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The joint effects of genetic liability and the death of close relatives on risk for major depression and alcohol use disorder in a Swedish national sample

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Abstract

Background. To determine whether genetic risk factors for major depression (MD) and alcohol use disorder (AUD) interact with a potent stressor – death of spouse, parent, and sibling – in predicting episodes of, respectively, MD and AUD.

Methods. MD and AUD registrations were assessed from national Swedish registries. In individuals born in Sweden 1960–1970, we identified 7586, 388 459, and 34 370 with the loss of, respectively, a spouse, parent, and sibling. We started following subjects at age 18 or the year 2002 with end of follow-up in 2018. We examined time to event – a registration for MD within 6 months or AUD within a year – on an additive scale, using the Nelson–Aalen estimator. Genetic risk was assessed by the Family Genetic Risk Score (FGRS).

Results. In separate models controlling for the main effects of death of spouse, parent, and sibling, FGRS, and sex, significant interactions were seen in all analyses between genetic risk for MD and death of relative in prediction of subsequent MD registration. A similar pattern of results, albeit with weaker interaction effects, was seen for genetic risk for AUD and risk for AUD registration. Genetic risk for bipolar disorder (BD) and anxiety disorders (AD) also interacted with event exposure in predicting MD.

Conclusions. Genetic risk for both MD and AUD act in part by increasing the sensitivity of individuals to the pathogenic effects of environmental stressors. For prediction of MD, similar effects are also seen for genetic risk for AD and BD.

A long tradition of research has examined the association between stressful life events (SLE) and risk for episode onset or recurrence of a range of psychiatric disorders, especially major depression (MD) (Brown & Harris, 1978; Brown, Harris, & Hepworth, 1995; Cohen, Murphy, & Prather, 2019; Holmes & Rahe, 1967; Kendler, Karkowski, & Prescott, 1998; Kessler, 1997; Paykel et al., 1969). A substantial proportion of this association appears to be causal (Kendler & Gardner, 2010a; Kendler, Karkowski, & Prescott, 1999). Most, but not all, such studies have also seen elevations in rates of alcohol misuse and alcohol use disorder (AUD) after SLEs (Boden, Fergusson, & Horwood, 2014; Gorman & Peters, 1990; Jennison, 1992; Keyes, Hatzenbuehler, & Hasin, 2011; Lee, Young Wolff, Kendler, & Prescott, 2012; Perreira & Sloan, 2001; Storr et al., 2021).

Along with evidence of a direct effect of SLEs on disease risk, our field has also been long interested in understanding how environmental traumatic experiences inter-relate with genetic risk. Much of this work has focused on whether genetic risk factors for disorders like MD act partly by rendering individuals more or less sensitive to the depressogenic effects of environmental stressors (Kendler & Eaves, 1986). Prior twin studies have generally found evidence for such an interaction between genetic risk and SLE exposure in risk for MD, with SLEs assessed by interview (Kendler et al., 1995; Kendler, Kuhn, & Prescott, 2004). After this twin work, a large literature on MD emerged testing the interaction of SLEs with various candidate gene variants. A large proportion of this 'gene × SLE interaction literature' focused on the serotonin transporter polymorphism (Dick & Kendler, 2012). These findings have generally failed the test of replication (Dick et al., 2015). However, with the recent availability of polygenic risk scores (PRS) calculated from genome wide association studies, a number of studies have examined the joint effects of a PRS score for MD and SLE exposure, with most (Arnau-Soler et al., 2019; Chuong et al., 2022; Coleman et al., 2020; Colodro-Conde et al., 2018; Peterson et al., 2018; Suppli et al., 2022) but not all (Mullins et al., 2016) finding interaction effects.

Studies examining interactions between stress exposure and PRS for AUD on risk for AUD have been rarer, with both positive (Kuo et al., 2023) and negative results (Mies et al., 2018).

In this report, we seek to contribute further to understanding the joint effects of genetic risk and environmental stressors for both MD and AUD using a different methodological approach. In a recent study (Kendler, Lönn, Sundquist, & Sundquist, 2023c), we showed, in a large general population Swedish sample, that the death of a parent, spouse, sibling or child produced a substantial increased risk for MD over the 6 months after death. A more modest and longer lasting increased risk was also seen for AUD. As a SLE, death in a close relative has the practical advantages for studies as it is temporally discrete, non-recurrent, can be assessed with high accuracy and is often a severe stressor (Brugha, Bebbington, Tennant, & Hurry, 1985; Holmes & Rahe, 1967; Kendler et al., 1998).

We here build on that prior study and adapt its methods to determine if levels of genetic risk for MD and AUD not only increase baseline risk for, respectively, MD and AUD, but also increase the sensitivity of the individuals to develop these disorders after the death of a close relative. This study permits us to study the question of gene-environment interaction using a large, representative population sample, a potent, non-recurrent stressor, and a quantitative well-validated measure of genetic risk – the familial genetic risk score (FGRS). We also address, for the first time to our knowledge, whether other genetic risks – in particular, bipolar disorder (BD) and anxiety disorders (AD) – also interact with a severe stressor in increasing disorder risk for MD.

Methods

We linked nationwide Swedish registers via the unique 10-digit identification number assigned to all Swedish residents which was replaced by a serial number to ensure confidentiality. To create our analysis dataset, we used the following sources: Multi-Generation Register, containing information about date of birth and death, sex and linking individuals born after 1932 to their parents and siblings; Total Population Register, containing yearly information of marital status from 1968, Hospital Discharge Register, containing hospitalizations for Swedish inhabitants from 1964 to 2018; Prescribed Drug Register, containing all prescriptions in Sweden picked up by patients from July 2005 to 2018; Outpatient Care Register, containing information from all outpatient clinics from 2001 to 2018; Crime Register that included national complete data on all convictions in lower court from 1973–2018; Swedish Suspicion Register that included national data on individuals strongly suspected of crime from 1998–2018; and the Mortality Register with dates and causes of death from 1952 until 2018. In addition, we had medical diagnosis from Primary Health Care clinics from nearly all counties in Sweden outlined in the online Appendix Table 1. The time periods vary due to the regions' different timing of digitalizing of the patient records.

Measures and sample

We defined MD using the following ICD-codes from Swedish medical registers, ICD-9 codes: 296B, 298A, and 300E, and ICD-10 codes: F32, and F33. AUD was defined from Swedish medical registers using the following ICD codes: ICD8: 571.0, 291, 303, 980; ICD9: V79B, 305A, 357F, 571A, 571B, 571C, 571D, 425F, 535D, 291, 303, 980; and ICD 10: E244, G312, G621, G721, I426, K292, K700, K701, K702, K703, K704, K709, K852, K860, O354, T510, T511, T512, T513, T518, T519, F101, F102, F103, F104, F105, F106, F107, F108, F109; and from the Prescribed Drug Register if prescribed disulfiram (Anatomical Therapeutic Chemical (ATC) Classification System N07BB01), acamprosate (N07BB03), or naltrexone (N07BB04). In addition, we identified AUD as convicted for, or suspected of, at least two alcohol-related crimes according to law 1951:649, paragraph 4 and 4A and law 1994:1009, Chapter 20, paragraph 4 and 5 from the Swedish Crime Register, and code 3005 and 3201 in the Suspicion register.

We assessed the genetic liability on risk for MD, AUD, AD and BD using a FGRS. Basically, the FGRS is calculated from morbidity risks for disorders in first-degree through fifth-degree relatives, controlling for age, sex, year of birth, country of residence and cohabitation effects with parents and siblings, and thus arises from phenotypes in extended pedigrees, not from molecular genetic data. For further details, see online Appendix Table 2. The FGRS was categorized into quartiles when included in the analysis.

We included men and women born in Sweden between 1960 and 1970 to Swedish born parents. This latter restriction was necessary because only for such individuals do we have information on enough relatives to calculate a meaningful FGRS. Most MD and medical AUD diagnosis are set in primary and outpatient care, and we therefore follow individuals from the year 2002 and onwards. We included only married couples who cohabited and identified death of spouse using marital status in the total population register. Siblings and parents were identified using the Multigeneration register. We included only the first marriage and the death of the first parent or sibling if occurring when the proband was over age 18.

Statistical methods

For the loss of spouse analysis, we followed individuals from the date of marriage or the year 2002 and for the loss of sibling and parent analysis we started following subjects at age 18 or the year 2002. End of follow-up was in 2018, emigration, or death. Because we wanted to analyze the time to event, MD or AUD on an additive scale, we used the Nelson–Aalen estimator (Martinussen & Scheike, 2006). Consequently, the assessed associations represent the expected number of new cases of MD/AUD per 10 000 person years, meaning that the interaction represent the additional number of cases we can expect if both predictors are present, beyond the additional risk of each predictor. We included all eligible individuals who were unexposed to death of a close relative at the start of follow-up and the SLE was included as a time dependent variable. We followed individuals until a registration of MD/AUD, or censoring. We allowed for registrations of MD/AUD both before and after the SLE but counted only the first episode of M/AUD in each time period.

We ran several consecutive analyses starting with a crude model including only the SLE and sex (model 1). For MD, our risk period was 6 months after the death of the relevant relative. Given prior evidence of a more prolonged risk for AUD post-relative death (Kendler et al., 2023c), the period of risk for AUD was set at one year. Next, we included the FGRS quartiles and the interaction between sex and the SLE (e.g. death of relative) to allow for sex differences (model 2), and, finally, to investigate whether the effect of the SLE is dependent on genetic risk, we added the interaction between the FGRS quartile and the SLE

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Table 1. Sample size of the three kinds of relatives examined and the number of probands exposed to their death

Kind of relative	Selected on	Total sample size	Number (%) exposed to death
Spouse	Being married	622 169	7586 (1.2%)
Parent	Having both parents living	777 719	388 459 (49.9%)
Sibling	Having at least one living sibling	773 621	34 370 (4.4%)

to the model (model 3). In addition, we investigated whether the genetic liability of BD and AD is associated with risk of MD by running models 2 and with the BD and AD FGRS respectively. Results, which reflect an additive approach to the analysis of G × E interaction (Kendler & Gardner, 2010a, 2010b), are presented as number of new cases of MD or AUD respectively per 10 000 person years, with 95% CIs. Analyses were conducted in R (RStudio Team, 2022; Team, 2022; Scheike, 2023).

Results

The key descriptive results from our three samples – (i) married individuals with and without loss of spouse, (ii) individuals selected for having both parents alive and who did *v.* did not have the loss of a parent, and (iii) individuals with at least one living sibling who did or did not lose a sibling – can be seen in Table 1. We had both the largest sample and by far the largest number of deaths in parents followed by siblings. The sample with loss of a spouse was much smaller and hence those analyses are more poorly powered.

Results for MD genetic liability on risk for MD

The main results for MD are presented in Table 2 in the form of three models. The dependent variable assessed was the number of new cases of MD per 10 000 person years (95% CIs) in the 6 months after the relative's death. Model 1 shows the main effect of the death of the three classes of relatives. The effect size is largest for loss of spouse, followed by loss of sibling and then loss of parent.

Model 2 adds the main effect of the genetic risk for MD ($FGRS_{MD}$) for the 2nd, 3rd and 4th quartiles compared to the 1st quartile of risk. Accounting for the death of the relative, sex effects, and a death × sex interaction (where positive effects indicate greater impact in females), we see, for death of spouse, parent, and sibling, a monotonic and consistently significant increase in the number of new MD cases associated with rising levels of genetic risk.

Our key results are contained in model 3 which adds to model 2 the interaction between genetic risk and death of relative. For loss of spouse, we see significant evidence for G × E interaction

Table 2. Risk for major depression after death of spouse, parent and sibling and interaction between death and genetic risk for major depression within 6 months of death

	(Average) number of new cases of MD per 10 000 person years (95% CIs)		
Follow-up time	Loss of spouse	Loss of parent	Loss of sibling
Model 1			
Death of first degree relative	1112.78 (999.64, 1244.92)	235.47 (237.46, 243.89)	330.03 (299.15, 360.90)
Women *v.* men	47.66 (45.45, 48.87)	55.98 (54.82, 57.15)	14.08 (13.78, 14.38)
Model 2			
Death of first degree relative	595.63 (455.33, 735.92)	148.49 (139.45 157.53)	220.62 (183.90, 257.33)
Women *v.* men	46.74 (45.53, 47.94)	51.64 (50.49, 52.78)	13.65 (13.35, 13.95)
2nd *v.* 1st quartile FGRS	10.06 (8.65, 11.47)	13.13 (11.81, 14.45)	3.51 (3.17, 3.86)
3rd *v.* 1st quartile FGRS	33.48 (31.89, 35.06)	40.82 (39.32, 42.31)	10.44 (10.05, 10.82)
4th *v.* 1st quartile FGRS	67.48 (65.66, 69.30)	80.74 (78.96, 82.52)	20.14 (19.71, 20.58)
Death × sex interaction stronger in females	794.05 (583.53, 1004.57)	170.50 (154.35, 186.65)	219.67 (157.54, 281.80)
Model 3			
Death of first degree relative	431.63 (201.71, 661.56)	53.60 (40.01, 67.20)	55.56 (−0.69, 111.82)
Women *v.* men	46.74 (45.53, 47.95)	51.70 (50.56, 52.84)	13.65 (13.36, 13.95)
2nd *v.* 1st quartile FGRS	10.08 (8.67, 11.48)	12.26 (10.96, 13.56)	3.52 (3.17, 3.86)
3rd *v.* 1st quartile FGRS	33.38 (31.80, 34.96)	38.70 (37.22, 40.17)	10.37 (9.98, 10.75)
4th *v.* 1st quartile FGRS	67.26 (65.45, 69.07)	75.97 (74.22, 77.71)	19.99 (19.56, 20.43)
Death × sex interaction	789.45 (578.88, 1000.02)	166.69 (150.57, 182.80)	209.44 (147.51, 271.37)
Death × 2nd quartile	−29.85 (−324.03, 264.32)	**38.38 (19.57, 57.18)**	14.34 (−59.03, 87.71)
Death × 3rd quartile	224.16 (−88.61, 536.93)	**112.22 (91.59, 132.85)**	**206.16 (124.64, 287.68)**
Death × 4th quartile	**451.08 (124.53, 777.63)**	**222.05 (199.46, 244.64)**	**342.07 (289.32, 424.83)**

Statistically significant interactions in model 3 are bolded.

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only in those in the highest quartile of $FGRS_{MD}$ noting the wide CIs in our findings. For loss of parent, we find significant G × E interactions increasing in magnitude from the 2nd to 4th quartiles of genetic risk with much more precise estimates. In death in siblings, significant and increasing evidence is found for G × E effects for those in the 3rd and 4th quartiles of $FGRS_{MD}$.

Looking at the raw results in the interaction effects for the 1st *v.* 4th quartile, the effect size is considerably greater in death of spouse, intermediate in death of siblings and smallest in death of parents. Not surprisingly, this is the same order of effect size seen in the main effect of death on MD risk. But, given the large CIs for our G × E effects, especially with spouse, we cannot be confident in our ability to order the interactions by effect size.

Results for AUD genetic liability on risk for AUD

As seen in Table 3, the results of model 1 show a much smaller effect size for death of relatives on risk for AUD than was seen in Table 2 for risk for MD. Furthermore, the order of size of effect differs as it is strongest for AUD in siblings and for MD in spouses. As expected, we also see the reversal of sex effects, with the impact of death of close relative on AUD having a stronger effect in males than females. Model 2 shows the main effect of AUD genetic risk on rates of AUD after death which much of that main effect packed into those in the highest risk quartile. Model 3 shows the results of greatest interest to us, presenting evidence of significant G × E effects for the 4th *v.* 1st quartile comparison for death of spouses, siblings, and parents. We also see significant effects for the 3rd *v.* 1st quartile comparison for loss of parents and siblings. Parental loss is associated with a less robust G × E effect in predicting registrations for AUD than is seen with loss of siblings and spouses.

Results for BD and AD genetic liability on risk for MD

We next examined risk for MD after death of a close relative but this time jointly with genetic risk factors for BD (Table 4). We can see in the results of model 2 in Table 4 compared to model 2 in Table 2, that the direct effect of $FGRS_{BD}$ on risk for MD in all three of our samples is much weaker than the direct effect of $FGRS_{MD}$. No significant interactions are seen with genetic risk for BD with death of spouse. Death of parent has significant interactions for the 4th *v.* 1st and the 3rd *v.* 1st quartiles of $FGRS_{BD}$. For death of siblings, significant interactions are only seen for the 4th *v.* 1st quartiles. As seen with the direct effect, the magnitude of the interactions with $FGRS_{BD}$ are considerably smaller than those we see with $FGRS_{MD}$.

Finally, we explored the interaction of the genetic risk for AD and death of close relatives in the prediction of MD after the death of close relatives (Table 5). In model 2, we can see that the direct effect of $FGRS_{AD}$ on risk for MD in all three of our samples is weaker than the direct effect of $FGRS_{MD}$ but stronger than that

Table 3. Risk for alcohol use disorder after death of spouse, parent and sibling and interaction between death and genetic risk for alcohol use disorder within 12 months of death

	(Average) number of new cases of AUD per 10 000 person years (95% CIs)		
Follow-up time	Loss of spouse	Loss of parent	Loss of sibling
Model 1			
Death of first degree relative	162.48 (131.59, 193.45)	73.60 (70.41, 76.79)	147.52 (133.09, 161.95)
Women *v.* men	−12.19 (−12.74, −11.63)	−22.51 (−23.13, −21.88)	−6.18 (−6.35, −6.01)
Model 2			
Death of first degree relative	261.36 (194.53, 328.33)	101.74 (96.44, 107.04)	325.55 (296.59, 354.50)
Women *v.* men	−12.23 (−12.78, −11.67)	−20.73 (−21.34, −20.12)	−6.18 (−6.35, −6.01)
2nd *v.* 1st quartile FGRS	−0.12 (−0.48, 0.72)	0.08 (−0.62, 0.77)	−0.17 (−0.36, −0.01)
3rd *v.* 1st quartile FGRS	4.68 (4.02, 5.35)	7.99 (7.26, 8.73)	2.15 (1.94, 2.36)
4th *v.* 1st quartile FGRS	21.92 (21.02, 22.82)	38.16 (37.11, 39.22)	10.55 (10.27, 10.582)
Death × sex interaction	−151.87 (−225.87, −77.86)	−61.27 (−67.61, −54.93)	−207.07 (−241.54, −172.61)
Model 3			
Death of first degree relative	207.31 (130.25, 284.37)	72.02 (65.80, 78.24)	99.31 (75.56, 123.07)
Women *v.* men	−12.23 (−12.78, −11.67)	−20.69 (−21.29, −20.08)	−6.18 (−6.35, −6.01)
2nd *v.* 1st quartile FGRS	0.15 (−0.45, 0.75)	0.26 (−0.42, 0.93)	−0.21 (−0.40, −0.02)
3rd *v.* 1st quartile FGRS	4.65 (3.99, 5.31)	7.40 (6.68, 8.11)	2.10 (1.89, 2.31)
4th *v.* 1st quartile FGRS	21.73 (20.84, 22.62)	34.25 (33.23, 35.27)	10.20 (9.92, 10.47)
Death × sex interaction	−154.23 (−228.91, −80.13)	−61.98 (−68.33, −55.63)	−135.13 (−163.93, −106.32)
Death × 2nd quartile	−23.23 (−90.87, 44.40,)	-0.26 (−7.13, 6.61)	35.19 (4.06, 66.32)
Death × 3rd quartile	35.77 (−43.18, 114.71)	**16.68 (8.81, 24.55)**	**46.58 (15.64, 77.52)**
Death × 4th quartile	**201.77 (104.55, 298.98)**	**97.44 (87.62, 107.25)**	**235.51 (200.67, 270.35)**

Statistically significant interactions in model 3 are bolded.

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Table 4. Risk for major depression after death of spouse, parent and sibling and interaction between death and genetic risk for bipolar disorder within 6 months of death

	(Average) number of new cases of MD per 10 000 person years (95% CIs)		
Follow-up time	Loss of spouse	Loss of parent	Loss of sibling
Model 1			
Death of first degree relative	1112.78 (999.64, 1244.92)	235.47 (237.46, 243.89)	330.03 (299.15, 360.90)
Women *v.* men	47.66 (45.45, 48.87)	55.98 (54.82, 57.15)	14.08 (13.78, 14.38)
Model 2			
Death of first degree relative	597.41 (457.11, 737.71)	152.15 (143.11, 161.19)	222.28 (185.56, 258.99)
Women *v.* men	47.45 (46.24, 48.66)	52.78 (51.63, 52.93)	14.00 (13.71, 14.30)
2nd *v.* 1st quartile FGRS	0.25 (−1.32, 2.01)	2.21 (0.65, 3.77)	−0.42 (−0.82, −0.01)
3rd *v.* 1st quartile FGRS	3.17 (1.50, 4.84)	2.78 (1.18, 4.38)	−0.56 (−0.96, −0.16)
4th *v.* 1st quartile FGRS	20.77 (18.97, 22.57)	22.64 (20.98, 24.31)	5.25 (4.82, 5.68)
Death × sex interaction stronger in females	793.89 (583.37, 1004.41)	170.90 (154.75, 187.05)	219.93 (157.80, 282.05)
Model 3			
Death of first degree relative	517.44 (268.97, 765.91)	110.81 (94.90, 126.73)	133.48 (80.61, 186.34)
Women *v.* men	47.45 (46.24, 48.66)	52.77 (51.62, 53.91)	14.00 (13.71, 14.30)
2nd *v.* 1st quartile FGRS	0.32 (−1.33, 1.98)	1.82 (0.29, 3.35)	−0.46 (−0.86, −0.06)
3rd *v.* 1st quartile FGRS	3.11 (1.44, 4.77)	2.17 (0.60, 3.74)	−0.61 (−1.01, −0.21)
4th *v.* 1st quartile FGRS	20.71 (18.92, 22.50)	20.59 (18.95, 22.23)	5.15 (4.72, 5.58)
Death × sex interaction	796.94 (586.14, 1007.75)	171.78 (155.62, 187.95)	222.17 (160.03, 284.30)
Death × 2nd quartile	50.63 (−270.90, 372.16)	21.25 (−0.38, 42.89)	78.69 (−3.20, 160.58)
Death × 3rd quartile	133.50 (−185.03, 452.04)	**33.74 (12.29, 55.20)**	78.62 (−5.30, 162.55)
Death × 4th quartile	117.36 (−203.55, 428.27)	**108.44 (84.97, 131.90)**	**202.85 (119.74, 285.95)**

Statistically significant interactions in model 3 are bolded.

seen with $FGRS_{BD}$. The interaction effects seen in model 5 between $FGRS_{AD}$ and death of a relative are statistically significant for the 4th *v.* 1st and the 3rd *v.* 1st quartiles of $FGRS_{AD}$ for death of spouse, parent, and siblings. The magnitudes of these interactions are similar to and in some cases modestly larger than those seen in our analyses with $FGRS_{MD}$.

Discussion

We asked three major questions all seeking to further understand how genetic risk and environmental stressors inter-relate in the etiology of MD and AUD. We will review our major findings in turn.

First, we examined the joint effects of the genetic risk for MD and death of three classes of close relatives – spouses, parents and siblings – on risk for MD in the 6 months following the death – the main risk period for MD per our prior analyses (Kendler et al., 2023c). Consistent with those prior results (Kendler et al., 2023c), we found a substantial direct effect of loss of relative on risk for MD in all three analyses. Also, as expected, we consistently saw direct effects of genetic liability on risk for MD. Of most interest, we also saw evidence of significant positive G × E interactions in each of the three groups – those who experienced the recent death of a spouse, parent, or sibling. In our additive statistical model, this means we observed more cases of MD than would have been predicted from the direct effects of genetic risk and our environmental stressor, death of relative, operating independently. These results, using a relatively different approach to stress assessment, provide confirmation of prior twin and PRS based studies most typically using SLEs as assessed by interview or questionnaire.

Second, in our first descriptive analysis of our data, we also found a more modest increased risk for AUD after the death of close relatives (Kendler et al., 2023c). Because most of the literature on G × E effects with substance use disorders focused on a quite different set of environmental exposures (that are permissive of or restrictive of deviant social behaviors (Dick & Kendler, 2012), we judged it of value to examine G × E effects for AUD with more traditional personal 'stressors' here. Indeed, we detected evidence for such effects in response to death of all three of the close relatives examined. Put in a different way, we found evidence that genetic risk for AUD partly acts by rendering individuals more or less sensitive to the pathogenic impact of loss of a relative on excess drinking and eventual development of AUD. We should note that the effect of death of a close relative on AUD risk could occur by two different pathways. The first would be a more traditional stress effect (e.g. emotional and potentially financial). The second, likely particularly important in married couples, is the loss of the protective effect of close relationships on risk for problematic drinking (Bachman et al., 2002; Staff et al., 2010). Indeed, we see a substantial reduction in AUD in married *v.* non-married individuals in Sweden (Kendler, Lonn,

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Table 5. Risk for major depression after death of spouse, parent and sibling and interaction between death and genetic risk for anxiety disorders within 6 months of death

	(Average) number of new cases of MD per 10 000 person years (95% CIs)		
Follow-up time	Loss of spouse	Loss of parent	Loss of sibling
Model 1			
Death of first degree relative	1112.78 (999.64, 1244.92)	235.47 (237.46, 243.89)	330.03 (299.15, 360.90)
Women *v.* men	47.66 (45.45, 48.87)	55.98 (54.82, 57.15)	14.08 (13.78, 14.38)
Model 2			
Death of first degree relative	595.05 (455.65, 736.24)	150.16 (141.11, 159.20)	220.85 (184.13, 257.56)
Women *v.* men	46.83 (45.62, 48.04)	52.52 (51.38, 52.67)	13.66 (13.36, 13.95)
2nd *v.* 1st quartile FGRS	9.72 (8.8.28, 11.16)	−2.34 (−3.84, −0.83)	3.61 (13.25, 3.96)
3rd *v.* 1st quartile FGRS	29.78 (28.19, 31.37)	9.80 (8.30, 11.30)	9.39 (9.01, 9.78)
4th *v.* 1st quartile FGRS	62.34 (60.52, 64.15)	41.08 (39.32, 42.84)	18.56 (18.13, 18.99)
Death × sex interaction stronger in females	793.67 (583.15, 1004.19)	170.81 (154.66, 186.96)	219.98 (157.85, 282.10)
Model 3			
Death of first degree relative	366.38 (143, 589.27)	117.62 (101.79, 133.45)	70.11 (11.46, 128.76)
Women *v.* men	46.83 (45.63, 48.04)	52.53 (51.39, 53.68)	13.66 (13.36, 13.95)
2nd *v.* 1st quartile FGRS	9.71 (8.27, 11.14)	−2.19 (−3.67, −0.71)	3.59 (3.24, 3.94)
3rd *v.* 1st quartile FGRS	29.61 (28.02, 31.19)	9.27 (7.79, 10.74)	9.35 (8.96, 9.73)
4th *v.* 1st quartile FGRS	62.10 (60.29, 63.91)	38.98 (37.25, 40.71)	18.41 (17.98, 18.84)
Death × sex interaction	789.23 (578.66, 999.82)	170.35 (154.20, 186.50)	215.30 (153.24, 277.37)
Death × 2nd quartile	22.49 (−268.08, 313.06)	−2.21 (−23.03, 18.61)	50 0.60 (−27.18, 128.38)
Death × 3rd quartile	**383.69 (73.36, 694.02)**	**30.06 (7.60, 52.52)**	**139.68 (59.57, 219.80)**
Death × 4th quartile	**491.57 (173.15, 809.99)**	**97.78 (74.67, 120.88)**	**327.93 (243.90, 411.95)**

Statistically significant interactions in model 3 are bolded.

Salvatore, Sundquist, & Sundquist, 2016a) and an increased AUD risk associated with the loss of a spouse through divorce (Kendler, Lonn, Salvatore, Sundquist, & Sundquist, 2017).

The third question we asked is whether G × E effects for depression associated with loss of close relatives might occur with other genetic liabilities. There is precedence for such an effect in model organisms where it is possible, through selection effects, to separate out genetic variants that impact on the mean of a trait *v.* impact on the sensitivity of that trait to relevant environmental changes (Mather & Jinks, 1982). We in fact see such effects here. High levels of genetic risk for BD and especially AD increased the sensitivity of individuals in our cohort to the depressogenic effect of the loss of close relatives. The stronger effect seen with ADs might relate, in part, to the particularly high correlation we see in our sample, consistent with other studies (Kendler, Gardner, Gatz, & Pedersen, 2006), between genetic risk for AD and MD (polychoric correlations = +0.56). These results are of theoretical interest as they open up a further research area in the study of gene-environment interactions in psychiatric and substance use disorders.

Limitations

This work should be interpreted in the context of five potentially important methodological limitations. First, its value depends on the quality of the diagnostic information obtained from the Swedish medical registries, which has been widely studied and supported (Ludvigsson et al., 2011). The validity of MD diagnoses is supported by its prevalence, sex ratio, sibling and twin correlations and associations with well-documented psychosocial risk factors (Kendler, Ohlsson, Lichtenstein, Sundquist, & Sundquist, 2018; Sundquist, Ohlsson, Sundquist, & Kendler, 2017). The validity of our definition of AUD is reinforced by the high rates of concordance for ascertainment across registries (Kendler et al., 2015), and the similarity of genetic epidemiological findings in Sweden compared to those in other samples (Kendler et al., 2015, 2016b).

Second, while death itself is a temporally discrete event, the process of dying can differ widely across individuals and present to their relative's variable stressors and care-giving burdens. We did see, in our initial report on this sample modest elevations of rates of MD and AUD also in the month's preceding death. We did not attempt to formally incorporate those results in our model which would lead to a modest conservative bias in our findings.

Third, while our assessment of the death of relatives is objective and accurately dated, our registry data does not permit us to assess a number of dimensions of the loss that require respondent report, such as long-term contextual threat developed by Brown and colleagues, which has been shown to robustly predict rates of subsequent episodes of MD (Brown & Harris, 1989; Kendler et al., 1998).

Fourth, the FGRS, a family phenotype-based measure to assess quantitative genetic risk distinct from PRS derived from genome wide association studies, has now been widely published and

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validated, (Kendler et al., in pressa, in pressb; Kendler, Ohlsson, Sundquist, & Sundquist, 2021a, 2021b; Kendler, Ohlsson, Sundquist, & Sundquist, 2023a, 2023b; Kendler, Rosmalen, Ohlsson, Sundquist, & Sundquist, 2023d) with evidence that it is not highly sensitive to assumptions involved in its calculation, that the correction for cohabitation effects performs appropriately, the method agrees well with other similar statistical approaches (Hujoel, Gazal, Loh, Patterson, & Price, 2020; Krebs et al., 2023). Furthermore, we have recently performed empirical analyses and simulations with Danish colleagues who have shown that an adaptation of our FGRS score applied to Danish registry data performs similarly to that seen in our Swedish analyses. These analyses further demonstrate that the observed modest correlations between FRGS-like statistics and PRS from the Danish iPsych study for psychiatric disorders are consistent with the hypothesis that current phenotype-based extended family measures and molecular based polygene scores are both fallible measures of the same underlying set of small effect genetic risk alleles that constitute most of the genetic liability to complex human disorders (Krebs et al., 2023).

Fifth, while the assessment of SLE by registry has many advantages such as lack of recall bias and precise dating, by its nature, this kind of data will be unlikely to capture the idiosyncratic nature of some depressogenic events which reflect how humans give significant personal meaning to particular environmental adversities.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003641.

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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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