



Research report

Lifetime manic spectrum episodes and all-cause mortality: 26-year follow-up of the NIMH epidemiologic catchment area study

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ABSTRACT

Background: While evidence suggests that depression is associated with medical morbidity and mortality, the potential role of mania has received less attention. This analysis evaluated the association between manic spectrum episodes and risk of all-cause mortality over a 26-year follow-up in a population-based study.

Methods: Participants included 14,870 adults (mean age 48.2 ± 20.3 ; 58.2% female; 31.1% non-white) from four sites of the Epidemiologic Catchment Area Study who completed the Diagnostic Interview Schedule (DIS) mania assessment between 1980 and 1983 and had vital status data available through 2007. Participants were grouped into four mutually exclusive categories based on DIS mania assessment: (1) *manic episode* ($n=46$); (2) *hypomanic episode* ($n=195$); (3) *sub-threshold manic symptoms* ($n=1041$); and (4) *no manic spectrum episodes* ($n=13,588$). To determine vital status, participants were matched with the National Death Index. Participants with manic spectrum episodes were compared to those without such episodes with regard to mortality after 26 years.

Results: After adjusting for major depressive symptoms and demographic differences, odds of mortality at follow-up for participants with lifetime manic spectrum episodes in the 30–44 and 45–64 year age cohorts at baseline were higher than those with no lifetime manic spectrum episodes in the same age cohorts ($OR=1.39$, 95% $CI=[1.00, 1.93]$ and $OR=1.41$, 95% $CI=[1.02, 1.95]$ respectively).

Conclusions: History of lifetime manic spectrum episodes in early to mid adulthood is associated with increased risk of all-cause mortality in mid to late life.

Limitations: Future studies of mania and mortality should evaluate specific causes of mortality.

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1. Introduction

Multiple studies have examined depression as a risk factor for mortality, and several systematic reviews have supported a positive association between depression and mortality (Lawson et al., 1999; Cuijpers and Smit, 2002; Sax and Dewwy, 2001; Cole et al., 1999). Meta-analyses have estimated a mortality rate among psychiatric inpatients and outpatients with depression that is 2.7 times higher as compared to the general population (Lawson et al., 1999) and 1.8 times higher for depressed compared to non-depressed individuals in the community (Cuijpers and Smit, 2002). Studies of depression in the community also support the association between minor and subclinical depression with increased risk of mortality (Cuijpers and Smit, 2002; Anda et al., 1993;

Zonderman et al., 1989; Thomas et al., 1992; Simonsick et al., 1995; Barefoot and Schroll, 1996; Pennix et al., 1999). These findings suggest that the association between depression and mortality may extend beyond cases of depression that are severe enough to result in hospitalization and includes milder cases identified among individuals in the community.

While many community-based studies have evaluated the association between depression and mortality, most studies examining the relationship between bipolar disorder and mortality are based on data from case-registers of patients diagnosed with bipolar disorder at a psychiatric or other health facility. Most of these studies have concluded that bipolar disorder is associated with an increased risk of all-cause and cause-specific mortality (Osby et al., 2001; Hoyer et al., 2000; Sharma and Markar, 1994; Black et al., 1987a; Laursen et al., 2007; Hoang et al., 2011; Chang et al., 2011; Angst et al., 2002; Tsai et al., 2005; Laursen, 2011a, 2011b). However, findings from previous case-register studies supporting an association between bipolar disorder and mortality can only be generalized to cases severe enough to warrant inpatient

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or outpatient treatment and not to the many individuals with bipolar disorder in the community who do not seek treatment or only rarely seek treatment. Past research indicates that many individuals with bipolar disorder are not diagnosed properly and do not receive proper psychiatric care (McAlpine and Mechanic, 2000; Hirschfeld et al., 2003; Kupfer et al., 2002). The average delay between onset of bipolar disorder symptoms and proper diagnosis and treatment has been estimated to be as long as 6 to 8 years, suggesting that there are many symptomatic but undiagnosed individuals in the community (Wang et al., 2005). Additionally, it has been estimated that only 32% of those meeting diagnostic criteria for bipolar I or bipolar II disorders had sought treatment in the past 12 months (Regier et al., 1993). Therefore, studies that extend beyond clinical populations are needed to fully understand the association between bipolar disorder and mortality in the general population. Furthermore, although the community prevalence of bipolar disorder type I and II account for an estimated 1–2% of the general population (Regier et al., 1993; Kessler, 1994), the latest evidence suggests that the prevalence of bipolar spectrum disorders may be as high as 6.4% (Judd and Akiskal, 1998). This higher prevalence takes into account subtler or milder presentations of manic symptoms that are common but often do not receive medical attention. However, the risk of increased mortality related to bipolar spectrum episodes in the community has not yet been investigated.

While research supports the association between unipolar depression and mortality as discussed above, the role of mania has received less attention. Individuals with bipolar disorder spend a substantial amount of their lifetime in both depressed (up to 31%) and manic (up to 9%) mood states (Judd et al., 2002), and it is possible that both depressed and manic mood states are independently responsible for the association between bipolar disorder and physical morbidities and mortality. To our knowledge, no study to date has examined risk of mortality in the community across the full spectrum of manic episodes either in the context of bipolar disorder or independent of a major depressive episode. Here we determined the association between manic spectrum symptoms and 26-year all-cause mortality in a large population-based study.

2. Methods

2.1. Study sample

The Epidemiologic Catchment Area (ECA) Program of research was initiated in response to the 1978 report of the President's Commission on Mental Health (President's Commission on Mental Health, 1978). The purpose was to collect data on the prevalence and incidence of mental disorders and on the use of and need for services by the mentally ill in a nationally representative sample. Initial data collection for the ECA Program took place across five sites (Baltimore, MD, Durham, NC, Los Angeles, CA, New Haven, CT, and St. Louis, MO) between 1980 and 1983. The study was comprised of a household survey and an institutional survey at each site and included a structured psychiatric diagnostic interview. Further details about the methods (Eaton and Kessler, 1985) and results (Robins and Regier, 1991) of the ECA study can be found elsewhere.

Of the five original sites, four (all except Los Angeles, CA) contributed data from which we could ascertain vital status. Our research team used this information to collect data on mortality of respondents through 2007 for these four sites. Participants were excluded if they: (1) had missing or incomplete data on the mania assessment section of the structured psychiatric interview ($N=1606$) (see Section 2.2); (2) had a less than “likely” quality

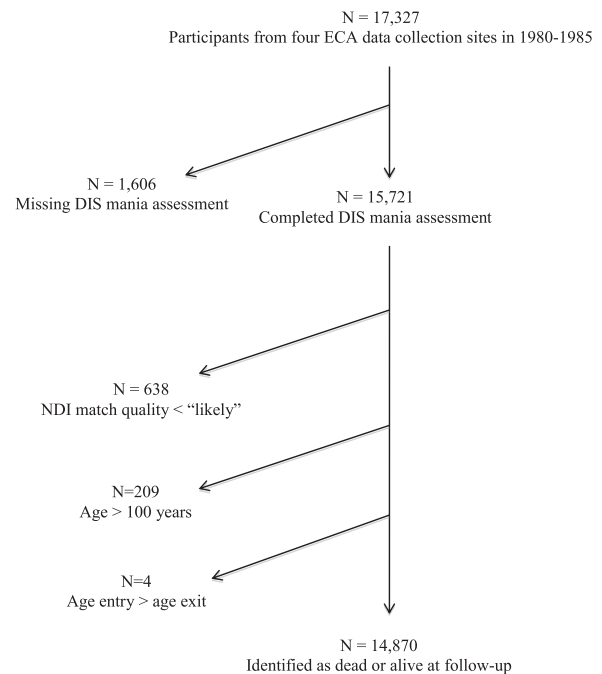


Fig. 1. Flow chart for study sample inclusion/exclusion.

of match with the National Death Index ($N=638$) (see Section 2.3); or (3) were projected to be over 100 years old at follow-up ($N=209$) (these participants were more likely to be deceased but not located). An additional four participants were excluded for apparent data entry errors where age of entry into the study was greater than the recorded age of death. Therefore, the sample for this analysis consisted of 14,870 of the original 17,327 participants from the four study sites (Fig. 1).

2.2. Psychiatric assessment: diagnostic interview schedule (DIS) (Robins et al., 1982)

The DIS is a structured interview designed to be administered by a trained lay interviewer and consists mostly of questions with yes/no response options designed to diagnose mental disorders based on the DSM-III criteria. Although the DIS has demonstrated high specificity in validation studies comparing DIS diagnosis of bipolar disorder to that of a psychiatrist, specificity varied a great deal across studies (15–60%) (Eaton and Kessler, 1985; Robins and Regier, 1991; Robins et al., 1982; Greist et al., 1987). Because our goal was to assess the risk of mortality across the full manic spectrum, we chose to include all DIS mania symptoms in our analysis, not just the full criteria for a DMS-III manic episode or bipolar disorder. For this analysis, participants were grouped into four mutually exclusive categories based on their responses to eight questions on the DIS designed to capture the DSM-III diagnostic criteria for a manic episode, as done previously by Judd and Akiskal (1998). These four groups are described below.

2.2.1. Participants with a history of one or more manic episodes (ManEp; $N=46$)

Participants in this group met DSM-III criteria for one or more lifetime manic episodes at the time of the ECA study assessment. Specifically, these participants reported having an elevated, expansive or euphoric mood for a week or more (DIS question 100) in addition to at least three other co-occurring manic symptoms, or at least four other manic symptoms if they reported irritable mood (DIS question 110A). These participants also were required

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