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The predictive effect of family genetic risk scores as an indirect measure of causal effects of one disorder on another

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Abstract

Background. One potential cause of comorbidity is the direct causal effect of one disorder – A – on risk for subsequent onset of disorder B. Could genetic risk scores be utilized to test for such an effect? If disorder A causally impacts on risk for disorder B, then genetic risk for disorder A should be lower in cases of disorder A with *v.* without a prior onset of B.

Methods. In all individuals ($n = 905\,736$) born in Sweden from 1980 to 1990, from six psychiatric and drug use disorders (major depression, anxiety disorders, alcohol use disorder, drug use disorder, bipolar disorder, and schizophrenia), we formed 14 pairs of disorders A and B. In these pairs, we compared, using Cox proportional hazards models, the predictive effect of the familial-genetic risk score (FGRS) for disorder B in those who had *v.* had not had a prior onset of disorder A.

Results. In all pairs, the impact of the FGRS for disorder B was significantly stronger in cases without *v.* with a prior history of disorder A. These effects were similar across sex, stable across levels of FGRS and not likely due to clinician bias. In many of our disorder pairs, previous clinical studies suggest a mechanism for a causal effect of disorder A on B.

Conclusions. Our findings provide indirect evidence that the occurrence of one psychiatric or substance use disorder often has a causal effect on risk for subsequent disorders. This mechanism may substantially contribute to the widespread comorbidity among psychiatric conditions.

Many clinical and epidemiological studies have demonstrated that comorbidity is the rule rather than the exception for psychiatric and substance use disorders (Kessler, 1997; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler et al., 1993, 2011). Studies of both epidemiological and clinical populations have repeatedly shown that most pairs of psychiatric and/or substance use disorders co-occur at rates substantially higher than would be expected by chance. A number of approaches have been taken to elucidate the causes of this comorbidity (Klein & Riso, 1993; Neale & Kendler, 1995). Most explanations focus on three possible causes: (i) overlapping diagnostic criteria, (ii) shared (or 'confounding') risk factors, including genetic ones, and (iii) a direct causal effect of one disorder on another.

In this paper, we examine a novel method to evaluate the third of these possible mechanisms for comorbidity – a direct causal effect of one disorder on another. Our approach is adapted from a classical family study by Bruno Schulz on the etiology of schizophrenia published in 1933 (Kendler & Klee, 2022; Schulz, 1933). In that study, Schulz evaluated possible physical and psychological environmental influences on the risk for schizophrenia. He notes

> in the cases without indication of [an] illness cause, [we] …find twice the schizophrenia frequency among the siblings, than among the siblings of the probands where a physical cause … was blamed… This raises the suspicion that … the probands with alleged physical causes … consist of cases in which the schizophrenia… only emerges when there is a triggering cause in the form of an infectious disease, pregnancy, or a fall on the head, etc. (Kendler & Klee, 2022; Schulz, 1933). p. 231

His most striking results were with head trauma. In his 55 cases of schizophrenia with a significant head trauma prior to onset, the total risk of schizophrenia in their siblings was 2.9%, compared to 8.3% in the 340 cases of schizophrenia without a known cause. That is, the familial risk for schizophrenia was appreciably lower in cases of schizophrenia with *v.* without head trauma. Schulz interprets these findings as suggesting that head trauma meaningfully contributes to the etiology of schizophrenia (Kendler & Klee, 2022; Schulz, 1933).

As Schulz wanted to know if prior head trauma contributed to the etiology of schizophrenia, we want to know if the prior occurrence of disorder A contributes causally to the risk of a

subsequent onset of disorder B. The logic of this model is outlined in Fig. 1. Like Schulz, we do this by comparing the impact of the genetic liability of disorder B on the risk for disorder B in individuals without *v.* with a prior history of disorder A. From Fig. 1, we predict that the stronger the causal effect of a prior occurrence of disorder A on disorder B (the Z path), the greater the X path – the impact of genetic liability for disorder B on risk for disorder B in the absence of a history of disorder A – will be compared t the Y path – the impact of genetic liability for disorder B on risk for disorder B in the presence of a history of disorder A. Put back into simple words, taking the example of major depression (MD) and alcohol use disorder (AUD), we predict that if prior MD contributes causally to the onset of subsequent AUD, then the genetic risk for AUD will have a weaker effect on AUD risk in individuals with *v.* without a prior history of MD.

We apply this analytic framework to population-based Swedish registries containing diagnostic information with dates at first registration from in-patient, out-patient specialist, and primary care and, for substance abuse disorders, also from criminal registries. Furthermore, we have developed in this population, a family genetic risk score (FGRS) utilizing registry based diagnoses in 1st through 5th degree relatives accounting for age, sex, year of birth, county of residence, and cohabitation effects. This FGRS has performed well in a number of empirical applications with simulations suggesting that is provides a good and relatively unbiased measure of genetic risk (Kendler, Ohlsson, Sundquist, & Sundquist, 2021a, 2021b, 2023c, 2023d; Kendler, Rosmalen, Ohlsson, Sundquist, & Sundquist 2023e; Kendler et al. 2023a, 2023b).

We apply the model outlined above to 14 pairs of psychiatric and substance use disorders taken to be illustrative of the wide array of potential kinds of comorbidity. These pairs where the onset of one always precedes that of the second, involve the following six disorders: MD, anxiety disorders (AD), AUD, drug use disorder (DUD), bipolar disorder (BD), and schizophrenia (SZ). Our key analysis is to compare the predictive power of the FGRS for the second disorder in the pair with *v.* without a history of a prior episode of the first disorder. So, returning to our MD-AUD pairing, we will examine whether the impact of the $FGRS_{AUD}$ on risk for AUD is weaker in those who have *v.* have not had a prior onset of MD.

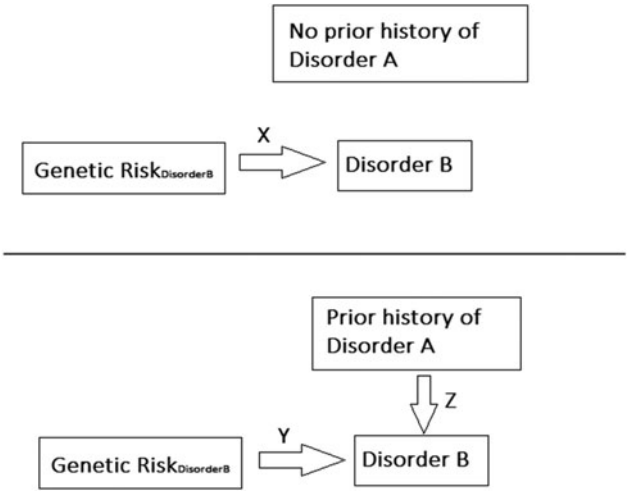

Figure 1. The conceptual design of this study –we assume two disorders, A and B. We examine cases of disorder B who have not had a prior episode of disorder A (top panel) and cases of disorder B who have had a prior episode of disorder A. The impact of the genetic liability for disorder B on risk for disorder B in the absence of a prior episode of disorder A (top panel) is quantified by the path coefficient X. The impact of the genetic liability for disorder B of risk for disorder B in the presence of a prior episode of disorder A (bottom panel) is quantified by the path coefficient Y. In the bottom panel, the magnitude of the causal effect of disorder A on risk for disorder B is quantified by coefficient Z. We predict that the stronger the impact of disorder A risk on disorder B (that is, the higher will be the value of Z), the greater the difference will be between our coefficient X and our coefficient Y. This is because the stronger the effect of disorder A on risk for disorder B is, the impact of the genetic liability for disorder B on risk for disorder B will be weaker.

Methods

We collected information on individuals from Swedish population-based registers with national coverage linking each person's unique personal identification number which, to preserve confidentiality, was replaced with a serial number by Statistics Sweden. We secured ethical approval for this study from the Regional Ethical Review Board in Lund (No. 2008/409 and later amendments). Participant consent was not required since the study used secondary register data.

Our database consisted of all individuals born in Sweden to Swedish born parents from 1980 to 1990. Utilizing ICD-9 and 10 codes from primary care, out-patient specialist, and hospital registries (for details, see appendix table 1), we included, in this database, the date of first registration for MD, AD, AUD, DUD, BD, and SZ (for their ICD-codes, see appendix table 2). Furthermore, we included individual family genetic risk scores (FGRS) for the six disorders. The FGRS are calculated from morbidity risks for specific disorders in first-degree through fifth-degree relatives, that controls for sex, year of birth, place of residence, genetic relationship with the proband and among first degree relatives, effects of cohabitation. The FGRS value is then standardized so a score of 0 and 0.5 means the genetic risk is, respectively, the average observed in the Swedish population *v.* 0.5 S.D.s above that mean value. It is important to note that the genetic information in the FGRS derives from phenotypes of members of extended pedigrees, and not from molecular genetic data. See appendix table 3 for further details of the FGRS.

The analyses focused on 14 pairs of psychiatric and substance use disorders (outlined in Table 1). We used Cox proportional hazards models to investigate the association between FGRS for disorder B and risk for disorder B controlling for year of birth and sex. We follow individuals from age 15 until end of follow-up (date of disorder B, death, emigration, or 12–31–2018, whatever came first). In the models we also included disorder A as a time dependent covariate (i.e. until the date of the disorder A the individual was considered free of exposure while from the date of disorder A the individual was considered exposed until end of follow-up) and an interaction term between disorder A and FGRS for disorder B. The inclusion of the interaction term allows us to examine whether the impact of FGRS (for disorder B) and disorder B is weaker among those who have *v.* have not had a prior onset of disorder A. All statistical analyses were performed using SAS 9.4 (SAS Institute, 2012).

Results

Descriptive analyses

Table 1 provides important descriptive information about our samples. We utilized a total population cohort of 905 736 individual (51.4% males), whom we followed from age 15 for a mean

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Table 1. Descriptive statistics of our sample of individuals born 1980 to 1990 in Sweden to Swedish-born parents ($N = 905\,736$)

		Rates disorder B			Rates disorder A*			
Disorder B	Disorder A	All (%)	Females (%)	Males (%)	All (%)	Females (%)	Males (%)	Tetrachoric correlation
AUD	DUD	4.0	2.9	5.2	5.5	3.3	7.7	0.49 (0.00)
DUD	AUD	6.4	3.8	8.9	2.8	2.2	3.4	0.40 (0.00)
MD	AD	14.3	18.6	10.2	10.8	13.5	8.1	0.36 (0.00)
AD	MD	15.4	20.0	11.2	10.3	13.2	7.5	0.45 (0.00)
MD	AUD	14.3	18.6	10.2	3.1	2.0	4.2	0.17 (0.00)
AUD	MD	4.0	2.9	5.2	13.2	17.6	9.1	0.14 (0.00)
AUD	BD	4.0	2.9	5.2	1.2	1.6	0.7	0.14 (0.01)
BD	AUD	1.4	1.9	0.9	3.9	2.7	5.0	0.28 (0.01)
DUD	SZ	6.4	3.8	8.9	0.1	0.1	0.2	0.14 (0.01)
SZ	DUD	0.2	0.1	0.3	6.3	3.7	8.8	0.33 (0.01)
AD	DUD	15.4	20.0	11.2	5.3	2.6	7.9	0.23 (0.00)
DUD	AD	6.4	3.8	8.9	13.6	18.4	9.1	0.06 (0.00)
AUD	SZ	4.0	2.9	5.2	0.2	0.1	0.2	0.14 (0.01)
SZ	AUD	0.2	0.1	0.3	4.0	2.8	5.1	0.25 (0.01)

*Registration has to occur prior to end of follow-up: AUD, alcohol use disorder; DUD, drug use disorder; MD, major depression; AD, anxiety disorders; BD, bipolar disorder; SZ, schizophrenia.

(S.D.) of 17.7 (3.9) years. Prevalences of our six disorders ranged widely, from 10–15% for MD and AD, 3–6% for DUD and AUD, ∼1.5% for BD and less than 0.2% for SZ, consistent with the narrow diagnostic approach to SZ long seen in Scandinavia in general and in Sweden specifically (Bech, 1990; Langfeldt, 1960). We see the expected female excess for MD, AD, and BD and a male excess for AUD, DUD, and SZ. The tetrachoric correlation, used here as an index of the magnitude of comorbidity between our pairs of disorders in this population cohort, varied widely from modest ($r < +0.15$), for DUD-AD, AUD-SZ,

Table 2. Descriptive results of relevant pairing of disorders for analysis

Disorder		Hazard ratios for control variables and key interaction term for prediction of risk for disorder B			Hazard ratios (± 95% CIs) for prediction of risk for disorder B from $FGRS_B$	
Disorder B	Disorder A	Year of birth	Male v. female	Interaction of $FGRS_B$ and history of prior disorder A in predicting disorder B	In the absence of a history of disorder A	In the presence of a history of disorder A
AUD	DUD	1.00 (1.00–1.01)	1.59 (1.55–1.63)	0.83 (0.81–0.84)	1.44 (1.43–1.46)	1.19 (1.18–1.21)
DUD	AUD	1.06 (1.06–1.06)	2.40 (2.35–2.44)	0.86 (0.84–0.87)	1.42 (1.41–1.43)	1.22 (1.19–1.24)
MD	AD	1.01 (1.01–1.02)	0.56 (0.56–0.57)	0.84 (0.83–0.85)	1.34 (1.34–1.35)	1.12 (1.11–1.14)
AD	MD	1.05 (1.04–1.05)	0.58 (0.58–0.59)	0.84 (0.83–0.85)	1.33 (1.32–1.34)	1.11 (1.10–1.13)
MD	AUD	1.03 (1.03–1.03)	0.50 (0.49–0.51)	0.91 (0.89–0.94)	1.34 (1.34–1.35)	1.23 (1.20–1.26)
AUD	MD	1.01 (1.00–1.01)	2.15 (2.10–2.20)	0.86 (0.84–0.88)	1.49 (1.46–1.51)	1.28 (1.26–1.30)
AUD	BD	1.02 (1.02–1.02)	1.91 (1.87–1.96)	0.83 (0.79–0.87)	1.48 (1.46–1.50)	1.23 (1.17–1.29)
BD	AUD	1.05 (1.05–1.06)	0.45 (0.43–0.47)	0.94 (0.91–0.97)	1.30 (1.27–1.32)	1.22 (1.19–1.25)
DUD	SZ	1.06 (1.06–1.06)	2.46 (2.41–2.51)	0.83 (0.75–0.91)	1.42 (1.41–1.43)	1.18 (1.07–1.30)
SZ	DUD	0.95 (0.93–0.96)	1.59 (1.43–1.76)	0.94 (0.91–0.97)	1.31 (1.19–1.24)	1.14 (1.11–1.17)
AD	DUD	1.06 (1.05–1.06)	0.48 (0.48–0.49)	0.92 (0.91–0.94)	1.32 (1.32–1.33)	1.22 (1.20–1.24)
DUD	AD	1.04 (1.04–1.05)	2.75 (2.70–2.80)	0.88 (0.87–0.90)	1.43 (1.42–1.44)	1.26 (1.24–1.28)
AUD	SZ	1.02 (1.02–1.02)	1.88 (1.84–1.92)	0.81 (0.72–0.90)	1.48 (1.46–1.50)	1.19 (1.06–1.33)
SZ	AUD	0.96 (0.95–0.98)	1.81 (1.64–2.00)	0.96 (0.92–1.00)	1.21 (1.19–1.24)	1.16 (1.12–1.20)

FGRS, family genetic risk score; AUD, alcohol use disorder; DUD, drug use disorder; MD, major depression; AD, anxiety disorders; BD, bipolar disorder; SZ, schizophrenia.

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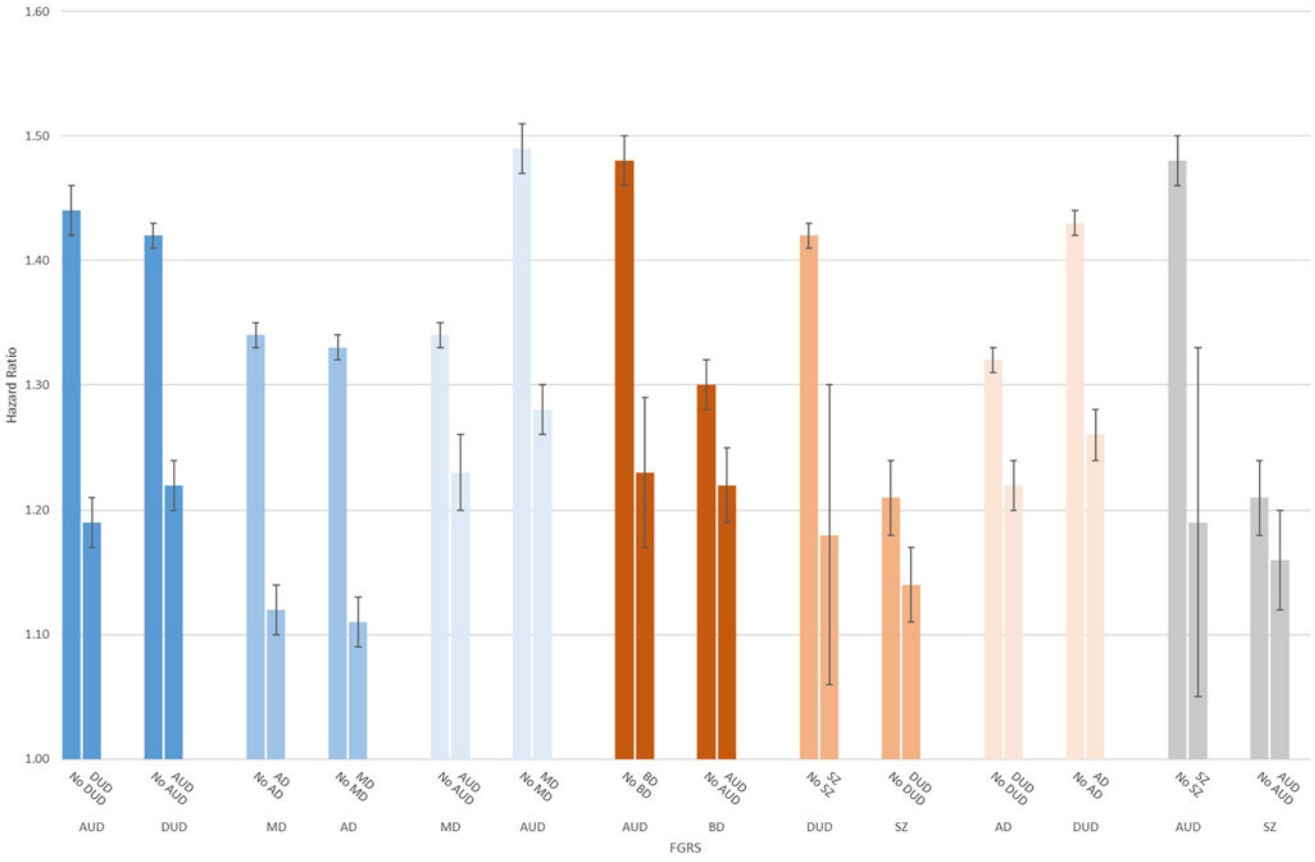

Figure 2. (*a*) The magnitude of interactions term (± 95% CIs) which reflects the differences in the genetic risk for disorder B – depicted at the bottom of the pairs of columns – in the absence of *v.* in the presence of a prior diagnosis of disorder A. The specific disorder A being considered is listed right below the two matched columns. For example, in the first two bars at the left edge of the figure, the left column shows the hazard ratio for $FGRS_{AUD}$ on AUD among individuals without a prior DUD registration ('No DUD') and the right column shows the hazard ratio for $FGRS_{AUD}$ on AUD among individuals with a prior DUD registration("DUD). The non-overlapping nature of the CIs seen for all pairs of columns, except the pair on the far right – SZ with or without a prior history of AUD – indicates that the hazard ratios are significantly different for the two analyses. (*b*) The magnitude, calculated separately in males and females, of the interaction term (± 95% CIs) which reflects the differences in the genetic risk for disorder B – depicted at the bottom of the pairs of columns – in the absence of versus in the presence of a prior diagnosis of disorder A, listed right below the two matched columns. In all sets of four columns, results for females are seen in bars 1 and 3 and males in bars 2 and 4.

DUD-SZ, AUD-MD, and AUD-BD to substantial ($r \geqslant +0.35$) for MD-AD, AD-MD, DUD-AUD, and AUD-DUD.

Primary analyses

The key results from our 14 pairs of disorders are presented in Table 2 and Fig. 2*a* where we predict the risk for disorder B. Table 2 includes the estimates (and 95% CIs) for the control variables year of birth and sex, the key result – the interaction between the FGRS for disorder B and the absence *v.* presence of a prior history of disorder A – and then, in the final two columns, the HRs for the FGRS for disorder B predicting risk for disorder B in the absence *v.* presence of a prior history of disorder A. Figure 1*a* illustrates those final two HRs for all the results, with disorder B given at the bottom of the pairs of columns representing the HRs for the FGRS in the absence *v.* presence of a history of disorder A.

In 13 of the 14 pairs (all but the prediction of risk for SZ from the $FGRS_{SZ}$ with *v.* without a prior history of AUD), the interactions were statistically significant. In all these pairs, the predictive effect of the FGRS for disorder B was considerably stronger in the absence than in the presence of a history of disorder A. The strongest effect was that the prediction of risk for AUD by the $FGRS_{AUD}$ which was substantially lower in individuals with a prior diagnosis of SZ – HR = 1.19 (1.06–1.33) – than in individuals with no history of SZ: HR = 1.48 (1.46–1.50). This produced an interaction term equal to 0.81 (0.72–0.90). A similar effect was seen for AUD and BD where the HR for $FGRS_{AUD}$ was significantly lower in individuals with *v.* without a prior BD diagnosis: 1.23 (1.17–1.29) *v.* 1.48 (1.46–1.50) [interaction – 0.83 (0.79–0.87)]. A very similar pattern of results is seen for risk of DUD with and without prior SZ.

Substantial effects were also seen for two closely related internalizing disorders: MD and AD. For example, the impact of the $FGRS_{MD}$ on MD was substantially greater in individuals without a prior diagnosis of AD (HR = 1.34, 1.34–1.35) *v.* those with a prior AD: HR = 1.12 (1.11–1.14), interaction – 0.84 (0.83–0.85). The results were nearly identical for the impact of $FGRS_{AD}$ on risk for AD in individuals with *v.* without a prior diagnosis of MD (Table 2).

In our two substance use disorders, AUD and DUD, results were similar. For example, the impact of the $FGRS_{AUD}$ on AUD risk was considerably stronger in individuals with no prior history of DUD (HR = 1.44, 1.43–1.46) than in those with a history of

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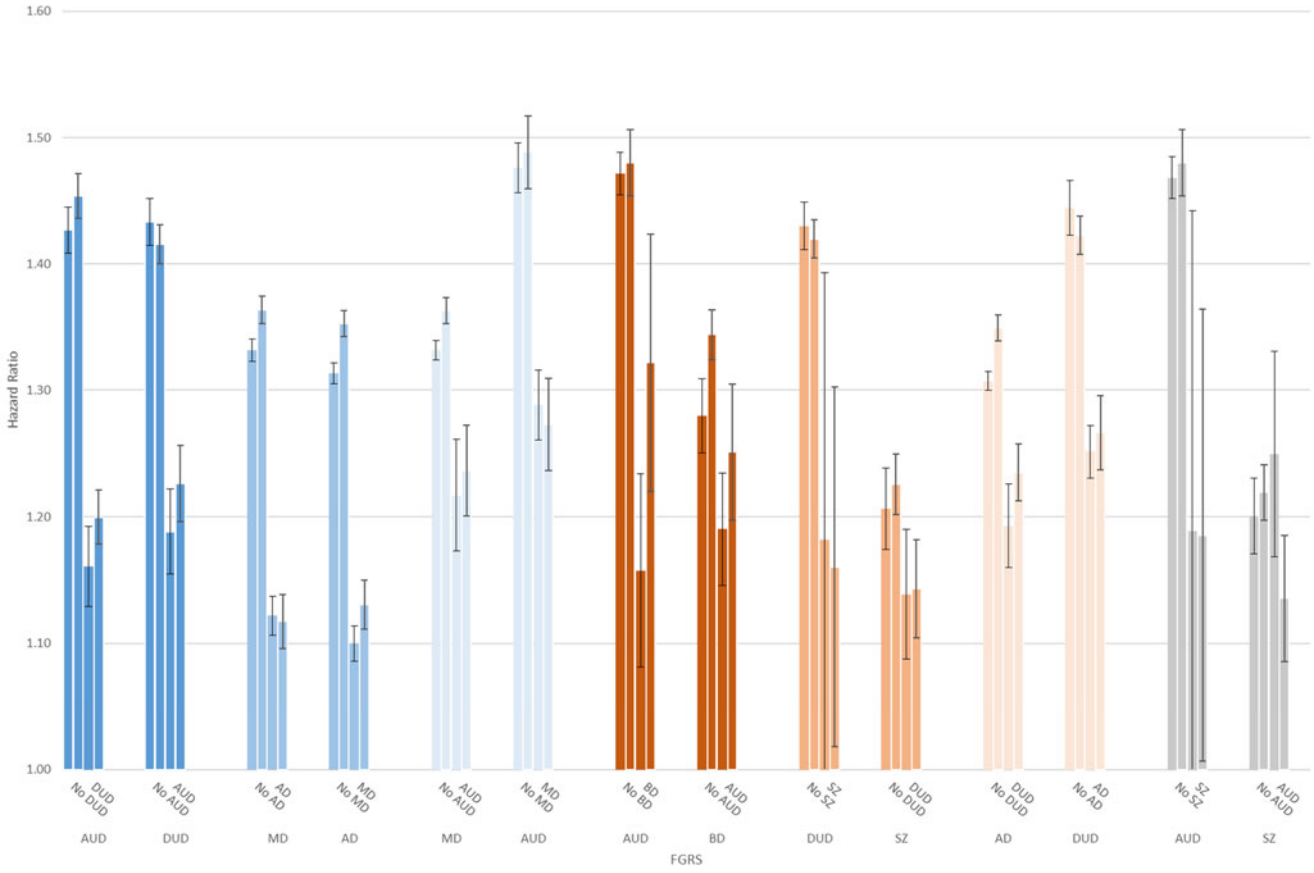

Figure 2. Continued.

DUD (HR = 1.19, 1.18–1.21) [interaction 0.83 (0.81–0.84)]. Very similar results were seen for the impact of $FGRS_{DUD}$ on risk for DUD in the presence *v.* absence of a prior history of AUD.

Several other findings were of substantial clinical and/or theoretical interest. The HR for $FGRS_{SZ}$ on risk for SZ was significantly lower in individuals with a prior history of DUD (1.14,1.11–1.17) compared to that seen in the absence of a DUD diagnosis: 1.31 (1.19–1.24) [interaction – 0.94 (0.91–0.97)]. The predictive effect of the $FGRS_{MD}$ on risk for MD was significantly lower in the presence *v.* the absence of a prior AUD diagnosis: 1.23 (1.20–1.26) *v.* 1.34 (1.34–1.35) [interaction 0.91 (0.89–0.94)]. Furthermore, the reverse was also seen as the predictive effect of the $FGRS_{AUD}$ on risk for AUD was significantly lower in the presence *v.* the absence of a prior MD diagnosis: 1.28 (1.26–1.30) *v.* 1.49 (1.46–1.51), interaction 0.86 (0.84–0.88).

Subsidiary analyses

We conducted three subsidiary analyses. First, we examined whether the pattern of results seen in Table 2 and Fig. 2*a* were similar across sexes. The primary results are presented in Fig. 2*b* which reveals qualitatively similar results across the sexes for our analyses. As seen in appendix table 4, a test of equality of the interaction terms between males and females for our 12 analyses revealed that none were significant at a Bonferroni corrected *p* value.

Second, several of the pairs of disorders (e.g. MD and AD) we have examined are known to be substantially genetically correlated (Kendler, Gardner, Gatz, & Pedersen, 2006; Kendler, Myers, & Prescott, 2007). Such correlations would predict that the average genetic risk for MD would be greater in an individual who had both MD and AD than AD alone. Indeed, in our cohort this is exactly what we find. Therefore, we wanted to insure that the results we were seeing in Fig. 2 did not arise from differences in levels of genetic risk for the non-comorbid *v.* comorbid cases. Therefore, we re-ran the analyses presented in Fig. 1 combining separate analyses within four groups of the FGRS (see appendix table 5 for explanation) for the given disorders, thereby matching for the level of genetic risk in the non-comorbid and comorbid cases. As seen in Fig. 3*a*, after controlling for level of genetic risk, our results are qualitatively similar to those seen in our initial analyses. We formally compared the interaction terms in the analyses presented in Fig. 3*a*, controlling for level of FGRS, with those presented in our main analyses in Fig. 2*a*. None of the 14 interactions differed significantly at a Bonferroni corrected *p* value of 0.003 (with one *p* value at 0.008 and the other 13 ranging from 0.07 to 0.92).

Third, we were concerned about our results being affected by clinician bias in which a treating physician either having diagnosed disorder A or see records of disorder A in the medical charts might be more prone to give a diagnosis of disorder B. We used one approach to rigorously test for this bias. While all of our psychiatric diagnoses were recorded only in medical records, our substance use disorder diagnoses came both from medical and from criminal registries. We reasoned that if clinical bias explained a substantial proportion of our observed effect, then our overall finding of lowered FGRS for disorder B after *v.*

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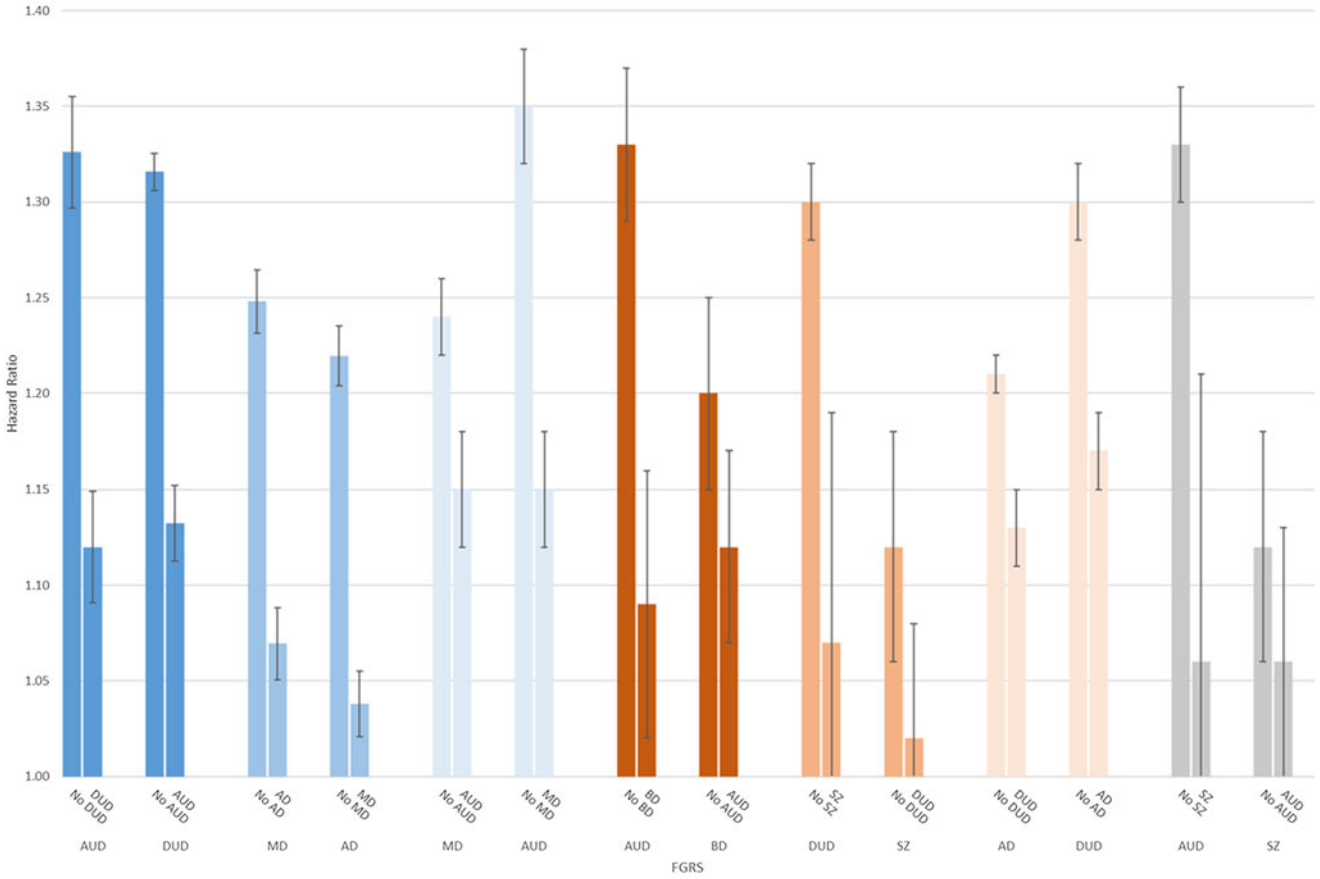

Figure 3. (*a*) The magnitude of interactions controlling for the level of FGRS, which reflects the differences in the genetic risk for disorder B – depicted at the bottom of the pairs of columns – in the presence of *v.* in the absence of a prior diagnosis of disorder A. The identity of disorder A is given right below the two matched columns. This was done by the division of the FGRS into four groups based on K-means clustering. Otherwise, the format of the results is the same as in (*a*). We tested for the heterogeneity of the interaction terms obtained with these analyses and the original analyses presented in (*a*). The resulting *p* value heterogeneity tests ranged from 0.072 to 0.97 for all comparison expect for MD (No AD v. AD) where the *p* value was 0.0075, all higher than the Bonferroni corrected *p* value of <0.004. Therefore, we could not reject the hypothesis that the interaction terms were similar across the two models. (b) This figure compares the interactions depicted in the above figures for disorder pairs involving alcohol use disorder (AUD) and drug use disorder (DUD) comparing the results obtained for AUD/DUD from medical registrations (Med) *v.* from criminal registrations (Cr). We tested the equality of the interaction terms between the two models (bars with the same color/shade in the figure). None were significant even at a nominal *p* value of <0.05.

before a diagnosis of disorder A should be much stronger when our AUD or DUD diagnoses arose from the medical *v.* the criminal registries. We present these results in Fig. 3*b*. In none of the 8 relevant analyses were the interactions significantly different from one another even at a nominal *p* value of 0.05 (with *p* values ranging from 0.06 to 0.86).

Discussion

We began this project with the hope that the availability of high quality family-based measures of genetic risk in the entire population of Sweden might provide insight into the vexed problem of the etiology of psychiatric and substance-use disorder comorbidity. Our approach was indirect and our goals modest. We did not seek to develop a statistically complex model that provides a full picture of the possible causes of comorbidity, nor did we attempt to calculate the percentage of comorbidity that might be due to a causal relationship between disorders. Instead, we sought to evaluate one important hypothesis – whether the prior occurrence of one psychiatric or substance use disorder contributes causally to the onset of a subsequent disorder? Our test of this hypothesis was based on the common-sense etiologic model (Fig. 1) that if a prior disorder A significantly increased the risk for the subsequent onset of B, then the genetic influences on the risk for disorder B should be stronger in cases without than in cases with a prior history as initially suggested by Schulz back in the 1930s.

Our results were consistent with that hypothesis. In 13 of our 14 pairs of disorders, chosen to represent a broadly representative set of psychiatric and substance use disorders, we found indirect evidence that the occurrence of the first of the pair of disorders contributed etiologically to the risk of onset of the second of the pair.

For many of these pairs, our results are congruent with prior findings and resulting theories from the clinical literature. For example, a leading explanation for the comorbidity between AUD and both MD and AD is the 'self-medication' hypothesis – that individuals affected with MD or AD will treat their dysphoria by self-medicating with alcohol or psychoactive drugs which can then lead to substance misuse and often to AUD or DUD (Khantzian, 1997; Turner, Mota, Bolton, & Sareen, 2018). Prior empirical studies, including some with genetic designs, have presented data consistent with this hypothesis (Kuo, Gardner, Kendler, & Prescott, 2006; Robinson, Sareen, Cox, & Bolton, 2011). This would be consistent with our findings for our MD-AUD and AD-DUD pairings. Self-medication has also

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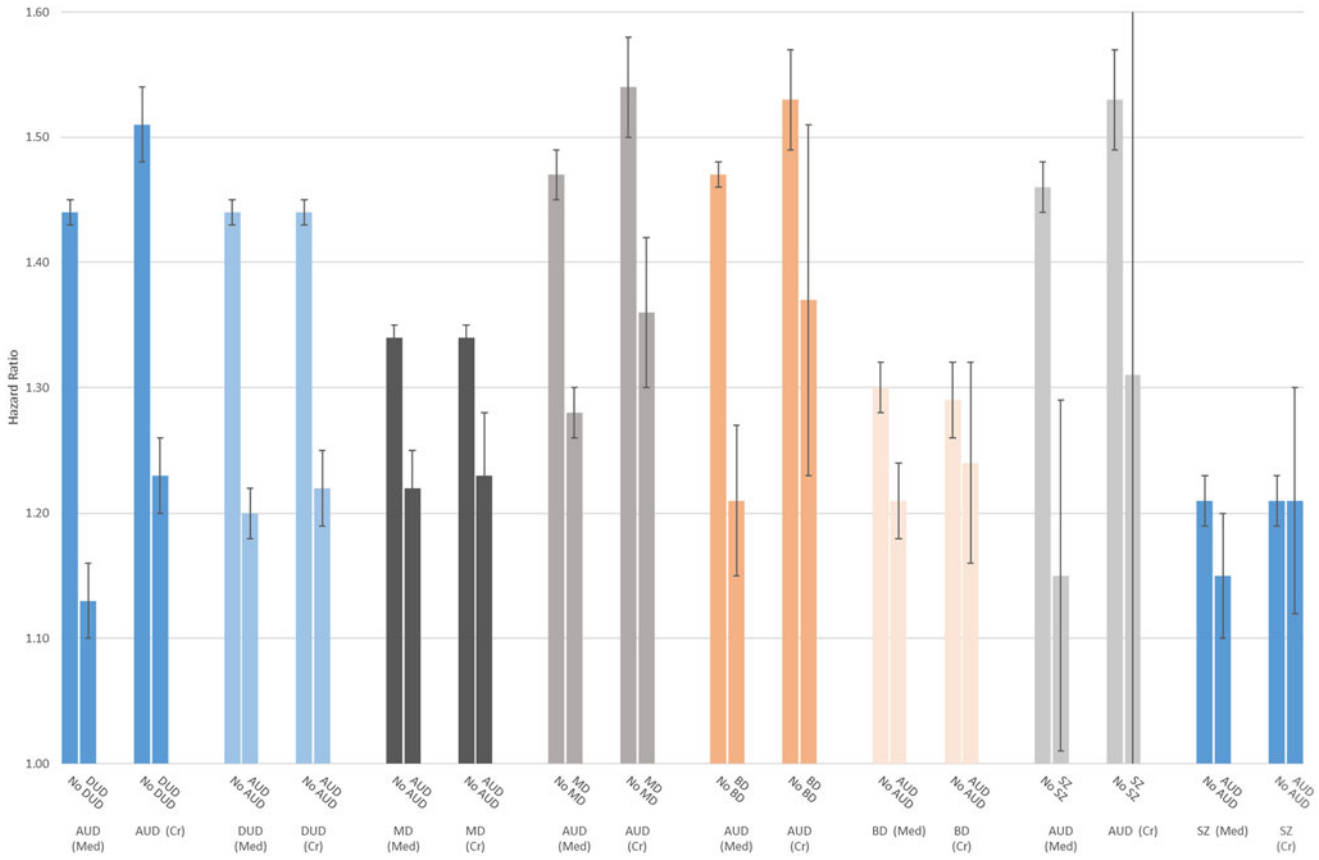

Figure 3. Continued.

been proposed as a pathway from SZ to substance use disorders (for example SZ patients reporting that their heavy alcohol intake reduces the intensity of their auditory hallucinations), consistent with the findings of our SZ-AUD and SZ-DUD pairings (Winklbaur, Ebner, Sachs, Thau, & Fischer, 2022). Excessive alcohol consumption has long been associated with manic episodes which may, over time, lead to excess risk for AUD as predicted by our results for the BD-AUD pairing (Reich, Himmelhoch, & Davies, 1974). Substantial recent interest has focused on the possibility of a causal relationship between cannabis use disorder and SZ (D'Souza et al., 2022; Johnson et al., 2021) and two recent large population based studies have shown that a substantial proportion of patients with substance-induced psychotic disorder, especially those related to cannabis and stimulant use, eventually transition to schizophrenia (Kendler, Ohlsson, Sundquist, & Sundquist, 2019; Rognli, Heiberg, Jacobsen, Høye, & Bramness, 2023). These findings are consistent with the results for our DUD-SZ disorder pair. Finally, a number of longitudinal studies have suggested bidirectional paths from AD to MD and MD to AD which may be, at least in part, causally mediated (Kessler et al., 2008; Lamers et al., 2011; Moffitt et al., 2007) (e.g. chronic anxiety leading to a reduction in self-esteem, social isolation and associated depressive symptoms), results that would be predicted from our findings in our AD-MD and MD-AD pairings.

Aside from our main results, we conducted three subsidiary analyses to examine further scientific questions and potential biases in our findings. First, we showed no evidence of significant sex effects in our models. With respect to potential causal effects of one disorder on another, including disorders like MD and AUD with large sex differences in prevalence, no major differences were seen between men and women in our modeling results. Second, we predicted that the genetic risk for disorder B in our pairs would be higher in those without a history of a prior disorder A diagnosis than in those with such a history. We saw this in our results. Could our results arise in part from the difference in genetic risk? We showed that this is unlikely as, after controlling for level of genetic risk, our results were qualitatively similar to those seen in our main analyses.

Third, we examined whether a clinician bias might have influenced our results. This might arise if a physician would be more likely to give a diagnosis of disorder B given a prior history of disorder A could explain our findings. We tested this for AUD and DUD because we had diagnoses from two entirely different registries for these conditions. Our analyses did not suggest that clinician bias likely influenced our findings.

In summary, given that polygenic risk scores are becoming available on more and more clinical samples, we hope that this report might encourage future attempts to replicate and generalize our findings. Furthermore, following more closely the goals of the original use of this method by Schulz in 1933, the wide availability of genetic risk scores provides an additional method to verify potential environmental risk factors for psychiatric and drug abuse disorders by finding weaker effects of genetic risk scores into cases with *v.* without exposure to the putative environmental risk factor.

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Limitations

These results should be interpreted in the context of three potential methodological limitations of our analyses. First, the value of our results is in part dependent on the validity of the diagnoses in the Swedish medical registries. These were not diagnoses made in research settings so variability in these clinical conditions is likely. The validities of the hospital diagnoses for SZ and BD in Sweden have, however, been well supported (Ekholm et al., 2005; Lichtenstein et al., 2006; Sellgren, Landen, Lichtenstein, Hultman, & Langstrom, 2011). The validity of the diagnosis of MD and AD are supported by their prevalence, sex ratio, sibling and twin correlations and associations with known psychosocial risk factors (Kendler, Ohlsson, Lichtenstein, Sundquist, & Sundquist, 2018b; Sundquist, Ohlsson, Sundquist, & Kendler, 2017). The validity of our definitions of AUD and DUD is supported by the high rates of concordance across ascertainment methods (Kendler, Lönn, Salvatore, Sundquist, & Sundquist, 2018a) (Kendler et al., 2015) and patterns of resemblance in relatives similar to those found in personally interviewed samples (Prescott & Kendler, 1999; Tsuang et al., 1996). Furthermore, in this study, we can only examine disorders seen in clinical settings (except for AUD and DUD that are also ascertained through criminal records). Having one psychiatric disorder could increase the chances of help-seeking for a second disorder which could impact on our findings of levels of genetic risk. If this was an important effect on our results, then we would expect the difference in risk for disorders occurring on their own or after other disorders should differ substantially if the first disorder is a psychiatric or substance use disorders – was the latter are ascertained in an entirely different fashion. That is not seen in our results suggesting that our overall pattern of results is unlikely to be largely attributed to the impact of help-seeking behavior.

Second, we do not have precise estimates of ages at onset in our samples and had to use, instead, their ages at first registration. Thus, is it likely that in some instances, we have incorrectly ordered the onsets of our pairs of disorders.

Third, as pointed out previously, we are inferring a causal process from differences in the strength of the prediction of disorders by genetic risk factors. Such inferences can be mistaken, and we cannot rule out that we have misinterpreted our results due to the operation of other causal factors. Further efforts to unravel the bases of the widespread comorbidities seen for psychiatric and drug use disorders would be well advised to pay special attention to causal processes and try to use a range of the non-experimental causal inference methods available in psychiatric epidemiology (Ohlsson & Kendler, 2020).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003847.

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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