Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls

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People with severe mental illness (SMI) – schizophrenia, bipolar disorder and major depressive disorder – appear at risk for cardiovascular disease (CVD), but a comprehensive meta-analysis is lacking. We conducted a large-scale meta-analysis assessing the prevalence and incidence of CVD; coronary heart disease; stroke, transient ischemic attack or cerebrovascular disease; congestive heart failure; peripheral vascular disease; and CVD-related death in SMI patients (N=3,211,768) versus controls (N=113,383,368) (92 studies). The pooled CVD prevalence in SMI patients (mean age 50 years) was 9.9% (95% CI: 7.4-13.3). Adjusting for a median of seven confounders, patients had significantly higher odds of CVD versus controls in cross-sectional studies (odds ratio, OR=1.53, 95% CI: 1.27-1.83; 11 studies), and higher odds of coronary heart disease (OR=1.51, 95% CI: 1.47-1.55) and cerebrovascular disease (OR=1.42, 95% CI: 1.21-1.66). People with major depressive disorder were at increased risk for coronary heart disease, while those with schizophrenia were at increased risk for coronary heart disease, cerebrovascular disease and congestive heart failure. Cumulative CVD incidence in SMI patients was 3.6% (95% CI: 2.7-5.3) during a median follow-up of 8.4 years (range 1.8-30.0). Adjusting for a median of six confounders, SMI patients had significantly higher CVD incidence than controls in longitudinal studies (hazard ratio, HR=1.78, 95% CI: 1.60-1.98; 31 studies). The incidence was also higher for coronary heart disease (HR=1.54, 95% CI: 1.30-1.82), cerebrovascular disease (HR=1.64, 95% CI: 1.26-2.14), congestive heart failure (HR=2.10, 95% CI: 1.64-2.70), and CVD-related death (HR=1.85, 95% CI: 1.53-2.24). People with major depressive disorder, bipolar disorder and schizophrenia were all at increased risk of CVD-related death versus controls. CVD incidence increased with antipsychotic use (p=0.008), higher body mass index (p=0.008) and higher baseline CVD prevalence (p=0.03) in patients vs. controls. Moreover, CVD prevalence (p=0.007), but not CVD incidence (p=0.21), increased in more recently conducted studies. This large-scale meta-analysis confirms that SMI patients have significantly increased risk of CVD and CVD-related mortality, and that elevated body mass index, antipsychotic use, and CVD screening and management require urgent clinical attention.

Key words: Cardiovascular disease, severe mental illness, schizophrenia, bipolar disorder, major depression, coronary heart disease, cerebrovascular disease, congestive heart failure, premature mortality

People with severe mental illness (SMI) – including schizophrenia, bipolar disorder, major depressive disorder, and their related spectrum disorders – have a life expectancy shortened of 10-17.5 years compared to the general population[1,2]. While suicide explains some of this reduced life expectancy[3], it is now established that physical diseases account for the overwhelming majority of premature mortality[4,5]. Among physical conditions, cardiovascular disease (CVD) is the main potentially avoidable contributor to early deaths in patients with SMI[4].

Given the importance of understanding the magnitude, contributors to and relative distribution of CVD risk in people with SMI, a number of disease-specific meta-analyses investigated if people with major depressive disorder, bipolar disorder or schizophrenia are at an increased risk of CVD compared to controls. These meta-analyses reported that people with depression (defined by the presence of depressive symptoms or a diagnosis of major depressive disorder) are at increased

CVD risk[6,7], including stroke (risk ratio, RR=1.34, 95% CI: 1.17-1.54), myocardial infarction (hazard ratio, HR=1.31, 95% CI: 1.09-1.57), coronary heart disease (RR=1.36, 95% CI: 1.24-1.49) and coronary heart disease-related death (HR=1.36, 95% CI: 1.14-1.63)[6-8]. While clearly informative, results concerning CVD were not specific for major depressive disorder defined according to established diagnostic criteria, possibly biasing such observed association towards a lower risk[9]. Another meta-analysis of longitudinal studies, which utilized standardized criteria to define bipolar disorder, reported mixed results, since people with that disorder were actually not at increased risk of myocardial infarction (RR=1.09, 95% CI: 0.96-1.24), whereas the risk of stroke was higher compared to controls (RR=1.74, 95% CI: 1.29-2.35)[10]. Among individuals with schizophrenia, previous meta-analyses[11,12] reported an overall increased risk of CVD compared to controls (RR=1.53, 95% CI: 1.27-1.86). This risk increase included stroke (up to RR=1.71,

95% CI: 1.19-2.46) and heart failure (RR=1.81, 95% CI: 1.42-2.29), but not coronary heart disease (RR=1.20, 95% CI: 0.93-1.53).

While the existing literature has provided relevant insights, several limitations are to be highlighted and important questions remain unanswered. First, some of the previous meta-analyses did not use standardized clinical assessments to identify and categorize SMI and/or cardiovascular events. Second, the exact prevalence and incidence of each type of CVD among people with SMI, both within and across major diagnostic SMI sub-groups, remains unclear. Third, the magnitude of premature CVD-related mortality risk in people with SMI versus controls is to be specified. Fourth, potential risk factors for increased CVD and related mortality risk across the SMI groups have not been elucidated via meta-analytic techniques, which could help identify targets for treatment guidelines, clinical standards and development of preventive and therapeutic programs. In this regard, large-scale pooled analyses in the SMI population can provide relevant information, allowing the investigation of potentially shared risk factors across many studies and participants, thus dissecting CVD risk factors associated with SMI and/or treatments for these disorders from factors which are non-specific or shared with the general population[13]. Additionally, pooling of data allows for the investigation of demographic, regional and treatment variables, both within and across major diagnostic categories.

Given the caveats mentioned above, the current gaps within the literature and the need to better understand CVD risk among people with SMI, we conducted a large scale meta-analysis investigating the prevalence, incidence and mortality attributed to CVD and their correlates among people with SMI, both within and across major diagnostic groups.

METHODS

This systematic review and meta-analysis adhered to the PRISMA statement[14], following a predetermined, but unpublished protocol.

Search strategy

An electronic literature search was conducted in PubMed, Embase and Scopus from database inception until August 2, 2016 by two independent reviewers, using the search terms ("bipolar disorder" OR mania OR schizophrenia OR schizoaffective OR psychosis OR "major depression" OR "serious mental illness") AND (cardiovascular OR stroke OR cerebrovascular OR "transient ischemic attack" OR "transient ischaemic attack" OR "peripheral vascular" OR "myocardial infarction" OR "coronary heart disease" OR" coronary artery disease" OR "ischemic heart disease" OR "ischaemic heart disease" OR "hypertensive heart disease" OR angina OR "cardiac failure" OR "heart failure" OR "congestive heart failure" OR "atrial fibrillation" OR "pulmonary embolism" OR "cardiovascular mortality"). Furthermore, bibliographies of included papers were reviewed.

Inclusion and exclusion criteria

We included studies with the following characteristics: a) reporting on patients with schizophrenia, schizophrenia spectrum or schizoaffective disorder, bipolar disorder or bipolar spectrum disorders, major depressive disorder or depressive episodes, or SMI (defined as at least two among major depressive spectrum, bipolar spectrum and schizophrenia spectrum disorders) according to DSM-III, DSM-IV, DSM-5, ICD-8, ICD-9 or ICD-10, or a medical record diagnosis based on a clinical interview; b) having a cross-sectional or a retrospective/prospective longitudinal design, either with or without a control group; c) using a standardized definition of CVD; d) reporting RR, HR or odds ratio (OR) comparing patients with region-specific controls, percentage or number of events at baseline (data used for cross-sectional analysis = prevalence) and/or follow-up (data used for longitudinal analysis = cumulative incidence).

We excluded studies that investigated cardiovascular risk estimates and/or factors, subclinical CVD, or SMI rates in populations with CVD. In case of multiple publications from the same study, only the most recent paper or the article with the longest follow-up was included. When required, we contacted the primary/corresponding authors of potential studies to confirm eligibility or acquire unpublished variables of interest.

Data extraction

Seven authors divided in four pairs independently extracted data in a standardized Microsoft Excel sheet, with reciprocal validation of data extraction results. The extracted data included: authors, year and country; geographic region; study design; data source; period of data collection; SMI diagnostic criteria; CVD diagnostic criteria; specific SMI and CVD diagnosis; case and control inclusion criteria; number of cases and controls; percentage or number with CVD, coronary heart disease, cerebrovascular disease and congestive heart failure at baseline; number of events at follow-up; follow-up duration; number and type of covariates considered in the analyses; OR, RR, rate ratio and HR with their respective 95% upper and lower CIs; mean age with standard deviation; mean body mass index with standard deviation; proportion of males; co-occurring obesity, alcohol and substance related disorders, diabetes, hypertension, and hyperlipidemia; married status; employment status; percentage of patients with poorest income and least urbanized; and percentage of patients taking antipsychotics. Rate ratios calculated with Cox regression models were included in HR analyses. When authors did not specify whether or not a rate ratio had been calculated with Cox regression models, we contacted them seeking clarification.

Outcomes

Primary outcomes were CVD prevalence and cumulative incidence plus CVD-related mortality in people with SMI, as

well as adjusted OR for prevalence and HR for incidence rates in SMI versus controls. Secondary outcomes were the same measures for specific CVDs (i.e., coronary heart disease, cerebrovascular disease, congestive heart failure) in SMI patients, as well as adjusted OR and HR versus controls.

Prevalence and OR were calculated from cross-sectional studies and from baseline results of longitudinal studies. Where available, incidence, RR and HR were calculated from longitudinal studies.

Quality assessment

For the purpose of this meta-analysis, a checklist (yes versus no) was used to assess the methodological quality of included studies. The evaluation of methodological quality across studies was based on the following factors: clear diagnostic criteria, presence of a control group, matching of the control group, covariate-adjusted outcomes, reported cardiovascular risk factors at baseline, and follow-up ≥ 5 years.

Data analysis

This meta-analysis was performed using Comprehensive Meta-Analysis V3[15]. All outcomes were meta-analyzed when at least two studies provided data. A random effects model[16,17] was used to account for between-study heterogeneity. We calculated pooled CVD prevalences and pooled CVD cumulative incidences, each with SMI subgrouping. For dichotomous primary and secondary outcomes comparing pooled SMI and SMI subgroups with controls, we calculated unadjusted as well as adjusted pooled OR for cross-sectional data, and unadjusted pooled RR, as well as adjusted pooled HR, for longitudinal data. Funnel plots were visually inspected, and Egger's test[18] and Begg-Mazumdar Kendall's tau[19] were used to determine if publication bias was likely. When publication bias was present, the trim and fill[20] procedure was run to evaluate if the results changed after imputing potentially missing studies.

Between-study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared $p < 0.05$ and I-squared $\geq 50\%$ indicating significant heterogeneity[21]. To identify potential moderators, meta-regression was run with Comprehensive Meta-Analysis V3 for unadjusted outcomes where heterogeneity was significant.

Since CVD rates in the general population vary across the world, we also performed a stratified analysis across geographic regions (Asia, Europe, North America, Oceania) regarding raw CVD prevalence and incidence in SMI populations, and compared patients to their respective region-specific general population controls (calculating RRs as well as adjusted ORs and HRs for the four regional strata and comparing them across the different regions whenever at least two studies provided data per each region).

The following study and patient characteristics were explored as potential moderators and mediators in addition to SMI status: geographical region of the sample; time of data collection; percentage of patients taking antipsychotics; and the difference between patient and control samples regarding age, body mass index, proportion of males and of those with married status, unemployed, with poorest income, least urbanized, and having co-occurring obesity, alcohol and substance-related disorders, diabetes, hypertension or hyperlipidemia.

RESULTS

Search results

Out of 18,064 initial hits across the searched electronic databases, 11,878 unduplicated hits were screened, and 11,576 were excluded through title/abstract reading. Altogether, 302 full texts were reviewed, and 210 were excluded with specific reasons. Among 92 studies meeting inclusion criteria, 27 had a cross-sectional design[22-48] and 65 studies had a retrospective or prospective longitudinal design[49-113] (Figure 1).

Characteristics of included studies

We included 92 studies, with a total population of 3,211,768 patients (mean age 50 years, 49% male) with SMI and 113,383,368 controls (mean age 51 years, 49% male), with a total of 116,595,136 subjects when summing those studies where patient and control sample sizes were not separately reported. Altogether, 27 studies (N=27,037,943) were cross-sectional and 65 studies (N=89,557,193) were longitudinal. Overall, 38 studies included patients with schizophrenia (of which 29 were longitudinal), 30 with bipolar disorder (21 longitudinal), 30 with major depressive disorder (22 longitudinal), and 14 with SMI (8 longitudinal). Taken together, six studies included only patients with SMI (N=884,412), 16 studies included only patients with bipolar disorder (N=71,832), 20 studies included only patients with major depressive disorder (N=111,360), and 29 studies included only patients with schizophrenia (N=1,591,106), while 19 studies included different subgroups of SMI, providing data for each of them separately (some studies included more than one diagnostic group, see Tables 1 and 2 for details).

Meta-analysis: cross-sectional results

The pooled CVD prevalence in SMI was 9.9% (95% CI: 7.4-13.3; 38 studies). Individual rates were 8.4% for people with bipolar disorder (95% CI: 5.4-12.6, 12 studies, N=66,911); 11.7% for those with major depressive disorder (95% CI: 3.6-32.2, 7 studies, N=83,965); 11.8% for those with schizophrenia (95% CI: 7.1-19.0, 13 studies, N=191,982), and 11.8% for those with SMI (95% CI: 4.1-29.4, 6 studies, N=17,286) (p<0.001 for SMI diagnostic subgroup comparisons).

Adjusting for a median of seven potential confounders, the adjusted pooled OR for CVD in SMI compared to controls was
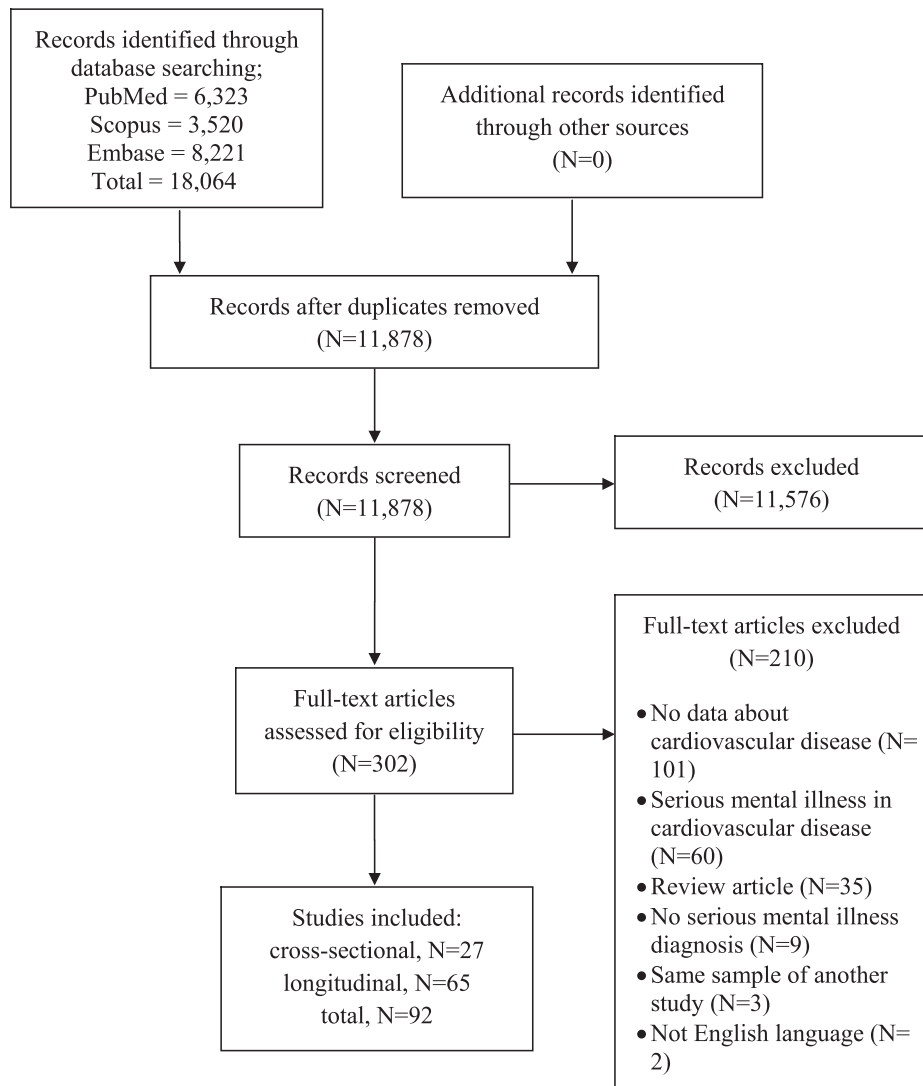
Figure 1 PRISMA flow chart

1.53 (95% CI: 1.27-1.83, p<0.001, 11 studies). For specific CVDs, pooled together, people with SMI had an increased risk of coronary heart disease (OR=1.51, 95% CI: 1.47-1.55, p<0.001, 5 studies) and cerebrovascular disease (OR=1.42, 95% CI: 1.21-1.66, p<0.001, 6 studies), with a strong statistical trend for congestive heart failure (OR=1.28, 95% CI: 0.99-1.65, p=0.06, 4 studies). Considering separately single types of SMI and CVD, in adjusted OR analyses, bipolar disorder was not significantly associated with CVD or its subtypes; major depressive disorder was significantly associated with CVD and coronary heart disease; and schizophrenia was significantly associated with coronary heart disease, cerebrovascular disease and congestive heart failure (Table 3). No adjusted ORs were available for mixed SMI groups.

All significant results were significantly heterogeneous. After adjusting for publication bias with the trim-and-fill method, all

pooled previously significant ORs remained statistically significant, confirming the association of CVD, coronary heart disease and cerebrovascular disease with SMI, while the OR for congestive heart failure became marginally significant (p=0.05).

Meta-analysis: longitudinal adjusted results

Among patients with SMI, 3.6% (95% CI: 2.7-5.3%) experienced a CVD event during a median follow-up period of 8.4 years (range 1.8-30.0) (65 studies). After adjusting for a median of six potential confounders, people with SMI were at significantly increased risk across longitudinal studies for CVD (HR=1.78, 95% CI: 1.60-1.98) (31 studies, N=671,384 cases vs. N=14,335,203 controls) as well as for specific CVDs, including coronary heart disease (HR=1.54, 95% CI: 1.30-1.82, 18 studies, N=194,017 cases vs. N=13,530,858 controls), cerebrovascular

Table 1 Cross-sectional studies: characteristics of included studies and samples

Study	Country	No. cases	No. controls	Period of data collection	SMI definition	Inclusion criteria for cases	No. covariates
Beyer et al[22]	USA	1,379	-	2001-2002	Medical records	Bipolar disorder	-
Bresee et al[23]	Canada	28,775	2,281,636	1995-2006	ICD-9,10	Schizophrenia	4
Bresee et al[24]	Canada	399	120,044	2005	Medical records	Schizophrenia	11
Chen et al[25]	Taiwan	80	-	2015	DSM-IV	Bipolar disorder, >60 years	-
Curkendall et al[26]	Canada	3,022	12,088	1994-1999	ICD-9	Schizophrenia	7
Devantier et al[27]	Denmark	28	27	2009-2011	ICD-10	Major depressive disorder, late onset	-
Hagg et al[28]	Sweden	269	-	2000-2003	DSM-IV	Schizophrenia, 20-69 years	-
Herbst et al[29]	USA	10,573 total population		2001-2002	DSM-IV	Major depressive disorder, >60 years	11
Huang et al[30]	Taiwan	117,987	21,356,304	2000-2003	ICD-9	Bipolar disorder or major depressive disorder	1
Hyde et al[31]	Australia	355	-	2008-2012	Medical records	Severe mental illness, prescribed clozapine	-
Kilbourne et al[32]	USA	8,083	-	2001	ICD-9	Severe mental illness, >60 years	-
Kilbourne et al[33]	USA	9,705	5,353	2000-2001	ICD-9	Bipolar disorder or severe mental illness, male	3
Lindegard[34]	Sweden	368	87,176	1966-1979	ICD-9, DSM-III	Major depressive disorder or bipolar disorder	-
Maina et al[35]	Italy	185	-	2006-2008	DSM-IV	Severe mental illness	-
Morden et al[36]	Canada	65,362	65,362	2000-2007	ICD-9	Schizophrenia	4
Munoli et al[37]	India	120	-	2011	ICD-10	Bipolar disorder	-
Nielsen et al[38]	Denmark	937	-	1969-2014	ICD-10	Schizophrenia	-
Niranjan et al[39]	USA	5,695	34,979	2007	DSM-IV	Major depressive disorder	6
Oreski et al[40]	Croatia	289	192	2011	ICD-10	Bipolar disorder or schizophrenia	-
Prieto et al[41]	USA	988	-	2009-2013	DSM-IV	Severe mental illness	-
Scherrer et al[42]	USA	628	6,903	1990-1992	DSM-III	Major depressive disorder, male twins	-
Scott et al[43]	Multicenter	52,095 total population		2001-2011	DSM-IV	Bipolar disorder or major depressive disorder	6
Shen et al[44]	Taiwan	203	2,036	2005-2007	ICD-9	Schizophrenia, in intensive care unit	6
Smith et al[45]	UK	9,677	1,414,701	2007	Medical records	Schizophrenia	3
Smith et al[46]	UK	2,582	1,421,796	2007	Medical records	Bipolar disorder	2
Swain et al[47]	Multicenter	45,288 total population		2001-2011	DSM-IV	Bipolar disorder or major depressive disorder	7
Zilkens et al[48]	Australia	656	349	2000-2009	ICD-8,9,10	Major depressive disorder, 65-84 years, developing dementia	-

SMI – severe mental illness

disease (HR=1.64, 95% CI: 1.26-2.14, 11 studies, N=188,841 cases vs. N=13,113,564 controls), congestive heart failure (HR=2.10, 95% CI: 1.64-2.70, 2 studies, N=409 cases vs. N=41,678 controls), peripheral vascular disease (only unadjusted RR=3.11, 95% CI: 2.46-3.91, three studies), and CVD-related death (HR=1.85, 95% CI: 1.53-2.24, 16 studies, N=353,407 cases vs. N=7,317,053 controls).

According to adjusted HRs, schizophrenia was significantly associated with CVD in longitudinal studies (HR=1.95, 95% CI: 1.41-2.70, 14 studies), as well as with coronary heart disease (HR=1.59, 95% CI: 1.08-2.35, 5 studies), cerebrovascular disease (HR=1.57, 95% CI: 1.09-2.25, 5 studies), and CVD-related death (HR=2.45, 95% CI: 1.64-3.65, 9 studies).

According to adjusted HRs, bipolar disorder was significantly associated with CVD in longitudinal studies (HR=1.57, 95% CI: 1.28-1.93, 10 studies) as well as with CVD-related death

(HR=1.65, 95% CI: 1.10-2.47, 3 studies), with a trend toward a significant association with cerebrovascular disease (HR=1.60, 95% CI: 0.99-2.57, 4 studies), but no significant association with coronary heart disease (HR=1.16, 95% CI: 0.76-1.78, 4 studies). One study reported a significant association with congestive heart failure (HR = 2.27, 95% CI: 1.49-3.45).

According to adjusted HRs, major depressive disorder was significantly associated with CVD in longitudinal studies (HR=1.72, 95% CI: 1.48-2.00, 18 studies) as well as with coronary heart disease (HR=1.63, 95% CI: 1.33-2.00, 9 studies), cerebrovascular disease (HR=2.04, 95% CI: 1.05-3.96, 3 studies), congestive heart failure (HR=2.02, 95% CI: 1.48-2.75, 2 studies), and CVD-related death (HR=1.63, 95% CI: 1.25-2.13, 7 studies).

According to adjusted HRs, mixed SMIs were significantly associated with CVD in longitudinal studies (HR=3.24, 95%

Table 2 Longitudinal studies: characteristics of included studies and samples

Study	Country	No. cases	No. controls	Period of data collection	SMI definition	Inclusion criteria for cases	No. covariates
Almeida et al[49]	Australia	1,503	35,691	1996-2010	ICD-9	Schizophrenia, bipolar disorder or major depressive disorder, 65-85 years, male	8
Bremmer et al[50]	The Netherlands	41	2,080	1992-2000	DSM-III	Major depressive disorder, >55 years	13
Butnoriene et al[51]	Lithuania	184	369	2003-2004	DSM-IV	Major depressive disorder, >45 years	4
Callaghan et al[52]	Canada	5,999	5,999	2002-2006	Medical records	Bipolar disorder	6
Callaghan et al[53]	Canada	9,815	9,815	2002-2006	ICD-10	Bipolar disorder	8
Carney et al[54]	USA	1,074	726,262	1996-2001	ICD-9	Schizophrenia or schizoaffective disorder	4
Chen et al[55]	Taiwan	63,913	63,913	2002-2008	ICD-9	Schizophrenia	8
Clouse et al[56]	USA	16	60	1982-1992	DSM-III	Major depressive disorder with diabetes	7
Coryell et al[57]	USA	903	-	1998-1999	RDC	Severe mental illness	-
Crump et al[58]	Sweden	6,618	6,580,418	2003-2009	ICD-10	Bipolar disorder	6
Crump et al[59]	Sweden	8,277	6,097,834	2003-2009	ICD-10	Schizophrenia, >25 years	6
Davis et al[60]	Hawaii	280	39,000	1999-2005	Medical records	Major depressive disorder	5
Davydow et al[61]	Denmark	68,137	5,912,158	1999-2013	ICD-9	Schizophrenia, schizoaffective disorder or bipolar disorder	5
Enger et al[62]	USA	1,920	9,600	1995-1999	ICD-9	Schizophrenia, on antipsychotic treatment, 15-64 years	-
Fiedorowicz et al[63]	USA	288	147	1978-1981	RDC	Bipolar disorder	8
Filik et al[64]	UK	482	1,998	1999-2002	DSM-IV	Schizophrenia, schizophreniform or schizoaffective disorder	6
Fors et al[65]	Sweden	255	1,275	1981-1991	DSM-II	Schizophrenia	3
Gasse et al[66]	Denmark	873,898	52,693,301	1995-2009	ICD-8,10	Severe mental illness (affective psychoses)	22
Goldstein et al[67]	USA	5,835	26,266	2001-2005	DSM-IV	Bipolar disorder or major depressive disorder	8
Healy et al[68]	UK	1,429	-	1875-1924; 1994-2010	Medical records	Schizophrenia	-
Hendrie et al[69]	USA	757	30,831	1999-2008	ICD-9	Schizophrenia, >65 years	-
Hou et al[70]	Taiwan	8,264	-	1985-2008	DSM-III or IV, ICD-9	Schizophrenia	-
Hsieh et al[71]	Taiwan	9,715	-	2001-2009	ICD-9	Schizophrenia	10
Huang et al[72]	Taiwan	7,937	31,748	1996-2006	ICD-9	Major depressive disorder	9
Ifteni et al[73]	Romania	7,189	-	1989-2011	DSM-IV	Schizophrenia, inpatients	-
Jakobsen et al[74]	Denmark	74,759	338,747	1977-2000	ICD-8,10	Schizophrenia or major depressive disorder	2
Janszky et al[75]	Sweden	646	48,675	1969-2007	ICD-8	Major depressive disorder, 18-20 years	7
Jokinen & Nordstrom[76]	Sweden	346	-	1980-2005	DSM-IV	Major depressive disorder or bipolar disorder	-
Joukamaa et al[77]	Finland	606	8,000	1977-1994	Medical records	Schizophrenia, mood disorder or severe mental illness	1
Kendler et al[78]	Sweden	5,647	24,727	1998-2003	ICD-10	Major depressive disorder, twins	-
Kiviniemi et al[79]	Finland	6,987	-	1998-2003	ICD-9	Schizophrenia, first onset	-
Lahti et al[80]	Finland	204	11,880	1969-2004	ICD-8,9,10	Schizophrenia	5
Lan et al[81]	Taiwan	3,681	-	2001-2006	ICD-9	Bipolar disorder	-
Laursen et al[82]	Denmark	22,294	2,411,852	1995-2007	ICD-8,10	Schizophrenia or bipolar disorder, 15-52 years	3
Laursen et al[83]	Denmark	1,454	59,256	1995-2006	ICD-8,10	Schizophrenia or bipolar disorder	4

Table 2 Longitudinal studies: characteristics of included studies and samples *(continued)*

Study	Country	No. cases	No. controls	Period of data collection	SMI definition	Inclusion criteria for cases	No. covariates
Lemogne et al[84]	France	4,336	16,621	1990-2010	ICD-9,10	Depression or severe mental illness (bipolar disorder, psychosis)	6
Li et al[85]	Taiwan	1,003	4,012	1996-2009	ICD-9	Major depressive disorder	6
Lin et al[86]	Taiwan	7,353	22,059	2000-2006	ICD-9	Schizophrenia	8
Lin et al[87]	Taiwan	2,289	16,413	1998-2003	ICD-9	Bipolar disorder	10
Lin et al[88]	Taiwan	5,001	10,002	1998-2003	ICD-9	Schizophrenia, <45 years	9
Maina et al[89]	Italy	309	-	2003-2011	DSM-IV	Bipolar disorder	-
McDermott et al[90]	USA	503	2,083	1990-2003	ICD-9	Schizophrenia or severe mental illness	9
Murray-Thomas et al[91]	UK	232,132	193,920	1997-2001	ICD-10	Schizophrenia, bipolar disorder or major depressive disorder	2
Olfson et al[92]	USA	1,138,853	-	2001-2007	ICD-10	Schizophrenia, 20-64 years	4
Osborn et al[93]	UK	38,824	-	1995-2010	Medical records	Bipolar disorder or severe mental illness, 30-90 years	-
Pratt et al[94]	USA	73	1,107	1981-1994	DSM-III	Major depressive disorder	11
Prieto et al[95]	USA	334	334	1966-1996	DSM-IV	Bipolar disorder	4
Rahman et al[96]	Sweden	6,822	29,832	1998-2002	ICD-7,8,9,10	Major depressive disorder, twin population study	7
Ramsey et al[97]	USA	129	1,339	1981-1982	DSM-III	Bipolar disorder or major depressive disorder	6
Saint Onge et al[98]	USA	548	10,821	1999-2006	ICD	Major depressive disorder	11
Scherrer et al[99]	USA	77,568	214,749	1999-2007	ICD-9	Major depressive disorder, 25-80 years	4
Schoepf & Heun[100]	UK	1,418	14,180	2000-2012	ICD-10	Schizophrenia, inpatients	-
Schoepf et al[101]	UK	621	6,210	2000-2012	ICD-10	Bipolar disorder	-
Shah et al[102]	USA	538	7,103	1988-2006	DSM-III	Major depressive disorder or bipolar disorder, 17-39 years	14
Stewart et al[103]	USA	235	-	NA	ICD-9	Major depressive disorder	-
Surtees et al[104]	UK	3,057	16,592	1996-2008	DSM-IV	Major depressive disorder, 45-80 years	11
Ting et al[105]	China	153	7,682	1996-2008	DSM-IV	Major depressive disorder with diabetes	18
Torniainen et al[106]	Sweden	21,492	214,920	2006-2015	ICD-10	Schizophrenia, 17-65 years	2
Tsai et al[107]	Taiwan	80,569	241,707	1999-2003	ICD-9	Schizophrenia	8
Tsan et al[108]	USA	49,173	-	2002-2009	ICD-9	Schizophrenia	-
van Marwijk et al[109]	The Netherlands	143	139	2002-2003	DSM-IV	Major depressive disorder, >55 years	-
Weeke et al[110]	Denmark	3,795	-	1950-1957; 1969-1977	ICD-8	Bipolar disorder	-
Westman et al[111]	Sweden	17,101	10,631,208	1987-2006	ICD-10	Bipolar disorder	3
Wu et al[112]	Taiwan	16,821	67,284	1999-2010	ICD-9	Bipolar disorder	9
Wu et al[113]	Taiwan	70,225	207,592	1996-2007	ICD-9	Schizophrenia or bipolar disorder	8

SMI – severe mental illness, RDC – Research Diagnostic Criteria

CI: 2.15-4.88, 3 studies) as well as with CVD-related death (HR=2.75, 95% CI: 1.32-5.73, 3 studies).

All significant results were significantly heterogeneous, except for mixed SMI and CVD risk, as well as all the congestive heart failure results. After trim and fill procedure, all results remained unchanged, and Egger test did not show any evidence of publication bias influencing the results (see Table 4 for details).

Quality assessment of included studies

Quality ratings of single studies are presented in Table 5. All studies used clear diagnostic criteria, by design. Among the 27 cross-sectional studies, all except 9 studies had a control group, 5 studies used a matched control sample, 13 studies adjusted analyses for relevant covariates, and all except 6 studies reported cardiovascular risk factors. Among the 65 longitudinal studies, all

Table 3 Meta-analysis of cross-sectional studies: unadjusted and adjusted odds ratios

	Meta-analysis of unadjusted and adjusted odds ratios								Meta-analysis of covariate adjusted odds ratios							
	No. studies	No. participants		Unadjusted and adjusted odds ratios				Heterogeneity I²	No. studies	No. participants		Adjusted odds ratios				Heterogeneity I²
Disorder		Patients	Controls	OR	95% CI		p			Patients	Controls	OR	95% CI		p	
Cardiovascular disease																
Bipolar disorder	4	19,562	1,526,110	**1.73**	**1.11**	**2.71**	**0.02**	91	4	2,640	1,423,135	1.28	0.90	1.80	0.17	52
Major depressive disorder	3	1,577	47,851	**2.08**	**1.51**	**2.88**	**<0.001**	58	7	7,050	43,570	**1.75**	**1.36**	**2.26**	**<0.001**	69
Schizophrenia	10	190,584	4,100,315	1.23	0.92	1.65	0.16	99	5	42,076	3,860,505	1.38	0.93	2.05	0.11	96
Severe mental illnesses	1	146	2,083	1.59	0.87	2.88	0.13	-	-	-	-	-	-	-	-	-
Pooled	14	211,869	7,808,603	**1.59ª**	**1.32**	**1.91**	**<0.001**	99	11	51,766	5,325,871	**1.53ᵉ**	**1.27**	**1.83**	**<0.001**	94
Coronary heart disease																
Bipolar disorder	3	19,504	1,524,771	**1.75**	**1.11**	**2.77**	**0.02**	94	1	2,582	1,421,796	0.94	0.79	1.11	0.49	-
Major depressive disorder	1	958	35,691	**2.44**	**2.13**	**2.79**	**<0.0001**	-	3	6,323	41,882	**2.52**	**1.81**	**3.52**	**<0.001**	93
Schizophrenia	8	187,359	4,086,191	1.03	0.85	1.25	0.76	98	1	399	120,044	**1.52**	**1.48**	**1.56**	**<0.001**	-
Severe mental illnesses	1	146	2,083	1.02	0.56	1.83	0.96	-	-	-	-	-	-	-	-	-
Pooled	8	207,967	4,160,030	**1.80ᵇ**	**1.62**	**2.00**	**<0.001**	98	5	9,304	1,583,722	**1.51ᶠ**	**1.47**	**1.55**	**<0.001**	90
Cerebrovascular disease																
Bipolar disorder	3	2,741	1,458,826	**1.68**	**1.07**	**2.63**	**0.03**	47	2	2,582	1,421,796	1.06	0.85	1.31	0.62	0
Major depressive disorder	3	1,577	47,851	**2.24**	**1.33**	**3.79**	**0.003**	81	2	656	349	1.64	0.96	2.78	0.07	72
Schizophrenia	5	41,071	37,77,039	**1.63**	**1.19**	**2.24**	**0.003**	96	3	32,196	2,413,768	**2.05**	**1.59**	**2.64**	**<0.001**	61
Severe mental illnesses	1	146	2,083	1.02	0.56	1.83	0.96	-	-	-	-	-	-	-	-	-
Pooled	10	45,535	5,454,785	**1.63ᶜ**	**1.31**	**2.02**	**<0.0001**	93	6	35,434	3,835,913	**1.42ᵍ**	**1.21**	**1.66**	**<0.001**	90
Congestive heart failure																
Bipolar disorder	1	2,582	1,421,796	**1.38**	**1.03**	**1.84**	**0.03**	-	1	2,582	1,421,796	1.11	0.80	1.54	0.53	0
Major depressive disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	5	40,984	3,743,431	**1.71**	**1.36**	**2.15**	**<0.001**	92	3	41,474	5,708,425	**1.60**	**1.06**	**2.40**	**0.02**	97
Severe mental illnesses	1	146	2,083	1.59	0.87	2.88	0.13	-	-	-	-	-	-	-	-	-
Pooled	6	43,712	5,167,189	**1.57ᵈ**	**1.32**	**1.87**	**<0.001**	88	4	44,056	7,130,221	1.28ʰ	0.99	1.65	0.06	96

Bold values represent significant results

Egger test for bias: ª2.24, p=0.53; ᵇ6.41, p=0.03 (Duval & Tweedie trim-and-fill procedure adjusted OR: 1.35, 95% CI: 0.98-1.83); ᶜ−1.69, p=0.24; ᵈ−2.39, p=0.15; ᵉ−1.73, p=0.18; ᶠ0.17, p=0.93; ᵍ−2.59, p=0.07; ʰ−5.26, p=0.20

Table 4 Meta-analysis of longitudinal studies with publication bias assessment

Disorder		Meta-analysis of unadjusted relative risk								Meta-analysis of covariate adjusted hazard ratio							
	No. studies	No. participants		Unadjusted relative risk				Hetero-geneity I²	No. studies	No. participants		Adjusted hazard ratio				Hetero-geneity I²
		Patients	Controls	RR	95% CI		p			Patients	Controls	HR	95% CI		p	
Cardiovascular disease																
Bipolar disorder	12	66,549	9,606,575	1.50	1.28	1.75	<0.0001	76	10	91,187	6,967,728	1.57	1.28	1.93	<0.0001	91
Major depressive disorder	13	328,431	800,718	1.29	0.92	1.81	0.14	99	18	282,621	682,045	1.72	1.48	2.00	<0.0001	67
Schizophrenia	16	361294	16,096,125	1.21	1.006	1.45	0.04	98	14	296,778	7,176,374	1.95	1.41	2.70	<0.0001	99
Severe mental illnesses	2	874022	52,709,922	2.44	1.13	5.25	0.02	74	3	798	31,724	3.24	2.15	4.88	<0.0001	0
Pooled	33	1,630,296	76,031,192	1.38[a]	1.23	1.54	<0.0001	98	31	671,384	14,335,203	1.78[g]	1.60	1.98	<0.0001	95
Coronary heart disease																
Bipolar disorder	4	25,286	9,200,196	1.95	1.20	3.17	0.007	96	4	19,129	6,789,683	1.16	0.76	1.78	0.49	87
Major depressive disorder	6	14,3671	515,187	1.15	0.71	1.85	0.57	98	9	99,028	392,210	1.63	1.33	2.00	<0.0001	80
Schizophrenia	8	169,507	15,446,625	0.93	0.81	1.08	0.33	87	5	75,860	6,348,965	1.59	1.08	2.35	0.02	95
Severe mental illnesses	1	873,898	52,693,301	1.80	1.74	1.86	<0.0001	-	-	-	-	-	-	-	-	-
Pooled	17	1,212,362	75,235,865	1.75[b]	1.69	1.80	<0.0001	99	18	194,017	13,530,858	1.54[h]	1.30	1.82	<0.0001	92
Cerebrovascular disease																
Bipolar disorder	6	32,898	9,082,511	1.92	1.13	3.26	0.02	97	4	23,831	6,649,375	1.60	0.99	2.57	0.05	85
Major depressive disorder	4	8,121	41,665	1.55	1.02	2.35	0.04	77	3	7,046	38,853	2.04	1.05	3.96	0.04	74
Schizophrenia	8	243,254	15,475,608	1.48	1.21	1.81	<0.0001	96	5	157,964	6,425,336	1.57	1.09	2.25	0.02	95
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	17	284,273	22,187,932	1.53[c]	1.29	1.82	<0.0001	96	11	188,841	13,113,564	1.64[i]	1.26	2.14	<0.0001	90

Table 4 Meta-analysis of longitudinal studies with publication bias assessment (*continued*)

Disorder	Meta-analysis of unadjusted relative risk								Meta-analysis of covariate adjusted hazard ratio							
	No. studies	No. participants		RR	95% CI		p	Heterogeneity I^2	No. studies	No. participants		HR	95% CI		p	Heterogeneity I^2
		Patients	Controls							Patients	Controls					
Congestive heart failure																
Bipolar disorder	1	6,215	2,411,852	11.52	9.37	23.14	<0.0001	-	1	58	1,339	2.27	1.49	3.45	<0.0001	0
Major depressive disorder	-	-	-	-	-	-	-	-	2	351	40,339	2.02	1.48	2.75	<0.0001	0
Schizophrenia	3	85,290	9,050,272	1.80	1.15	2.79	0.009	84	-	-	-	-	-	-	-	-
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	4	91,505	11,459,059	8.24[d]	6.84	9.94	<0.0001	99	2	409	41,678	2.10	1.64	2.70	<0.0001	0
Peripheral vascular disease																
Bipolar disorder	1	6,215	2,411,852	3.44	2.70	4.38	<0.0001	-	-	-	-	-	-	-	-	-
Major depressive disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	3	85,290	9,050,272	0.96	0.43	2.17	0.92	93	-	-	-	-	-	-	-	-
Severe mental illnesses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pooled	3	91,505	11,402,868	3.11[e]	2.46	3.91	<0.0001	98	-	-	-	-	-	-	-	-
Death due to cardiovascular disease																
Bipolar disorder	5	37,144	356,298	1.31	0.94	1.83	0.11	75	3	17,420	162,231	1.65	1.10	2.47	0.02	88
Major depressive disorder	5	18,112	283,746	1.30	0.59	2.86	0.51	99	7	183,297	282,014	1.63	1.25	2.13	<0.0001	81
Schizophrenia	9	53,779	7,179,454	1.26	0.84	1.90	0.27	96	9	152,690	6,872,808	2.45	1.64	3.65	<0.0001	96
Severe mental illnesses	3	874,146	52,714,134	2.99	2.84	3.13	<0.0001	0	3	798	31,724	2.75	1.32	5.73	0.007	75
Pooled	18	1,151,181	60,287,400	2.89[f]	2.75	3.03	<0.0001	99	16	353,407	7,317,053	1.85[i]	1.53	2.24	<0.0001	95

Egger test for bias: [a] −0.44, p=0.80; [b] −1.24, p=0.71; [c] 0.03, p=0.96; [d] 8.07, p=0.37; [e] 3.08, p=0.60; [f] −3.66, p=0.20; [g] 1.16, p=0.31; [h] −0.13, p=0.92; [i] 2.57, p=0.07; [j] −1.19, p=0.43

Table 5 Quality assessment of included studies

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Cross-sectional studies						
Beyer et al[22]	Y	N	N	N	Y	N
Bresee et al[23]	Y	Y	N	Y	Y	N
Bresee et al[24]	Y	Y	N	Y	Y	N
Chen et al[25]	Y	N	N	N	Y	N
Curkendall et al[26]	Y	Y	Y	Y	Y	N
Devantier et al[27]	Y	Y	Y	N	Y	N
Hagg et al[28]	Y	N	N	N	Y	N
Herbst et al[29]	Y	Y	N	Y	N	N
Huang et al[30]	Y	Y	N	Y	Y	N
Hyde et al[31]	Y	N	N	N	Y	N
Kilbourne et al[32]	Y	N	N	N	Y	N
Kilbourne et al[33]	Y	Y	N	Y	Y	N
Lindegard[34]	Y	Y	N	N	N	N
Maina et al[35]	Y	N	N	N	Y	N
Morden et al[36]	Y	Y	Y	Y	Y	N
Munoli et al[37]	Y	N	N	N	Y	N
Nielsen et al[38]	Y	N	N	N	Y	N
Niranjan et al[39]	Y	Y	N	Y	Y	N
Oreski et al[40]	Y	Y	N	N	Y	N
Prieto et al[41]	Y	N	N	N	Y	N
Scherrer et al[42]	Y	Y	N	N	N	N
Scott et al[43]	Y	Y	N	Y	N	N
Shen et al[44]	Y	Y	Y	Y	Y	N
Smith et al[45]	Y	Y	N	Y	Y	N
Smith et al[46]	Y	Y	N	Y	Y	N
Swain et al[47]	Y	Y	N	Y	N	N
Zilkens et al[48]	Y	Y	Y	N	N	N
Longitudinal studies						
Almeida et al[49]	Y	Y	Y	N	Y	Y
Bremmer et al[50]	Y	Y	Y	N	Y	Y
Butnoriene et al[51]	Y	Y	Y	N	N	Y
Callaghan et al[52]	Y	Y	Y	Y	Y	N
Callaghan et al[53]	Y	Y	Y	Y	Y	N
Carney et al[54]	Y	Y	Y	N	Y	N
Chen et al[55]	Y	Y	Y	Y	Y	Y
Clouse et al[56]	Y	Y	Y	N	Y	Y
Coryell et al[57]	Y	Y	N	N	N	Y
Crump et al[58]	Y	Y	Y	N	N	Y
Crump et al[59]	Y	Y	Y	N	Y	Y
Davis et al[60]	Y	Y	Y	N	Y	N
Davydow et al[61]	Y	Y	Y	N	N	Y

Table 5 Quality assessment of included studies *(continued)*

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Enger et al[62]	Y	Y	Y	Y	Y	N
Fiedorowicz et al[63]	Y	Y	Y	N	Y	Y
Filik et al[64]	Y	Y	Y	N	Y	N
Fors et al[65]	Y	Y	Y	Y	N	Y
Gasse et al[66]	Y	Y	Y	N	N	Y
Goldstein et al[67]	Y	Y	Y	N	Y	N
Healy et al[68]	Y	Y	N	N	N	Y
Hendrie et al[69]	Y	Y	Y	N	Y	Y
Hou et al[70]	Y	Y	N	N	N	Y
Hsieh et al[71]	Y	Y	N	N	N	N
Huang et al[72]	Y	Y	Y	Y	Y	Y
Ifteni et al[73]	Y	Y	N	N	N	Y
Jakobsen et al[74]	Y	Y	Y	Y	N	Y
Janszky et al[75]	Y	Y	Y	N	Y	Y
Jokinen & Nordstrom et al[76]	Y	Y	N	N	N	Y
Joukamaa et al[77]	Y	Y	Y	N	N	Y
Kendler et al[78]	Y	Y	Y	N	N	Y
Kiviniemi et al[79]	Y	Y	N	N	N	Y
Lahti et al[80]	Y	Y	Y	N	Y	Y
Lan et al[81]	Y	Y	N	N	Y	Y
Laursen et al[82]	Y	Y	Y	N	N	Y
Laursen et al[83]	Y	Y	Y	N	N	Y
Lemogne et al[84]	Y	Y	Y	N	Y	Y
Li et al[85]	Y	Y	Y	Y	Y	Y
Lin et al[86]	Y	Y	Y	Y	Y	Y
Lin et al[87]	Y	Y	Y	Y	Y	Y
Lin et al[88]	Y	Y	Y	Y	Y	Y
Maina et al[89]	Y	Y	N	N	N	Y
McDermott et al[90]	Y	Y	Y	N	N	Y
Murray-Thomas et al[91]	Y	Y	Y	N	N	N
Olfson et al[92]	Y	Y	N	N	N	Y
Osborn et al[93]	Y	Y	Y	N	Y	Y
Pratt et al[94]	Y	Y	Y	N	Y	Y
Prieto et al[95]	Y	Y	Y	Y	Y	Y
Rahman et al[96]	Y	Y	Y	Y	Y	N
Ramsey et al[97]	Y	Y	Y	N	Y	Y
Saint Onge et al[98]	Y	Y	Y	N	Y	Y
Scherrer et al[99]	Y	Y	Y	N	Y	Y
Schoepf & Heun[100]	Y	Y	Y	Y	N	Y
Schoepf et al[101]	Y	Y	Y	Y	Y	Y
Shah et al[102]	Y	Y	Y	N	Y	Y
Stewart et al[103]	Y	Y	N	N	N	Y
Surtees et al[104]	Y	Y	Y	N	N	Y

Table 5 Quality assessment of included studies *(continued)*

Study	Clear diagnostic criteria	Control group	Matched controls	Coavariate adjusted analyses	Reported cardiovascular risk factors at baseline	Follow-up at least 5 years
Ting et al[105]	Y	Y	Y	N	Y	Y
Torniainen et al[106]	Y	Y	Y	Y	N	Y
Tsai et al[107]	Y	Y	Y	Y	Y	Y
Tsan et al[108]	Y	Y	N	N	Y	Y
van Marwijk et al[109]	Y	Y	Y	Y	Y	N
Weeke et al[110]	Y	Y	N	N	N	N
Westman et al[111]	Y	Y	Y	N	N	Y
Wu et al[112]	Y	Y	Y	Y	Y	Y
Wu et al[113]	Y	Y	Y	N	Y	Y

N – no, Y – yes

Table 6 Prevalence and incidence of cardiovascular disease (CVD) in severe mental illness stratified by region

Regional strata	Analysis details	Prevalence of CVD	Incidence of CVD	Risk ratios for incident CVD	Adjusted hazard ratios for incident CVD
Asia	Pooled estimate, % (95% CI)	5.4 (4.3-6.7)	2.6 (1.9-3.6)	1.63 (1.31-2.04)	1.75 (1.38-2.22)
	p value	<0.0001	<0.0001	<0.0001	<0.0001
	Heterogeneity, I^2 (p value)	98 (<0.0001)	100 (<0.0001)	99 (<0.0001)	96 (<0.0001)
	No. comparisons	8	12	9	10
Europe	Pooled estimate, % (95% CI)	9.7 (6.5-14.2)	3.4 (2.2-5.3)	1.17 (0.96-1.42)	1.88 (1.44-2.46)
	p value	<0.0001	<0.0001	0.11	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	97 (<0.0001)	96 (<0.0001)
	No. comparisons	9	35	20	22
North America	Pooled estimate, % (95% CI)	14.6 (12.0-17.7)	4.6 (3.4-6.2)	1.39 (0.91-2.12)	1.88 (1.62-2.19)
	p value	<0.0001	<0.0001	0.13	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	97 (<0.0001)	62 (0.003)
	No. comparisons	17	15	11	11
Oceania	Pooled estimate, % (95% CI)	20.6 (10.9-35.4)	26.3 (24.1-28.6)	1.52 (1.40-1.66)	1.58 (1.41-1.78)
	p value	<0.0001	<0.0001	<0.0001	<0.0001
	Heterogeneity, I^2 (p value)	97 (<0.0001)	100 (<0.0001)	0 (0.72)	0 (0.84)
	No. comparisons	4	3	3	3
	p (difference between regions)	<0.0001	<0.0001	0.08	0.29

had a control group, which was matched in all but 12 studies, only 19 studies adjusted for covariates, 38 studies reported on cardiovascular risk factors, and all except 12 studies had a follow-up of at least 5 years.

Regional CVD prevalence, incidence and longitudinal risk

Raw CVD prevalence and incidence rates consistently increased from Asia, through Europe and North America, to Oceania (Asia: 5.4% and 2.6%; Europe: 9.7% and 3.4%; North America: 14.6% and 4.6%; Oceania: 20.6% and 26.3%; p<0.0001 for both prevalence and incidence). However, when comparing CVD risk in SMI patients in each region with their respective control groups, there was no statistically significant difference anymore across regions, with both RRs and adjusted HRs showing comparably increased CVD incidence risk in the SMI population (RRs ranging from 1.17 in Europe to 1.63 in Asia, p=0.08; and HRs ranging from 1.58 in Oceania to 1.88 in both Europe and North America, p=0.29) (Table 6). There were insufficient numbers of studies to perform this analysis for adjusted ORs

regarding prevalence rates across regions, or for adjusted ORs, RRs or HRs pertaining to specific CVD subgroups.

Meta-regression

Due to heterogeneous or partial reporting of possible moderator variables in the included studies, all meta-regression analyses were based on a much reduced number of studies. Hence, all analyses were less powered in comparison with the large sets of data used for cross-sectional prevalence and longitudinal incidence analyses. Nonetheless, CVD incidence increased significantly with a higher percentage of patients using antipsychotics (12 studies; β=0.04, 95% CI: 0.01-0.08, p=0.008), higher baseline body mass index in patients vs. controls (6 studies; β=0.24, 95% CI: 0.06-0.42, p=0.008), and higher CVD prevalence at baseline in patients vs. controls (7 studies; β=0.07, 95% CI: 0.01-0.14, p=0.03). CVD prevalence increased in more recent studies (38 studies; β=0.07, 95% CI: 0.02-0.12, p=0.007), whereas the same was not true for CVD incidence (65 studies; β=−0.02, 95% CI=−0.07 to 0.01, p=0.21).

DISCUSSION

To our knowledge, this is the first large scale meta-analysis providing comprehensive quantitative data on the prevalence and incidence of CVD in people with SMI, including both pooled data and comparisons across CVD and SMI diagnostic subgroups. Our results establish that approximately 10% of people with SMI with a mean age of 50 years have at least one comorbid CVD. Moreover, our longitudinal analysis documents a 3.6% incidence rate of CVD during a median of 8.4 years of follow-up. Patients with SMI show a 53% higher risk for having CVD, a 78% higher risk for developing CVD, and an 85% higher risk of death from CVD compared to the regionally matched general population.

This study provides a worldwide epidemiologic representation of CVD prevalence and incidence rates in SMI, reporting the lowest absolute prevalence and incidence in Asia, increasing through Europe and North America, and reaching the highest levels in Oceania. However, in analyses with sufficient numbers of available studies, neither RRs nor adjusted HRs indicated significantly different CVD incidence risk across regions, meaning that SMI patients are at an increased risk across the world and that CVD risk-reducing interventions in SMI are needed with the same urgency across all regions of the world. Moreover, while the prevalence and incidence of each CVD in people with SMI show some minor variations, people with major depressive disorder, bipolar disorder and schizophrenia are clearly all at an increased risk of CVD-related deaths compared to population-stratified controls, calling for urgent action.

We were able to identify some important and actionable moderators of increased CVD risk, including antipsychotic use, elevated body mass index and elevated baseline CVD. Based on these results, it is imperative that clinicians: a) only utilize antipsychotics, particularly for non-psychotic conditions, when alternative treatment options with lower CVD risk potential have been tried sufficiently; and b) screen for and manage emerging and existing CVDs as well as their risk factors, including weight gain and elevated body mass index. Our data, adding to research demonstrating a significantly higher prevalence of metabolic syndrome in people with SMI compared to controls[114], clearly suggest there is an urgent need to prevent and manage CVD risk in this population.

Our results demonstrating a higher CVD prevalence in SMI populations versus controls in more recent studies are also concerning, as they support accumulating data indicating that secondary prevention has been much less successful in the SMI population that in the general population, leading to a widening of the mortality gap in recent years[49,115,116]. Our findings confirm prior reports that antipsychotic medication use is associated with higher CVD risk[13,117,118]. However, due to limitations in the published data, we were unable to explore variations in CVD risk profiles between different antipsychotic medications[13,117-120]. Previous research has suggested that the highest cardio-metabolic risks are associated with clozapine and olanzapine, whilst the lowest risk is with aripiprazole, ziprasidone, lurasidone, amisulpride and high potency typical antipsychotics[13,117-122]. However, in this context it is also important to note that antipsychotic medications can decrease CVD-related mortality, as reported for example in Finnish[79] and Swedish[123] national database studies, that are highly generalizable. These data underscore that symptom control and functional improvement benefit both psychiatric and overall health, as severe psychiatric illness negatively affects lifestyle behaviors, medical care seeking and adherence to medical treatments. Thus, benefits of improved psychiatric status with antipsychotics and other psychotropic agents need to be carefully weighed against their potential for elevated cardiometabolic risk, which differs across available agents[13,117].

Since antipsychotic medication use moderates CVD risk and since antipsychotics are increasingly used as first line treatments for much more prevalent non-psychotic conditions, including bipolar disorder[124] and major depressive disorder with suboptimal response to antidepressant treatment[125], the pool of people at an increased CVD risk is greatly enlarged. Therefore, research on the underlying mechanisms for the increased CVD risk after pharmacotherapy initiation is even more urgently needed to develop more effective and targeted preventive and interventional treatments. Studies should also examine whether different clinical subtypes of depression (i.e., melancholic, psychotic, atypical or undifferentiated) and bipolar disorder (e.g., type 1 or 2, cyclothymic disorder), certain mood states (manic, depressive, mixed or euthymic), or different antipsychotics, antidepressants or mood stabilizers[13] significantly moderate CVD risk.

Furthermore, the pathophysiology underlying the association between SMI and CVD risk is complex and not well understood, clearly requiring further investigation. Emerging

evidence suggests that SMI and CVD share pathophysiological features, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, peripheral immune activation, neuro-inflammation, oxidative and nitrosative stress, as well as common genetic links and epigenetic interactions[126]. However, since these different mechanisms probably interact, research that integrates these pathways is urgently needed. Beyond mechanistic evaluations, such studies also need to investigate the general and specific effects of physical health improvements on SMI outcomes.

Future research should also investigate optimal monitoring regimens across stratified patient subgroups as well as the most effective timing and efficacy of primary, secondary and tertiary preventive interventions[120,127]. In this regard, studies should comprehensively assess relevant moderator and mediator variables of CVD risk, including type and duration of specific psychotropic medications use, physical activity (including using passive monitoring via actimetry or mobile phone technology), diet, smoking, body mass index, personal and family history of CVD, in order to identify subgroups of patients who may require different monitoring and or interventions schemes. Long-term follow-up studies are also required to accurately document the emergence of more distal physical and mental health as well as health economic outcomes in relationship to the early identification and management of CVD risk factors and manifest CVD conditions in people with SMI.

Finally, since people with SMI engage in unhealthy lifestyle and often take psychotropic medication for extensive periods, long-term follow-up studies are needed that assess whether current predictor models based on the magnitude of traditional CVD risk factor effects observed in the general population apply or need to be adjusted for the SMI population[93], in whom CVD risk factors also emerge at a far earlier age[117,128].

While this is the most comprehensive meta-analysis of CVD risk in people with SMI conducted to date, we acknowledge several limitations that are largely related to factors in the primary data. First, lifestyle behavior information (e.g., physical activity) was inadequately reported, precluding meta-analytic assessment of these important factors as moderating or mediating variables. People with SMI are less likely than the general population to engage in physical activity and have higher levels of sedentary behaviour[129], smoke more[130], consume diets that are high in saturated fats and refined sugars, while being low in fruit and vegetables[131], all factors relevant for CVD risk. Second, variables such as clinical subtypes of major depressive disorder and bipolar disorder, negative symptom severity in people with schizophrenia, and concomitant or previous use of specific antipsychotics, antidepressants and mood stabilizers were not reported or were insufficiently reported or controlled for in most available studies. Third, as expected when combining observational data[132], many of the results were moderately to highly heterogeneous. However, in accordance with the MOOSE guidelines[133], we conducted meta-regression analyses and were able to explain some of the observed heterogeneity. In addition, all of our results remained robust after adjustment for potential publication bias with the trim and fill analysis.

In conclusion, SMIs pooled together were significantly associated in cross-sectional studies with CVD, coronary heart disease, cerebrovascular disease and CVD-related death. Additionally, in longitudinal studies, each specific diagnostic SMI group was significantly associated with CVD and CVD-related death. Furthermore, schizophrenia was associated with coronary heart disease and cerebrovascular disease, while bipolar disorder was associated with congestive heart failure, and major depressive disorder was associated with coronary heart disease, cerebrovascular disease, and congestive heart failure.

Importantly, our data confirm that CVDs are associated with an increased risk of mortality in people with SMI, which to a large part explains the shortened life expectancy of people with SMI compared to the general population[2,4,5]. Furthermore, we showed geographical variations in raw CVD prevalence and incidence risk in SMI populations, but no significant regional variance in the difference in CVD risk compared to the region-specific general population. Finally, the fact that antipsychotic use, higher body mass index and baseline CVD significantly increased the risk for CVD morbidity and mortality underscores the urgent need to limit antipsychotic use to those populations truly requiring them, choosing the lowest risk antipsychotic agents first in the treatment algorithm, screening all SMI patients regularly for CVD risk factors and conditions, and addressing any identified abnormalities aggressively.

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