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Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden.

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Article summary

Article focus

- To estimate mortality in cardiovascular disease and its subgroups cerebrovascular and coronary heart disease and acute myocardial infarction among 17,101 persons diagnosed with bipolar disorder during 1987 to 2006 in Sweden compared to the general population in a national register study with a 20-year follow-up.

Key messages

- Persons with bipolar disorder died of CVD approximately ten years early. Excess mortality from CVD and other somatic diseases was three times higher (1,812 deaths) than suicide and other unnatural causes (675 deaths). MRRs for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high compared to the general population. Despite the increased mortality, hospital admissions for CVD treatment were only slightly increased.

- The increased cardiovascular mortality in persons with bipolar disorder calls for more resources to prevent and treat somatic diseases. Specifically, our findings imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as the population.

Strengths and limitations of this study

- A large cohort with comprehensive data on patient characteristics was studied. Mortality data from the Swedish cause of death register are of high quality.
- Clinical information on symptoms and treatment were lacking.

ABSTRACT (word count: 261)

Objective: To estimate cardiovascular mortality among persons with bipolar disorder in Sweden compared to the general population.

Design: Population register based cohort study with a 20-year follow-up.

Setting: Sweden.

Participants: The entire population of Sweden (n=10.6 million) of whom 17,101 persons were diagnosed with bipolar disorder between 1987 and 2006.

Main outcome measures: Mortality rate ratios (MRR), excess mortality (excess deaths), cardiovascular disorders (CVD) and specifically cerebrovascular disease, coronary heart disease, and acute myocardial infarction, hospital admission rate ratios (ARR).

Results: Persons with bipolar disorder died of CVD approximately ten years earlier than did persons of the general population. More than two thirds (73%) of all deaths in persons with bipolar disorder were caused by CVD and other somatic diseases, whereas suicide and other unnatural causes accounted for less than a third of all deaths (27%). Excess mortality of CVD and other somatic diseases was three times higher (1,812 deaths) than that of suicide and other unnatural causes (675 deaths). MRRs for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high in persons with bipolar disorder compared to the general population. Despite the increased mortality of CVD, ARRs for CVD treatment were only slightly increased in persons with bipolar disorder when compared to the general population.

Conclusions: The increased cardiovascular mortality in persons with bipolar disorder calls for more resources to prevent and treat somatic diseases in this group. Specifically, our findings further imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as persons without bipolar disorder.

Introduction

Cardiovascular disease (CVD) is the main cause of death in many developed countries.[1] CVD encompasses a broad range of different conditions that are potentially life threatening. In Sweden, although mortality from CVD in the population has almost halved in the last two decades, CVD still accounts for more than 40% of all deaths in the country.[2] Premature death in patients with severe mental health disorders, especially patients with schizophrenia and bipolar disorder, has been generally attributed to suicide rather than CVD, despite studies showing that CVD leads to shorter life spans than does suicide in those patients.[3] Persons with bipolar disorder have an increased risk of CVD and have been observed to die due to CVD twice as often as the general population.[4-6] Although previous studies have shown an association between bipolar disorder and mortality from CVD, few studies have addressed mortality rates in different CVD subgroups, or examined their use of health care. An improved understanding of the causes behind and magnitude of CVD among bipolar patients is warranted along with an in-depth evaluation of different diagnostic CVD subgroups. The answers to these questions, which are far less investigated than among patients with schizophrenia, are essential in the efforts to address the problem of premature deaths due to CVD in bipolar patients.

The aim of this study was to evaluate excess mortality from CVD, such as cerebrovascular disease and coronary heart disease with acute myocardial infarction as its most important component, and also CVD hospitals admissions, in people with bipolar disorder in Sweden between 1987 and 2006 compared to the population.

Methods

Cohort and follow-up

All persons who resided in Sweden between the 1st of January 1987 and the 31st of December 2006 (n=10,631, 208) were identified using the Swedish Total Population Register (TPR). The TPR was established in 1968 and contains information on sex, date and place of birth, date of migration of every resident in Sweden. Information on hospital admission, medical diagnosis, and cause of death was obtained by linking the TRP with the national Swedish Cause-of-Death Register and the National Patient Register (NPR) using each resident's unique personal identification number.

The NPR, which is maintained by the National Board of Health and Welfare, contains information on all hospital in-patient treatments carried out in Sweden since 1987. For psychiatric in-patient care the register has nationwide coverage dating back from 1973. For each hospitalization, the unique national registration number, date of admission and discharge, and diagnosis are registered in NPR. In Sweden, all hospital diagnoses are classified according to the WHO International Classification of Diseases (ICD). Since the diagnostic definitions of affective disorders were substantially changed in ICD-9 and ICD-10 as compared with ICD-8, only patients diagnosed with bipolar disorder according to ICD-9 or ICD-10 were included in the study. Bipolar diagnoses recorded between 1987 and 1996 were identified using ICD-9 (296A, C, E, 298B). From 1997 and later, ICD-10 (F30-F31) was used to identify bipolar diagnoses. The Swedish Cause of Death Register (CDR) includes all individuals who were registered in Sweden at the time of death. The register provides information on date of death as well as main (underlying) and secondary causes of death based on death certificates. Definitions regarding causes of death and ICD codes used in this study are shown in Figure 1.

A total of 20,248 patients admitted to hospital between 1st of January 1987 and 31st of December 2006 with a main diagnosis of bipolar disorder (ICD-9; ICD-10) were identified in the NPR. Of the 20,248 patients, 3,147 had been previously diagnosed with schizophrenia (ICD-8: 295; ICD-9: 295; ICD-10; F20, F25) and were consequently excluded. Thus, the total risk population of the study comprised 17,101 patients with bipolar disorder.

The follow-up period was 20 years (1987-2006). Immigrants were included from the date of immigration to Sweden. Each person was followed until December 31, 2006, or date of death or emigration, depending on which came first. Inclusion in the risk population started from the date of first hospital admission (discharge diagnosis) during the study period.

Statistical analysis

Person years at risk, number of cause-specific deaths and hospital admissions due to CVD for both bipolar patients and the general population were determined. Person time was stratified by sex, calendar year and age. Mortality rate ratios (MRR) and Admission rate ratios (ARR) and predicted mortality rates were calculated with corresponding 95% confidence intervals (CI) using Poisson regression models with the GENMOD procedure using statistical software SAS (version 9.2). All models were adjusted for or stratified by sex, attained age and year of follow-up.

To calculate the excess mortality for patients with bipolar disorder the observed number of deaths was compared with the expected number of deaths among patients with bipolar disorder. The expected number of deaths was calculated by applying age, sex and calendar specific mortality rates in the general population to the time at risk among the patients. The risk of dying from CVD after first hospital admission was analyzed by estimating cause-specific survival curves using the Kaplan-Meier method. Additional adjusted hazard ratios with 95% CIs were estimated using Cox proportional hazard models.

When hospital admission due to CVD (Admission Rate Ratios, ARR) was the event of interest, follow-up ended on the day of first admission. To ensure that the observed cases were incident, a three-year run-in period was created to compensate for the lack of CVD coverage in the NPR before 1987. Hence, all bipolar patients analyzed had no hospital admissions due to CVD recorded for at least three years before follow-up.

Results

Causes of death

Total mortality (death from any cause) between 1987 and 2006 in Sweden was more than twice as high among patients with bipolar disorder compared to the general population (MRR 2.40; 95% CI 2.33-2.47). Specifically, 2,489 excess deaths in patients with bipolar disorder

were observed (Table 1). With mortality causes subdivided into CVD, other somatic, and unnatural causes of death, we found that men and women with bipolar disorder were twice as likely to die of CVD compared to the general population (MRR 2.03; 95% CI 1.93-2.13), with 824 excess deaths due to CVD. Mortality from other somatic causes was also doubled (MRR 2.10; 95% CI 2.00-2.19), with 988 excess deaths. Unnatural causes of death, such as suicide and accidents, were increased more than nine times in bipolar patients (MRR 9.66; 95% CI 8.99-10.37), with 675 excess deaths. As far as CVD subgroups were concerned, mortality from coronary heart disease and cerebrovascular disease was twice as high in bipolar patients, with 377 excess deaths (MRR 1.95; 95% CI 1.81-2.09) and 184 excess deaths (MRR 2.00; 95% CI 1.81-2.09), respectively. Mortality from acute myocardial infarction was almost twice as high in bipolar patients (MRR 1.83; 95% CI 1.67-2.01), with 200 excess deaths. Bipolar women and men of all ages had an equally increased mortality from CVD (data not shown).

Age and cause of death

MRR for CVD was increased for bipolar patients across all ages but was particularly pronounced in the young age groups (Figure 2b). Patients with bipolar disorder who died of CVD were younger than people in the general population. The same finding was observed when we subdivided CVD into cerebrovascular disease, coronary heart disease and acute myocardial infarction (Figure 2e-g). For acute myocardial infarction and coronary heart disease the increased risk was most apparent in the 55-65 years age groups (2f-g). In the ages below 50 years the results should be interpreted with caution because there were very few events in these ages. Death by suicide and other unnatural deaths were 15 times more common among bipolar patients below 30 years of age compared to persons of the same age in the general population (Figure 2d). Overall, the MRR for suicide and other unnatural deaths decreased with increasing age. However, it should be noted that it remained significantly increased in persons aged between 70-74 years (MRR 6.88; CI 95% 5.06-9.35) (Figure 2d).

Admission rates

Hospital admission rates for CVD among patients with bipolar disorder were similar to those for the general population even though MRR for CVD was almost twice as high, independent of the specific CVD cause (Tables 1 and 2). Survival rates five years after first hospital admission for CVD were significantly lower among bipolar patients than among the general population (Figure 4).

Discussion

Key findings

In this nationwide study of mortality among persons with bipolar disorder in Sweden compared to the population, somatic illness was the main cause of death. Bipolar patients died of CVD around ten years earlier than the general population. Mortality from cerebrovascular disease, coronary heart disease, and acute myocardial infarction was twice as high in bipolar patients as in the general population, while the frequency of hospital admissions due to these diseases was not increased. Our findings clearly showed that CVD and other somatic diseases in persons with bipolar disorder accounted for a substantial number of excess deaths (n=1,812), larger than suicide and other unnatural causes of death (n=675).

Strengths and limitations

The Swedish National Patient Register and Cause of Death Register include everyone who resides in the country and are considered unique, comprehensive and highly credible. Currently more than 99% of all somatic and psychiatric hospital discharges are recorded in the National Patient Register.[7] Swedish hospitals and government agencies are obliged by law to enter medical information in the National Patient Register. All diagnoses in the National Patient and Cause of Death registers were given by patients' doctors using international classification standards (ICD codes). Being register based, this study used information about clinical diagnoses from hospital admissions in Sweden. During the study period, the ICD diagnostic definitions were specific for bipolar disorder. A validation of the Swedish clinical bipolar diagnoses has shown high validity, sufficient for epidemiological studies.[8] One limitation of this study was that it was based on in-patient diagnoses, which may have generated a selective bias towards severely ill patients. However, most individuals at severe stages of bipolar disorder are admitted to hospital in Sweden. In a previous study, we have shown that the number and frequency of hospital admissions due to bipolar disorder remained relatively unchanged in Sweden during recent years, while the overall number of psychiatric admissions was drastically reduced.[9] We did not have access to medical records or information on medical treatment, which would have been of interest since antidepressants use have been linked to increased risk of fatal coronary heart disease.[10] In terms of the validity of the data on causes of death, in CVD deaths we found a slightly higher autopsy rate (28%)

among patients with bipolar disorder than in the general population (22%). It is unlikely that these small differences affected the outcome of the study.

Findings from other studies

The findings of this study add to the growing body of evidence that somatic diseases, particularly CVD, contribute to a shorter lifespan among bipolar patients. Findings from several large register-based studies from different parts of the world indicate that cardiovascular disease is responsible for the majority of excess deaths, with up to 2.5-fold increased mortality.[3 5 6 11-15] Studies using registers from the Nordic countries have shown than bipolar patients run almost twice the risk of dying from CVD than do persons in the general population, the mechanisms for which are currently unknown.[4 5] Possible risk factors for the increased mortality from CVD among bipolar patients may include adverse effects of medication,[16 17] high levels of smoking,[18] unhealthy diet,[19 20] lack of physical activity,[19] and low social-economic status.[21] In addition, effects of genetic associations, such as those reported between Type 2 diabetes, CHD and schizophrenia,[22] could not be excluded. One of the most important locus of genetic polymorphism linked to bipolar disease and depression is around the ATP-activated ion-channel receptor *P2X7*.[23] Recently, a polymorphism in the *P2X7* gene was linked to increased risk of stroke and acute myocardial infarction,[24] and the same polymorphism has also recently been shown to be linked to cognitive symptoms in bipolar disorder,[25] indicating that common genetic factors could have effect on both cardiovascular disease and bipolar disorder.

CVD undertreated in bipolar disorder

Studies of patients with bipolar disorder have shown that the patients run an increased risk of metabolic syndrome,[26] i.e. increased blood glucose,[27]and cholesterol levels,[28] higher blood pressure,[29] and higher prevalence of overweight and obesity[19], closely associated with CVD. To prevent and treat metabolic disorders in patients with severe mental illnesses such as bipolar disorder, new guidelines have been drawn up for clinicians in Sweden.[30] However the effects of those guidelines are still to be evaluated.

Our finding that patients with bipolar disorder showed only slightly increased hospital admissions rates for CVD despite their twice as high cardiovascular mortality, strongly suggests that CVD is undertreated in bipolar patients when compared to the general population. Our register data alone cannot offer an explanation for this finding. However, the

MRR and ARR patient populations are slightly different, in the respect that the ARR patients are identified at their first index admission, while the MRR patients may have several admissions, and thus being more severely affected. Unequal access to health care (i.e. receiving cardiac treatment of lower quality) for reasons other than financial has been previously suggested as a contributor to excess CVD mortality in patients with severe mental disorders, such as schizophrenia,[31] and may be indicated by our findings of increased mortality after discharge from hospital compared to the population. These factors have not been studied extensively in bipolar patients. Health care in Sweden is free and is financed primarily through taxes. Therefore, it is unlikely that patients with bipolar disorder do not seek hospital care for lack of financial means.

Many mechanisms can contribute to the under-treatment of CVD among people with bipolar disorder. Our results indicate a failure of the health care system to identify and address the health needs of those patients, which has also been shown in other studies of people with severe mental disorders.[32] The levels of CVD mortality in our bipolar persons are similar to those in schizophrenia, where adverse effects of antipsychotic medication have been considered the main contributing factor. When compared with schizophrenia, a recent study of bipolar disorder in Stockholm County found only 29% of bipolar patients medicating with antipsychotics, as compared to practically all schizophrenia patients, which raises the question of the importance of adverse effects of antipsychotics in CVD.[33]

Conclusions

The observed number of deaths from cardiovascular diseases in patients with bipolar disorders was almost twice as the expected number when comparing with the general population, suggesting that more resources are needed for the prevention of these diseases in this patient group. Targeted interventions by effective cooperation between primary health care and psychiatric professionals would be crucial in the efforts to reduce excess CVD mortality in patients with bipolar disorder. Finally, effective cardiac treatment would ensure longevity and improved quality of life for bipolar patients.

Contributors: UÖ had the idea of the study and is guarantor of the study together with JH, who has performed the statistical analyses. JW has contributed to the design of the study and drafted the manuscript together with UÖ. KW, DE and LA have contributed to the design of the study and with revisions of the manuscript. All authors have approved the final version of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). JW, KW, LA, DE, UÖ has declared no support from any organization for the submitted work, no financial relationship with any organizations that would have interest in the submitted work in the previous three years, and no other activities that could appear to have influenced the submitted work. UÖ has declared traveling expenses from Janssen-Cilag for attending a course in October 2012 unrelated to the study.

Ethical approval: This study was approved by the ethical review board in Stockholm County. The ethical review board determined that informed consent from participating individuals was not required.

Data sharing: The analysis data set for this study is available from the National Board of Health and Welfare (Socialstyrelsen) in Sweden. Please contact JH for further information.

Figure 1. ICD-coding and disease classification

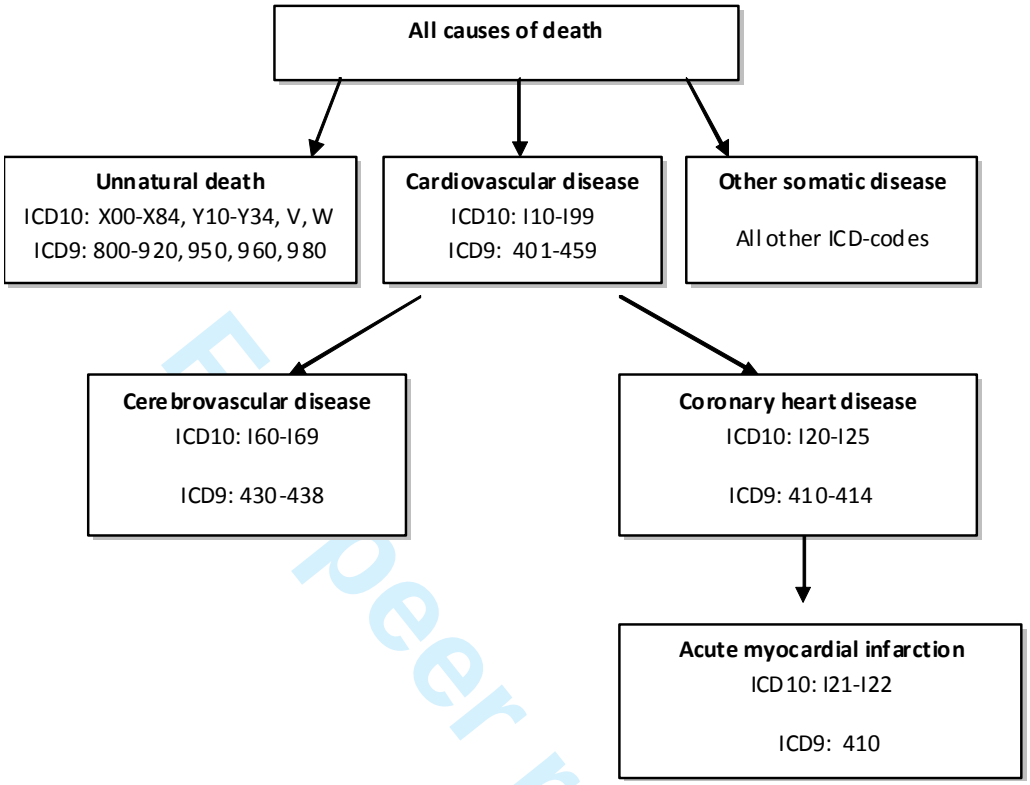


Table 1. Mortality rate ratios for bipolar patients between 1987 and 2006

	Men		Women		Total (both sexes)		
Cause of death	**Cases**	**MRR (95% CI)**	**Cases**	**MRR (95% CI)**	**Cases**	**MRR (95% CI)**	**Excess cases (95% CI)**
All causes of death	1874	2.48 (2.37-2.59)	2393	2.34 (2.25-2.44)	4267	2.40 (2.33-2.47)	2489 (2361-2617)
Cardiovascular disease	733	2.16 (2.01-2.33)	892	1.93 (1.81-2.06)	1625	2.03 (1.93-2.13)	824 (745-903)
Other somatic deaths	735	1.97 (1.83-2.11)	1154	2.19 (2.06-2.32)	1889	2.10 (2.00-2.19)	988 (902-1073)
Unnatural deaths	406	9.37 (8.50-10.33)	347	10.02 (9.01-11.13)	753	9.66 (8.99-10.37)	675 (621-729)
Cerebrovascular disease	144	2.29 (1.94-2.70)	224	1.86 (1.63-2.12)	368	2.00 (1.81-2.22)	184 (147-222)
Coronary heart disease	385	2.00 (1.81-2.21)	391	1.89 (1.71-2.09)	776	1.95 (1.81-2.09)	377 (323-432)
Acute myocardial infarction	227	1.89 (1.66-2.15)	213	1.78 (1.55-2.03)	440	1.83 (1.67-2.01)	200 (159-241)

Table 2. Admission rate ratios for bipolar patients during 1990 to 2006

	Men		Women		Total (both sexes)		
Hospital admissions	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Excess cases (95% CI)
Cardiovascular disease	540	1.27 (1.16-1.38)	696	1.33 (1.24-1.43)	1236	1.30 (1.23-1.38)	287 (218-356)
Cerebrovascular disease	179	1.32 (1.14-1.53)	271	1.43 (1.27-1.62)	450	1.39 (1.26-1.52)	125 (84-167)
Coronary heart disease	212	1.02 (0.89-1.17)	207	1.06 (0.92-1.21)	419	1.04 (0.94-1.14)	15 (-25-55)
Acute myocardial infarction	133	0.96 (0.81-1.14)	137	1.11 (0.94-1.31)	270	1.03 (0.92-1.16)	8 (-24-41)

Figure 2a. Mortality Rate Ratios (MRR) for all causes of death by age at death in bipolar disorder patients and the general population.

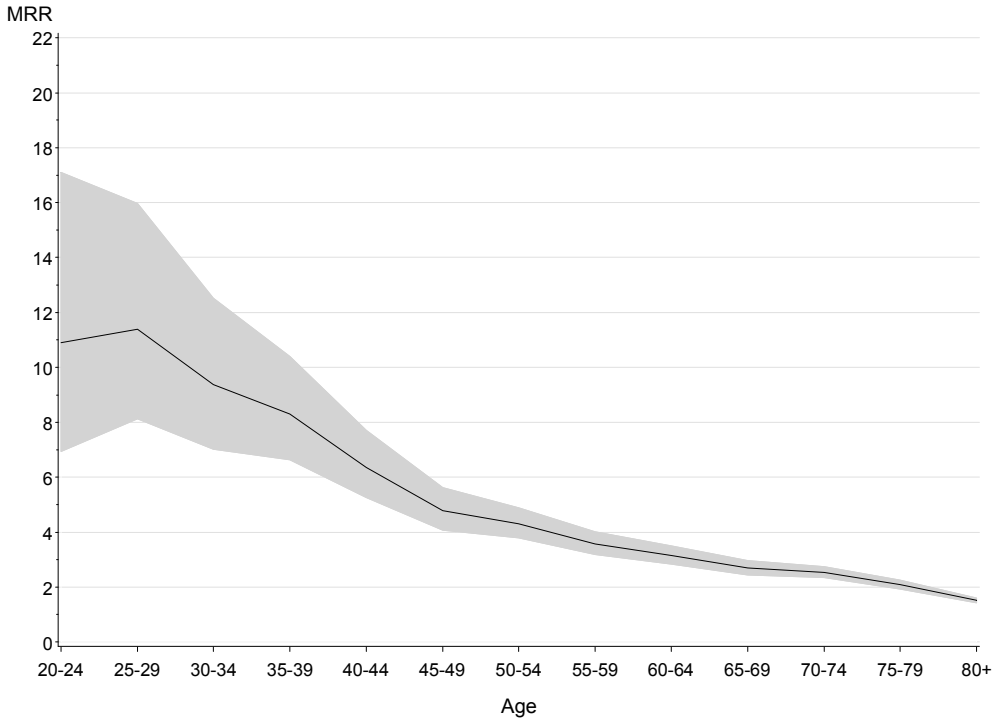


Figure 2b. Mortality Rate Ratios (MRR) for cardiovascular death by age at death in bipolar disorder patients and the general population.

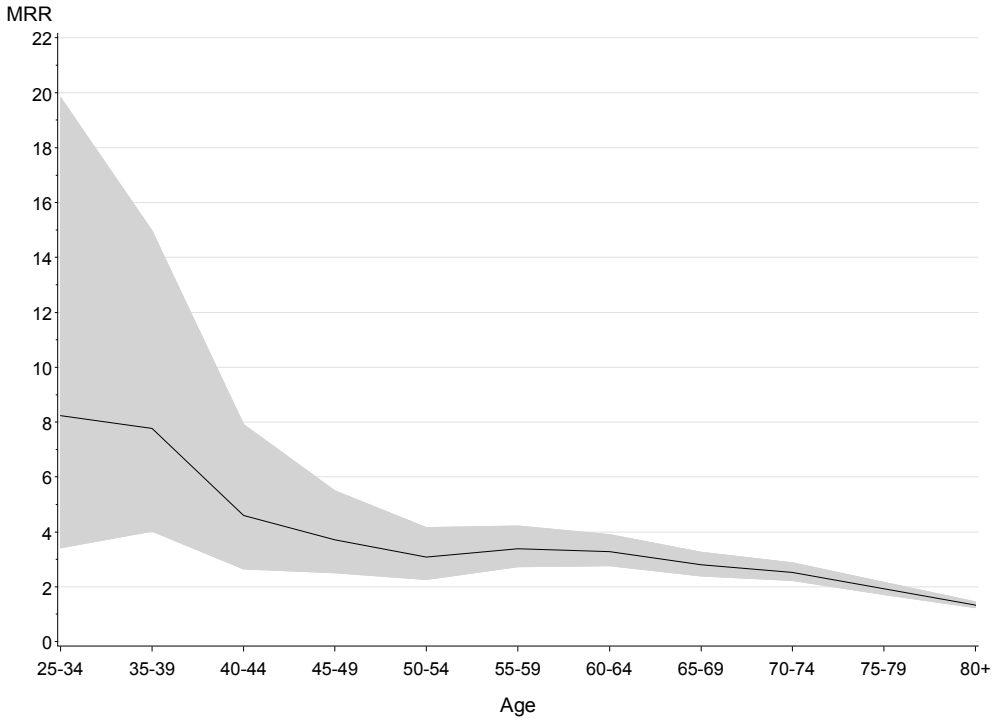


Figure 2c. Mortality Rate Ratios (MRR) for other somatic death by age at death in bipolar disorder patients and the general population.

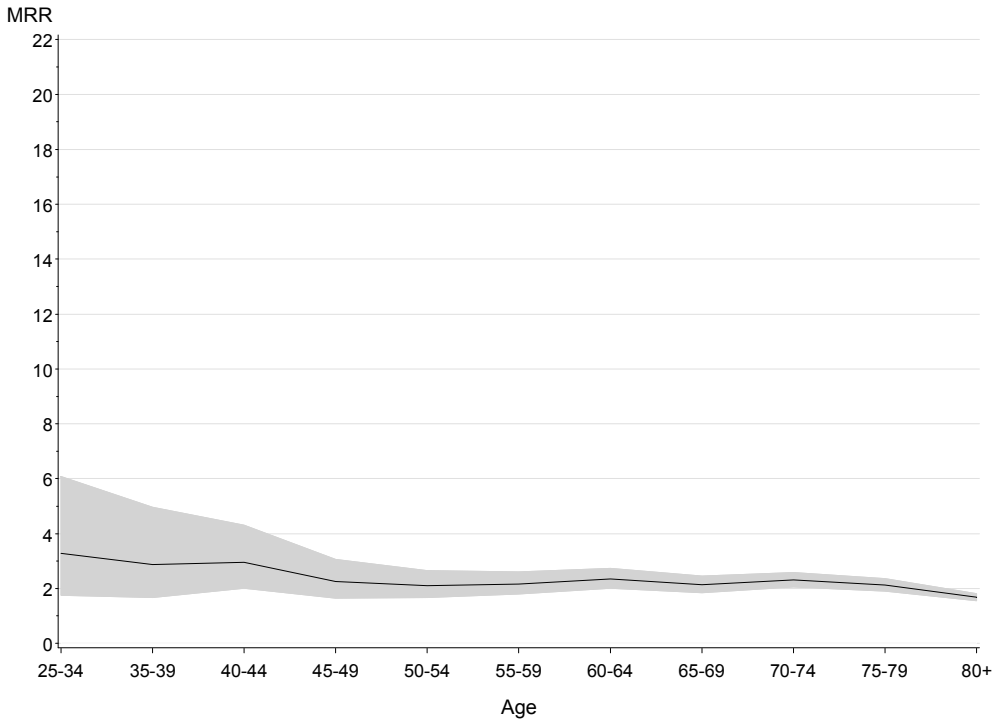


Figure 2d. Mortality Rate Ratios (MRR) of suicide and other unnatural deaths by age at death in patients with bipolar disorder and the general population.

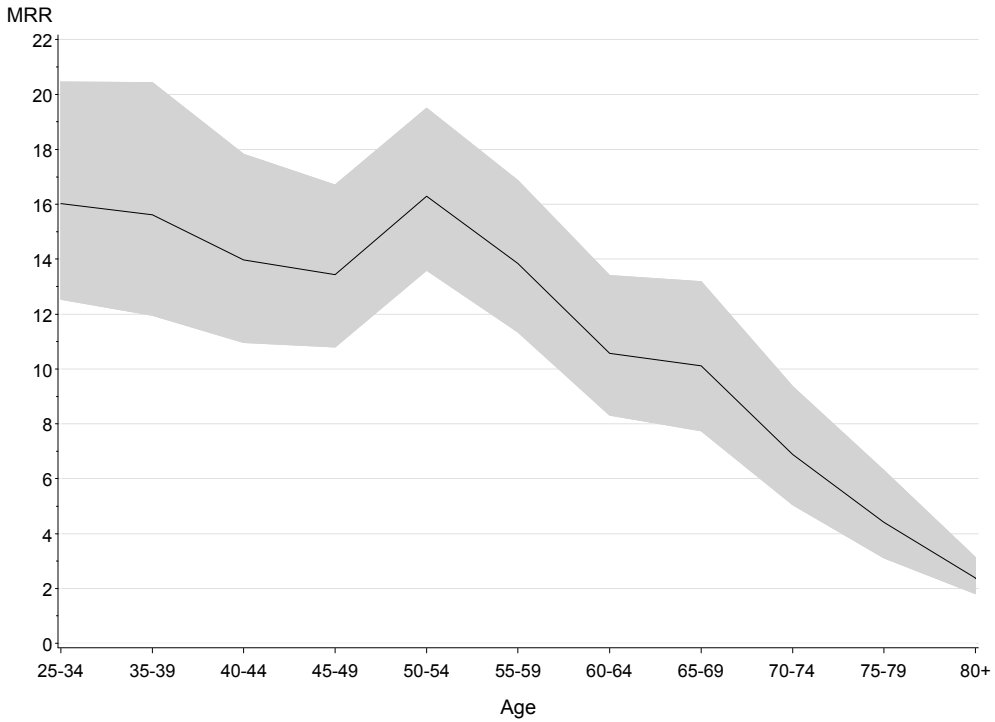


Figure 2e. Mortality Rate Ratios (MRR) of cerebrovascular disease by age at death in patients with bipolar disorder and the general population.

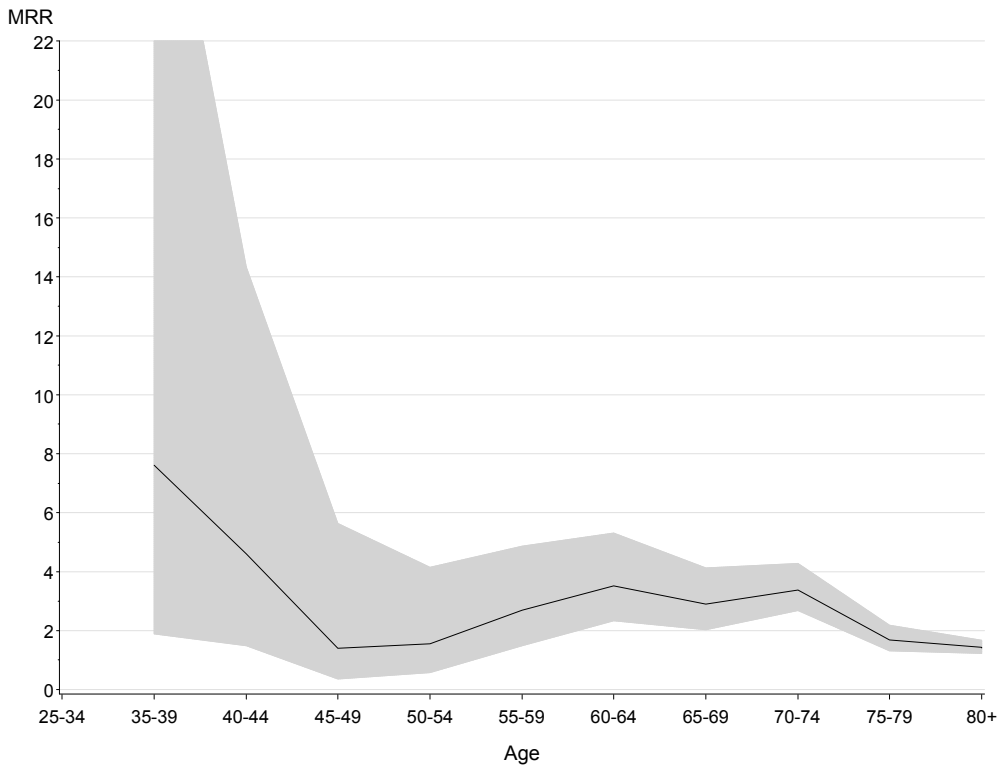


Figure 2f. Mortality Rate Ratios (MRR) of coronary heart disease by age at death in patients with bipolar disorder and the general population.

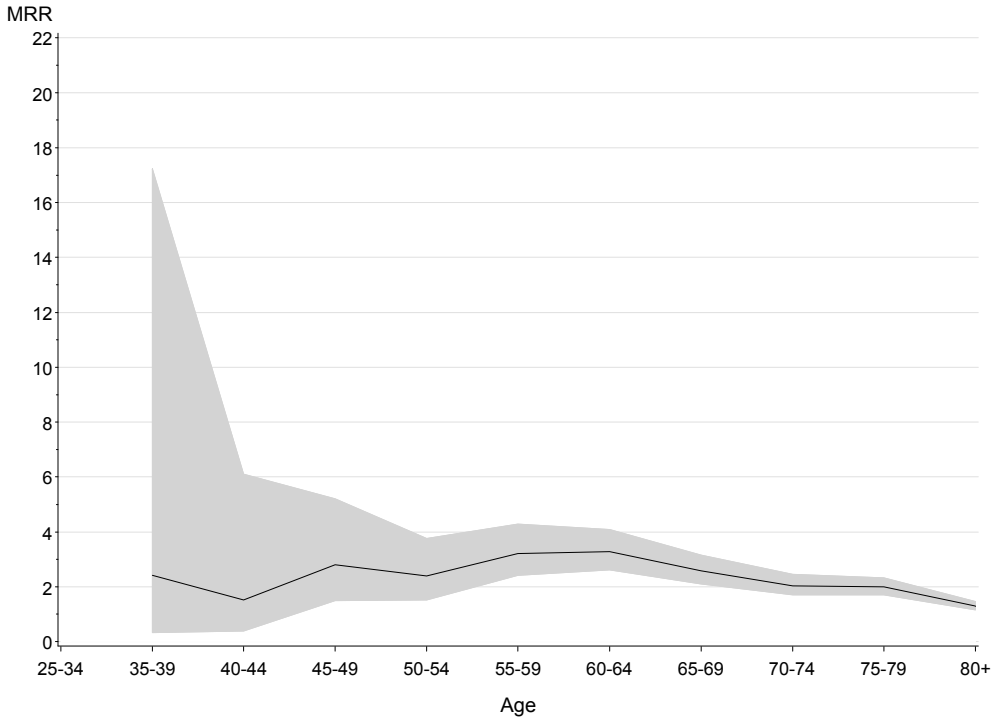


Figure 2g. Mortality Rate Ratios (MRR) of acute myocardial infarction by age at death in patients with bipolar disorder and the general population.

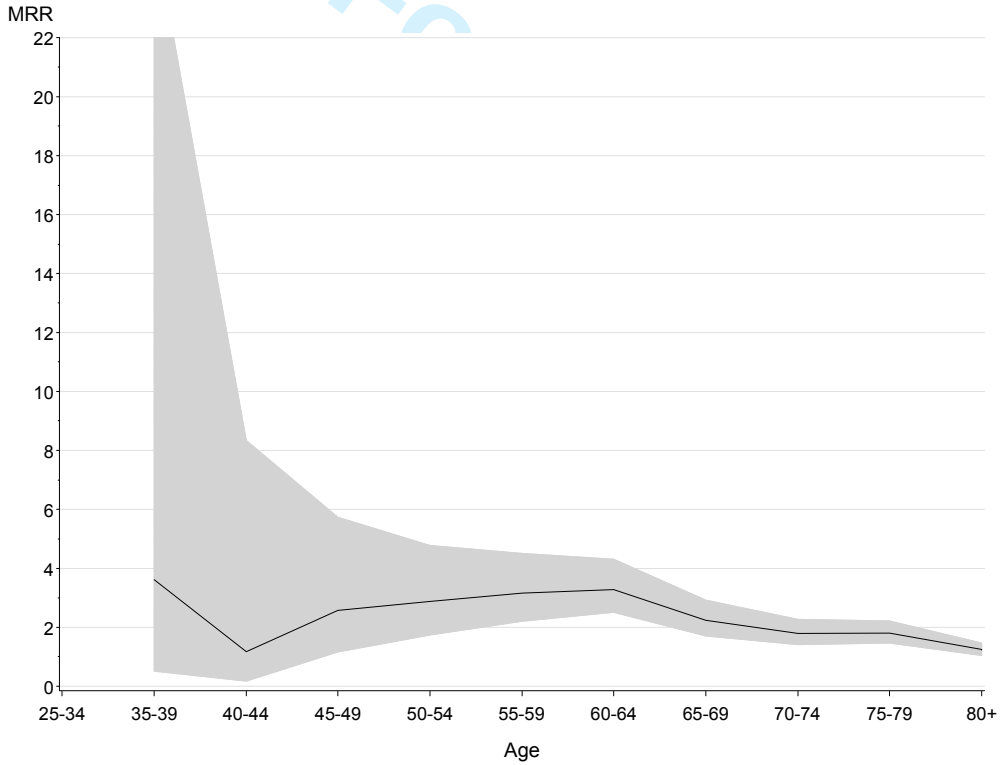


Figure 3a. Mortality of coronary heart disease per 1000 person-years in patients with bipolar disorder and the general population adjusting for sex and calendar year.

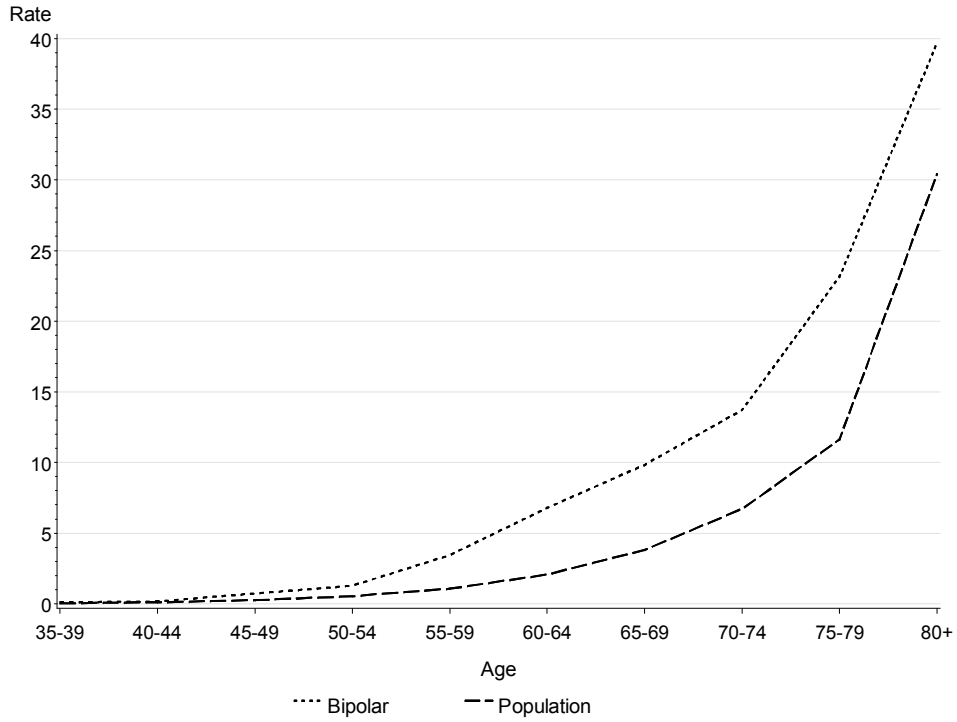


Figure 3b. Acute myocardial infarction

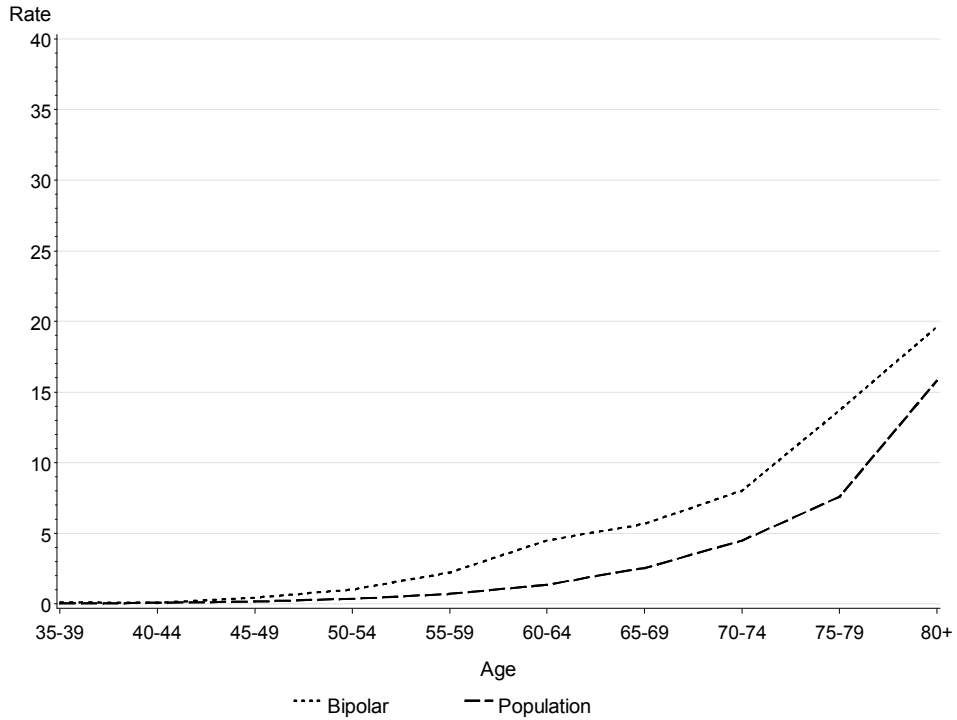


Figure 3c. Cerebrovascular disease

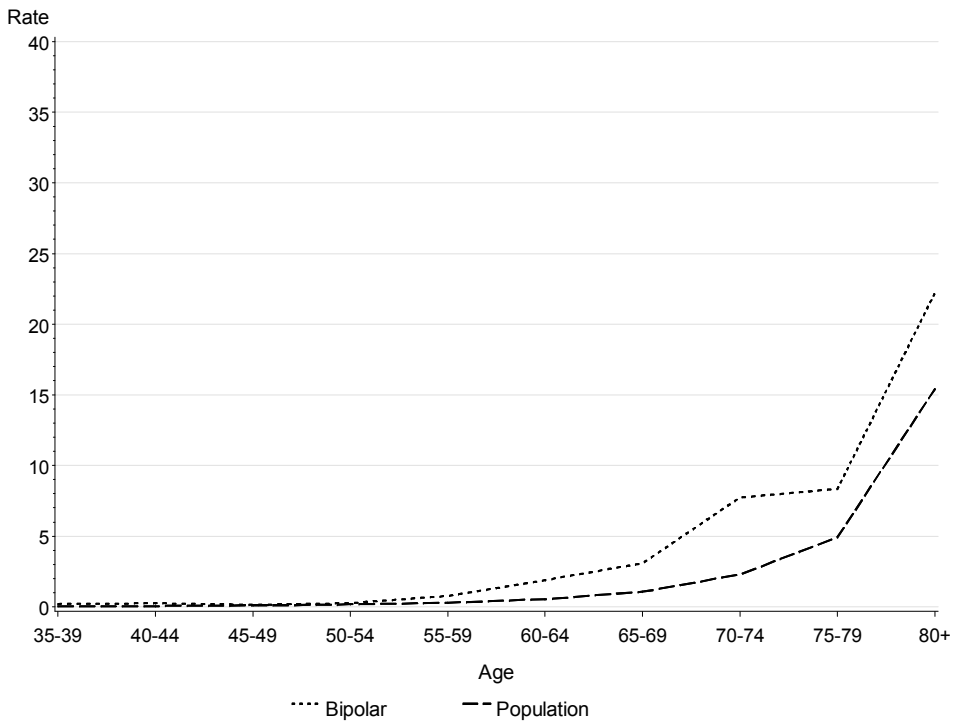
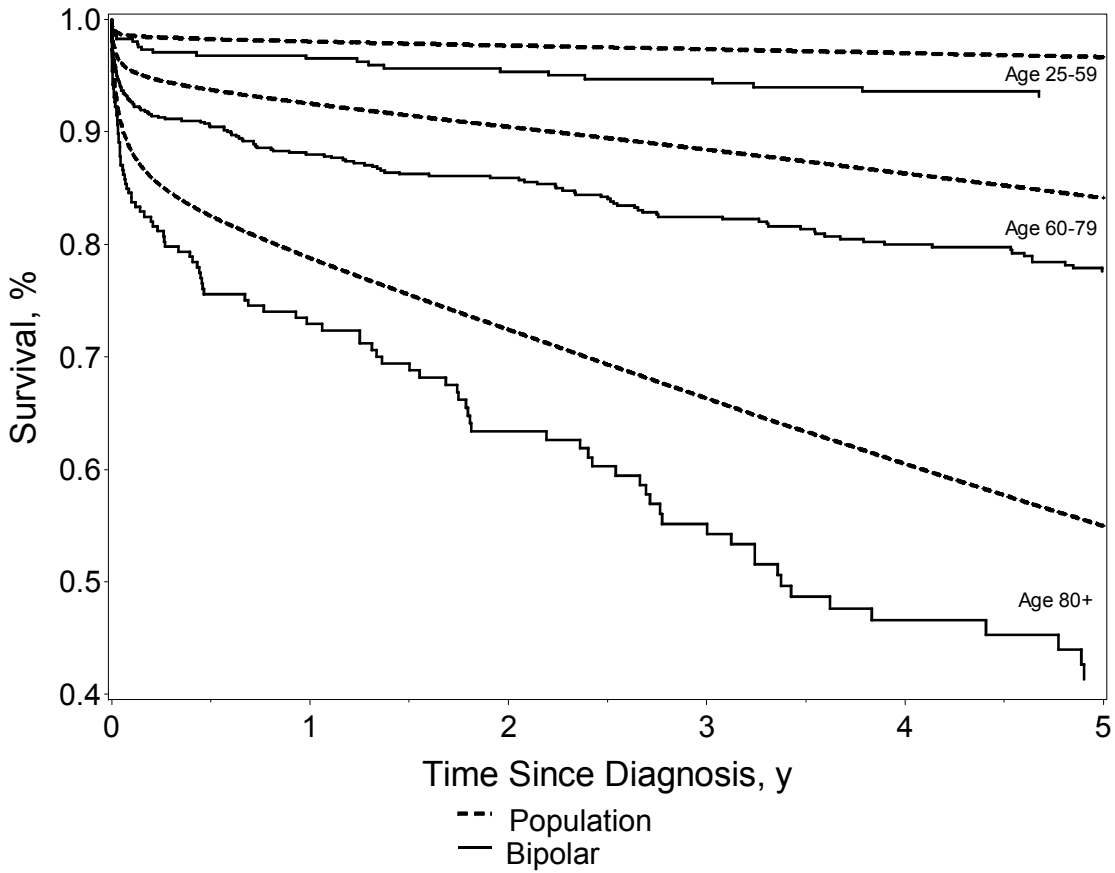


Figure 4. Five-year survival of cardiovascular disease after disharge from first cardiovascular admission stratified by age at hospital contact.



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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). JW, KW, LA, DE, UÖ has declared no support from any organization for the submitted work, no financial relationship with any organizations that would have interest in the submitted work in the previous three years, and no other activities that could appear to have influenced the submitted work. UÖ has declared traveling expenses from Janssen-Cilag for attending a course in October 2012 unrelated to the study.

CONTRIBUTORSHIP

UÖ had the idea of the study and is guarantor of the study together with JH, who has performed the statistical analyses. JW has contributed to the design of the study and drafted the manuscript together with UÖ. KW, DE and LA have contributed to the design of the study and with revisions of the manuscript. All authors have approved the final version of the study.

DATA SHARING

The analysis data set for this study is available from the National Board of Health and Welfare (Socialstyrelsen) in Sweden. Please contact JH for further information.

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Our manuscript have been checked towards the STROBE Statement.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies*** -

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden

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Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden.

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Article summary

Article focus

- To estimate mortality in cardiovascular disease (CVD) and its subgroups cerebrovascular and coronary heart disease and acute myocardial infarction among 17,101 persons diagnosed with bipolar disorder in Sweden, compared to the general population in a national register study with a 20-year follow-up.

Key messages

- Persons with bipolar disorder died of CVD approximately ten years early. Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was higher than that of suicide and other external causes (n=675 deaths). Mortality rate ratios (MRR) for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high compared to the general population. Despite the increased mortality, hospital admissions, admission rate ratios (ARR) for CVD treatment in persons with bipolar disorder were only slightly increased.

- The increased cardiovascular mortality in persons with bipolar disorder calls for renewed efforts to prevent and treat somatic diseases. Specifically, our findings imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as the population.

Strengths and limitations of this study

- A large national cohort with comprehensive data on patient characteristics was studied. Mortality data from the Swedish cause of death register are of high quality.
- Clinical information on symptoms and treatment were lacking.

ABSTRACT (word count: 265)

Objective: To estimate cardiovascular mortality among persons with bipolar disorder in Sweden compared to the general population.

Design: Population register based cohort study with a 20-year follow-up.

Setting: Sweden.

Participants: The entire population of Sweden (n=10.6 million) of whom 17,101 persons were diagnosed with bipolar disorder between 1987 and 2006.

Main outcome measures: Mortality rate ratios (MRR), excess mortality (excess deaths), cardiovascular disorders (CVD) and specifically cerebrovascular disease, coronary heart disease, acute myocardial infarction, sudden cardiac deaths, and hospital admission rate ratios (ARR).

Results: Persons with bipolar disorder died of CVD approximately ten years earlier than the general population. One third (38%) of all deaths in persons with bipolar disorder were caused by CVD, and almost half (44%) by other somatic diseases, whereas suicide and other external causes accounted for less than a fifth of all deaths (18%). Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was higher than that of suicide and other external causes (n=675 deaths). MRRs for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high in persons with bipolar disorder compared to the general population. Despite the increased mortality of CVD, hospital admissions (ARR) for CVD treatment were only slightly increased in persons with bipolar disorder when compared to the general population.

Conclusions: The increased cardiovascular mortality in persons with bipolar disorder calls for renewed efforts to prevent and treat somatic diseases in this group. Specifically, our findings further imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as persons without bipolar disorder.

Introduction

Cardiovascular disease (CVD) is the main cause of death in many developed countries.[1] CVD encompasses a broad range of different conditions that are potentially life threatening. In Sweden, although mortality from CVD in the population has almost halved in the last two decades, CVD still accounts for more than 40% of all deaths in the country.[2] Premature death in patients with severe mental health disorders, especially patients with schizophrenia and bipolar disorder, has historically been attributed to suicide. However, more recent studies have shown that CVD leads to more reduced life spans than does suicide in those patients.[3] Persons with bipolar disorder have an increased risk of CVD and have been observed to die due to CVD twice as often as the general population.[4-6] Although previous studies have shown an association between bipolar disorder and mortality from CVD, few studies have addressed mortality rates in different types of vascular mortality, or examined their use of health care. An improved understanding of the causes behind and magnitude of CVD among bipolar patients is warranted along with an in-depth evaluation of different diagnostic CVD subgroups. The answers to these questions, which are far less investigated than among patients with schizophrenia, are essential in the efforts to address the problem of premature deaths due to CVD in bipolar patients, and they are the focus of the present Swedish national register-based study, which extends earlier Swedish findings[5] both by more specific CVD mortality analyses and more recent patient data.

The aim of this study was to evaluate excess mortality from CVD, such as cerebrovascular disease and coronary heart disease with acute myocardial infarction as its most important component, and also CVD hospitals admissions, in persons with bipolar disorder in Sweden between 1987 and 2006 compared to the population.

Methods

Cohort and follow-up

All persons who resided in Sweden between the 1st of January 1987 and the 31st of December 2006 (n=10,631, 208) were identified using the Swedish Total Population Register (TPR). The TPR was established in 1968 and contains information on sex, date and place of birth, date of migration of every resident in Sweden. Information on hospital admission, medical diagnosis, and cause of death was obtained by linking the TRP with the national Swedish Cause-of-Death Register and the National Patient Register (NPR) using each resident's unique personal identification number.

The NPR, which is maintained by the National Board of Health and Welfare, contains information on all hospital in-patient treatments carried out in Sweden since 1987. For psychiatric in-patient care the register has nationwide coverage dating back from 1973. For each hospitalization, the unique national registration number, date of admission and discharge, and diagnosis are registered in NPR. In Sweden, all hospital diagnoses are classified according to the WHO International Classification of Diseases (ICD). Since the diagnostic definitions of affective disorders were substantially changed in ICD-9 and ICD-10 as compared with ICD-8, only patients diagnosed with bipolar disorder according to ICD-9 or ICD-10 were included in the study. Bipolar diagnoses recorded between 1987 and 1996 were identified using ICD-9 (296A, C, E, 298B). From 1997 and later, ICD-10 (F30-F31) was used to identify bipolar diagnoses. The Swedish Cause of Death Register (CDR) includes all individuals who were registered in Sweden at the time of death. The register provides information on date of death as well as main (underlying) and secondary causes of death based on death certificates. Definitions regarding causes of death and ICD codes used in this study are shown in Figure 1.

A total of 20,248 patients admitted to hospital between 1st of January 1987 and 31st of December 2006 with a main diagnosis of bipolar disorder (ICD-9; ICD-10) were identified in the NPR. Of the 20,248 patients, 3,147 had been previously diagnosed with schizophrenia (ICD-8: 295; ICD-9: 295; ICD-10; F20, F25) and were consequently excluded. Thus, the total risk population of the study comprised 17,101 patients with bipolar disorder. The follow-up period was 20 years (1987-2006). Immigrants were included from the date of immigration to Sweden. Each person was followed until December 31, 2006, or date of death or emigration,

depending on which came first. Inclusion in the risk population started from the date of first hospital admission (discharge diagnosis) during the study period.

Statistical analysis

Person years at risk, number of cause-specific deaths and hospital admissions due to CVD for both bipolar patients and the general population were determined. Person time was stratified by sex, calendar year and age. Mortality rate ratios (MRR) and Admission rate ratios (ARR) and predicted mortality rates were calculated with corresponding 95% confidence intervals (CI) using Poisson regression models with the GENMOD procedure using statistical software SAS (version 9.2). All models were adjusted for or stratified by sex, attained age and year of follow-up.

To calculate the excess mortality for patients with bipolar disorder the observed number of deaths was compared with the expected number of deaths among patients with bipolar disorder. The expected number of deaths was calculated by applying age, sex and calendar specific mortality rates in the general population to the time at risk among the patients.
The risk of dying from CVD after first hospital admission was analyzed by estimating cause-specific survival curves using the Kaplan-Meier method. Additional adjusted hazard ratios with 95% CIs were estimated using Cox proportional hazard models.

When hospital admission due to CVD (Admission Rate Ratios, ARR) was the event of interest, follow-up ended on the day of first admission. To ensure that the observed cases were incident, a three-year run-in period was created to compensate for the lack of CVD coverage in the NPR before 1987. Hence, all bipolar patients analyzed had no hospital admissions due to CVD recorded for at least three years before follow-up.

Results

Causes of death

Total mortality (death from any cause) between 1987 and 2006 in Sweden was more than twice as high among patients with bipolar disorder compared to the general population (MRR 2.40; 95% CI 2.33-2.47). Specifically, 2,489 excess deaths in patients with bipolar disorder were observed (Table 1). With mortality causes subdivided into CVD, other somatic, and external causes of death, we found that men and women with bipolar disorder were twice as

likely to die of CVD compared to the general population (MRR 2.03; 95% CI 1.93-2.13), with 824 excess deaths due to CVD. Mortality from other somatic causes was also doubled (MRR 2.10; 95% CI 2.00-2.19), with 988 excess deaths. External causes of death, such as suicide, homicides, and accidents, were increased more than nine times in bipolar patients (MRR 9.66; 95% CI 8.99-10.37), with 675 excess deaths. As far as CVD subgroups were concerned, mortality from coronary heart disease and cerebrovascular disease was twice as high in bipolar patients, with 377 excess deaths (MRR 1.95; 95% CI 1.81-2.09) and 184 excess deaths (MRR 2.00; 95% CI 1.81-2.09), respectively. Mortality from acute myocardial infarction was almost twice as high in bipolar patients (MRR 1.83; 95% CI 1.67-2.01), with 200 excess deaths. Mortality from sudden cardiac death, cardiac arrest/ventricular fibrillation, was also increased (MRR 1.85; 95% CI 1.42-2.41), with 25 excess deaths. Bipolar women and men of all ages had an equally increased mortality from CVD (data not shown).

Age and cause of death

MRR by age at death for all causes of death is shown in Fig 2a and subdivided into cardiovascular death (Fig 2b), other somatic death (Fig 2c), suicide and other external causes of death (Fig 2c). Cerebrovascular death (Fig 2e), death by coronary heart disease (Fig 2f), and death from acute myocardial infarction (Fig 2g) are reported separately.

MRR for CVD was increased for bipolar patients across all ages but was particularly pronounced in the young age groups (Figure 2b). Patients with bipolar disorder who died of CVD were younger than people in the general population. The same finding was observed when we subdivided CVD into cerebrovascular disease, coronary heart disease and acute myocardial infarction (Figure 2e-g). For acute myocardial infarction and coronary heart disease the increased risk was most apparent in the 55-65 years age groups (2f-g). In the ages below 50 years the results should be interpreted with caution because there were very few events in these ages. Death by suicide and other external causes of death were 15 times more common among bipolar patients below 30 years of age compared to persons of the same age in the general population (Figure 2d). Overall, the MRR for suicide and other external causes ofdeath decreased with increasing age. However, it should be noted that it remained significantly increased in persons aged between 70-74 years (MRR 6.88; CI 95% 5.06-9.35) (Figure 2d).

Age differences at death between persons with bipolar disorder and the population from coronary heart disease, acute myocardial infarction and cerebrovascular disease is shown in Figure 3a-3c. The earlier age at death for persons with bipolar disorder is clearly shown for all these causes of death.

Admission rates

Hospital admission rates for CVD among patients with bipolar disorder were similar to those for the general population even though MRR for CVD was almost twice as high, independent of the specific CVD cause (Tables 1 and 2). Survival rates five years after first hospital admission for CVD were significantly lower among bipolar patients than among the general population (Figure 4).

Discussion

Key findings

In this nationwide study of mortality among persons with bipolar disorder in Sweden compared to the population, somatic illness was the main cause of death. Bipolar patients died of CVD around ten years earlier than the general population. Mortality from cerebrovascular disease, coronary heart disease, and acute myocardial infarction was twice as high in bipolar patients as in the general population, while the frequency of hospital admissions due to these diseases was not increased. Our findings showed that CVD in persons with bipolar disorder accounted for 824 excess deaths and other somatic diseases 988 excess deaths, taken together 1,812 excess deaths, both larger than suicide and other external causes of death (n=675). Interestingly, sudden cardiac death was also increased.

Strengths and limitations

The Swedish National Patient Register and Cause of Death Register include everyone who resides in the country and are considered unique, comprehensive and highly credible. Currently more than 99% of all somatic and psychiatric hospital discharges are recorded in the National Patient Register.[7] Swedish hospitals and government agencies are obliged by law to enter medical information in the National Patient Register. All diagnoses in the National Patient and Cause of Death registers were given by patients' doctors using international classification standards (ICD codes). Being register based, this study used information about clinical diagnoses from hospital admissions in Sweden. During the study period, the ICD diagnostic definitions were specific for bipolar disorder. A validation of the Swedish clinical

bipolar diagnoses has shown high validity, sufficient for epidemiological studies.[8] One limitation of this study was that it was based on in-patient diagnoses, which may have generated a selective bias towards severely ill patients. However, most individuals at severe stages of bipolar disorder are admitted to hospital in Sweden. Since medical care is free in Sweden, there is no bias by costs for hospital care leading to differences in health-seeking behavior. In a previous study, we have shown that the number and frequency of hospital admissions due to bipolar disorder remained relatively unchanged in Sweden during recent years, while the overall number of psychiatric admissions was drastically reduced.[9] We did not have access to medical records or information on medical treatment. In terms of the validity of the data on causes of death, in CVD deaths we found a slightly higher autopsy rate (28%) among patients with bipolar disorder than in the general population (22%). It is unlikely that these small differences affected the outcome of the study. Although MRR for CVD deaths were generally lower for women than for men but not significantly, the absolute numbers of deaths was larger among women. Thus, the lower MRR for women with bipolar disorder relates to differences in CVD mortality between women and men in the general population.

Findings from other studies

The findings of this study add to the growing body of evidence that somatic diseases, particularly CVD, contribute to a shorter lifespan among bipolar patients. Findings from several large register-based studies from different parts of the world indicate that cardiovascular disease is responsible for the majority of excess deaths, with up to 2.5-fold increased mortality.[3 5 6 10-14] Studies using registers from the Nordic countries have shown that bipolar patients run almost twice the risk of dying from CVD than do persons in the general population, the mechanisms for which are currently unknown.[4 5] There is also a growing body of evidence from studies in other countries, and similar findings have been observed in a representative study of the US population.[15] Studies have shown a higher cardiovascular mortality in persons with bipolar disorder type I compared to bipolar disorder type II or major depressive disorder.[16 17] In our Swedish data, bipolar disorder type I, can not be separated from bipolar disorder type II. However, patients with bipolar disorder type I are much more likely to be hospitalized and thus to be included in our sample. Earlier age of CVD has been shown in several studies,[15] and is also confirmed in our findings of increased cardiovascular death at a younger age compared to the population in Sweden. Possible risk factors for the increased mortality from CVD among bipolar patients may include adverse effects of

medication,[18 19] high levels of smoking,[20] unhealthy diet,[21 22] lack of physical activity,[21] low social-economic status,[23] and lower rates of nutritional counceling.[24] Studies have shown that bipolar disorder patients deviate from age-based norms on arterial stiffness measures.[25] In addition, effects of genetic associations, such as those reported between Type 2 diabetes, CHD and schizophrenia,[26] could not be excluded. One of the most important locuses of genetic polymorphisms linked to bipolar disease and depression is around the ATP-activated ion-channel receptor *P2X7*.[27] Recently, a polymorphism in the *P2X7* gene was linked to increased risk of stroke and acute myocardial infarction,[28] and the same polymorphism has also recently been shown to be linked to cognitive symptoms in bipolar disorder,[29] indicating that common genetic factors could have effect on both cardiovascular disease and bipolar disorder. Also, inflammation has been pointed out as a potential biological cause of increased CVD in bipolar disorder [30 31] together with endothelial dysfunction. [32]

CVD undertreated in persons with bipolar disorder

Studies of patients with bipolar disorder have shown that the patients run an increased risk of metabolic syndrome,[33] i.e. increased blood glucose,[34]and cholesterol levels,[35] higher blood pressure,[36] and higher prevalence of overweight and obesity[21], closely associated with CVD. To prevent and treat metabolic disorders in patients with severe mental illnesses such as bipolar disorder, new guidelines have been drawn up for clinicians in Sweden.[37] However, the substantially younger age at CVD disease among persons with bipolar disorder compared to the population need to be further emphasized. The effects of those guidelines are still to be evaluated.

Our finding that patients with bipolar disorder showed only slightly increased hospital admissions rates for CVD despite their twice as high cardiovascular mortality, strongly suggests that CVD is undertreated in bipolar patients when compared to the general population. In a Danish study, the rates of invasive heart disease procedures were 40% lower among persons with bipolar disorder than in the general population.[4] Although the younger age at cardiac events in bipolar disorder compared to the population may reduce detection, this possible contributing factor is unlikely to cause the reduced rates of invasive heart procedures. Sudden cardiac mortality from cardiac arrest/ventricular fibrillation was increased among patients with bipolar disorder (MRR: 1.85), but the 25 excess cases does not explain the difference in hospital admissions in terms of increased sudden death before hospitalization. Thus, the reasons for CVD undertreatment in bipolar disorder is not explained

by the current findings. In our study, the MRR and ARR patient populations are slightly different, in the respect that the ARR patients are identified at their first index admission, while the MRR patients may have several admissions, and thus being more severely affected. Unequal access to health care (i.e. receiving cardiac treatment of lower quality) for reasons other than financial has been previously suggested as a contributor to excess CVD mortality in patients with severe mental disorders, such as schizophrenia,[38] and may be indicated by our findings of increased mortality after discharge from hospital compared to the population. These factors have not been studied extensively in bipolar patients. Health care in Sweden is free and is financed primarily through taxes. Therefore, it is unlikely that patients with bipolar disorder do not seek hospital care for lack of financial means.

Many mechanisms can contribute to the under-treatment of CVD among people with bipolar disorder. Our results indicate a failure of the health care system to identify and address the health needs of those patients, which has also been shown in other studies of people with severe mental disorders.[39] The levels of CVD mortality in our bipolar persons are similar to those in schizophrenia, where adverse effects of antipsychotic medication have been considered the main contributing factor. When compared with schizophrenia, a recent study of bipolar disorder in Stockholm County found only 29% of bipolar patients medicating with antipsychotics, as compared to practically all schizophrenia patients, which raises the question of the importance of adverse effects of antipsychotics in CVD.[40]

Conclusions

The observed number of deaths from cardiovascular diseases in patients with bipolar disorders was almost twice as the expected number when comparing with the general population, suggesting that more resources are needed for the prevention of these diseases in this patient group. Targeted interventions by effective cooperation between primary health care and psychiatric professionals would be crucial in the efforts to reduce excess CVD mortality in patients with bipolar disorder. Finally, effective cardiac treatment would ensure longevity and improved quality of life for patients with bipolar disorder.

Contributors: UÖ had the idea of the study and is guarantor of the study together with JH, who has performed the statistical analyses. JW has contributed to the design of the study and drafted the manuscript together with UÖ. KW, DE and LA have contributed to the design of the study and with revisions of the manuscript. All authors have approved the final version of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). JW, KW, LA, DE, UÖ has declared no support from any organization for the submitted work, no financial relationship with any organizations that would have interest in the submitted work in the previous three years, and no other activities that could appear to have influenced the submitted work. UÖ has declared traveling expenses from Janssen-Cilag for attending a course in October 2012 unrelated to the study.

Ethical approval: This study was approved by the ethical review board in Stockholm County. The ethical review board determined that informed consent from participating individuals was not required.

Data sharing: The analysis data set for this study is available from the National Board of Health and Welfare (Socialstyrelsen) in Sweden. Please contact JH for further information.

Figure 1. ICD-coding and classification of disease and mortality.

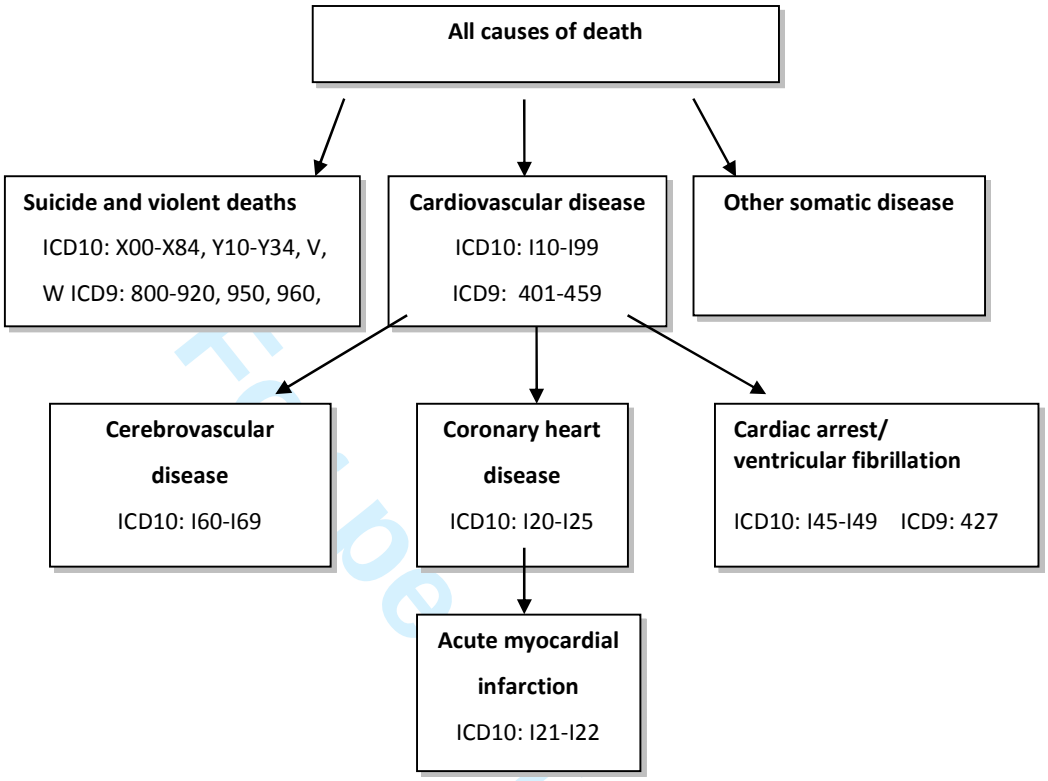


Table 1. Mortality rate ratios for bipolar patients between 1987 and 2006

	Men		Women		Total (both sexes)		
Cause of death	**Cases**	**MRR (95% CI)**	**Cases**	**MRR (95% CI)**	**Cases**	**MRR (95% CI)**	**Excess cases (95% CI)**
All causes of death	1874	2.48 (2.37-2.59)	2393	2.34 (2.25-2.44)	4267	2.40 (2.33-2.47)	2489 (2361-2617)
Cardiovascular disease	733	2.16 (2.01-2.33)	892	1.93 (1.81-2.06)	1625	2.03 (1.93-2.13)	824 (745-903)
Other somatic deaths	735	1.97 (1.83-2.11)	1154	2.19 (2.06-2.32)	1889	2.10 (2.00-2.19)	988 (902-1073)
Suicide and other External deaths	406	9.37 (8.50-10.33)	347	10.02 (9.01-11.13)	753	9.66 (8.99-10.37)	675 (621-729)
Cerebrovascular disease	144	2.29 (1.94-2.70)	224	1.86 (1.63-2.12)	368	2.00 (1.81-2.22)	184 (147-222)
Coronary heart disease	385	2.00 (1.81-2.21)	391	1.89 (1.71-2.09)	776	1.95 (1.81-2.09)	377 (323-432)
Acute myocardial infarction	227	1.89 (1.66-2.15)	213	1.78 (1.55-2.03)	440	1.83 (1.67-2.01)	200 (159-241)
Cardiac arrest/Ventricular fibrillation	23	2.29 (1.52-3.45)	32	1.62 (1.15-2.30)	55	1.85 (1.42-2.41)	25 (12-42)

Table 2. Admission rate ratios for bipolar patients during 1990 to 2006

	Men		Women		Total (both sexes)		
Hospital admissions	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Excess cases (95% CI)
Cardiovascular disease	540	1.27 (1.16-1.38)	696	1.33 (1.24-1.43)	1236	1.30 (1.23-1.38)	287 (218-356)
Cerebrovascular disease	179	1.32 (1.14-1.53)	271	1.43 (1.27-1.62)	450	1.39 (1.26-1.52)	125 (84-167)
Coronary heart disease	212	1.02 (0.89-1.17)	207	1.06 (0.92-1.21)	419	1.04 (0.94-1.14)	15 (-25-55)
Acute myocardial infarction	133	0.96 (0.81-1.14)	137	1.11 (0.94-1.31)	270	1.03 (0.92-1.16)	8 (-24-41)

Figure 2a. Mortality Rate Ratios (MRR) for all causes of death by age at death in bipolar disorder patients and the general population.

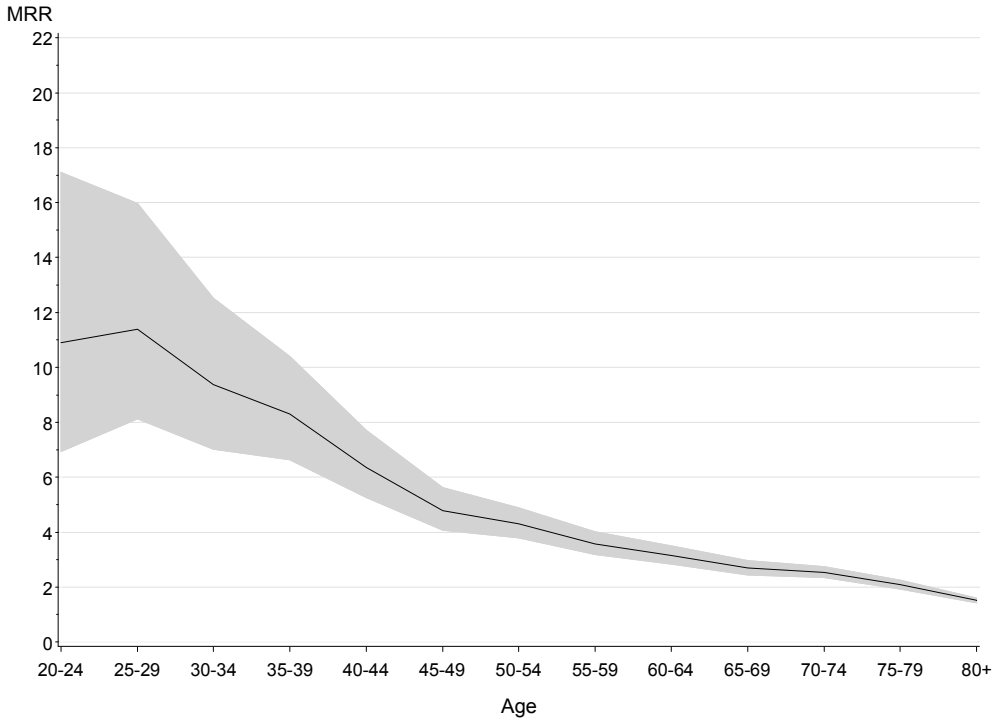


Figure 2b. Mortality Rate Ratios (MRR) for cardiovascular death by age at death in persons with bipolar disorder patients and the general population.

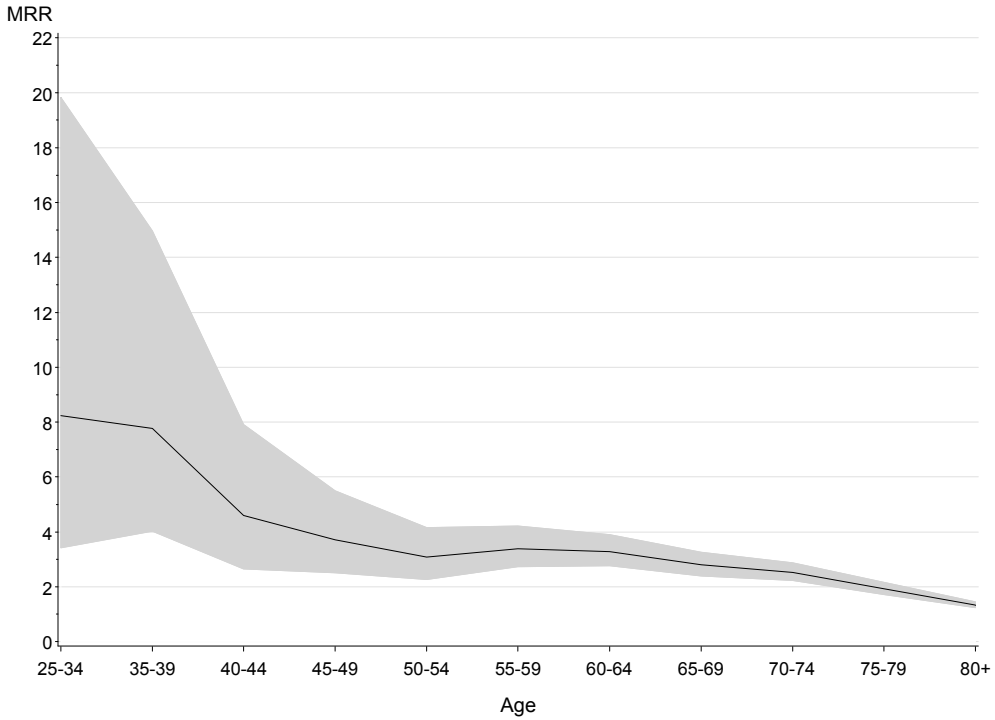


Figure 2c. Mortality Rate Ratios (MRR) for other somatic death by age at death in patients with bipolar disorder and the general population.

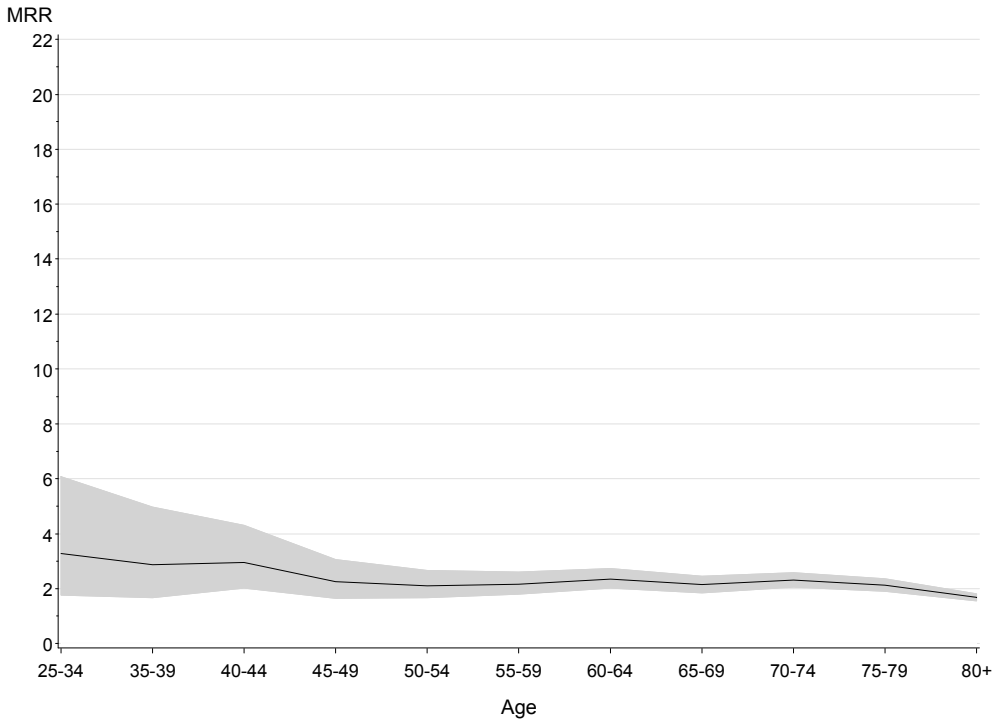


Figure 2d. Mortality Rate Ratios (MRR) of suicide and other external causes of death by age at death in patients with bipolar disorder and the general population.

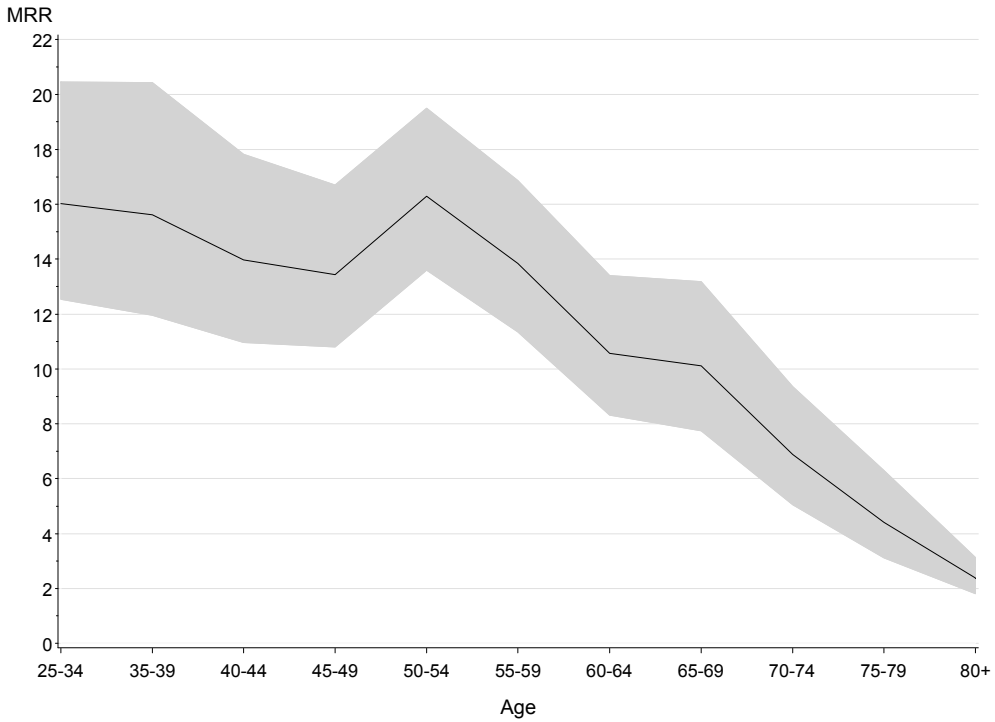


Figure 2e. Mortality Rate Ratios (MRR) of cerebrovascular disease by age at death in patients with bipolar disorder and the general population.

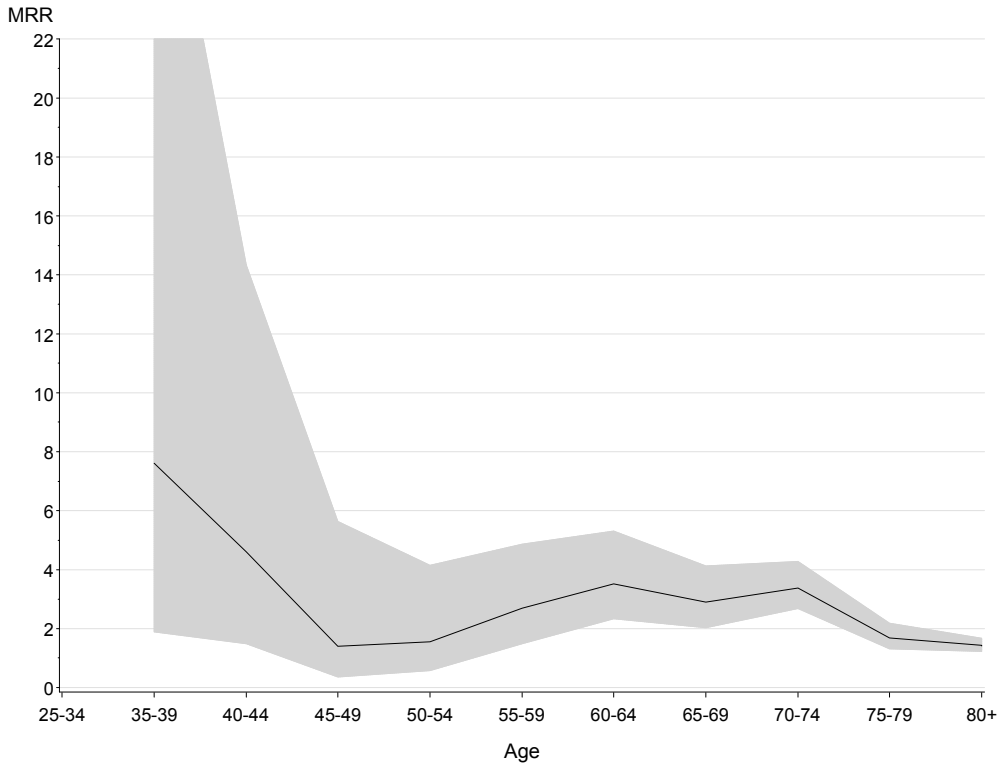


Figure 2f. Mortality Rate Ratios (MRR) of coronary heart disease by age at death in patients with bipolar disorder and the general population.

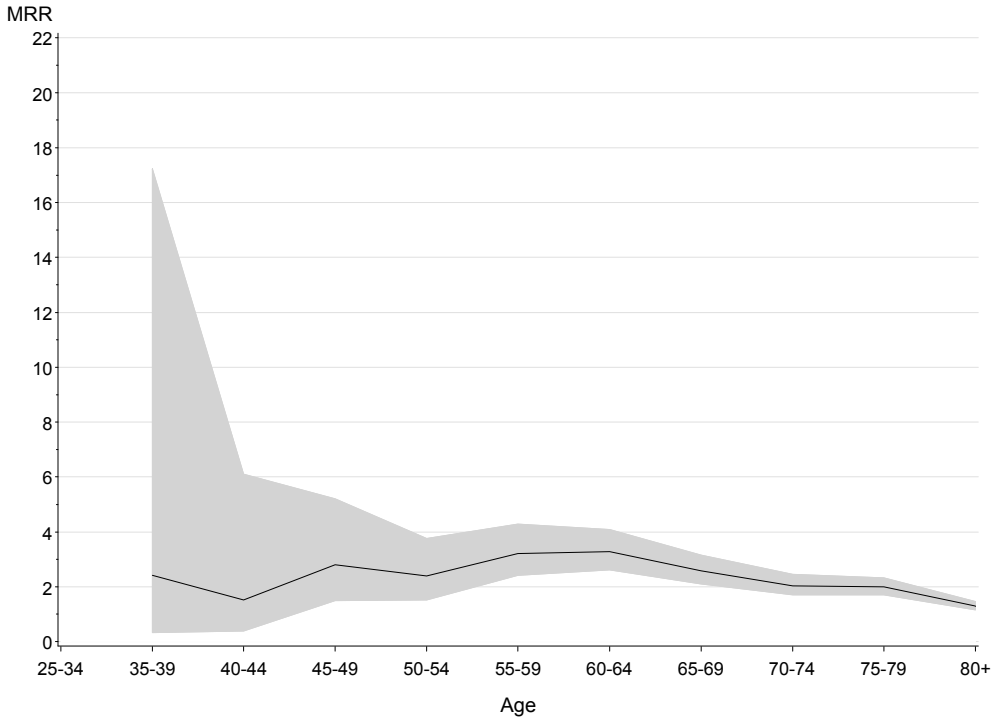


Figure 2g. Mortality Rate Ratios (MRR) of acute myocardial infarction by age at death in patients with bipolar disorder and the general population.

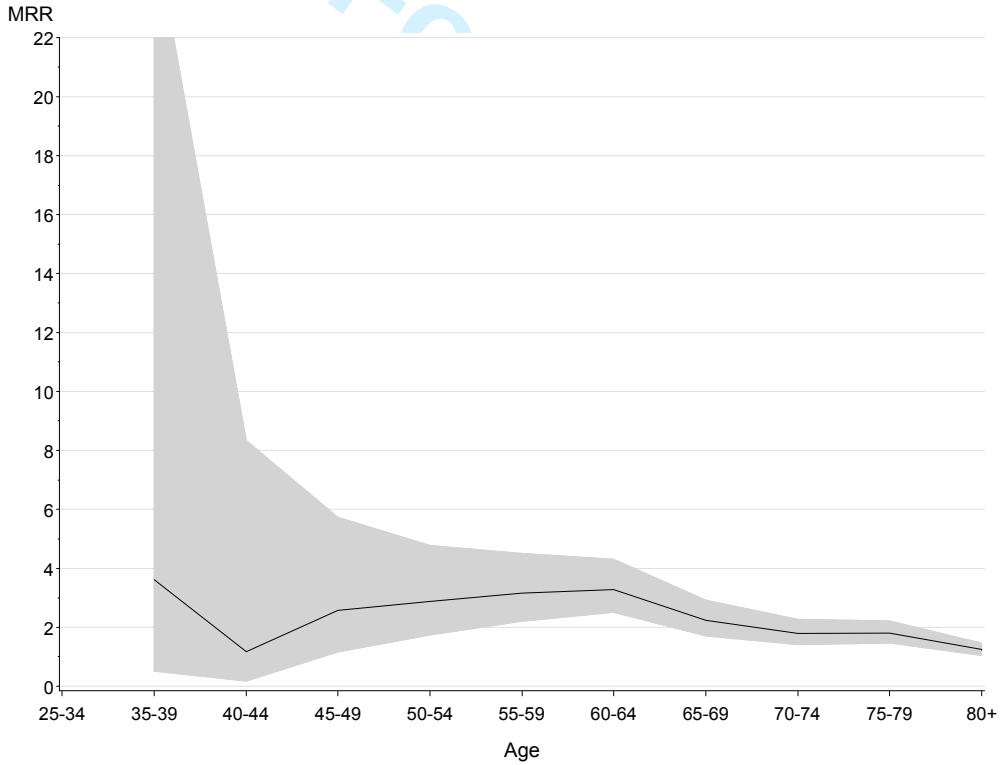


Figure 3a. Mortality of coronary heart disease per 1000 person-years in patients with bipolar disorder and the general population adjusting for sex and calendar year.

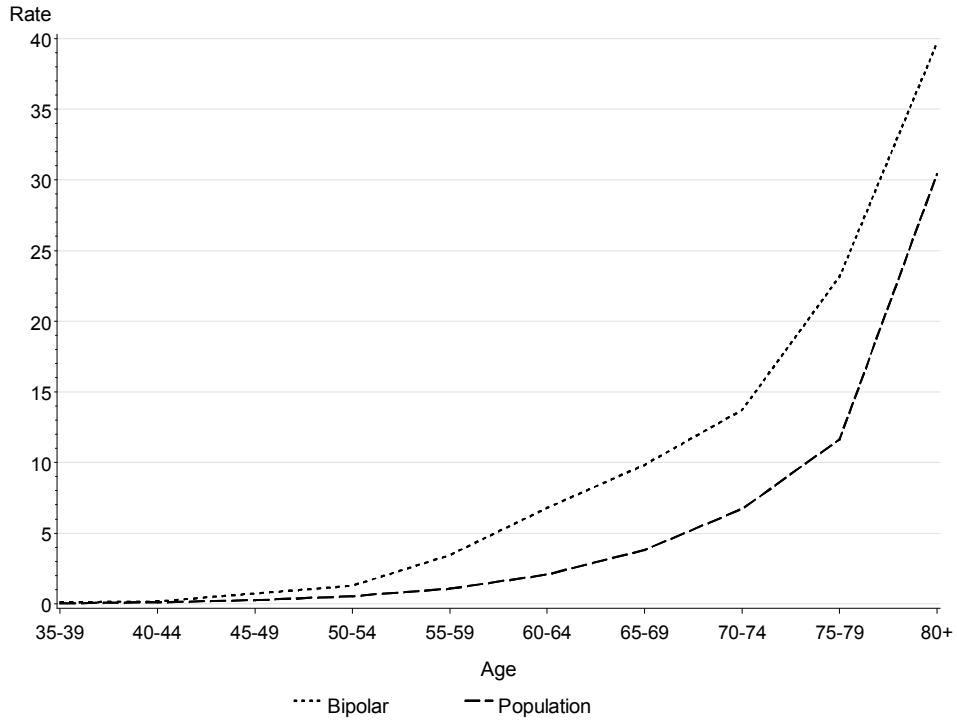


Figure 3b. Acute myocardial infarction

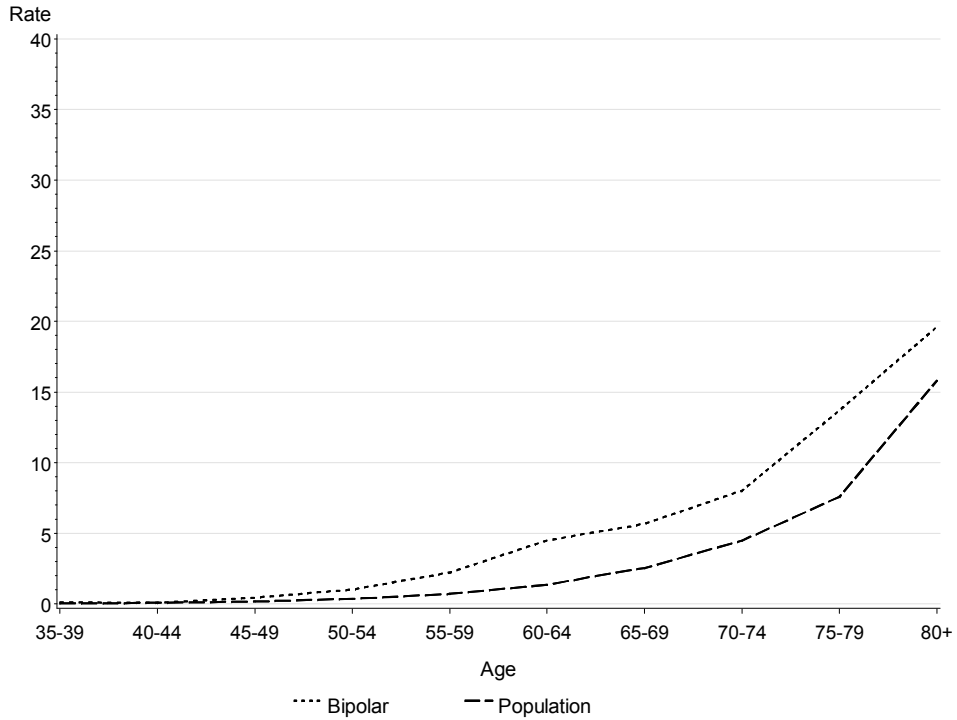


Figure 3c. Cerebrovascular disease

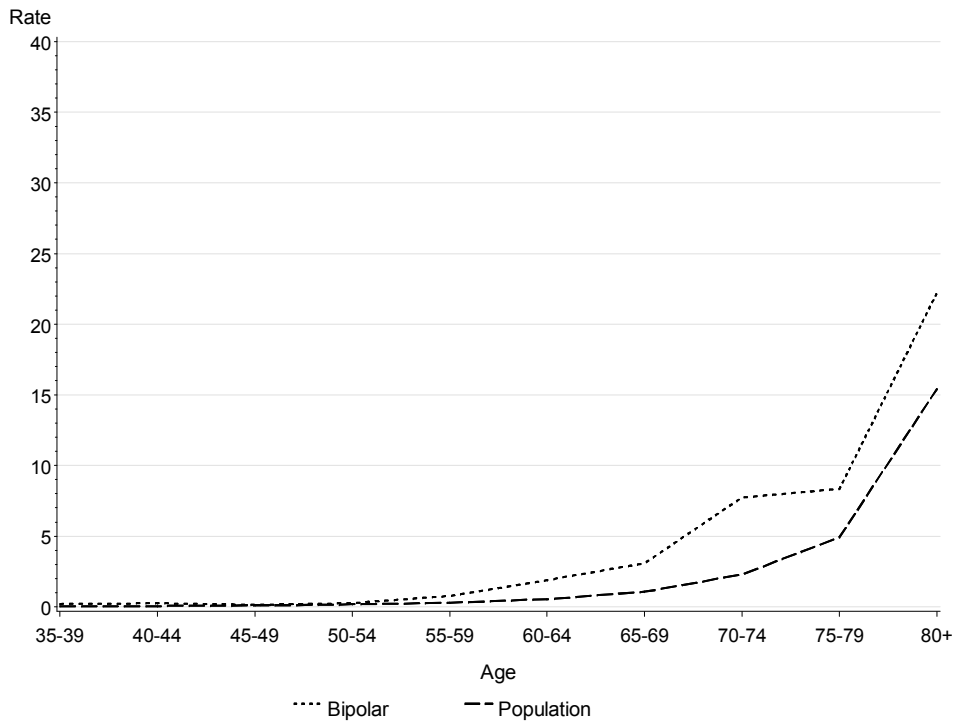
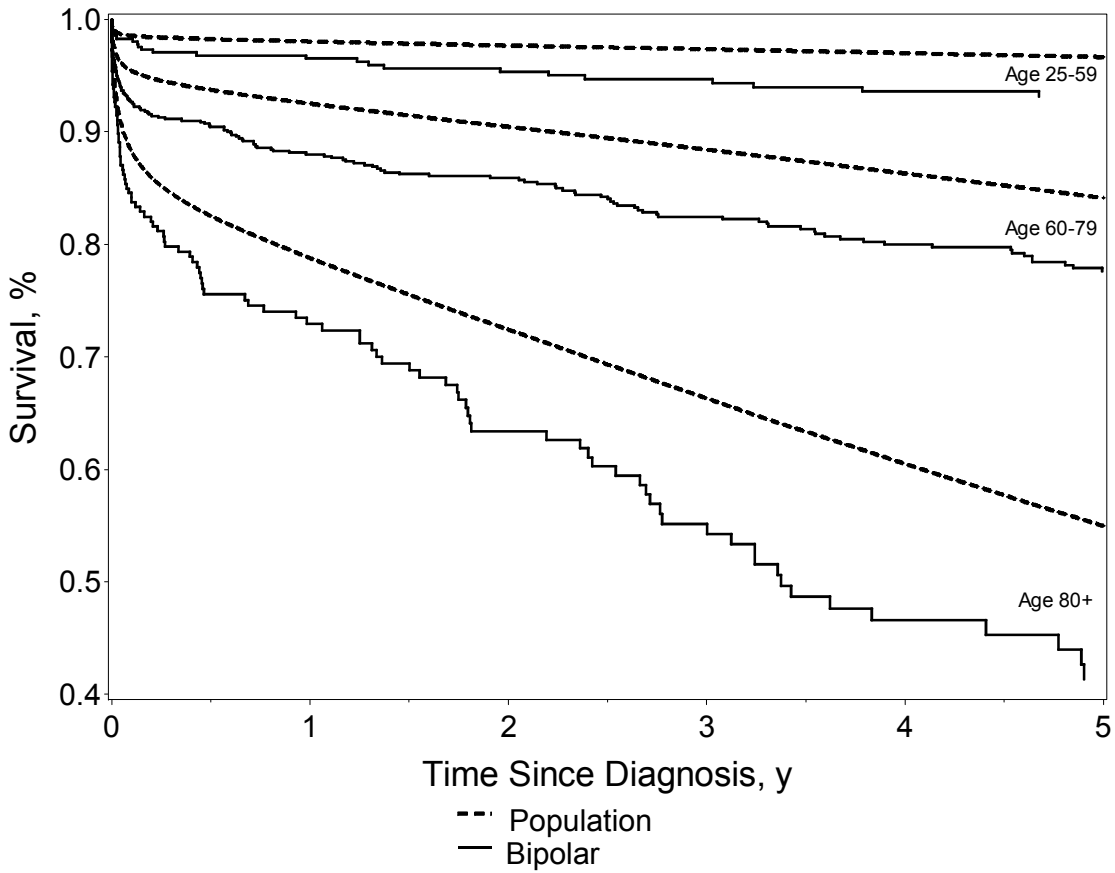


Figure 4. Five-year survival of cardiovascular disease after disharge from first cardiovascular admission stratified by age at hospital contact.



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Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden.

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Article summary

Article focus

- To estimate mortality in cardiovascular disease (CVD) and its subgroups cerebrovascular and coronary heart disease and acute myocardial infarction among 17,101 persons diagnosed with bipolar disorder ~~during 1987 to 2006~~ in Sweden, compared to the general population in a national register study with a 20-year follow-up.

Key messages

- Persons with bipolar disorder died of CVD approximately ten years early. Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was higher than that of suicide and other external causes (n=675 deaths). ~~Excess mortality from CVD and other somatic diseases was three times higher (1,812 deaths) than suicide and other external unnatural causes (675 deaths).~~ Mortality rate ratios (MRR~~s~~) for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high compared to the general population. Despite the increased mortality, hospital admissions, admission rate ratios (ARR) for CVD treatment in persons with bipolar disorder were only slightly increased.

- The increased cardiovascular mortality in persons with bipolar disorder calls for renewed efforts~~more resources~~ to prevent and treat somatic diseases. Specifically, our findings imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as the population.

Strengths and limitations of this study ~~of this study~~

- A large national cohort with comprehensive data on patient characteristics was studied. Mortality data from the Swedish cause of death register are of high quality.
- Clinical information on symptoms and treatment were lacking.

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ABSTRACT (word count: 2651)

Objective: To estimate cardiovascular mortality among persons with bipolar disorder in Sweden compared to the general population.

Design: Population register based cohort study with a 20-year follow-up.

Setting: Sweden.

Participants: The entire population of Sweden (n=10.6 million) of whom 17,101 persons were diagnosed with bipolar disorder between 1987 and 2006.

Main outcome measures: Mortality rate ratios (MRR), excess mortality (excess deaths), cardiovascular disorders (CVD) and specifically cerebrovascular disease, coronary heart disease, and acute myocardial infarction, sudden cardiac deaths, and hospital admission rate ratios (ARR).

Results: Persons with bipolar disorder died of CVD approximately ten years earlier than did persons of the general population. More than twoOne third (3783%) of all deaths in persons with bipolar disorder were caused by CVD, and almost half (44%) by other somatic diseases, whereas suicide and other unnaturalexternal causes accounted for less than a fifththan a third of all deaths (1278%). Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was three times higher (1,812 deaths) than that of suicide and other external unnatural causes (n=675 deaths). MRRs for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high in persons with bipolar disorder compared to the general population. Despite the increased mortality of CVD, hospital admissions (ARR)s for CVD treatment were only slightly increased in persons with bipolar disorder when compared to the general population.

Conclusions: The increased cardiovascular mortality in persons with bipolar disorder calls for renewed effortsmore resources to prevent and treat somatic diseases in this group. Specifically, our findings further imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as persons without bipolar disorder.

Introduction

Cardiovascular disease (CVD) is the main cause of death in many developed countries.[1] CVD encompasses a broad range of different conditions that are potentially life threatening. In Sweden, although mortality from CVD in the population has almost halved in the last two decades, CVD still accounts for more than 40% of all deaths in the country.[2] Premature death in patients with severe mental health disorders, especially patients with schizophrenia and bipolar disorder, has historically been ~~generally~~ attributed to suicide~~, rather than CVD, despite~~ However, more recent studies have show~~i~~n~~g~~ that CVD leads to more reduced~~shorter~~ life spans than does suicide in those patients.[3] Persons with bipolar disorder have an increased risk of CVD and have been observed to die due to CVD twice as often as the general population.[4-6] Although previous studies have shown an association between bipolar disorder and mortality from CVD, few studies have addressed mortality rates in different ~~CVD subgroups~~types of vascular mortality, or examined their use of health care. An improved understanding of the causes behind and magnitude of CVD among bipolar patients is warranted along with an in-depth evaluation of different diagnostic CVD subgroups. The answers to these questions, which are far less investigated than among patients with schizophrenia, are essential in the efforts to address the problem of premature deaths due to CVD in bipolar patients, and they are the focus of the present Swedish national register-based study, which extends earlier Swedish findings[5] both by more specific CVD mortality analyses and more recent patient data.

The aim of this study was to evaluate excess mortality from CVD, such as cerebrovascular disease and coronary heart disease with acute myocardial infarction as its most important component, and also CVD hospitals admissions, in ~~people with bipolar disorder~~persons with bipolar disorder in Sweden between 1987 and 2006 compared to the population.

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Methods

Cohort and follow-up

All persons who resided in Sweden between the 1st of January 1987 and the 31st of December 2006 (n=10,631, 208) were identified using the Swedish Total Population Register (TPR). The TPR was established in 1968 and contains information on sex, date and place of birth, date of migration of every resident in Sweden. Information on hospital admission, medical diagnosis, and cause of death was obtained by linking the TRP with the national Swedish Cause-of-Death Register and the National Patient Register (NPR) using each resident's unique personal identification number.

The NPR, which is maintained by the National Board of Health and Welfare, contains information on all hospital in-patient treatments carried out in Sweden since 1987. For psychiatric in-patient care the register has nationwide coverage dating back from 1973. For each hospitalization, the unique national registration number, date of admission and discharge, and diagnosis are registered in NPR. In Sweden, all hospital diagnoses are classified according to the WHO International Classification of Diseases (ICD). Since the diagnostic definitions of affective disorders were substantially changed in ICD-9 and ICD-10 as compared with ICD-8, only patients diagnosed with bipolar disorder according to ICD-9 or ICD-10 were included in the study. Bipolar diagnoses recorded between 1987 and 1996 were identified using ICD-9 (296A, C, E, 298B). From 1997 and later, ICD-10 (F30-F31) was used to identify bipolar diagnoses. The Swedish Cause of Death Register (CDR) includes all individuals who were registered in Sweden at the time of death. The register provides information on date of death as well as main (underlying) and secondary causes of death based on death certificates. Definitions regarding causes of death and ICD codes used in this study are shown in Figure 1.

A total of 20,248 patients admitted to hospital between 1st of January 1987 and 31st of December 2006 with a main diagnosis of bipolar disorder (ICD-9; ICD-10) were identified in the NPR. Of the 20,248 patients, 3,147 had been previously diagnosed with schizophrenia (ICD-8: 295; ICD-9: 295; ICD-10; F20, F25) and were consequently excluded. Thus, the total risk population of the study comprised 17,101 patients with bipolar disorder. The follow-up period was 20 years (1987-2006). Immigrants were included from the date of immigration to Sweden. Each person was followed until December 31, 2006, or date of death or emigration,

depending on which came first. Inclusion in the risk population started from the date of first hospital admission (discharge diagnosis) during the study period.

Statistical analysis

Person years at risk, number of cause-specific deaths and hospital admissions due to CVD for both bipolar patients and the general population were determined. Person time was stratified by sex, calendar year and age. Mortality rate ratios (MRR) and Admission rate ratios (ARR) and predicted mortality rates were calculated with corresponding 95% confidence intervals (CI) using Poisson regression models with the GENMOD procedure using statistical software SAS (version 9.2). All models were adjusted for or stratified by sex, attained age and year of follow-up.

To calculate the excess mortality for patients with bipolar disorder the observed number of deaths was compared with the expected number of deaths among patients with bipolar disorder. The expected number of deaths was calculated by applying age, sex and calendar specific mortality rates in the general population to the time at risk among the patients.
The risk of dying from CVD after first hospital admission was analyzed by estimating cause-specific survival curves using the Kaplan-Meier method. Additional adjusted hazard ratios with 95% CIs were estimated using Cox proportional hazard models.

When hospital admission due to CVD (Admission Rate Ratios, ARR) was the event of interest, follow-up ended on the day of first admission. To ensure that the observed cases were incident, a three-year run-in period was created to compensate for the lack of CVD coverage in the NPR before 1987. Hence, all bipolar patients analyzed had no hospital admissions due to CVD recorded for at least three years before follow-up.

Results

Causes of death

Total mortality (death from any cause) between 1987 and 2006 in Sweden was more than twice as high among patients with bipolar disorder compared to the general population (MRR 2.40; 95% CI 2.33-2.47). Specifically, 2,489 excess deaths in patients with bipolar disorder were observed (Table 1). With mortality causes subdivided into CVD, other somatic, and ~~unnatural~~external causes of death, we found that men and women with bipolar disorder were

twice as likely to die of CVD compared to the general population (MRR 2.03; 95% CI 1.93-2.13), with 824 excess deaths due to CVD. Mortality from other somatic causes was also doubled (MRR 2.10; 95% CI 2.00-2.19), with 988 excess deaths. ~~Unnatural~~ External causes of death, such as suicide, homicides, and accidents, were increased more than nine times in bipolar patients (MRR 9.66; 95% CI 8.99-10.37), with 675 excess deaths. As far as CVD subgroups were concerned, mortality from coronary heart disease and cerebrovascular disease was twice as high in bipolar patients, with 377 excess deaths (MRR 1.95; 95% CI 1.81-2.09) and 184 excess deaths (MRR 2.00; 95% CI 1.81-2.09), respectively. Mortality from acute myocardial infarction was almost twice as high in bipolar patients (MRR 1.83; 95% CI 1.67-2.01), with 200 excess deaths. Mortality from sudden cardiac death, cardiac arrest/ventricular fibrillation, was also increased (MRR 1.85; 95% CI 1.42-2.41), with 25 excess deaths. Bipolar women and men of all ages had an equally increased mortality from CVD (data not shown).

Age and cause of death

MRR by age at death for all causes of death is shown in Fig 2a and subdivided into cardiovascular death (Fig 2b), other somatic death (Fig 2c), suicide and other external causes of death (Fig 2c). Cerebrovascular death (Fig 2e), death by coronary heart disease (Fig 2f), and death from acute myocardial infarction (Fig 2g) are reported separately.

MRR for CVD was increased for bipolar patients across all ages but was particularly pronounced in the young age groups (Figure 2b). Patients with bipolar disorder who died of CVD were younger than people in the general population. The same finding was observed when we subdivided CVD into cerebrovascular disease, coronary heart disease and acute myocardial infarction (Figure 2e-g). For acute myocardial infarction and coronary heart disease the increased risk was most apparent in the 55-65 years age groups (2f-g). In the ages below 50 years the results should be interpreted with caution because there were very few events in these ages. Death by suicide and other ~~unnatural~~external causes of death~~s~~ were 15 times more common among bipolar patients below 30 years of age compared to persons of the same age in the general population (Figure 2d). Overall, the MRR for suicide and other ~~unnatural~~ external causes of ~~-~~death~~s~~ decreased with increasing age. However, it should be noted that it remained significantly increased in persons aged between 70-74 years (MRR 6.88; CI 95% 5.06-9.35) (Figure 2d).

Age differences at death between persons with bipolar disorder and the population from coronary heart disease, acute myocardial infarction and cerebrovascular disease is shown in Figure 3a-3c. The earlier age at death for persons with bipolar disorder is clearly shown for all these causes of death.

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Admission rates

Hospital admission rates for CVD among patients with bipolar disorder were similar to those for the general population even though MRR for CVD was almost twice as high, independent of the specific CVD cause (Tables 1 and 2). Survival rates five years after first hospital admission for CVD were significantly lower among bipolar patients than among the general population (Figure 4).

Discussion

Key findings

In this nationwide study of mortality among persons with bipolar disorder in Sweden compared to the population, somatic illness was the main cause of death. Bipolar patients died of CVD around ten years earlier than the general population. Mortality from cerebrovascular disease, coronary heart disease, and acute myocardial infarction was twice as high in bipolar patients as in the general population, while the frequency of hospital admissions due to these diseases was not increased. Our findings ~~clearly~~ showed that CVD in persons with bipolar disorder accounted for 824 excess deaths and other somatic diseases 988 ~~in persons with bipolar disorder accounted for a substantial number of~~ excess deaths, taken together ~~(n=~~1,812~~)~~ excess deaths, both larger than suicide and other ~~unnatural~~external causes of death (n=675). Interestingly, sudden cardiac death was also increased.

Strengths and limitations

The Swedish National Patient Register and Cause of Death Register include everyone who resides in the country and are considered unique, comprehensive and highly credible. Currently more than 99% of all somatic and psychiatric hospital discharges are recorded in the National Patient Register.[7] Swedish hospitals and government agencies are obliged by law to enter medical information in the National Patient Register. All diagnoses in the National Patient and Cause of Death registers were given by patients' doctors using international classification standards (ICD codes). Being register based, this study used information about

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clinical diagnoses from hospital admissions in Sweden. During the study period, the ICD diagnostic definitions were specific for bipolar disorder. A validation of the Swedish clinical bipolar diagnoses has shown high validity, sufficient for epidemiological studies.[8] One limitation of this study was that it was based on in-patient diagnoses, which may have generated a selective bias towards severely ill patients. However, most individuals at severe stages of bipolar disorder are admitted to hospital in Sweden. Since medical care is free in Sweden, there is no bias by costs for hospital care leading to differences in health-seeking behavior. In a previous study, we have shown that the number and frequency of hospital admissions due to bipolar disorder remained relatively unchanged in Sweden during recent years, while the overall number of psychiatric admissions was drastically reduced.[9] We did not have access to medical records or information on medical treatment., ~~which would have been of interest since antidepressants use have been linked to increased risk of fatal coronary heart disease.~~[10] In terms of the validity of the data on causes of death, in CVD deaths we found a slightly higher autopsy rate (28%) among patients with bipolar disorder than in the general population (22%). It is unlikely that these small differences affected the outcome of the study. Although MRR for CVD deaths were generally lower for women than for men but not significantly, the absolute numbers of deaths was larger among women. Thus, the lower MRR for women with bipolar disorder relates to differences in CVD mortality between women and men in the general population.

Findings from other studies

The findings of this study add to the growing body of evidence that somatic diseases, particularly CVD, contribute to a shorter lifespan among bipolar patients. Findings from several large register-based studies from different parts of the world indicate that cardiovascular disease is responsible for the majority of excess deaths, with up to 2.5-fold increased mortality.[3 5 6 10-14]~~[3 5 6 11 15]~~ Studies using registers from the Nordic countries have shown that~~n~~ bipolar patients run almost twice the risk of dying from CVD than do persons in the general population, the mechanisms for which are currently unknown.[4 5] There is also a growing body of evidence from studies in other countries, and similar findings have been observed in a representative study of the US population.[15] ~~(Goldstein et al 2009).~~ Studies have shown a higher cardiovascular mortality in persons with bipolar disorder type I compared to bipolar disorder type II or major depressive disorder.~~ (~~[16 17] ~~Fiedorowicz 2009, Angst 2012).~~ In our Swedish data, bipolar disorder type I, can not be separated from bipolar disorder type II. However, patients with bipolar disorder type I are much more likely to be hospitalized and

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thus to be included in our sample. Earlier age of CVD has been shown in several studies,[15] and is also confirmed in ~~which~~our findings of increased cardiovascular death at a younger age compared to the population in Sweden~~also confirm findings of increased cardiovascular disease at a younger age compared to the population~~. Possible risk factors for the increased mortality from CVD among bipolar patients may include adverse effects of medication,[18 19~~16~~ ~~17~~] high levels of smoking,[20~~18~~] unhealthy diet,[21 22~~19~~ ~~20~~] lack of physical activity,[21~~19~~] ~~and~~ low social-economic status,~~s~~[23~~21~~] and lower rates of nutritional counceling.[24] Studies have shown that bipolar disorder patients ~~-~~deviate from age-based norms on arterial stiffness measures.[25] In addition, effects of genetic associations, such as those reported between Type 2 diabetes, CHD and schizophrenia,[26~~22~~] could not be excluded. One of the most important locuses of genetic polymorphisms linked to bipolar disease and depression is around the ATP-activated ion-channel receptor *P2X7*.[27~~23~~] Recently, a polymorphism in the *P2X7* gene was linked to increased risk of stroke and acute myocardial infarction,[28~~24~~] and the same polymorphism has also recently been shown to be linked to cognitive symptoms in bipolar disorder,[29~~25~~] indicating that common genetic factors could have effect on both cardiovascular disease and bipolar disorder. Also, inflammation has been pointed out as a potential biological cause of increased CVD in bipolar disorder[30 31] together with endothelial dysfunction.[32]

CVD undertreated in ~~bipolar disorder~~persons with bipolar disorder

Studies of patients with bipolar disorder have shown that the patients run an increased risk of metabolic syndrome,[33~~26~~] i.e. increased blood glucose,[34~~27~~] and cholesterol levels,[35~~28~~] higher blood pressure,[36~~29~~] and higher prevalence of overweight and obesity[21~~19~~], closely associated with CVD. To prevent and treat metabolic disorders in patients with severe mental illnesses such as bipolar disorder, new guidelines have been drawn up for clinicians in Sweden.[37~~30~~] However, the substantially younger age at CVD disease among persons with bipolar disorder compared to the population need to be further emphasized. ~~t~~The effects of those guidelines are still to be evaluated.

Our finding that patients with bipolar disorder showed only slightly increased hospital admissions rates for CVD despite their twice as high cardiovascular mortality, strongly suggests that CVD is undertreated in bipolar patients when compared to the general population. In a Danish study, the rates of invasive heart disease procedures were 40% lower among persons with bipolar disorder than in the general population.[4] Although the younger

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age at cardiac events in bipolar disorder compared to the population may reduce detection, this possible contributing factor is unlikely to cause the reduced rates of invasive heart procedures. Sudden cardiac mortality from cardiac arrest/ventricular fibrillation was increased among patients with bipolar disorder (MRR: 1.85), but the 25 excess cases does not explain the difference in hospital admissions in terms of increased sudden death before hospitalization. Thus, the reasons for CVD undertreatment in bipolar disorder is not explained by the current findings. ~~Our register data alone cannot offer an explanation for this finding.~~ In our study, the MRR and ARR patient populations are slightly different, in the respect that the ARR patients are identified at their first index admission, while the MRR patients may have several admissions, and thus being more severely affected. Unequal access to health care (i.e. receiving cardiac treatment of lower quality) for reasons other than financial has been previously suggested as a contributor to excess CVD mortality in patients with severe mental disorders, such as schizophrenia,[38~~31~~] and may be indicated by our findings of increased mortality after discharge from hospital compared to the population. These factors have not been studied extensively in bipolar patients. Health care in Sweden is free and is financed primarily through taxes. Therefore, it is unlikely that patients with bipolar disorder do not seek hospital care for lack of financial means.

Many mechanisms can contribute to the under-treatment of CVD among people with bipolar disorder. Our results indicate a failure of the health care system to identify and address the health needs of those patients, which has also been shown in other studies of people with severe mental disorders.[39~~32~~] The levels of CVD mortality in our bipolar persons are similar to those in schizophrenia, where adverse effects of antipsychotic medication have been considered the main contributing factor. When compared with schizophrenia, a recent study of bipolar disorder in Stockholm County found only 29% of bipolar patients medicating with antipsychotics, as compared to practically all schizophrenia patients, which raises the question of the importance of adverse effects of antipsychotics in CVD.[40~~33~~]

Conclusions

The observed number of deaths from cardiovascular diseases in patients with bipolar disorders was almost twice as the expected number when comparing with the general population, suggesting that more resources are needed for the prevention of these diseases in this patient group. Targeted interventions by effective cooperation between primary health care and psychiatric professionals would be crucial in the efforts to reduce excess CVD

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mortality in patients with bipolar disorder. Finally, effective cardiac treatment would ensure longevity and improved quality of life for ~~bipolar~~ patients with bipolar disorder.

Contributors: UÖ had the idea of the study and is guarantor of the study together with JH, who has performed the statistical analyses. JW has contributed to the design of the study and drafted the manuscript together with UÖ. KW, DE and LA have contributed to the design of the study and with revisions of the manuscript. All authors have approved the final version of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). JW, KW, LA, DE, UÖ has declared no support from any organization for the submitted work, no financial relationship with any organizations that would have interest in the submitted work in the previous three years, and no other activities that could appear to have influenced the submitted work. UÖ has declared traveling expenses from Janssen-Cilag for attending a course in October 2012 unrelated to the study.

Ethical approval: This study was approved by the ethical review board in Stockholm County. The ethical review board determined that informed consent from participating individuals was not required.

Data sharing: The analysis data set for this study is available from the National Board of Health and Welfare (Socialstyrelsen) in Sweden. Please contact JH for further information.

Figure 1. ICD-coding and ~~disease~~ classification of disease and mortality.

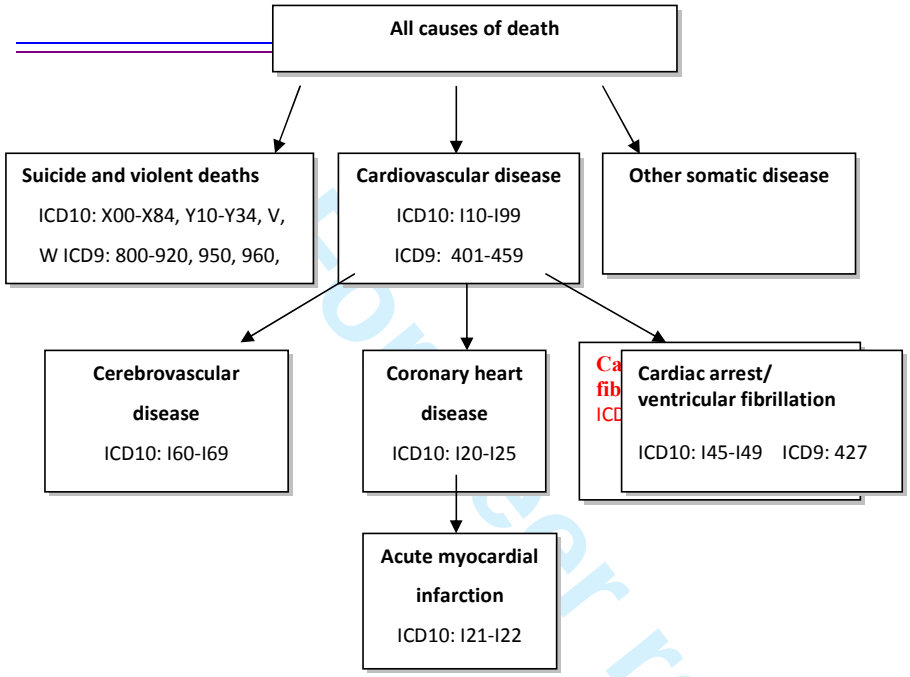

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Table 1. Mortality rate ratios for bipolar patients between 1987 and 2006

	Men		Women		Total (both sexes)		
Cause of death	Cases	MRR (95% CI)	Cases	MRR (95% CI)	Cases	MRR (95% CI)	Excess cases (95% CI)
All causes of death	1874	2.48 (2.37-2.59)	2393	2.34 (2.25-2.44)	4267	2.40 (2.33-2.47)	2489 (2361-2617)
Cardiovascular disease	733	2.16 (2.01-2.33)	892	1.93 (1.81-2.06)	1625	2.03 (1.93-2.13)	824 (745-903)
Other somatic deaths	735	1.97 (1.83-2.11)	1154	2.19 (2.06-2.32)	1889	2.10 (2.00-2.19)	988 (902-1073)
~~Unnatural~~Suicide and other External deaths	406	9.37 (8.50-10.33)	347	10.02 (9.01-11.13)	753	9.66 (8.99-10.37)	675 (621-729)
Cerebrovascular disease	144	2.29 (1.94-2.70)	224	1.86 (1.63-2.12)	368	2.00 (1.81-2.22)	184 (147-222)
Coronary heart disease	385	2.00 (1.81-2.21)	391	1.89 (1.71-2.09)	776	1.95 (1.81-2.09)	377 (323-432)
Acute myocardial infarction	227	1.89 (1.66-2.15)	213	1.78 (1.55-2.03)	440	1.83 (1.67-2.01)	200 (159-241)
Cardiac arrest ~~-~~/-Ventricular fibrillation	23	2.29 (1.52-3.45)	32	1.62 (1.15-2.30)	55	1.85 (1.42-2.41)	25 (12-42)

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Table 2. Admission rate ratios for bipolar patients during 1990 to 2006

	Men		Women		Total (both sexes)		
Hospital admissions	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Excess cases (95% CI)
Cardiovascular disease	540	1.27 (1.16-1.38)	696	1.33 (1.24-1.43)	1236	1.30 (1.23-1.38)	287 (218-356)
Cerebrovascular disease	179	1.32 (1.14-1.53)	271	1.43 (1.27-1.62)	450	1.39 (1.26-1.52)	125 (84-167)
Coronary heart disease	212	1.02 (0.89-1.17)	207	1.06 (0.92-1.21)	419	1.04 (0.94-1.14)	15 (-25-55)
Acute myocardial infarction	133	0.96 (0.81-1.14)	137	1.11 (0.94-1.31)	270	1.03 (0.92-1.16)	8 (-24-41)

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Figure 2a. Mortality Rate Ratios (MRR) for all causes of death by age at death in bipolar disorder patients and the general population.

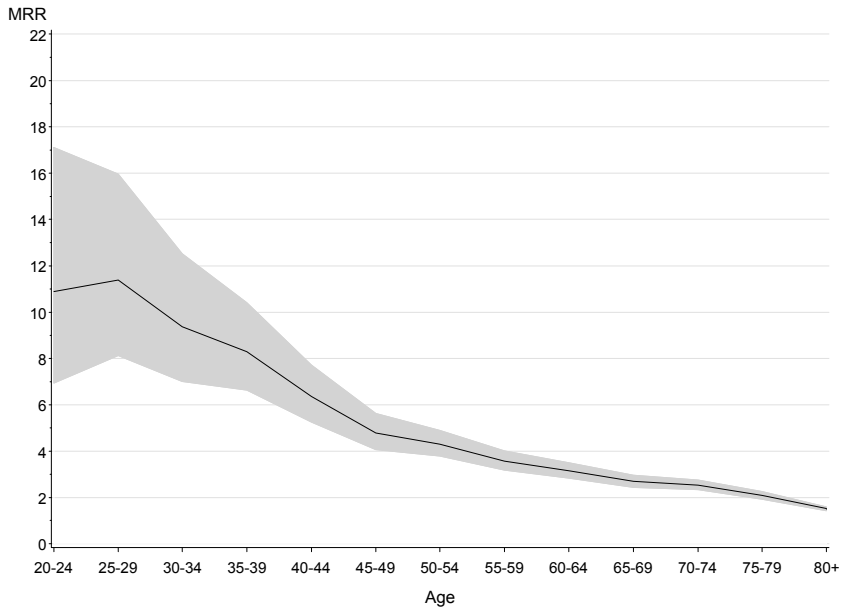
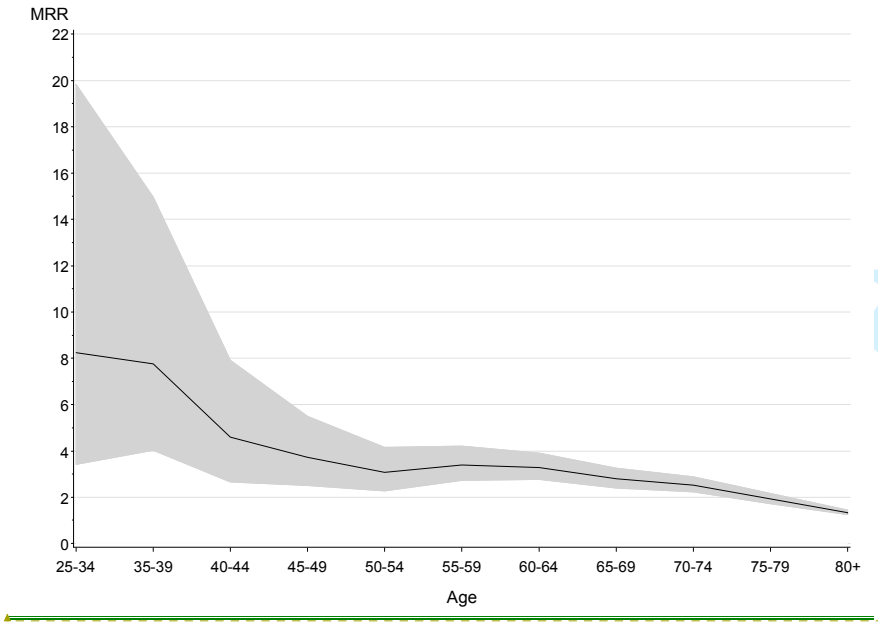


Figure 2b. Mortality Rate Ratios (MRR) for cardiovascular death by age at death in ~~bipolar disorder~~persons with bipolar disorder patients and the general population.



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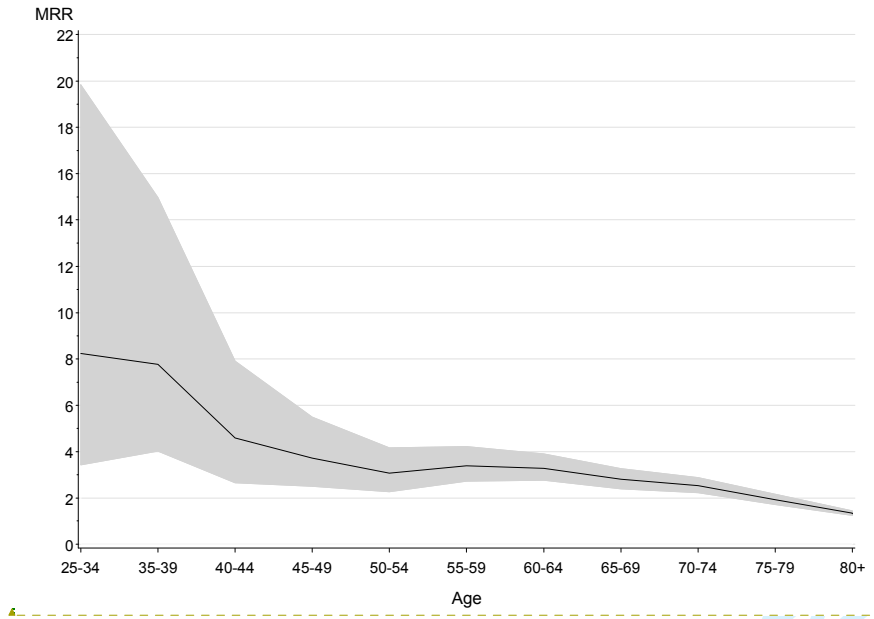
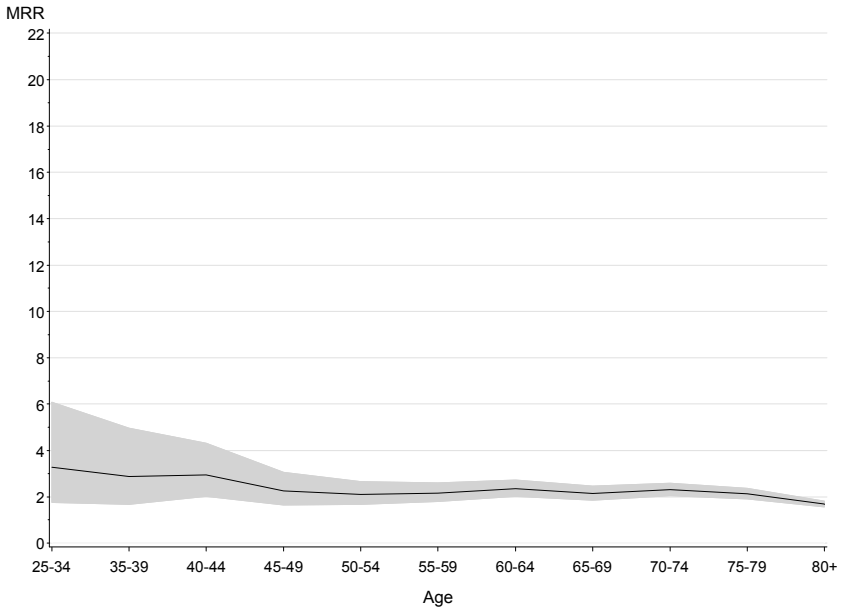


Figure 2c. Mortality Rate Ratios (MRR) for other somatic death by age at death in patients with bipolar disorder ~~patients~~ and the general population.


MRR
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35-39
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55-59
60-64
65-69
70-74
75-79
80+
Age

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Figure 2d. Mortality Rate Ratios (MRR) of suicide and other ~~unnatural~~ external causes of death~~s~~ by age at death in patients with bipolar disorder and the general population.

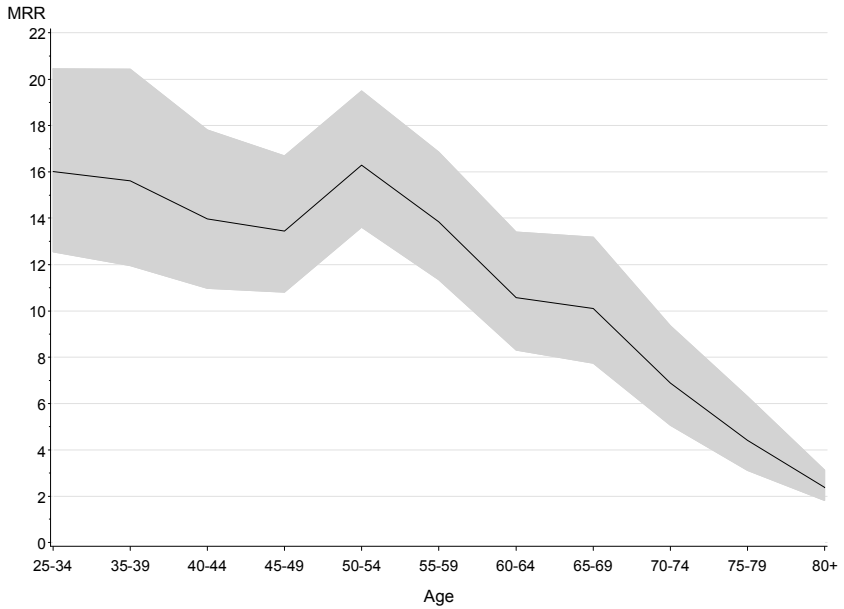

Figure 2e. Mortality Rate Ratios (MRR) of cerebrovascular disease by age at death in patients with bipolar disorder and the general population.

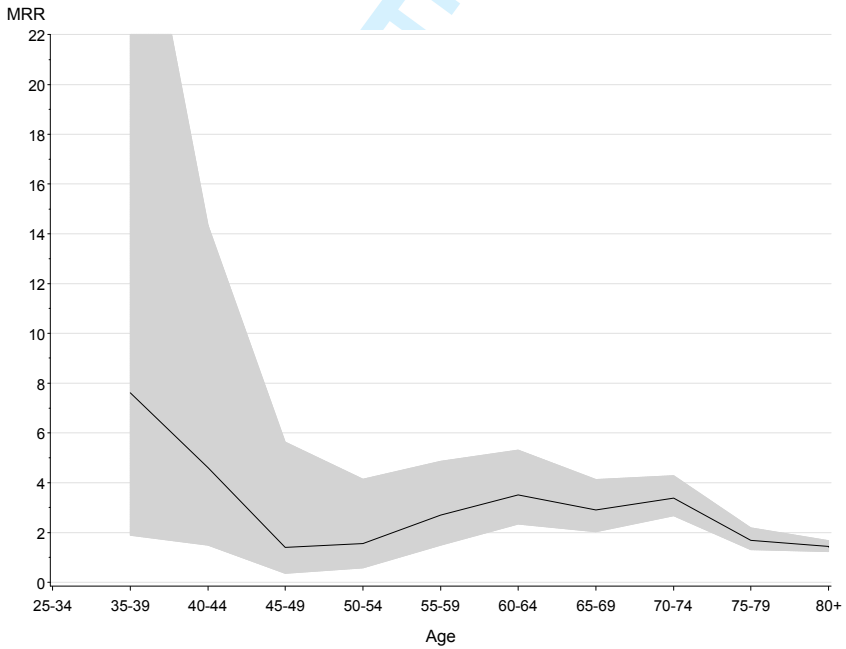

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Figure 2f. Mortality Rate Ratios (MRR) of coronary heart disease by age at death in patients with bipolar disorder and the general population.

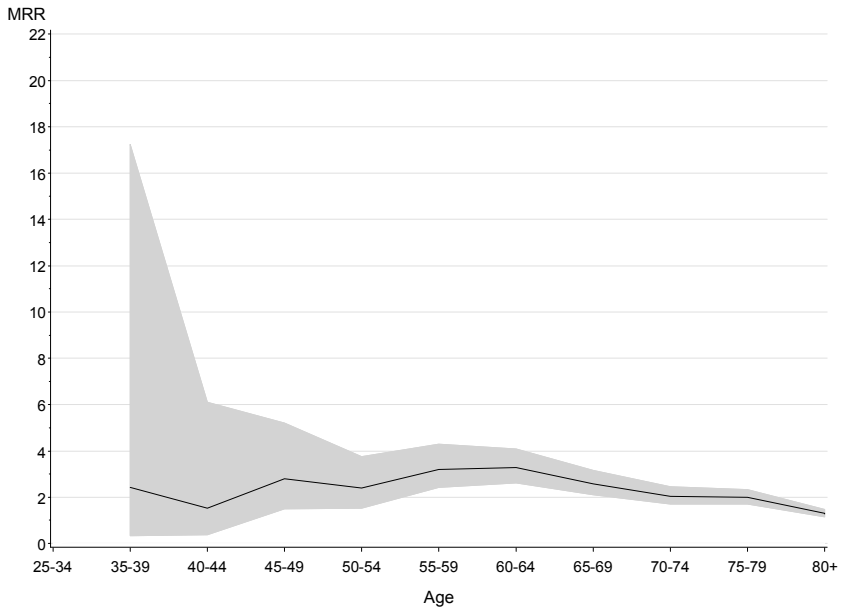

Figure 2g. Mortality Rate Ratios (MRR) of acute myocardial infarction by age at death in patients with bipolar disorder and the general population.

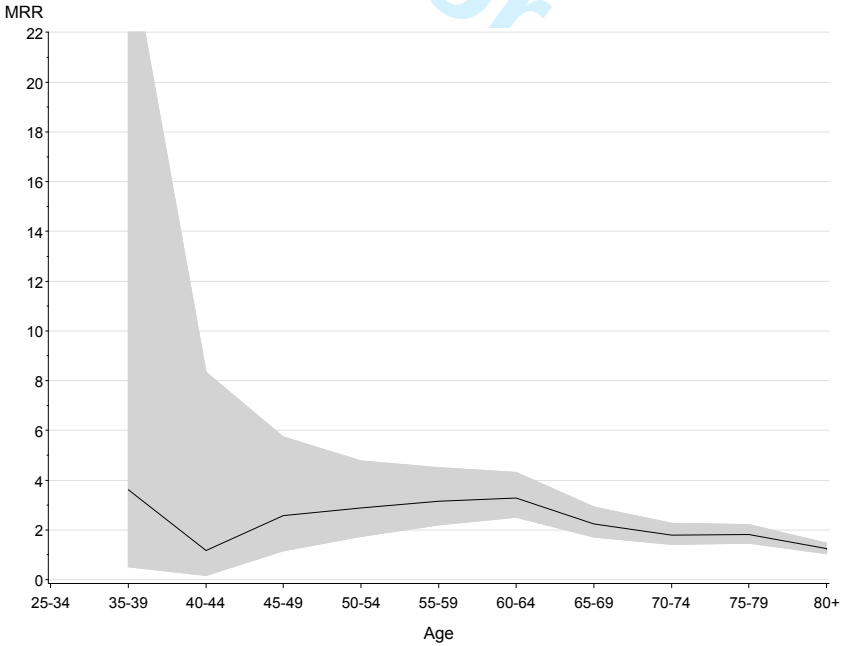

Figure 3a. Mortality of coronary heart disease per 1000 person-years in patients with bipolar disorder and the general population adjusting for sex and calendar year.

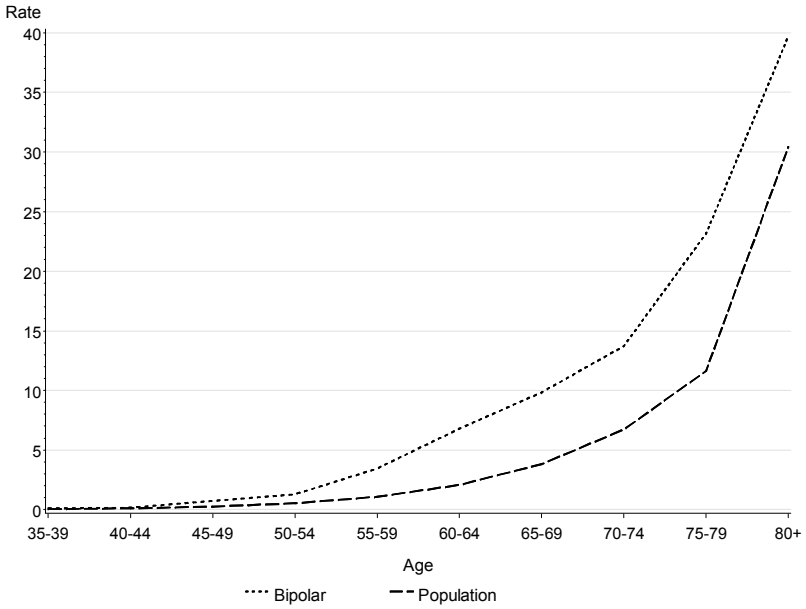

Figure 3b. Acute myocardial infarction

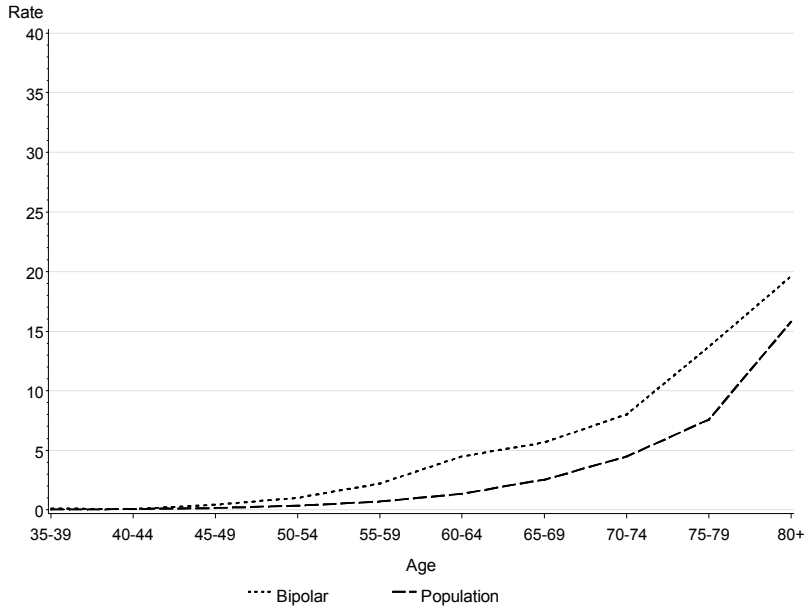

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Figure 3c. Cerebrovascular disease

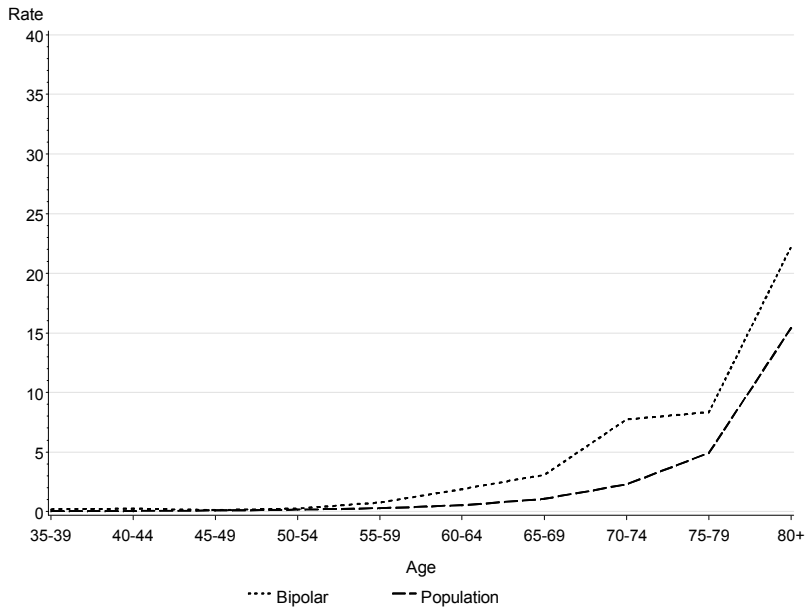
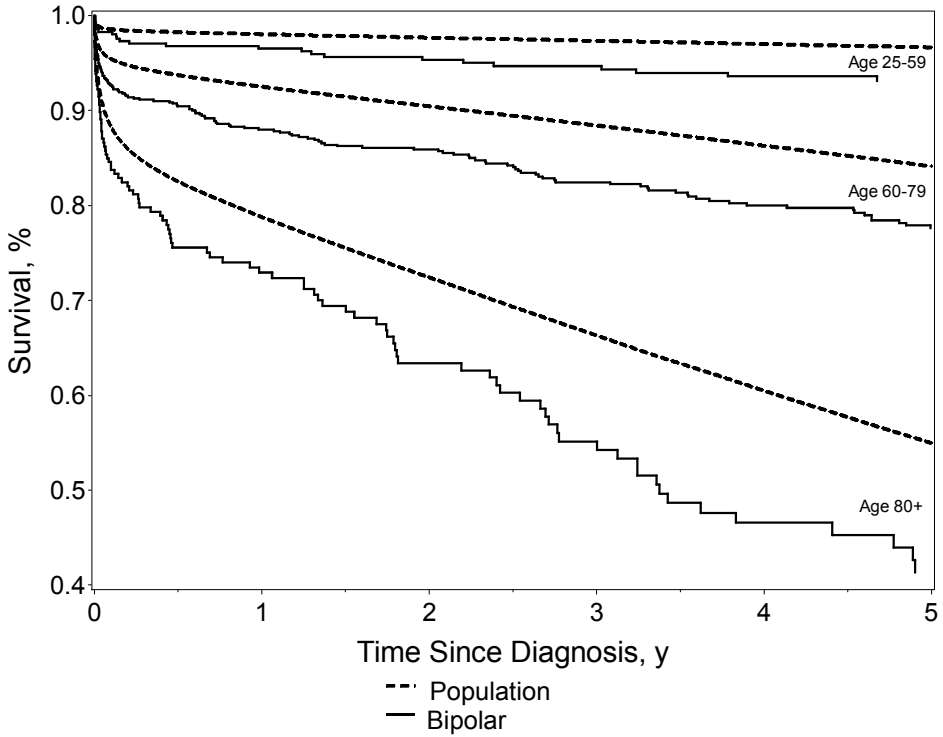


Figure 4. Five-year survival of cardiovascular disease after disharge from first cardiovascular admission stratified by age at hospital contact.



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Our manuscript have been checked towards the STROBE Statement.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies*** -

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden

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Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden.

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Article summary

Article focus

- To estimate mortality in cardiovascular disease (CVD) and its subgroups cerebrovascular and coronary heart disease and acute myocardial infarction among 17,101 persons diagnosed with bipolar disorder in Sweden, compared to the general population in a national register study with a 20-year follow-up.

Key messages

- Persons with bipolar disorder died of CVD approximately ten years early. Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was higher than that of suicide and other external causes (n=675 deaths). Mortality rate ratios (MRR) for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high compared to the general population. Despite the increased mortality, hospital admissions, admission rate ratios (ARR) for CVD treatment in persons with bipolar disorder were only slightly increased.

- The increased cardiovascular mortality in persons with bipolar disorder calls for renewed efforts to prevent and treat somatic diseases. Specifically, our findings imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as the population.

Strengths and limitations of this study

- A large national cohort with comprehensive data on patient characteristics was studied. Mortality data from the Swedish cause of death register are of high quality.
- Clinical information on symptoms and treatment were lacking.

ABSTRACT (word count: 265)

Objective: To estimate cardiovascular mortality among persons with bipolar disorder in Sweden compared to the general population.

Design: Population register based cohort study with a 20-year follow-up.

Setting: Sweden.

Participants: The entire population of Sweden (n=10.6 million) of whom 17,101 persons were diagnosed with bipolar disorder between 1987 and 2006.

Main outcome measures: Mortality rate ratios (MRR), excess mortality (excess deaths), cardiovascular disorders (CVD) and specifically cerebrovascular disease, coronary heart disease, acute myocardial infarction, sudden cardiac deaths, and hospital admission rate ratios (ARR).

Results: Persons with bipolar disorder died of CVD approximately ten years earlier than the general population. One third (38%) of all deaths in persons with bipolar disorder were caused by CVD, and almost half (44%) by other somatic diseases, whereas suicide and other external causes accounted for less than a fifth of all deaths (18%). Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was higher than that of suicide and other external causes (n=675 deaths). MRRs for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high in persons with bipolar disorder compared to the general population. Despite the increased mortality of CVD, hospital admissions (ARR) for CVD treatment were only slightly increased in persons with bipolar disorder when compared to the general population.

Conclusions: The increased cardiovascular mortality in persons with bipolar disorder calls for renewed efforts to prevent and treat somatic diseases in this group. Specifically, our findings further imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as persons without bipolar disorder.

Introduction

Cardiovascular disease (CVD) is the main cause of death in many developed countries.[1] CVD encompasses a broad range of different conditions that are potentially life threatening. In Sweden, although mortality from CVD in the population has almost halved in the last two decades, CVD still accounts for more than 40% of all deaths in the country.[2] Premature death in patients with severe mental health disorders, especially patients with schizophrenia and bipolar disorder, has historically been attributed to suicide. However, more recent studies have shown that CVD leads to more reduced life spans than does suicide in those patients.[3] Persons with bipolar disorder have an increased risk of CVD and have been observed to die due to CVD twice as often as the general population.[4-6] Although previous studies have shown an association between bipolar disorder and mortality from CVD, few studies have addressed different types of vascular mortality, or examined related use of health care. An improved understanding of the causes behind and magnitude of CVD among bipolar patients is warranted along with an in-depth evaluation of different diagnostic CVD subgroups. The answers to these questions, which are far less investigated in bipolar disorder than in schizophrenia, are essential in the efforts to address the problem of premature deaths due to CVD in persons with bipolar disorder. These questions are the focus of the present national register-based study, which extends earlier Swedish findings[5] both by more specific CVD mortality analyses and more recent patient data.

The aim of this study was to evaluate excess mortality from CVD, such as cerebrovascular disease and coronary heart disease with acute myocardial infarction as its most important component, and also CVD hospitals admissions, in persons with bipolar disorder in Sweden between 1987 and 2006 compared to the population.

Methods

Cohort and follow-up

All persons who resided in Sweden between the 1st of January 1987 and the 31st of December 2006 (n=10,631,208) were identified using the Swedish Total Population Register (TPR). The TPR was established in 1968 and contains information on sex, date and place of birth, and date of migration of every resident in Sweden. Information on hospital admission, medical diagnosis, and cause of death was obtained by linking the TRP with the national Swedish Cause-of-Death Register and the National Patient Register (NPR) using each resident's unique personal identification number.

The NPR, which is maintained by the National Board of Health and Welfare, contains information on all hospital in-patient treatments in Sweden since 1987. For psychiatric in-patient care the register has nationwide coverage dating back from 1973. For each hospitalization, the unique national registration number, date of admission and discharge, and diagnosis are registered in NPR. In Sweden, all hospital diagnoses are classified according to the WHO International Classification of Diseases (ICD). Since the diagnostic definitions of affective disorders were substantially changed in ICD-9 and ICD-10 as compared with ICD-8, only patients diagnosed with bipolar disorder according to ICD-9 or ICD-10 were included in the study. Bipolar diagnoses recorded between 1987 and 1996 were identified using ICD-9 (296A, C, E, 298B). From 1997 and later, ICD-10 (F30-F31) was used to identify bipolar diagnoses. The Swedish Cause of Death Register (CDR) includes all individuals who were registered in Sweden at the time of death. The register provides information on date of death as well as main (underlying) and secondary causes of death based on death certificates. Definitions regarding causes of death and ICD codes used in this study are shown in Figure 1.

A total of 20,248 patients admitted to hospital between 1st of January 1987 and 31st of December 2006 with a main diagnosis of bipolar disorder (ICD-9; ICD-10) were identified in the NPR. Of the 20,248 patients, 3,147 had been previously diagnosed with schizophrenia (ICD-8: 295; ICD-9: 295; ICD-10; F20, F25) and were consequently excluded. Thus, the total risk population of the study comprised 17,101 patients with bipolar disorder. The follow-up period was 20 years (1987-2006). Immigrants were included from the date of immigration to Sweden. Each person was followed until December 31, 2006, or date of death or emigration,

depending on which came first. Inclusion in the risk population started from the date of first hospital admission (discharge diagnosis) during the study period.

Statistical analysis

Person years at risk, number of cause-specific deaths and hospital admissions due to CVD for both bipolar patients and the general population were determined. Person time was stratified by sex, calendar year and age. Mortality rate ratios (MRR) and Admission rate ratios (ARR) and predicted mortality rates were calculated with corresponding 95% confidence intervals (CI) using Poisson regression models with the GENMOD procedure using statistical software SAS (version 9.2). All models were adjusted for or stratified by sex, attained age and year of follow-up.

To calculate the excess mortality for patients with bipolar disorder the observed number of deaths was compared with the expected number of deaths among patients with bipolar disorder. The expected number of deaths was calculated by applying age, sex and calendar specific mortality rates in the general population to the time at risk among the patients.
The risk of dying from CVD after first hospital admission was analyzed by estimating cause-specific survival curves using the Kaplan-Meier method. Additional adjusted hazard ratios with 95% CIs were estimated using Cox proportional hazard models.

When hospital admission due to CVD (Admission rate ratios, ARR) was the event of interest, follow-up ended on the day of first admission. To ensure that the observed cases were incident, a three-year run-in period was created to compensate for the lack of CVD coverage in the NPR before 1987. Hence, all bipolar patients analyzed had no hospital admissions due to CVD recorded for at least three years before follow-up.

Results

Causes of death

Total mortality (death from any cause) between 1987 and 2006 in Sweden was more than twice as high among patients with bipolar disorder compared to the general population (MRR 2.40; 95% CI 2.33-2.47). Specifically, 2,489 excess deaths in patients with bipolar disorder were observed (Table 1). With mortality causes subdivided into CVD, other somatic, and external causes of death, we found that men and women with bipolar disorder were twice as

likely to die of CVD compared to the general population (MRR 2.03; 95% CI 1.93-2.13), with 824 excess deaths due to CVD. Mortality from other somatic causes was also doubled (MRR 2.10; 95% CI 2.00-2.19), with 988 excess deaths. External causes of death, such as suicide, homicides, and accidents, were increased more than nine times in bipolar patients (MRR 9.66; 95% CI 8.99-10.37), with 675 excess deaths. As far as CVD subgroups were concerned, mortality from cerebrovascular disease and coronary heart disease was twice as high in bipolar patients, with 184 excess deaths (MRR 2.00; 95% CI 1.81-2.22) and 377 excess deaths (MRR 1.95; 95% CI 1.81-2.09), respectively. Mortality from acute myocardial infarction was almost twice as high in bipolar patients (MRR 1.83; 95% CI 1.67-2.01), with 200 excess deaths. Mortality from sudden cardiac death, cardiac arrest/ventricular fibrillation, was also increased (MRR 1.85; 95% CI 1.42-2.41), with 25 excess deaths. Bipolar women and men of all ages had an equally increased mortality from CVD (data not shown).

Age and cause of death

MRR by age at death for all causes of death is shown in Fig 2a and subdivided into cardiovascular death (Fig 2b), other somatic death (Fig 2c), suicide and other external causes of death (Fig 2c). Cerebrovascular death (Fig 2e), death by coronary heart disease (Fig 2f), and death from acute myocardial infarction (Fig 2g) are reported separately.

MRR for CVD was increased for bipolar patients across all ages but was particularly pronounced in the young age groups (Figure 2b). Patients with bipolar disorder who died of CVD were younger than people in the general population. The same finding was observed when we subdivided CVD into cerebrovascular disease, coronary heart disease and acute myocardial infarction (Figure 2e-g). For acute myocardial infarction and coronary heart disease the increased risk was most apparent in the 55-65 years age groups (2f-g). In the ages below 50 years the results should be interpreted with caution because there were very few events in these ages. Death by suicide and other external causes of death were 15 times more common among bipolar patients below 30 years of age compared to persons of the same age in the general population (Figure 2d). Overall, the MRR for suicide and other external causes ofdeath decreased with increasing age. However, it should be noted that it remained significantly increased in persons aged between 70-74 years (MRR 6.88; CI 95% 5.06-9.35) (Figure 2d).

Age differences at death between persons with bipolar disorder and the population from coronary heart disease, acute myocardial infarction and cerebrovascular disease is shown in Figure 3a-3c. The earlier age at death for persons with bipolar disorder is clearly shown for all these causes of death.

Admission rates

Hospital admission rates for CVD among patients with bipolar disorder were similar to those for the general population even though MRR for CVD was almost twice as high, independent of the specific CVD cause (Tables 1 and 2). Survival rates five years after first hospital admission for CVD were significantly lower among bipolar patients than among the general population (Figure 4).

Discussion

Key findings

In this nationwide study of mortality among persons with bipolar disorder in Sweden compared to the population, somatic illness was the main cause of death. Bipolar patients died of CVD around ten years earlier than the general population. Mortality from cerebrovascular disease, coronary heart disease, and acute myocardial infarction was twice as high in bipolar patients as in the general population, while the frequency of hospital admissions due to these diseases was not increased. Our findings showed that CVD in persons with bipolar disorder accounted for 824 excess deaths and other somatic diseases 988 excess deaths, taken together 1,812 excess deaths, both larger than suicide and other external causes of death (n=675). Interestingly, sudden cardiac death was also increased.

Strengths and limitations

The Swedish National Patient Register and Cause of Death Register include everyone who resides in the country and are considered unique, comprehensive and highly credible. Currently more than 99% of all somatic and psychiatric hospital discharges are recorded in the National Patient Register.[7] Swedish hospitals and government agencies are obliged by law to enter medical information in the National Patient Register. All diagnoses in the National Patient and Cause of Death registers were given by patients' doctors using international classification standards (ICD codes). Being register based, this study used information about clinical diagnoses from hospital admissions in Sweden. During the study period, the ICD

diagnostic definitions were specific for bipolar disorder. A validation of the Swedish clinical bipolar hospital diagnoses has shown high validity, sufficient for epidemiological studies.[8] One limitation of this study was that it was based on in-patient diagnoses, which may have generated a selective bias towards severely ill patients. However, most individuals at severe stages of bipolar disorder are admitted to hospital in Sweden. Since medical care is free in Sweden, there is no bias by costs for hospital care leading to differences in health-seeking behavior. In a previous study, we have shown that the number and frequency of hospital admissions due to bipolar disorder remained relatively unchanged during recent years, while the overall number of psychiatric admissions was drastically reduced.[9] We did not have access to medical records or information on medical treatment. In terms of the validity of the data on causes of death, in CVD deaths we found a slightly higher autopsy rate (28%) among patients with bipolar disorder than in the general population (22%). It is unlikely that these small differences affected the outcome of the study. An advantage with the present study is the analysis of specific causes of death.

Findings from other studies

The findings of this study add to the growing body of evidence that somatic diseases, particularly CVD, contribute to a shorter lifespan among bipolar patients. Findings from several large register-based studies from different parts of the world indicate that cardiovascular disease is responsible for the majority of excess deaths, with up to 2.5-fold increased mortality.[3 5 6 10-14] Studies using registers from the Nordic countries have shown that bipolar patients run almost twice the risk of dying from CVD than do persons in the general population, the mechanisms for which are currently unknown.[4 5] There is a growing body of evidence from studies in other countries, and findings similar to ours have been observed in a representative study of the US population.[15] In our previous study,[5] SMR for CVD but not for cerebrovascular mortality was higher for women compared to men. This difference was not found in our present study. SMR and MRR are relative measurements, affected both by population trends and trends among the cases. Thus, the different findings could be related both to changing mortality rates in the population and to changes among persons with bipolar disorder, or a combination of those factors. CVD contains several different causes of mortality, which may have different trends over time. However, the specific causes of death related to the sex difference in CHD mortality previously found cannot be answered in our study.

Studies have shown a higher cardiovascular mortality in persons with bipolar disorder type I compared to bipolar disorder type II or major depressive disorder.[16 17] In our Swedish data, bipolar disorder type I cannot be separated from bipolar disorder type II. However, patients with bipolar disorder type I are much more likely to be hospitalized and thus to be included in our sample. Earlier age of CVD has been shown in several studies,[15] and is also confirmed in our findings of increased cardiovascular death at a younger age compared to the population in Sweden. Possible risk factors for the increased mortality from CVD among bipolar patients may include adverse effects of medication,[18 19] high levels of smoking,[20] unhealthy diet,[21 22] lack of physical activity,[21] low social-economic status,[23] and lower rates of nutritional counceling.[24] Studies have shown that bipolar disorder patients deviate from age-based norms on arterial stiffness measures.[25] Also, inflammation has been pointed out as a potential biological cause of increased CVD in bipolar disorder [30 31] together with endothelial dysfunction. [32] In addition, effects of genetic associations, such as those reported between Type 2 diabetes, CHD and schizophrenia,[26] could not be excluded. One of the most important locuses of genetic polymorphisms linked to bipolar disease and depression is around the ATP-activated ion-channel receptor *P2X7*.[27] Recently, a polymorphism in the *P2X7* gene was linked to increased risk of stroke and acute myocardial infarction,[28] and the same polymorphism has also recently been shown to be linked to cognitive symptoms in bipolar disorder,[29] indicating that common genetic factors could have effect on both cardiovascular disease and bipolar disorder.

CVD undertreated in persons with bipolar disorder

Studies of patients with bipolar disorder have shown that the patients have an increased risk of metabolic syndrome,[33] i.e. increased blood glucose,[34] and cholesterol levels,[35] higher blood pressure,[36] and higher prevalence of overweight and obesity,[21] closely associated with CVD. To prevent and treat metabolic disorders in patients with severe mental illnesses such as bipolar disorder, new guidelines for clinicians in Sweden were drawn up in 2009, thus after the end of this study, by psychiatrists, diabetologists, endocrionologists, cardiologists and general practitioners in collaboration.[37] The guidelines can be found on the website of the Swedish Psychiatric Association (www.svenskpsykiatri.se). In the guidelines, there is a strong emphasis on the increased metabolic risks at younger age, with focus both on primary and secondary prevention strategies and the need for collaboration between the different medical specialties. The effects of those guidelines are still to be evaluated.

Our finding that patients with bipolar disorder showed only slightly increased hospital admissions rates for CVD despite their twice as high cardiovascular mortality, strongly suggests that CVD is undertreated in bipolar patients when compared to the general population. In a Danish study, the rates of invasive heart disease procedures were 40% lower among persons with bipolar disorder than in the general population.[4] Although the younger age at cardiac events in bipolar disorder compared to the population may reduce detection, this factor is unlikely to cause the reduced rates of invasive heart procedures, since younger age at detection would rather be expected to lead to more intensive treatment. The lower rate of invasive heart disease procedures among persons with bipolar disorder is yet to be explained. Sudden cardiac mortality from cardiac arrest/ventricular fibrillation was increased among patients with bipolar disorder (MRR: 1.85), but the 25 excess cases does not explain the difference in CVD admissions in terms of increased sudden death before hospital admission. Thus, the reasons for CVD undertreatment in bipolar disorder is not explained by the current findings. In our study, the MRR and ARR patient populations are slightly different, in the respect that the ARR patients are identified at their first index admission, while the MRR patients may have several admissions, and thus being more severely affected. Unequal access to health care (i.e. receiving cardiac treatment of lower quality) for reasons other than financial has been previously suggested as a contributor to excess CVD mortality in patients with severe mental disorders, such as schizophrenia,[38] and may be indicated by our findings of increased mortality after discharge from hospital compared to the population. These factors have not been studied extensively in bipolar patients. Health care in Sweden is free and is financed primarily through taxes. Therefore, it is unlikely that patients with bipolar disorder do not seek hospital care for lack of financial means.

Many mechanisms can contribute to the under-treatment of CVD among people with bipolar disorder. Our results indicate a failure of the health care system to identify and address the health needs of those patients, which has also been shown in other studies of people with severe mental disorders.[39] The levels of CVD mortality in our bipolar persons are similar to those in schizophrenia, where adverse effects of antipsychotic medication have been considered the main contributing factor. When compared with schizophrenia, a recent study of bipolar disorder in Stockholm County found only 29% of bipolar patients medicating with antipsychotics, as compared to practically all schizophrenia patients, which raises the question of the importance of adverse effects of antipsychotics in CVD.[40]

Conclusions

The observed number of deaths from cardiovascular diseases in patients with bipolar disorders was almost twice as the expected number when comparing with the general population, suggesting that more resources are needed for the prevention of these diseases in this patient group. Targeted interventions by effective cooperation between primary health care and psychiatric professionals would be crucial in the efforts to reduce excess CVD mortality in patients with bipolar disorder. Finally, effective cardiac treatment would ensure longevity and improved quality of life for patients with bipolar disorder.

Contributors: UÖ had the idea of the study and is guarantor of the study together with JH, who has performed the statistical analyses. JW has contributed to the design of the study and drafted the manuscript together with UÖ. KW, DE and LA have contributed to the design of the study and with revisions of the manuscript. All authors have approved the final version of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). JW, KW, LA, DE, UÖ has declared no support from any organization for the submitted work, no financial relationship with any organizations that would have interest in the submitted work in the previous three years, and no other activities that could appear to have influenced the submitted work. UÖ has declared traveling expenses from Janssen-Cilag for attending a course in October 2012 unrelated to the study.

Ethical approval: This study was approved by the ethical review board in Stockholm County. The ethical review board determined that informed consent from participating individuals was not required.

Data sharing: The analysis data set for this study is available from the National Board of Health and Welfare (Socialstyrelsen) in Sweden. Please contact JH for further information.

Figure 1. ICD-coding and classification of disease and mortality.

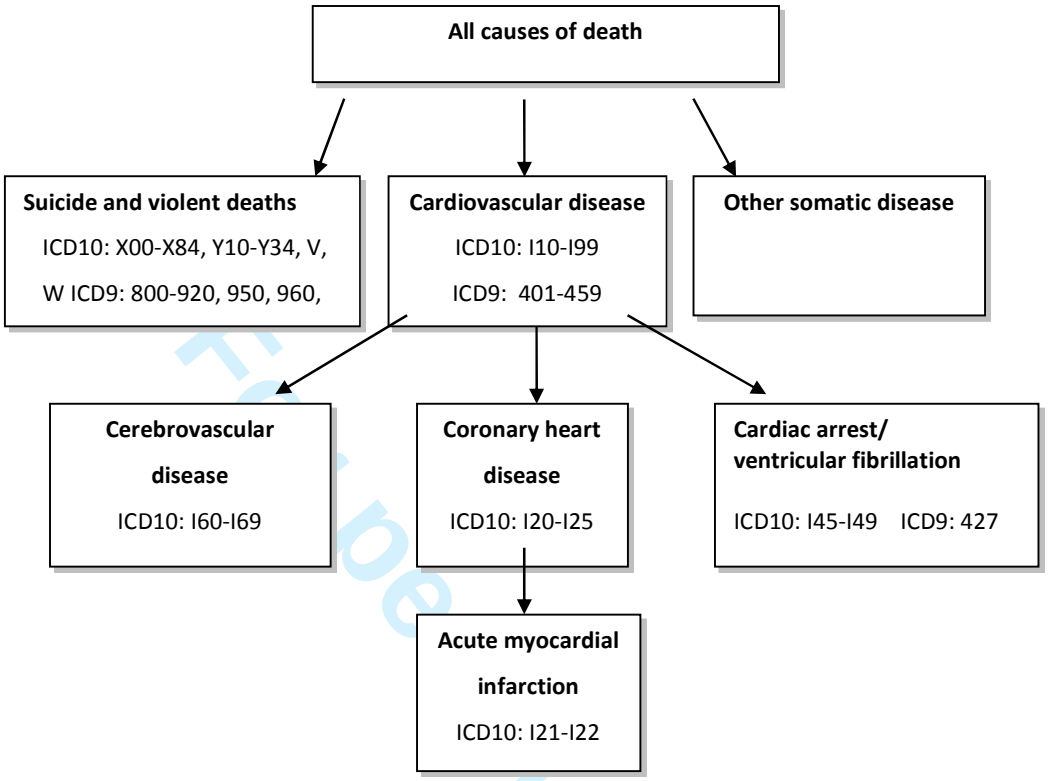


Table 1. Mortality rate ratios (MRR) for persons with bipolar disorder between 1987 and 2006

	Men		Women		Total (both sexes)		
Cause of death	**Cases**	**MRR (95% CI)**	**Cases**	**MRR (95% CI)**	**Cases**	**MRR (95% CI)**	**Excess cases (95% CI)**
All causes of death	1874	2.48 (2.37-2.59)	2393	2.34 (2.25-2.44)	4267	2.40 (2.33-2.47)	2489 (2361-2617)
Cardiovascular disease	733	2.16 (2.01-2.33)	892	1.93 (1.81-2.06)	1625	2.03 (1.93-2.13)	824 (745-903)
Other somatic deaths	735	1.97 (1.83-2.11)	1154	2.19 (2.06-2.32)	1889	2.10 (2.00-2.19)	988 (902-1073)
Suicide and other External deaths	406	9.37 (8.50-10.33)	347	10.02 (9.01-11.13)	753	9.66 (8.99-10.37)	675 (621-729)
Cerebrovascular disease	144	2.29 (1.94-2.70)	224	1.86 (1.63-2.12)	368	2.00 (1.81-2.22)	184 (147-222)
Coronary heart disease	385	2.00 (1.81-2.21)	391	1.89 (1.71-2.09)	776	1.95 (1.81-2.09)	377 (323-432)
Acute myocardial infarction	227	1.89 (1.66-2.15)	213	1.78 (1.55-2.03)	440	1.83 (1.67-2.01)	200 (159-241)
Cardiac arrest/Ventricular fibrillation	23	2.29 (1.52-3.45)	32	1.62 (1.15-2.30)	55	1.85 (1.42-2.41)	25 (12-42)

Table 2. Admission rate ratios (ARR) for persons with bipolar disorder during 1990 to 2006

	Men		Women		Total (both sexes)		
Hospital admissions	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Excess cases (95% CI)
Cardiovascular disease	540	1.27 (1.16-1.38)	696	1.33 (1.24-1.43)	1236	1.30 (1.23-1.38)	287 (218-356)
Cerebrovascular disease	179	1.32 (1.14-1.53)	271	1.43 (1.27-1.62)	450	1.39 (1.26-1.52)	125 (84-167)
Coronary heart disease	212	1.02 (0.89-1.17)	207	1.06 (0.92-1.21)	419	1.04 (0.94-1.14)	15 (-25-55)
Acute myocardial infarction	133	0.96 (0.81-1.14)	137	1.11 (0.94-1.31)	270	1.03 (0.92-1.16)	8 (-24-41)

Figure 2a. Mortality rate ratios (MRR) for all causes of death by age at death in persons with bipolar disorder and the general population.

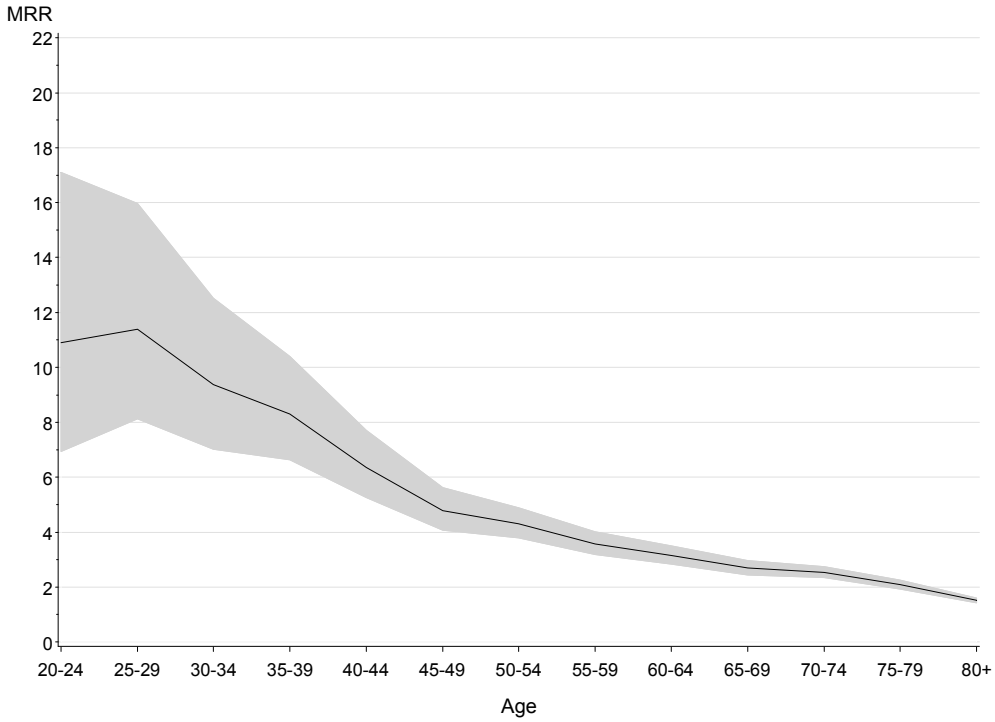


Figure 2b. Mortality rate ratios (MRR) for cardiovascular death by age at death in persons with bipolar disorder and the general population.

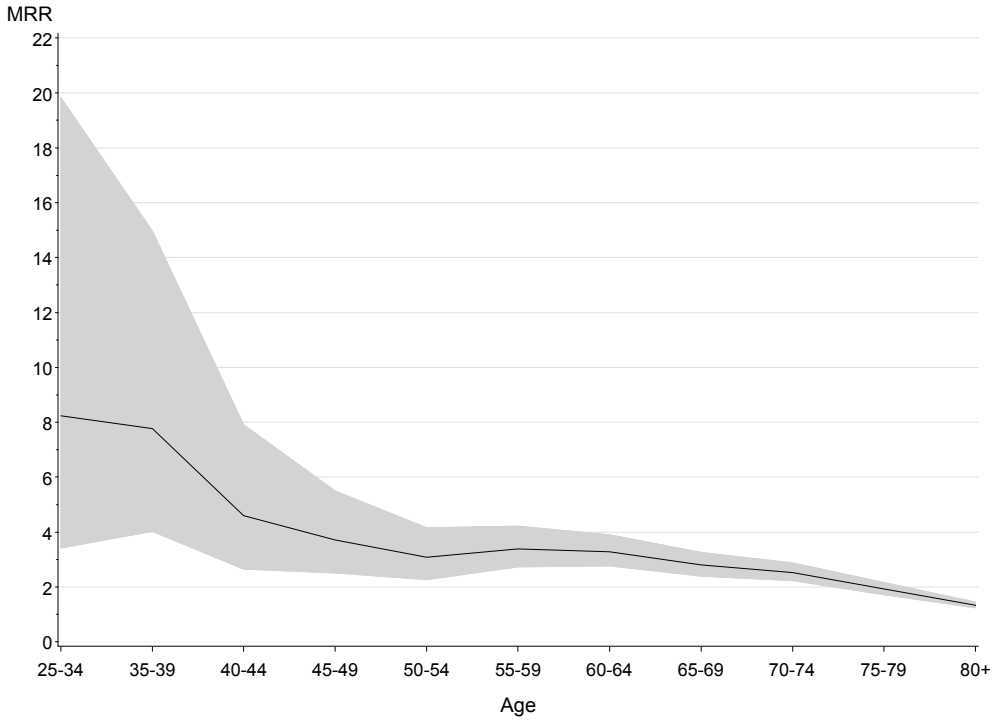


Figure 2c. Mortality rate ratios (MRR) for other somatic death by age at death in patients with bipolar disorder and the general population.

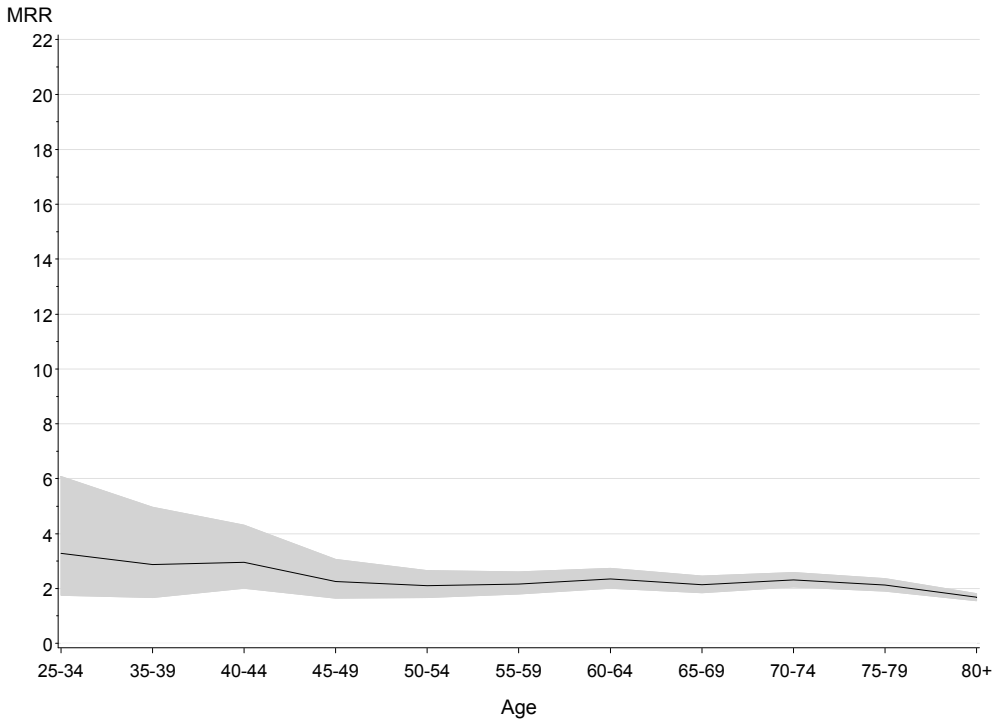


Figure 2d. Mortality rate ratios (MRR) of suicide and other external causes of death by age at death in patients with bipolar disorder and the general population.

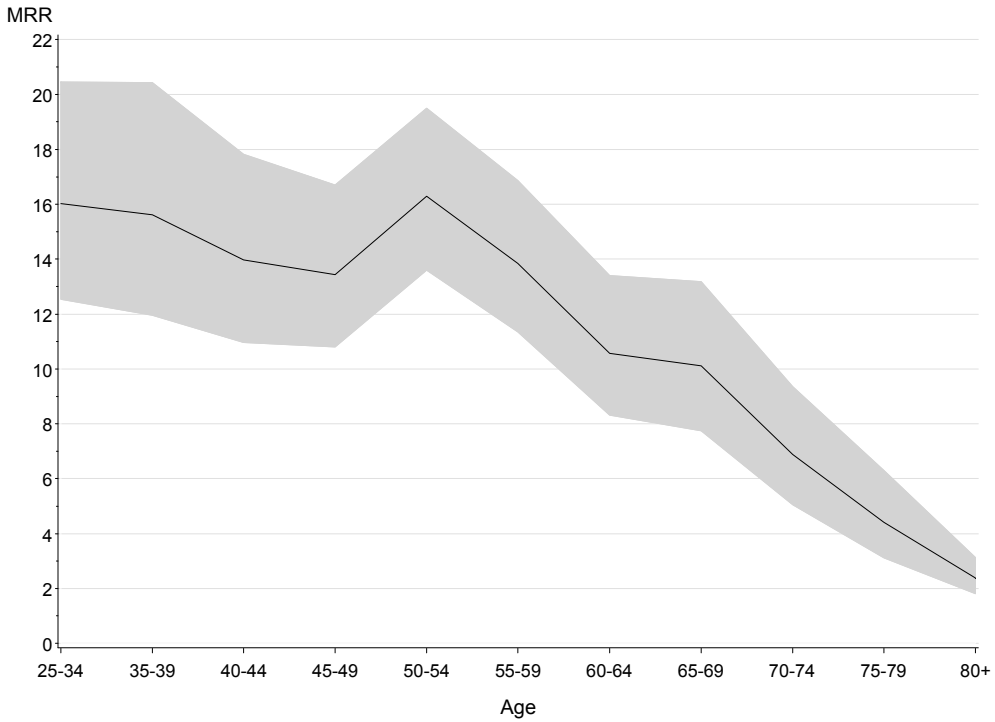


Figure 2e. Mortality rate ratios (MRR) of cerebrovascular disease by age at death in persons with bipolar disorder and the general population.

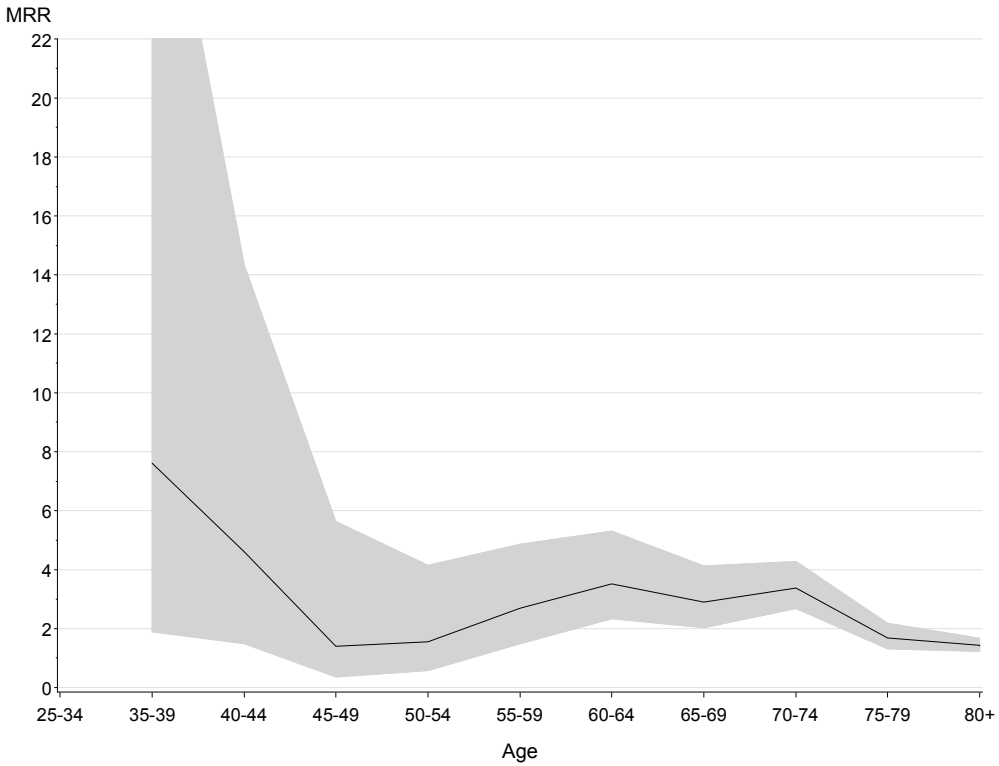


Figure 2f. Mortality rate ratios (MRR) of coronary heart disease by age at death in persons with bipolar disorder and the general population.

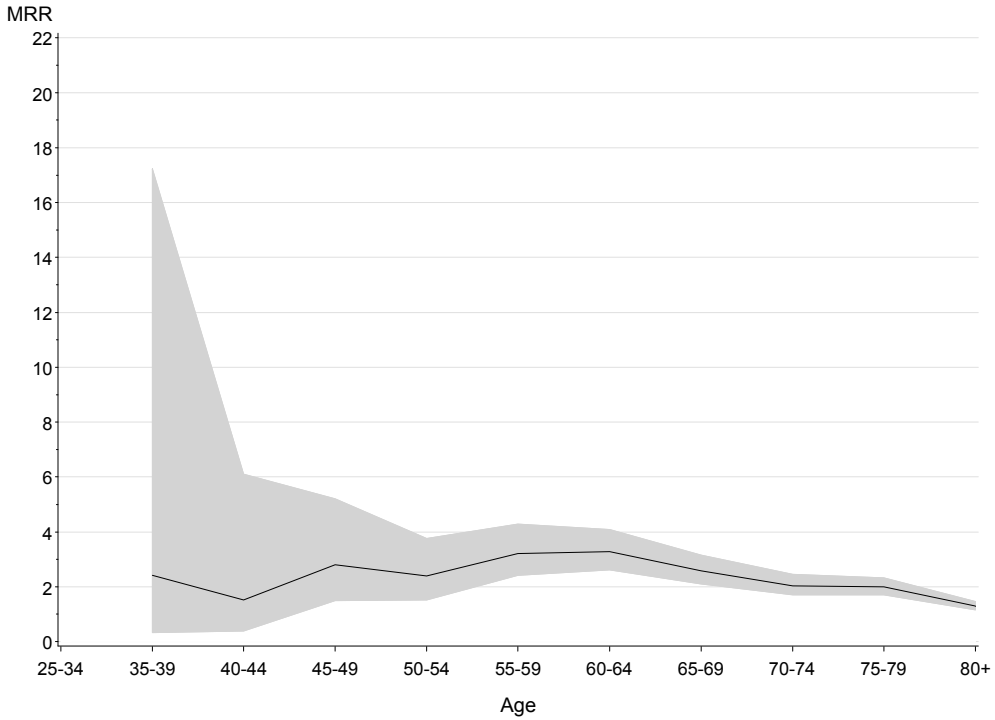


Figure 2g. Mortality rate ratios (MRR) of acute myocardial infarction by age at death in persons with bipolar disorder and the general population.

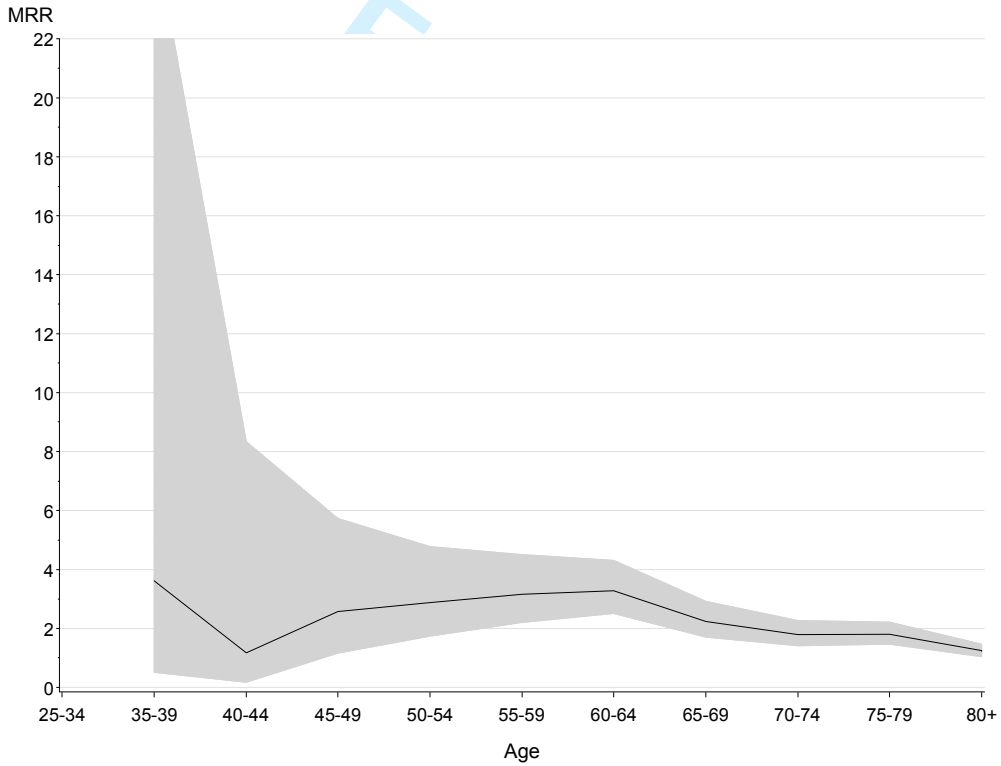


Figure 3a. Mortality of coronary heart disease per 1,000 person-years in persons with bipolar disorder and the general population adjusting for sex and calendar year.

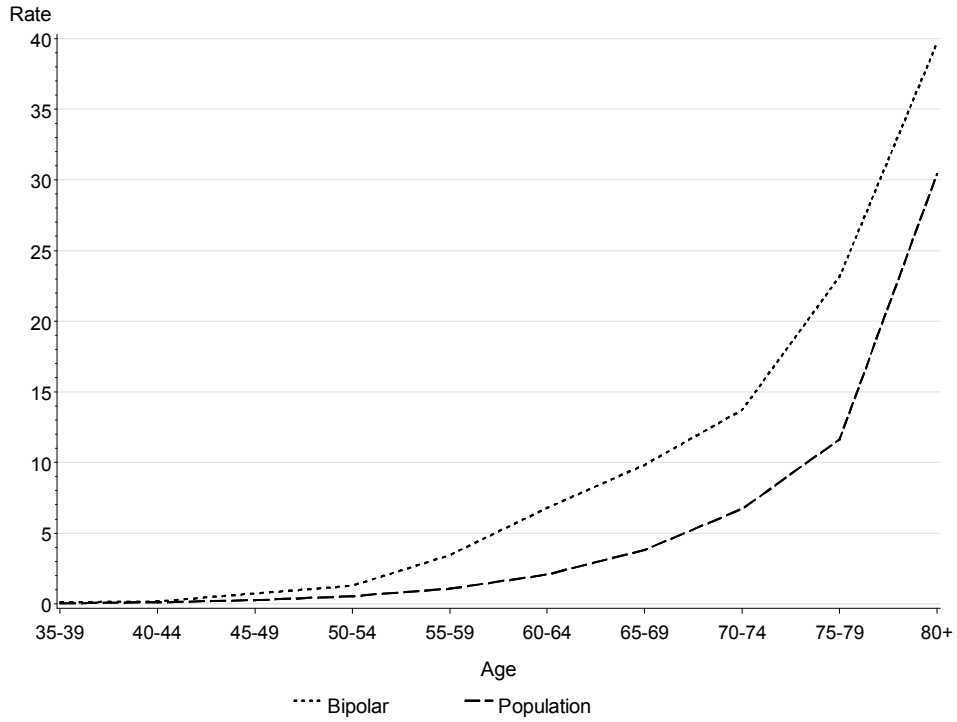


Figure 3b. Mortality of acute myocardial infarction per 1,000 person-years in persons with bipolar disorder and the general population adjusting for sex and calendar year.

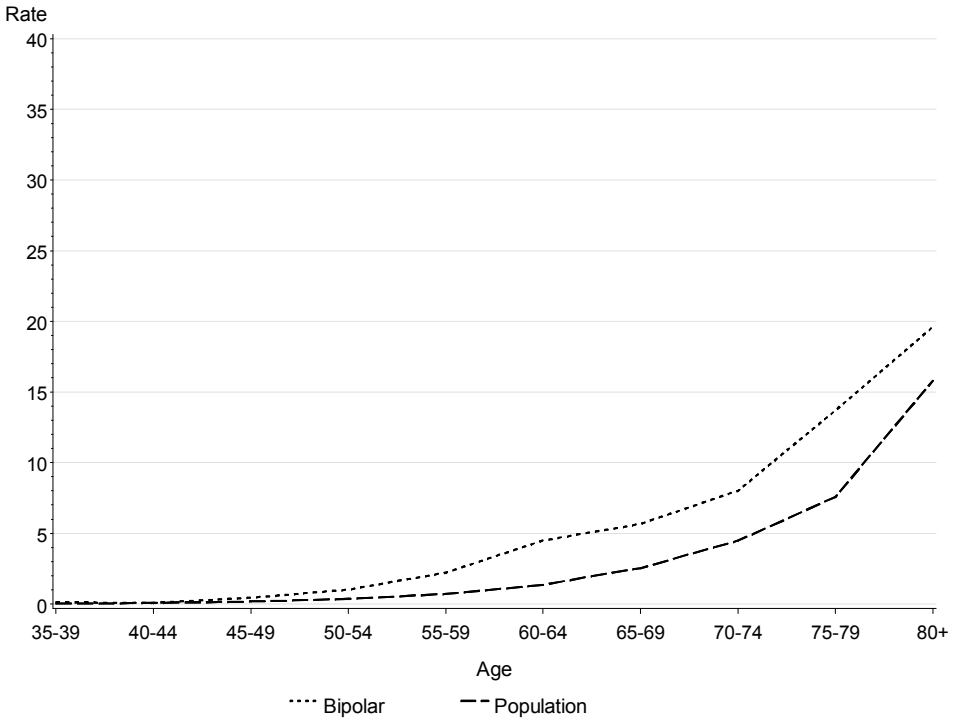


Figure 3c. Mortality of cerebrovascular disease per 1,000 person-years in persons with bipolar disorder and the general population adjusting for sex and calendar year.

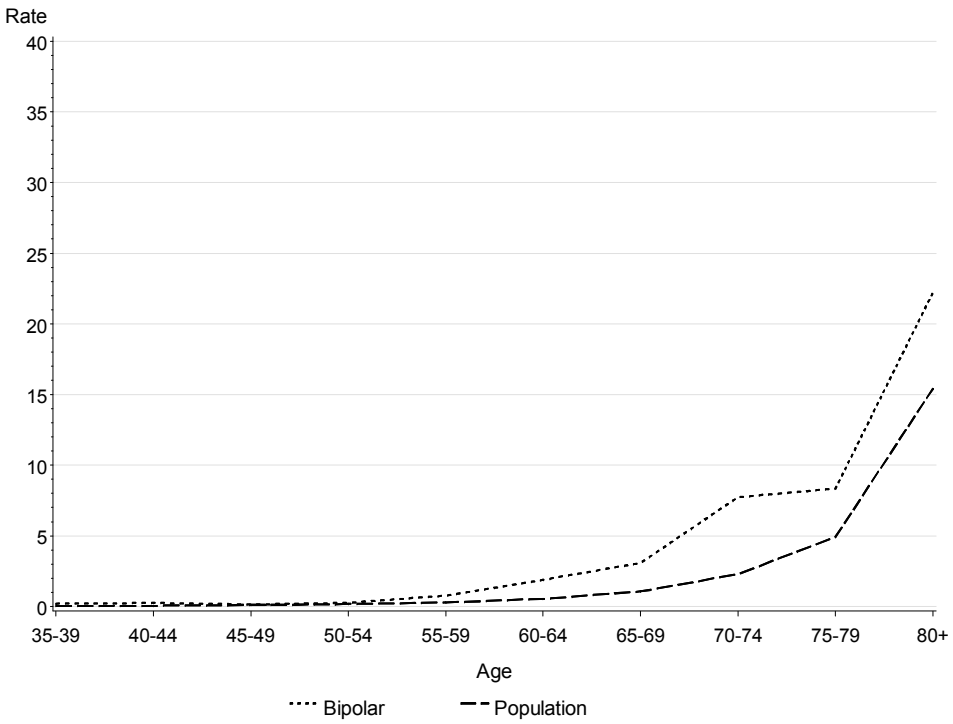
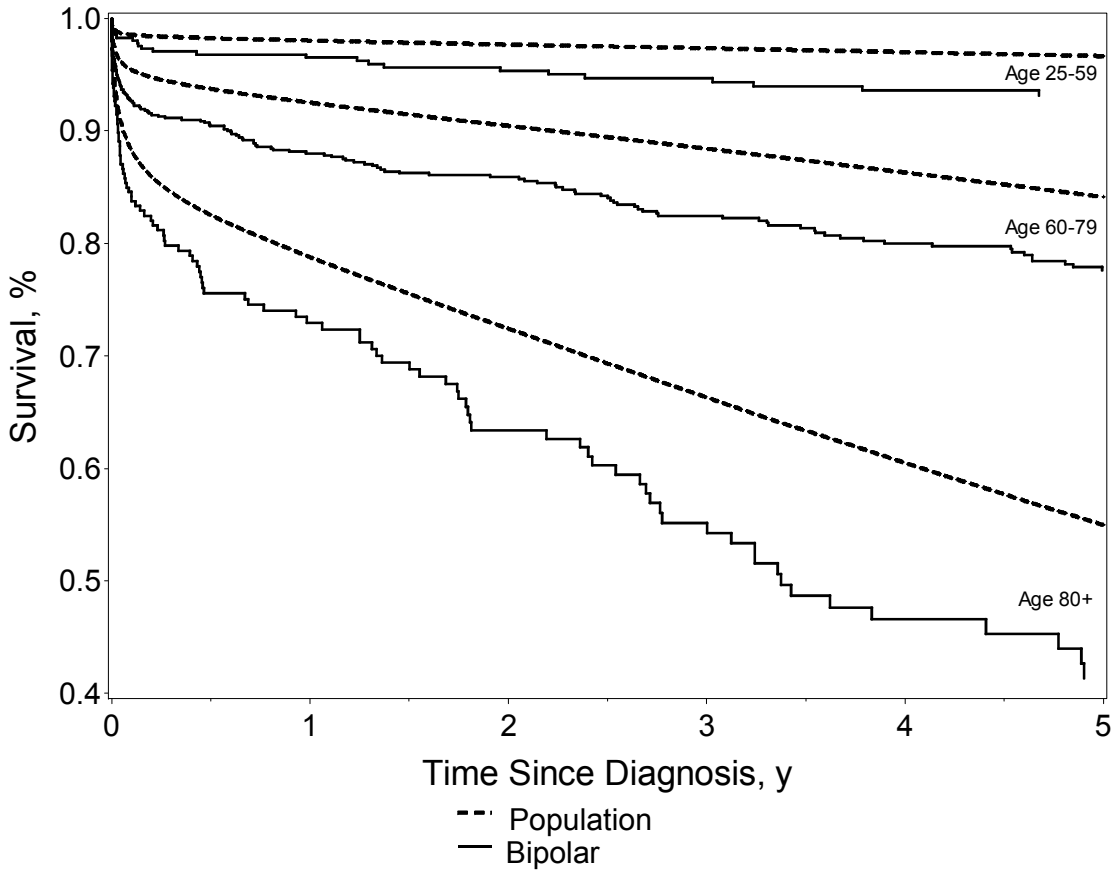


Figure 4. Five-year survival of cardiovascular disease in persons with bipolar disorder after discharge from first cardiovascular admission stratified by age at hospital contact.



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Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden.

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Article summary

Article focus

- To estimate mortality in cardiovascular disease (CVD) and its subgroups cerebrovascular and coronary heart disease and acute myocardial infarction among 17,101 persons diagnosed with bipolar disorder ~~during 1987 to 2006~~ in Sweden, compared to the general population in a national register study with a 20-year follow-up.

Key messages

- Persons with bipolar disorder died of CVD approximately ten years early. Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was higher than that of suicide and other external causes (n=675 deaths). ~~Excess mortality from CVD and other somatic diseases was three times higher (1,812 deaths) than suicide and other external unnatural causes (675 deaths).~~ Mortality rate ratios (MRR~~s~~) for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high compared to the general population. Despite the increased mortality, hospital admissions, admission rate ratios (ARR) for CVD treatment in persons with bipolar disorder were only slightly increased.

- The increased cardiovascular mortality in persons with bipolar disorder calls for renewed efforts~~more resources~~ to prevent and treat somatic diseases. Specifically, our findings imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as the population.

Strengths and limitations of this study ~~of this study~~

- A large national cohort with comprehensive data on patient characteristics was studied. Mortality data from the Swedish cause of death register are of high quality.
- Clinical information on symptoms and treatment were lacking.

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ABSTRACT (word count: 2651)

Objective: To estimate cardiovascular mortality among persons with bipolar disorder in Sweden compared to the general population.

Design: Population register based cohort study with a 20-year follow-up.

Setting: Sweden.

Participants: The entire population of Sweden (n=10.6 million) of whom 17,101 persons were diagnosed with bipolar disorder between 1987 and 2006.

Main outcome measures: Mortality rate ratios (MRR), excess mortality (excess deaths), cardiovascular disorders (CVD) and specifically cerebrovascular disease, coronary heart disease, and acute myocardial infarction, sudden cardiac deaths, and hospital admission rate ratios (ARR).

Results: Persons with bipolar disorder died of CVD approximately ten years earlier than did persons of the general population. More than twoOne third (3783%) of all deaths in persons with bipolar disorder were caused by CVD, and almost half (44%) by other somatic diseases, whereas suicide and other unnaturalexternal causes accounted for less than a fifththan a third of all deaths (1278%). Excess mortality of both CVD (n=824) and other somatic diseases (n=988) was three times higher (1,812 deaths) than that of suicide and other external unnatural causes (n=675 deaths). MRRs for cerebrovascular disease, coronary heart disease, and acute myocardial infarction, were twice as high in persons with bipolar disorder compared to the general population. Despite the increased mortality of CVD, hospital admissions (ARR)s for CVD treatment were only slightly increased in persons with bipolar disorder when compared to the general population.

Conclusions: The increased cardiovascular mortality in persons with bipolar disorder calls for renewed effortsmore resources to prevent and treat somatic diseases in this group. Specifically, our findings further imply that it would be critical to ensure that persons with bipolar disorder receive the same quality care for CVD as persons without bipolar disorder.

Introduction

Cardiovascular disease (CVD) is the main cause of death in many developed countries.[1] CVD encompasses a broad range of different conditions that are potentially life threatening. In Sweden, although mortality from CVD in the population has almost halved in the last two decades, CVD still accounts for more than 40% of all deaths in the country.[2] Premature death in patients with severe mental health disorders, especially patients with schizophrenia and bipolar disorder, has historically been ~~generally~~ attributed to suicide~~, rather than CVD, despite~~ However, more recent studies have show~~i~~n~~g~~ that CVD leads to more reduced~~shorter~~ life spans than does suicide in those patients.[3] Persons with bipolar disorder have an increased risk of CVD and have been observed to die due to CVD twice as often as the general population.[4-6] Although previous studies have shown an association between bipolar disorder and mortality from CVD, few studies have addressed ~~mortality rates in~~ different ~~CVD subgroups~~types of vascular mortality, or examined ~~their~~ related use of health care. An improved understanding of the causes behind and magnitude of CVD among bipolar patients is warranted along with an in-depth evaluation of different diagnostic CVD subgroups. The answers to these questions, which are far less investigated in bipolar disorder than in ~~among patients with~~ schizophrenia, are essential in the efforts to address the problem of premature deaths due to CVD in persons with bipolar disorder~~, patients~~ These questions are the focus of the present national register-based study, which extends earlier Swedish findings[5] both by more specific CVD mortality analyses and more recent patient data.

The aim of this study was to evaluate excess mortality from CVD, such as cerebrovascular disease and coronary heart disease with acute myocardial infarction as its most important component, and also CVD hospitals admissions, in ~~people with bipolar disorder~~persons with bipolar disorder in Sweden between 1987 and 2006 compared to the population.

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Methods

Cohort and follow-up

All persons who resided in Sweden between the 1st of January 1987 and the 31st of December 2006 (n=10,631,-208) were identified using the Swedish Total Population Register (TPR). The TPR was established in 1968 and contains information on sex, date and place of birth, and date of migration of every resident in Sweden. Information on hospital admission, medical diagnosis, and cause of death was obtained by linking the TRP with the national Swedish Cause-of-Death Register and the National Patient Register (NPR) using each resident's unique personal identification number.

The NPR, which is maintained by the National Board of Health and Welfare, contains information on all hospital in-patient treatments ~~carried out~~ in Sweden since 1987. For psychiatric in-patient care the register has nationwide coverage dating back from 1973. For each hospitalization, the unique national registration number, date of admission and discharge, and diagnosis are registered in NPR. In Sweden, all hospital diagnoses are classified according to the WHO International Classification of Diseases (ICD). Since the diagnostic definitions of affective disorders were substantially changed in ICD-9 and ICD-10 as compared with ICD-8, only patients diagnosed with bipolar disorder according to ICD-9 or ICD-10 were included in the study. Bipolar diagnoses recorded between 1987 and 1996 were identified using ICD-9 (296A, C, E, 298B). From 1997 and later, ICD-10 (F30-F31) was used to identify bipolar diagnoses. The Swedish Cause of Death Register (CDR) includes all individuals who were registered in Sweden at the time of death. The register provides information on date of death as well as main (underlying) and secondary causes of death based on death certificates. Definitions regarding causes of death and ICD codes used in this study are shown in Figure 1.

A total of 20,248 patients admitted to hospital between 1st of January 1987 and 31st of December 2006 with a main diagnosis of bipolar disorder (ICD-9; ICD-10) were identified in the NPR. Of the 20,248 patients, 3,147 had been previously diagnosed with schizophrenia (ICD-8: 295; ICD-9: 295; ICD-10; F20, F25) and were consequently excluded. Thus, the total risk population of the study comprised 17,101 patients with bipolar disorder. The follow-up period was 20 years (1987-2006). Immigrants were included from the date of immigration to Sweden. Each person was followed until December 31, 2006, or date of death or emigration,

depending on which came first. Inclusion in the risk population started from the date of first hospital admission (discharge diagnosis) during the study period.

Statistical analysis

Person years at risk, number of cause-specific deaths and hospital admissions due to CVD for both bipolar patients and the general population were determined. Person time was stratified by sex, calendar year and age. Mortality rate ratios (MRR) and Admission rate ratios (ARR) and predicted mortality rates were calculated with corresponding 95% confidence intervals (CI) using Poisson regression models with the GENMOD procedure using statistical software SAS (version 9.2). All models were adjusted for or stratified by sex, attained age and year of follow-up.

To calculate the excess mortality for patients with bipolar disorder the observed number of deaths was compared with the expected number of deaths among patients with bipolar disorder. The expected number of deaths was calculated by applying age, sex and calendar specific mortality rates in the general population to the time at risk among the patients.
The risk of dying from CVD after first hospital admission was analyzed by estimating cause-specific survival curves using the Kaplan-Meier method. Additional adjusted hazard ratios with 95% CIs were estimated using Cox proportional hazard models.

When hospital admission due to CVD (Admission rRate rRatios, ARR) was the event of interest, follow-up ended on the day of first admission. To ensure that the observed cases were incident, a three-year run-in period was created to compensate for the lack of CVD coverage in the NPR before 1987. Hence, all bipolar patients analyzed had no hospital admissions due to CVD recorded for at least three years before follow-up.

Results

Causes of death

Total mortality (death from any cause) between 1987 and 2006 in Sweden was more than twice as high among patients with bipolar disorder compared to the general population (MRR 2.40; 95% CI 2.33-2.47). Specifically, 2,489 excess deaths in patients with bipolar disorder were observed (Table 1). With mortality causes subdivided into CVD, other somatic, and unnaturalexternal causes of death, we found that men and women with bipolar disorder were

twice as likely to die of CVD compared to the general population (MRR 2.03; 95% CI 1.93-2.13), with 824 excess deaths due to CVD. Mortality from other somatic causes was also doubled (MRR 2.10; 95% CI 2.00-2.19), with 988 excess deaths. ~~Unnatural~~ External causes of death, such as suicide, homicides, and accidents, were increased more than nine times in bipolar patients (MRR 9.66; 95% CI 8.99-10.37), with 675 excess deaths. As far as CVD subgroups were concerned, mortality from cerebrovascular disease and coronary heart disease ~~and cerebrovascular disease~~ was twice as high in bipolar patients, with ~~377 excess deaths (MRR 1.95; 95% CI 1.81-2.09) and~~ 184 excess deaths (MRR 2.00; 95% CI 1.81-2.2209) and ~~;~~ 377 excess deaths (MRR 1.95; 95% CI 1.81-2.09), respectively. Mortality from acute myocardial infarction was almost twice as high in bipolar patients (MRR 1.83; 95% CI 1.67-2.01), with 200 excess deaths. Mortality from sudden cardiac death, cardiac arrest/ventricular fibrillation, was also increased (MRR 1.85; 95% CI 1.42-2.41), with 25 excess deaths. Bipolar women and men of all ages had an equally increased mortality from CVD (data not shown).

Age and cause of death

MRR by age at death for all causes of death is shown in Fig 2a and subdivided into cardiovascular death (Fig 2b), other somatic death (Fig 2c), suicide and other external causes of death (Fig 2c). Cerebrovascular death (Fig 2e), death by coronary heart disease (Fig 2f), and death from acute myocardial infarction (Fig 2g) are reported separately.

MRR for CVD was increased for bipolar patients across all ages but was particularly pronounced in the young age groups (Figure 2b). Patients with bipolar disorder who died of CVD were younger than people in the general population. The same finding was observed when we subdivided CVD into cerebrovascular disease, coronary heart disease and acute myocardial infarction (Figure 2e-g). For acute myocardial infarction and coronary heart disease the increased risk was most apparent in the 55-65 years age groups (2f-g). In the ages below 50 years the results should be interpreted with caution because there were very few events in these ages. Death by suicide and other ~~unnatural~~external causes of death~~s~~ were 15 times more common among bipolar patients below 30 years of age compared to persons of the same age in the general population (Figure 2d). Overall, the MRR for suicide and other ~~unnatural~~ external causes of ~~-~~death~~s~~ decreased with increasing age. However, it should be noted that it remained significantly increased in persons aged between 70-74 years (MRR 6.88; CI 95% 5.06-9.35) (Figure 2d).

Age differences at death between persons with bipolar disorder and the population from coronary heart disease, acute myocardial infarction and cerebrovascular disease is shown in Figure 3a-3c. The earlier age at death for persons with bipolar disorder is clearly shown for all these causes of death.

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Admission rates

Hospital admission rates for CVD among patients with bipolar disorder were similar to those for the general population even though MRR for CVD was almost twice as high, independent of the specific CVD cause (Tables 1 and 2). Survival rates five years after first hospital admission for CVD were significantly lower among bipolar patients than among the general population (Figure 4).

Discussion

Key findings

In this nationwide study of mortality among persons with bipolar disorder in Sweden compared to the population, somatic illness was the main cause of death. Bipolar patients died of CVD around ten years earlier than the general population. Mortality from cerebrovascular disease, coronary heart disease, and acute myocardial infarction was twice as high in bipolar patients as in the general population, while the frequency of hospital admissions due to these diseases was not increased. Our findings ~~clearly~~ showed that CVD in persons with bipolar disorder accounted for 824 excess deaths and other somatic diseases 988 ~~in persons with bipolar disorder accounted for a substantial number of~~ excess deaths, taken together ~~(n=~~1,812~~)~~ excess deaths, both larger than suicide and other ~~unnatural~~external causes of death (n=675). Interestingly, sudden cardiac death was also increased.

Strengths and limitations

The Swedish National Patient Register and Cause of Death Register include everyone who resides in the country and are considered unique, comprehensive and highly credible. Currently more than 99% of all somatic and psychiatric hospital discharges are recorded in the National Patient Register.[7] Swedish hospitals and government agencies are obliged by law to enter medical information in the National Patient Register. All diagnoses in the National Patient and Cause of Death registers were given by patients' doctors using international

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classification standards (ICD codes). Being register based, this study used information about clinical diagnoses from hospital admissions in Sweden. During the study period, the ICD diagnostic definitions were specific for bipolar disorder. A validation of the Swedish clinical bipolar hospital diagnoses has shown high validity, sufficient for epidemiological studies.[8] One limitation of this study was that it was based on in-patient diagnoses, which may have generated a selective bias towards severely ill patients. However, most individuals at severe stages of bipolar disorder are admitted to hospital in Sweden. Since medical care is free in Sweden, there is no bias by costs for hospital care leading to differences in health-seeking behavior. In a previous study, we have shown that the number and frequency of hospital admissions due to bipolar disorder remained relatively unchanged ~~in Sweden~~ during recent years, while the overall number of psychiatric admissions was drastically reduced.[9] We did not have access to medical records or information on medical treatment., ~~which would have been of interest since antidepressants use have been linked to increased risk of fatal coronary heart disease.~~[10] In terms of the validity of the data on causes of death, in CVD deaths we found a slightly higher autopsy rate (28%) among patients with bipolar disorder than in the general population (22%). It is unlikely that these small differences affected the outcome of the study. An advantage with the present study is the analysis of specific causes of death.

Findings from other studies

The findings of this study add to the growing body of evidence that somatic diseases, particularly CVD, contribute to a shorter lifespan among bipolar patients. Findings from several large register-based studies from different parts of the world indicate that cardiovascular disease is responsible for the majority of excess deaths, with up to 2.5-fold increased mortality.[3 5 6 10-14] ~~3 5 6 11 15~~ Studies using registers from the Nordic countries have shown that ~~in~~ bipolar patients run almost twice the risk of dying from CVD than do persons in the general population, the mechanisms for which are currently unknown.[4 5] There is a growing body of evidence from studies in other countries, and findings similar to ours have been observed in a representative study of the US population.[15] In our previous study,[5] SMR for CVD but not for cerebrovascular mortality was higher for women compared to men. This difference was not found in our present study. SMR and MRR are relative measurements, affected both by population trends and trends among the cases. Thus, the different findings could be related both to changing mortality rates in the population and to changes among persons with bipolar disorder, or a combination of those factors. CVD contains several different causes of mortality, which may have different trends over time. However, the

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specific causes of death related to the sex difference in CHD mortality previously found cannot be answered in our study.

~~There is also a growing body of evidence from studies in other countries, and similar findings have been observed in a representative stuy of the US population (Goldstein et al 2009).~~ Studies have shown a higher cardiovascular mortality in persons with bipolar disorder type I compared to bipolar disorder type II or major depressive disorder. ~~(~~[16 17] ~~Fiedorowicz 2009, Angst 2012).~~ In our Swedish data, bipolar disorder type I can ~~not~~ be separated from bipolar disorder type II. However, patients with bipolar disorder type I are much more likely to be hospitalized and thus to be included in our sample. Earlier age of CVD has been shown in several studies,[15] ~~,~~ and is also confirmed in ~~which~~our- findings of increased cardiovascular death at a younger age compared to the population in Sweden~~also confirm findings of increased cardiovascular disease at a younger age compared to the population~~. Possible risk factors for the increased mortality from CVD among bipolar patients may include adverse effects of medication,[18 19~~16 17~~] high levels of smoking,[20~~18~~] unhealthy diet,[21 22~~19 20~~] lack of physical activity,[21~~19~~] ~~and~~ low social-economic status,~~s.~~[23~~21~~] and lower rates of nutritional counceling.[24] ~~,~~ Studies have shown that bipolar disorder patients ~~deviate from age-based norms on arterial stiffness measures.~~[25] Also, inflammation has been pointed out as a potential biological cause of increased CVD in bipolar disorder [30 31] together with endothelial dysfunction. [32] In addition, effects of genetic associations, such as those reported between Type 2 diabetes, CHD and schizophrenia,[26~~22~~] could not be excluded. One of the most important locuses of genetic polymorphisms linked to bipolar disease and depression is around the ATP-activated ion-channel receptor *P2X7*.[27~~23~~] Recently, a polymorphism in the *P2X7* gene was linked to increased risk of stroke and acute myocardial infarction,[28~~24~~] and the same polymorphism has also recently been shown to be linked to cognitive symptoms in bipolar disorder,[29~~25~~] indicating that common genetic factors could have effect on both cardiovascular disease and bipolar disorder.

CVD undertreated in ~~bipolar disorder~~persons with bipolar disorder

Studies of patients with bipolar disorder have shown that the patients have~~run~~ an increased risk of metabolic syndrome,[33~~26~~] ~~,~~ i.e. increased ~~-~~blood glucose,[34~~27~~] and cholesterol levels,[35~~28~~] higher blood pressure,[36~~29~~] and higher prevalence of overweight and obesity,[21~~19~~] ~~,~~ closely associated with CVD. To prevent and treat metabolic disorders in patients with severe mental

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illnesses such as bipolar disorder, new guidelines for clinicians in Sweden were drawn up in 2009, thus after the end of this study, by psychiatrists, diabetologists, endocrionologists, cardiologists and general practitioners in collaboration~~have been drawn up for clinicians in Sweden~~.[37]~~[30]~~ ~~However, the effects of those guidelines are still to be evaluated.~~ The guidelines can be found on the website of the Swedish Psychiatric Association (www.svenskpsykiatri.se). In the guidelines, there is a strong emphasis on the increased metabolic risks at younger age, with focus both on primary and secondary prevention strategies and the need for collaboration between the different medical specialties. The effects of those guidelines are still to be evaluated.

Our finding that patients with bipolar disorder showed only slightly increased hospital admissions rates for CVD despite their twice as high cardiovascular mortality, strongly suggests that CVD is undertreated in bipolar patients when compared to the general population. In a Danish study, the rates of invasive heart disease procedures were 40% lower among persons with bipolar disorder than in the general population.[4] Although the younger age at cardiac events in bipolar disorder compared to the population may reduce detection, this factor is unlikely to cause the reduced rates of invasive heart procedures, since younger age at detection would rather be expected to lead to more intensive treatment. The lower rate of invasive heart disease procedures among persons with bipolar disorder is yet to be explained. Sudden cardiac mortality from cardiac arrest/ventricular fibrillation was increased among patients with bipolar disorder (MRR: 1.85), but the 25 excess cases does not explain the difference in CVD~~hospital~~ admissions in terms of increased sudden death before hospital admission~~ization~~. Thus, the reasons for CVD undertreatment in bipolar disorder is not explained by the current findings. ~~Our register data alone cannot offer an explanation for this finding.~~ In our study, the MRR and ARR patient populations are slightly different, in the respect that the ARR patients are identified at their first index admission, while the MRR patients may have several admissions, and thus being more severely affected. Unequal access to health care (i.e. receiving cardiac treatment of lower quality) for reasons other than financial has been previously suggested as a contributor to excess CVD mortality in patients with severe mental disorders, such as schizophrenia,[38]~~[31]~~ and may be indicated by our findings of increased mortality after discharge from hospital compared to the population. These factors have not been studied extensively in bipolar patients. Health care in Sweden is free and is financed primarily through taxes. Therefore, it is unlikely that patients with bipolar disorder do not seek hospital care for lack of financial means.

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Many mechanisms can contribute to the under-treatment of CVD among people with bipolar disorder. Our results indicate a failure of the health care system to identify and address the health needs of those patients, which has also been shown in other studies of people with severe mental disorders.[39~~32~~] The levels of CVD mortality in our bipolar persons are similar to those in schizophrenia, where adverse effects of antipsychotic medication have been considered the main contributing factor. When compared with schizophrenia, a recent study of bipolar disorder in Stockholm County found only 29% of bipolar patients medicating with antipsychotics, as compared to practically all schizophrenia patients, which raises the question of the importance of adverse effects of antipsychotics in CVD.[40~~33~~]

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Conclusions

The observed number of deaths from cardiovascular diseases in patients with bipolar disorders was almost twice as the expected number when comparing with the general population, suggesting that more resources are needed for the prevention of these diseases in this patient group. Targeted interventions by effective cooperation between primary health care and psychiatric professionals would be crucial in the efforts to reduce excess CVD mortality in patients with bipolar disorder. Finally, effective cardiac treatment would ensure longevity and improved quality of life for ~~bipolar~~ patients with bipolar disorder.

Contributors: UÖ had the idea of the study and is guarantor of the study together with JH, who has performed the statistical analyses. JW has contributed to the design of the study and drafted the manuscript together with UÖ. KW, DE and LA have contributed to the design of the study and with revisions of the manuscript. All authors have approved the final version of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author). JW, KW, LA, DE, UÖ has declared no support from any organization for the submitted work, no financial relationship with any organizations that would have interest in the submitted work in the previous three years, and no other activities that could appear to have influenced the submitted work. UÖ has declared traveling expenses from Janssen-Cilag for attending a course in October 2012 unrelated to the study.

Ethical approval: This study was approved by the ethical review board in Stockholm County. The ethical review board determined that informed consent from participating individuals was not required.

Data sharing: The analysis data set for this study is available from the National Board of Health and Welfare (Socialstyrelsen) in Sweden. Please contact JH for further information.

Figure 1. ICD-coding and ~~disease~~ classification of disease and mortality.

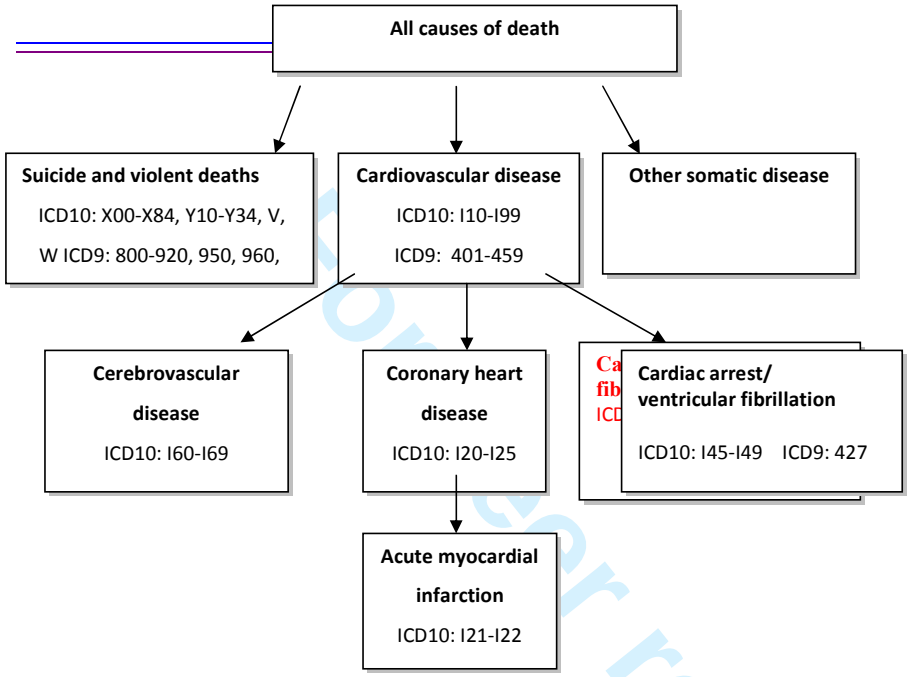

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Table 1. Mortality rate ratios (MRR) for ~~bipolar patients~~ persons with bipolar disorder between 1987 and 2006

	Men		Women		Total (both sexes)		
Cause of death	Cases	MRR (95% CI)	Cases	MRR (95% CI)	Cases	MRR (95% CI)	Excess cases (95% CI)
All causes of death	1874	2.48 (2.37-2.59)	2393	2.34 (2.25-2.44)	4267	2.40 (2.33-2.47)	2489 (2361-2617)
Cardiovascular disease	733	2.16 (2.01-2.33)	892	1.93 (1.81-2.06)	1625	2.03 (1.93-2.13)	824 (745-903)
Other somatic deaths	735	1.97 (1.83-2.11)	1154	2.19 (2.06-2.32)	1889	2.10 (2.00-2.19)	988 (902-1073)
~~Unnatural~~Suicide and other External deaths	406	9.37 (8.50-10.33)	347	10.02 (9.01-11.13)	753	9.66 (8.99-10.37)	675 (621-729)
Cerebrovascular disease	144	2.29 (1.94-2.70)	224	1.86 (1.63-2.12)	368	2.00 (1.81-2.22)	184 (147-222)
Coronary heart disease	385	2.00 (1.81-2.21)	391	1.89 (1.71-2.09)	776	1.95 (1.81-2.09)	377 (323-432)
Acute myocardial infarction	227	1.89 (1.66-2.15)	213	1.78 (1.55-2.03)	440	1.83 (1.67-2.01)	200 (159-241)
Cardiac arrest ~~-~~/-Ventricular fibrillation	23	2.29 (1.52-3.45)	32	1.62 (1.15-2.30)	55	1.85 (1.42-2.41)	25 (12-42)

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Table 2. Admission rate ratios (ARR) for ~~bipolar patients~~ persons with bipolar disorder during 1990 to 2006

	Men		Women		Total (both sexes)		
Hospital admissions	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Cases	ARR (95% CI)	Excess cases (95% CI)
Cardiovascular disease	540	1.27 (1.16-1.38)	696	1.33 (1.24-1.43)	1236	1.30 (1.23-1.38)	287 (218-356)
Cerebrovascular disease	179	1.32 (1.14-1.53)	271	1.43 (1.27-1.62)	450	1.39 (1.26-1.52)	125 (84-167)
Coronary heart disease	212	1.02 (0.89-1.17)	207	1.06 (0.92-1.21)	419	1.04 (0.94-1.14)	15 (-25-55)
Acute myocardial infarction	133	0.96 (0.81-1.14)	137	1.11 (0.94-1.31)	270	1.03 (0.92-1.16)	8 (-24-41)

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Figure 2a. Mortality rRate rRatios (MRR) for all causes of death by age at death in persons with bipolar disorder ~~patients~~ and the general population.

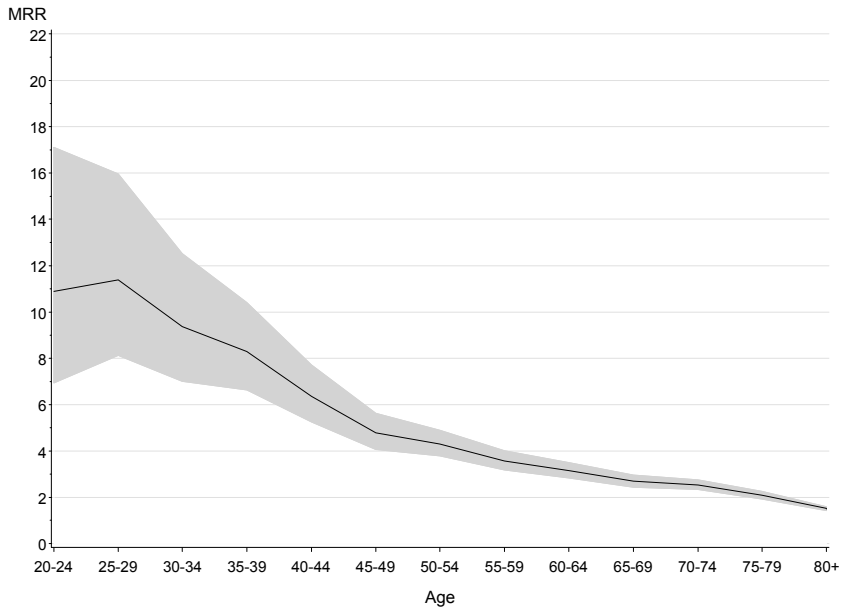
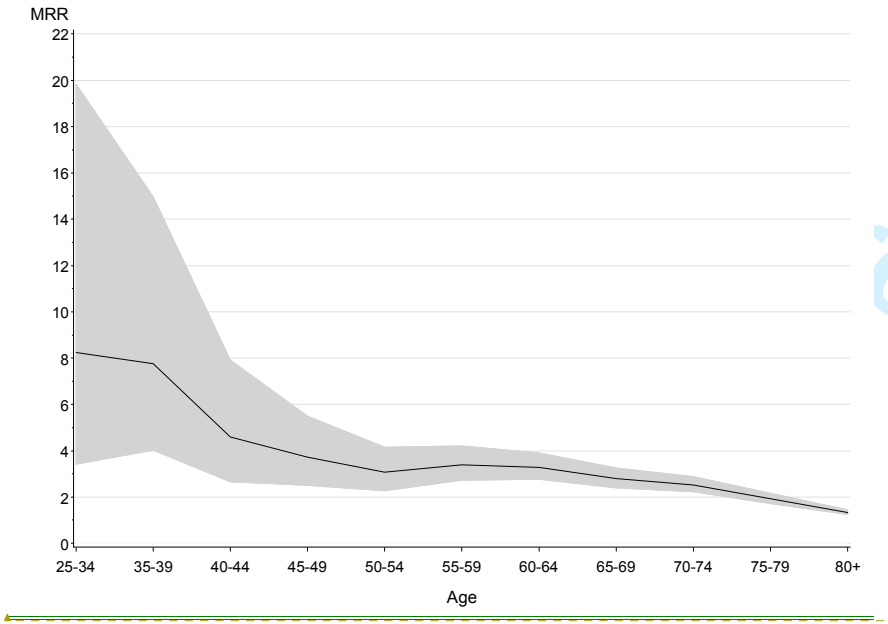


Figure 2b. Mortality rRate rRatios (MRR) for cardiovascular death by age at death in ~~bipolar disorder~~persons with bipolar disorder ~~patients~~ and the general population.



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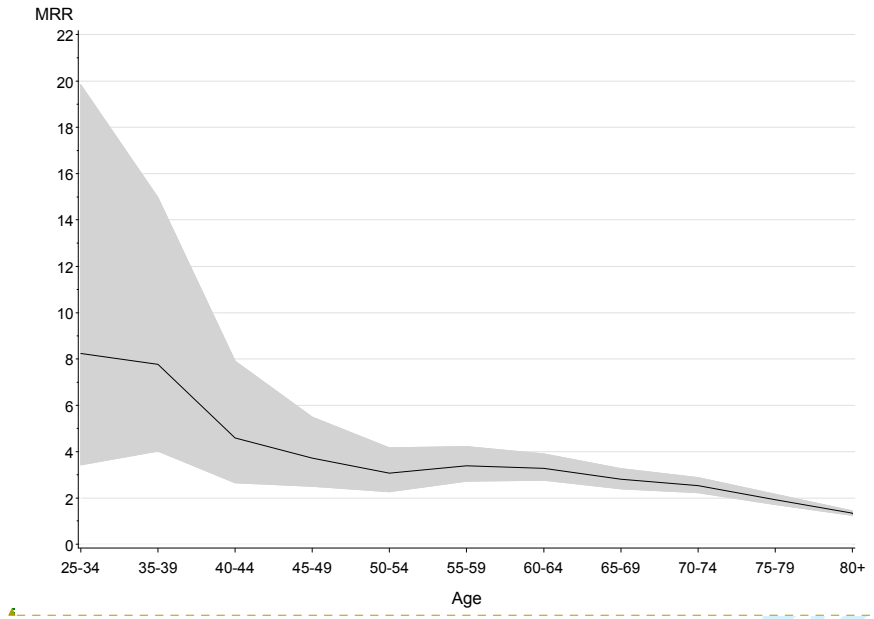
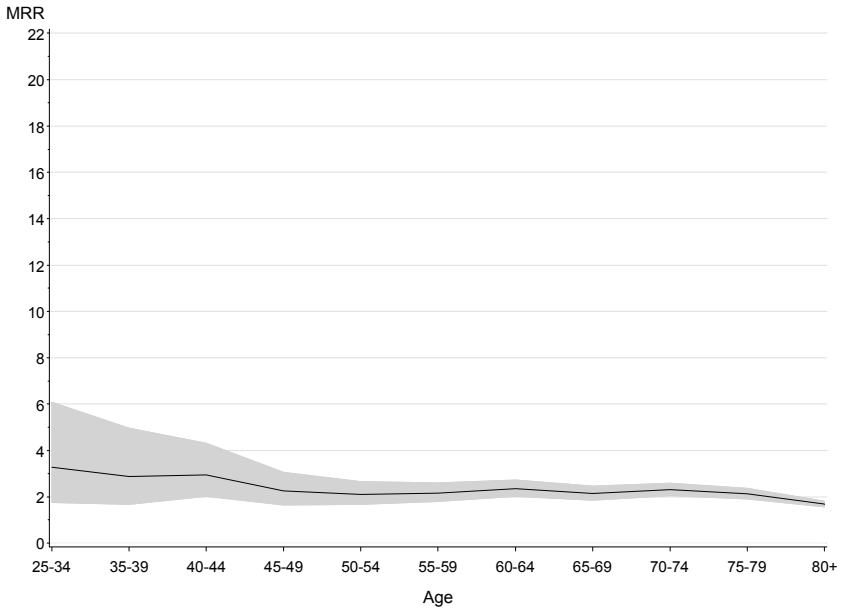


Figure 2c. Mortality rRate rRatios (MRR) for other somatic death by age at death in patients with bipolar disorder ~~patients~~ and the general population.


MRR
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80+
Age

Figure 2d. Mortality r~~R~~ate r~~R~~atios (MRR) of suicide and other ~~unnatural~~ external causes of death~~s~~ by age at death in patients with bipolar disorder and the general population.

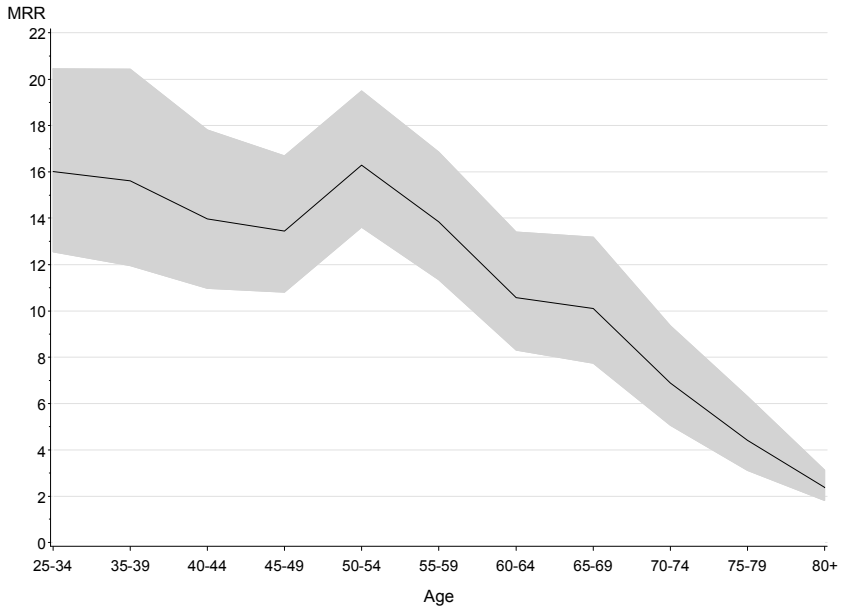

Figure 2e. Mortality rRate rRatios (MRR) of cerebrovascular disease by age at death in personsatients with bipolar disorder and the general population.

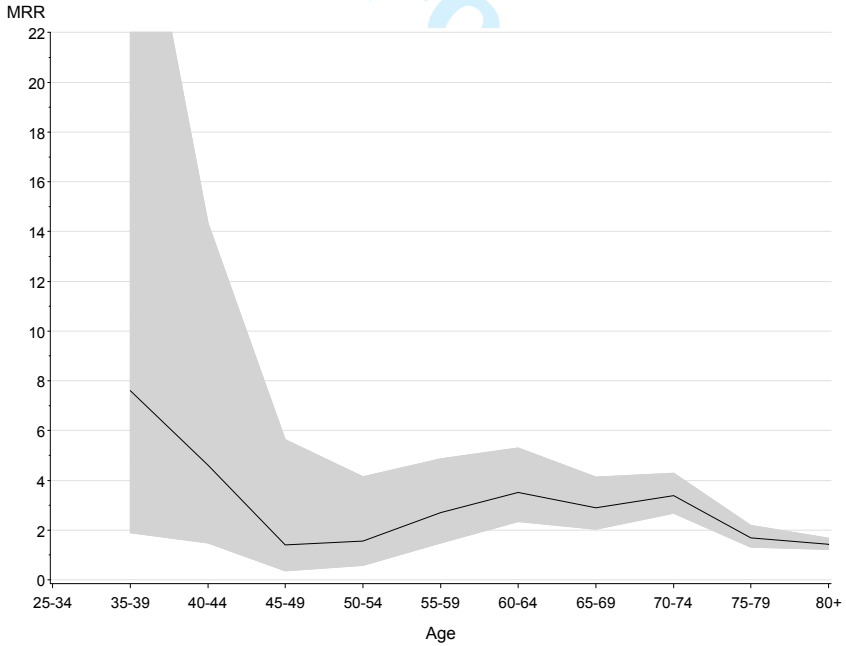

Figure 2f. Mortality rRate rRatios (MRR) of coronary heart disease by age at death in persons ~~atients~~ with bipolar disorder and the general population.

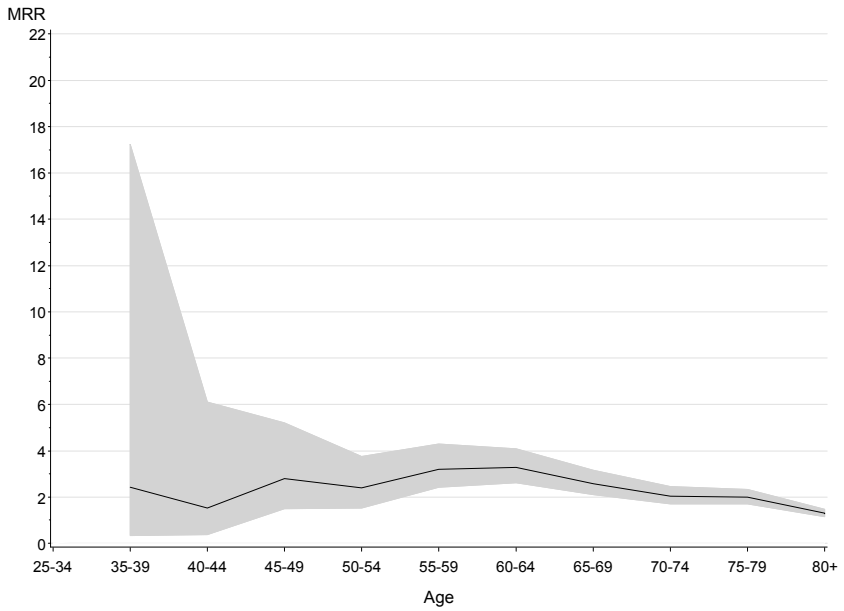

Figure 2g. Mortality rRate rRatios (MRR) of acute myocardial infarction by age at death in personsatients with bipolar disorder and the general population.

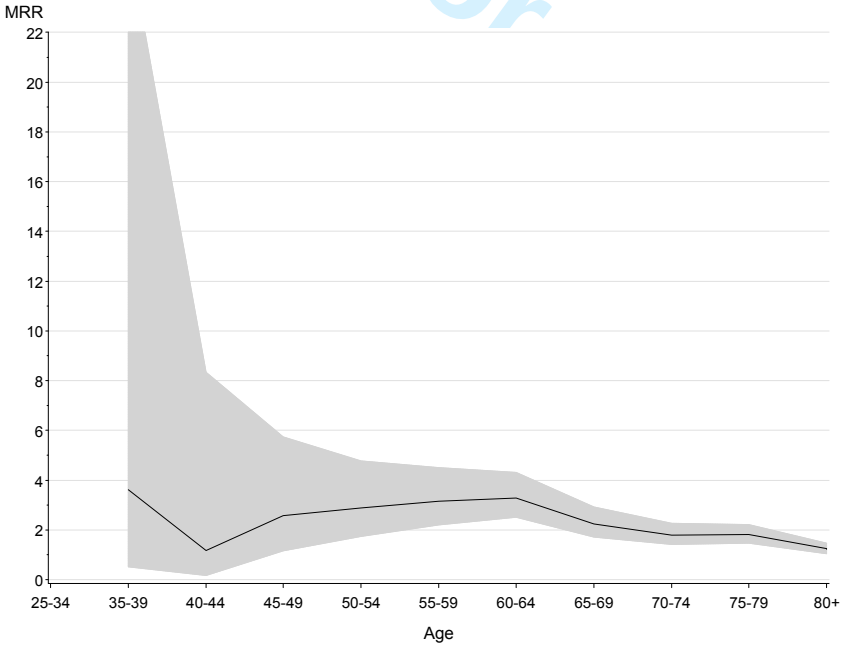

Figure 3a. Mortality of coronary heart disease per 1,000 person-years in persons~~atients~~ with bipolar disorder and the general population adjusting for sex and calendar year.

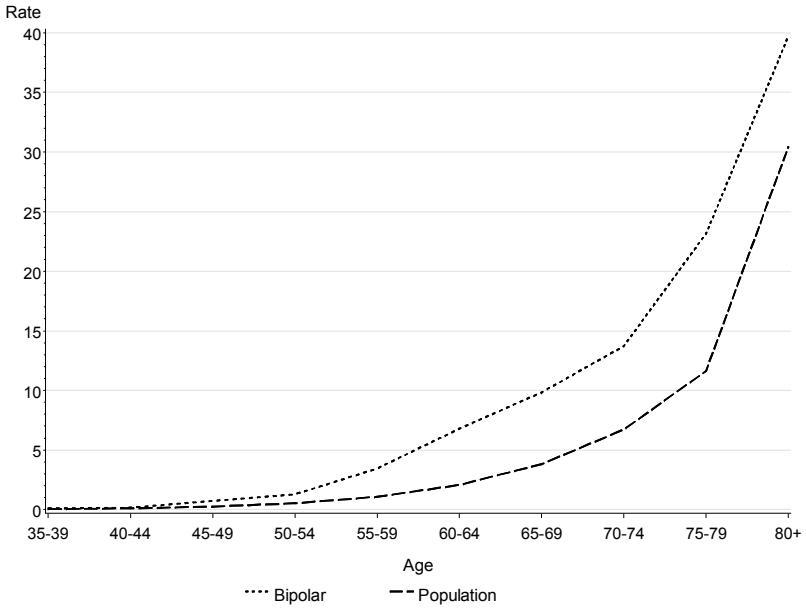

Figure 3b. Mortality of a~~A~~cute myocardial infarction per 1,000 person-years in persons with bipolar disorder and the general population adjusting for sex and calendar year.

~~Acute myocardial infarction~~

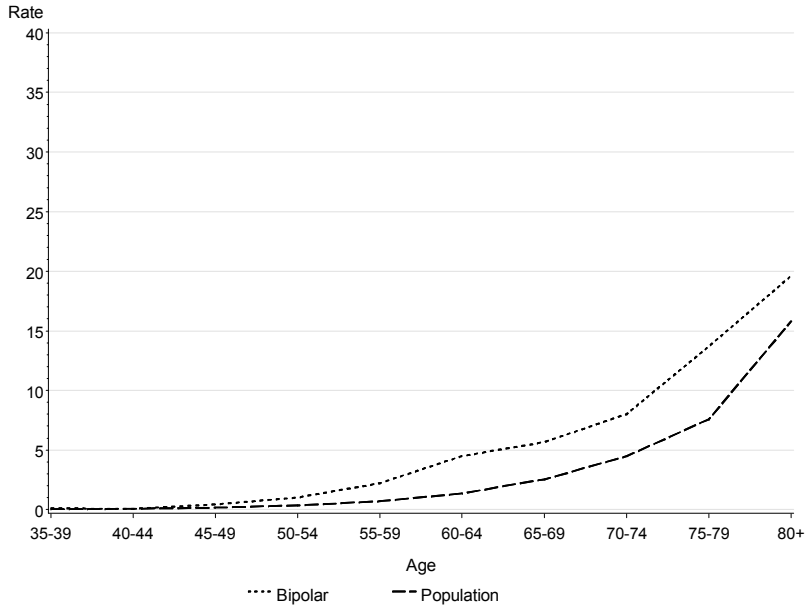

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Figure 3c. ~~Cerebrovascular disease~~Mortality of cerebrovascular disease per 1,000 person-years in persons with bipolar disorder and the general population adjusting for sex and calendar year.

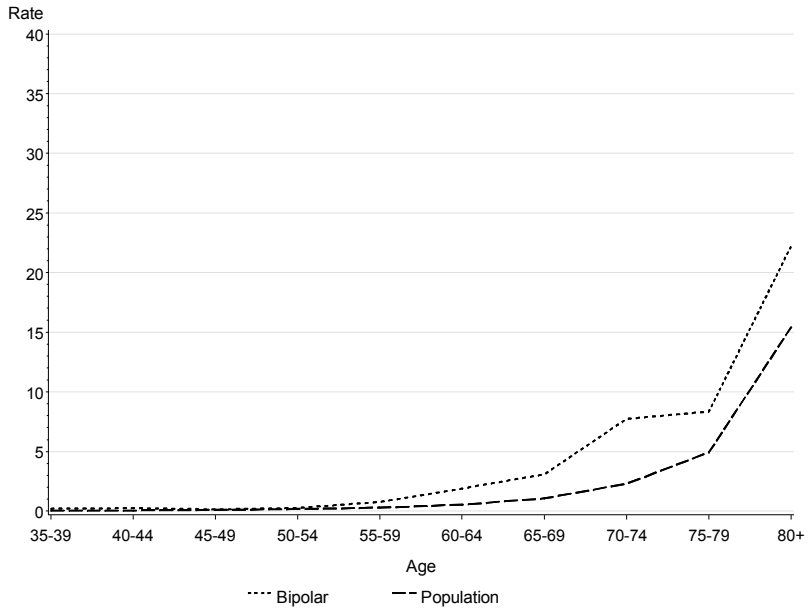
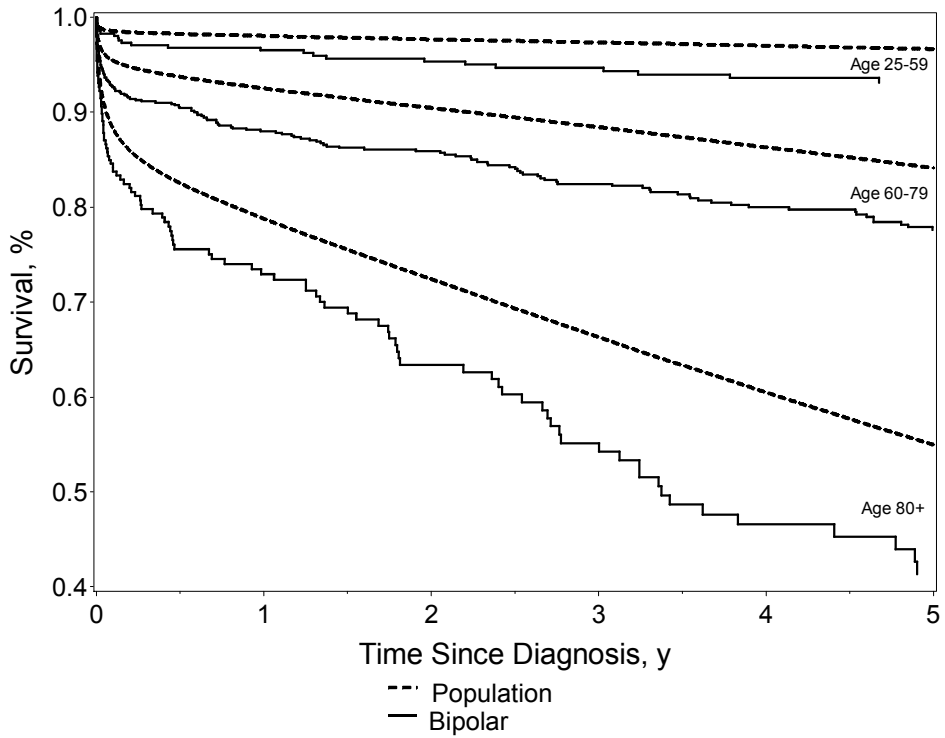


Figure 4. Five-year survival of cardiovascular disease in persons with bipolar disorder after discharge from first cardiovascular admission stratified by age at hospital contact.



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Our manuscript have been checked towards the STROBE Statement.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies*** -

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.