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**Figures: 2**

**Tables: 3**

**Supplementary tables: 7**

**Title: Disparities in screening and treatment of cardiovascular diseases in patients with mental disorders across the world**

**Subtitle: Systematic review and meta-analysis of 47 observational studies**

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**Summary 249/250**

**Objectives.** This meta-analysis aims to measure disparities in cardiovascular disease (CVD) screening/treatment in people with mental disorders, given the increased CVD incidence and mortality.

**Methods.** PRISMA/MOOSE compliant systematic search, Pubmed/PsycInfo, last search June 31st, 2020 (protocol https://osf.io/b8rvs/), with random-effect meta-analysis of observational studies comparing CVD screening/treatment in people with vs. without mental disorders. Primary outcome was Odds Ratios (ORs) for CVD screening/treatment. Sensitivity analyses on screening/treatment separately, on specific procedures, as well as country/confounding subgroup analyses, and meta-regressions were run. Publication bias and quality (Newcastle-Ottawa Scale (NOS)) were assessed.

**Results.** Forty-seven studies (n=24,400,452, 1,283,602 with mental disorders), from North America (k=26), Europe (k=16), Asia (k=4), and Australia (k=1) were meta-analyzed. Lower rates of screening/treatment in mental disorders emerged for any CVD (k=47, OR=0.773, 95%CI=0.742-0.804, p<0.001), coronary artery disease (k=34, OR=0.734, 95%CI=0.690-0.781, p<0.001), cerebrovascular disease (k=8, OR=0.810, 95%CI=0.779-0.842, p<0.001), or other mixed CVDs (k=11, OR=0.839, 95%CI=0.761-0.924, p<0.001). Significant disparities emerged for any screening, any intervention, catheterization/revascularization in coronary artery disease, intravenous thrombolysis for stroke, and treatment with any and specific medications for CVD across all mental disorders (except for CVD medications in mood disorders). Disparities were largest for schizophrenia, and differed across countries. Median quality was high (NOS=8), higher quality studies found larger disparities, and publication bias did not affect results.

**Conclusions**. People with mental disorders (schizophrenia in particular) receive less screening and lower quality treatment for CVD. It is of paramount importance to address under-prescribing of CVD medications and under-utilization of diagnostic and therapeutic procedures across all mental disorders.

**Keywords:** Mental illness; disparities; cardiovascular disease; screening; treatment; gender medicine; prevention; life expectancy, psychosis.

**Introduction**

People with mental disorders (schizophrenia spectrum disorders/bipolar disorder/depressive disorders, among others) have poorer physical health than the general population,(1,2) with a higher burden of risk factors for cardiovascular diseases (CVDs), diabetes,(3) metabolic syndrome,(4) poor nutritional habits,(5,6) more sedentary behavior(7) and smoking behavior.(1) Pharmacological treatment of mental disorders, including second-generation antipsychotics also contribute to poor metabolic status.(8) According to a large-scale meta-analysis,(9) those with mental disorders have a high CVD prevalence (9.9%) and roughly 80% increased CVD incidence in those with severe mental disorders compared with the general population. Mental disorders appear to be independent risk factors for cardiovascular disease and a variety of putative causal mechanisms may explain this(10). This independent relationship has best studied and established for depression(11) although there is compelling evidence of independent associations from prospective studies for other mental disorders on cardiovascular disease and mortality, especially for bipolar disorder and schizophrenia(9,12), and less so for the anxiety disorders(10,12).

Several medical conditions and CVDs contribute the largest absolute risk to the reduced longevity of 10-20 years amongst those with mental disorders (which is only partially due to suicide, which accounts for the largest relative mortality risk).(13–17) Beyond increased incidence, the stage at which medical comorbidities are diagnosed, the quality and timeliness of care play a role in determining disease course and outcome. For instance, while the overall incidence of cancer in people with mental disorders is similar to that of the general population, mortality from cancer in both sexes is increased,(18) with higher fatality rates for cervical/breast/overall cancer compared with the general population (100, 23, 50% increased mortality risk, respectively).(19,20) Such increased cancer fatality in mental disorders might be explained by poor cancer screening , barriers to access to treatment, or lower quality treatment. While the latter remains to be investigated, disparities in cancer screening exist. Specifically, a recent meta-analysis that included 4,717,839 subjects (501,559 of whom with mental disorders) showed that people with mental disorders are less likely to be screened for any/breast/cervical/prostate cancer (Odds Ratio (OR)=0·76/0.65/0·89/0·78, respectively – women with schizophrenia in particular).(21)

Similarly, disparities in CVD screening may also exist for people with mental disorders.(22,23) Moreover, consistent with general medical care, (24,25) the problem might go beyond CVD screening and extend to CVD treatment. Disparities in CVD screening/treatment might in part explain why people with mental disorders show an approximate 80% increased risk of CVD-related death compared with the general population.(9,26,27)

A rigorous synthesis of the available evidence is paramount to determine whether disparities of this kind exist and to assess their type and extent. However, no recent comprehensive meta-analysis, without restriction in types of CVDs or types of mental disorders, has investigated disparities in CVD screening and treatment. To the best of the authors' knowledge, the latest systematic reviews on disparities in medical prescriptions in people with mental illness vs. the general population was published by Mitchell et al., in 2012,(24) with the

last search conducted in 2010. Since then, a number of studies have been published, reporting alarming disparities in CVD screening/treatment in people with vs without mental disorders.(28) Furthermore, assessing sources of bias in observational evidence is crucial.(29) Particularly, confounding by indication, i.e., not accounting for the expected higher frequency of screening and/or treatment for CVD in groups with a higher base rate of CVD (i.e., mentally ill people) can lead to underestimation of disparities in observational evidence.(30,31) Conversely, given increased rates of undetected/untreated CVD in subjects with mental disorders, studies comparing CVD screening/treatment without restricting the selection criteria to people with underlying CVD, might also underestimate screening/treatment disparities.

Based on the above, we conducted a systematic review with meta-analysis of studies measuring disparities in CVD screening/treatment in people with vs. without mental disorders. Our hypothesis was that significant disparities exist for both suboptimal/reduced screening and treatment of CVD, both across CVD and mental disorders groups.

## Methods

*Search, inclusion criteria*

We followed an *a priori* protocol (https://osf.io/b8rvs/), following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)(32) (eTable 1, supplementary material, page 3) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (33) guidelines (eTable 2, supplementary material, page 5). We performed an electronic search from database inception and without language restriction on 7/31/2020, via Ovid, searching MEDLINE/PsycInfo (see Research in Context for specific search key). In addition to systematic database searches, reference lists of previous reviews/included studies were hand-searched.

Inclusion criteria were observational studies (real-world data), published in any language, focusing on screening, diagnosis and treatment of CVDs, in people with mental disorders, defined according to structured criteria, validated scales, or clinical records, and which reported comparative effect sizes of CVD screening and/or treatment between people with mental disorders and the general population, or raw frequencies in both groups. Whether a person was or was not hospitalized due to CVD was not considered, since this does automatically indicate quality of care.

Two authors (LP, MD) independently conducted the searches and selected eligible papers. Any disagreement was resolved by consensus, or by a third author (MS).

*Data extraction*

The following information was extracted into a pre-defined spreadsheet: author, year, country, study design, diagnostic criteria for CVDs/mental disorders, specific CVD/mental disorder, specific procedure (i.e., coronary catheterization, intravenous thrombolysis), age, sex, presence of confounding by indication (i.e., assessing treatment for CVD without restricting to people with CVD), association measures quantifying disparities in CVD screening/treatment between the two groups, raw frequencies to compute the association measure. When studies provided unadjusted and adjusted effect sizes, we considered the (most) adjusted effect size. When

studies provided association measures at different time-points, we considered the result at the longest time point. Two authors (LP, MD) independently extracted data. Any disagreement was resolved by consensus, or by a third author (MS).

*Quality assessment*

Two authors (LP, MD) independently assessed the quality of the included studies with the Newcastle-Ottawa Scale (NOS), with a score ≥7 (out of 9) indicating high quality.(34)

*Meta-analysis*

We performed a random-effect meta-analysis,(35,36) using comprehensive meta-analysis (CMA, version 2 - meta-analysis.com). We calculated the OR and 95%CI of any CVD screening/treatment in people with mental disorders versus the general population (primary outcome). When multiple outcomes were reported in one study, we considered the mean estimate to avoid double counting participants (and artificially inflating sample size). In sensitivity analyses we analyzed screening and treatment separately, across mental disorders and across specific procedures (catheterization in coronary artery disease (CAD), revascularization in CAD, intravenous thrombolysis in stroke, medications in any CVD) in mental disorders. Finally, subgroup analyses were run by country, and by presence of confounding by indication, each across mental disorders.

Heterogeneity was assessed with the $I^2$ statistics (with significant heterogeneity being indicated by $I^2 \geq 50\%$).(37) Publication bias was assessed via visual inspection of funnel plots and Egger's bias test.(38) We also calculated the fail-safe number (estimated number of studies needed to move the effect size from significant to non-significant), and trim and fill adjusted analysis(39) in case of publication bias (Egger's test p-value <0.1). Random-effect meta-regression was conducted to explore sex, age, sample size, and quality of included studies as potential moderators of the primary outcome.

**Results**

*Search results and study characteristics*

Search results and the study selection process are illustrated in Figure 1. Out of 5,074 initial hits and 25 additional records identified through manual search, we screened 5,095 studies (after removing duplicates) at the title/abstract level, selecting 116 studies for full-text assessment. We excluded 69 studies for specific reasons after full-text assessment (see eTable 3, Supplementary material, page 7), and ultimately included 47 studies.

Detailed characteristics and references of included studies are reported in eTable 4 (supplementary material, page 9). Overall, this meta-analysis reports data from 24,400,452 subjects, including 1,283,602 with mental disorders. Mean or median age was >65 years in 15 studies. Among people with mental disorders, 873,268 (68.0%) were diagnosed with mood disorders, 279,177 (21.8%) with schizophrenia-spectrum disorders, and 131,157 (10.2%) with other mental disorders (anxiety disorders, dementia, personality disorders, post-traumatic stress disorder, substance use disorders, other mixed disorders). Thirty studies (63.8%) included subjects with different disorders, 13 (27.7%) subjects with schizophrenia-spectrum disorders, and four (8.5%) people with mood disorders. Twenty-eight (59.6%) studies included subjects with CAD, including acute

myocardial infarction (AMI), 15 (31.9%) with different CVDs, and four (8.5%) with cerebrovascular disease (CBVD), including stroke.

All continents except Africa and South America were represented. Specifically, 21 studies were conducted in the USA, seven in Denmark, five in Canada, three in the United Kingdom, two in Finland, two in Israel, two in Norway, and one each in France, Taiwan, Australia, Hong-Kong, and The Netherlands. Overall, five studies were affected by confounding by indication. The quality of included studies was high (NOS score $\geq$7) in 41 out of 47 studies, with a median score of 8 (IQR =7-8) (eTable 4, Supplementary material, page 7).

*Primary outcome: screening or treatment for CVD*

Main results for the primary outcome are reported in Table 1. Patients with mental disorders had significantly lower rates of screening/treatment for any CVD (k=47, OR=0.773, 95%CI=0.742-0.805, p<0.001), CAD (k=34, OR=0.734, 95%CI=0.690-0.781, p<0.001), CBVD (k=8, OR=0.810, 95%CI=0.779-0.842, p<0.001), or mixed CVDs (k=11, OR=0.839, 95%CI=0.761-0.924, p<0.001). Disparities were confirmed for patients with mood disorders for any CVD (k=19, OR=0.842, 95%CI=0.786-0.901, p<0.001), CAD (k=13, OR=0.827, 95%CI=0.750-0.911, p<0.001) and for CBVD (k=4, OR=0.811, 95%CI=0.768-0.857, p<0.001), but not for mixed CVDs (p=0.397). Larger disparities emerged for schizophrenia-spectrum disorders, for any CVD (k=29, OR=0.615, 95%CI=0.564-0.671, p<0.001), CAD (k=21, OR=0.564, 95%CI=0.513-0.620, p<0.001), CBVD (k=5, OR=0.717, 95%CI=0.626-0.821, p<0.001), and for mixed CVDs (k=6, OR=0.764, 95%CI=0.674-0.866, p<0.001). Finally, for those with mixed mental disorders, disparities were also confirmed for any CVD (k=25, OR=0.836, 95%CI=0.787-0.887, p<0.001), CAD (k=18, OR=0.819, 95%CI=0.760-0.883, p<0.001), CBVD (k=4, OR=0.849, 95%CI=0.808-0.892, p<0.001), but not for any mixed CVDs (p=0.111).

*Screening for cardiovascular disease*

Meta-analyses on CVD screening disparities are reported in Table 2. Regarding screening for any CVD, disparities emerged for any/mood/schizophrenia-spectrum/other mental disorders (OR=0.757/0.877/0.611/0.812, all p-values<0.05). Similar results emerged for CAD, in any/mood/schizophrenia spectrum/other mental disorders (OR=0.718/0.830/0.552/0.856, all p-values<0.05). For CBVD, a significant gap in CVD screening was confirmed in any/schizophrenia spectrum disorders (OR=0.683/0.591, both p-values<0.05), while one study only was included for mood, and mixed mental disorders. For mixed CVDs, subjects with any/schizophrenia spectrum/ mixed mental disorders had lower rates of CVD screening (OR=0.786/0.775/0.730, all p-values<0.05), while no difference emerged in those with mood disorders.

*Treatment of cardiovascular disease*

Meta-analyses on CVD treatment disparities are shown in Table 3. Regarding treatment for CVD, across any/mood/schizophrenia spectrum/ mixed mental disorders, disparities emerged for any CVD (OR=0.765/0.816/0.597/0.843, all p-values<0.05), CAD (OR=0.728/0.830/0.556/0.816, all p-values<0.05),

and CBVD (OR=0.811/0.813/0.719/0.849, all p-values<0.05). For mixed CVDs, treatment was significantly less likely to be administered only for 'any mental illness' (OR=0.837, p<0.05) and schizophrenia-spectrum disorder (OR=0.683, p<0.05), but not for mood disorders, or other mental disorders.

*Specific procedures and medications for CVDs*

Disparities in specific procedures for CVDs across mental disorders are reported in Figure 2. For catheterization in CAD, disparities emerged for any/mood/schizophrenia-spectrum disorders (OR=0.736/0.771/0.505, all p-values<0.05), but not for mixed mental disorders. Similarly, in CAD, lower rates of revascularization emerged across any/mood/schizophrenia spectrum or mixed mental disorders (OR=0.763/0.818/0.559/0.806, all p-values<0.05), as well as of coronary artery bypass grafting (OR=0.694/0.682/0.504/0.798, all p-values<0.05). A significantly lower frequency of intravenous thrombolysis in stroke emerged for any/mood/schizophrenia-spectrum disorders/ mixed mental disorders (OR=0.845/0.813/0.716/0.849, all p-values<0.05). A gap in treatment with CVD-targeting medications emerged in any/schizophrenia-spectrum disorders (OR=0.840/0.701, both p-values<0.05), but not for mood/ mixed mental disorders.

Notably, there was a significant gap for antiplatelet/anticoagulant treatment in any/schizophrenia-spectrum disorders (OR=0.858/0.735, all p-values<0.05), but not in mood/mixed mental disorders. Antihypertensives were less frequently used in any/mood disorders (OR=0.797/0.649, all p-values<0.05), but not in schizophrenia-spectrum/mixed mental disorders. In any/schizophrenia spectrum/mixed mental disorders there was also lower prescribing for lipid-lowering agents (OR=0.679/0.613/0.784, all p-values<0.05) and beta-blockers (OR=0.824/0.691/0.911, all p-values<0.05) , but this was not the case in mood disorders.

*Subgroup analyses*

Subgroup analyses (supplementary material, page 19-20) showed significant differences across countries regarding disparities in screening/treatment for any CVD (largest in Taiwan/OR=0.384, 95%CI=0.289-0.510, non-significant in France/OR=1.163, 95%CI =.979-1.381, subgroup comparison p<0.001), for CAD (largest in Taiwan/OR=0.384, 95%CI 0.289-0.510, smallest in Finland/OR=0.893, 95%CI 0.868-0.919, subgroup comparison p<0.001) and for mixed CVDs (largest in United Kingdom/OR=0.289, 95%CI 0.150-0.559, absent in France/OR=1.163, 95%CI 0.979-1.381, subgroup comparison p<0.001), but not for CBVD (p=0.505).

Meta-analytic estimates from studies vulnerable to confounding by indication failed to identify disparities in screening/treatment for any CVD/CAD/CBVD/mixed CVD disorders. Subgroup differences emerged in screening/treatment for any CVD (p<0.05), and CAD (p<0.05).

*Meta-regression*

Higher study quality (beta=-0.018, standard error=0.009, p=0.046) and females percentage (beta=-0.003, standard error=0.001, p=0.004) moderated larger disparities. Age (p=0.232) and sample size (p=0.950) were not significant moderators.

*Publication bias*

In main analyses on the primary outcome, publication bias was present in one association, and among sensitivity analyses in six associations. All associations remained significant after trim and fill analysis. The median fail-safe number in main/sensitivity analysis was 364/476 (interquartile range 163-3,666/171-2,652).

**Discussion**

This systematic review/meta-analysis investigated any CVD and specific CVD screening and treatment procedures disparities in over 1.25 million people with vs. over 23 million people without mental disorders from four continents. Results indicate that people with mental disorders suffer from significantly lower screening/treatment of any CVD/CAD/CBVD/other CVD, including heart failure, and that these disadvantages extend across different mental disorders, being highest in people with schizophrenia-spectrum disorders.

These findings extend previous narrative reviews and confirm the hypothesis that people with mental disorders undergo less screening/treatment procedures for CVDs than the general population, although people with mental illness have a greater likelihood of having and dying from CVDs.(40,41) The results are consistent with previous work from Mitchell and colleagues, who showed that people treated with antipsychotics receive lower metabolic screening than mandated by guidelines(42) and that people with mental disorders receive lower metabolic quality of care for CVD in general,(43) less frequent revascularization in coronary artery disease,(26) and fewer prescriptions of medications for physical disorders.(24) However, our data expand the findings of that previous systematic review, by including any mental disorder, any screening and treatment procedures, and for any CVD, in one quantitative evidence synthesis and by having a more than tenfold larger sample size. These results show that disparities in physical healthcare of people with mental disorders clearly and concerningly extend beyond cancer screening,(21) diabetes care (44,45) and treatment of metabolic syndrome. (46–48)

There are many possible reasons for these disparities in CVD management of people with mental disorders. First, mental health professionals reportedly undertake physical examinations in less than 50% of people with mental disorders.(49) Second, mental health professionals often do not feel confident in prescribing physical health medications, and leave the task to physicians in primary care, internal medicine or specific medical specialties.(24) Third, family doctors spend less time with persons with mental disorders than with other patients,(43,50) because they have to deal with frequently overly busy schedules and the competing demands of other patients.(51,52) Similarly, low mental health literacy in non-mental health professionals may results in stigma and barrier in offering treatment.(53)Indeed, overshadowing of mental disorders limiting healthcare

for physical disorders frequently occurs. Fourth, symptoms and impairment in (social) functioning and in cognition, reduced illness insight, non-adherence, as well as financial and/or insurance problems may compromise healthcare access and utilization, especially when people with mental illness live in poverty or have no fixed address.(21) In this context, social withdrawal, avoidance behaviour, depressed mood, among other symptoms could contribute to the patient's loss of interest in self-care, including medical care. (21) Core symptomatology could be a determining factor in schizophrenia, as patients with schizophrenia reportedly have fewer medical visits and fewer documented medical problems compared with people with depression.(54) This factor could explain the fact that disparities in CVD screening/treatment are largest in schizophrenia. Ultimately patients with schizophrenia frequently also do not accept proposed treatments, after AMI for instance.(55) Fifth, physicians may disregard physical complaints by mentally ill patients, due to diagnostic overshadowing (the assumption that the complaint results from the mental condition).(56,57) Sixth, physical and mental healthcare providers often deliver care in silos, limiting comprehensive care for both physical and mental illness. (58) Seventh, people with mental disorders tend to receive CVD care too late, when the disease is already well-established, rather than receiving preventive care when risk factors, such as diabetes and hypertension, first appear. This problem has been shown in comparison with the general private insurance companies Medicaid and Medicare managed care populations in the US,(58) and people with mental illness are less likely to receive blood glucose or lipid test, hospital care, or medications for diabetes.(59)

Importantly, the present results suggest that disparities in CVD status between people with vs without mental disorders are actually larger than previously reported.(9) If those with mental disorders are infrequently screened for CVD, many may die without their CVD ever being diagnosed or treated. Such a hypothesis is supported by evidence from a study reporting on 72,451 subjects dying from CVD, showing that study participants with schizophrenia and female participants with BD were 66% and 38% less likely to be diagnosed of CVD before their CVD-related death.(60) Conversely, timely pharmacological treatment of CVDs could substantially reduce the high/premature mortality rates typically observed in people with mental disorders.(61) Specific interventions should be tested in future RCTs. A possible approach to avoid delaying CVD diagnosis and treatment, could be to routinely offer a CVD risk assessment to those accessing mental health services, and to establish a close, efficient collaboration with cardiology services where patients with elevated CVD risk can be referred.(62) Mental health professionals could then follow-up with patients regarding cardiologists' prescription, to promote compliance. The effectiveness and cost-effectiveness of this pathway could be tested in cluster RCTs, with centres randomly assigned to either CVD screening plus dedicated cardiologist referral (experimental arm) or treatment as usual (control arm). Experimental arm should be tailored to specific healthcare organizations across different countries, also in light of different magnitude of disparities across countries. Indeed, any rehabilitative treatment should aim to promote autonomy and recovery, ultimately leading patients with mental disorders to autonomously use health services as the general population does. However, real-world evidence included in this work just shows this autonomy remains to be achieved, and that

currently specific adjustments to facilitate CVD screening and treatment are needed, to contrast both lack of prescription of and compliance with CVD screening and care in those with mental disorders.

Importantly, the need for improving screening and treatment for physical conditions in those with mental disorders extend to a more intense acute setting healthcare services utilization (hospitalization, emergency department) for physical health,(63) suggesting disparities in screening and treatment of physical disorders might go beyond CVD, despite effective options are available.(64)Finally, our findings are also important from a methodological standpoint. The result clearly show that studies biased by confounding by indications either underestimate the gap in CVD screening/treatment due to undetected CVDs in people with mental illness and/or overestimate screening/treatment due to higher frequencies of CVDs in people with mental illness vs the general population, failing to find existing disparities in CVD screening/treatment for people with mental disorders. Additionally, studies with relatively lower quality reported relatively smaller disparities.

This work has several strengths. It is the largest and most comprehensive evidence synthesis on CVD screening/treatment disparities in people with mental disorders. It includes high-quality observational studies. It sheds light on mechanisms underlying poor CVD status, with considerable clinical and service organization implications. It supports the research and evidence-synthesis recommendations from The Lancet Commission: a blueprint for protecting physical health in people with mental illness.(40)

However, the present work is also not without limitations. First, virtually all analyses showed high heterogeneity. However, we identified moderators, which could be responsible for heterogeneous estimates, such as country, confounding by indication, and study quality. Second, observational studies are affected by several types of bias, which even high-quality meta-analytic methodology can only partially address.(29) Finally, scant evidence was available from low- and middle-income countries.

**Conclusions**

People with mental disorders receive CVD screening and/or treatment procedures significantly less frequently than the general population. Such disparities are not confined to a particular mental disorder, although they are most pronounced for those with schizophrenia-spectrum disorders. Such gaps in screening and treatment for CVDs may contribute to increased mortality and lower life expectancy in men and women with mental disorders. With nearly a two-fold elevation in risk for cardiovascular mortality, this situation represents a dramatic but modifiable health disparity. Targeted efforts to address this public health disparity are urgent. Given the persistent mortality gap, seen over several decades affecting people with mental disorders compared with the general population, which is largely attributed to CVDs, a collaborative model of care, involving preventive screening and collaboration among primary care clinicians, medical specialists and mental health care providers/prescribers should be tested and implemented widely after efficacy is demonstrated.

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**Authors' contributions**

MS, CUC, LS, JIS, JF, AFC, PFP and BS ideated or drafted the protocol of the study. MS, LP, MD, MA, AH, IH conducted the screening and data extraction. MS, CUC run the analyses. MS, AFC, PFP, JF, SC, DJC, MSe, CUC, HL drafted the manuscript circulated among all co-authors. All authors read, modified, and approved the final version of the submitted manuscript.

**Conflict of interest statements**

MS has received honoraria from Angelini, and Lundbeck, outside of this work. PFP has received research or personal fees from Lundbeck, Angelini, Menarini, Boehringer Ingelheim, outside of this work. HL has served as a speaker for Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda outside of this work. SC declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD

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**Data sharing**

Data are available from author upon request.

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Figure 1. PRISMA flow-chart

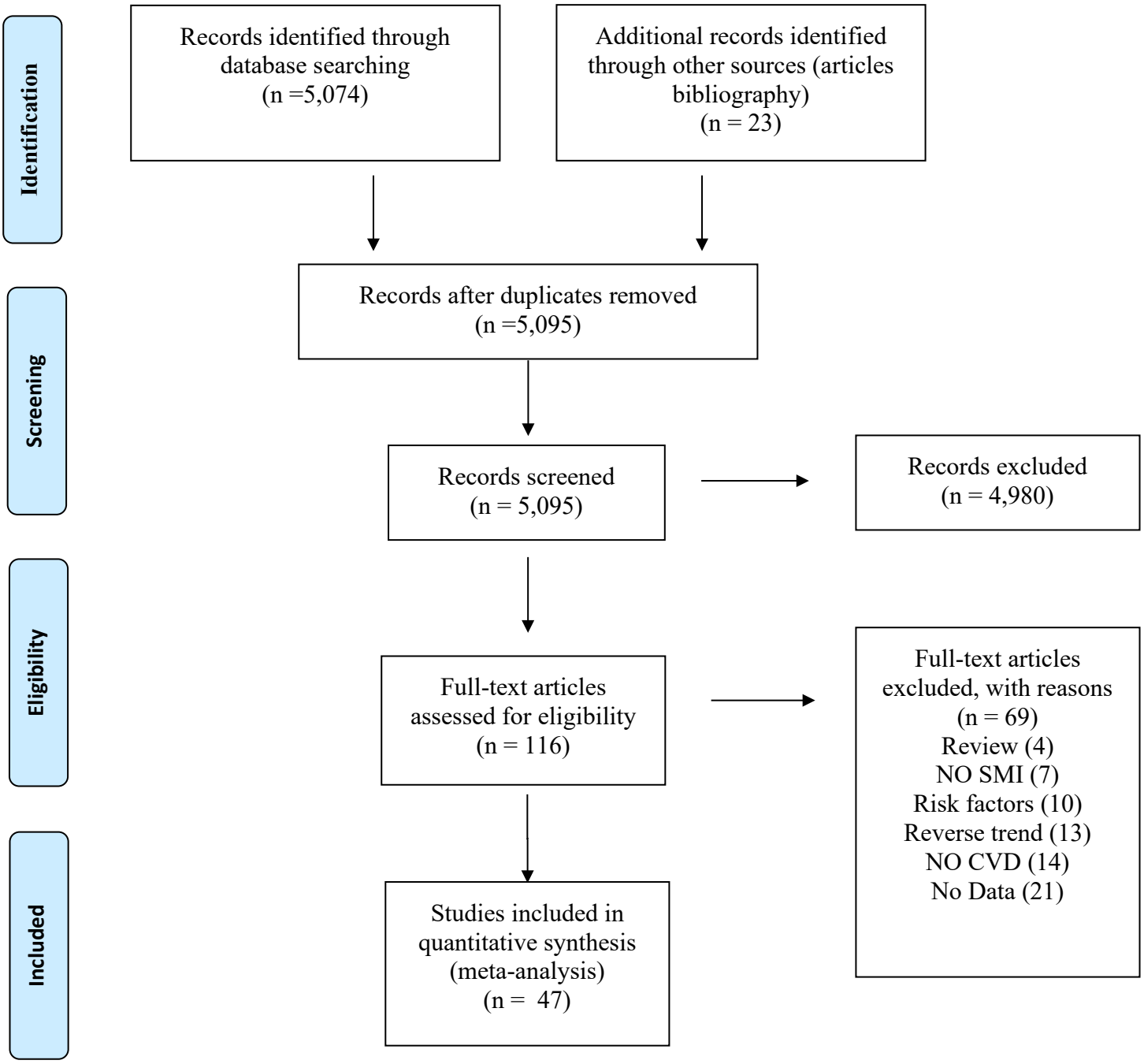

Figure 2. Lower frequency of specific screening/treatment procedures/medications for cardiovascular disease in subjects with vs without mental disorders

Legend. CABG, Coronary artery bypass grafting; CAD, coronary artery disease; CVD, cardiovascular disease; IVT, intravenous thrmobolysis; OR, odds ratio

Table 1. Disparities in any procedure for any and specific cardiovascular diseases across mental disorders.

| Mental illness | Cardiovascular disease | Procedure | Publication/diagnostic samples | OR | 95%CI | p | $I^2$ | Egger's test p value; fail safe N; effect size after trim and fill (in case of publication bias) |
|---|---|---|---|---|---|---|---|---|
| **Any cardiovascular disease (primary outcome)** | | | | | | | | |
| Any | Any | Any | 47/90 | 0.773 | 0.742-0.805 | <0.001 | 93.577 | 0.265; 8,599 |
| Mood disorders | Any | Any | 19/26 | 0.842 | 0.786-0.901 | <0.001 | 93.532 | 0.876; 1,484 |
| Schizophrenia spectrum disorder | Any | Any | 29/30 | 0.615 | 0.564-0.671 | <0.001 | 93.237 | 0.018; 7,967; 0.625, 95%CI 0.573-0.682 |
| Mixed* | Any | Any | 25/34 | 0.836 | 0.787-0.887 | <0.001 | 91.485 | 0.411; 2,714 |
| **Acute myocardial infarction, ischemic heart disease** | | | | | | | | |
| Any | CAD | Any | 34/63 | 0.733 | 0.690-0.781 | <0.001 | 94.830 | 0.122; 8,716 |
| Mood disorders | CAD | Any | 13/15 | 0.827 | 0.750-0.911 | <0.001 | 90.884 | 0.457; 339 |
| Schizophrenia spectrum disorder | CAD | Any | 21/21 | 0.564 | 0.513-0.620 | <0.001 | 84.590 | 0.212; 4,617 |
| Mixed* | CAD | Any | 18/26 | 0.819 | 0.760-0.883 | <0.001 | 92.314 | 0.524; 1,750 |
| **Cerebrovascular disease, stroke, transient ischemic attack** | | | | | | | | |
| Any | CBVD | Any | 8/19 | 0.810 | 0.779-0.842 | <0.001 | 70.617 | 0.625; 1,045 |
| Mood disorders | CBVD | Any | 4/6 | 0.811 | 0.768-0.857 | <0.001 | 57.463 | 0.341; 364 |
| Schizophrenia spectrum disorder | CBVD | Any | 5/5 | 0.717 | 0.626-0.821 | <0.001 | 45.877 | 0.141; 151 |
| Mixed* | CBVD | Any | 4/8 | 0.849 | 0.808-0.892 | <0.001 | 29.354 | 0.936; 54 |
| **Mixed cardiovascular disease** | | | | | | | | |
| Any | Mixed | Any | 11/16 | 0.839 | 0.761-0.924 | <0.001 | 83.160 | 0.742; 234 |
| Mood disorders | Mixed | Any | 4/4 | 0.933 | 0.794-1.096 | 0.397 | 33.299 | NP |
| Schizophrenia spectrum disorder | Mixed | Any | 6/6 | 0.764 | 0.674-0.866 | <0.001 | 68.076 | 0.348; 151 |
| Mixed* | Mixed | Any | 6/6 | 0.869 | 0.731-1.033 | 0.111 | 85.198 | 0.231; 13 |

Legend. CAD, coronary artery disease; CBVD, cerebrovascular disease; CI, confidence interval; NP, not pertinent; OR, odds ratio; *, mixed disorders, included anxiety disorders, post-traumatic stress disorder, substance related disorders, other disorders.

Table 2. Disparities in screening for any and specific cardiovascular diseases across mental disorders.

| Mental illness | Cardiovascular disease | Procedure | Publication/samples | OR | 95%CI | p | $I^2$ | Egger's test p value; fail safe N; effect size after trim and fill (in case of publication bias) |
|---|---|---|---|---|---|---|---|---|
| **Any cardiovascular disease** | | | | | | | | |
| Any | Any | Screening | 23/38 | 0.757 | 0.719-0.797 | <0.001 | 92.900 | 0.43; 5,391; 0.813, 95%CI 0.769-0.859 |
| Mood disorders | Any | Screening | 8/9 | 0.877 | 0.792-0.973 | 0.013 | 84.358 | 0.80; 241 |
| Schizophrenia spectrum disorder | Any | Screening | 15/16 | 0.611 | 0.554-0.673 | <0.001 | 91.055 | 0.005; 2,709; 0.728, 95%CI 0.660-0.803 |
| Mixed* | Any | Screening | 10/13 | 0.812 | 0.733-0.899 | <0.001 | 92,982 | 0.695; 603 |
| **Acute myocardial infarction, ischemic heart disease** | | | | | | | | |
| Any | CAD | Screening | 16/29 | 0.718 | 0.670-0.770 | <0.001 | 94.461 | 0.048; 3,302; 0.800, 95%CI 0.745-0.860 |
| Mood disorders | CAD | Screening | 6/7 | 0.830 | 0.732-0.941 | <0.001 | 82.248 | 0.697; 240 |
| Schizophrenia spectrum disorder | CAD | Screening | 12/13 | 0.552 | 0.490-0.622 | <0.001 | 88.030 | 0.06; 1,861;0.673, 95%CI 0.597-0.757 |
| Mixed* | CAD | Screening | 6/9 | 0.856 | 0.748-0.980 | <0.001 | 93.625 | 0.993; 277 |
| **Cerebrovascular disease, stroke, transient ischemic attack** | | | | | | | | |
| Any | CBVD | Screening | 3/ 4 | 0.683 | 0.533-0.87 | 0.003 | 0 | 0.078; 5; unchanged |
| Mood disorders | CBVD | Screening | One study only | | | | | |
| Schizophrenia spectrum disorder | CBVD | Screening | 2/2 | 0.591 | 0.388-0.899 | <0.001 | 0 | NP |
| Mixed* | CBVD | Screening | One study only | | | | | |
| **Mixed cardiovascular disease** | | | | | | | | |
| Any | Mixed | Screening | 7/ 10 | 0.786 | 0.712-0.868 | <0.001 | 88.739 | 0.397; 326 |
| Mood disorders | Mixed | Screening | 3/ 3 | 1.011 | 0.935-1.094 | 0.784 | 0 | 0.610; NP |
| Schizophrenia spectrum disorder | Mixed | Screening | 4/ 4 | 0.775 | 0.719-0.835 | <0.001 | 46.769 | 0.017; 149; 0.797, 95%CI 0.733-0.867 |
| Mixed* | Mixed | Screening | 3/3 | 0.730 | 0.552-0.966 | <0.001 | 95.934 | 0.514; 48 |

Legend. CAD, coronary artery disease; CBVD, cerebrovascular disease; CI, confidence interval; NP, not pertinent; OR, odds ratio; *, mixed disorders, included anxiety disorders, post-traumatic stress disorder, substance related disorders, other disorders.

Table 3. Disparities in treatment of any and specific cardiovascular diseases across mental disorders.

| Mental illness | Cardiovascular disease | Procedure | Publication/samples | OR | 95%CI | p | $I^2$ | Egger's test p value; fail safe N; effect size after trim and fill (in case of publication bias) |
|---|---|---|---|---|---|---|---|---|
| **Any cardiovascular disease** | | | | | | | | |
| Any | Any | Treatment | 45/86 | 0.765 | 0.730-0.801 | <0.001 | 94.613 | 0.276; 6,062 |
| Mood disorders | Any | Treatment | 17/21 | 0.816 | 0.755-0.882 | <0.001 | 94.829 | 0.858; 1,361 |
| Schizophrenia spectrum disorder | Any | Treatment | 27/28 | 0.597 | 0.538-0.662 | <0.001 | 93.97 | 0.046; 6,723; 0.609, 95%CI 0.549-0.674 |
| Mixed* | Any | Treatment | 25/37 | 0.843 | 0.792-0.898 | <0.001 | 91.792 | 0.310; 2,483 |
| **Acute myocardial infarction, ischemic heart disease** | | | | | | | | |
| Any | CAD | Treatment | 33/61 | 0.728 | 0.681-0.778 | <0.001 | 95.661 | 0.115; 8,254 |
| Mood disorders | CAD | Treatment | 12/14 | 0.830 | 0.755-0.912 | <0.001 | 91.470 | 0.251; 255 |
| Schizophrenia spectrum disorder | CAD | Treatment | 20/21 | 0.556 | 0.489-0.633 | <0.001 | 93.470 | 0.140; 4,444 |
| Mixed* | CAD | Treatment | 18/26 | 0.816 | 0.754-0.884 | <0.001 | 92.637 | 0.511; 1,726 |
| **Cerebrovascular disease, stroke, transient ischemic attack** | | | | | | | | |
| Any | CBVD | Treatment | 7/17 | 0.811 | 0.779-0.844 | <0.001 | 74.451 | 0.511; 985 |
| Mood disorders | CBVD | Treatment | 3/5 | 0.813 | 0.766-0.863 | <0.001 | 71.612 | 0.239; 349 |
| Schizophrenia spectrum disorder | CBVD | Treatment | 4/4 | 0.719 | 0.619-0.835 | <0.001 | 56.059 | 0.266; 132 |
| Mixed* | CBVD | Treatment | 4/8 | 0.849 | 0.807-0.894 | <0.001 | 31.973 | 0.901; 54 |
| **Mixed cardiovascular disease** | | | | | | | | |
| Any | Mixed | Treatment | 9/12 | 0.837 | 0.723-0.969 | 0.017 | 84.441 | 0.113; 46 |
| Mood disorders | Mixed | Treatment | 2/2 | 0.667 | 0.447 | 0.995 | 0.047 | NP |
| Schizophrenia spectrum disorder | Mixed | Treatment | 4/4 | 0.683 | 0.492-0.947 | 0.022 | 81.197 | 0.101; 22 |
| Mixed* | Mixed | Treatment | 6/6 | 0.940 | 0.805-1.097 | 0.433 | 78.478 | 0.452; NP |

Legend. CAD, coronary artery disease; CBVD, cerebrovascular disease; CI, confidence interval; OR, odds ratio; *, mixed disorders, included anxiety disorders, post-traumatic stress disorder, substance related disorders, other disorders.