Cardiovascular disease and subsequent risk of psychiatric disorders: a nationwide sibling-controlled study

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Abstract

Background

The association between cardiovascular disease (CVD) and selected psychiatric disorders has frequently been suggested while the potential role of familial factors and comorbidities in such association has rarely been investigated.

Methods

We identified 869 056 patients newly diagnosed with CVD from 1987 to 2016 in Sweden with no history of psychiatric disorders, and 910 178 full siblings of these patients as well as 10 individually age- and sex-matched unrelated population controls (N=8 690 560). Adjusting for multiple comorbid conditions, we used flexible parametric models and Cox models to estimate the association of CVD with risk of all subsequent psychiatric disorders, comparing rates of first incident psychiatric disorder among CVD patients with rates among unaffected full siblings and population controls.

Results

The median age at diagnosis was 60 years for patients with CVD and 59.2% were male. During up to thirty years of follow-up, the crude incidence rates of psychiatric disorder were 7.1, 4.6 and 4.0 per 1000 person-years for patients with CVD, their siblings and population controls. In the sibling comparison, we observed an increased risk of psychiatric disorder during the first year after CVD diagnosis (hazard ratio [HR], 2.74; 95% confidence interval [CI], 2.62-2.87) and thereafter (1.45; 95% CI, 1.42-1.48). Increased risks were observed for all types of psychiatric disorders and among all diagnoses of CVD. We observed similar associations in the population comparison. CVD patients who developed a comorbid psychiatric disorder during the first year after diagnosis were at elevated risk of subsequent CVD death compared to patients without such comorbidity (HR 1.55; 95% CI 1.44-1.67).

Conclusions

Patients diagnosed with CVD are at an elevated risk for subsequent psychiatric disorders independent of shared familial factors and comorbid conditions. Comorbid psychiatric disorders in patients with CVD are associated with higher risk of cardiovascular mortality suggesting that surveillance and treatment of psychiatric comorbidities should be considered as an integral part of clinical management of newly diagnosed CVD patients.

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Key words: cardiovascular disease, psychiatric disorder, sibling, family design

Introduction

Being diagnosed and living with a major life-threatening disease is stressful and associated with multiple biologic processes that, when combined, may contribute to the development of psychiatric disorders. It is for instance demonstrated that a cancer diagnosis is associated with subsequent risk of psychiatric disorders[1] and self-inflicted injury,[2] which in turn might be associated with a compromised cancer survival.[3] Psychiatric comorbidities have also been reported among patients with cardiovascular disease (CVD), e.g., stroke,[4] heart failure,[5] and myocardial infarction,[6,7] with indications of elevated risk of overall mortality.[8,9] Yet, evidence on the association between CVD and subsequent development of psychiatric disorders is still limited as previous research has mainly relied on selected patient populations instead of complete follow-up of general population as well as limited control of reverse causality and important confounding factors, e.g., familial factors and comorbidities.[10–12]

We thoroughly searched the existing literature on the association between CVD and clinically confirmed psychiatric disorders or psychiatric symptoms. After excluding most studies with either cross-sectional or retrospective designs, we only found 12 prospective cohort studies investigating the risk of selected psychiatric disorders following a diagnosis of CVD (Supplementary File 1a). While these prospective studies suggest a positive association of hypertension, heart disease, and stroke with depressive symptoms[11,13–15] and stress-related disorders,[16] they were limited to elderly populations,[17,18] and used self-reported ascertainment of psychiatric outcomes.[17,18] Only few of these studies addressed incident or first diagnosed psychiatric disorders among patients with CVD, e.g., excluding patients with history of psychiatric disorders, and no study addressed the issue of familial confounding. Indeed, genetic correlation has recently been document between these two complex disease groups[19–21] as well as the importance of early life environment for the development of both CVD[22] and psychiatric disorders.[23] It is therefore unknown to what extent the reported association

between CVD and psychiatric disorder can be explained by unmeasured confounding shared within families.[19–21] Thus, a comprehensive evaluation of the association between all CVDs and risk of any incident psychiatric disorder, addressing the abovementioned shortcomings, is warranted.

With up to thirty years of follow-up and with nationwide complete information on family links in Sweden, we aimed to investigate the association between CVD diagnosed in specialist care and subsequent risk of incident psychiatric disorders while accounting for familial factors through a sibling comparison. We further aimed to estimate the potential role of psychiatric comorbidity in cardiovascular mortality among patients with CVD.

Materials and Methods

Study Design

The Swedish Patient Register contains national information on inpatient care with complete coverage since 1987 and outpatient specialized care since 2001.[25] The Swedish Multi-Generation Register includes nearly complete familial information for Swedish residents born since 1932.[26] Using personal identification numbers assigned to all Swedish residents, we identified all individuals born in Sweden after 1932 who received a first diagnosis of any CVD and attended inpatient or outpatient specialized care between 1 January 1987 and 31 December 2016 (N=986 726). Patients diagnosed with CVD before age 5 (N=6 091, probable congenital heart disease) or with a history of any psychiatric disorder before the diagnosis of CVD (N=111 579) were excluded, leaving 869 056 patients in the analysis (Supplementary File 2). Date of first CVD diagnosis was used as the index date for the exposed patients.

We constructed a sibling-controlled matched cohort to control for familial confounding according to guidelines for designing family-based studies.[24] Through the Multi-Generation

Register, we identified all full siblings of patients with CVD (58·6% of all CVD patients) who were alive and free of CVD and psychiatric disorder at the time when their affected sibling was diagnosed (N=910 178). In addition, for each patient with CVD, we randomly selected 10 age- and sex-matched individuals from the general population who were free of CVD or psychiatric disorder when the index patient was diagnosed (N=8 690 560). The date of CVD diagnosis for the index patient was used as the index date for their unaffected siblings and matched population controls.

All study participants were followed from the index date until first diagnosis of any psychiatric disorder, death, emigration, first diagnosis of CVD (for unaffected siblings and matched population controls), or the end of the study period (31 December 2016), whichever occurred first.

Ascertainment of CVD and Psychiatric Disorder

We defined CVD as any first inpatient or outpatient hospital visit with CVD as the primary diagnosis from the Swedish Patient Register. Incident psychiatric disorder was defined as any first inpatient or outpatient hospital visit with psychiatric disorder as the primary diagnosis. We used the 9th and 10th Swedish revisions of the International Classification of Diseases (ICD-9 and 10) codes to identify CVD and psychiatric disorders and their subtypes (Supplementary File 1b). In line with previous study,[27] we classified CVD as ischemic heart disease, cerebrovascular disease, emboli/thrombosis, hypertensive disease, heart failure, and arrhythmia/conduction disorder. We classified psychiatric disorders as non-affective psychotic disorders, affective psychotic disorders, alcohol or drug misuse, mood disorders excluding psychotic symptoms, anxiety and stress-related disorders, eating disorders, and personality disorders.[28]

Covariates

We extracted socioeconomic information for each participant, including educational level, individualized family income and cohabitation status, from the Longitudinal Integration Database for Health Insurance and Labor Market.[29] Missing information on socioeconomic status was categorized as unknown or missing group. A history of somatic diseases was defined as having any of the following conditions before the index date: chronic pulmonary disease, connective tissue disease, diabetes, renal diseases, liver disease, ulcer diseases, malignancies, and HIV infection/AIDS (Supplementary File 1b). We defined a family history of psychiatric disorders as a diagnosis of any psychiatric disorder among biological parents and full siblings of the study participants before the index date according to the Swedish Patient Register.

Statistical Analysis

We used flexible parametric survival models to estimate the time-varying association between CVD and subsequent risk of incident psychiatric disorders,[30] by comparing the rates of incident psychiatric disorders in CVD patients with the corresponding rates in their unaffected full siblings and matched population controls. As we observed a marked risk increase of psychiatric disorders immediately following the CVD diagnosis, we separately assessed the association within one year of CVD diagnosis and beyond one year. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were derived from stratified Cox regression models, using time since the index date as the underlying time scale. We estimated HRs for any psychiatric disorder and categories of psychiatric disorders. We performed subgroup analyses by sex, age at index date (<50, 50-60, or >60 years), age at follow-up (<60 or ≥60 years), history of somatic diseases (no or yes), and family history of psychiatric disorder (no or yes). We also performed subgroup analysis by calendar year at index date (1987-1996, 1997-2006, or 2007-2016) to check for potentially different associations over time (i.e., due to lifestyle

177 factors that changed over time, including smoking and alcohol use).[31] In the sibling
178 comparison, all Cox models were stratified by sibling sets and adjusted for sex, birth year,
179 educational level, individualized family income, cohabitation status, and history of somatic
180 diseases. In the population comparison, all Cox models were stratified by the matching
181 variables birth year and sex and adjusted for all abovementioned covariates plus family
182 history of psychiatric disorder.

183 To study the impact of additional cardiovascular comorbidity (i.e., patients with another type
184 of CVD after diagnosis of the first CVD), we analyzed the association by presence or absence
185 of cardiovascular comorbidity after the index date according to the type of first CVD. This
186 analysis was restricted to follow-up beyond one year to focus on patients who survived their
187 first CVD to be able to receive the diagnosis of another CVD. As a patient with CVD might
188 have different types of CVD, we identified all diagnoses of CVD during follow-up and
189 considered CVD comorbidity as a time-varying variable through splitting the person-time
190 according to each diagnosis.

191 Because the Swedish Patient Register includes only information related to specialist care, we
192 might have misclassified patients with a history of milder psychiatric disorders diagnosed
193 before index date attended only in primary care. To account for the reverse causality of
194 having undetected psychiatric disorders or symptoms before the incident CVD, we performed
195 a sensitivity analysis additionally excluding study participants with prescribed use of
196 psychotropic drugs before the index date (ascertained from the Swedish Prescribed Drug
197 Register including information on all prescribed medication use in Sweden since July 2005),
198 and followed the remaining participants during 2006-2016. Use of psychotropic drugs during
199 follow-up was also considered as having psychiatric disorder in this analysis.

200 To study rate of cardiovascular mortality (ascertained from the Swedish Causes of Death
201 Register) in relation to psychiatric comorbidities after CVD diagnosis, we estimated Kaplan-

Meier survival curves beyond the first year of follow-up for CVD patients with or without a diagnosis of psychiatric disorder during the first year of follow-up, separately. We estimated the survival curves by types of first diagnosed CVD as well as by types of psychiatric comorbidities. In addition to this 1-year time window, we also studied six months or two years since CVD diagnosis, to assess the robustness of these survival curves. We calculated the HRs of cardiovascular mortality for these two groups of patients using Cox model. To account for potential impact of unmeasured confounding due to lifestyle factors, we performed a sensitivity analysis excluding individuals with a history of alcoholic cirrhosis of liver (ICD-10 code K703) or chronic obstructive pulmonary disease (COPD, ICD-10 code J44), as proxies for heavy drinking or smoking.

Analyses were performed in STATA 17.0 (StataCorp LP). All tests were two sided and $P<0.05$ was considered statistically significant. The study was approved by the Ethical Vetting Board in Stockholm, Sweden (DNRs 2012/1814-31/4 and 2015/1062-32).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The median age at index date was 60 years for CVD patients and 55 years for their unaffected full siblings (Table 1). 59·2% of the CVD patients and 48·4% of their unaffected siblings were male. CVD patients were more likely to have a history of somatic diseases than their unaffected siblings and matched population controls (15·6% vs. 8·8% and 11·0%). The most common diagnoses among the CVD patients were ischemic heart diseases (24·5%), arrhythmia/conduction disorders (24·2%), and hypertensive diseases (17·3%). The majority

of the CVD patients had only one CVD diagnosis (without additional CVD comorbidities) during follow-up (69·7%).

Table 1. Characteristics of CVD patients diagnosed in Sweden between 1987 and 2016, their unaffected siblings and matched population controls.

Characteristics	Sibling comparison			Population comparison	
	CVD patients (N=509 467)	Unaffected full siblings (N=910 178)		CVD patients (N=869 056)	Matched population controls (N=8 690 560)
Median age at index date in years (IQR)	57 (48-65)	55 (46-63)		60 (51-68)	60 (51-68)
Median follow-up time in years (IQR)	8.1 (3.7-13.7)	8.1 (3.8-13.7)		7.7 (3.3-13.2)	7.1 (3.2-12.4)
Male sex	308 203 (60.5)	440 177 (48.4)		514 388 (59.2)	5 143 880 (59.2)
Educational level					
<9 years	149 555 (29.4)	261 752 (28.8)		272 960 (31.4)	2 294 482 (26.4)
9-12 years	225 548 (44.3)	413 702 (45.5)		376 917 (43.4)	3 548 338 (40.8)
>12 years	134 364 (26.4)	234 724 (25.8)		219 179 (25.2)	2 847 740 (32.8)
Yearly individualized family income level					
Top 20%	1 079 90 (21.2)	175 658 (19.3)		139 098 (16.0)	1 757 726 (20.2)
Middle	301 706 (59.2)	549 842 (60.4)		535 109 (61.6)	5 152 938 (59.3)
Lowest 20%	99 485 (19.5)	184 588 (20.3)		192 858 (22.2)	1 706 931 (19.6)
Unknown	286 (0.1)	90 (0.0)		1 991 (0.2)	72 965 (0.8)
Cohabitation status					
Non-cohabitating	223 134 (43.8)	392 256 (43.1)		373 337 (43.0)	3 744 116 (43.1)
Cohabitating	286 047 (56.2)	517 832 (56.9)		493 728 (56.8)	4 873 479 (56.1)
Missing	286 (0.1)	90 (0.0)		1 991 (0.2)	72 965 (0.8)
History of somatic disease[a]	71 273 (14.0)	79 679 (8.8)		135 473 (15.6)	955 030 (11.0)
Family history of psychiatric disorder[b]	133 094 (26.1)	251 237 (27.6)		209 957 (24.2)	2 003 161 (23.1)
Type of first onset CVD					
Ischemic heart disease	122 084 (24.0)	-		212 737 (24.5)	-
Cerebrovascular disease	71 030 (13.9)	-		126 860 (14.6)	-
Emboli and thrombosis	25 338 (5.0)	-		42 857 (4.9)	-
Hypertensive disease	89 818 (17.6)	-		150 337 (17.3)	-
Heart failure	15 726 (3.1)	-		30 469 (3.5)	-
Arrhythmia/conduction disorder	126 738 (24.9)	-		210 654 (24.2)	-
Others	58 733 (11.5)	-		95 142 (11.0)	-
Number of cardiovascular diagnoses during follow-up					
One	365 266 (71.7)	-		605 615 (69.7)	-
Two	99 921 (19.6)	-		179 472 (20.7)	-
Three or more	44 280 (8.7)	-		83 969 (9.7)	-

IQR: interquartile range. CVD: cardiovascular disease

[a] History of somatic diseases included chronic pulmonary disease, connective tissue disease, diabetes, renal diseases, liver diseases, ulcer diseases and HIV infection/AIDS that diagnosed before index date.

[b] The difference between exposed patients and unaffected full siblings was due to different number of siblings for exposed patients. The family history of psychiatric disorder was constant within each family.

During up to thirty years of follow-up, the crude incidence rates of psychiatric disorder were 7·1, 4·6 and 4·0 per 1000 person-years among CVD patients, their unaffected full siblings, and matched population controls, respectively (Supplementary File 1c). Compared with unaffected siblings, CVD patients showed an elevated risk of incident psychiatric disorder, especially immediately after diagnosis (Figure 1). The risk increase declined rapidly within the first few months after diagnosis and decreased gradually thereafter: the HR was 2·74 (95% CI 2·62 to 2·87) within first year and 1·45 (95% CI 1·42 to 1·48) beyond first year (Supplementary File 1d). The risk increment was noted in all types of psychiatric disorders within and beyond first year of follow-up (Fig 2ure and Supplementary File 1e). Overall, the observed positive association was similar in sibling and population comparisons, although the HR of non-affective psychotic disorders beyond one year of CVD diagnosis was smaller in the sibling comparison than in the population comparison. During the entire follow-up, we found similar positive associations across sex, age at index date, age at follow-up, history of somatic diseases and family history of psychiatric disorders (Supplementary File 1c). A greater risk increment was observed in recent calendar years than earlier years.

We found a higher risk of incident psychiatric disorder among all groups of CVD patients, with the most marked risk elevation observed among patients with cerebrovascular disease and heart failure (Figure 3 and Supplementary File 1f). A greater risk increment of incident psychiatric disorder was noted among CVD patients with additional cardiovascular comorbidities beyond one year of first CVD diagnosis compared with CVD patients without such comorbidities, except among those with heart failure (Figure 3 - figure supplement 1). We found a similar positive association between CVD and risk of incident psychiatric disorder, when including use of psychotropic drugs as a definition of psychiatric disorder (Supplementary File 1g).

CVD patients diagnosed with subsequent psychiatric disorder showed a lower CVD-specific survival compared with patients without such diagnosis (Figure 4, and Figure 4 – figure supplement 1). The HR of CVD death was 1·55 (95% CI 1·44 to 1·67) when comparing CVD patients with a diagnosis of psychiatric disorder to patients without such diagnosis (mortality rate, 9·2 and 7·1 per 1 000 person-years, respectively). The compromised CVD-specific survival differed by types of CVD, and was most pronounced for hypertensive disease, ischemic heart disease, and arrhythmia/conduction disorder (Figure 4 – figure supplement 2). When studying categories of psychiatric disorders, we found that the compromised survival among CVD patients was confined to those with comorbid non-affective and affective psychotic disorders, as well as alcohol or drug misuse (Figure 4 – figure supplement 3).

Discussion

Our large population-based sibling-controlled cohort study including all patients diagnosed with first-onset CVD between 1987 and 2016 in Sweden, their unaffected full siblings, as well as a set of randomly selected unaffected population controls reveals a robust association between CVD and subsequent risk of incident psychiatric disorder. We found that patients with CVD were at elevated risk of various types of psychiatric disorders, independent of confounding factors shared within families and history of somatic diseases. The risk increment was greatest during the year after CVD diagnosis, indicating an opportunity for clinical surveillance in a high-risk time window. Further, an occurrence of psychiatric comorbidity after CVD diagnosis was associated with an approximately 55% higher risk of subsequent death from cardiovascular causes. This finding further underscores the importance of surveillance and, if needed, treatment of psychiatric comorbidities among newly diagnosed CVD patients.

Comparison with other studies

Our findings are consistent with the existing literature suggesting a positive association between CVD and different types of psychiatric disorders. In previous studies, an increased risk of depression[13–15] and anxiety[11] was noted after diagnosis of stroke,[11,13–15] hypertension,[17] coronary artery disease[32] and atrial fibrillation.[33] Such risk elevations have been suggested to be persistent over time,[10,34,35] and, in parallel with our findings, associated with compromised survival.[8,36,37] However, the evidence from prospective cohort studies with a long and complete follow-up as well as with a thorough control of confounding factors and comorbid conditions has, up to this point, been limited. Our study therefore complements previous findings revealing a positive association between a broader range of CVDs and subsequent risk of incident psychiatric disorder, using a large cohort with control of various confounding factors. We found the association to be robust both in sibling and population comparisons, and after additional adjustment for various comorbidities including other additional CVDs, indicating that the association is unlikely explained by shared familial factors and various comorbidities. In addition to common psychiatric disorders, the evidence on CVD and other psychiatric disorders, e.g., eating disorder, is limited. Our study therefore provides valuable indication on this association that deserves further research attention. We showed that CVD patients with psychiatric comorbidity was associated with an increased risk of subsequent CVD death, highlighting the importance of surveillance and prevention on psychiatric comorbidities for the newly diagnosed CVD patients. The associations remained similar after excluding individuals with liver cirrhosis and COPD, as proxies for heavy alcohol consumption and smoking, suggesting that residual confounding due to unmeasured lifestyle factors might not have overly substantial impact on the results.

The association between CVD and psychiatric disorders was noted both in men and women, across all age groups and calendar periods, as well as among individuals with or without a history of somatic diseases and family history of psychiatric disorders. Previous studies have

311 indicated that major depression was more commonly recognized among individuals with
312 multimorbidity (more than one CVD diagnosis) than those with only one condition.[38] In our
313 study, about 30% of the CVD patients developed one or more cardiovascular comorbidities
314 during follow-up, and a higher risk of psychiatric disorder was indeed noted among patients
315 with multiple CVD diagnoses. A compromised survival from CVD cause was indeed
316 observed among most patients with common types of first CVD diagnosis and comorbid with
317 psychiatric disorder, in particular among patients with hypertensive disease, ischemic heart
318 disease, and arrhythmia/conduction disorder. Thus, particular clinical attention is needed for
319 CVD patients with comorbid psychiatric disorders, particularly alcohol or drug misuse or
320 psychotic disorders.

321 **Potential mechanisms**

322 The pathophysiological mechanisms linking CVD and psychiatric disorders are complex and
323 not well understood, and may vary with specific diagnoses of CVD and psychiatric disorders.
324 The highly increased risk noted immediately after CVD diagnosis may indicate a direct
325 impact of stress reaction of being diagnosed with a life-threatening disease.[39] In addition, it
326 has been proposed that biological alterations in the cardiovascular system to a severe stress
327 response may increase the risk of various psychiatric disorders.[40] For example, cardiovascular
328 risk factors including hypercoagulability, dyslipidemia, and an impaired immune response
329 have been associated with impaired psychological health.[40] Some biological changes in
330 patients with coronary heart disease (e.g., decreased heart rate variability, increased arterial
331 stiffness, and endothelial dysfunction) have been observed in patients with depressive and
332 anxiety disorders.[41–43] Chronic inflammation may induce the development of atherosclerosis
333 and arterial thrombosis, and elevation in inflammatory biomarkers (i.e., IL-6 and C-reactive
334 protein) has been reported in various psychiatric disorders including post-traumatic stress

disorder and major depression.[44–46] Other behavioral and psychosocial factors may as well interact with these pathways and need to be understood further.

Strengths and Limitations

The strengths of our study include its large sample size of the entire Swedish nation and the prospective study design with sibling comparison that significantly alleviates concerns of familial confounding from shared genetic and environmental factors between siblings. The Swedish population and health registers provide the opportunity to obtain complete follow-up as well as the prospectively and independently collected information on disease identification, minimizing the risk of selection and information biases. The large sample size of our study further enables detailed subgroup analyses by types of CVD, types of psychiatric disorders, and patient characteristics.

Some limitations need to be acknowledged. First, we identified patients with CVD and psychiatric disorder through inpatient or outpatient hospital visit. The later inclusion of outpatient records in the Swedish Patient Register may lead to underestimation of the actual numbers of patients with CVD and psychiatric disorder, especially those with relatively milder symptoms. Second, we missed individuals attending primary care only, which may underestimate the proportion of individuals with history of psychiatric disorders at cohort entry. To alleviate such concerns, we additionally considered the use of prescribed psychotropic drugs as a proxy of psychiatric disorders and found similar results. Further, patients with CVD have an established contact with health care and may therefore be more likely than others to be diagnosed with psychiatric disorder. Although such surveillance bias may to some extent explain the increased risks during the first few months after CVD diagnosis, it is unlikely that the risk elevation during the entire follow-up is attributed to such bias. Finally, although we found similar results with and without excluding individuals with a history of liver cirrhosis or COPD, as proxies for heavy drinking or smoking (Supplementary

File 1h). We did not have direct access to hazardous behaviors that could potentially modify this association, and therefore cannot exclude the possibility of residual confounding.

Conclusions

Using a large population-based sibling-controlled cohort with up to thirty years of follow-up, we found patients with CVD are at elevated risk of newly diagnosed psychiatric disorder, independent of familial background shared between siblings, history of somatic diseases, and other cardiovascular comorbidities. Our study further observes higher cardiovascular mortality among CVD patients with subsequent psychiatric comorbidities, providing evidence for increased surveillance of psychiatric comorbidity among newly diagnosed patients with CVD.

Competing interest: The authors declare that there is no conflict of interest.

Role of the Funder: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical approval: The study was approved by the Ethical Vetting Board in Stockholm, Sweden (DNRs 2012/1814-31/4 and 2015/1062-32). Informed consent to each participant was waived by Swedish law in nationwide registry data.

Data availability statement: Data analyses were performed in STATA 17.0 (StataCorp LP). STATA script used in the primary analyses has been made available as supplementary

appendix. Aggregated data used for generating figures are available in supplementary appendix. The original data used in this study are owned by the Swedish National Board of Health and Welfare and Statistics Sweden. The authors are not able to make the dataset publicly available according to the Public Access to Information and Secrecy Act in Sweden. Any researchers (including international researchers) interested in accessing the data can send request to the authorities for data application by: 1) apply for ethical approval from local ethical review board; 2) contact the Swedish National Board of Health and Welfare (https://bestalladata.socialstyrelsen.se/, email: registerservice@socialstyrelsen.se) and/or Statistics Sweden (https://www.scb.se/vara-tjanster/bestall-data-och-statistik/, email: scb@scb.se) with the ethical approval and submit a formal application for access to register data. The same contacts can be used for detailed information about how to apply for access to register data for research purposes."

Transparency declaration: UV affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figure legends

Figure 1. Time-varying hazard ratios for an incident psychiatric disorder among CVD patients, compared with their unaffected full siblings (sibling comparison) or matched population controls (population comparison), by time of follow-up (<1 year and >=1 year from CVD diagnosis)[*]

A. Sibling comparison
B. Population comparison

* CVD: cardiovascular disease. Time-varying hazard ratios and 95% confidence intervals were derived from flexible parametric survival models, allowing the effect of psychiatric disorder to vary over time. A spline with 5 df was used for the baseline rate, and 3 df was used for the time-varying effect. All models were adjusted for age at index date, sex, educational level, yearly individualized family income, cohabitation status, history of somatic diseases, as well as family history of psychiatric disorder (for population comparison).

Figure 2. Hazard ratios with 95% confidence intervals for different types of psychiatric disorder among CVD patients compared with their full siblings and matched population controls, by time of follow-up (<1 or >=1 year from CVD diagnosis)[*]

* CVD: cardiovascular disease. Cox regression models were stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison, controlling for age at index date, sex, educational level, individualized family income, cohabitation status, history of somatic diseases, and family history of psychiatric disorder (in population comparison). Time since index date was used as underlying time scale.

Figure 3. Hazard ratios with 95% confidence intervals for psychiatric disorders among different groups of CVD patients compared with their full siblings and matched population controls, by time of follow-up (<1 or >=1 year from CVD diagnosis)[*]

* CVD: cardiovascular disease. Cox regression models were stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison, controlling for age at index date, sex, education level, individualized family income, cohabitation status, history of somatic diseases, and family history of psychiatric disorder (in population comparison). Time since index date was used as underlying time scale. We identified all cardiovascular diagnoses during follow-up and considered CVD comorbidity as a time-varying variable by grouping the person-time according to each diagnosis.

Figure 3 – figure supplement 1. Crude incidence rates and hazard ratios with 95% confidence intervals (CIs) for an incident psychiatric disorder among different types of CVD patients compared with their full siblings or matched population controls, by number of CVD diagnoses during >=1 year of follow-up[a]

CVD: cardiovascular disease.
[a]Cox regression models, stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison, and controlled for educational level, individualized family income, cohabitation status, as well as sex and birth year (in sibling comparison). Time since index date was used as underlying time scale. For patients with two or more CVD diagnoses, follow up time started from diagnosis of that cardiovascular comorbidity.

Figure 4. Estimated Kaplan-Meier curves of CVD death in CVD patients with and without incident psychiatric disorder during the first year of follow-up[a]

[a] CVD: cardiovascular disease. Time since index date was used as underlying time scale. 90.4% of CVD patients (N=785 287) survived the first year of follow-up and included in this analysis.

Figure 4 – figure supplement 1. Estimated Kaplan-Meier curves of CVD death in CVD patients with and without incident psychiatric disorder during 1) six months or 2) two years of follow-up

CVD: cardiovascular disease.

[a] Time since index date was used as underlying time scale. 94.1% of CVD patients (N=817 748) survived the six months of follow-up and included in this analysis. The hazard ratio of cardiovascular death was 1.40 (95% confidence interval 1.27 to 1.54) when comparing CVD patients with psychiatric disorder to patients without such a psychiatric diagnosis (mortality rate, 8.1 and 7.0 per 1000 person-years, respectively).

[b] Time since index date was used as underlying time scale. 83.8% of CVD patients (N=728 179) survived the two years of follow-up and included in this analysis. The hazard ratio of cardiovascular death was 1.52 (95% confidence interval 1.43 to 1.62) when comparing CVD patients with psychiatric disorder to patients without such a psychiatric diagnosis (mortality rate, 9.1 and 7.4 per 1000 person-years, respectively).

Figure 4 – figure supplement 2. Estimated Kaplan-Meier curves of CVD death in CVD patients with and without incident psychiatric disorder during the first year of follow-up, according to types of first CVD diagnosis[a]

CVD: cardiovascular disease.

[a] Time since index date was used as underlying time scale. 90.4% of CVD patients (N=785 287) survived the first year of follow-up and included in this analysis.

Figure 4 – figure supplement 3. Estimated Kaplan-Meier curves of CVD death in CVD patients with and without incident psychiatric disorder during the first year of follow-up, according to types of incident psychiatric disorder[a]

CVD: cardiovascular disease.

[a] Time since index date was used as underlying time scale. 90.4% of CVD patients (N=785 287) survived the first year of follow-up and included in this analysis.

Supplementary File 1 legends

1a. Summary of prospective cohort studies addressing the association between various indications of cardiovascular disease and risk of psychiatric disorders/psychiatric symptoms.

1b. International Classification of Diseases (ICD) codes for exposure, outcome and covariates identifications.

1c. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for incident psychiatric disorder among CVD patients compared with their full siblings or matched population controls, by patient characteristics

CVD: cardiovascular disease.

[a]Cox regression models, stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison, adjusting for sex, birth year, educational level, individualized family income,

cohabitation status, history of somatic disease and family history of psychiatric disorder. Time since index date was used as underlying time scale.

1d. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for incident psychiatric disorders among CVD patients compared with their full siblings or matched population controls, by time of follow-up (<1 or >=1 year from CVD diagnosis)

CVD: cardiovascular disease.
[a]Cox regression models, stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison. Time since index date was used as underlying time scale.

1e. Crude incidence rates (IRs) of different types of psychiatric disorder among CVD patients, their full siblings, and matched population controls, by time of follow-up (<1 or >=1 year from CVD diagnosis)

CVD: cardiovascular disease.

1f. Crude incidence rates (IRs) for psychiatric disorders among different groups of CVD patients, their full siblings and matched population controls, by time of follow-up (<1 or >=1 year from CVD diagnosis)[a]

CVD: cardiovascular disease.
[a] We identified all cardiovascular diagnoses during follow-up and considered CVD comorbidity as a time-varying variable by grouping the person-time according to each diagnosis.

1g. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for psychiatric disorders among CVD patients compared with their full siblings or matched population controls, excluding CVD patients medicated with psychotropic drugs, by time of follow-up (<1 or >=1 year from CVD diagnosis)[a]

CVD: cardiovascular disease.
[a] CVD patients diagnosed during 2006-2016 were included in this analysis due to the availability of data on prescribed drug. In sibling comparison, 27.8% CVD patients and 23.5% siblings were excuded due to prior medicaiton of psychotropic drugs before index date. In population comparison, 30.6% CVD patients and 25.0% population controls were excluded due to prior medicated with psychotropic drugs before index date.
[b] Cox regression models, stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison. Time since index date was used as underlying time scale. Definition of psychiatric disorder included hospital visits as well as use of psychotropic drugs during follow-up.

1h. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for incident psychiatric disorder among CVD patients compared with their full siblings or matched population controls, restricting study period to 2001-2016 and excluding individuals with a history of alcoholic cirrhosis of liver or COPD, by time of follow-up (<1 or >=1 year from CVD diagnosis).

COPD, chronic obstructive pulmonary disease;
§ In sibling comparison, 1.14% exposed patients and 0.55% siblings were excluded due to a history of alcoholic cirrhosis or COPD before index date. In population comparison, 1.44% exposed patients and 1.01% population controls were excluded due to having a history of alcoholic cirrhosis or COPD before index date.

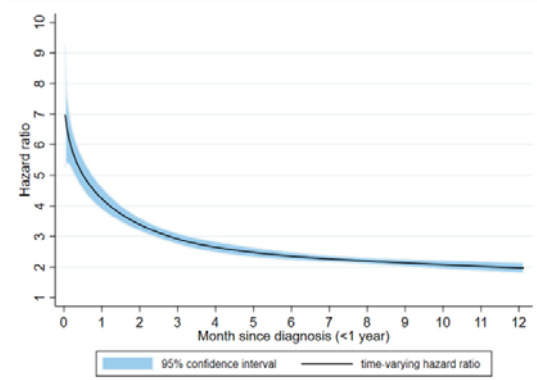
*Cox regression models, stratified by family identifier for sibling comparison or matching identifier (birth year and sex) for population comparison. Time since index date was used as underlying time scale. Definition of psychiatric disorder included hospital visits as well as use of psychotropic drugs during follow-up.

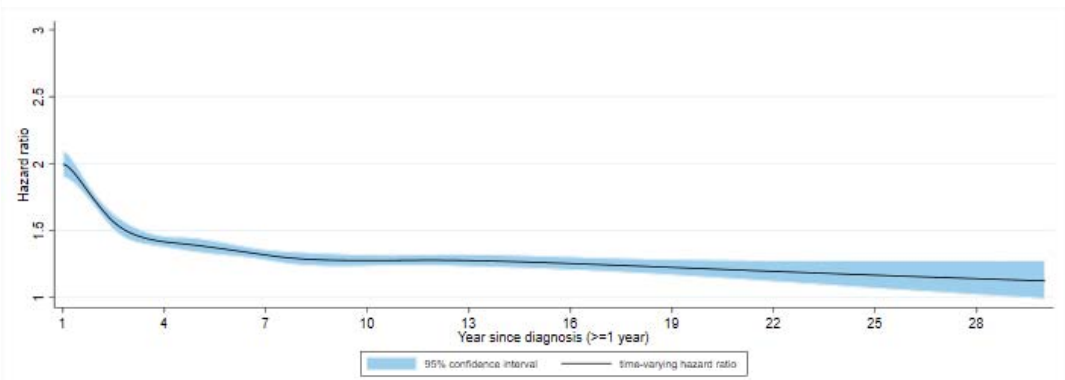
Supplementary File 2 legends

Study design

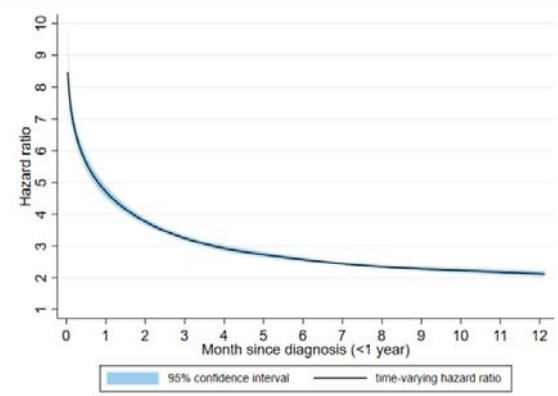
CVD: cardiovascular disease.
* 67 745 families had more than one sibling affected by CVD.

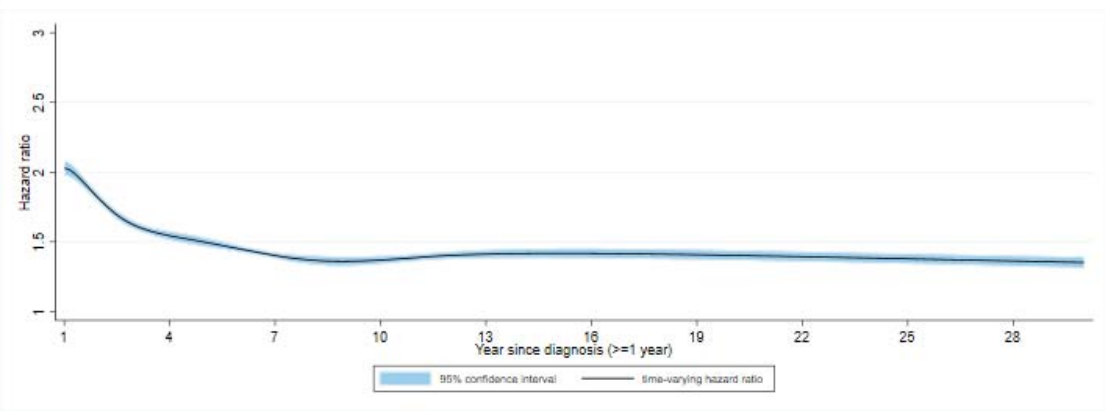
A. Sibling comparison

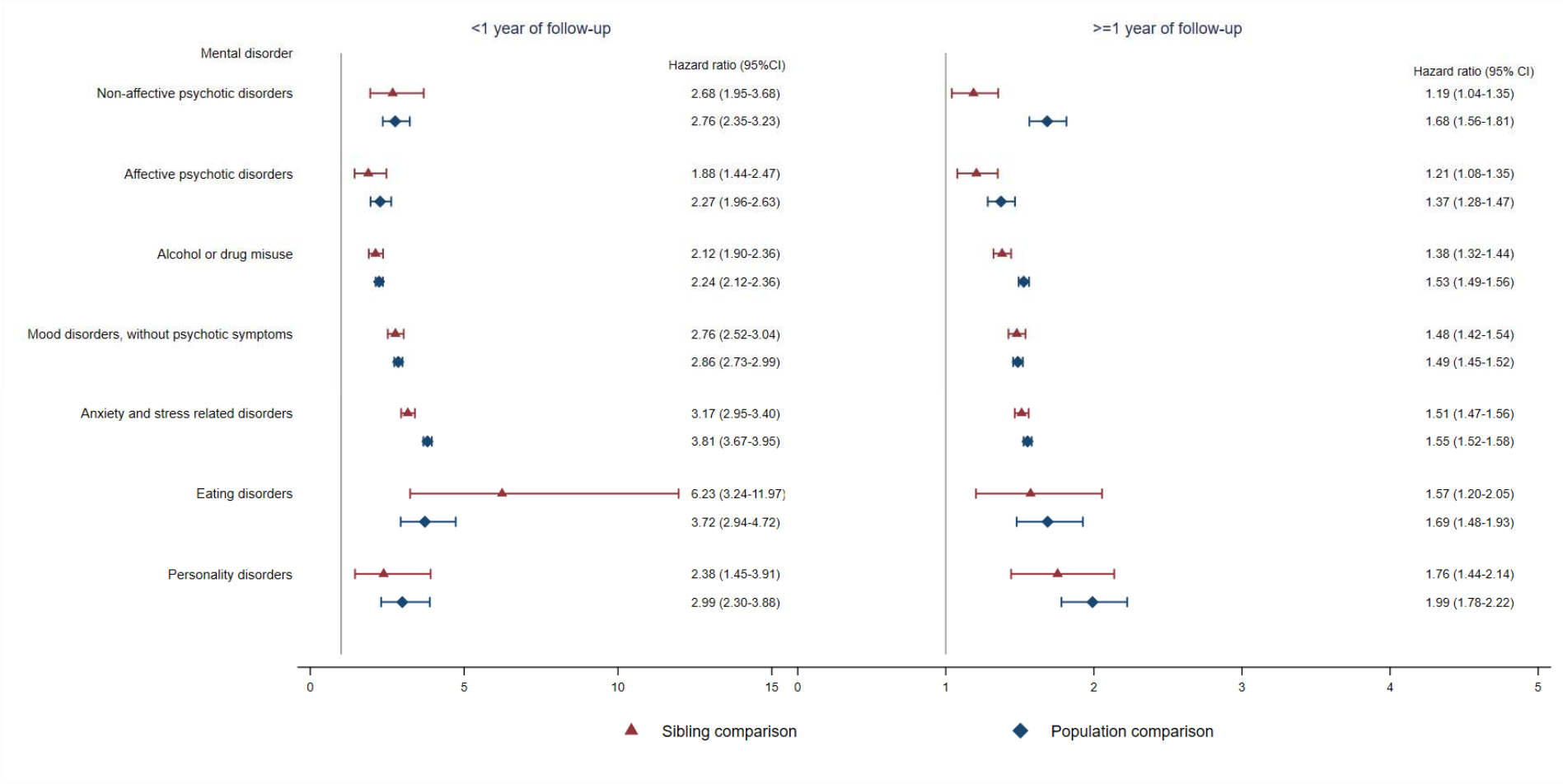




B. Population comparison






<1 year of follow-up
>=1 year of follow-up
Mental disorder
Hazard ratio (95%CI)
Hazard ratio (95% CI)
Non-affective psychotic disorders
2.68 (1.95-3.68)
1.19 (1.04-1.35)
2.76 (2.35-3.23)
1.68 (1.56-1.81)
Affective psychotic disorders
1.88 (1.44-2.47)
1.21 (1.08-1.35)
2.27 (1.96-2.63)
1.37 (1.28-1.47)
Alcohol or drug misuse
2.12 (1.90-2.36)
1.38 (1.32-1.44)
2.24 (2.12-2.36)
1.53 (1.49-1.56)
Mood disorders, without psychotic symptoms
2.76 (2.52-3.04)
1.48 (1.42-1.54)
2.86 (2.73-2.99)
1.49 (1.45-1.52)
Anxiety and stress related disorders
3.17 (2.95-3.40)
1.51 (1.47-1.56)
3.81 (3.67-3.95)
1.55 (1.52-1.58)
Eating disorders
6.23 (3.24-11.97)
1.57 (1.20-2.05)
3.72 (2.94-4.72)
1.69 (1.48-1.93)
Personality disorders
2.38 (1.45-3.91)
1.76 (1.44-2.14)
2.99 (2.30-3.88)
1.99 (1.78-2.22)
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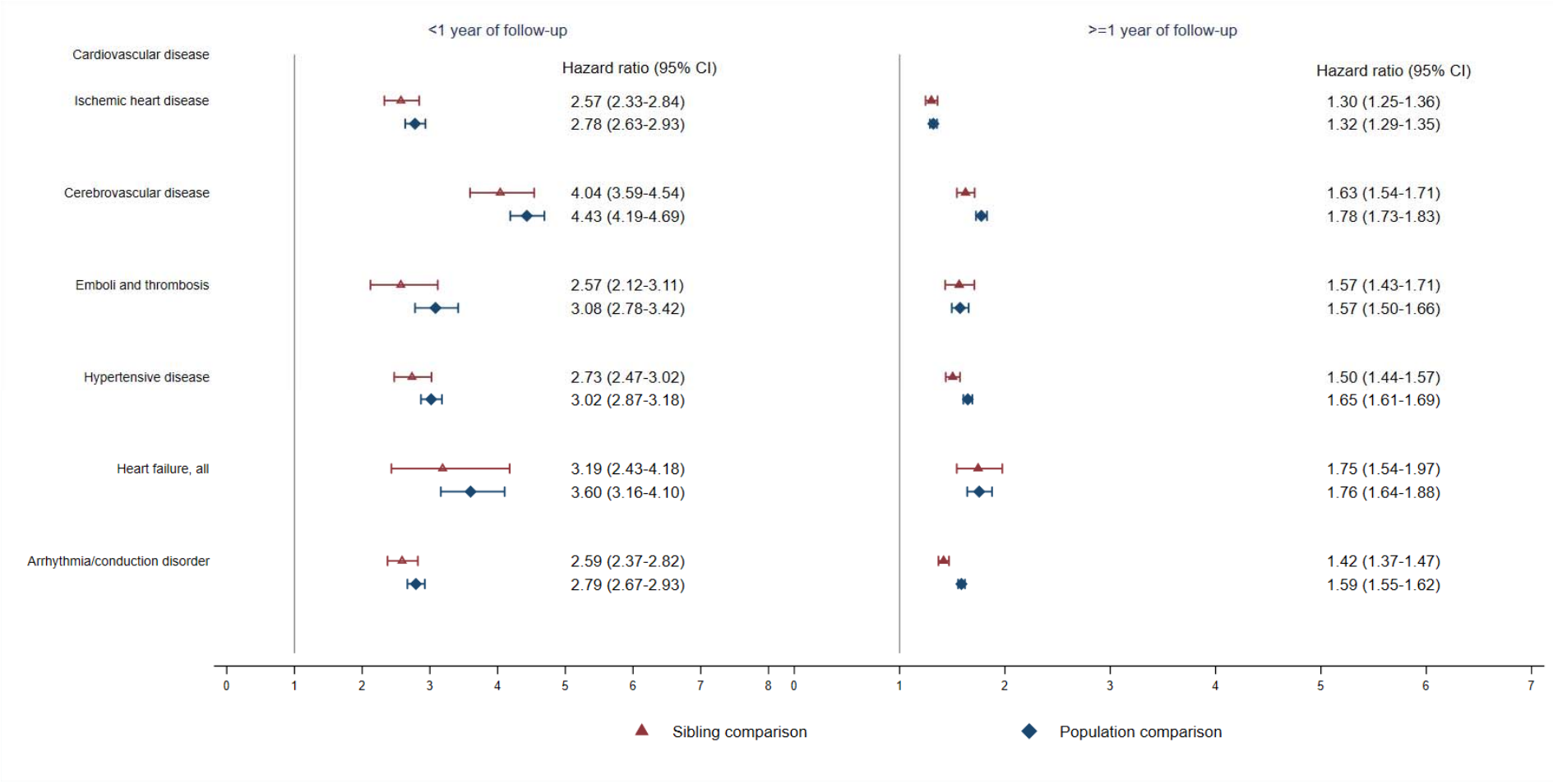
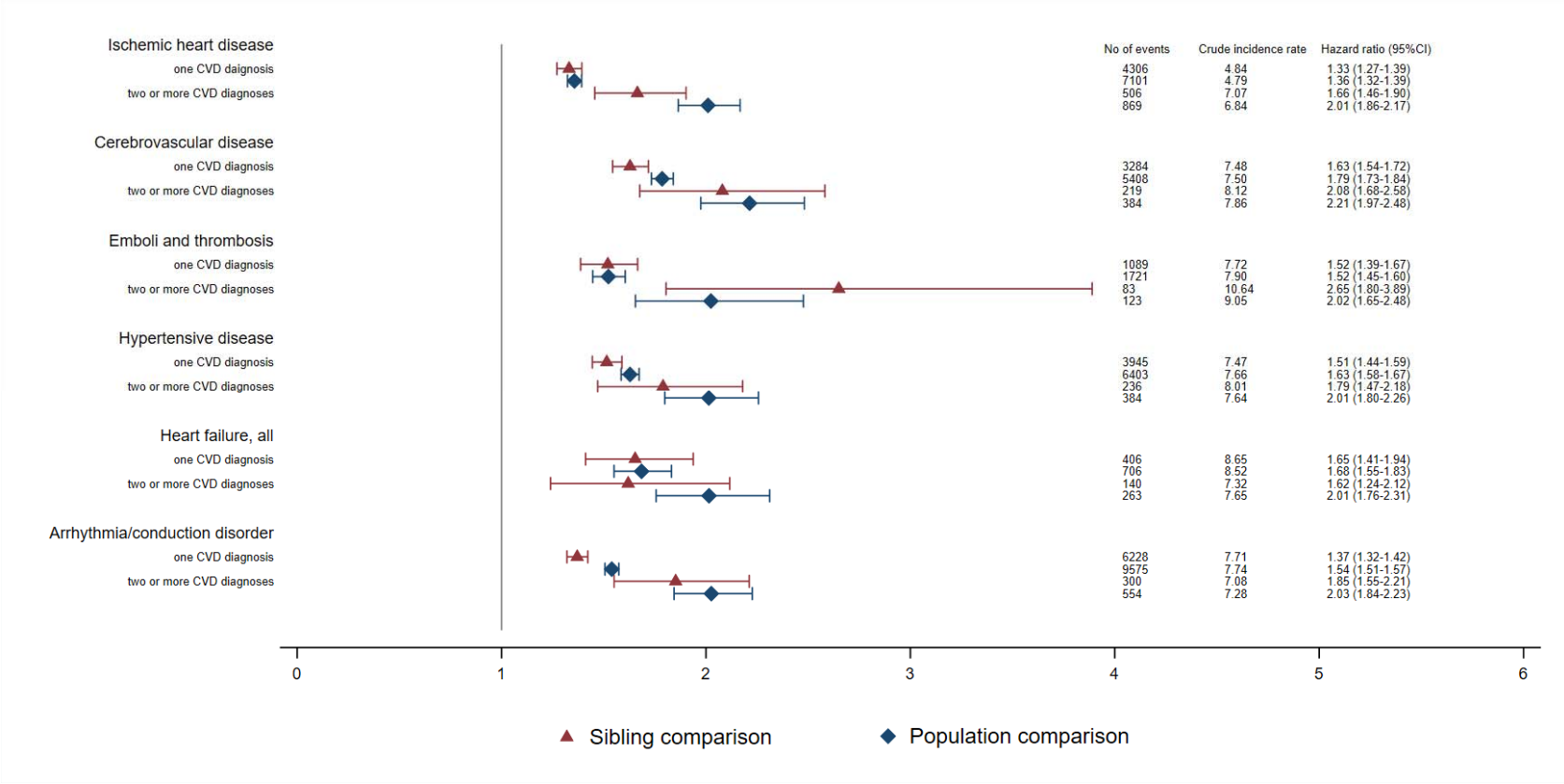
Sibling comparison
Population comparison


<1 year of follow-up
>=1 year of follow-up
Cardiovascular disease
Hazard ratio (95% CI)
Hazard ratio (95% CI)
Ischemic heart disease
2.57 (2.33-2.84)
2.78 (2.63-2.93)
1.30 (1.25-1.36)
1.32 (1.29-1.35)
Cerebrovascular disease
4.04 (3.59-4.54)
4.43 (4.19-4.69)
1.63 (1.54-1.71)
1.78 (1.73-1.83)
Emboli and thrombosis
2.57 (2.12-3.11)
3.08 (2.78-3.42)
1.57 (1.43-1.71)
1.57 (1.50-1.66)
Hypertensive disease
2.73 (2.47-3.02)
3.02 (2.87-3.18)
1.50 (1.44-1.57)
1.65 (1.61-1.69)
Heart failure, all
3.19 (2.43-4.18)
3.60 (3.16-4.10)
1.75 (1.54-1.97)
1.76 (1.64-1.88)
Arrhythmia/conduction disorder
2.59 (2.37-2.82)
2.79 (2.67-2.93)
1.42 (1.37-1.47)
1.59 (1.55-1.62)
0 1 2 3 4 5 6 7 8
0 1 2 3 4 5 6 7
Sibling comparison
Population comparison


Ischemic heart disease
one CVD daignosis
two or more CVD diagnoses
Cerebrovascular disease
one CVD diagnosis
two or more CVD diagnoses
Emboli and thrombosis
one CVD diagnosis
two or more CVD diagnoses
Hypertensive disease
one CVD diagnosis
two or more CVD diagnoses
Heart failure, all
one CVD diagnosis
two or more CVD diagnoses
Arrhythmia/conduction disorder
one CVD diagnosis
two or more CVD diagnoses
No of events
Crude incidence rate
Hazard ratio (95%CI)
4306 4.84 1.33 (1.27-1.39)
7101 4.79 1.36 (1.32-1.39)
506 7.07 1.66 (1.46-1.90)
869 6.84 2.01 (1.86-2.17)
3284 7.48 1.63 (1.54-1.72)
5408 7.50 1.79 (1.73-1.84)
219 8.12 2.08 (1.68-2.58)
384 7.86 2.21 (1.97-2.48)
1089 7.72 1.52 (1.39-1.67)
1721 7.90 1.52 (1.45-1.60)
83 10.64 2.65 (1.80-3.89)
123 9.05 2.02 (1.65-2.48)
3945 7.47 1.51 (1.44-1.59)
6403 7.66 1.63 (1.58-1.67)
236 8.01 1.79 (1.47-2.18)
384 7.64 2.01 (1.80-2.26)
406 8.65 1.65 (1.41-1.94)
706 8.52 1.68 (1.55-1.83)
140 7.32 1.62 (1.24-2.12)
263 7.65 2.01 (1.76-2.31)
6228 7.71 1.37 (1.32-1.42)
9575 7.74 1.54 (1.51-1.57)
300 7.08 1.85 (1.55-2.21)
554 7.28 2.03 (1.84-2.23)
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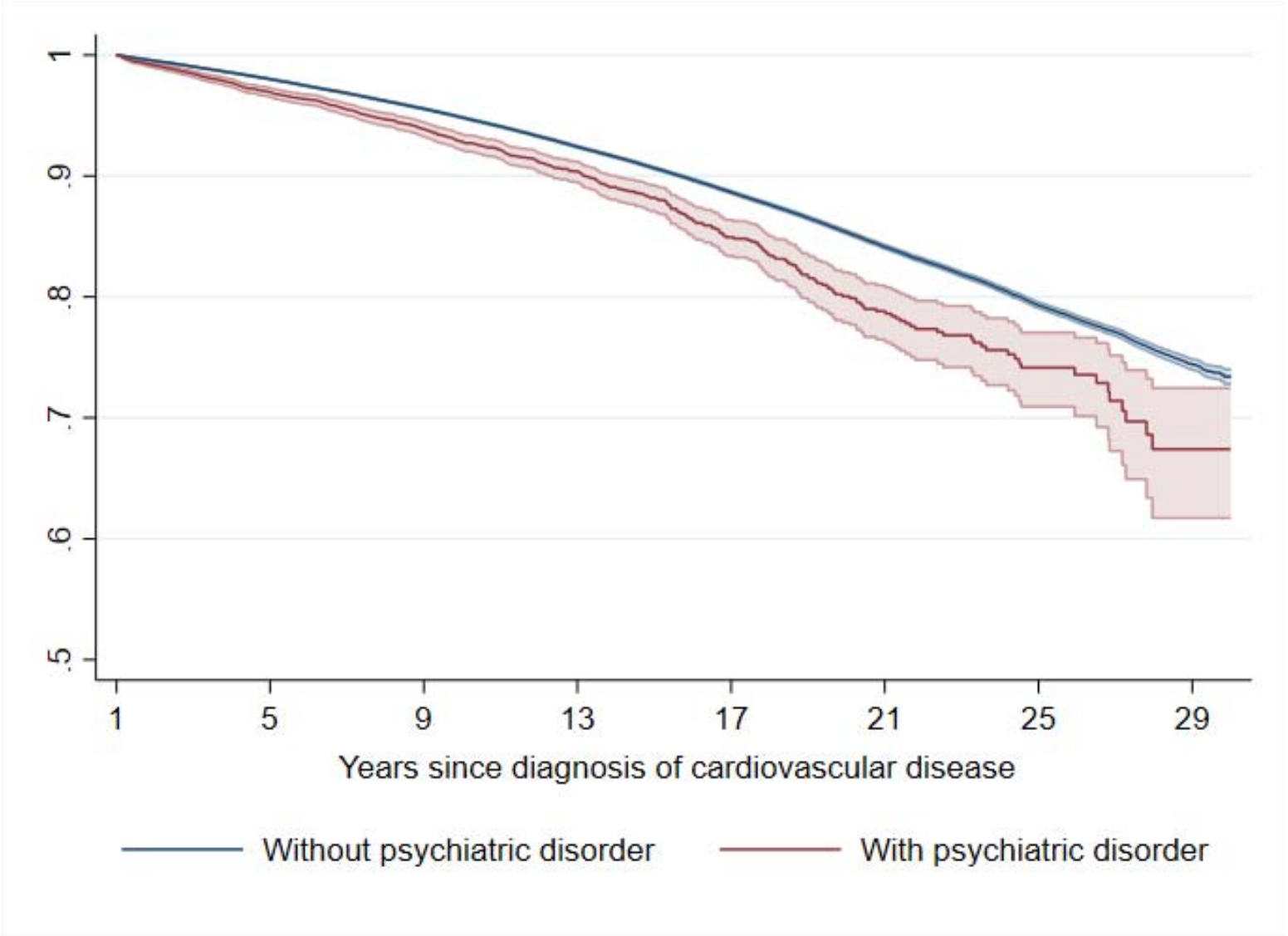
Sibling comparison
Population comparison


1
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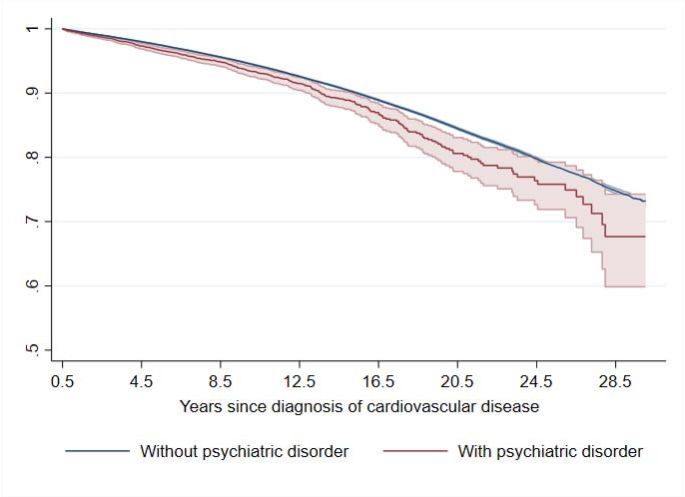
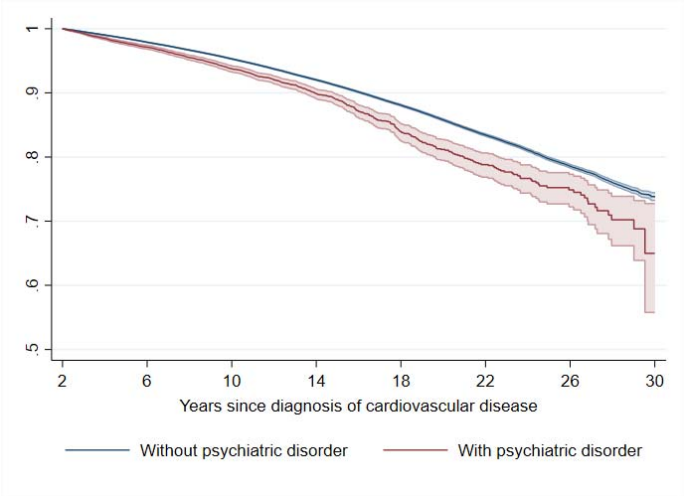
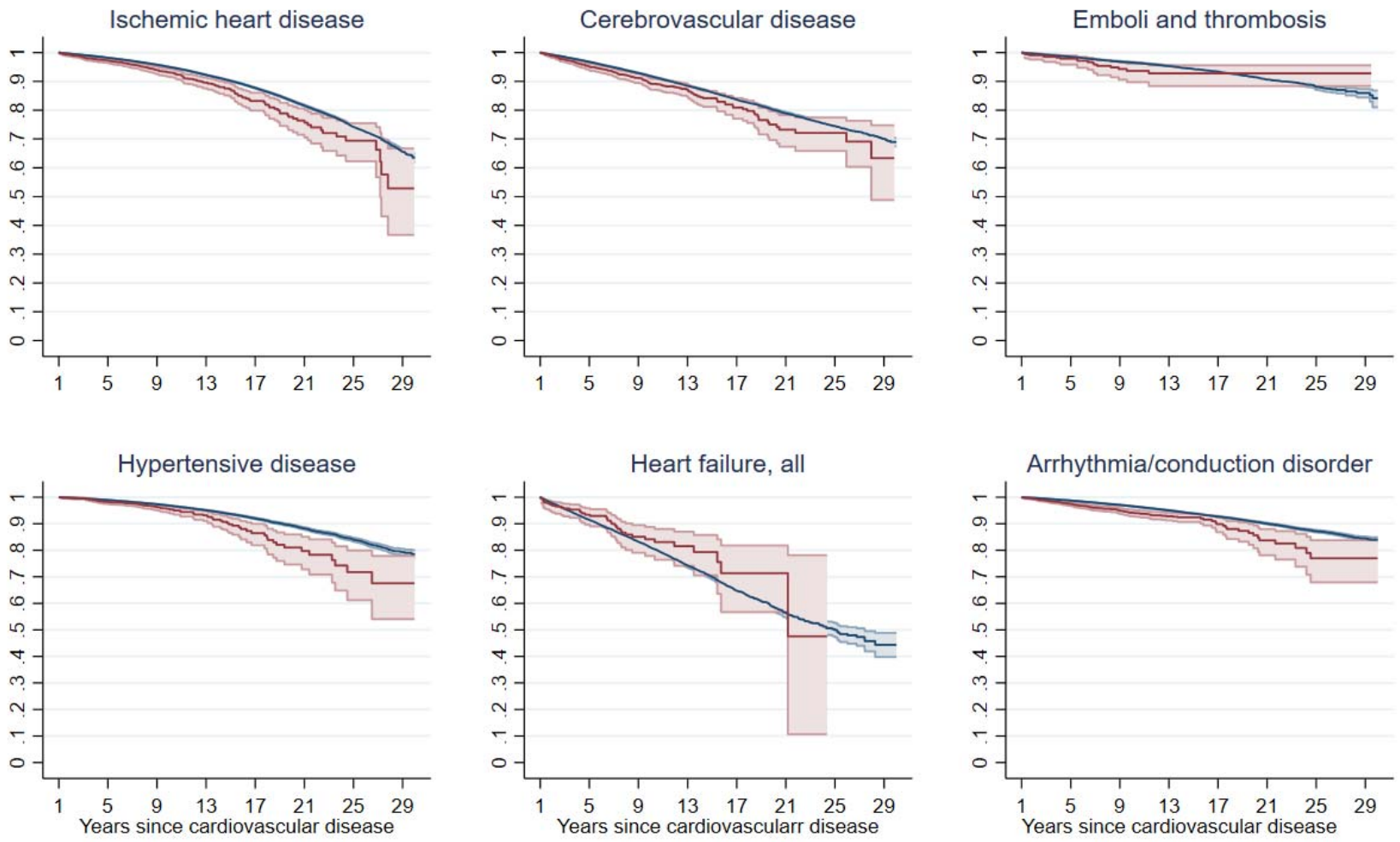
Years since diagnosis of cardiovascular disease
Without psychiatric disorder
With psychiatric disorder

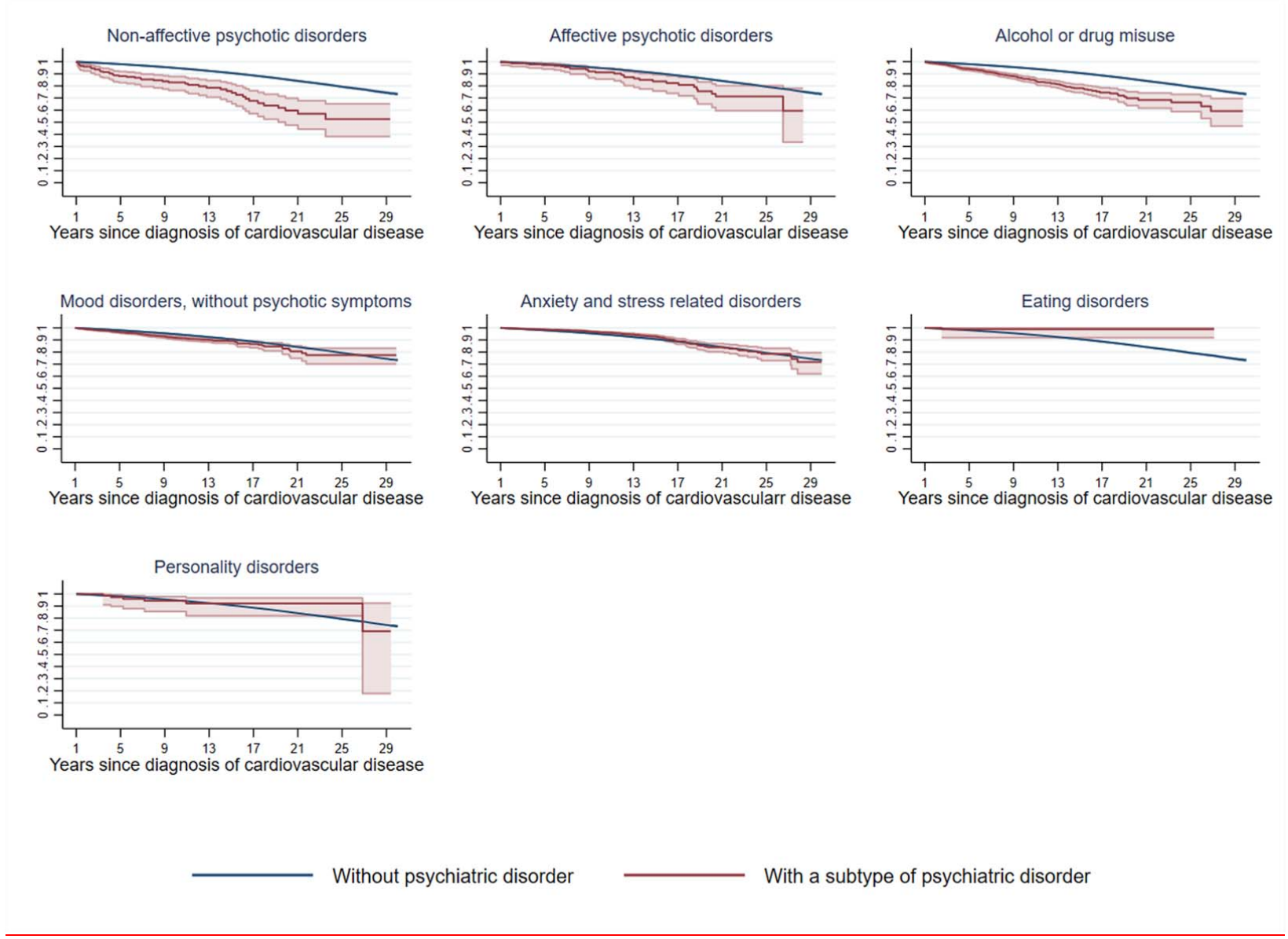
1) six months of follow-up[a]



2) two years of follow-up[b]




Ischemic heart disease
Cerebrovascular disease
Emboli and thrombosis
Hypertensive disease
Heart failure, all
Arrhythmia/conduction disorder
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
1 5 9 13 17 21 25 29
Years since cardiovascular disease
Years since cardiovascularr disease
Without psychiatric disorder
With psychiatric disorder


Non-affective psychotic disorders
Affective psychotic disorders
Alcohol or drug misuse
Mood disorders, without psychotic symptoms
Anxiety and stress related disorders
Eating disorders
Personality disorders
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
1 5 9 13 17 21 25 29
Years since diagnosis of cardiovascular disease
Years since diagnosis of cardiovascularr disease
Without psychiatric disorder
With a subtype of psychiatric disorder