

Cause-specific excess mortality after first diagnosis of bipolar disorder: population-based cohort study

Tapio Paljärvi ¹, Kimmo Herttua ¹, Heidi Taipale,^{1,3,4} Markku Lähteenvuo,¹ Antti Tanskanen,^{1,3} Seena Fazel ^{5,6}, Jari Tiihonen^{1,3}

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¹Niuvanniemi Hospital, Kuopio, Finland

²Department of Public Health, University of Southern Denmark, Esbjerg, Denmark

³Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

⁴School of Pharmacy, University of Eastern Finland, Kuopio, Finland

⁵Department of Psychiatry, University of Oxford, Oxford, UK

⁶Oxford Health NHS Foundation Trust, Oxford, UK

Correspondence to

Dr Tapio Paljärvi, Niuvanniemi Hospital, Kuopio 70240, Finland; tapio.paljarvi@niuva.fi

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ABSTRACT

Background Bipolar disorder (BD) is associated with increased mortality, but evidence on cause-specific mortality is limited.

Objective To investigate cause-specific premature excess mortality in BD.

Methods Finnish nationwide cohort study of individuals with and without a diagnosis of BD who were aged 15–64 years during 2004–2018. Standardised mortality ratios (SMRs) with 95% CIs were calculated for BD using the mortality rates in the Finnish general population without BD as weights. Causes of death were defined by the International Classification of Diseases, 10th revision codes.

Findings Of the included 47 018 individuals with BD, 3300 (7%) died during follow-up. Individuals with BD had sixfold higher mortality due to external causes (SMR: 6.01, 95% CI: 5.68, 6.34) and twofold higher mortality due to somatic causes (SMR: 2.06, 95% CI: 1.97, 2.15). Of the deaths due to external causes, 83% (1061/1273) were excess deaths, whereas 51% (1043/2027) of the deaths due to somatic causes were excess. About twice the number of potential years of life were lost in excess due to external causes than due to somatic causes. Alcohol-related causes contributed more to excess mortality than deaths due to cardiovascular disease.

Conclusion External causes of death contributed more to the mortality gap than somatic causes after controlling for age-specific background general population mortality.

Clinical implication A balanced consideration between therapeutic response, different treatment options and risk of cause-specific mortality is needed to prevent premature mortality in BD and to reduce the mortality gap.

BACKGROUND

Bipolar affective disorder (BD) is a severe mental illness characterised by overlapping or alternating episodes of depression and manic episodes of varying intensity and duration. It is estimated to have a lifetime prevalence of around 1% in most countries.¹ Manic episodes often involve also psychotic symptoms, which is why manic episodes frequently lead to contact with healthcare.²

All-cause mortality in BD is consistently reported to be about twofold higher than in the general population.³ An increasing mortality gap between BD and the general population has been reported in some countries,^{4,5} while in other countries, stable or decreasing trends have been reported.^{6–8} These

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bipolar disorder (BD) is associated with increased mortality, but the role of somatic and external causes of death in excess mortality is unclear.

WHAT THIS STUDY ADDS

⇒ External causes of death contributed more to premature mortality than somatic causes in those aged 15–64 years. Excess mortality due to external causes was substantial in all age groups. Alcohol-related causes contributed more to excess mortality than cardiovascular disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Improved interventions aimed at reducing the risk of death due to external causes, and alcohol abuse should be developed to prevent premature excess mortality associated with BD.

differences may reflect changes in the underlying patterns of cause-specific mortality risks.⁹ While the excess all-cause mortality in BD has been reported consistently across different countries, evidence on cause-specific mortality is limited. The relative risk of death due to external causes, suicides in particular,^{10–12} is markedly higher in BD than in the general population, but deaths due to somatic causes have been reported to substantially contribute to the excess mortality in BD and thus also to the mortality gap.^{3 13–15} However, most studies have reported effects for all age groups combined and thus potentially important information on age-specific mortality rates and patterns has not been captured. Premature mortality in the ages between 15 and 64 years has a high impact on society in terms of potential years of life lost (PYLL), and deaths in this age group should be mostly avoidable by timely and effective interventions.

OBJECTIVE

The purpose of this study, therefore, is to investigate cause-specific mortality gap between individuals with BD and the general population in those aged 15–64 years. This information could be used in developing better ways to identify high-risk persons, in developing more targeted interventions to reduce the mortality gap and to inform healthcare



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service provision. Furthermore, we will add to the evidence base by quantifying both relative excess mortality and absolute excess mortality. This approach will provide a more comprehensive and balanced understanding of the excess cause-specific mortality in BD than what is currently available.

METHODS

We used Finnish nationwide registers to identify all individuals diagnosed with BD. The hospital discharge register maintained by the National Institute for Health and Welfare includes information on all inpatient and specialised outpatient care contacts, and the registers maintained by the Social Insurance Institution and the Centre for Pensions include information on reimbursed disability-related benefits, including sickness allowances (sick leaves ≥ 14 days) and disability pensions. The quality and validity of the hospital discharge register have been shown to be good overall and in relation to severe mental illnesses.^{16–18} The cause of death register maintained by the Statistics Finland was used to identify causes of deaths. We used information from these registers for the years between 1998 and 2018 (for sickness absences from 2004 onwards). All diagnoses were identified using the International Classification of Diseases, 10th revision (ICD-10), Finnish modification codes (online supplemental eTable 1). The record linkage was done by the National Institute for Health and Welfare using a unique personal identification number issued to all permanent residents in Finland. Because the study used administrative pseudonymised register data, no institutional review board approval or informed consent were needed. The study design and record linkages were approved by the review boards of the institutions maintaining the registers: The Finnish National Institute for Health and Welfare (635/5.05.00/2019), the Social Insurance Institution of Finland (31/522/2019), Finnish Centre for Pensions (19023) and Statistics Finland (TK-53-569-19). The number of cause-specific deaths in the general population and the number of individuals in each age group were extracted from publicly available aggregate-level data from the Statistics Finland website. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹⁹

Design

We identified all individuals with the first diagnosis of BD between the years 1998 and 2018 according to the ICD-10 criteria (ICD-10: F30, F31). The best coverage of ICD-10 codes in the hospital discharge register is from 1998 onwards. Furthermore, information on outpatient care is available only from 1998 onwards. Because the purpose of this study was to quantify cause-specific excess mortality associated with the first diagnosis of BD, we excluded those who had pre-existing diagnoses of schizophrenia-spectrum disorders and censored the follow-up time for those who later received a diagnosis for schizophrenia-spectrum disorders (ICD-10: F20–F29). From a diagnostic point of view, we thus considered that a later diagnosis of schizophrenia-spectrum disorder replaced the diagnosis of BD in line with the consensus hierarchical approach to these diagnoses. During follow-up, 5% of the individuals (2402/47 018) with an initial diagnosis of BD received a diagnosis of schizophrenia-spectrum disorder and were thus censored. Of these individuals, 7% (160/2402) died. Individuals with BD were identified from inpatient and outpatient specialised care contacts, sickness allowances and disability pensions.²⁰ Because the focus of this analysis was on premature excess mortality, individuals were eligible if they were aged 15–64 years during the study period

(years 2004–2018). Individuals were followed up until diagnosis of schizophrenia-spectrum disorders, 65th birthday, death or the end of 2018, whichever came first. Because of the small number of deaths in the younger age groups, age at death was categorised into 10-year intervals: 15–24, 25–34, 35–44, 45–54 and 55–64. The number of individuals with BD and the number of deaths in them were subtracted from the corresponding numbers of the general population to represent the general population without BD. For the general population, we used end-of-year information on the population size and number of deaths in each study year.

There were 10 034 individuals with BD who were aged 65 or above and were thus excluded from the analyses. Of those individuals, 2773 (28%) died during the study period. Of all deaths in those aged 65+ years, 92% (2560/2773) were due to somatic causes and 8% (213/2773) were due to external causes (online supplemental eTable 2). The highest number of deaths was due to cardiovascular diseases (CVDs) (36%, 996/2773). In other words, the age group of 15–64 years represented 82% (47 018/57 052) of the individuals with BD, and the deaths in them represented 54% (3300/6073) of all deaths in the total BD population aged 15+ years. In the Finnish general population, there were 759 755 deaths during the study period. Of these deaths, 19% (144 816/759 755) were in those aged 15–64 years and 81% (614 939/759 755) were in those aged 65+ years.

Measurements

Covariates were sex, age at diagnosis, year of diagnosis and age at death. The outcome measures were all-cause mortality; deaths due to external causes, including accidents, suicides, violence and events of undetermined intent; and deaths due to somatic causes, including, for example, alcohol-related causes, CVD and cancer (online supplemental eTable 1). Events of undetermined intent were combined with suicides. Because cancers, CVD, alcohol-related causes, accidents and suicides had enough deaths across age groups for separate analyses, some of the results are shown separately by these categories. Any somatic cause of death was defined as any other death that did not belong to the category of external causes of death. This definition is equivalent to dividing deaths into natural and unnatural causes of death.³ Accidental alcohol poisoning was considered as an indicator of alcohol abuse and thus these were included in alcohol-related deaths and excluded from external causes of death. In defining the cause of death, information on the main cause of death was used, because only this information is available to the general population. In BD, person-years were calculated based on the actual at-risk time each individual contributed, whereas for the general population, we used the number of persons at the end of each year as the number of person-years, that is, each person contributed 1 full year to the at-risk time.

Statistical analyses

We calculated SMRs per 1000 person-years with 95% CIs by using the Finnish general population without BD as a reference. In this method, expected mortality rates in BD were calculated by using the age-specific mortality rates from the reference population as weights. SMR is a measure of relative excess mortality. We used the number of PYLL as an additional measure of premature mortality. PYLL was calculated, for each individual with BD who died, as the number of years not lived up to the age of 65 or 75 (PYLL-65 and PYLL-75, respectively). The age of 75 was used as an approximation for life expectancy in this population. Because our focus was on those who died the age of 15–64 years,

deaths occurring after the age of 64 were not included in the calculation. There were no missing data in the analysis variables. We used the SAS 9.4 STDRATE procedure to estimate the SMRs.

FINDINGS

We included 47 018 individuals with BD, of whom 57% (26 717) were women, and their mean age at the start of follow-up was 38 years (SD: 13). Median follow-up time was about 8 years (IQR: 7, 4–11 years). Total number of person-years in the BD population was 3 77 386 years and there were 3300 deaths (7%, 3300/47 018). Total number of person-years in the reference Finnish general population was 52 144 411 years and there were 141 536 deaths in this population; after the BD population was excluded from these numbers.

Of the persons with BD who died during the follow-up, 65% (2137/3300) were men. Mean age at death was 50 years (SD: 11), both in men and women. Of the observed deaths, 61% (2027/3300) were due to somatic causes. Of these deaths, the highest number of deaths was due to alcohol-related causes (29%, 595/2027); followed by CVD (27%, 552/2027); cancer (22%, 442/2027); respiratory diseases (4%, 78/2027), mainly due to chronic obstructive pulmonary disease; deaths due to diabetes mellitus (2%, 41/2027) and deaths due to substance use-related mental and behavioural disorders other than alcohol (1%, 23/2027). Of the alcohol-related deaths, the highest number of deaths was due to diseases of the liver (48%, 289/595), followed by accidental alcohol poisonings (28%, 165/595) and alcohol dependence (10%, 60/595). Of the deaths due to external causes (39%, 1273/3300), the highest number of

deaths was due to suicide (58%, 740/1273). Nearly half (48%, 353/740) of the suicides were due to overdoses by psychotropic medicines, including medicines used to treat BD (ICD-10: X41), which represented 64% of the intentional self-poisonings (226/353). Other larger groups of suicides were suffocation-related deaths, including drowning (24%, 179/740), and impact-related deaths, including falls and deaths involving the crashing of a motor vehicle (15%, 109/740). Of the accidental deaths, excluding alcohol poisonings, half of the deaths were due to poisonings (52%, 265/509), followed by impact-related deaths (22%, 111/509) and suffocation-related deaths (11%, 58/509). Of the accidental poisonings, 46% (123/265) were due to overdoses by psychotropic medications and 44% (117/265) were due to overdoses of narcotics and hallucinogens, including drugs of abuse (ICD-10: X42).

In absolute numbers, 64% (2104/3300) of the observed deaths due to any cause were excess deaths (table 1). Of the observed deaths due to somatic causes, 51% (1043/2027) were excess deaths, whereas 83% (1061/1273) of the observed deaths due to external causes were excess deaths. In other words, 51% of the observed somatic deaths were attributable to BD, whereas 83% of the deaths due to external causes were attributable to BD. Most of the excess deaths due to somatic causes were either due to alcohol-related causes (40%, 414/1043), CVD (26%, 267/1043) or cancer (10%, 100/1043). Of the excess deaths due to external causes, 61% (651/1061) were due to suicide.

Most of the excess deaths due to somatic causes (81%, 846/1043) and about half (49%, 523/1061) of the excess deaths due to external causes were in those aged 45–64 years; meaning

Table 1 Excess deaths in bipolar disorder

	Total person-years of follow-up	Observed deaths, n	Expected deaths, n	Excess deaths, n (%)	PYLL-65, total years, n	Excess PYLL-65/100 person-years, n	PYLL-75, total years, n	Excess PYLL-75/100 person-years, n
Age group	All-cause mortality							
15–24	23 442	88	12	76 (86)	3707	13.6	4567	16.7
25–34	78 640	323	56	267 (83)	11 141	11.7	14 301	15.1
35–44	84 788	503	111	392 (78)	12 685	11.7	17 705	16.3
45–54	95 016	1022	310	712 (70)	15 101	11.1	25 271	18.6
55–64	95 500	1364	707	657 (48)	6978	3.5	20 568	10.3
15–64	377 386	3300	1196	2104 (64)	49 612	8.4	82 412	14.0
Age group	Mortality due to external causes*							
15–24	23 442	76	9	67 (88)	3187	12.0	3927	14.7
25–34	78 640	252	34	218 (87)	8963	9.9	11 493	12.7
35–44	84 788	292	40	252 (86)	8099	8.2	11 269	11.4
45–54	95 016	368	60	308 (84)	6868	6.1	11 348	10.0
55–64	95 500	285	70	215 (75)	1954	1.5	5284	4.1
15–64	377 386	1273	212	1061 (83)	29 072	6.4	43 321	9.5
Age group	Mortality due to somatic causes†							
15–24	23 442	12	3	9 (75)	520	1.7	640	2.0
25–34	78 640	71	22	49 (69)	2178	1.9	2808	2.5
35–44	84 788	211	71	140 (66)	4586	3.6	6436	5.0
45–54	95 016	654	250	404 (62)	8233	5.4	13 923	9.1
55–64	95 500	1079	637	442 (41)	5024	2.1	15 284	6.6
15–64	377 386	2027	984	1043 (51)	20 541	2.8	39 091	5.3

Number of deaths in individuals aged 15–64 years during 2004–2018. Age-specific mortality rates in the Finnish general population were used in calculating expected deaths for bipolar disorder. Excess deaths proportion is calculated as the number of excess deaths/observed deaths. Causes of death are defined according to the International Classification of Diseases, 10th revision.

*Excluding accidental alcohol poisoning.

†Including accidental alcohol poisoning.

PYLL, potential years of life lost.

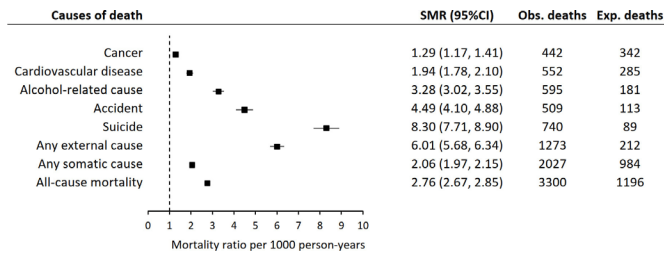


Figure 1 Standardised mortality ratios (SMR) per 1000 person-years for all-cause and cause-specific deaths in individuals with bipolar disorder aged 15–64 years during 2004–2018. Finnish general population as a reference. Error bars represent 95% CIs. Accidental alcohol poisoning included in somatic causes of death and excluded from external causes of death. Exp. deaths, expected deaths; Obs. deaths, observed deaths.

that this age group had a high burden of both somatic and external causes of death. In relation to total excess mortality, deaths due to external causes represented 38% (523/1369) of the total mortality in the age group of 45–64 years, whereas in the age group of 15–44 years, this proportion was 73% (537/735).

About 10 years of potential life were lost in excess per 100 person-years due to external causes in those who died aged 15–64 years, assuming that they would have lived until the age of 75 years (table 1). This was twice the number of PYLLs in excess due to somatic causes (5/100 person-years). Only in the oldest age group, that is, 55–64 years, the number of excess PYLLs due to somatic causes was higher than due to external causes. In other age groups, the number of PYLLs was several times higher in deaths due to external causes than due to somatic causes. Comparable associations were found when excess PYLLs were calculated for the age of 65 years.

Because no difference between men and women was observed in relative excess mortality, overall or by age group (online supplemental eFigure 1), subsequent results are not reported separately for men and women. In BD, all-cause mortality was about threefold higher (SMR: 2.76, 95% CI: 2.67, 2.85), mortality due to somatic causes was about twofold higher (SMR: 2.06, 95% CI: 1.97, 2.15) and mortality due to external causes was about sixfold higher (SMR: 6.01, 95% CI: 5.68, 6.34) than in the general population without BD (figure 1). Highest relative excess mortality due to somatic causes was from alcohol-related deaths, that is, about threefold higher (SMR: 3.28, 95% CI: 3.02, 3.55), followed by mortality due to CVD (SMR: 1.94, 95% CI: 1.78, 2.10). Highest relative excess mortality was due to suicides, which was about eightfold higher (SMR: 8.30, 95% CI: 7.71, 8.90) than in the general population.

Across most cause-of-death categories, relative excess mortality was higher in the younger age groups (figure 2). While the highest relative cause-specific excess mortality was in the younger age groups, excess deaths in the age group of 45–64 years represented 84% (223/264) of the deaths due to CVD, 80% (333/414) of the deaths due to alcohol-related causes and about half (47%, 305/651) of the deaths due to suicide. Therefore, while the highest relative excess mortality rates were consistently found in the youngest age groups, the older age groups contributed to the excess mortality in absolute numbers either equally or more than the younger age groups.

Online supplemental eTable 3 presents different population mortality models in which cause-specific mortality would be reduced by 50% equally across all age groups, and how these reductions would affect the relative excess all-cause mortality,

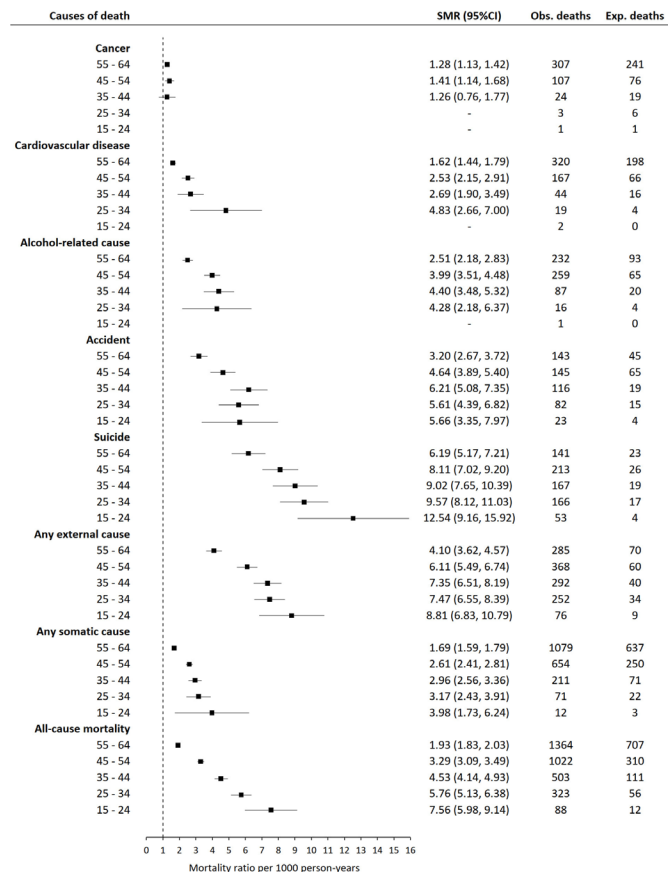


Figure 2 Standardised mortality ratios (SMRs) per 1000 person-years for all-cause and cause-specific mortality by age group in individuals with bipolar disorder during 2004–2018. Finnish general population as a reference. Error bars represent 95% CIs. Estimates for age groups with less than 10 deaths omitted. Accidental alcohol poisoning included in somatic causes of death and excluded from external causes of death. Exp. deaths, expected deaths; Obs. deaths, observed deaths.

that is, the mortality gap. Reducing mortality due to external causes would have twice the effect of reducing mortality due to CVD, and roughly the same effect as reducing both mortality due to alcohol-related causes and CVD. These results suggest that reducing mortality due to external causes would likely have a greater effect on the mortality gap than reducing mortality due to somatic causes. This is because deaths due to external causes were common in all age groups.

Online supplemental eTable 4 shows SMRs for accidents and for any external causes when accidental alcohol poisonings were included in these cause of death categories, rather than in somatic causes, that is, in alcohol-related causes of death. No marked differences in age-specific SMRs were observed in comparison with the SMRs showed in figures 1 and 2.

DISCUSSION

In this population-level cohort study, we followed up over 47 000 individuals diagnosed with BD for over 377 000 person-years to investigate patterns of cause-specific excess mortality across age groups. We found that external causes of death contributed more to the mortality gap in BD than somatic causes, when focusing on age-specific excess mortality rather than on total mortality. While half of the observed somatic deaths were attributable to BD, over three-quarters of the deaths due to external causes were attributable to BD. Most of the excess deaths in those aged

15–44 years were due to external causes. In contrast, in those aged 45–64 years, external causes and somatic causes contributed in nearly equal numbers to the excess mortality. Alcohol-related causes contributed more to the age group-specific excess mortality than CVD. Although premature mortality due to CVD was common in those aged 15–64 years, it had a relatively smaller role in explaining the mortality gap than external causes of death or alcohol-related causes of death.

Our results showed that the excess risk of death due to external causes was substantial in all age groups. A key implication of the high number of excess deaths due to suicide is the need for personalised approaches to prediction and prevention. In prediction, simple scalable models have been developed and validated in people with BDs that can assist with risk stratification.²¹ If this can be linked to effective interventions aimed at suicide prevention, such as safety planning, this may have a role in reducing the mortality gap further. Similar prediction models could be developed for premature mortality from other causes as well. For example, well-calibrated prediction models exist in cardiovascular medicine for low-base rate events, and these are used to inform treatment and prognosis.²² In particular, further research on risk prediction tools also for deaths due to overdose by prescription medicines and other substances, including alcohol, is needed. Given the similar profile of causes of death determined as accidents on one hand and as suicides on the other, a detailed analysis of underlying intentionality in deaths due to external causes is warranted. In addition to known effective pharmacological treatment with mood stabilisers, accidental deaths could be prevented by psychosocial interventions targeting treatment compliance and risk-taking behaviours, particularly those associated with substance abuse.

Furthermore, we showed that the excess risk of death due to alcohol abuse was substantial in the older age groups. The role of alcohol abuse, and other substances, is likely underestimated here because alcohol is a contributory factor also in various other causes of death that are not explicitly defined as related to alcohol. Alcohol-related morbidity and mortality are important determinants of absolute and relative health disparities in many high-income countries.²³ We showed that in BD, deaths due to alcohol-related causes were increased by about threefold compared with the general population. Alcohol-related causes also had the highest number of excess deaths within somatic causes, by about twofold compared with deaths due to CVD, which was the second largest group of deaths due to somatic causes. Although substance use disorders are a known and relatively common comorbidity in BD,^{13 24} we are not aware of previous studies that would have quantified alcohol-related excess mortality in BD. Further research is thus warranted on alcohol-related excess morbidity and mortality in BD. Interventions aimed at preventing deaths related to substance abuse will thus likely have additional effects in reducing total excess mortality in BD.

A consistent excess all-cause mortality of about twofold to threefold compared with the general population has been reported in many countries,²⁵ also outside Europe and North America.^{8 9} Evidence on cause-specific mortality is less consistent.^{25 26} This variability may be partly explained by context-specific factors, because the mortality risk in BD is affected by the background general population mortality risk and the factors directly determining the mortality risk associated with BD, such as diagnosis, treatment and management of BD and its comorbidities. There is debate over the relative contribution of cardiovascular deaths, or somatic causes in general, and deaths due to external causes in determining excess mortality

in severe mental illness.³ The conclusion has often been that cardiovascular causes are more important than external causes in determining the mortality gap.^{15 27 28} This conclusion has typically been based on the observed total number of deaths across all age groups. For example, in Sweden, CVD deaths represented about 38% of all deaths in BD, whereas deaths from external causes represented only 18%.¹⁵ We also found that when all age groups were included, CVD was the leading cause of death and that somatic causes of death represented the majority of all deaths in BD. However, this finding reflects the fact that, in many high-income countries, most of the deaths are due to somatic causes, with CVD, cancers, and diseases of the nervous system as the leading causes of death in the older age groups. Evidence consistently shows that the relative excess mortality in BD decreases with increasing age.^{25 29} In other words, the older the BD population, the more the mortality pattern converges toward the general population mortality, and thus the mortality gap is smallest in the older age groups. We showed that in the population aged 15–64 years, about half of the deaths due to CVD were excess deaths, whereas most of the deaths due to external causes were excess deaths. Similar proportions have been reported also elsewhere.^{15 30} However, we also showed that, although the relative excess mortality due to external causes decreased with age, the absolute excess mortality did not. Similarly, the relative excess mortality due to CVD decreased with increasing age, but, in contrast, the absolute excess mortality increased with age. Furthermore, the mortality difference in relation to the general population in those aged under 65 years is important also because over half of all BD deaths were in those aged 15–64 years, whereas in the Finnish general population, only about one-fifth of all deaths were in this age group. Age-specific prevention strategies that will take into account different mortality patterns across age groups are thus needed in reducing the mortality gap.

Study strengths and limitations

The major strengths of our study were the improved precision of the effect estimates due to the large number of individuals diagnosed with BD and the large number of deaths in the dataset. This enabled us to establish cause-specific mortality estimates across age groups. Using various nationwide registers enabled us to identify individuals with BD also from other sources than inpatient care. This improved generalisability of our results in relation to many previous studies which have mostly included individuals identified from inpatient contacts. We standardised the mortality estimates for sex and age, but because administrative registers do not include information on various explanatory covariates, such as various clinical characteristics, we did not identify the factors that potentially explain the observed excess mortality in BD. Excluding those with a history of schizoaffective disorder has likely underestimated excess mortality in BD particularly due to external causes, because a history of persistent symptoms of psychosis, delusions and hallucinations is known to be associated with markedly increased mortality. Future studies should thus aim to establish cause-specific excess mortality across age groups in those with mixed diagnostic history before the diagnosis of BD.^{31 32} The diagnosis of BD is done typically in specialised care, and because we used information on both inpatient and outpatient specialised care contacts in combination with other register data, we were probably able to capture most individuals with the first diagnosis of BD. However, the mortality estimates for BD may be underestimated because an unknown

proportion of individuals in the general population were either not diagnosed or were misdiagnosed as having, for example, depression, and thus the deaths in those individuals were not attributed correctly to BD. The known substantial delay in BD diagnosis is an important factor in the misclassification of deaths, especially in relation to deaths due to external causes because these deaths are more likely to occur before the BD diagnosis is recorded. Because these results apply to mortality associated with diagnosed BD, the results are relevant in terms of preventable excess mortality due to BD. Because excess mortality estimates are affected by the underlying general population mortality rates, future studies should aim to replicate these findings in other populations.

CLINICAL IMPLICATIONS

Because of the observed high total number of deaths due to CVD, much of the recent research on mortality associated with BD has emphasised the importance of preventing CVD deaths.²⁸ Therefore, the cardiometabolic tolerability of medicines for treating BD has also received increased attention among clinicians.^{33–35} However, our findings show that the contribution of external causes of death has been underestimated because most previous studies have not considered age-specific excess mortality. Deaths due to external causes are an important cause of excess mortality in those aged 15–64 years. This calls for a re-evaluation of the current emphasis on preventing somatic mortality to reduce the mortality gap between BD and the general population. A balanced consideration between therapeutic response, potential serious long-term somatic side effects of different medicines and risk of cause-specific premature mortality is needed, especially in younger persons.^{35–36} Targeting preventive interventions for substance abuse will likely reduce the mortality gap both due to external causes and somatic causes. Suicide prevention remains a priority, and better awareness of the risk of overdose and other poisonings is warranted.

Contributors TP, HT and JT designed the study. HT contributed to the linkage of the data sources. TP did the statistical analysis. TP wrote the first draft of the manuscript. All authors reviewed and revised the manuscript. JT is the guarantor. TP and HT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Patient consent for publication Not applicable.

Ethics approval The study design and record linkages were approved by the review boards of the institutions maintaining the registers: The Finnish National Institute for Health and Welfare (635/5.05.00/2019), the Social Insurance Institution of Finland (31/522/2019), Finnish Centre for Pensions (19023), and Statistics Finland (TK-53-569-19)

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study may be obtained from the institutions maintaining the registers used in this study. Restrictions apply to the availability of these data.

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ORCID iDs

Tapio Paljärvi <http://orcid.org/0000-0002-5324-9825>

Kimmo Herttua <http://orcid.org/0000-0003-2004-779X>

Seena Fazel <http://orcid.org/0000-0002-5383-5365>

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