Psychiatric disorders and subsequent risk of cardiovascular disease: a longitudinal matched cohort study across three countries

Supplementary Appendix

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Table S1. Summary of longitudinal cohort studies on the association between various types of psychiatric disorders and risk of subsequent cardiovascular disease.

Paper	Study design and database	Exposure	Outcome	Sample size and follow-up	Main findings with adjustment	Controlled for	
						familial factors?	other psychiatric comorbidities?
Non-affective and affective psychotic disorders							
Søgaard M, 2017[1]	A nationwide registry-based matched cohort study in Denmark	Inpatient or hospital-based outpatient diagnosis of schizophrenia, severe depression, or bipolar disorder, among patients with atrial fibrillation (AF)	Stroke, fatal thromboembolic events, and bleeding using hospital diagnoses in the National Patient Register.	253,741 patients with AF with mean age of 73 years, and 47% were female; followed up to 5 years	Compared with matched AF patients without any mental disorder, HR of ischemic stroke was 1.37 (95% CI 0.88 to 2.14) for schizophrenia and 1.04 (95% CI 0.69 to 1.56) for bipolar disorder. HR of fatal thromboembolic events was 3.16 (95% CI 1.78 to 5.61) for schizophrenia and 1.53 (95% CI 0.93 to 2.53) for bipolar disorder.	No	alcohol intake
Foroughi M, 2022[2]	A population-based historical cohort study using the Rochester Epidemiology Project.	Bipolar disorder (BP) diagnosis was validated by chart review.	The primary outcome was the incidence of major adverse cardiac events (MACEs), defined as the composite outcome of myocardial infarction, ischemic and hemorrhagic stroke, percutaneous coronary intervention, coronary artery bypass graft, and death obtained from the electronical medical records.	288 with BP and 35,326 individuals without BD. Median follow-up was 16.5 years. Mean age was 49.8 years.	Multivariate regression adjusting for age and sex yielded an association between BD and MACE (hazard ratio [HR] = 1.93; 95% confidence interval [CI] = 1.43–2.52). The association remained significant after further adjustment.	No	alcohol use disorder, substance use disorder and major depressive disorder.
Wu S-I, 2015[3]	A population-based cohort study using nationwide	Schizophrenia or bipolar disorder at age 18 or above	Incident acute myocardial infarction (AMI) diagnosed from	70,225 patients with schizophrenia or bipolar disorder and 207,592	HR in men was 1.15 (95% CI 1.01~1.32) for schizophrenia and 1.37 (1.08~1.73) for bipolar	No	alcohol use disorder,

	administrative data in Taiwan		ambulatory care, emergency service, or hospitalization during 1996 to 2007	randomly selected reference people without serious mental illness; mean age of around 40 years, and about 52% were male; followed up for 11 years	disorder; HR in women was 1.85 (1.58~2.18) and 1.88(1.47~2.41) respectively.		antipsychotic agents, antidepressants, and mood stabilizers
Davydow DS, 2016[4]	A nationwide population-based cohort study in Denmark	Serious mental illnesses (SMIs) (e.g., schizophrenia or bipolar disorder) using The Danish Psychiatric Central Register	Hospitalizations for ambulatory care-sensitive conditions (ACSCs) and rehospitalization for the same or another ACSC, within 30 days	42,558 patients with schizophrenia/schizoaffective disorder and 25,648 patients with bipolar disorder; mean age of 38.4 years (45% male); followed up over 10 years	SMI was associated with increased risk for hospitalizations for angina (IRR: 1.14, 95% CI, 1.04–1.25), and congestive heart failure exacerbation (IRR: 1.25; 95% CI, 1.16–1.35)	no	substance abuse
Prieto ML, 2016[5]	A population-based cohort study utilizing a records-linkage system spanning 30 years (1966–1996) in the US	Bipolar I disorder as a manic episode confirmed by DSM-IV criteria, or a clinical diagnosis of a manic episode in the medical record	Incident fatal and non-fatal myocardial infarction (MI) and stroke confirmed by board-certified cardiologist/neurologist	334 patients with bipolar I disorder and 334 age- and sex-matched referents (median age of 37 years, and 52% female); median follow-up of 18.7 years	There was an increased risk of fatal or non-fatal MI or stroke (as a composite outcome) in patients with bipolar I disorder [HR 1.54, 95% CI 1.02, 2.33]. After adjusting for baseline cardiovascular risk factors (alcoholism, hypertension, diabetes, and smoking), the risk was no longer significantly increased (HR 1.19, 95% CI 0.76, 1.86).	no	alcohol use disorder
Krieger I, 2019[6]	A nationwide cohort study based on nationwide data, derived from the Clalit Health Services (CHS) databases in Israel	Schizophrenia registered by a senior psychiatrist or when listed in the diagnoses of discharge letters from a psychiatric hospital	Ischemic heart disease (IHD) diagnosed by a physician	Individuals with schizophrenia (n=10,502) and a matched sample of smoking healthy controls (n=10,502), mean age of both groups was 49.7; mean follow-up time of 12.6 years	Individuals with schizophrenia were at a lower risk of developing IHD (OR=0.76, 95%CI = 0.67-0.85) compared to healthy controls. After controlling for sociodemographic and clinical variables, this association became non-significant (adjusted OR=0.92, 95% CI=0.83-1.03)	no	alcohol abuse, and drug abuse
Non-psychotic mood disorders							

Søgaard M, 2017[1]	A nationwide registry-based matched cohort study in Denmark	Inpatient or hospital-based outpatient diagnosis of schizophrenia, severe depression, or bipolar disorder, among patients with atrial fibrillation (AF)	Stroke, fatal thromboembolic events, and bleeding using hospital diagnoses in the National Patient Register.	253,741 patients with AF with mean age of 73 years, and 47% were female; followed up to 5 years	Compared with matched referents, HR of ischemic stroke was 1.36 (95% CI 0.89 to 2.08) for depression. HR of fatal thromboembolic events was 1.31 (95% CI 0.67 to 2.56) for depression.	no	alcohol intake
Davydow DS, 2015[7]	Retrospective cohort study with a population-based sample of Americans >50 years participating in the Health and Retirement Study (HRS) (1998-2008)	Depression was defined as either a score of ≥4 on the 8-item Center for Epidemiologic Studies Depression Scale (CES-D-8) at the baseline interview or a depression diagnosis in the Medicare claims	Hospitalized ischemic stroke	7,031 Americans >50 years old, and 42% male; followed up from 1998 or 2000 until 2008 or death	Co-occurring depression and cognitive impairment without dementia (OR: 1.65, 95%CI: 1.24, 2.18) was associated with odds of ischemic stroke. Depression alone was not associated with odds of ischemic stroke (OR: 1.11, 95%CI: 0.88, 1.40)	no	comorbidities using Charlson Index
Egeberg A, 2015[8]	A Danish nationwide register-based cohort study	Patients with psoriasis with concurrent depression (prescription of antidepressant medication from pharmacy)	Incident atrial fibrillation (AF) and stroke from registers	5,251,888 adults including 67,853 patients with psoriasis, mean age 42.9 and 49.3% male; followed up during 1997-2011	HR for AF was 1.19 (95% CI 1.06–1.33) in patients with mild psoriasis and depression, and 1.74 (95% CI 1.43–2.11) in patients with severe psoriasis and depression. HR of stroke was 1.63 (95% CI 1.43–1.85) and 2.47 (95% CI 2.07–2.95), respectively.	no	comorbidities using Charlson Index
Fenger-Grøn M, 2019[9]	A Danish nationwide register-based matched cohort study	Depression and subsequent antidepressant treatment as identified by first-time antidepressant prescription redemption in the registered period	Incident atrial fibrillation (AF) from inpatient or outpatient records	785,254 depressed patients and 1:5 matched population controls, 40.8% male; followed up from 2000 to 2013	During the first month after antidepressant therapy initiation, the HR was 3.18 (95% CI: 2.98–3.39) for AF. This association gradually attenuated over the following year (HR=1.37; 95% CI: 1.31–1.44 during 2–6 months after, and HR=1.11; 95% CI: 1.06–1.16 during 6–12 months after the initiation.	no	comorbidities including history of Schizophrenia or schizoaffective disorder, bipolar disorder, and substance abuse

Huang C-J, 2013[10]	A matched cohort study with a random sample from the Taiwan National Health Insurance Program	Newly diagnosed depression on at least two occasions between 2000 and 2007	Composite of coronary events including myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) procedures	39,685 individuals (7937 with depression and 31,748 without depression) aged 20–99 years were followed up for a median period of 8.76 years; 37.4% were male	The HR for newly detected coronary events was 1.49 (95% CI= 1.29–1.74) for individuals with depression compared to age- and gender- matched individuals without depression.	no	no
Jee YH, 2019[11]	A Korean population-based cohort study using the Database of National Health Insurance System	Depression was defined as the hospital outpatient use and diagnosis of depression or history of medication for depression	First atherosclerotic cardiovascular disease (ASCVD) from hospital admission or death	481,355 Koreans (260,695 men and 220,660 women) aged 40–80 years who had a biennial health check-up between 2002 and 2005; mean age 52.8 years	Depression increased the risk of developing ASCVD by 41% for men and 48% for women. In men, 3–4 outpatient visits for depression increased the risk of angina pectoris by 2.12 times (95% CI 1.55 to 2.90) and acute myocardial infarction by 2.29 times (95% CI 1.33 to 3.95). Depression was also associated with stroke in men (HR 1.29, 95% CI 1.19 to 1.39) and women (HR 1.37, 95% CI 1.29 to 1.46).	no	no
Lee CW-S, 2015[12]	A population-based retrospective cohort study using data from the Longitudinal Health Insurance Database 2000 of Taiwan (2000-2011)	Newly diagnosed depression from the Longitudinal Health Insurance Database	Venous thromboembolism (VTE) was determined by linking patient records with ambulatory and inpatient care data	35,274 depressed patients and a non-depression cohort comprising 70,548 patients matched according to sex, age, and index year; mean age of 48 years and 38.4% male	Depressed patients had a 1.38-fold greater risk (95% CI= 1.09–1.73) of developing VTE.	no	no
Liu N, 2016[13]	A mega-cohort of Chinese adults from the China Kadoorie Biobank (CKB) Study with over 0.5 million adults aged 30 to 79 years	Major depression (MD) was measured with the modified Chinese version of Composite International Diagnostic Interview-Short Form at baseline	Incident ischemic heart disease (IHD) was identified through linkage to established disease registries and national health insurance claim databases	486,541 participants with a median age of 51 years, and 40.9% were male; median follow-up of 7.2 years	MD patients had a higher risk of IHD (HR 1.32; 95% CI 1.15–1.53).	no	no
Mathur R, 2016[14]	A prospective cohort study between 2005 and 2015	Anxiety and depressive disorders were selected from the primary care database	Incident non-fatal myocardial infarction (MI) and stroke	524,952 patients with mean age of 35.9 years,	Depression was independently associated with both MI (HR 1.21,	no	anxiety

	from the east London primary care database			and 52.8% were male; followed up to 10 years	95% CI 1.05-1.39) and stroke (HR 1.29, 95% CI 1.00-1.66).		
O'Neil A, 2016[15]	A prospective longitudinal study of a representative sample of women enrolled in the Geelong Osteoporosis Study (1993–2011) in Australia	Depressive disorder using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders	Incident coronary heart disease (CHD) from hospital medical records	860 women with mean age of 48 years; followed up for 18 years	Baseline depression predicted 18-year incidence, adjusting for anxiety (OR:2.39; 95% CI:1.19–4.82)	no	anxiety
Parkin L, 2017[16]	A large prospective study of UK women recruited through the National Health Service Breast Screening Programme in England and Scotland	Depression and regular use of medications from questionnaire	Venous thromboembolism (VTE) through linkage to routinely collected National Health Service statistics	734,092 women with a mean age of 59.9 years; followed up for an average of 7.3 years	Antidepressant users had a higher risk of VTE than women had neither depression nor use of psychotropic drugs (HR, 1.39; 95% CI, 1.23–1.56). VTE risk was not increased in women being treated for depression or anxiety but not using antidepressants or other psychotropic drugs (HR, 1.19; 95% CI, 0.95–1.49).	no	use of other antipsychotics
Patten SB, 2008[17]	A longitudinal population-based cohort study from the Canadian National Population Health Survey (NPHS) every 2 years between 1994 and 2002	Major depression (MD) assessed from the composite International Diagnostic Interview Short Form	Chronic medical conditions including heart disease and hypertension, from self-reported survey	15,254 respondents with age over 12 years	The risk was elevated for heart disease (HR, 1.4,1.0-2.1) and hypertension (HR1.6, 1.2-2.2) in relation to MD at baseline interview.	no	no
Pelletier R, 2015[18]	DECADE (Depression Effects on Coronary Artery Disease Events), a prospective observational study of patients referred at the Montreal Heart Institute	Depression and anxiety disorders were assessed at baseline using the Primary Care Evaluation of Mental Disorders (PRIME-MD)	Major adverse cardiovascular events (MACE), including cardiac mortality, non-fatal myocardial infarction (MI), revascularization procedures, and cerebrovascular events (i.e., stroke), among patients with and without	2,390 patients with mean age of around 56 years, and 30-40% were female; followed for 8.8 years, between 1998 and 2009	Neither depression nor anxiety was associated with MACE among patients with or without CAD.	no	anxiety

			coronary artery disease (CAD)				
Ting RZW, 2013[19]	A 7-year prospective study of the Hong Kong Diabetes Registry	Major depression assessed by psychiatrists in public hospitals	Cardiovascular disease (CVD) was defined as coronary heart disease (CHD) and/or stroke and/or peripheral vascular disease	7835 Hong Kong Chinese with type 2 diabetes (median age of 56), and 47% were male; median follow-up of 7.4 years	Depression independently predicted CVD [HR=2.18 (95% CI=1.45-3.27)], mainly due to stroke [HR=3.55 (95% CI = 2.15-5.84)]	no	no
Tsai T-Y, 2017[20]	A population-based matched cohort study using Taiwan's Longitudinal Health Insurance Database (1997-2010)	Rheumatoid arthritis (RA) comorbid with depression from insurance claims data	Incident stroke	8045 subjects with a newly diagnosed RA, together with 32,600 subjects without RA matched by age, gender and index date; mean age of 55 years; 31% were male	Patients with RA with comorbid depression had increased risk of stroke (HR 2.18; 95% CI 1.87 to 2.54). Those with RA only or those with depression only had also a higher risk of stroke by 43% and 57% as compared with individuals without either condition.	no	no
White JR, 2015[21]	Veterans Aging Cohort Study (VACS)	Major depressive disorder (MDD) comorbid with HIV infection from medical records	Incident heart failure (HF) from medical records	81,427 individuals with a mean age of 48; 95% were male; 5.8 years of follow-up	HIV+ individuals with MDD had a higher risk of HF (HR, 1.68; 95% CI, 1.45–1.95) compared with HIV− individuals without MDD. MDD was associated with HF among both HIV− and HIV+ individuals (HR 1.21; 95% CI, 1.06–1.37; and HR, 1.29; 95% CI, 1.11–1.51, respectively).	no	alcohol abuse and cocaine abuse
Yuan HW, 2012[22]	A multi-centered prospective cohort study among patients with acute stroke in China	Poststroke depression (PSD) was diagnosed according to the criteria set by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)	Recurrent stroke at 1 year followed up via face-to-face or phone interview	1713 patients with acute stroke with mean age of 61.5 years, and 34.4% were female; 1 year of follow up	There was a 49% increased odds of recurrent stroke in patients with PSD, compared to patients without PSD (OR = 1.49, 95%CI: 1.03–2.15). There was no significant association between use of antidepressant drugs and the risk of recurrent stroke (OR = 1.96, 95%: CI 0.95–4.04)	no	high alcohol consumption
Zivin K, 2015[23]	A retrospective cohort study in the Veterans Health Administration in the United States who	Depression based on depression diagnoses recorded during an inpatient stay or any	Cause of death was obtained from the National Death Index (NDI)	5,078,082 patients treated in Veterans Health Administration (VHA) settings with mean age of	Depression was associated with a higher hazard of three-year mortality from heart disease (HR 1.155, 1.133-1.177),	no	psychiatric hospitalizations (0, ≥1); psychiatric

	received treatment in a VA facility at least once during fiscal year 2006	outpatient visit during two years prior to the index date		62.6 years, and 91.7% were male; followed up for 3 years	cerebrovascular disease (HR 1.437, 1.376-1.502), and hypertension (HR 1.184, 1.080-1.297).		comorbidities (anxiety and/or PTSD, serious mental illness (bipolar disorder, schizophrenia, and other psychoses), nicotine use, and substance use disorder)
Pratt LA, 1996[24]	Prospective data from the Baltimore cohort of the Epidemiologic Catchment Area Study	Major depressive episode	Self-reported myocardial infarction (MI)	1551 respondents free of heart trouble, and 26-40% were male; followed up for 13 years	A history of major depressive episode was associated with a higher risk of MI (OR 4.54; 95% CI, 1.65 to 12.44), independent of coronary risk factors.	no	alcohol abuse, panic disorder, and phobia
Khambaty T, 2016[25]	A veterans aging cohort study with HIV-infected adults in the US	Major depressive disorder (MDD) and dysthymic disorder	Incident acute myocardial infarction (AMI) defined by discharge summary documentation, enzyme/electrocardiography evidence of AMI, inpatient ICD-9 code for AMI, or AMI as underlying cause of death	26,144 HIV-infected veterans (mean age 48 years) and 97% were male; followed up for 5.8 years	Baseline MDD was associated with incident AMI after adjusting for demographics (HR, 1.31; 95% CI, 1.05-1.62), CVD risk factors (HR, 1.29; 95% CI, 1.04-1.60), and HIV-specific factors (HR, 1.30; 95% CI, 1.05-1.62). Further adjustment for hepatitis C, renal disease, substance abuse, and hemoglobin level (HR, 1.25; 95% CI, 1.00-1.56) and antidepressant use (HR, 1.12; 95% CI, 0.87-1.42) attenuated the associations. Baseline dysthymic disorder was not associated with incident AMI.	no	substance abuse and antidepressant use
Sun J, 2016[26]	A prospective study of 0.5 million Chinese adults using the China Kadoorie Biobank cohort	Major depressive episodes (MDE) using a WHO composite international diagnostic interview-Short Form	Stroke events were ascertained through death certificates, medical records, and health insurance data	199,294 men and 288,083 women aged 30 to 79 years (mean age of 51 years; 40.9% male); followed	Past year MDE was marginally associated with a 15% increased risk of stroke (adjusted HR, 1.15; 95% CI, 0.99–1.33). There was a positive dose–response relationship	no	alcohol use

				from 2004 to 2013, median of follow-up 7.2 years	between the number of depression symptoms and increased stroke risk (P_{trend}=0.011).		
Almas A, 2019[27]	A longitudinal cohort study on mental health, work, and relations in Sweden	Depression assessed using the Major Depression Inventory (MDI) and self-reported data on non-cardiovascular morbidity in 1998–2000	Outcomes of cardiovascular disease (CVD) were assessed using the National Patient Register	10,443 adults (aged 20–64 years) with median age of 41-52 years, and 44% were male; followed from 2001 to 2014	Both depression (HR 1.5; 95% CI, 1.1, 2.0) and non-cardiovascular morbidity (HR 2.0; 95% CI, 1.8, 2.6) were associated with an increased future risk of CVD. The combined effect of depression and non-cardiovascular comorbidity on future CVD was HR 2.1 (95%, CI 1.3, 3.4) after adjusting for age, gender and socioeconomic position.	no	psychiatric disorders (other than depression) and hazardous alcohol use
Prigge R, 2022[28]	A large prospective cohort study based on UK Biobank.	Depression was defined as at least one of: self-report of depression or antidepressant use; or hospital record of depression at baseline.	Major cardiovascular events (MCVE), defined as first-ever fatal or non-fatal stroke or myocardial infarction from routinely collected health and death records.	466,238 UK Biobank participants, aged 40–69 years without cardiovascular disease, bipolar disorder or schizophrenia at baseline. Median age was 57 years and 44.2% was male.	Depression was associated with increased risks of MCVE (adjusted HR, 95% CI: 1.28, 1.19–1.38;)	no	no
Anxiety and stress-related disorders							
Jackson CA, 2016[29]	An Australian longitudinal study on women's health, surveyed every 3 years from 1998 to 2013	Anxiety defined using self-reported doctor-diagnosis	Incident hypertension was defined as first reported occurrence of hypertension from self-reported survey	9126 women, mean age 49.5 years with follow-up of 12 years	Anxiety was associated with increased odds of hypertension (OR 1.24, 95% CI 1.09 to 1.42), but this association became non-significant after adjusting for all factors (OR 1.06, 95% CI 0.90 to 1.24).	no	depression
Mathur R, 2016[14]	A prospective cohort study between 2005 and 2015 from the east London primary care database	Anxiety and depressive disorders were selected from the primary care database	Incident non-fatal myocardial infarction (MI) and stroke	524,952 patients with mean age of 35.9 years, and 52.8% were male; followed up to 10 years	Anxiety was not associated with MI (HR 1.08, 95% CI 0.92-1.24) or stroke (HR 1.06, 95% CI 0.81-1.38).	no	depression

Pelletier R, 2015[18]	DECADE (Depression Effects on Coronary Artery Disease Events), a prospective observational study of patients referred at the Montreal Heart Institute	Depression and anxiety disorders were assessed at baseline using the Primary Care Evaluation of Mental Disorders (PRIME-MD)	Major adverse cardiovascular events (MACE) including cardiac mortality, non-fatal myocardial infarction (MI), revascularization procedures, and cerebrovascular events (i.e., stroke), among patients with and without coronary artery disease (CAD)	2390 patients with mean age of around 56 years, and 30-40% were female; followed for 8.8 years, between 1998 and 2009	Neither depression nor anxiety was associated with MACE among patients with or without CAD.	no	depression
Chang WH, 2017[30]	A nationwide longitudinal cohort study including individuals aged over 60 years from the National Health Insurance Research Database (2000-2008)	Coexisting geriatric anxiety and depressive disorders	Ischemic heart disease mortality defined as in-hospital death or critical discharge (discharged with a terminal condition for death at home)	1086 elderly individuals with anxiety disorders (44.8% male, mean follow-up 6.5 years) and 50,554 elderly controls (57.2% male, mean follow-up 7.7 years) without anxiety disorders	The risk of mortality in patients with anxiety disorders was higher than controls, and was even higher when the patients had coexisting anxiety and depressive disorder (RR = 1.60; 95% CI: 1.14–2.24)	no	no
Tsai M-T, 2016[31]	An 11-year population-based retrospective cohort study used the National Health Insurance Research Database in Taiwan	Comorbid anxiety in patients with diabetes defined by both a clinical diagnosis of the DSM-IV (ICD-9-CM) and prescriptions for anxiolytic medications	Stroke including an ischemic stroke event or a hemorrhagic stroke event	4124 patients with diabetes and 41% were male; followed up during 2001-2011	Diabetic patients with comorbid anxiety were at a higher risk of stroke compared to patients without comorbid anxiety (HR: 1.33, 95% CI: 1.02–1.72).	no	psychiatric disorders (including depression, bipolar disorder, or schizophrenia) and psychiatric medications
Chen M-H, 2015[32]	A longitudinal study based on data from the Taiwan's National Health Insurance	Post-traumatic stress disorder (PTSD) identified from the Taiwan National Health Insurance Research Database	Diagnoses of any stroke, ischemic stroke and hemorrhagic stroke given by neurologists, neurosurgeons, and emergency room doctors	5217 individuals with PTSD and 20,868 age- and gender-matched controls (mean age of 36.6 years and 20.9% were male); enrolled between 2002 and 2009, and followed up until 2011	Individuals with PTSD had an increased risk of developing any stroke (HR=3.37, 95% CI 2.44–4.67) and ischemic stroke (HR = 3.47, 95% CI 2.23–5.39) after adjusting for demographic data and medical comorbidities.	no	major depression

Lin C-E, 2019[33]	A nationwide cohort study in Taiwan based on The National Health Insurance (NHI) program	Posttraumatic stress disorder (PTSD)	Metabolic syndrome (MetS) including hypertension, dyslipidemia, and diabetes mellitus in inpatient or outpatient medical records with concomitant medication prescriptions	953 individuals in the PTSD cohort and 3812 individuals in the control cohort (49% were male); followed up to 3 years	HR for developing any metabolic parameter of MetS was 4.451 (95% CI: 2.109–5.001) in relation to PTSD.	no	depression
Rosman L, 2019[34]	A prospective cohort study of 1.1 million young adults through the Veterans Health Administration	Posttraumatic stress disorder (PTSD) obtained from a clinical diagnosis based on ICD codes (ICD-9 code 309.81)	Incident atrial fibrillation (AF)	988,090 young and middle-aged veterans (mean age, 30.29) and 87.8% were male; mean follow-up of 4.8 years	PTSD was associated with incident AF in unadjusted models (HR, 1.31; 95% CI, 1.19–1.43) and models adjusted for demographics, lifestyle factors, cardiovascular risk factors, and depression (HR, 1.13; 95% CI, 1.02–1.24).	no	depression and substance abuse
Rosman L, 2019[35]	A prospective cohort study of 1.1 million young adults through the Veterans Health Administration	Posttraumatic stress disorder (PTSD) obtained from a clinical diagnosis based on ICD codes (ICD-9 code 309.81)	First onset of transient ischemic attack (TIA) and ischemic stroke	987,855 young and middle-aged Veterans (mean age, 30.29) and 87.8% were male; up to 13 years of follow-up	The association between PTSD and incident TIA (HR, 1.61; 95% CI,1.27–2.04) and ischemic stroke (HR, 1.36; 95% CI, 1.22–1.52) remained significant in fully adjusted models. The effect of PTSD on ischemic stroke risk was stronger in men than in women.	no	major depressive disorder and generalized anxiety disorder, and substance abuse
Song H, 2019[36]	A population based, sibling controlled cohort study in Sweden	Stress related disorders, including post-traumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions	Primary diagnosis of incident cardiovascular disease—any or specific subtypes (ischemic heart disease, cerebrovascular disease, emboli/ thrombosis, hypertensive diseases, heart failure, arrhythmia/conduction disorder, and fatal cardiovascular disease)	136,637 patients (37% male), 171,314 unaffected full siblings (50% male) and 1,366,370 (37% male) matched population controls; median age of 36 years; followed up from 1987 to 2013 (median follow-up of 6 years)	In sibling-based comparisons, the hazard ratio for any cardiovascular disease was 1.64 (95% CI 1.45 to 1.84). Except for fatal cardiovascular diseases, these associations were not modified by the presence of psychiatric comorbidity. Analyses within the population matched cohort yielded similar results.	Yes, full siblings	other psychiatric comorbidities

Ebrahimi R,2021[37]	Retrospective, longitudinal cohort study of the national Veterans Health Administration (VHA) electronic medical records among women Veterans	Posttraumatic stress disorder (PTSD), diagnosis codes from inpatient or outpatient encounters	Incident ischemic heart disease (IHD), defined as new-onset coronary artery disease, angina, or myocardial infarction	398,769 female veterans; mean age of 40.1 years; median follow-up of 4.9 years	PTSD was associated with greater risk of developing IHD (HR, 1.44; 95% CI, 1.38-1.50).	no	anxiety, de-pression, schizophrenia, alcohol dependence, and nonalco-hol drug dependence
Gradus JL, 2015[38]	Prospective cohort study utilizing Danish national registry data	Post-traumatic stress disorder (PTSD) and adjustment disorder	Cardiovascular disease (CVD) events including myocardial infarction (MI), stroke, ischemic stroke, and venous thromboembolism (VTE)	PTSD (n=4724) and adjustment disorder (n=64,855) cohorts compared with the general population of Denmark from 1995 to 2011 (39% male)	Associations were found between PTSD and all 4 CVD events ranging from 1.5 (95% CI 1.1 to 1.9) for MI to 2.1 (95% CI 1.7 to 2.7) for VTE. Associations that were similar in magnitude were also found for adjustment disorder and all 4 CVD events: 1.5 (95% CI 1.4 to 1.6) for MI to 1.9 (95% CI 1.8 to 2.0) for VTE.	no	depression and alcohol abuse
Gomez-Caminero A, 2005[39]	A cohort study of a national managed care database in United States	Panic disorder (PD) from database from 1997 through 2002	Coronary heart disease (CHD) defined as presence of an acute myocardial infarction, unstable angina, or angina pectoris	39,920 PD patients (68% female) and an equal number of patients without PD (59% female); mean age of 36 years; average follow up of 1.5 years	Patients with PD were observed to have nearly a 2-fold increased risk for CHD (HR=1.87, 95% CI=1.80 – 1.91). Patients with a comorbid diagnosis of depression were almost 3 times more likely to develop CHD (HR=2.60, 95% CI=2.30 – 3.01).	no	depression
Isomura K, 2021[40]	A population-based, sibling-controlled cohort study in Sweden	Obsessive-compulsive disorder (OCD) diagnosed between 1973 and 2013	Cardiovascular disease (CVD) defined from the National Patient Register by the record of an inpatient or outpatient visit and additionally from VAL by diagnoses records in visits to primary care or from the Cause of Death Register	33,561 OCD patients, 23,263 clusters of full siblings and 10 times matched population controls (56.7% women); average follow-up time of 27 years	OCD was associated with an increased risk of a broad range of CVD (HR for any CVD = 1.25 [95% CI, 1.22–1.29]). These associations were strongest for venous thrombo-embolism (HR = 1.48 [95% CI, 1.38–1.58]) and heart failure (HR = 1.37 [95% CI, 1.28–1.46]). When comparing OCD exposed individuals with their non-exposed full siblings, results were largely similar. Exclusion of several groups of psychiatric comorbidities	yes, sibling controlled	other psychiatric comorbidities

					resulted in comparable results, albeit attenuated.		
Chen MH, 2021[41]	A longitudinal matched cohort study in Taiwan	Diagnosis of OCD obtained from the Health Insurance Research Database with data collected between 2001-2010	Ischemic and hemorrhagic stroke during follow-up (from enrollment to end of 2011) were identified from the insurance database.	28,064 adult patients with OCD and 28,064 age-, sex-, and comorbidity-matched controls were included in this study, with an average age of 37 years and female predominance (51.8%). Mean follow-up time was 6.5 years.	Patients with OCD (hazard ratio [HR], 3.02 [95% CI, 1.91–4.77]), especially middle-aged (HR, 2.66 [95% CI, 1.34–5.29]) and elderly adults (HR, 3.46 [95% CI, 1.70–7.05]), had an elevated risk of developing ischemic stroke during the follow-up period compared with non-OCD controls.	no	schizophrenia, bipolar disorder, and major depressive disorder
Vaccarino V, 2014[42]	A prospective study of middle-aged male twins from the Vietnam Era Twin Registry	Post-traumatic stress disorder (PTSD) diagnosis based on the Diagnostic Interview Schedule (DIS) for psychiatric disorders	Clinical events (myocardial infarction, other hospitalizations for coronary heart disease [CHD] and coronary revascularization)	A total of 562 twins (281 pairs) were included with mean age of 42.6 yrs at baseline;all males; median follow-up of 13 years	The incidence of CHD was more than double in twins with PTSD (22.6%) than those without PTSD (8.9%; p<0.001). The association remained robust after adjusting for lifestyle factors, other CHD risk factors and major depression (OR=2.2, 95% confidence interval, 1.2-4.1). Associations were only mildly attenuated within 117 twin pairs discordant for PTSD.	yes, twin pairs	major depression
Scherrer JF, 2019[43]	A longitudinal cohort study with eligible patients used 1 of 5 Veterans Health Affairs medical centers distributed across the United States	2 separate visits with an *ICD-9* code for PTSD (*ICD-9*: 309.81) within a 12-month period or 1 inpatient stay to classify patients as having post-traumatic stress disorder (PTSD)	Incident CVD was defined by ICD-9 codes and Current Procedural Terminology codes for cardiovascular revascularization procedures.	2519 Veterans Health Affairs patients had PTSD diagnoses and 1659 did not; mean=50.1 years, SD±11.0 , mostly male (87.0%); Patients could enter the cohort between 2008 and 2012 with follow-up until 2015.	The age-adjusted association between PTSD and incident CVD was significant (hazard ratio=1.41; 95% CI: 1.21–1.63). After adjustment for metabolic conditions, the association between PTSD and incident CVD was attenuated but remained significant (hazard ratio=1.23; 95% CI: 1.06–1.44). After additional adjustment for smoking, sleep disorder, substance use disorder, anxiety disorders, and depression, PTSD was not associated with incident CVD (hazard ratio=0.96; 95% CI: 0.81–1.15).	no	substance use disorder, anxiety disorders, and depression

Eating disorder							
Tith RM, 2020[44]	A longitudinal cohort study using the Maintenance and Use of Data for the Study of Hospital Clientele registry from Quebec, Canada	Hospitalization for bulimia nervosa between 2006 and 2016	Incidence of cardiovascular disease from Hospital Clientele registry with discharge abstracts of all hospitalizations in Quebec	416,709 women (including 818 women hospitalized for bulimia nervosa and 415,891 for pregnancy-related events); mean age of 28.3 years; followed up to 12 years	Women hospitalized for bulimia nervosa had 4.25 (95% CI, 2.98-6.07) times the risk of any cardiovascular disease and 4.72 (95% CI, 2.05-10.84) times the risk of death compared with women hospitalized for pregnancy-related events. Bulimia nervosa was found to be associated with ischemic heart disease (HR, 6.63; 95% CI, 3.34-13.13), atherosclerosis (HR, 6.94; 95% CI, 3.08-15.66), and cardiac conduction defects (HR, 2.99; 95% CI, 1.57-5.71).	no	depression, anxiety, bipolar disorder, schizophrenia, and alcohol, tobacco, or substance use
Personality disorder							
Chen M-H, 2017[45]	A nationwide longitudinal study using the Taiwan National Health Insurance Research Database	Borderline personality disorder (BPD) by board-certificated psychiatrists	Stroke diagnosis given by neurologists, neurosurgeons, internal medicine physicians, or emergency room physicians after brain image examinations	5969 borderline patients and 23,876 age-and sex-matched controls; average age of 28.55 years; 69.7% female; followed up from between 2002 and 2009, to 2011	BPD was associated with an increased risk of developing any stroke (HR: 4.82, 95% CI: 2.77–8.40) and ischemic stroke (HR: 5.67, 95% CI: 2.49–12.93).	no	major depression, PTSD, bipolar disorder, alcohol-related disorders, substance use disorder
Others/all types							
Gale CR, 2014[46]	Cohort study including all non-adopted men born in Sweden	Mental disorders were assessed by psychiatric interview on conscription and data on hospital admissions	Coronary heart disease (CHD) obtained from the Cause of Death Register and the Swedish Patient Register	1,107,524 men with average age of 18.3 years; mean follow-up of 22.6 years	Age-adjusted HR (95% CI) according to diagnoses at conscription ranged from 1.30 (1.05, 1.60) (depressive disorders) to 1.92 (1.60, 2.31) (alcohol-related disorders). The equivalent figures	no	risky use of alcohol and intelligence

					according to diagnoses during hospital admission ranged from 1.49 (1.24, 1.80) (schizophrenia) to 2.82 (2.53, 3.13) (other substance use disorders).		
Sung C, 2022[47]	A population-based retrospective matched cohort study based on the Taiwan National Health Insurance Research Database from 2000 to 2013.	Alcohol use disorder (AUD) defined as a newly diagnosis of AUD, namely alcoholic psychosis, alcohol abuse and alcohol dependency syndrome obtained from the database.	CVD was identified using the diagnostic codes for ischemic heart disease (IHD) and stroke from the database.	7,420 patients with AUD and 29,680 age- and sex-matched controls without AUD. The patients were predominantly men (92.84%), with an average age of 43.12 ± 11.85 years.	The AUD group also exhibited a significantly higher incidence of CVD than the control group (adjusted hazard ratio [AHR] =1.447, 95% confidence interval [CI] =1.372–1.52 5,P<0.001).	no	anxiety, depression

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Table S2. International Classification of Diseases (ICD) codes for exposure, outcome, and covariates

	ICD-9	ICD-10
Any psychiatric disorder	291,292, 295-311, 314, 317-319	F10-F69, F70-F73, F78, F79, F84, F90
Non-affective psychotic disorders	295, 297, 298, excluding 295H and 298B	F20-24, F28-29
- Schizophrenia	295A-295E, 295G, 295W, 295X	F200-F206, F208, F209
Affective psychotic disorders	296, 295H, 298B	F25, F30-31, F32.3, F33.3
- Schizoaffective disorder	295H	F25
- Bipolar disorder	296A-296H, 296W, 296X	F30-F31
Substance misuse	291, 292, 303, 304	F10-16, F18-19
- Alcohol	303A, 303X	F100-F109
- Drug	304A-304H, 304W, 304X	F110-F119, F190-F199
Non-psychotic mood disorders	300E, 311	F32-34, F38-39, excluding F32.3 and F33.3
Anxiety and stress-related disorders	300A-D, 300F-H, 300W-X, 306, 307A, 308, 309	F40-48
- Anxiety disorder	300A, 300C	F400-F402, F408, F409, F410-F413, F418, F419
- Obsessive-compulsive disorder	300D	F420-422, F428, F429
- Post-traumatic stress disorder	308A-308E, 308X, 309A-309E, 309W, 309X	F430-F432, F438, F439
Eating disorders	307B, 307F	F500, F501, F502, F503, F509
- Anorexia nervosa	307B	F500, F501
- Bulimia nervosa	-	F502, F503
Personality disorders	301	F60-63, F68-69
Attention deficit hyperactivity disorder (ADHD)	314, 314A-314C, 314J, 314W, 314X	F90, F900, F901, F908
Autism spectrum disorder (ASD)	299A	F840, F841, F845

Intellectual disability	317, 318, 318A, 318B, 318C, 319	F70-F73, F78, F79
Any cardiovascular disease	390-438, 440,444,445	I00-I70, I730, I74- I75
Ischemic heart disease	410-414	I20-I24, I25 (excluding I25.5)
Cerebrovascular disease	430-434, 436-438	I60-I69
Emboli and thrombosis	415, 444,445	I26, I74, I75
Hypertensive disease	401-405	I10-I16, I674
Heart failure	428	I25.5, I42.0, I42.8, I42.9, I50
Arrhythmia/conduction disorder	426, 427	I44-I49
Covariates: history of severe somatic conditions		
Chronic pulmonary disease	500-505, 506C	J60-J67, J684, J70, J703
Connective tissue disease	710A, 710B, 710E, 714A, 714B, 714C, 714W,714X, 725	M05, M06, M315, M32-M34, M351, M353, M360
Diabetes	250A, 250G	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149
Diabetes with end organ damage	250D-250F	E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147
Moderate or severe renal disease	582, 583A, 583B, 583C, 583E,	I120, I131, N032-N037, N052-N057, N18, N19, N250, Z490-Z492, Z940, Z992
Mild liver disease	583G, 583H, 585, 586, 588	B18, K700-K703, K709, K713-K715, K717, K73, K74, K760, K762--K764, K768, K769, Z944
Moderate or severe liver disease	571C, 571E,571F, 571G	I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767
Ulcer disease	572C, 572D, 572E, 572W, 456A, 456B, 456C	K25-K28

Any malignancy, including leukemia and lymphoma	140-172, 174-195, 200-208	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97
Metastatic cancer	196,197,198,199A, 199B	C77- C80
HIV/AIDS	042, 043, 044	B20-B22, B24

Table S3. Number and median age at the index date among patients with psychiatric disorders in the sibling as well as population comparisons of the Swedish cohort

Characteristics	Sibling comparison			Population comparison	
	Exposed patients (N=619,289)	Median age at index date in years (IQR)		Exposed patients (N=900,240)	Median age at index date in years (IQR)
Type of first-onset psychiatric disorder					
1. Non-affective psychotic disorders	16,765 (2,71)	33 (25-45)		24,023 (2,67)	35 (25-48)
1.1 Schizophrenia	2,602 (0,42)	32 (25-44)		3,782 (0.42)	34 (25-47)
2. Affective psychotic disorders	14,449 (2,33)	37 (26-49)		21,421 (2,38)	39 (27-51)
2.1 Schizoaffective disorder	311 (0.05)	35 (23-46)		452 (0.05)	35 (24-47)
2.2 Bipolar disorder	7,347 (1.19)	35 (25-48)		11,074 (1.23)	36 (25-50)
3. Substance misuse	107,464 (17,35)	28 (19-46)		161,192 (17,91)	30 (20-48)
3.1 Alcohol misuse	79,884 (12.90)	31 (19-49)		117,995 (13.11)	35 (19-51)
3.2 Drug disuse	14,536 (2.35)	26 (21-35)		22,893 (2.54)	26 (21-35)
4. Non-psychotic mood disorders	121,439 (19,61)	31 (21-45)		176,450 (19,60)	33 (21-47)
5. Anxiety and stress related disorders	200,143 (32,32)	31 (21-44)		291,644 (32,40)	32 (21-45)
5.1 Anxiety disorder	98,503 (15.91)	28 (20-41)		144,689 (16.07)	29 (20-43)
5.2 Obsessive-compulsive disorder (OCD)	9,618 (1.55)	22 (16-31)		13,081 (1.45)	22 (16-32)
5.3 Post-traumatic stress disorder (PTSD)	68,633 (11.08)	35 (24-46)		100,578 (11.17)	35 (24-46)
6. Eating disorders	20,136 (3,25)	17 (15-22)		25,665 (2,85)	17 (15-22)
6.1 Anorexia nervosa	8,014 (1.29)	17 (15-20)		9,853 (1.09)	17 (15-20)
6.2 Bulimia nervosa	2,071 (0.33)	23 (19-27)		2,745 (0.30)	23 (19-28)
7. Personality disorders	9,049 (1,46)	28 (21-39)		13,575 (1.51)	28 (21-39)
8. Attention deficit hyperactivity disorder (ADHD)	54,706 (8,83)	13 (10-18)		79,039 (8,78)	13 (10-18)
9. Autism spectrum disorder (ASD)	18,762 (3,03)	12 (7-17)		26,186 (2,91)	12 (6-18)
10. Intellectual disability	13,432 (2,17)	13 (8-20)		19,018 (2,11)	13 (7-21)
11. Others	42,944 (6,93)	26 (16-42)		62,027 (6,89)	27 (16-43)

IQR: interquartile range;

Table S4. Characteristics of patients with psychiatric disorders, their unaffected siblings, and matched reference population - a Danish register-based replication cohort

Characteristics	Sibling comparison			Population comparison	
	Exposed patients (N=404,023)	Unaffected full siblings (N=625,710)		Exposed patients (N=875,634)	Matched reference population (N=8,756,340)
Median age at index date in years (IQR)	22.32 (18.10)	22.99 (19.89)		28.85 (23.73)	28.85 (23.75)
Median follow-up time in years (IQR)	9.72 (12.69)	10.76 (13.65)		9.72 (13.72)	10.46 (14.78)
Female sex	196,869 (48.73)	303,800 (48.55)		433,576 (49.52)	4,335,760 (49.52)
History of somatic diseases*	92,329 (22.85)	103,294 (16.51)		280,416 (32.02)	1,748,782 (19.97)
Family history of cardiovascular disease†	190,085 (47.05)	-		281,744 (32.18)	2,209,335 (25.23)
Type of psychiatric disorders					
1. Psychiatric and behavioral disorders due to psychoactive substance use	147,096 (35.79)	-		353,391 (40.36)	-
2. Schizophrenia and related disorders	42,295 (10.29)	-		104,594 (11.94)	-
3. Mood disorders	104,209 (25.36)	-		246,749 (28.18)	-
4. Anxiety disorders	177,850 (43.28)	-		369,703 (42.22)	-
5. Eating disorders	19,244 (4.68)	-		29,567 (3.38)	-
6. Personality disorders	55,028 (13.39)	-		131,973 (15.07)	-
7. Intellectual disabilities	18,973 (4.62)			34,311 (3.92)	
8. Developmental disorders	36,538 (8.89)			56,620 (6.47)	
9. Behavioral and emotional disorders	72,974 (17.76)			118,894 (13.58)	
Number of psychiatric diagnoses					
One	248,363 (60.44)	-		519,117 (59.28)	-
Two	95,464 (23.23)	-		211,866 (24.20)	-
Three or more	67,126 (16.33)	-		144,651 (16.52)	-

IQR: interquartile range.

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

† The difference between exposed patients and unaffected full siblings was due to different number of siblings per exposed patient. The family history of cardiovascular disease was constant within each family.

Table S5. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for incident cardiovascular disease among patients with any psychiatric disorder, compared with their unaffected full siblings or matched reference population, by patient characteristics*

	Sibling comparison					Population comparison				
	Unaffected full siblings		Exposed group			Matched population		Exposed group		
	No. of cases	IR (per 1,000 person years)	No. of cases	IR (per 1,000 person years)	HR (95% CI)*	No. of cases	IR (per 1,000 person years)	No. of cases	IR (per 1,000 person years)	HR (95% CI)*
Overall	65774	7,38	33893	8,61	1.40 (1.38-1.43)	550007	7,06	54189	9,71	1.45 (1.44-1.46)
By sex										
male	38345	8,51	19719	10,23	1.41 (1.37-1.45)	315085	8,28	31132	11,39	1.47 (1.46-1.49)
female	27429	6,22	14174	7,06	1.37 (1.33-1.42)	234922	5,90	23057	8,10	1.42 (1.40-1.44)
By age at cohort entry										
≤22	3991	1,42	2908	1,98	1.28 (1.20-1.36)	40498	1,54	4016	2,02	1.42 (1.38-1.47)
23-41	15003	4,41	8102	5,68	1.48 (1.42-1.54)	135089	4,27	13633	6,29	1.58 (1.56-1.61)
≥42	46780	17,36	22883	21,96	1.36 (1.34-1.39)	374420	18,87	36540	25,73	1.41 (1.39-1.42)
By age during follow-up										
<35	5421	2,03	4140	2,88	1.27 (1.20-1.35)	49651	2,06	5856	2,97	1.31 (1.27-1.35)
≥35	60353	9,66	29753	11,91	1.40 (1.37-1.42)	500356	9,30	48333	13,39	1.44 (1.42-1.45)
By calendar year at cohort entry										
1987-1996	23864	8,69	10033	9,94	1.42 (1.38-1.47)	184370	8,54	15591	10,98	1.48 (1.46-1.51)
1997-2006	27537	7,51	14434	8,76	1.37 (1.34-1.40)	227197	7,07	22614	9,80	1.41 (1.39-1.43)
2007-2016	14373	5,73	9426	7,36	1.42 (1.38-1.47)	138440	5,73	15984	8,63	1.46 (1.44-1.49)
By history of somatic diseases										
No	61574	7,08	30664	8,09	1.41 (1.38-1.43)	513934	6,75	48455	9,04	1.46 (1.45-1.48)
Yes	4200	19,21	3229	21,98	1.60 (1.38-1.87)	36073	21,10	5734	25,87	1.25 (1.18-1.32)

By family history of cardiovascular disease among first degree relatives										
No	19861	3,66	11284	4,45	1.44 (1.40-1.49)	201350	3,96	19417	5,44	1.48 (1.45-1.51)
Yes	45913	13,16	22609	16,12	1.38 (1.35-1.41)	348657	12,89	34772	17,31	1.41 (1.39-1.42)

*Cox regression models, stratified by family identifiers in sibling comparison and matching identifiers (birth year and sex) in population comparison, adjusting for sex, birth year, educational level, individualized family income, cohabitation status, history of somatic disease and family history of cardiovascular disease. Time since index date was used as underlying time scale.

Table S6. Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for incident cardiovascular disease among patients with any psychiatric disorder, compared to their unaffected full siblings (sibling comparison) or matched reference population (population comparison), by time since psychiatric diagnosis (<1 or ≥1 year)

	Sibling comparison			Population comparison		
	No. of cases	IR (per 1,000 person years)	HR (95% CI)*	No. of cases	IR (per 1,000 person years)	HR (95% CI)*
<1 year follow-up						
Full siblings/matched population controls	4,396	4,58	1.0	39,850	4,62	1.0
Psychiatric patients_controlled for sex, birth year, educational level, individualized family income and cohabitation status	4,214	7,77	1.91 (1.82-2.00)	7,224	9,19	1.96 (1.91-2.01)
As above + history of somatic diseases			1.88 (1.79-1.98)			1.91 (1.86-1.96)
As above + family history of cardiovascular disease			-			1.91 (1.86-1.96)
≥1 year follow-up						
Full siblings/matched population controls	63,468	7,95	1.0	528,869	7,62	1.0
Psychiatric patients_controlled for sex, birth year, educational level, individualized family income and cohabitation status	34,910	9,14	1.38 (1.35-1.40)	55,525	10,26	1.43 (1.42-1.44)
As above + history of somatic diseases			1.37 (1.34-1.39)			1.41 (1.40-1.43)
As above + family history of cardiovascular disease			-			1.41 (1.40-1.43)

*Cox regression models, stratified by family identifiers in sibling comparison or matching identifiers (birth year and sex) in population comparison. Time since index date was used as underlying time scale.

Table S7. Crude incidence rates (IRs) for different types of incident cardiovascular disease among patients with any psychiatric disorder, their unaffected full siblings and matched reference population, by time since psychiatric diagnosis (<1 or ≥1 year)

	Sibling comparison				Population comparison			
	Unaffected siblings		Exposed group		Matched population		Exposed group	
	No. of cases	IR (per 1000 person years)	No. of cases	IR (per 1000 person years)	No. of cases	IR (per 1000 person years)	No. of cases	IR (per 1000 person years)
<1 year follow up								
Ischemic heart disease	930	0,97	656	1,21	8457	0,98	1157	1,47
Cerebrovascular disease	598	0,62	712	1,31	5893	0,68	1240	1,58
Emboli and thrombosis	229	0,24	262	0,48	1865	0,22	476	0,61
Hypertensive disease	850	0,89	772	1,42	7468	0,87	1364	1,74
Heart failure	146	0,15	205	0,38	1219	0,14	348	0,44
Arrhythmia/conduction disorder	1105	1,15	1105	2,04	9764	1,13	1807	2,30
Fatal cardiovascular event	43	0,04	89	0,16	488	0,06	174	0,22
>=1 year follow up								
Ischemic heart disease	15099	1,89	7544	1,97	116950	1,69	12058	2,23
Cerebrovascular disease	8778	1,10	5604	1,47	80052	1,15	9262	1,71
Emboli and thrombosis	3366	0,42	2080	0,54	26806	0,39	3307	0,61
Hypertensive disease	12094	1,52	5917	1,55	100567	1,45	9139	1,69
Heart failure	2224	0,28	1683	0,44	18887	0,27	2867	0,53
Arrhythmia/conduction disorder	15059	1,89	7893	2,07	127084	1,83	12331	2,28
Fatal cardiovascular event	794	0,10	697	0,18	6891	0,10	1240	0,23

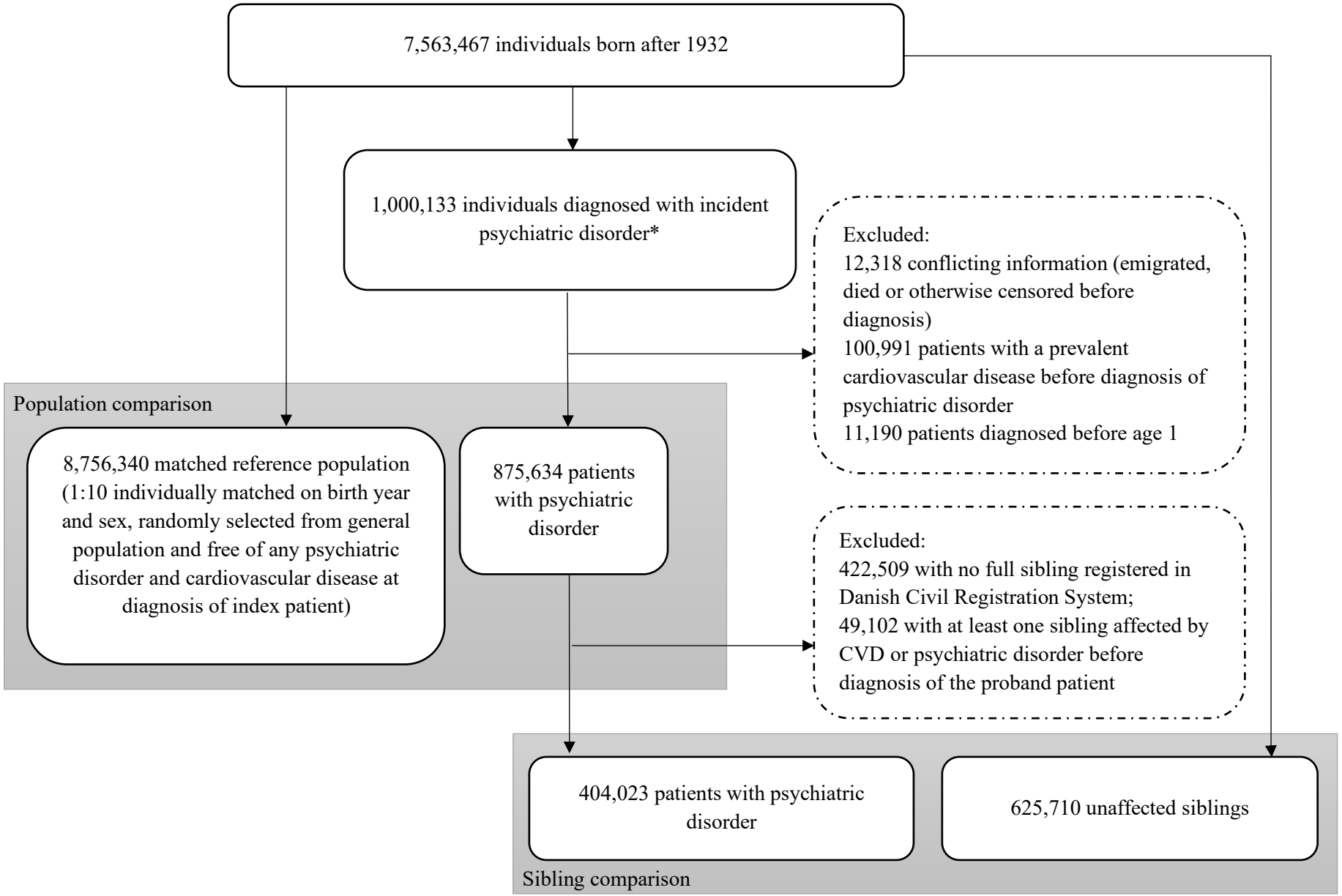
Table S8. Crude incidence rates (IRs) and hazard ratios (HRs) and 95% confidence intervals (CI) for incident cardiovascular disease among patients with different types of psychiatric disorder, compared to their unaffected full siblings (sibling comparison) or matched reference population (population comparison), by time since psychiatric diagnosis (<1 year or ≥1 year)[*]

	Sibling comparison			Population comparison		
	No. of cases	IR (per 1000 person years)	HR (95% CI)	No. of cases	IR (per 1000 person years)	HR (95% CI)
<1 year follow up						
Full siblings/matched population controls	4396	4,58	1.0	39850	4,62	1.0
1. Non-affective psychotic disorders	124	9,06	2.12 (1.61-2.78)	229	11,70	2.02 (1.75-2.33)
1.1 Schizophrenia	14	6,10	3.62 (1.36-9.64)	31	9,30	1.36 (0.93-1.98)
1.2 non-affective psychotic disorders excluding schizophrenia	110	9,66	2.02 (1.52-2.68)	198	12,20	2.19 (1.87-2.55)
2. Affective psychotic disorders	115	9,74	1.72 (1.30-2.29)	178	10,18	1.62 (1.38-1.90)
2.1 Schizoaffective disorder	1	3,99	1.10 (0.08-15.08)	3	8,25	0.98 (0.30-3.24)
2.2 Bipolar disorder	57	9,35	1.60 (1.08-2.36)	93	10,15	1.55 (1.24-1.93)
2.3 other affective psychotic disorders	57	10,43	1.90 (1.26-2.88)	82	10,31	1.76 (1.39-2.23)
3. Substance misuse	1056	11,01	2.11 (1.91-2.34)	1880	13,14	1.98 (1.88-2.08)
3.1 Alcohol misuse	916	12,47	2.08 (1.87-2.32)	1622	15,03	1.95 (1.84-2.05)
3.2 Drug disuse	84	6,97	2.80 (1.93-4.05)	148	7,79	2.39 (1.99-2.87)
3.3 Other substance misuse	56	5,40	1.81 (1.19-2.74)	110	6,83	2.05 (1.67-2.52)
4. Non-psychotic mood disorders	828	8,18	1.61 (1.45-1.78)	1447	9,87	1.70 (1.60-1.79)
5. Anxiety and stress related disorders	1443	8,49	1.88 (1.74-2.04)	2477	10,04	1.94 (1.86-2.03)
5.1 Anxiety disorder	752	9,17	2.13 (1.90-2.38)	1297	10,81	2.18 (2.05-2.31)
5.2 Obsessive-compulsive disorder (OCD)	17	2,04	0.83 (0.45-1.53)	29	2,58	0.91 (0.62-1.33)
5.3 Post-traumatic stress disorder (PTSD)	432	7,45	1.71 (1.48-1.96)	734	8,67	1.84 (1.70-2.00)
5.4 Other stress-related disorder	242	11,19	1.73 (1.43-2.09)	417	13,59	1.67 (1.50-1.85)
6. Eating disorders	62	3,80	5.90 (3.55-9.81)	77	3,70	2.98 (2.31-3.85)
6.1 Anorexia nervosa	33	4,89	21.36 (6.22-73.32)	36	4,34	4.91 (3.29-7.33)
6.2 Bulimia nervosa	4	2,34	2.28 (0.54-9.54)	5	2,22	1.17 (0.46-2.96)
6.3 Other eating disorder	25	3,18	3.87 (1.97-7.62)	36	3,51	2.52 (1.75-3.65)
7. Personality disorders	39	5,11	2.42 (1.46-4.00)	70	6,14	1.60 (1.24-2.06)
8. Attention deficit hyperactivity disorder (ADHD)	147	2,99	2.02 (1.56-2.62)	201	2,83	2.49 (2.13-2.91)
9. Autism spectrum disorder (ASD)	19	1,14	1.27 (0.66-2.45)	33	1,42	1.34 (0.93-1.93)
10. Intellectual disability	60	4,77	2.26 (1.49-3.41)	89	5,01	2.16 (1.71-2.73)
11. Others	242	6,26	1.62 (1.34-1.95)	424	7,62	1.89 (1.70-2.10)
>=1 year follow up						

Full siblings/matched population controls	63468	7,95	1.0	528869	7,62	1.0
1. Non-affective psychotic disorders	1051	9,02	1.18 (1.08-1.29)	1690	10,49	1.16 (1.10-1.22)
1.1 Schizophrenia	218	8,83	1.21 (0.99-1.47)	372	10,78	1.15 (1.03-1.28)
1.2 non-affective psychotic disorders excluding schizophrenia	833	9,07	1.18 (1.07-1.30)	1318	10,42	1.16 (1.10-1.23)
2. Affective psychotic disorders	918	10,14	1.17 (1.07-1.29)	1491	11,54	1.08 (1.03-1.14)
2.1 Schizoaffective disorder	17	5,92	0.78 (0.41-1.50)	25	6,28	0.79 (0.52-1.19)
2.2 Bipolar disorder	326	10,77	1.10 (0.94-1.29)	525	11,94	1.08 (0.99-1.19)
2.3 Other affective psychotic disorders	575	10,03	1.24 (1.09-1.39)	941	11,59	1.09 (1.02-1.17)
3. Substance misuse	8597	13,06	1.56 (1.50-1.61)	13860	14,50	1.62 (1.59-1.65)
3.1 Alcohol misuse	7278	14,37	1.55 (1.49-1.61)	11800	16,33	1.59 (1.56-1.63)
3.2 Drug disuse	730	8,51	1.57 (1.40-1.77)	1129	8,52	1.88 (1.76-2.00)
3.3 Other substance misuse	589	8,91	1.67 (1.46-1.90)	931	9,25	1.60 (1.49-1.72)
4. Non-psychotic mood disorders	6065	10,19	1.24 (1.20-1.29)	9795	11,62	1.27 (1.25-1.30)
5. Anxiety and stress related disorders	10884	9,13	1.33 (1.29-1.36)	17304	10,22	1.37 (1.34-1.39)
5.1 Anxiety disorder	4319	8,84	1.39 (1.33-1.46)	7077	10,11	1.41 (1.38-1.45)
5.2 Obsessive-compulsive disorder (OCD)	222	4,32	0.99 (0.82-1.20)	340	4,96	1.09 (0.98-1.23)
5.3 Post-traumatic stress disorder (PTSD)	4435	9,20	1.29 (1.24-1.35)	6899	10,00	1.35 (1.32-1.38)
5.4 Other stress-related disorder	1908	11,24	1.32 (1.23-1.41)	2988	12,76	1.34 (1.29-1.39)
6. Eating disorders	325	2,66	1.60 (1.36-1.88)	410	2,65	1.21 (1.09-1.34)
6.1 Anorexia nervosa	120	2,24	1.46 (1.12-1.91)	152	2,34	1.20 (1.01-1.42)
6.2 Bulimia nervosa	31	3,00	1.08 (0.67-1.73)	38	2,84	1.34 (0.96-1.89)
6.3 Other eating disorder	174	2,98	1.87 (1.49-2.35)	220	2,88	1.19 (1.04-1.37)
7. Personality disorders	519	6,67	1.28 (1.13-1.46)	825	7,27	1.36 (1.26-1.46)
8. Attention deficit hyperactivity disorder (ADHD)	535	2,65	1.40 (1.23-1.59)	824	2,85	1.81 (1.68-1.95)
9. Autism spectrum disorder (ASD)	144	1,55	1.05 (0.82-1.33)	214	1,71	1.08 (0.93-1.24)
10. Intellectual disability	456	4,34	1.40 (1.22-1.61)	703	4,83	1.44 (1.33-1.56)
11. Other mental disorders	3750	9,03	1.40 (1.34-1.47)	5861	10,06	1.50 (1.46-1.55)

*Cox regression models, stratified by family identifiers in sibling comparison and matching identifiers (birth year and sex) in population comparison, adjusting for sex, birth year, educational level, individualized family income, cohabitation status, history of somatic disease and family history of cardiovascular disease. Time since index date was used as underlying time scale.

Figure S1. Flowchart of study design and study participants for Danish replication cohort



* Incident psychiatric disorders (main and auxiliary) were identified from the Danish National Patient Register (1977-01-01 to 2016-12-31) and Danish Psychiatric Central Research Register (1969-01-01 to 2016-12-31).

Figure S2. Schematic diagram for analyses and used datasets across three countries.

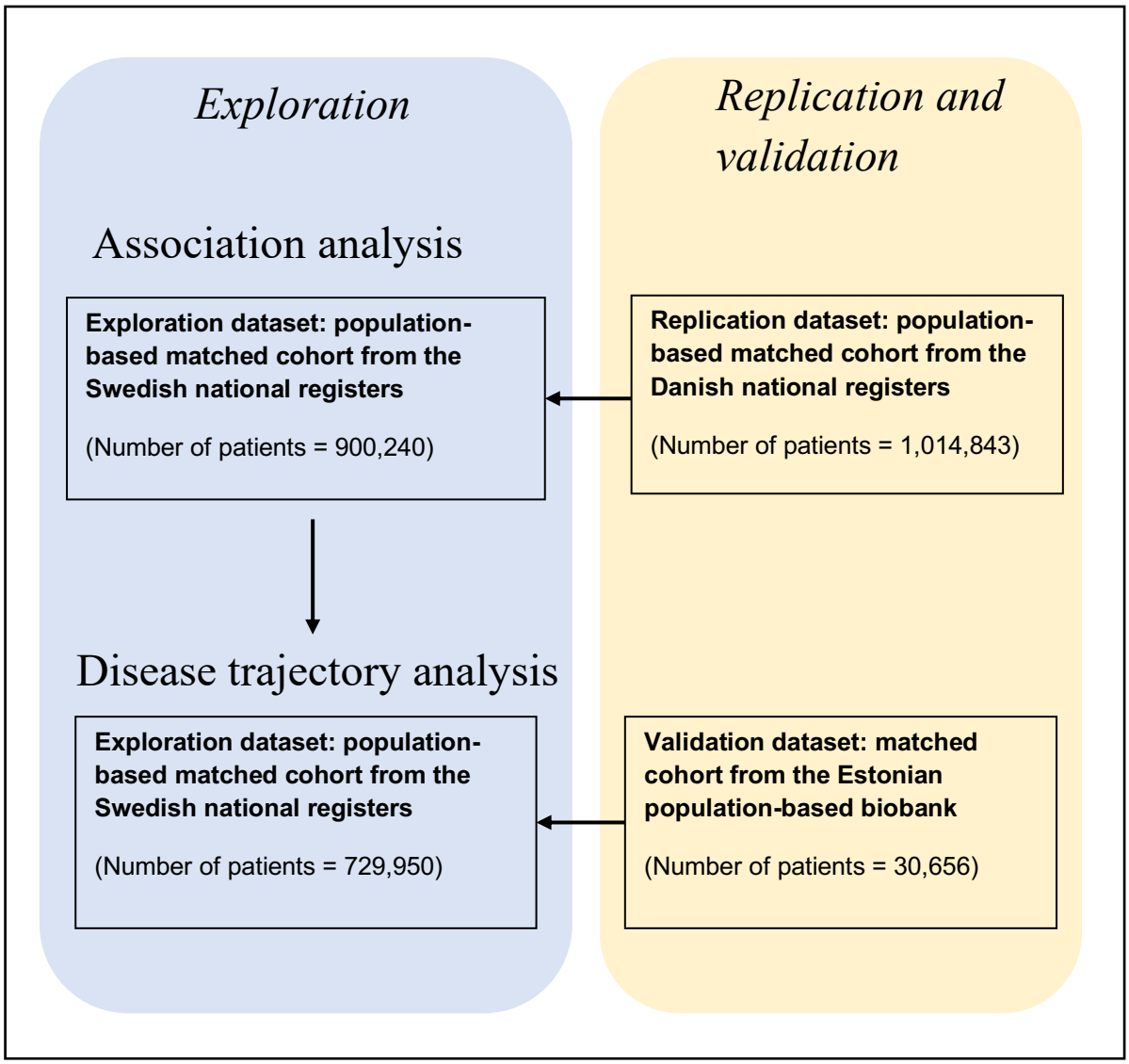
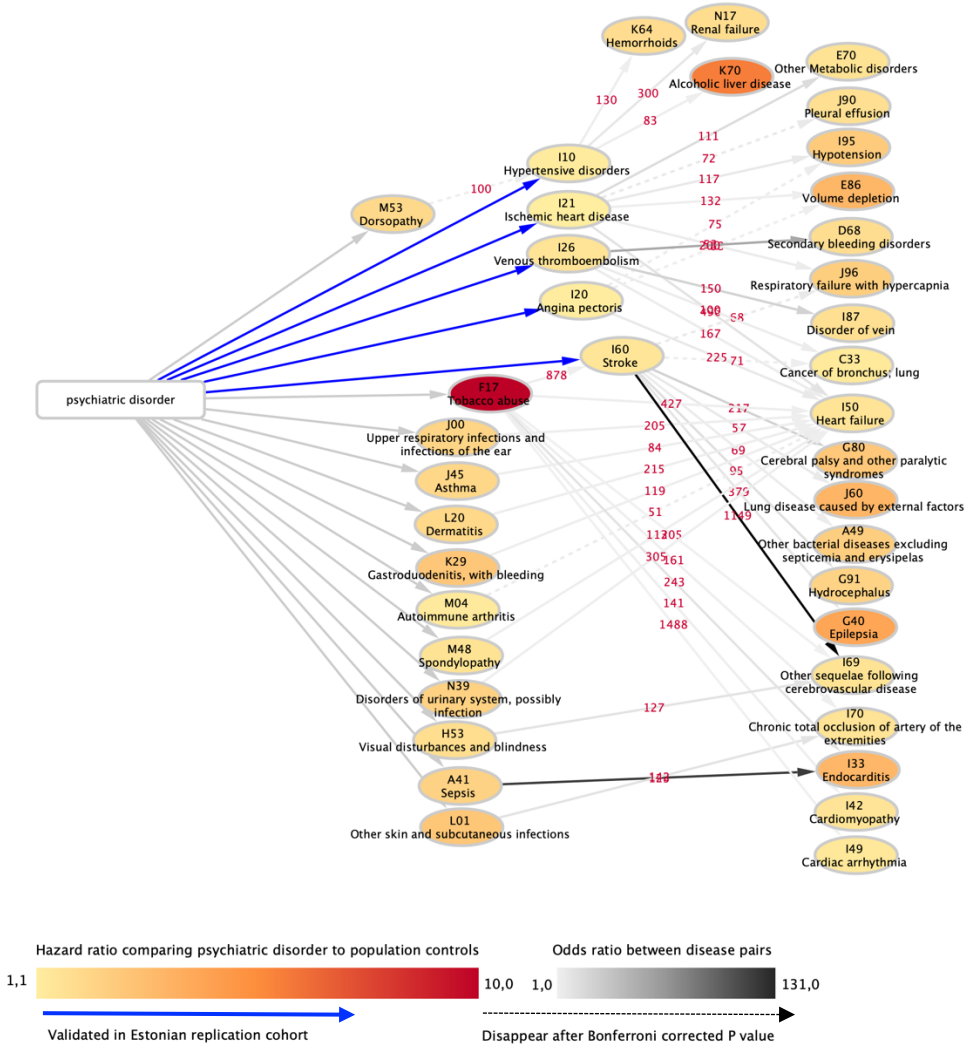


Figure S3. Disease trajectories toward different cardiovascular diseases among patients with psychiatric disorders (except for autism, N=729 950)*

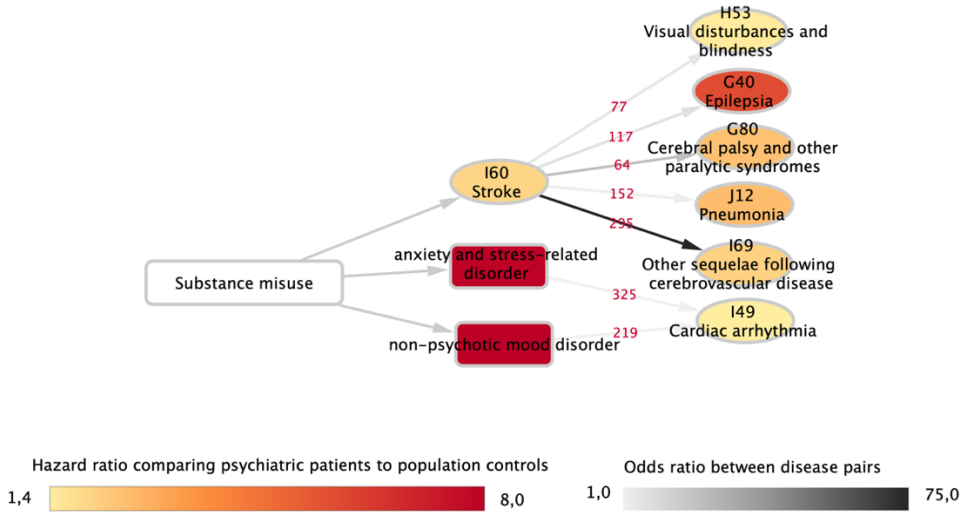


*This figure illustrates disease trajectories with direct and indirect links between psychiatric disorders and incident cardiovascular disease. The ICD codes used to cluster medical conditions are shown in circle. The color of each circle represents the magnitude of the association (hazard ratio) between psychiatric disorders and each medical condition. The color of arrows connecting two circles indicates the odds ratio of the association between two medical conditions among psychiatric patients. The number on the arrow corresponds to the number of pairs with both medical conditions among psychiatric patients. The blue color of arrows indicates the trajectories were validated in Estonian replication cohort.

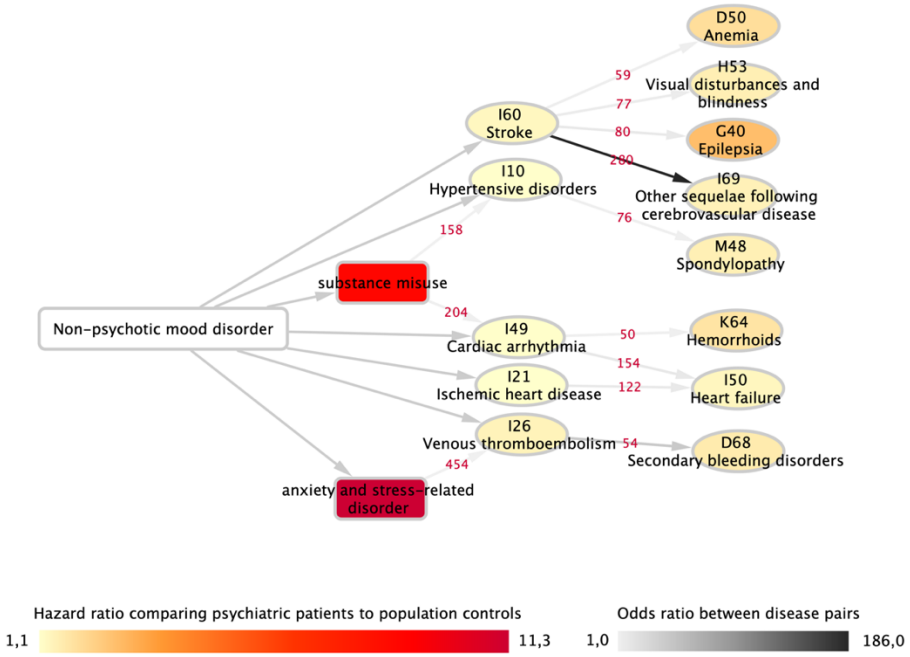
Figure S4. Disease trajectories toward different cardiovascular diseases among patients with substance misuse, non-psychotic mood disorders, and anxiety and stress-related disorders*

*This figure illustrates disease trajectories with direct and indirect links between psychiatric disorders and incident cardiovascular disease. The ICD codes used to cluster medical conditions are shown in circle. The color of each circle represents the magnitude of the association (hazard ratio) between psychiatric disorders and each medical condition. The color of arrows connecting two circles indicates the odds ratio of the association between two medical conditions among psychiatric patients. The number on the arrow corresponds to the number of pairs with both medical conditions among psychiatric patients.

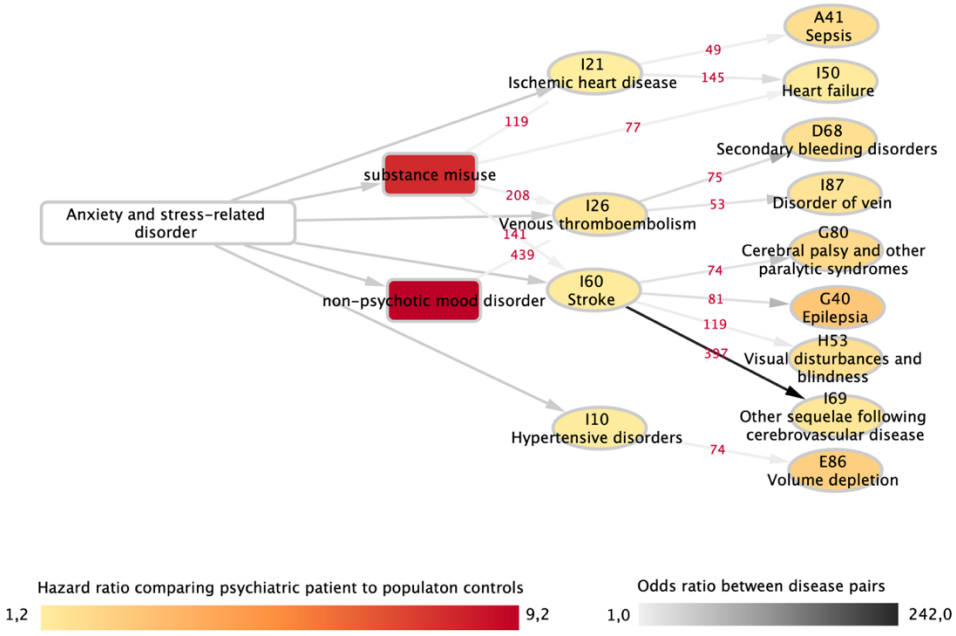
A. Patients with substance misuse



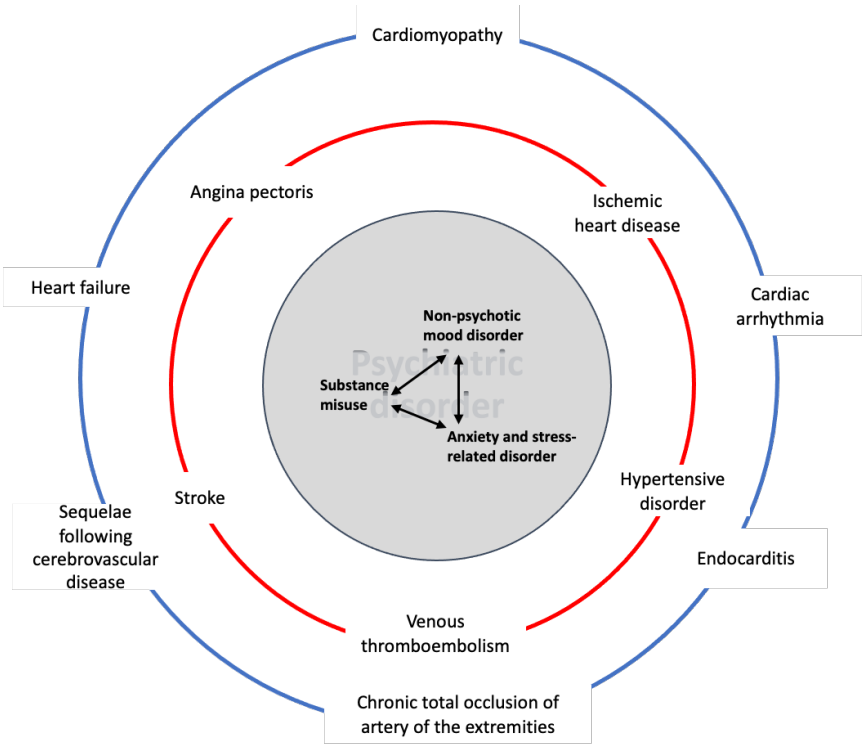
B. Patients with non-psychotic mood disorders



C. Patients with anxiety and stress-related disorders



D. Illustration of cardiovascular disease identified from A-C. Red circle denotes direct links and blue circle denotes indirect links.


Cardiomyopathy
Angina pectoris
Ischemic heart disease
Heart failure
Cardiac arrhythmia
Non-psychotic mood disorder
Psychiatric disorder
Substance misuse
Anxiety and stress-related disorder
Stroke
Hypertensive disorder
Sequelae following cerebrovascular disease
Endocarditis
Venous thromboembolism
Chronic total occlusion of artery of the extremities

Section 1: Description of method - Danish replication cohort

We identified a population of 7,563,467 persons residing during 1968-2016 in Denmark. Using personal identification numbers uniquely assigned to all Danish residents, we found in total 1,000,133 individuals diagnosed with a first-onset of any psychiatric disorder between 1 January 1977 and 31 December 2016 from the Danish National Patient Register,[1] as well as between 1 January 1969 and 31 December 2016 from the Danish Psychiatric Central Research Register.[2] Patients diagnosed with psychiatric disorders under age 1 (N=11,190, possible congenital/developmental anomalies), with a prevalent CVD before diagnosis of psychiatric disorders (N=100,991), or with conflicting information (emigrated, died or otherwise censored before diagnosis, N=12,318) were excluded, leaving 875,634 patients with a newly diagnosed psychiatric disorder in the analysis (Appendix Figure S1 flowchart). We ascertained date of first psychiatric diagnosis as the index date for the exposed patients.

The Danish Civil registration system is complete from 1968 from when it includes all individuals born in Denmark. Through linkage with the Danish National Patient register (since 1977) and the Danish Psychiatric Central Research Register (since 1969) diagnostic information can be obtained. The Danish Multi-Generation Register includes nearly complete familial linkage for Danish residents born since 1968. Through the Register, we identified 625,710 unaffected full siblings for 404,023 patients with psychiatric disorders (46.1 % of all exposed patients) who were alive and free of psychiatric disorders and CVD before diagnosis of the index patient. We randomly selected up to 10 age- and sex-matched individuals from the study base using the method of incidence density sampling per exposed individual (N=8,756,340). The date of psychiatric diagnosis for the index patient was used as the index date for unaffected siblings and matched reference population.

All study participants were followed from the index date until first diagnosis of any CVD, death, emigration, first diagnosis of psychiatric disorders (for unaffected siblings and matched

reference population), or the end of the study period (31 December 2016), whichever occurred first.

Ascertainment of Psychiatric Disorders and Cardiovascular Disease

We used the 8th and 10th revision of the International Classification of Diseases (ICD-8 and 10) codes to identify psychiatric disorders and CVD that were attended by specialized care, and their subtypes (ICD codes in below Table). We defined incident psychiatric disorders as any inpatient, emergency or outpatient visit with a psychiatric disorder as the main and auxiliary diagnoses from the Danish National Patient Register, or any visit as the main diagnosis from the Danish Psychiatric Central Research Register. CVD was ascertained as any first inpatient, emergency or outpatient visit with CVD as the primary diagnosis (according to Danish National Patient Register). We also identified fatal cardiovascular event as any death within 30 days of incident CVD according to the Danish Causes of Death Register and the Danish National Patient Register. We classified psychiatric disorders as Psychiatric and behavioral disorders due to psychoactive substance use (e.g., use of alcohol, cannabis, cocaine, opioids, etc.), schizophrenia and related disorders (e.g., schizoaffective disorders and other psychotic disorders), mood disorders(e.g., bipolar, and depressive disorders), anxiety disorders (e.g., neurotic, stress-related, and somatoform disorders: anxiety due to phobias, and obsessive-compulsive disorders), eating disorders (e.g., anorexia and bulimia nervosa), specific personality disorders, intellectual disabilities, developmental disorders (e.g., language and scholastic skill deficits, autism spectrum disorders) and behavioral and emotional disorders (e.g., attention-deficit hyperactivity disorder, conduct disorders). We categorized CVD as ischemic heart disease, cerebrovascular disease, emboli and thrombosis, hypertensive disease, heart failure, and arrhythmia/conduction disorder.

Covariates

Having any of the following conditions before the index date was defined as having a history of somatic diseases: dyslipidemia, diabetes melittus (diabetes melittus type 1, diabetes melittus type 2, gestational diabetes melittus), chronic pulmonary diseases, connective tissue diseases, renal diseases (including chronic kidney diseases), liver diseases (including chronic liver diseases), ulcer diseases, HIV infection/AIDS, any malignancy (including leukemia, lymphoma and metastatic cancer). We considered a family history of CVD as a diagnosis of any CVD among biological parents and full siblings of the study participants before the index date according to the Danish National Patient Register.

Table. International Classification of Diseases (ICD) codes for exposure, outcome, and covariates used in Danish replication cohort.

Psychiatric disorders	Abbreviation	ICD-10	ICD-8 equivalents	Start of follow-up (earliest possible age at onset, years)
Psychiatric and behavioral disorders due to psychoactive substance use E.g., use of alcohol, cannabis, cocaine, opioids, etc.	Substance use disorders	F10-F19	291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9	10
Schizophrenia and related disorders E.g., schizoaffective disorders and other psychotic disorders	Schizophrenia	F20-F29	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83	10
Mood disorders E.g., bipolar, and depressive disorders	Mood disorders	F30-F39	296.x9 (excluding 296.89), 298.09, 298.19, 300.19, 300.49	10
Anxiety disorders E.g., neurotic, stress-related, and somatoform disorders: anxiety due to phobias, and obsessive-compulsive disorders	Anxiety disorders	F40-F48	300.x9 (excluding 300.49), 305.x9, 305.68, 307.99	5
Eating disorders, E.g., anorexia and bulimia nervosa	Eating disorders	F50	305.60, 306.50, 306.58, 306.59	1
Specific personality disorders	Personality disorders	F60	301.x9 (excluding 301.19), 301.80, 301.81, 301.82, 301.84	10
Intellectual disabilities	Intellectual disorders	F70-F79	311.xx, 312.xx, 313.xx, 314.xx, 315.xx	1
Developmental disorders E.g., language and scholastic skill deficits, autism spectrum disorders	Developmental disorders	F80-F84	299.00, 299.01, 299.02, 299.03	1
Behavioral and emotional disorders E.g., attention-deficit hyperactivity disorder, conduct disorders	Behavioral disorders	F90-F98	306.x9, 308.0x	1

References:

1.The Danish National Patient Register - Elsebeth Lynge, Jakob Lynge Sandegaard, Matejka Rebolj, 2011. Accessed November 1, 2022. https://journals.sagepub.com/doi/10.1177/1403494811401482

2.Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health. 2011;39(7_suppl):54-57. doi:10.1177/1403494810395825

Section 2: Description of method - disease trajectory analysis

Disease trajectory analysis was performed to identify all disease trajectories following any psychiatric disorder, as well as after each type of psychiatric disorder, including non-affective psychotic disorder, affective psychotic disorder, substance misuse, non-psychotic mood disorder, anxiety and stress-related disorder, eating disorder, and attention deficit hyperactivity disorder (ADHD). We included psychiatric patients diagnosed during 2001 and 2016, due to the inclusion of outpatient health visit from 2001 and onward became largely available in the Swedish Patient Register. We used 3-digit ICD-10 codes for medical condition identification and diagnoses of medical conditions were based on main diagnosis in the register. We excluded diagnoses related to pregnancy, childbirth, perinatal conditions and unclassified symptoms or signs. We considered the diagnosis and date of first health record if multiple records with same medical condition were identified for the same patient.

Steps of analysis

Step 1: Phenome-wide association analyses (PheWAS) using conditional Cox regression model, to investigate the risk of all medical conditions in individuals with a psychiatric disorder compared to matched population controls. For each outcome in Cox regression analysis, a sub-cohort was formed by excluding individuals with a previous history of the outcome disease before start of follow-up (i.e., date of psychiatric disorder or index date), and follow-up of the individuals in the sub-cohort ended on date of the outcome disease diagnosis, death, emigration or end of study, whichever came first. To ensure statistical power, we limited the analyses to diseases that occurred in at least 100 patients with a psychiatric disorder. After the PheWAS, only medical conditions with p-value<Bonferroni corrected threshold and hazard ratio (HR)>1 were considered in the second step.

Step 2: to identify disease 1 (D1) and disease 2 (D2) pairs with explicit temporal order (i.e., disease 2 occurred after disease 1) among patients with a psychiatric disorder. When assessing disease trajectories related to cardiovascular diseases (CVD), we included only D1 or D2 to be any type of CVD in this step. D1 and D2 can be any medical condition when identifying disease trajectories of any medical condition. For each D1→D2 disease pair that was experienced by at least 50 psychiatric patients, binomial test was conducted to investigate whether significantly more patients (>50%) had D1 diagnosed before D2 among those with both D1 and D2 diagnoses. Patients with the same D1 and D2 diagnoses date were not included in the analysis. D1→D2 disease pairs with binomial test p-value<0.0001 (Bonferroni corrected P value in sensitivity analysis) threshold were forwarded to the third step.

Step 3: We used nested case-control study design and conditional logistic regression analyses to assess the magnitude of the associations between each disease pair. For each disease pair included, we constructed a nested case-control dataset using intensity density sampling, by considering D2 as outcome and D1 as exposure. In each case-control dataset, at most 2 controls were matched to each case, based on sex and year of birth as well as year of psychiatric diagnosis. Psychiatric patients with a history of D1 or D2 before start of follow-up were not included in the analysis.

Section 3: Replication of disease trajectories with direct link to incident cardiovascular diseases in Estonian Biobank (EstBB)

1. Description of the EstBB database

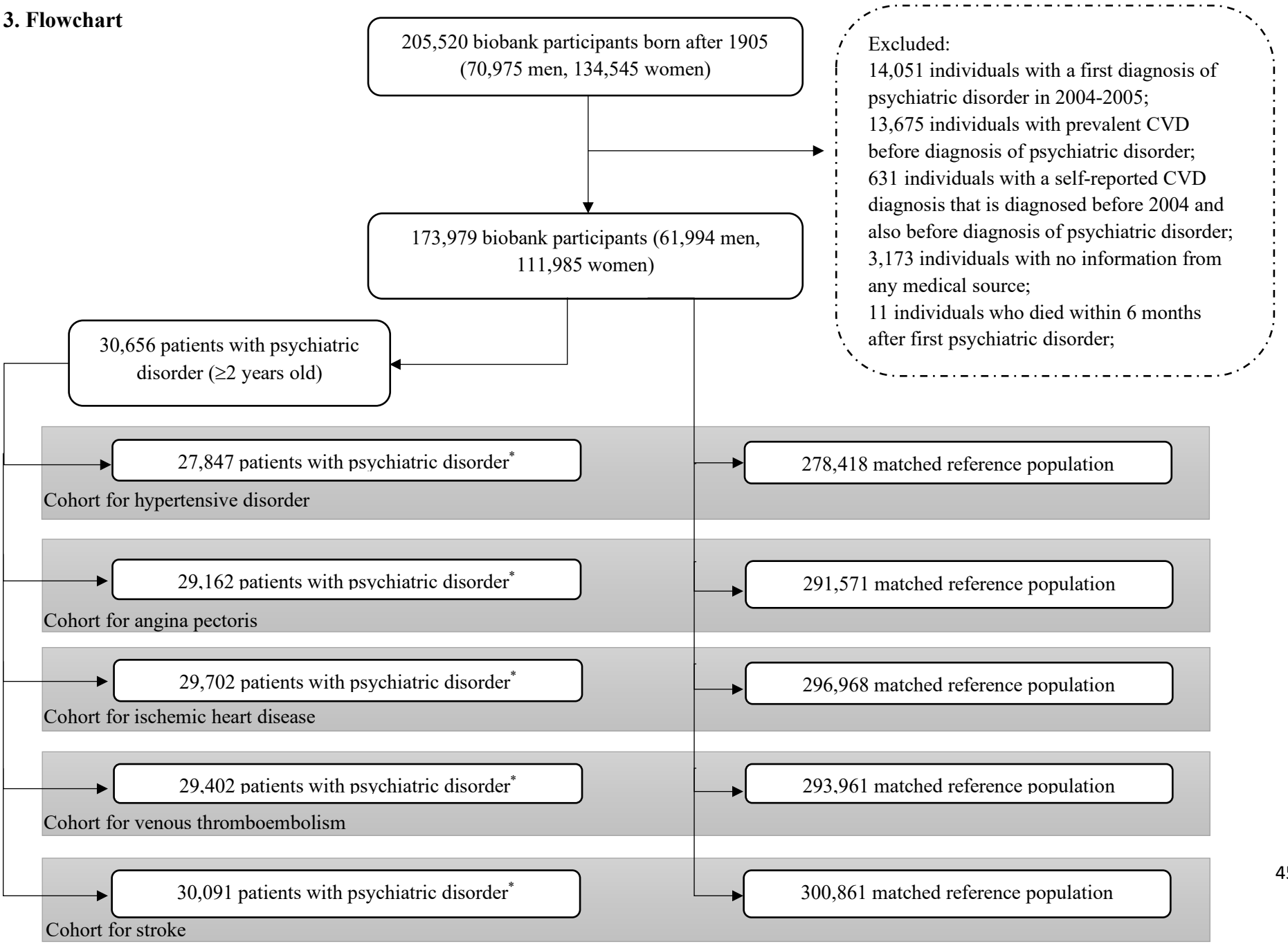
The Estonian Biobank (EstBB) is a population-based biobank of the Institute of Genomics at the University of Tartu. The current cohort size is more than 207,000 individuals, reflecting the age, sex and geographical distribution of the adult population in Estonia. All activities at the EstBB are conducted according to the Human Genes Research Act of Estonia and all the participants have signed a broad informed consent. In addition to self-reported data about participants' health status, lifestyle, and diet, the EstBB database is regularly linked with national registries, hospital databases, and the database of the national health insurance fund, which holds the treatment and service bills.

2. Construction of replication cohort

For the replication analysis of the association between psychiatric disorder and first-onset cardiovascular disease, the diagnoses in ICD-10 coding for every participant (N = 205,520) were obtained from the national health insurance fund from January 1, 2004 until December 31, 2020 (flowchart below). For individuals with chronic disorders (e.g, any psychiatric disorder, hypertension, ischemic heart disease) or angina pectoris, we restricted to individuals with at least two diagnoses within six months. For individuals with stroke or venous thromboembolism, one diagnosis was sufficient.

In order to study the association between first psychiatric disorder and subsequent cardiovascular disease (CVD), individuals diagnosed with any psychiatric disorder in 2004-2005 were excluded (*N*=14,501). Also, patients with a prevalent CVD before diagnosis of psychiatric disorder based on the registry data or self-reported data before 2004 were excluded (*N*=13,675 and *N*=631, respectively). In addition, we excluded individuals without information from any of the databases (*N*=3,173) or who died within six months after the first psychiatric diagnosis (*N*=11). The final dataset for the replication analyses included 173,979 individuals. Of them, 30,656 were individuals diagnosed with any psychiatric disorder.

3. Flowchart


205,520 biobank participants born after 1905 (70,975 men, 134,545 women)
Excluded:
14,051 individuals with a first diagnosis of psychiatric disorder in 2004-2005;
13,675 individuals with prevalent CVD before diagnosis of psychiatric disorder;
631 individuals with a self-reported CVD diagnosis that is diagnosed before 2004 and also before diagnosis of psychiatric disorder;
3,173 individuals with no information from any medical source;
11 individuals who died within 6 months after first psychiatric disorder;
173,979 biobank participants (61,994 men, 111,985 women)
30,656 patients with psychiatric disorder (≥2 years old)
27,847 patients with psychiatric disorder*
278,418 matched reference population
Cohort for hypertensive disorder
29,162 patients with psychiatric disorder*
291,571 matched reference population
Cohort for angina pectoris
29,702 patients with psychiatric disorder*
296,968 matched reference population
Cohort for ischemic heart disease
29,402 patients with psychiatric disorder*
293,961 matched reference population
Cohort for venous thromboembolism
30,091 patients with psychiatric disorder*
300,861 matched reference population
Cohort for stroke

*Each patient with a psychiatric disorder was matched with up to 10 reference population, based on birth year and sex. Psychiatric patients with outcome disease diagnosed within six months of psychiatric diagnosis were excluded from each cohort.

4. Methods

We estimated the risk of five CVDs following the diagnosis of any psychiatric disorder identified from disease trajectory analysis in Swedish cohort. The identified five CVDs were: hypertensive disorder, angina pectoris, ischemic heart disease, venous thromboembolism, stroke (ICD-10 codes and combined codes shown below). We assessed hazard ratios of these five CVDs comparing psychiatric patients to matched reference population using stratified Cox regression models.

Disease	Combined code	ICD-10 codes
Hypertensive disorders	I10	I10-I15
Angina pectoris	I20	I20
Ischemic heart disease	I21	I21-I25
Venous thromboembolism	I26	I26, I80-I82
Stroke	I60	I60-I67

For each individual with a psychiatric disorder, we selected 6-10 controls among individuals who were free of any psychiatric disorder and outcome disease within six months of the diagnosis of the index patient. Of note, individuals with at least one occurrence of chronic disorder (e.g, any psychiatric disorder, hypertension, ischemic heart disease) or angina pectoris that did not meet the requirement of two occurrence within six months were not selected as controls.

Stratified Cox regression was used to assess the risk of CVD in psychiatric patients compared to matched reference population. The start of follow-up was six months after indexed diagnosis of psychiatric disorder. The end of follow-up was the date of the CVD diagnosis of interest, date of death or end of follow-up period (December 31st, 2020), whichever occurred first. The R code used for modelling is shown below.

coxph(Surv(time = entry, time2 = exit, event = outcome_disease) ~ psychiatric_disorder + strata(Set), data)

The proportional hazard assumption was assessed based on the scaled Schoenfeld residuals using the *cox.zph()* function in R and graphical tests.

Section 4: Output from each step of disease trajectory analysis

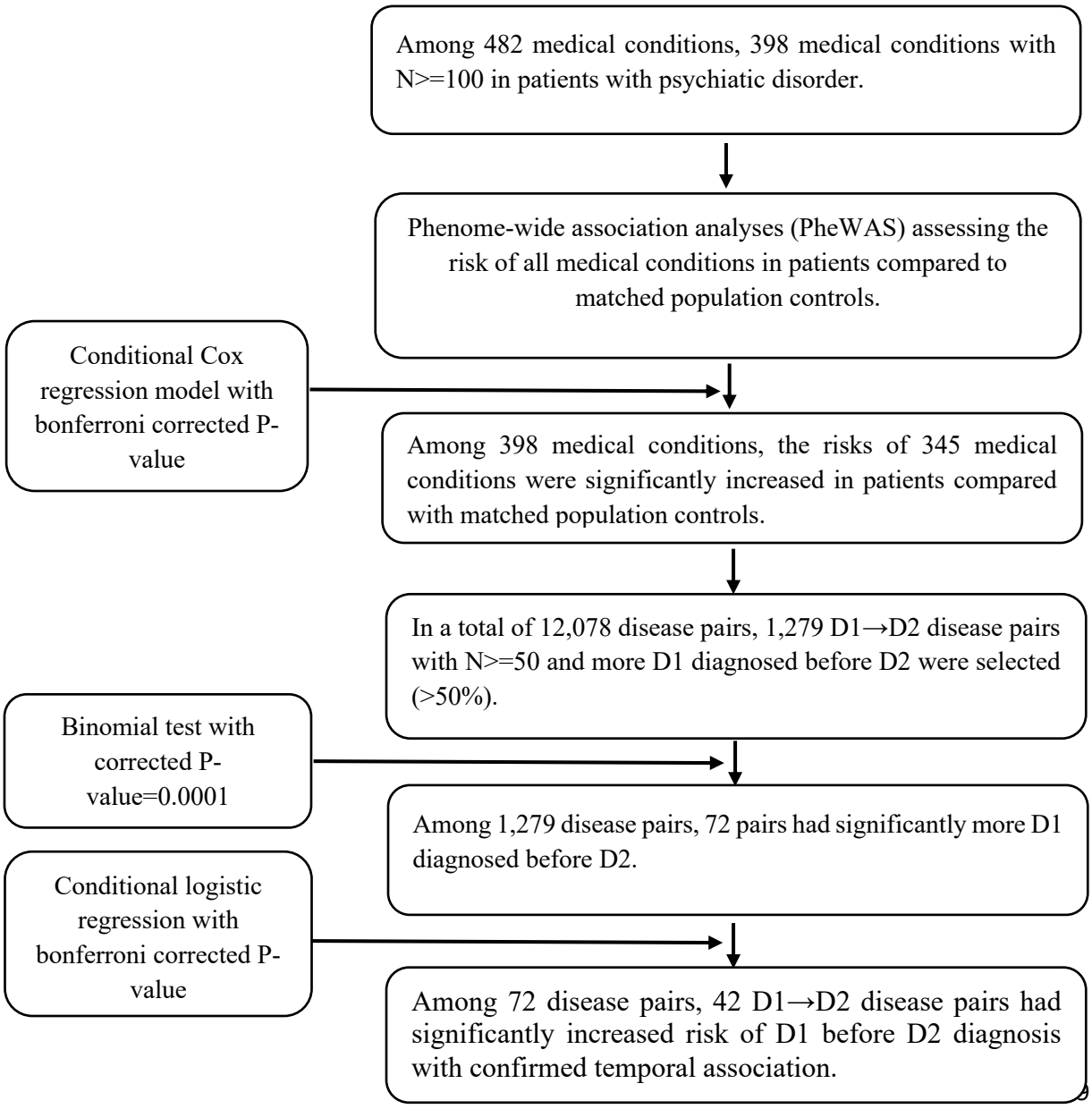
1. All psychiatric disorders (except for autism, N=729,950)

Step 1: A total of 482 medical conditions, 398 medical conditions with N>=100 in patients with psychotic disorder. Among 398 medical conditions, the risks of 345 medical conditions were significantly increased in patients with psychotic disorder, compared with matched population controls.

Step 2: In a total of 12,078 disease pairs, 1,279 D1→D2 disease pairs had D1 or D2 as CVD, with N>=50 and more D1 diagnosed before D2 (>50%) were selected. 72 D1→D2 disease pairs were identified with significantly more patients had D1 before D2.

Step 3: Among 72 disease pairs, 42 D1→D2 disease pairs had significantly increased risk of D1 before D2 diagnosis.

Flowchart



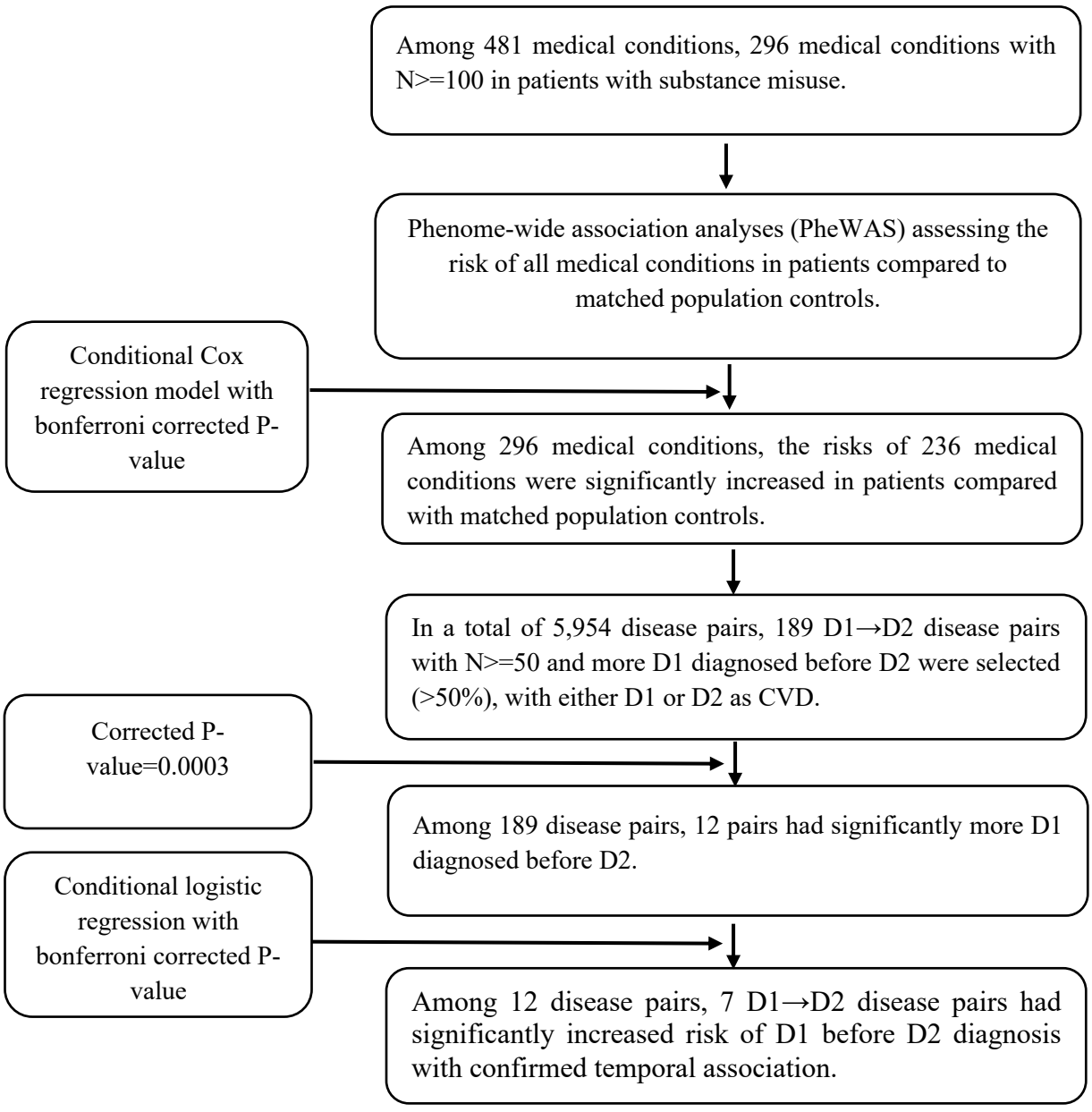
2. Substance misuse (N=124,189)

Step 1: A total of 481 medical conditions, 296 medical conditions with N>=100 in patients with substance misuse. Among 296 medical conditions, the risks of 236 medical conditions were significantly increased in patients with substance misuse, compared with matched population controls.

Step 2: In a total of 5,954 disease pairs, 189 D1→D2 disease pairs had D1 or D2 as CVD, with N>=50 and more D1 diagnosed before D2 (>50%) were selected. 12 D1→D2 disease pairs were identified with significantly more patients had D1 before D2.

Step 3: Among 12 disease pairs, 7 D1→D2 disease pairs had significantly increased risk of D1 before D2 diagnosis.

Flowchart



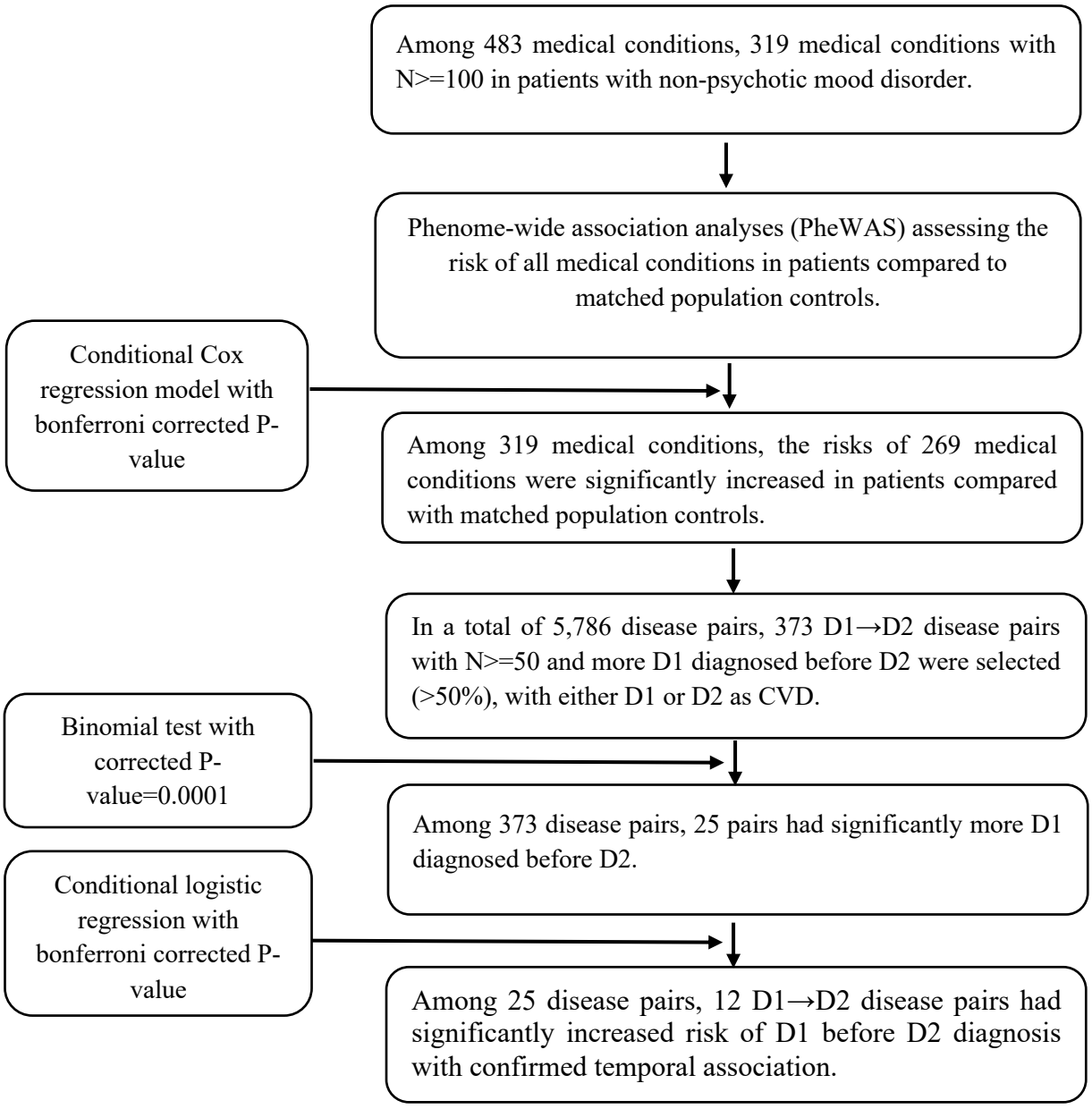
3. Non-psychotic mood disorders (N=159,055)

Step 1: A total of 483 medical conditions, 319 medical conditions with N>=100 in patients with non-psychotic mood disorder. Among 319 medical conditions, the risks of 269 medical conditions were significantly increased in patients with non-psychotic mood disorder, compared with matched population controls.

Step 2: In a total of 5,786 disease pairs, 373 D1→D2 disease pairs had D1 or D2 as CVD, with N>=50 and more D1 diagnosed before D2 (>50%) were selected. 25 D1→D2 disease pairs were identified with significantly more patients had D1 before D2.

Step 3: Among 25 disease pairs, 12 D1→D2 disease pairs had significantly increased risk of D1 before D2 diagnosis.

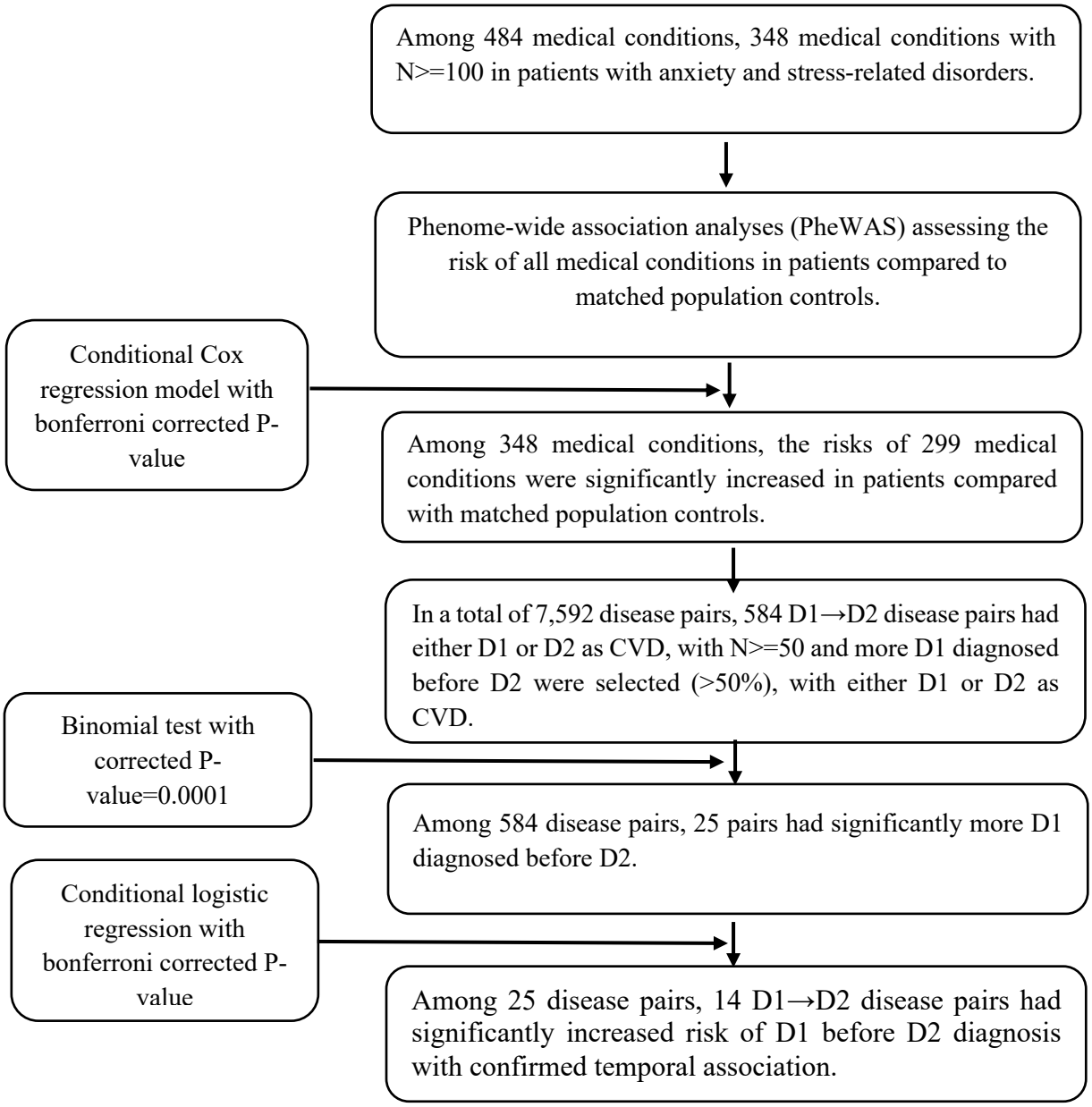
Flowchart



4. Anxiety and stress-related disorders (N=260,110)

Step 1: A total of 484 medical conditions, 348 medical conditions with N>=100 in patients with anxiety and stress-related disorders. Among 348 medical conditions, the risks of 299 medical conditions were significantly increased in patients with anxiety and stress-related disorders, compared with matched population controls.

Step 2: In a total of 7,592 disease pairs, 548 D1→D2 disease pairs had either D1 or D2 as CVD, with N>=50 and more D1 diagnosed before D2 (>50%) were selected, among which, 25 D1→D2 disease pairs were identified with significantly more patients had D1 before D2.

Step 3: Among 25 disease pairs, 14 D1→D2 disease pairs had significantly increased risk of D1 before D2 diagnosis.

Flowchart