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Risk of specific cardiovascular diseases in obsessive-compulsive disorder

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ABSTRACT

Individuals with obsessive-compulsive disorder (OCD) may have an increased risk of cardiovascular disease (CVD), but evidence for specific types of CVD is limited. This population-based, sibling-controlled cohort study investigated the risk of specific CVD in individuals with OCD. Linking data from various Swedish population-based registers, we explored the risk of a range of CVD in a cohort of individuals diagnosed with OCD between 1973 and 2013 (n = 33,561), compared to matched (1:10) unaffected individuals (n = 335,610). Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using conditional Cox proportional hazards regression models, adjusting for history of somatic diseases. To control for familial confounders, we analyzed 23,263 clusters of full siblings discordant for OCD. Individuals with psychiatric comorbidities were systematically excluded to assess the impact of these comorbidities. Over an average follow-up time of 27 years, OCD was associated with an increased risk of a broad range of CVD (adjusted HR [aHR] for any CVD = 1.25 [95% confidence interval [CI], 1.22–1.29]). These associations were strongest for the subtypes venous thrombo-embolism (aHR = 1.48 [95% CI, 1.38–1.58]) and heart failure (aHR = 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 resulted in comparable results, albeit attenuated. Individuals with OCD have a moderately increased risk of CVD-related morbidity, independent from history of somatic diseases, familial confounders, and psychiatric comorbidities. The time may be ripe for the development and evaluation of lifestyle interventions to help reduce the risk of cardiovascular morbidity in OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is an impairing psychiatric condition with a lifetime prevalence of about 2% (Ruscio et al., 2010). While OCD has been previously associated with a significantly increased risk of mortality (Meier et al., 2016), very little is known about the reasons leading to the reduced life expectancy of these individuals. Cardiovascular diseases (CVD) are the number one cause of death globally, accounting for 31% of all deaths (World Health Organization, 2017). In general, individuals with psychiatric disorders are a group of particularly high risk of CVD, with increased rates of both CVD-related morbidity and mortality (Harris and Barraclough, 1998; Lawrence et al., 2013; Momen et al., 2020; Roest et al., 2010; Song et al., 2019; Tiihonen et al., 2016), but OCD has rarely been studied separately from

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broader groups of anxiety or 'neurotic' disorders. This is important as the risks of CVD following a diagnosis of a psychiatric disorder vary considerably between disorders, and these risks also vary by specific CVD (Momen et al., 2020).

Only a handful of studies have explored the association between OCD and CVD, with mixed results. In a German population-based survey, Witthauer et al. (2014) did not find differences in the 12-month prevalence of self-reported cardiac diseases or hypertension when comparing a group of 239 individuals with OCD or subthreshold OCD and 3571 individuals without obsessive-compulsive symptoms. Similarly, a telephone survey conducted in Singapore (Chong et al., 2012) did not find an increased risk of self-reported cardiovascular disorders and hypertension and high blood pressure when comparing OCD cases with the general population. By contrast, a Swedish register-based study by our group showed that, compared to the general population, individuals with OCD (n = 25,415) had a 44% increased risk of broadly-defined circulatory system diseases (Isomura et al., 2018).

In this study, we aimed to further extend the results of our previous work on the association between OCD and cardiometabolic disorders (Isomura et al., 2018). Specifically, in our previous work, we used a single composite variable encompassing a wide range of circulatory system diseases. Thus, our understanding of the risks of specific groups of CVD in OCD is very limited. This is important to inform the rational development of prevention and treatment strategies, which may vary substantially depending on which specific CVD are most strongly associated with OCD. Hence, here we explored the risk of specific, rationally-defined groups of CVD in persons with OCD, while strictly controlling for somatic and psychiatric comorbidities, as well as potential familial confounders.

2. Material and methods

The study was approved by the Regional Ethical Review Board in Stockholm. The requirement for informed consent was waived since the study is register-based and the individuals are not identifiable at any time.

2.1. Data sources

In this population-based, sibling controlled-study, we linked several Swedish nationwide population-based registers by using the unique personal identification numbers assigned to all Swedish residents (Ludvigsson et al., 2009). Demographic data were derived from the Swedish Total Population Register, which contains information on all Swedish inhabitants since 1968 (Ludvigsson et al., 2016). The Migration Register contains a record on every immigration into and emigration out of Sweden (Ludvigsson et al., 2016). The Multi-Generation Register connects every person born in Sweden since 1932 or ever registered as living in Sweden after 1960 to their parents, enabling researchers to obtain a family pedigree for each subject (Ekbom, 2011). The National Patient Register (NPR) comprises information on inpatient care (since 1969 and 1973 for somatic and psychiatric disorders, respectively, with complete national coverage from 1987) and outpatient specialist services (since 2001) in Sweden, with all procedures and primary and supplementary diagnoses documented per visit for each individual. Diagnoses in the NPR are based on the International Classification of Diseases system in its eight (ICD-8; 1969–1986), ninth (ICD-9; 1987–1996), and tenth (ICD-10, 1997–2013) revisions (Ludvigsson et al., 2011). The Cause of Death Register contains a record of all deaths in Sweden since 1952, with compulsory reporting nationwide and also based on ICD codes (Brooke et al., 2017). In order to improve coverage of CVD that do not necessarily require specialist care, we also collected information from the Stockholm Regional Healthcare Data Warehouse (VAL in its Swedish acronym, *Vårdanalysdatabasen*) (Zarrinkoub et al., 2013), which contains information on all ICD-10 diagnoses given in primary care in the Stockholm Region since 2003.

2.2. Population matched cohort

Individuals born in Sweden who received a diagnosis of OCD at the age of 6 years or above between January 1, 1973 and December 31, 2013 were identified from the NPR and constituted the exposed cohort. Along the lines of prior register-based OCD research (Isomura et al., 2018), we considered individuals with OCD to be entering the cohort at their sixth birthday or on January 1, 1973, whichever occurred later (henceforth, the cohort entry date). This cohort entry date was chosen – instead of the date of first diagnosis – because OCD is an early onset, chronic disorder (American Psychiatric Association, 2013), but substantial delays in help-seeking or diagnosis are typical (Fullana et al., 2009; Garcia-Soriano et al., 2014; Torres et al., 2007); hence, the recorded date of first diagnosis in the NPR is a poor reflection of the disorder's actual date of onset. We therefore assume that individuals with a diagnosis of OCD were exposed at the time they entered the cohort, irrespective of the actual date of diagnosis. Individuals born earlier than 1932 were excluded to enable identification of the cohort members' full siblings from the Multi-Generation Register. Additionally, we excluded individuals with a diagnosis of CVD recorded before the cohort entry date, those that died or emigrated from Sweden before the cohort entry date, and those with conflicting information (e.g., individuals that appeared as having died or emigrated before being diagnosed with OCD). Unlike Isomura et al. (2018), the current study did not exclude individuals on the basis of any comorbidities, resulting on a larger cohort of OCD-diagnosed individuals than in our previous study. Then, for each of the exposed individuals, we identified and matched 10 unexposed controls randomly selected from the general population and that were free from a diagnosis of OCD during the study period. To be considered for matching, unexposed individuals had to be living in Sweden and free from any CVD at the date when OCD patients entered the cohort. The controls were selected from the Total Population Register and matched to OCD patients by sex, birth year, and county of birth. The cohorts of OCD-exposed individuals and matched controls were followed up from January 1, 1973 or their sixth birthday, whichever occurred last (i.e., from the cohort entry date), to the date of the outcome (see below), death, emigration from Sweden or end of the study period (i.e., December 31, 2013), whichever occurred first.

2.3. Sibling cohort

In order to control for shared familial confounders, the full siblings of OCD-exposed individuals were identified from the Multi-Generation Register. Family identification numbers were created for the linkage. Full siblings of OCD patients were considered for inclusion if they were singleton births, living in Sweden, free from a diagnosis of OCD during the study period, and did not have a diagnosis of any CVD before their sixth birthday or 1973, whichever occurred last. For the sibling comparison, each sibling was followed from age 6 or 1973, whichever occurred last, up to the date of outcome diagnosis, death, emigration from Sweden or end of the study period, whichever occurred first.

2.4. Exposure variable: obsessive-compulsive disorder

OCD was defined as at least one diagnosis during the study period, according to ICD-8 (code 300.3), ICD-9 (code 300D) or ICD-10 (code F42) recorded at the age of 6 years or older, in order to avoid misclassification of cases (Isomura et al., 2018). The ICD codes for OCD in the NPR have been previously validated by comparing the registered diagnoses with information in the medical records (Rück et al., 2015). The ICD-10 codes have excellent interrater reliability and validity, with positive predictive values (PPVs) ranging from 0.91 to 0.96, while ICD-8 and ICD-9 codes for OCD have moderate validity (PPV = 0.55 and PPV = 0.64, respectively).

2.5. Outcome variables: cardiovascular diseases

Cases of CVD (any, specific subtypes – including ischemic heart disease, cerebrovascular disease, venous thrombo-embolism, hypertensive diseases, heart failure, and arrhythmias – or individual events; see complete list and ICD codes in Supplemental Table 1) were defined from the NPR 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 through the underlying or contributory cause of death, using the same ICD codes. A number of CVD have been validated in the NPR, with PPVs ranging from 0.68 (non-fatal strokes) to 1.00 (myocardial infarction) (Ludvigsson et al., 2011).

2.6. Covariates

For each study participant, information on diagnoses of severe somatic diseases registered during the study period was collected from the NPR if ever recorded before the end of follow-up, including the records of chronic pulmonary disease, connective tissue disease, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS (ICD codes are listed in Supplemental Table 2).

Psychiatric comorbidities registered during the study period were also obtained from the NPR. Diagnoses were grouped into: 1) pervasive developmental disorders, 2) anxiety disorders, 3) stress-related disorders, 4) eating disorders, 5) depression and other mood-related disorders, 6) bipolar disorder, 7) schizophrenia and other psychotic disorders, and 8) substance use disorders (see Supplemental Table 3 for ICD codes).

2.7. Statistical analysis

Conditional Cox proportional hazards regression analyses were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for CVD in individuals with a diagnosis of OCD, compared to matched unexposed individuals without a diagnosis of OCD, taking time in days after the start of the follow-up as the underlying time scale. The analysis was first conducted for 'any CVD' as an outcome and then separately for each specific subtype and individual events. The initial model was stratified by the matching identifiers including birth year, sex, and county of birth (henceforth, unadjusted model) and was followed by a model additionally adjusted for history of severe somatic diseases. In subgroup analyses, we calculated the risk by sex.

In the subsample of full sibling clusters, all siblings within a family were compared to each other using stratified Cox proportional hazards regression models. By design, this analysis adjusts for all non-measured familial factors shared between siblings, including about 50% of the genetic load and shared environmental factors such as childhood sociodemographic status, parental medical history or parental level of education (D'Onofrio et al., 2013). The models were adjusted for sex, birth year, and county of birth, and then additionally adjusted for history of severe somatic diseases.

To further explore the impact of psychiatric comorbidities on the association between OCD and CVD, the analyses adjusted for history of severe somatic diseases were repeated after excluding individuals with different groups of comorbid psychiatric disorders, one disorder group at a time. This was done to explore the specific contribution to each group of psychiatric comorbidities, as the magnitude of their associated CVD risks is known to vary (Momen et al., 2020).

Finally, we performed four sensitivity analyses. First, because some of the outcomes under study may not necessarily require specialist care (e.g., hypertensive disorders, arrhythmia/conduction disorder) and to improve coverage, we repeated the main analysis ascertaining the CVD under study both from the NPR and from the primary care (i.e., VAL) database (Stockholm Region only). Within the subset of individuals living in Stockholm Region between 2003 (start date of VAL database) and 2013, those OCD-exposed individuals were matched to 10 unexposed individuals by the same matching identifiers as in the main analysis. Individuals were then followed-up from January 1, 2003, their sixth birthday or the date of moving to Stockholm county, whichever occurred last, to the date of the outcome (as in the main analysis), death, moving out of the Stockholm county or the end of the study. Second, we changed the definition for the 'cohort entry date' and followed OCD-exposed and unexposed individuals from the actual date of OCD diagnosis among the exposed. Individuals exposed to OCD were excluded if the diagnosis of any CVD preceded the diagnosis of OCD. For each exposed, 10 unexposed individuals were selected if they were free from OCD and CVD at the date when the exposed individuals received OCD diagnosis (matched by the same matching identifiers as in the main analysis). For unexposed individuals, the follow-up was additionally censored at the date of their first OCD diagnosis under the study, if any. Cox proportional hazards regression models were stratified by the matching identifiers and further adjusted for history of severe somatic diseases. Third, in the subgroup of individuals with data available from age 6, the expected cumulative incidence of 'any CVD' for exposed and unexposed individuals by the end of the follow-up (i.e., at age 46 years) was calculated using Kaplan-Meier survival estimates (under the assumption of no competing risks). The main analysis was repeated in this subgroup in order to ensure complete follow-up from this age, thus avoiding issues with left truncation (i.e., exposure and/or outcome happening before the register started and thus missing). Lastly, since the validity of the ICD-8 and ICD-9 codes in the NPR is somewhat lower (Rück et al., 2015) and the diagnoses from the NPR, if recorded prior to 2001, solely represent inpatient care, we repeated the main analyses among the individuals diagnosed with the exposure and the outcome from 2001 onwards to reduce a potential misclassification and avoid bias from more severe cases.

Data management and analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA) and STATA version 15.1 (StataCorp LLC, College Station, TX, USA). All tests employed two-tailed significance set at $p < 0.05$ and robust standard errors.

3. Results

3.1. Population matched and sibling cohorts

After applying all inclusion and exclusion criteria (Fig. 1), we identified 33,561 individuals with a diagnosis of OCD and 335,610 matched unexposed population controls (see characteristics in Table 1). Frequencies and proportions of each subtype of CVD in cases and controls are shown in Supplemental Table 4. After controlling for history of severe somatic diseases, the cohort of individuals with OCD had a 25% increased risk of any CVD, compared to the matched controls (adjusted HR [aHR] = 1.25 [95% CI, 1.22–1.29]). Similarly, the risk of each specific CVD subtype or individual event was also significantly higher in individuals with OCD, compared to the matched controls, except for the individual events acute coronary syndrome, subarachnoidal bleeding, hemorrhagic stroke, ischemic cardiomyopathy, AV-block II-III, and atrial fibrillation/fludder (Table 2).

Overall, subgroup results by sex were largely comparable, with slightly higher estimates for women across most outcomes. Women showed significantly increased risks for ischemic heart disease (aHR = 1.21) and all the individual events in this category, while men had an increased risk of sick sinus syndrome (aHR = 2.07), which was not present in women (Supplemental Table 5).

When unexposed siblings were used as controls (23,263 identified clusters of full siblings discordant for OCD among 2,463,173 families with at least two singleton children), we obtained comparable results to those in the population matched-cohort analyses (Table 2). The significant associations of OCD and CVD outcomes that were observed in the main analysis persisted in the sibling analysis or became stronger for some outcomes (e.g., individual events chronic coronary syndrome and heart failure and individual event ischemic heart disease). The only

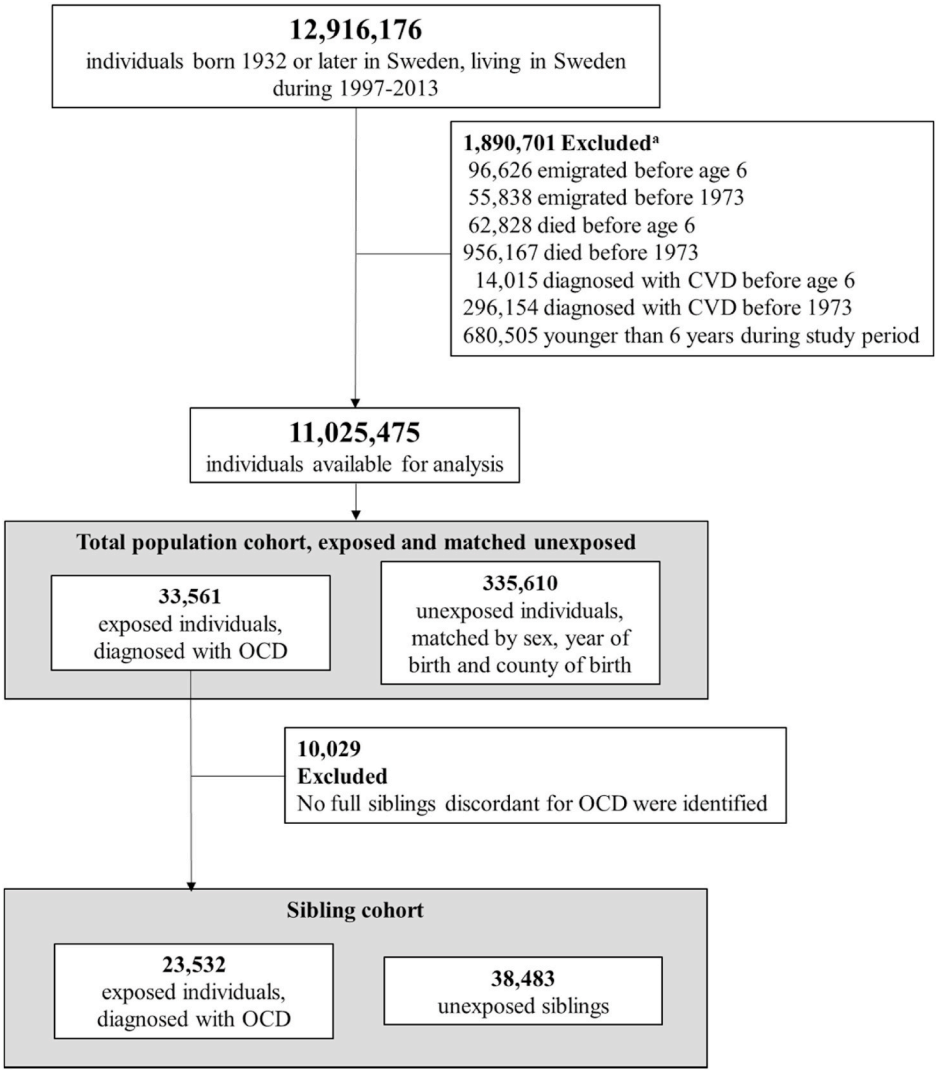

Fig. 1. Study design.
Abbreviations: CVD, cardiovascular disease; OCD, obsessive-compulsive disorder.
a The frequencies of the reasons for exclusion may not add up to the total number of excluded cases since the individuals excluded may have had more than one of these reasons to be excluded.

Table 1
Characteristics of study cohorts.

	Individuals with OCD n = 33,561		Individuals without OCD n = 335,610	
	median	IQR	median	IQR
Follow-up time, years	27.00	18.00–37.00	26.00	18.00–37.16
	n	%	n	%
Women	19,017	56.66	190,170	56.66
Any severe somatic disease	4571	13.62	31,965	9.52
Any psychiatric disorder[a]	25,947	77.31	42,530	12.67
Pervasive developmental disorders	3739	11.14	2319	0.69
Anxiety disorders	16,687	49.72	15,321	4.57
Stress-related disorders	5917	17.63	9345	2.78
Eating disorders	2594	7.73	2422	0.72
Depression and other mood-related disorders	14,962	44.58	17,976	5.36
Bipolar disorder	3375	10.06	3029	0.90
Schizophrenia and other psychotic disorders	4065	12.11	3815	1.14
Substance use disorders	5961	17.76	14,401	4.29

[a] Individuals may be diagnosed with more than one psychiatric condition.

exceptions were the association with supraventricular tachycardia, which lost significance in the sibling comparison, and the associations with acute coronary syndrome and AV-block II-III, which became statistically significant, compared to the main analysis.

When different groups of psychiatric comorbidities were excluded from the main analysis, the results remained mainly comparable, albeit the magnitude of the estimates was attenuated. When anxiety disorders, depression and other mood disorders, and substance use disorders were excluded, this attenuation was particularly notable for the ischemic heart disease, hypertensive diseases, and arrhythmias subgroups (Table 3).

3.2. Sensitivity analyses

Results restricted to the Stockholm Region, including CVD diagnoses given both in specialist services and in primary care, were overall comparable to those with CVD diagnoses retrieved from specialist services only in the Stockholm Region (e.g., for any CVD: aHR = 1.31 [95% CI, 1.22–1.40] in the NPR and VAL *vs.* 1.43 [95% CI, 1.32–1.56] in the NPR only; for diagnoses generally diagnosed in primary care: aHR for hypertensive diseases subtype = 1.16 [95% CI 1.07–1.26] *vs.* 1.36 [95% CI, 1.22–1.52], respectively; aHR for arrhythmias subtype = 1.25 [95% CI, 1.04–1.49] *vs.* 1.26 [95% CI, 1.05–1.51], respectively) (Supplemental Table 6).

Table 2
Risk of cardiovascular disease in individuals with obsessive-compulsive disorder, compared to matched unaffected individuals from the general population and to their unaffected full siblings.

	Population matched comparison cohort		Sibling comparison cohort	
	HR (95%CI), unadjusted	HR (95%CI), adjusted for history of severe somatic diseases	HR (95%CI), unadjusted	HR (95%CI), adjusted for history of severe somatic diseases
Any cardiovascular disease	1.26 (1.23–1.30)	1.25 (1.22–1.29)	1.36 (1.29–1.42)	1.34 (1.28–1.40)
Ischemic heart disease	1.09 (1.03–1.14)	1.08 (1.03–1.14)	1.31 (1.18–1.46)	1.29 (1.16–1.43)
Acute coronary syndrome (ACS)	1.03 (0.97–1.10)	1.03 (0.97–1.10)	1.23 (1.08–1.41)	1.21 (1.06–1.38)
Chronic coronary syndrome (without ACS)	1.12 (1.05–1.20)	1.12 (1.05–1.19)	1.41 (1.24–1.59)	1.39 (1.23–1.57)
Cerebrovascular disease	1.25 (1.18–1.33)	1.25 (1.18–1.33)	1.35 (1.21–1.52)	1.35 (1.20–1.52)
Subarachnoidal bleeding	1.05 (0.84–1.31)	1.05 (0.85–1.31)	0.87 (0.62–1.21)	0.88 (0.62–1.25)
Hemorrhagic stroke	1.12 (0.96–1.30)	1.12 (0.96–1.30)	1.25 (0.95–1.63)	1.27 (0.97–1.66)
Ischemic stroke	1.26 (1.17–1.37)	1.26 (1.17–1.36)	1.44 (1.23–1.68)	1.42 (1.22–1.67)
Other cerebrovascular disease	1.33 (1.23–1.45)	1.34 (1.23–1.45)	1.41 (1.20–1.65)	1.41 (1.20–1.66)
Venous thrombo-embolism	1.50 (1.40–1.60)	1.48 (1.38–1.58)	1.68 (1.50–1.88)	1.65 (1.47–1.85)
Deep vein thrombosis	1.45 (1.33–1.58)	1.42 (1.30–1.55)	1.60 (1.40–1.83)	1.56 (1.36–1.79)
Pulmonary emboli	1.54 (1.39–1.71)	1.54 (1.39–1.71)	1.91 (1.58–2.30)	1.90 (1.57–2.30)
Hypertensive diseases	1.17 (1.12–1.22)	1.14 (1.10–1.19)	1.30 (1.22–1.39)	1.26 (1.18–1.35)
Essential hypertension	1.18 (1.13–1.23)	1.15 (1.10–1.20)	1.31 (1.23–1.40)	1.27 (1.19–1.36)
Other hypertensive disease	1.23 (1.11–1.36)	1.21 (1.09–1.34)	1.36 (1.14–1.62)	1.28 (1.07–1.53)
Heart failure	1.39 (1.30–1.48)	1.37 (1.28–1.46)	1.72 (1.50–1.98)	1.67 (1.45–1.93)
Heart failure	1.40 (1.31–1.50)	1.38 (1.29–1.48)	1.80 (1.55–2.09)	1.75 (1.51–2.04)
Ischemic cardiomyopathy	1.39 (0.95–2.04)	1.38 (0.94–2.01)	1.76 (0.75–4.11)	1.71 (0.72–4.06)
Other cardiomyopathy	1.70 (1.43–2.03)	1.70 (1.43–2.03)	1.40 (1.07–1.83)	1.39 (1.06–1.82)
Arrhythmias	1.17 (1.10–1.24)	1.17 (1.10–1.24)	1.27 (1.15–1.40)	1.27 (1.15–1.41)
Bradyarrhythmias	1.30 (1.07–1.59)	1.30 (1.07–1.58)	1.93 (1.36–2.74)	2.03 (1.42–2.90)
Sick sinus syndrome	1.57 (1.07–2.29)	1.60 (1.09–2.35)	2.86 (1.29–6.34)	3.03 (1.27–7.26)
AV-block II-III	1.22 (0.97–1.53)	1.21 (0.96–1.52)	1.75 (1.18–2.59)	1.90 (1.26–2.85)
Takyarrhythmias	1.10 (1.03–1.17)	1.10 (1.03–1.18)	1.20 (1.08–1.33)	1.21 (1.09–1.35)
Atrial fibrillation/fludder	0.99 (0.91–1.06)	0.99 (0.92–1.07)	1.01 (0.87–1.16)	1.01 (0.88–1.17)
Supraventricular tachycardia	1.18 (1.01–1.38)	1.18 (1.01–1.38)	1.00 (0.81–1.24)	1.04 (0.84–1.30)
Ventricular tachycardia	1.83 (1.58–2.11)	1.83 (1.58–2.11)	1.97 (1.57–2.48)	2.00 (1.59–2.52)
Cardiac arrest	1.60 (1.38–1.85)	1.57 (1.36–1.82)	1.60 (1.20–2.15)	1.53 (1.13–2.07)

Note: HRs were derived from the analyses of individuals who were followed from age 6 or 1973, whichever occurred last.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Another sensitivity analysis was conducted among individuals exposed and unexposed to OCD who were followed from the actual date of OCD diagnosis among the exposed. Results were overall comparable to those in the main analysis (e.g., for any CVD, aHR = 1.29 [95% CI, 1.25–1.34]), although the associations became considerably stronger for some outcomes (e.g., subtypes ischemic heart disease, cerebrovascular disease, and heart failure and individual events hearth failure and cardiac arrest) and some associations lost its significance (e.g., the subtype hypertensive diseases and all the individual events within this group) (Supplemental Table 7).

In the subcohort of individuals who were followed from age 6 (n = 22,884 individuals with OCD and 228,840 matched controls), the Kaplan-Meier expected cumulative incidence of any CVD at the end of the follow-up was 15.12% (95% CI, 13.61%–16.78%) for the OCD group and 9.28% (95% CI, 8.90%–9.67%) for the controls (Fig. 2). The risks of CVD using this subgroup were overall slightly higher to those in the main analysis using the whole cohort (e.g., for any CVD: aHR = 1.56 [95% CI, 1.46–1.65]) (Supplemental Table 8).

Finally, the analyses including cases of OCD and CVD diagnosed from 2001, when the outpatient records were included in the NPR, also showed considerably higher estimates (e.g., for any CVD, aHR = 1.39 [95% CI, 1.33–1.44]) than that in the main analysis (Supplemental Table 9).

4. Discussion

This is the first study to examine the risk of specific CVD morbidity in patients with OCD. OCD-diagnosed individuals had an overall 25% increased risk of a broad range of CVD. Individuals with OCD seemed particularly vulnerable to the subtypes venous thrombo-embolism (48% increased risk) and heart failure (37% increased risk). Other specific events such as ventricular tachycardia, other cardiomyopathy, sick sinus syndrome, cardiac arrest, and pulmonary emboli were also particularly associated to an OCD diagnosis (83%, 70%, 57%, and 54% increased risk, respectively). Results were largely comparable in women and men with OCD, and the reported associations were independent from history of severe somatic diseases and shared familial factors.

The exclusion of relevant groups of psychiatric comorbidities did not alter the results considerably, although when anxiety disorders, depression and other mood disorders, and substance use disorders were excluded, the associations were attenuated. This was somewhat expected since these disorders have been previously linked to CVD in their own right (Roest et al., 2010; Shi et al., 2017; Thylstrup et al., 2015). However, the exclusion of other groups of psychiatric comorbidities also known to be linked to cardiovascular outcomes (e.g., schizophrenia and other psychotic disorders, stress-related disorders) (Correll et al., 2017; Song et al., 2019) did not influence the risk, indicating that the associations of interest were not likely to be explained by these combinations of psychiatric disorders.

These results expand previous findings from our group which had shown an increased risk of broadly-defined circulatory system diseases in individuals with OCD, compared with non-exposed individuals from the general population (Isomura et al., 2018). The results are consistent with those of a small naturalistic, cross-sectional study including 162 young Italian patients with OCD from a specialist clinic where 14% reported to have CVD (Aguglia et al., 2018) *vs.*15.4% in the current study. However, the results contrast with those of two previous cross-sectional surveys that collected information on CVD via self-report and did not find an association (Chong et al., 2012; Witthauer et al., 2014). Our estimates are in line with previous literature reporting elevated cardiovascular risk in other psychiatric disorders (Momen et al., 2020; Roest et al., 2010; Song et al., 2019). However, head-to-head comparisons between disorders are difficult given the wide range of methods previously used to explore this question. A study also using the Swedish

Table 3
Risk of cardiovascular diseases in individuals with obsessive-compulsive disorder, compared to matched unaffected individuals from the general population, after excluding different groups of psychiatric disorders (one group at the time).

	Excluding pervasive developmental disorders	Excluding anxiety disorders	Excluding stress-related disorders	Excluding eating disorders	Excluding depression and other mood disorders	Excluding bipolar disorder	Excluding schizophrenia and other psychotic disorders	Excluding substance use disorders
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Any cardiovascular disease	1.25 (1.21–1.29)	1.09 (1.05–1.13)	1.20 (1.16–1.24)	1.23 (1.20–1.27)	1.16 (1.11–1.20)	1.23 (1.19–1.27)	1.23 (1.20–1.27)	1.16 (1.12–1.20)
Ischemic heart disease	1.08 (1.03–1.14)	0.96 (0.90–1.03)	1.04 (0.98–1.10)	1.08 (1.02–1.14)	1.04 (0.97–1.12)	1.08 (1.02–1.14)	1.07 (1.01–1.13)	0.99 (0.93–1.05)
Acute coronary syndrome (ACS)	1.03 (0.97–1.10)	0.91 (0.84–0.99)	0.99 (0.92–1.05)	1.03 (0.96–1.09)	1.02 (0.94–1.10)	1.03 (0.96–1.10)	1.03 (0.96–1.10)	0.94 (0.88–1.01)
Chronic coronary syndrome (without ACS)	1.12 (1.05–1.20)	0.99 (0.91–1.07)	1.05 (0.98–1.13)	1.12 (1.05–1.19)	1.03 (0.95–1.13)	1.12 (1.04–1.19)	1.13 (1.05–1.21)	1.04 (0.96–1.11)
Cerebrovascular disease	1.25 (1.17–1.33)	1.20 (1.11–1.30)	1.21 (1.13–1.29)	1.24 (1.16–1.32)	1.15 (1.06–1.25)	1.23 (1.16–1.32)	1.22 (1.14–1.30)	1.18 (1.10–1.27)
Subarachnoidal bleeding	1.03 (0.82–1.29)	1.18 (0.89–1.57)	1.14 (0.90–1.45)	1.06 (0.85–1.32)	1.16 (0.87–1.56)	1.05 (0.83–1.32)	1.17 (0.93–1.48)	1.02 (0.79–1.31)
Hemorrhagic stroke	1.13 (0.97–1.31)	1.09 (0.90–1.32)	1.13 (0.97–1.33)	1.11 (0.95–1.29)	1.23 (1.01–1.49)	1.15 (0.98–1.34)	1.09 (0.92–1.29)	1.02 (0.86–1.22)
Ischemic stroke	1.26 (1.16–1.36)	1.20 (1.08–1.33)	1.20 (1.10–1.30)	1.25 (1.15–1.35)	1.12 (1.01–1.25)	1.24 (1.14–1.35)	1.21 (1.11–1.32)	1.19 (1.09–1.30)
Other cerebrovascular disease	1.34 (1.23–1.45)	1.25 (1.13–1.39)	1.28 (1.17–1.39)	1.33 (1.22–1.44)	1.17 (1.04–1.31)	1.31 (1.20–1.43)	1.31 (1.19–1.43)	1.24 (1.14–1.36)
Venous thrombo-embolism	1.48 (1.38–1.59)	1.24 (1.12–1.37)	1.37 (1.27–1.48)	1.47 (1.37–1.58)	1.32 (1.19–1.46)	1.42 (1.31–1.53)	1.35 (1.25–1.46)	1.32 (1.22–1.43)
Deep vein thrombosis	1.44 (1.32–1.57)	1.23 (1.09–1.40)	1.31 (1.19–1.45)	1.42 (1.30–1.55)	1.30 (1.15–1.48)	1.36 (1.24–1.49)	1.31 (1.19–1.45)	1.29 (1.17–1.42)
Pulmonary emboli	1.51 (1.36–1.68)	1.23 (1.05–1.43)	1.45 (1.29–1.62)	1.52 (1.36–1.68)	1.35 (1.16–1.58)	1.47 (1.32–1.65)	1.41 (1.25–1.59)	1.37 (1.21–1.55)
Hypertensive diseases	1.15 (1.11–1.20)	0.97 (0.92–1.03)	1.08 (1.03–1.13)	1.14 (1.09–1.19)	0.98 (0.92–1.04)	1.12 (1.07–1.17)	1.17 (1.12–1.22)	1.05 (1.00–1.10)
Essential hypertension	1.16 (1.11–1.22)	0.97 (0.91–1.03)	1.09 (1.04–1.14)	1.15 (1.10–1.20)	0.98 (0.92–1.05)	1.12 (1.07–1.18)	1.18 (1.13–1.24)	1.06 (1.01–1.12)
Other hypertensive disease	1.21 (1.09–1.34)	1.07 (0.93–1.23)	1.13 (1.01–1.27)	1.20 (1.08–1.34)	1.09 (0.95–1.26)	1.18 (1.06–1.31)	1.21 (1.08–1.36)	1.10 (0.98–1.24)
Heart failure	1.36 (1.27–1.45)	1.29 (1.19–1.41)	1.35 (1.26–1.45)	1.37 (1.28–1.46)	1.34 (1.23–1.46)	1.35 (1.26–1.45)	1.29 (1.20–1.39)	1.28 (1.19–1.38)
Heart failure	1.37 (1.28–1.46)	1.29 (1.18–1.40)	1.36 (1.27–1.46)	1.38 (1.29–1.47)	1.35 (1.23–1.47)	1.37 (1.28–1.47)	1.31 (1.21–1.41)	1.29 (1.20–1.39)
Ischemic cardiomyopathy	1.42 (0.97–2.07)	1.56 (0.95–2.54)	1.29 (0.84–1.99)	1.39 (0.95–2.04)	0.80 (0.41–1.54)	1.42 (0.95–2.10)	1.42 (0.93–2.16)	1.27 (0.81–1.99)
Other cardiomyopathy	1.79 (1.49–2.14)	1.87 (1.47–2.39)	1.71 (1.40–2.07)	1.73 (1.45–2.08)	2.06 (1.63–2.60)	1.57 (1.29–1.91)	1.60 (1.30–1.96)	1.72 (1.39–2.12)
Arrhythmias	1.16 (1.09–1.23)	0.98 (0.91–1.07)	1.16 (1.09–1.23)	1.14 (1.07–1.21)	1.12 (1.03–1.21)	1.16 (1.09–1.23)	1.15 (1.08–1.23)	1.09 (1.02–1.16)
Bradyarrhythmias	1.24 (1.01–1.52)	1.20 (0.93–1.55)	1.28 (1.04–1.58)	1.24 (1.01–1.53)	1.11 (0.83–1.48)	1.34 (1.09–1.65)	1.25 (1.01–1.56)	1.28 (1.03–1.59)
Sick sinus syndrome	1.49 (1.00–2.21)	1.33 (0.81–2.18)	1.65 (1.11–2.44)	1.55 (1.05–2.28)	1.22 (0.70–2.13)	1.65 (1.12–2.43)	1.59 (1.05–2.41)	1.47 (0.96–2.26)
AV-block II-III	1.17 (0.92–1.48)	1.17 (0.87–1.57)	1.16 (0.91–1.48)	1.15 (0.91–1.46)	1.11 (0.80–1.53)	1.24 (0.98–1.58)	1.18 (0.92–1.51)	1.21 (0.94–1.56)
Takyarrhythmias	1.10 (1.03–1.17)	0.91 (0.83–0.99)	1.08 (1.01–1.16)	1.08 (1.01–1.15)	1.05 (0.96–1.15)	1.10 (1.02–1.17)	1.11 (1.04–1.20)	1.05 (0.97–1.13)
Atrial fibrillation/ fludder	1.00 (0.92–1.08)	0.85 (0.77–0.94)	0.99 (0.92–1.08)	0.99 (0.91–1.06)	0.96 (0.87–1.06)	0.98 (0.90–1.06)	1.00 (0.92–1.09)	0.96 (0.88–1.04)
Supraventricular tachycardia	1.23 (1.05–1.45)	1.01 (0.79–1.29)	1.13 (0.94–1.35)	1.19 (1.01–1.40)	1.11 (0.89–1.39)	1.25 (1.07–1.47)	1.23 (1.04–1.45)	1.16 (0.97–1.38)
Ventricular tachycardia	1.74 (1.49–2.03)	1.26 (1.00–1.60)	1.72 (1.47–2.03)	1.70 (1.45–1.98)	1.64 (1.33–2.03)	1.81 (1.55–2.11)	1.81 (1.54–2.13)	1.62 (1.36–1.92)
Cardiac arrest	1.55 (1.34–1.80)	1.33 (1.09–1.62)	1.59 (1.36–1.86)	1.51 (1.30–1.75)	1.62 (1.33–1.99)	1.52 (1.30–1.77)	1.37 (1.15–1.62)	1.34 (1.13–1.59)

Note: The results are reported from the model adjusted for history of severe somatic disorders.
Abbreviations: CI, confidence interval; HR, hazard ratio.

registers but a slightly different analytical approach showed that individuals with stress-related disorders, including posttraumatic stress disorder, had a 64% increased risk of a similar group of any CVD, higher than our reported figures (Song et al., 2019). In the study by Momen et al. (2020), the group of 'neurotic' disorders had a 43% increased risk of circulatory disorders, lower than the 68% in behavioral disorders or the 55% in eating disorders. This indicates that not all psychiatric disorders carry the same risks of CVD morbidity, and that OCD might be a "medium risk group," compared to other psychiatric conditions.

While our study cannot provide definite evidence about the underlying pathophysiology explaining these associations, the fact that the results of the sibling analyses were very similar to those of the main

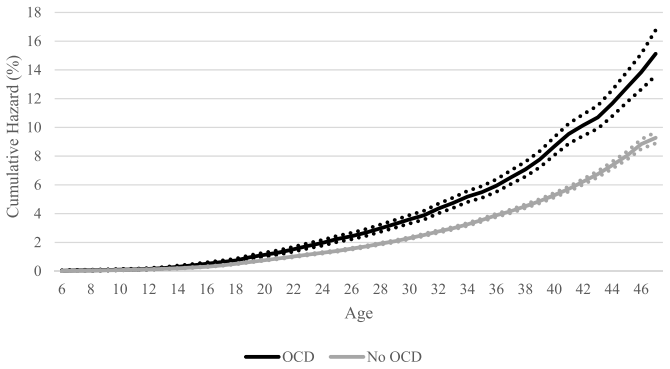

Fig. 2. Cumulative incidence under the assumption of no competing risks estimated as 1-the Kaplan-Meier estimate of survival function (with 95% confidence intervals) for any cardiovascular disorder in individuals with obsessive-compulsive disorder and controls without the disorder matched by sex, birth year, and county of birth, using the subgroup of individuals who were followed from age 6 (n = 22,884 individuals with obsessive-compulsive disorder and 228,840 matched controls).
Abbreviations: OCD, obsessive-compulsive disorder.

analyses suggests that the observed associations are not due to shared familial/genetic factors but may instead be related to modifiable lifestyle factors. In fact, most CVD subtypes in our study have been previously linked to a series of modifiable, individual risk factors related to lifestyle, including lack of physical activity, smoking or alcohol intake (Florido et al., 2018; Lindqvist et al., 2009; Pandey et al., 2015; Severinsen et al., 2009). Both psychosocial stress (Rosengren et al., 2008) and other psychiatric conditions (Strudsholm et al., 2005) have been associated with venous thrombo-embolism. The mechanisms are unknown, but effects on coagulation and fibrinolytic factors have been suggested (Rosengren et al., 2008). Also, the reason for the association between OCD and heart failure, ventricular tachycardias, and cardiac arrest is unknown; it probably includes traditional risk factors but may also include increase in sympathetic drive and neurohormonal activation (van der Wal et al., 2017; Ziaeian and Fonarow, 2016).

Our results contribute to the scarce but unambiguous body of research suggesting a strong association between OCD and a range of health complications (Aguglia et al., 2018; Albert et al., 2013; Drummond et al., 2011; Isomura et al., 2018; Witthauer et al., 2014). Additionally, we provide, for the first time, accurate estimates for the association between OCD and specific types of CVD. The study has relevant clinical implications and supports the need to monitor cardiovascular health in patients with OCD as it is routinely done in other severe psychiatric disorders such as schizophrenia (Marder et al., 2004). Further, the development and evaluation of interventions and prevention strategies that go beyond the focus on psychiatric symptoms and incorporate other variables amenable to change such as lifestyle habits is warranted (Mataix-Cols et al., 2020).

This study is not without limitations. First, despite the nationwide coverage of the Swedish registers, our cohort only includes individuals who have sought help for OCD and/or CVD. Similarly, the NPR only includes diagnoses from outpatient care since 2001 and we only had primary care available for the Stockholm Region, and only from 2003. Thus, our results may not generalize to individuals with milder symptoms who do not seek help. However, some of the CVD outcomes are serious and coverage is likely to be better. Second, the frequency of some of the individual events under study was reported to be low (e.g., ischemic cardiomyopathy, sick sinus syndrome, AV-block II-III, subarachnoidal bleeding) and therefore the results referring to these outcomes need to be interpreted with caution. Third, there are several behavioral variables, which are known to have strong links with CVD (e.g., sedentary lifestyle, unhealthy diet, smoking) (Alberti et al., 2009), that are not available in the registers and therefore their impact on the associations could not be explored. Fourth, we did not include medication status among the variables under study. While some psychotropic drugs have been associated with weight gain and metabolic risk (Blumenthal et al., 2014; Corruble et al., 2015; Serretti and Mandelli, 2010), previous epidemiological studies have associated the use of psychiatric medication with reduced risks of cardiometabolic health and mortality in psychiatric disorders (Brander et al., 2019; Isomura et al., 2018; Tiihonen et al., 2016). Other designs such as randomized controlled trials may be better suited to study the impact of medication on these outcomes. Finally, sibling analyses have inherent limitations and results from these comparisons should be interpreted accordingly (D'Onofrio et al., 2013).

5. Conclusions

OCD is associated with a moderately increased risk of a broad range of CVD. These risks seem to be independent from history of somatic diseases and shared familiar confounders. The time may be ripe for the development and evaluation of lifestyle interventions to help reduce the risk of cardiovascular morbidity in persons with OCD.

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CRediT authorship contribution statement

Kayoko Isomura: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft. **Anna Sidorchuk:** Conceptualization, Methodology, Software, Writing - original draft. **Gustaf Brander:** Methodology, Software, Writing - review & editing. **Tomas Jernberg:** Writing - review & editing. **Andreas Rück:** Writing - review & editing. **Huan Song:** Methodology, Writing - review & editing. **Unnur A. Valdimarsdóttir:** Methodology, Writing - review & editing. **Paul Lichtenstein:** Resources, Writing - review & editing. **Henrik Larsson:** Resources, Writing - review & editing. **Christian Rück:** Writing - review & editing. **David Mataix-Cols:** Conceptualization, Resources, Writing - review & editing, Supervision. **Lorena Fernández de la Cruz:** Conceptualization, Methodology, Resources, Writing - original draft, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

Henrik Larsson has served as a speaker for Evolan Pharma, Eli-Lilly, and Shire, and has received research grants from Shire; all outside the submitted work. David Mataix-Cols receives royalties for contributing articles to UpToDate, Wolters Kluwer Health and for editorial work from Elsevier. Lorena Fernández de la Cruz receives royalties for contributing articles to UpToDate, Wolters Kluwer Health. All other authors report no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.12.066.

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