Comorbidity of substance misuse with anxiety-related and depressive disorders: A genetically informative population study of 3 million individuals in Sweden

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Abstract

Background Causes of the comorbidity of substance misuse with anxiety-related and depressive disorders (anxiety/depression) remain poorly known. We estimated associations of substance misuse and anxiety/depression in the general population and tested them while accounting for genetic and shared environmental factors.

Methods We studied individuals born in Sweden 1968-1997 (n=2,996,398) with follow-up in nationwide register data for 1997–2013. To account for familial effects, stratified analyses were conducted within siblings and twin pairs. Substance misuse was defined as ICD-10 alcohol or drug use disorder or an alcohol/drug-related criminal conviction. Three dimensions of ICD-10 anxiety and depressive disorders and a substance misuse dimension were identified through exploratory factor analysis.

Results Substance misuse was associated with a 4.5-fold (95% CI: 4.50–4.58) elevated risk of lifetime generalized anxiety/depression, 4.7-fold (95% CI: 4.63–4.82) elevated risk of panic disorder and agora/social phobia, and 2.9-fold elevated risk of phobias/OCD (95% CI: 2.82–3.02) as compared to those without substance misuse. The associations were attenuated in within-family analyses but we found elevated risks in monozygotic twin pairs discordant for substance misuse as well as significant non-shared environmental correlations. The association between anxiety/depression and substance misuse was mainly driven by generalized anxiety/depression, whereas other anxiety/depression dimensions had minor or no independent associations with substance misuse.

Conclusions Substance misuse and anxiety/depression are associated at the population level, and these associations are partially explained by familial liabilities. Our findings indicate a common genetic etiology but are also compatible with a potential partially causal relationship between substance misuse and anxiety/depression.

Introduction

Substance use disorders (SUDs) and anxiety-related and depressive disorders (anxiety/depression) are among the leading causes of disability and are associated with increased mortality (Saraceno, 2002; Wittchen *et al*., 2011; Whiteford *et al*. 2013; Laramee *et al*., 2015; Westman et *al*., 2015; Meier *et al*., 2016). Epidemiologic surveys have revealed substantial comorbidity between SUDs and anxiety/depression (Regier *et al*., 1990; Merikangas *et al*., 1998; Swendsen *et al*., 1998; Teesson *et al*., 2000; Farrell *et al*., 2001; Burns *et al*., 2002; de Graaf *et al*., 2002; Kessler *et al*., 2005; Pirkola *et al*., 2005; Conway *et al*., 2006; Flensborg-Madsen *et al*., 2009; Toftdahl *et al*., 2016; Plana-Ripoll *et al*., 2019), which is associated with even higher disability, poorer treatment outcomes, and elevated mortality (Blanco *et al*., 2006; Meier *et al*., 2016).

A meta-analysis found individuals with SUDs to have two to three times the odds of having any anxiety disorder compared to those without SUDs (Lai *et al*., 2015). On the other hand, mixed associations between specific disorders with SUDs have been found. In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the Epidemiologic Catchment Area Study (ECA), of all anxiety disorders, panic disorder had the strongest and specific phobias the weakest association with SUDs, whereas mood-related disorders (depression, dysthymia) had stronger associations with SUDs than did anxiety disorders (Regier *et al*., 1990; Conway *et al*., 2006). In contrast, the associations between all types of anxiety/depressive disorders and SUDs were similar in the National Comorbidity Survey (NCS) (Swendsen *et al*., 1998). The British National Household Survey found that mixed anxiety was the most prevalent anxiety/depressive disorder among those with SUD (Farrell *et al*., 2001). Differences in the associations between specific anxiety and depressive disorders and SUDs remain uncertain, as many of the prior studies have not used formal statistical tests to verify them. Additionally, previous studies have often assessed the comorbidity of SUDs and anxiety or depression without accounting for other comorbid disorders. Potential sex differences in the comorbidity also remain poorly understood, as some

studies report no differences (Swendsen *et al*., 1998; Farrell *et al*., 2001; Conway *et al*., 2006), whereas others find stronger associations among women (Farrell *et al*., 2001; de Graaf *et al*., 2002; Conway *et al*., 2006) or men (Conway *et al*., 2006) for specific disorder combinations.

Importantly, the underlying causes of the comorbidity remain unclear. Several not mutually exclusive mechanisms are possible: unidirectional or reciprocal causal effects between SUDs and anxiety/depression, or shared etiological factors such as genetic liability or environmental influences could explain the associations (Schuckit *et al.*, 2006; Saraceno *et al*., 2009; Turner *et al*., 2018). Ordinary epidemiological studies cannot exclude shared underlying liabilities. Therefore, to better understand the potential direct effects between SUDs and anxiety/depression, genetically informative data is needed. Family and twin studies have found shared genetic and environmental influences to partly explain the comorbidity between SUDs and post-traumatic stress disorder (Xian *et al*., 2000; Sartor *et al*., 2011), as well as between alcohol use and anxiety (Tambs *et al*., 1997; Merikangas *et al*., 1998b). Other studies have found familial liabilities for SUDs and anxiety/depression to be primarily separate (Kendler *et al*., 1995; Pickens *et al*., 1995; Kendler *et al.*, 2003; Savage *et al*., 2016). However, many findings were based on relatively small samples and focused only on specific combinations of SUDs and anxiety and depressive disorders.

To a large degree, psychiatric comorbidity has been studied in voluntary surveys. Survey studies may be biased due to sample selection, as individuals with severe mental illness are less likely to participate (Galea and Tracy, 2007; Markkula *et al*., 2015). Further, retrospective recall may bias estimates of comorbidity (Takayanagi *et al*., 2014). Using prospective data from population-based health registers could help overcome these limitations, but very few studies have investigated the SUD-anxiety/depression comorbidity using nationwide register data (Toftdahl *et al*., 2016; Plana-Ripoll *et al*., 2019). Previous register-based studies have not studied comorbidity separately for different anxiety/depression diagnoses, nor have they taken into account shared underlying liabilities.

To describe the comorbidity between substance misuse and anxiety/depression in the population and to better understand the causes of comorbidity, we used Swedish nationwide register data to (1) estimate associations of substance misuse and anxiety/depression in the general population, and (2) test the associations while taking into account genetic and shared environmental factors by conducting stratified analyses and quantitative genetic models within siblings and twin pairs.

Methods

Study population

The study population included individuals born in Sweden between January 1968 and December 1997. The cohort was followed up from January 1997 to December 2013. Several Swedish population registers, linked with the unique personal identity number (Ludvigsson *et al*., 2009), were utilized. Individuals selected from the Total Population Register were linked to the Cause of Death Register, the Migration Register, the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), census data from Statistics Sweden, and the Multi-Generation Register with information available on demographic variables: sex, birth year, death and emigration date, parental education, and family socio-economic status. The sample included 2,996,398 individuals after excluding individuals with a diagnosis dated before age five (n=110), those whose parents could not be identified from the Multi-Generation Register (n=42,365), and those who had died (n=28,621) or emigrated (n=98,326) before January 1997. The Multi-Generation Register and the Swedish Twin Registry were used to identify full siblings, maternal/paternal half-siblings, and monozygotic (MZ) and dizygotic (DZ) twins (Ekbom, 2011).

Psychiatric diagnoses

Psychiatric diagnoses were retrieved from The National Patient Register (NPR) which covers inpatient (1973–) and outpatient (2001–) diagnoses nationwide (Ludvigsson *et al*., 2011). ICD-10 was implemented in Sweden in 1997, introducing fine-grained distinctions among different anxiety-related disorders (World Health Organization, 1992). Year 1997 was thus chosen as the baseline for the follow-up of the cohort. The diagnoses included in the analyses were: drug and alcohol use disorders (F10–F16, F18–F19), anxiety disorders (F40–F43), and depressive disorders (F32–F34, F38–F39) (eTable 1). Personality disorders (F60.0–F60.9) were used in a sensitivity analysis. The cohort members' diagnoses were the main exposure and outcome variables. Parental history of psychopathology was included as a covariate, defined as either parent having any psychiatric diagnosis (ICD-8, ICD-9 or ICD-10) in the NPR.

Criminal convictions

Convictions of driving under the influence of alcohol/drugs, and possession, manufacturing, trafficking, or sales of narcotics were included from the Crime Register to capture a wider range of substance use-related problems. Of those with substance-related convictions (n=126,391), 32% had a SUD diagnosis in the NPR.

Statistical analyses

Factor analysis

To reduce the number of associations to be analyzed, we used exploratory factor analysis and combined correlated diagnoses based on the factor structure (Supplement). Four factors best explained the data: 1) one representing SUDs and substance-related crimes (substance misuse), and three anxiety/depression factors representing 2) depressive disorders and non-specific, generalized

anxiety; 3) specific phobias and obsessive-compulsive disorder; and 4) panic disorder, agoraphobia and social phobia, respectively (eFigure 3).

We did no utilize factor scores, but instead used dichotomous variables as proxies for the factors. Having any of the disorders loading on the factor was coded as 1 and having no diagnoses within the factor was coded as 0. We refer to these variables as "diagnostic dimensions".

Association between substance misuse and anxiety/depression dimensions

We report comorbidity both as absolute and relative risks. Absolute risks describe the proportion of individuals with anxiety/depression among those with substance misuse and vice versa. In the main analyses, we estimated relative risks as Risk Ratios (RR) between lifetime (i.e. present at any time during the follow-up) substance misuse and anxiety/depression dimensions. RRs were chosen because it allowed for separate estimates for the relative risk of anxiety/depression given the person had substance misuse, and vice versa. Lifetime associations were estimated instead of time-dependent associations between prior substance misuse and subsequent anxiety/depression, and vice versa, because the diagnostic registration dates do not correspond with disorder onset, thus rendering it uncertain which disorder had developed first.

Sex and birth year were adjusted for in the first model. The second model further adjusted for parental education, family socioeconomic status, parental history of psychopathology, and parental immigration status. The non-independence of observations due to familial clustering was accounted for by using a cluster-robust sandwich estimator for standard errors.

Sex differences were examined by comparing tetrachoric correlation coefficients in men and women. Tetrachoric correlations use the probit link and differences in the coefficients are thus

interpretable as differences in an underlying normally distributed liability. Sex-stratified RRs were estimated in case the correlation coefficients suggested sex differences.

Within-family analyses

To examine the associations controlling for familial influences, we conducted fixed effects regression models (Gunasekara *et al*., 2014) which rule out all factors which are constant within sibling clusters. Fixed effects models use information from all families; informative clusters are the ones with discordance in the exposure. Discordance in substance misuse, for example, is then assigned if at least one sibling has either ICD-10 substance use disorder or a substance use related criminal conviction while the other siblings do not have any substance use diagnoses or substance-related criminal convictions.

Individual-level associations may be explained by 1) genetic factors which are shared completely by MZ co-twins, on average 50% shared by full siblings and DZ co-twins, and on average 25% shared by half-siblings, 2) shared environmental factors assumed to correlate perfectly among all siblings reared together, and 3) non-shared environmental factors which make siblings different from one another. The contribution of genetic and shared environmental factors can be examined by comparing individual-level estimates to those obtained from stratified analyses in different sibling types (Lahey and D'Onofrio, 2010; D'Onofrio *et al*., 2014). If within-family estimates are similar to the individual-level estimates, the association is not due to familial factors and may be causal. A situation where the association is reduced equally in MZ twins and full siblings suggests shared environmental variables partly explain the association. In contrast, the association being attenuated more in MZ twins than in other types of siblings suggests the contribution of genetic factors (D'Onofrio *et al*., 2014).

Quantitative genetic models

To complement the within-family regression models, we also fitted quantitative genetic models for MZ (n pairs=5647) and same-sex DZ (n pairs=4359) twins in the data to estimate the contributions of genetic and environmental sources to the co-variation between substance misuse and each of the three anxiety/depression dimensions. In quantitative genetic modeling, the phenotypic variance is decomposed into additive genetic (A), common or shared-environmental (C), and unique environmental (E) effects. In a bivariate model the covariance between two traits is partitioned into the A, C and E components using the Cholesky decomposition model (Neale and Cardon, 1992). All analyses were conducted using a liability-threshold model, where the categories (diagnosis present versus not present) were assumed to reflect an imprecise measurement of an underlying normal distribution of liability (Rijsdijk and Sham, 2002). All models were adjusted for birth year and sex.

Sensitivity analyses

While the main analyses estimated lifetime RRs during the study period, the baseline risks for substance misuse and anxiety/depression may be dependent on age. Further, the main analysis did not consider the order of the diagnoses. As a sensitivity analysis, Cox proportional hazards regression was conducted to estimate the effect of substance misuse as a time-varying covariate on the relative hazard of subsequent anxiety/depression, and vice versa, in a subsample born 1985–1997 (n=1,408,355) followed up from their 12th birthday until December 2013. The underlying time scale was attained age; individuals were followed until the date of first anxiety/depression diagnosis or substance misuse event, emigration, death, or the end of the follow-up, whichever occurred first. To control for familial confounding, stratified models within sibling clusters were conducted. We adjusted for all covariates in the model. Time-varying coefficients were also tested but there was no evidence for systematic age differences in the coefficients.

In further sensitivity analyses, we tested whether (i) the anxiety/depression dimensions had independent associations with substance misuse by including all dimensions simultaneously as predictors, and (ii) if the associations were confounded by personality disorders. Personality disorders were examined because they may increase the risk of addiction among those who are treated with benzodiazepines for anxiety. Comorbid personality disorders also affect the severity of anxiety/depression symptoms among those with SUDs (Langas *et al*., 2012; Kasteenpohja *et al.*, 2016).

Further, in order to investigate the effect of disease load, i.e. having more than one diagnosed disorder within each diagnostic dimension, we conducted Poisson regressions to estimate the associations between counts of different registered anxiety/depression disorders within dimensions and counts of different substance misuse registrations. Fixed-effects Poisson models were conducted within siblings and twin pairs.

We also estimated RRs between alcohol use disorder and anxiety/depression dimensions to elucidate potentially different associations of drug and alcohol use disorders with anxiety/depression.

Finally, to investigate comorbidity between less severe cases of substance misuse and anxiety/depression, we examined associations between diagnoses from primary care in the Stockholm county in 2003–2015 (Supplement).

Factor analysis was performed using the "psych" package (Ravelle, 2018) in R 3.4.1, Stata 14 was used for regression analyses, and quantitative genetic modeling was conducted with the OpenMx package in R version 3.4.1.

Results

Table 1 presents descriptive statistics of the cohort. The frequencies of diagnostic dimensions and covariates are shown for the entire sample, while the age at first diagnosis is reported for the sub-sample born 1985–1997. Frequencies describing the absolute risks of comorbidity are presented in Table 2.

Association between substance misuse and anxiety/depression

Those with lifetime exposure to substance misuse were at 2.9–4.7-fold elevated risk of having anxiety/depression compared to those without substance misuse (Table 3). Relative risks were similar for generalized anxiety/depression and the panic disorder and agora/social phobia dimension, whereas the association was weaker between substance misuse and phobias/OCD. In within-family analyses, the associations were attenuated but elevated risk of anxiety/depression was still found in all models. There was evidence of sex differences, with tetrachoric correlations being higher in women than in men (eTable 4). The relative risk of anxiety/depression was higher in women except for generalized anxiety/depression for which no sex differences were found.

Association between anxiety/depression and substance misuse

Individuals with a lifetime diagnosis of anxiety-related or depressive disorders had 2.5–4.5 times the risk of substance misuse compared to those without anxiety/depression (Table 4). The estimates and the overall pattern of results were similar to analyses with substance misuse as the exposure and anxiety/depression as the outcome.

Quantitative genetic models

The covariances between substance misuse and the three anxiety/depression dimensions were best explained by additive genetic and non-shared environmental influences (eTable 5). Approximately 76% of the covariance between substance misuse and generalized anxiety/depression was explained by genetic factors, and the remaining 24% by non-shared environmental factors. Genetic and non-shared environmental correlations were 0.60 (95% CI: 0.50–0.69) and 0.30 (95% CI: 0.16–0.44), respectively. The covariance between substance misuse and panic disorder and agora/social phobia was best explained by genetic (77%) and non-shared environmental factors (23%), and genetic and non-shared environmental correlations were 0.47 (95% CI: 0.28–0.66) and 0.23 (95% CI: -0.03–0.47). Similarly, the association between substance misuse and phobias/OCD was explained by genetic (53%) and non-shared environmental influences (47%), with genetic and non-shared environmental correlations being 0.24 (95% CI: 0.00–0.47) and 0.29 (95% CI: -0.03–0.60), respectively.

Sensitivity analyses

The results of the fully adjusted Cox regression models were consistent with estimates from the main analyses with the difference that most within-MZ-pair estimates, while all above 1, were statistically non-significant (Table 5).

Further, analyses mutually adjusting for the diagnostic dimensions suggested the association between lifetime anxiety/depression and substance misuse was mainly driven by generalized anxiety/depression (RR=4.15, 95% CI: 4.11–4.20), whereas the association of the panic disorder and agora/social phobia dimension with substance misuse was modest (RR=1.46, 95% CI: 1.43–1.48). Phobias/OCD, when adjusted for other anxiety and depressive dimensions, were not associated with substance misuse (RR=0.97, 95% CI: 0.95–1.00). Controlling for personality disorders significantly reduced but did not eliminate the associations between anxiety/depression

dimensions and substance misuse (eTable 6).Exposure to alcohol use disorder was associated with similar relative risks of anxiety/depression as compared to the estimates in Table 3, where the exposure was any substance misuse. In model 2, we entered a variable for all other substance use disorders (coding: 1 = any ICD-10 substance use disorder other than alcohol present, 0 = not present) to the model. The associations between alcohol use disorder and anxiety/depression dimensions attenuated significantly. In these models, RRs of drug use disorders (RR ~ 4.0) were systematically higher than those for alcohol use disorders (eTable 7). When alcohol use disorder was used as the outcome and anxiety/depression dimensions as the exposures (eTable 8), the RRs were slightly higher than the estimates in Table 4 where the outcome was substance misuse. Thus, individuals with anxiety/depression diagnoses had a higher relative risk of having alcohol use disorder than substance misuse in general.

The models using count measures instead of dichotomous indicator variables showed positive associations between the number of different types of registrations within the substance misuse dimension and the number of different anxiety/depression diagnoses (eTables 9 and 10), and similar to the main analyses significant associations were also found within MZ pairs.

Finally, associations between substance misuse and anxiety/depression in primary care were consistent with the NPR associations (eFigure 4).

Discussion

Using a prospective design with clinician-diagnosed disorders in 3 million individuals from Swedish nationwide registers we found an elevated risk of anxiety-related and depressive disorders in individuals with substance misuse and vice versa. Our results confirm previous studies using other designs (Lai *et al*., 2015), but also extend them by showing associations independent of genetic and shared environmental factors, which are consistent with a partially causal hypothesis.

Our main contribution was the finding of associations between substance misuse and anxiety/depression even after accounting for all genetic and shared environmental factors, suggesting that the observed associations were not completely explained by familial liabilities. This was confirmed with quantitative genetic models showing non-shared environmental correlations between substance misuse and anxiety/depression dimensions. The associations were gradually attenuated in the within-sibling analyses and often appeared weaker in MZ twins than in full siblings, suggesting shared genetic background. The results from quantitative genetic models supported this conclusion with genetic correlations ranging from 0.24 to 0.60. However, elevated risks were still observed within MZ twin pairs. Taken together, the pattern of results indicates that genetic and environmental influences, such as socioeconomic factors (Kessler *et al*., 1994), partially explain the comorbidity, in line with previous findings of shared genetic and environmental influences on SUDs and anxiety/depression (Tambs *et al*., 1997; Merikangas *et al*., 1998; Xian *et al*., 2000; Sartor *et al.*, 2011). On the other hand, other studies found primarily separate genetic and shared environmental liabilities for disorders in the internalizing and externalizing dimensions (Kendler *et al*., 1995; Kendler *et al*., 2003). While strong genetic correlations were found within the internalizing and externalizing spectrums, these studies also show weaker associations between the externalizing and internalizing disorders (Kendler *et al*., 2003), indicating modest familial liabilities likely detected in our well-powered study. Importantly, our findings also suggest that besides shared liabilities, causal effects between substance misuse and anxiety/depression may exist. A partially causal association would imply that interventions or treatments for one of the disorders should also reduce the risk of developing the other disorder. However, further studies with other causally informative research designs are still needed.

The absolute risks of comorbidity were substantial, with up to 45% of women with substance misuse having anxiety/depression during the follow-up. Generalized anxiety/depression had the

strongest association with substance misuse, consistent with earlier findings (Regier *et al*., 1990; Farrell *et al*., 2001; Pirkola *et al*., 2005; Conway *et al*., 2006). Further, exposure to substance misuse was associated with over 4.5-fold risk of having either generalized anxiety/depression or panic disorder and agora/social phobia. Studies in the NESARC and the ECA samples have also shown strong links between panic disorder and SUDs (Regier *et al*., 1990; Conway *et al*., 2006). In contrast, the association between panic disorder and agora/social phobia and substance misuse was mostly explained by comorbid generalized anxiety/depression. A Finnish study also suggested that depression may mediate the relationship between anxiety and substance use problems (Fröjd *et al*., 2011). Similar to earlier studies, we found that specific phobias/OCD had the weakest association with substance misuse (Regier *et al*., 1990; Conway *et al*., 2006); in fact, the association appeared to be entirely explained by the comorbid generalized anxiety/depression dimension. Phobias and OCD have been suggested to be protective of substance misuse due to traits such as risk aversion (Bejerot *et al*., 1999; Kessler *et al*., 2005b). Our findings thus highlight the importance of distinguishing between different types of anxiety-related disorders and taking generalized anxiety/depression into account in associations with substance misuse.

The severity of comorbidity in substance misuse, i.e. the number of different substance use diagnoses/drug-offence registrations was associated with a higher number of different anxiety/depression diagnoses, and vice versa. These results are in line with earlier findings showing increase in the magnitude of psychiatric comorbidity according to the level of severity of substance problems (Merikangas *et al*. 1998).

We also estimated associations between alcohol use disorder and anxiety/depression. When alcohol and drug use disorders were entered to the same model as distinct categories, we found associations of alcohol use disorders with anxiety/depression to be systematically attenuated. This suggests that a large proportion of the association between alcohol use disorder and anxiety/depression is explained by comorbid drug use. Previous studies have found similar results, reporting stronger

associations between drug use disorders and anxiety/depression than between alcohol use disorder and anxiety/depression (Merikangas *et al*. 1998, Kessler *et al*. 2005b). Further, when alcohol use disorder was treated as an outcome, the RRs were slightly higher than in associations between anxiety/depression and substance misuse. Thus, individuals with anxiety/depression had a higher relative risk of having alcohol use disorder than substance misuse in general, which in our study included drug-related criminal offences.

Expressed as relative risks, comorbidity was stronger in women than in men with the exception of generalized anxiety/depression given substance misuse. Thus, sex differences seem to depend on the specific substance misuse and anxiety/depression combination examined (Swendsen *et al*., 1998; Farrell *et al*., 2001; de Graaf *et al*., 2002; Conway *et al*., 2006). However, these results should be interpreted with caution as they may reflect differences in treatment seeking, as well as in diagnostic accuracy.

Identifying comorbidities is important during the initial clinical assessment, because a dual-diagnosis complicates the prognosis and planning of treatment (Kranzler and Rosenthal, 2003). However, our findings underline the importance of monitoring comorbid symptoms throughout the treatment, as substance misuse or anxiety/depression can develop later due to the prior condition.

Our study had some important limitations. First, we have not included all cases of anxiety/depression and SUDs in the population, because the NPR only captures diagnosed cases among the treatment-seeking population in inpatient and outpatient clinics, and the indexing of disorders also changed during the follow-up as the outpatient specialist information did not cover the entire period. Moreover, individuals with multiple diagnoses are more likely seek treatment, which may inflate the comorbidity estimates. We examined comorbidity also in primary care patients and found similar associations. A study by Sundquist *et al*. (2017) reported slightly lower correlations between anxiety, depression, and substance use disorders in a different sample of

Swedish primary care patients and using somewhat different groupings of diagnoses. As we used data from Stockholm county only, it is possible that the associations in our data differ from the associations found in other counties or in Swedish primary care population overall. A further limitation concerns the timing of disorders. In the main analysis, we did not explore whether substance misuse preceded anxiety/depression or vice versa because the first registered diagnosis date does not correspond with disorder onset. Due to the structure of the register data, individuals in the sample also had different follow-up periods. To account for these factors, all models were adjusted for birth year, and survival analysis was conducted as a sensitivity analysis in a sub-sample. Only the association between generalized anxiety/depression and substance misuse remained significant within monozygotic twins in the sub-sample that was followed longitudinally, which is compatible with the possibility of a self-medication pathway from generalized anxiety/depression to substance misuse. However, this finding needs to be replicated in a sample with more reliable timing for disorder onset. In these data, first registrations occurred at an average age of 18–19 for substance misuse, generalized anxiety/depression, and phobias/OCD, while the first panic disorder or agora/social phobia diagnoses were registered slightly later. However, anxiety disorders typically have a much earlier onset, at a median age of 11 (Kessler *et al*., 2005b). Further, diagnostic misclassification may introduce bias which appears as evidence for genetic confounding in within-family analyses (McGue *et al*., 2010; D'Onofrio *et al*., 2013). On the other hand, individual-specific confounding factors, such as early traumatic experiences associated with both substance misuse and other psychiatric disorders (De Bellis, 2002), cannot be fully ruled out in within-family analyses (McGue *et al*., 2010). Thus, instead of a causal effect, elevated risks in MZ co-twins might reflect factors such as the common method bias: correlations between diagnoses acquired from a single source such as the NPR might reflect treatment/diagnostic policies rather than actual relationships between disorders. To partially address this issue, we also included substance use-related criminal convictions in our definition of substance misuse.

Conclusion

To the best of our knowledge, the present study is the first to use nationwide register data to estimate associations between substance misuse and different types of anxiety and depressive disorders while accounting for familial influences. We found familial liabilities to partially explain the associations, but substantial comorbidity remained after accounting for genetic and shared environmental factors, compatible with a partially causal relationship between substance misuse and anxiety/depression. Future studies should examine developmental mechanisms of the comorbidity in more detail.

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Conflicts of interests

Dr Larsson has served as a speaker for Evolan Pharmaand Shire and has received research grants from Shire, all outside the submitted work. Professor Mataix-Cols receives royalties from Wolters Kluwer Health and Elsevier, all outside the submitted work. Other authors declare no conflicts of interest.

References

Bejerot S and Humble M (1999) Low prevalence of smoking among patients with obsessive-compulsive disorder. *Comprehensive Psychiatry* **40**, 268–272.

Blanco C, Xu Y, Brady K, Pérez-Fuentes G, Okuda M and Wang S (2013) Comorbidity of posttraumatic stress disorder with alcohol dependence among US adults: results from National Epidemiological Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence* **132**, 630–638.

Burns L and Teesson M (2002) Alcohol use disorders comorbid with anxiety, depression and drug use disorders: Findings from the Australian National Survey of Mental Health and Well Being. *Drug and Alcohol Dependence* **68**, 299–307.

Conway KP, Compton W, Stinson FS and Grant BF (2006) Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry* **67**, 247–257.

De Bellis MD (2002) Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology* **27**, 155–170.

D'Onofrio BM, Lahey BB, Turkheimer E and Lichtenstein P (2013) Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *American Journal of Public Health* **103**, 46–55.

de Graaf R, Bijl RV, Smit F, Vollebergh WA and Spijker J (2002) Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *American Journal of Psychiatry* **159**, 620–629.

Ekbom A (2011) The Swedish Multi-generation Register. *Methods in Molecular Biology* **675**, 215–220.

Farrell M, Howes S, Bebbington P, Brugha T, Jenkins R, Lewis G, and Meltzer H (2001) Nicotine, alcohol and drug dependence and psychiatric comorbidity: results of a national household survey. *British Journal of Psychiatry* **179**, 432–437.

Flensborg-Madsen T, Mortensen EL, Knop J, Becker U, Sher L and Grønbæk M (2009) Comorbidity and temporal ordering of alcohol use disorders and other psychiatric disorders: results from a Danish register-based study. *Comprehensive Psychiatry* **50**, 307–314.

Fröjd S, Ranta K, Kaltiala-Heino R and Marttunen M (2011) Associations of social phobia and general anxiety with alcohol and drug use in a community sample of adolescents. *Alcohol and Alcoholism* **46**, 192–199.

Galea S and Tracy M (2007) Participation rates in epidemiologic studies. *Annals of Epidemiology* **17**, 643–653.

Gunasekara F, Richardson K, Carter K and Blakely T (2014) Fixed effects analysis of repeated measures data. *International Journal of Epidemiology* **43**, 264–269.

Kasteenpohja T, Marttunen M. Aalto-Setälä T, Perälä J, Saarni SI and Suvisaari J (2016) Treatment adequacy of anxiety disorders among young adults in Finland. *BMC Psychiatry* **16**, 63–76.

Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC and Eaves LJ (1995) The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry* **52**, 374–383.

Kendler KS, Prescott CA, Myers J and Neale MC (2003) The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry* **60**, 929–937.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S and Kendler KS (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry* **51**, 8–19.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR and Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Kessler RC, Chiu WT, Demler O and Walters EE (2005b) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 617–627.

Kranzler HR and Rosenthal RN (2003) Dual diagnosis: Alcoholism and co-morbid psychiatric disorders. *American Journal on Addictions* **12**, 26-40.

Lahey BB and D'Onofrio BM (2010) All in the family: comparing siblings to test causal hypotheses regarding environmental influences on behavior. *Current Directions in Psychological Science* **19**, 319–323.

Lai HMX, Cleary M, Sitharthan T and Hunt GE (2015) Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. *Drug and Alcohol Dependence* **154**, 1–13.

Langas AM, Malt UF and Opjordsmoen S (2012) In-depth study of personality disorders in first-admission patients with substance use disorders. *BMC Psychiatry* **12**, 180–190.

Laramee P, Leonard S and Buchanan-Hughes A (2015) Risk of all-cause mortality in alcohol-dependent individuals: a systematic literature review and meta-analysis. *EBioMedicine* **2**, 1394–1404.

Ludvigsson JF, Otterblad-Olausson P, Pettersson BU and Ekbom A (2009) The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology* **24**, 659–667.

Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M and Otterblad Olausson P (2011) External review and validation of the Swedish National Inpatient Register. *BMC Public Health* **11**, 450–466.

Markkula N, Suvisaari J, Saarni SI, Pirkola S, Peña S, Saarni S, Ahola K, Mattila AK, Viertiö S, Strehle J, Koskinen S and Härkänen T (2015) Prevalence and correlates of major depressive disorder and dysthymia in an eleven-year follow-up--results from the Finnish Health 2011 Survey. Journal of Affective Disorders **1**, 73–80.

McGue M, Osler M and Christensen K (2010) Causal inference and observational research: The utility of twins. *Perspectives in Psychological Science* **5**, 546–556.

Meier SM, Mattheisen M, Mors O, Mortensen PB, Laursen TM and Penninx BW (2016) Increased mortality among people with anxiety disorders: total population study. *British Journal of Psychiatry* **209**, 216–221.

Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, Kolody B, Vega WA, Wittchen HU and Kessler RC (1998) Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addictive Behaviors* **23**, 893–907.

Merikangas KR, Stevens DE, Fenton B, Stolar M, O'Malley S, Woods SW and Risch N (1998b) Co-morbidity and familial aggregation of alcoholism and anxiety disorders. *Psychological Medicine* **28**, 773–788.

Neale MCCL and Cardon LR (1992). *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic Publishers.

Pickens RW, Svikis DS, McGue M and LaBuda MC (1995) Common genetic mechanisms in alcohol, drug, and mental disorder comorbidity. *Drug and Alcohol Dependence* **39**, 129–138.

Pirkola SP, Isometsä E, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, Koskinen S, Aromaa A and Lönnqvist JK (2005) DSM-IV mood-, anxiety-and alcohol use disorders and their comorbidity in the Finnish general population. *Social Psychiatry and Psychiatric Epidemiology* **40**, 1–10.

Plana-Ripoll O, Pedersen CB, Holtz Y, Benros ME, Dalsgaard S, de Jonge P, Fan CC, Degenhardt L, Ganna A, Greve AN, Gunn J, Iburg KM, Kessing LV, Lee BK, Lim CCW, Mors O, Nordentoft M, Prior A, Roest AM, Saha S, Schork A, Scott JG, Scott KM, Stedman T, Sørensen HJ, Werge T, Whiteford HA, Laursen TM, Agerbo E, Kessler RC, Mortensen PB and McGrath JJ (2019) Exploring Comorbidity Within Mental Disorders Among a Danish National Population. *JAMA Psychiatry*. Published online January 16, 2019. doi:10.1001/jamapsychiatry.2018.3658

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL and Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *JAMA* **264**, 2511–2518.

Revelle W (2018) *Psych: Procedures for Personality and Psychological Research*. Northwestern University, Evanston, Illinois, USA, https://CRAN.R-project.org/package=psych; Version = 1.8.4.

Rijsdijk FV and Sham PC (2002) Analytic approaches to twin data using structural equation models. *Briefings in Bioinformatics* **3**, 119–133.

Saraceno B (2002) The WHO world health report 2001 on mental health. *Epidemiologia e Psichiatria Sociale* **11**, 83–87.

Saraceno L, Munafó M, Heron J, Craddock N and Van Den Bree MB (2009) Genetic and non-genetic influences on the development of co-occurring alcohol problem use and internalizing symptomatology in adolescence: a review. *Addiction* **104**, 1100–1121.

Sartor CE, McCutcheon VV, Pommer NE, Nelson EC, Grant JD, Duncan A, Waldron M, Bucholz KK, Madden PA and Heath AC (2011) Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychological Medicine* **41**, 1497–1505.

Savage JE, Kaprio J, Korhonen T, Pulkkinen L, Rose RJ, Verhulst B and Dick DM (2016) The effects of social anxiety on alcohol and cigarette use across adolescence: Results from a longitudinal twin study in Finland. *Psychology of Addictive Behaviors* 30, 462–474.

Schuckit MA (2006) Comorbidity between substance use disorders and psychiatric conditions. *Addiction* **101**, 76–88.

Sundquist J, Ohlsson H, Sundquist K and Kendler KS (2017) Common adult psychiatric disorders in Swedish primary care where most mental health patients are treated. *BMC Psychiatry* **17**, 234–244.

Swendsen JD, Merikangas KR, Canino GJ, Kessler RC, Rubio-Stipec M and Angst J (1998) The comorbidity of alcoholism with anxiety and depressive disorders in four geographic communities. *Comprehensive Psychiatry* **39**, 176–184.

Takayanagi Y, Spira AP, Roth KB, Gallo JJ, Eaton WW and Mojtabai R (2014) Accuracy of reports of lifetime mental and physical disorders: results from the Baltimore Epidemiological Catchment Area study. *JAMA Psychiatry* **71**, 273–280.

Tambs K, Harris JR and Magnus P (1997) Genetic and environmental contributions to the correlation between alcohol consumption and symptoms of anxiety and depression. Results from a bivariate analysis of Norwegian twin data. *Behavior Genetics* **27**, 241–250.

Teesson M, Hall W, Lynskey M and Degenhardt L (2000) Alcohol-and drug-use disorders in Australia: Implications of the National Survey of Mental Health and Wellbeing. *The Australian and New Zealand Journal of Psychiatry* **34**, 206–213.

Toftdahl NG, Nordentoft M and Hjorthøj C (2016) Prevalence of substance use disorders in psychiatric patients: a nationwide Danish population-based study. *Social Psychiatry and Psychiatric Epidemiology* 51, 129–140.

Turner S, Mota N, Bolton J and Sareen J (2018) Self-medication with alcohol or drugs for mood and anxiety disorders: A narrative review of the epidemiological literature. *Depression and Anxiety* **35**, 851–860.

Westman J, Wahlbeck K, Laursen TM, Gissler M, Nordentoft M, Hällgren J and Ösby U (2015) Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden. *Acta Psychiatrica Scandinavica* **131**, 297–306.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ and Vos T (2013) Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *Lancet* **382**, 1575–1586

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R and Steinhausen HC (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology* **21**, 655–679

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva, Switzerland.

Xian H, Chantarujikapong SI, Scherrer JF, Eisen SA, Lyons MJ, Goldberg J and True WR (2000) Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. *Drug and Alcohol Dependence* 61, 95–102.

TABLES

Table 1. Sample characteristics (Total n = 2,996,398; Men n = 1,539,816; Women n = 1,456,582)

	Men		Women		Total	
	n (mean)	% (SD)	n (mean)	% (SD)	n (mean)	% (SD)
Substance misuse						
Any diagnosis /conviction	145,997	9.5	62,542	4.3	208,541	7.0
Two or more diagnoses /convictions	35,581	2.3	14,422	1.0	50,003	1.7
Age at first diagnosis /conviction	19.4	2.9	18.6	3.1	19.1	3.0
Generalized anxiety/depression						
Any diagnosis	86,110	5.6	140,222	9.6	226,332	7.6
Two or more diagnoses	25,851	1.7	50,716	3.5	76,567	2.6
Age at first diagnosis	19.6	3.7	19.2	3.4	19.3	3.5
Panic disorder and agora/social phobia						
Any diagnosis	21,494	1.4	32,442	2.2	53,936	1.8
Two or more diagnoses	3,289	0.2	4,903	0.3	8,192	0.3
Age at first diagnosis	20.5	3.4	20.0	3.3	20.2	3.4
Phobias/OCD						
Any diagnosis	9855	0.6	15,128	1.0	24,983	0.8
Two or more diagnoses	257	0.002	633	0.004	890	0.003
Age at first diagnosis	18.1	4.2	19.0	4.0	18.6	4.1
Birth year	1983	8.8	1983	8.7	1983	8.8
Family SES						
Low	447,221	29.0	423,939	29.1	871,160	29.1
Medium	380,998	24.7	359,389	24.6	740,387	24.7
High	278,038	18.1	261,107	17.9	539,145	18.0
Unknown	433,560	28.2	412,151	28.3	845,711	28.2
Mother's education						
Primary school	265,538	17.2	250,872	17.2	516,410	17.2
High school	757,334	49.2	717,916	49.3	147,5250	49.2
University	503,287	32.7	474,895	32.6	978,182	32.7
Doctorate	10,492	0.7	9,954	0.7	20,446	0.7
Unknown	3,166	0.2	2,949	0.2	6,115	0.2
Father's education						
Primary school	384,432	25.0	364,718	25.0	749,150	25.0
High school	730,327	47.4	690,738	47.4	1,421,065	47.4
University	391,379	25.4	369,093	25.4	760,472	25.4
Doctorate	24,362	1.6	23,123	1.6	47,485	1.6
Unknown	9,317	0.6	8,914	0.6	18,231	0.6
Parental immigrant status						
None	1,287,127	83.6	1,217,163	83.6	2,504,290	83.6

One parent immigrant	152,560	9.9	145,003	9.9	297,563	9.9
Both parents immigrants	100,130	6.5	94,420	6.5	19,4550	6.5
Parental history of psychopathology						
Substance misuse	254,635	16.5	24,242	16.6	497,055	16.6
Anxiety/depression	268,487	17.4	253,499	17.4	521,986	17.4
Any psychiatric disorder	419,924	27.3	398,544	27.4	818,465	27.3

Note: Number of diagnoses refers to the number of different diagnoses present within the diagnostic dimension; age at first diagnosis/conviction is reported for the sub-sample born 1985-1997; Substance misuse = SUDs and substance-related criminal convictions; SES = Socioeconomic status; OCD = Obsessive-compulsive disorder

Table 2. Absolute risks of comorbidity between substance misuse and anxiety/depression

	Men		Women	
	Frequency	%	Frequency	%
Substance misuse				
No comorbidity	113,273	77.6	34,385	55.0
Comorbidity with				
Any anxiety/depression	32,724	22.4	28,157	45.0
Generalized anxiety/depression	30,471	20.9	26,881	43.0
Panic disorder and agora/social phobia	7,767	5.3	6,862	11.0
Phobias/OCD	2,129	1.5	2,354	3.8
Generalized anxiety/depression				
No comorbidity	55,639	64.6	113,340	80.8
Comorbidity with substance misuse	30,471	35.4	26,881	19.2
Panic disorder and agora/social phobia				
No comorbidity	13,727	63.9	25,579	78.8
Comorbidity with substance misuse	7,767	36.1	6,862	21.2
Phobias/OCD				
No comorbidity	7,726	78.4	12,774	84.4
Comorbidity with substance misuse	2,129	21.6	2,354	15.6

Note: Substance misuse = Substance use disorders and substance-related criminal convictions; OCD = Obsessive-compulsive disorder

Table 3. Risk ratios (95% CIs) between substance misuse (exposure) and anxiety/depression (outcome)

	Substance misuse – Generalized anxiety/depression	Substance misuse – Panic disorder	Substance misuse – Phobias/OCD
Individual level models			
Model 1	5.13 (5.09–5.18)	5.47 (5.37–5.57)	3.21 (3.11–3.32)
Model 2	4.54 (4.50–4.58)	4.73 (4.63–4.82)	2.92 (2.82–3.02)
Within-family models			
Half-siblings[1]	3.40 (3.28–3.51)	3.36 (3.12–3.61)	2.39 (2.12–2.69)
Full siblings & DZ twins[2]	3.29 (3.23–3.35)	3.33 (3.21–3.47)	2.35 (2.21–2.51)
MZ twins[3]	1.69 (1.31–2.19)	2.10 (1.04–4.24)	5.50 (1.22–24.81)
Evidence of sex differences	Yes	Yes	Yes
Men	4.51 (4.45–4.57)	4.44 (4.32–4.57)	2.40 (2.29–2.52)
Women	4.55 (4.50–4.60)	4.97 (4.84–5.10)	3.56 (3.40–3.72)

Note: Model 1 adjusted for sex and birth year; Model 2 adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology; Within-family and sex-stratified models adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology. Substance misuse = Substance use disorders and substance-related criminal convictions; Panic disorder = Anxiety/depression dimension including panic disorder and agora/social phobia; OCD = Obsessive-compulsive disorder; DZ = Dizygotic; MZ = Monozygotic; Full and half-siblings include both same-sex and opposite-sex siblings

[1] N individuals from families discordant for substance misuse = 81,519

[2] N individuals from families discordant for substance misuse = 1,038,339

[3] N individuals from pairs discordant for substance misuse = 1,534

Table 4. Risk ratios (95% CIs) between anxiety/depression (exposure) and substance misuse (outcome)

	Generalized anxiety/depression – Substance misuse	Panic disorder – Substance misuse	Phobias/OCD – Substance misuse
Individual level models			
Model 1	5.14 (5.10–5.19)	4.32 (4.26–4.39)	2.81 (2.73–2.88)
Model 2	4.45 (4.41–4.49)	3.60 (3.55–3.66)	2.51 (2.44–2.58)
Within-family models			
Half-siblings[1]	3.33 (3.22–3.44)	2.48 (2.35–2.61)	2.05 (1.87–2.25)
Full siblings & DZ twins[2]	3.43 (3.37–3.50)	2.61 (2.53–2.69)	2.15 (2.04–2.26)
MZ twins[3]	1.90 (1.39–2.61)	1.79 (1.04–3.08)	3.25 (1.22–8.66)
Evidence of sex differences	Yes	Yes	Yes
Men	3.69 (3.65–3.73)	3.11 (3.06–3.17)	2.05 (1.97–2.12)
Women	6.05 (5.96–6.15)	4.34 (4.24–4.44)	3.13 (3.01–3.25)

Note: Model 1 adjusted for sex and birth year; Model 2 adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology; Within-family and sex-stratified models adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology. Substance misuse = Substance use disorders and substance-related criminal convictions; Panic disorder = Anxiety/depression dimension including panic disorder and agora/social phobia; OCD = Obsessive-compulsive disorder; DZ = Dizygotic; MZ = Monozygotic; Full and half-siblings include both same-sex and opposite-sex siblings

[1] N individuals from families discordant for generalized anxiety/depression; panic disorder; phobias/OCD = 78,844; 22,245; 8,816

[2] N individuals from families discordant for generalized anxiety/depression; panic disorder; phobias/OCD = 1,076,717; 825,882; 776,733

[3] N individuals from pairs discordant for generalized anxiety/depression; panic disorder; phobias/OCD = 1,879; 573; 299

Table 5. Hazard Ratios (95% CIs) between substance misuse and anxiety/depression dimensions

	Substance misuse – Generalized anxiety/depression	Substance misuse – Panic disorder	Substance misuse – Phobias/OCD
Individual level models			
Total	3.70 (3.63–3.78)	3.42 (3.29–3.56)	2.17 (2.03–2.33)
Men	3.65 (3.55–3.76)	3.35 (3.15–3.55)	1.73 (1.55–1.94)
Women	3.61 (3.51–3.72)	3.41 (3.23–3.60)	2.62 (2.40–2.86)
Within-family models			
Half-siblings	2.91 (2.49–3.40)	2.41 (1.79–3.25)	1.88 (1.01–3.51)
Full siblings & DZ twins	2.66 (2.52–2.82)	2.22 (2.00–2.46)	1.65 (1.40–1.94)
MZ twins	1.40 (0.62–3.15)	1.50 (0.25–8.98)	1.50 (0.25–8.98)
	Generalized anxiety/depression – Substance misuse	Panic disorder – Substance misuse	Phobias/OCD – Substance misuse
Individual level models			
Total	4.20 (4.11–4.29)	3.31 (3.17–3.47)	2.02 (1.88–2.16)
Men	3.37 (3.26–3.48)	2.70 (2.51–2.90)	1.51 (1.37–1.68)
Women	5.57 (5.41–5.74)	4.21 (3.96–4.47)	2.84 (2.59–3.12)
Within-family models			
Half-siblings	2.88 (2.48–3.35)	2.20 (1.52–3.18)	1.52 (1.02–2.43)
Full siblings & DZ twins	3.55 (3.35–3.77)	2.82 (2.48–3.20)	1.83 (1.55–2.16)
MZ twins	2.44 (1.13–5.31)	1.50 (0.42–5.32)	2.00 (0.18–22.06)

Note: Upper part: Hazard ratios between substance misuse (exposure) and anxiety/depression (outcome), lower part: HRs between anxiety/depression (exposure) and substance misuse (outcome); Models were adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology. Substance misuse = Substance use disorders and substance-related criminal convictions; Panic disorder = Anxiety/depression dimension including panic disorder and agora/social phobia; OCD = Obsessive-compulsive disorder