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Familial resemblance in mental health symptoms, social and cognitive vulnerability, and personality: A study of patients with depressive and anxiety disorders and their siblings

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ABSTRACT

Background: Investigating siblings of probands with affective disorders enables the identification of psychopathology-related risk features. Leveraging data from an older adult sample, as compared to most previous sibling studies, enabled us to study more definitive clinical profiling across the lifespan. We examined prevalence of depressive/anxiety disorders in siblings, proband-sibling resemblance in psychopathology-related features, and whether unaffected siblings showed higher levels of these features than healthy controls.

Methods: The sample (N=929; M_{age}=50.6) consisted of 256 probands with lifetime depressive and/or anxiety disorders, their 380 siblings, and 293 healthy controls without affected relatives. Fifteen psychopathology-related features were investigated across four domains: mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality.

Results: Lifetime disorders were present in 50.3% of siblings. Prevalence was 2-3 times higher than Dutch population frequencies. We found small to medium probandsibling resemblance across psychopathology-related features (ρ=0.10-0.32). Unaffected siblings reported poorer interpersonal functioning and more negative life events, childhood trauma, and rumination than healthy controls.

Limitations: Due to the cross-sectional study design, the directionality of effects cannot be determined. No inferences can be made about potential differences in familial resemblance in psychopathology-related features between high- and low-risk families.

Conclusions: Siblings of probands with affective disorders are at higher risk for depressive/anxiety disorders. Even when unaffected, still show higher psychosocial vulnerability than healthy controls. Nevertheless, the only modest proband-sibling resemblance across psychopathology-related features suggests that individual mechanisms differentiate clinical trajectories across the lifespan. Identification of these mechanisms is crucial to improve resilience in subjects with familial risk.

1. Introduction

Depressive and anxiety disorders are highly prevalent disorders with a substantial impact on public health (Vos et al., 2012). One of the strongest risk factors for the onset of depressive and anxiety disorders is a family history of these disorders (Lawrence et al., 2019; Maciejewski

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et al., 2018; Rasic et al., 2014; Van Sprang et al., 2020). A two- to three-fold increased risk of these disorders is found in siblings of depressed and/or anxious probands as compared to persons without affected relatives (Li et al., 2011, 2008; Steinhausen et al., 2009). Due to shared genes and upbringing, at-risk siblings may also have elevated levels of features commonly associated with the development and onset of depressive and anxiety disorders (Goldstein and Klein, 2014), such as (subclinical) mental health symptoms (Holma et al., 2011; Tozzi et al., 2008), social vulnerabilities (e.g. poor interpersonal functioning, adverse events; Jansen et al., 2016; Watters et al., 2013; Zimmermann et al., 2008), cognitive vulnerabilities (e.g. cognitive reactivity, anxiety sensitivity; Aldao et al., 2010; Dong et al., 2018), and certain personality traits (e.g. neuroticism; Kotov et al., 2010). As such, these features may be important targets in preventative strategies in a high-risk population of unaffected siblings of affected probands.

There is little scientific insight into the degree of resemblance among probands with depressive and/or anxiety disorders and their siblings (i.e. proband-sibling resemblance) in (subclinical) mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality. Within at-risk families, higher proband-sibling resemblance in these features may increase the risk for depressive and anxiety disorders for all siblings in the family as probands' siblings may (have) experience(d) similar adversities. However, findings from previous studies in young adult samples investigating differences in these features between unaffected siblings and healthy controls have been inconsistent. While some studies found elevated vulnerability in unaffected relatives (i.e. depressive/anxiety symptoms, poor interpersonal functioning, childhood trauma, negative cognitive bias, neuroticism) as compared to healthy controls (Lauer et al., 1997; Modell et al., 2003; Van Oostrom et al., 2013; Watters et al., 2013), others found no differences between groups (i.e. depressive symptoms, state/trait anxiety, hopelessness, neuroticism, introversion; Farmer et al., 2002; Lauer et al., 1997; Modell et al., 2003; Ouimette et al., 1996). So, it remains unclear whether unaffected siblings have elevated (subclinical) mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality as compared to healthy controls.

The majority of previous sibling studies has been performed in children or young adult samples, when siblings still largely share their rearing environment. As compared to older adult samples, these studies have for example reported generally high estimates of proband-sibling resemblance in different subtypes of childhood trauma (Hines et al., 2006; MacMillan et al., 2013). However, it is unknown to what extent findings extend to older populations, in which long-term individual developmental trajectories and environmental factors may have impacted proband-sibling resemblance measured at younger age. Examining proband-sibling resemblance at relatively older age allows for an examination of more definite clinical profiles (e.g. psychiatric disorder status in siblings is more clear given the relatively long exposure time-frame) and individual differences that emerged across the lifespan. So far, the few studies in adult samples reported low to medium proband-sibling resemblance in depressive/anxiety symptoms, worry, hopelessness (Moskvina et al., 2008), introversion, and neuroticism (Farmer et al., 2002), and low to high proband-sibling resemblance in different subtypes of childhood trauma (Kullberg et al., 2020).

The present study aimed to assess familial resemblance in features commonly associated with the development and onset of depressive and anxiety disorders in a relatively older adult sample (mean age 51 years) including probands with lifetime depressive and/or anxiety disorders, their siblings, and healthy controls without affected relatives. First, we examined the prevalence of depressive and anxiety disorders in siblings. Second, we investigated the degree of proband-sibling resemblance in (subclinical) mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality within families with affected probands. Third, we examined whether unaffected siblings have elevated levels of these features as compared to healthy controls.

2. Methods

The present study is a substudy of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study (2004-present) investigating the long-term course and consequences of depressive (i.e. major depressive disorder and dysthymia) and anxiety disorders (i.e. generalized anxiety disorder, panic disorder with and without agoraphobia, social phobia, and agoraphobia only). The NESDA baseline sample consisted of 2,981 participants, including 2,319 persons with a lifetime depression/anxiety diagnosis and 652 healthy controls. Participants were assessed in face-to-face interviews at baseline, and 2-, 4-, 6-, and 9-year follow-up. A detailed description of the NESDA study design and sampling procedure has been reported elsewhere (Penninx et al., 2008). The NESDA study protocol was approved by Medical Ethics Review Board of Amsterdam University Medical Centre, location Vrije Universiteit and by local review boards of each participating center - approval: 2003/183. All participants provided written informed consent. During the 9-year follow-up (2014-2017), siblings of lifetime affected participants were additionally recruited for the NESDA family study (NESDA-FS) to investigate the development of psychopathology, psychosocial functioning, and health (behavior) within the family context.

2.1. Sample and procedure

The sample used in this study included 929 participants, of whom 256 probands with lifetime depressive and/or anxiety disorders, their 380 siblings, with and without a lifetime depressive and/or anxiety disorders (hereafter referred to as 'affected siblings' and 'unaffected siblings', respectively), and 293 unrelated healthy controls. In siblings, lifetime depressive and/or anxiety disorders were assessed with the Composite Interview Diagnostic Instrument (CIDI, see below; WHO) at 9-year follow-up and indicated the presence of current disorder(s) or disorder(s) earlier in life.

See *Figure S1* of the supplementary materials for an inclusion flowchart of probands, siblings, and healthy controls into NESDA-FS. Inclusion criteria for probands of which siblings were invited were: (i) a depressive and/or anxiety disorder diagnosis (i.e. current, in between two waves, or earlier in life before baseline) assessed with the CIDI on at least two NESDA waves; (ii) 100% the same biological parents as their siblings; (iii) participated in at least three out of four NESDA face-to-face interviews prior to the 9-year follow-up (i.e., from baseline to 6-year follow-up); (iv) availability of genetic data; (v) provided approval of contacting siblings for research purposes; and (vi) participated at the 9-year follow-up face-to-face interview. The requirement of a diagnosis at two or more waves was chosen in order to ensure that there was at least some psychiatric burden in the patient. For instance, we wanted to prevent including targets and their siblings, where the target only suffered from a mild depressive episode 20 years ago. Moreover, our data showed that a vast majority of our lifetime affected targets fulfilled the criteria of having a diagnosis during at least two waves (61.83%), which is in line with the finding that that depressive and anxiety disorders are usually quite chronic conditions with frequent recurrences over an extended time (Verduijn et al., 2017).

Siblings of probands were included if they were: (i) currently living in the Netherlands; (ii) aged between 18 and 78 years; and (iii) consented to participate in a face-to-face interview. Most siblings were recruited at 9-year follow-up (N=367), but were enriched with 13 siblings of 10 probands that already participated in the original NESDA cohort based on genetic data. Unrelated (from each other and from siblings/probands) healthy controls from the original NESDA cohort were selected as a comparison group if they had: (i) no lifetime depressive and/or anxiety disorder diagnosis at any of the NESDA waves; and (ii) no parent and/or sibling with a lifetime depressive and/or anxiety disorder based on the Family Tree Inventory (Fyer and Weissman, 1999) or pedigree data.

Based on the inclusion criteria, 540 probands were excluded due to drop-out at the 9-year follow-up face-to-face interview, a further 622 were excluded because they did not give permission to contact their siblings, 3 were excluded because they did not participate in two of the first four NESDA face-to-face assessment, 25 were excluded because they did not have 100% the same biological parents, and 361 were excluded because they had a diagnosis at fewer than two NESDA waves. Of these 768 targets, siblings were approached (N=2027). Of those, 367 were eligible and agreed to participate. We compared included and excluded lifetime-affected targets on sex, age, and years of education. Results showed that included targets were significantly more often female (73% versus 67%; $p = .05$), younger (39.45 years versus 42.05 years; $p = .003$), and had more years of education (12.89 versus 11.91; $p < .001$). In our analyses, we controlled for these covariates. Healthy controls were mainly derived from the 9-year follow-up (N=219) but were enriched with unrelated controls of whom we had baseline data (N=74) to match the proband, sibling, and healthy control groups on age.

2.2. Measures

An overview of time points of assessment of the instruments can be found in *Table S1* in the supplementary materials. The present study used data mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality from the 9-year follow-up for most participants, that is, probands, their siblings, and healthy controls identified for NESDA-FS at 9-year follow-up; healthy controls identified at baseline were included with baseline data. However, for probands and healthy controls identified for NESDA-FS at 9-year follow-up, baseline or 6-year follow-up data were used for measures that were not administered at the 9-year follow-up in these participants. A detailed description of scale- and variable characteristics, including information on missing data, can be found in *Table S2* and *Table S3* of the supplementary materials. In the present sample, the internal consistency of (subscale) sum-scores was adequate to excellent (range α=.71-.96), except for neuroticism (α=.64).

2.2.1. Psychopathology

The presence of lifetime and current DSM-IV-TR (Association American Psychiatric, 2000) diagnoses of depressive and anxiety disorders was determined using the CIDI (lifetime version 2.1; WHO). The CIDI is a comprehensive diagnostic instrument developed for use in epidemiological studies with high validity for depressive and anxiety disorders (Wittchen, 1994). For the affected targets, the CIDI that was conducted at baseline assessed lifetime depressive and/or anxiety. The CIDI at the following waves assessed depressive and/or anxiety disorders since the previous assessment. A lifetime disorder was defined as either a lifetime disorder at baseline and/or a disorder since the previous assessment at the subsequent waves (based on all available waves from baseline to 9-year follow-up). For siblings, a lifetime diagnosis was based on a one-time lifetime CIDI interview. A lifetime diagnosis was operationalized as any depression or anxiety disorder that met DSM criteria and that took place earlier in life.

2.2.2. Mental health symptoms

The Inventory of Depressive Symptomatology-Self Report (IDS-SR; Rush et al., 1996) was used to assess past week severity and number of depressive symptoms. The IDS-SR contains all symptoms of depressive disorder as defined by the DSM-IV-TR (Association American Psychiatric, 2000) and symptoms commonly associated with depression. Past week severity of panic symptoms was measured using the Beck Anxiety Inventory (BAI; Beck et al., 1988). The Fear Questionnaire (FQ; Marks and Mathews, 1979) was used to assess the level of external avoidance behavior, reflecting the severity of phobia symptoms.

2.2.3. Social vulnerabilities

Poor interpersonal functioning was measured with the short version of the Inventory of Interpersonal Problems (IIP-32; Barkham et al., 1996), which assesses a person's most salient interpersonal problems on eight different domains: hard to be assertive, hard to be sociable, hard to be supportive, too caring, too dependent, too aggressive, hard to be involved, too open (Barkham et al., 1994). The List of Threatening Experiences (LTE) was used to assess the total number of past-year exposures to two different types of negative life events: (i) independent events, which are independent of a person's symptoms and unlikely to be influenced by the person as they are usually outside of a person's control (e.g. death of a loved one) and (ii) dependent events, which are likely, but do not have to be, influenced by a person and are therefore more controllable (e.g. job loss; Brugha et al., 1985; Liu, 2013; Maciejewski et al., 2021). The Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003) was used to assess childhood trauma before the age of 16 on five domains of trauma: sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect.

2.2.4. Cognitive vulnerabilities

The extent to which persons worry frequently and extensively was assessed with a shortened version of the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990), which included positively scored items of worry engagement only. Hopelessness and rumination were measured using subscales of the Leiden Index of Depression Sensitivity-Revised (LEIDS-R questionnaire; Van Der Does, 2002), which assessed cognitive reactivity to sad mood. The Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1992) was used to assess anxiety sensitivity, reflecting the extent to which persons fear potentially negative consequences of anxiety-related somatic sensations. Consistent with previous NESDA studies (Drost et al., 2012; Struijs et al., 2018), two subscales of the ASI were used: physical concerns and social-cognitive concerns.

2.2.5. Personality

The Dutch NEO-FFI (Hoekstra et al., 1996) was used to assess two personality domains: neuroticism, the propensity to experience negative emotions, and introversion, the tendency to behave in a reserved and solitary fashion. The Mastery Scale (Pearlin and Schooler, 1978) was used to assess external locus of control, which represents the degree to which persons believe that outcomes in their lives are mainly due to chance or fate.

2.3. Statistical analyses

First, psychopathology risk in siblings of probands (research aim 1) were reported as current (past 12-month) and lifetime prevalence (%) of depressive and anxiety disorders and, as a 'bench-mark', compared to population-based estimates as assessed by the national representative and large-scale (N=6,646) Netherlands Mental Health Survey and Incidence Study (NEMESIS; De Graaf et al., 2012). For this, no formal statistical testing was used. The assessment of psychopathology was similar between NEMESIS and NESDA. Both used information on only one CIDI assessment that measured both lifetime as well as current recency of diagnoses. The NESDA sibling sample had a mean age of 50.5 years (SD = 13.25; range = 20-78), 62% were female, and the sample had on average 13.2 years of education (SD = 3.2; range = 6-18). The NEMESIS-2 sample (De Graaf et al., 2012) had a mean age of 44.3 years (SD = 12.5; range = 18-64) and 55% were female. The study did not provide data on years of education. However, similar with NESDA, the level of education was quite high, with 35.3% of participants having completed higher professional education (i.e., university).

For subsequent analyses (research aims 2 and 3), multilevel regression analyses were conducted using clustered bootstrapping (5000 bootstrap samples) and with 'family-ID' as random intercept to account for within-family clustering. To investigate the degree of resemblance among probands and their siblings in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (research aim 2), intraclass correlations (ICC) were calculated, which have previously

been used as indicators of familial/proband-sibling resemblance in (genetic) epidemiology (see e.g. Farmer et al., 2002; Ferentinos et al., 2015; Kullberg et al., 2020; Moskvina et al., 2008). A total of 15 ICCs, one for each outcome measure, was calculated by dividing the between-family variance by the total family variance of a measure. Family variance components were obtained from unconditional means models. Based on previous research, ICC values <0.15 were considered as 'small', values ≥0.15 and <0.3 as 'medium', and values ≥0.3 as 'large' resemblance among probands and siblings of the same family (Bliese, 2000; James, 1982). If ICC values were significantly different from zero, this indicated the presence of proband-sibling resemblance. We controlled ICCs for covariates age, gender, and years of education to reduce residual error (Shoukri et al., 2013). Then, to test whether unaffected siblings showed elevated mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality as compared to healthy controls (research aim 3), 15 multilevel regression models were assessed: one for each outcome measure, with a group identifier (healthy controls '0' vs. unaffected siblings '1') added as predictor, and age, gender, and years of education as covariates. All *p*-values were derived from bootstrapped 95% confidence intervals (CI) according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within the two research aims to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values <.05 were considered to be statistically significant. Participants with missing values for an outcome measure were removed from the analyses for that measure (see *Table S2* of the supplementary materials for detailed information on missing data).

Data cleaning, preparation, and subsequent analyses were performed in R version 3.6.1 (Team, 2018). This paper, including the R code for the analyses, was pre-registered on the Open Science Framework (https://osf.io/9vn68/?view_only=fc54de1af6d94e6eb8bd50244fdaa291).

3. Results

3.1. Descriptive statistics

Family characteristics are reported in *Table 1*. The total of 256 proband-sibling families consisted of 2 (*N*=168 families), 3 (*N*=61 families), 4 (*N*=20 families), 5 (*N*=5 families), and 6 (*N*=2 families) family members. The sibling constellation was mixed-sex for 53.1%, female-only for 35.9%, and male-only for 10.9% of the families. For 90.6% of families, the maximum absolute age difference between probands and siblings from the same family ranged from 0 to 10 years. In the remaining families (9.3%), this difference ranged from 11 to 19 years.

Table 1
Family characteristics of proband-sibling families (*N*=256).

Family characteristics	*N*	%
Number of participating siblings[a] per family		
2	168	65.6
3	61	23.8
4	20	7.8
5	5	1.9
6	2	0.8
Total number of siblings[a,b] per family		
2	82	32.0
3	73	28.5
4	43	16.4
5	23	9.0
6	21	8.2
≥7	15	5.9
Gender constellation of siblings[a] per family		
Same sex – male	28	10.9
Same sex – female	92	35.9
Mixed sex	136	53.1
Maximum age difference between siblings[a] per family		
0-5 years	147	57.4
6-10 years	85	33.2
11-15 years	18	7.0
16-19 years	6	2.3

[a] Including probands.
[b] Based on Family Tree Inventory (Fyer and Weissman, 1999) data from the 9-year follow-up of NESDA.

The mean age of the sample (*N*=929) was 50.6 years (*SD*=13.4, range 20-78), mean years of education was 13.2, and 61.9% was female. Sample characteristics of the healthy control, sibling, and proband groups can be found in *Table 2*. Unaffected siblings were more often male as compared to healthy controls (*p*=.001), but did not differ in age (*p*=.100) and years of education (*p*=.366). At 9-year follow-up, 37.5% (96/265) of probands had a current (12-month) depressive and/or anxiety disorders, while 62.5% (160/256) was remitted.

3.2. Prevalence of depressive and anxiety disorders in siblings

Table 3 displays current (12-month) and lifetime prevalence of depressive and anxiety disorders in (i) siblings of lifetime depressed and/or anxious probands in the present sample and (ii) the Dutch population as found in the NEMESIS study (De Graaf et al., 2012). Of the 380 siblings included, 50.3% had a lifetime depressive and/or anxiety disorder (i.e. 'affected siblings'), while 49.7% had not (i.e. 'unaffected siblings'). As compared to what would be expected based on Dutch population frequencies, siblings of lifetime depressed and/or anxious probands showed a higher prevalence of current (26.8% vs. 10.0%; ~2.7 times higher) and lifetime (50.3% vs. 26.9%; ~1.9 times higher) depressive and/or anxiety disorders. Prevalence was higher quite similarly for all diagnoses. Specifically, current disorders were present in 13.2% of siblings for any depressive disorder (vs. 5.3% of the Dutch population; ~2.5 times higher) and in 19.5% of siblings for any anxiety disorder (vs. 6.3% of the Dutch population; ~3.1 times higher). Lifetime disorders were present in 38.9% of siblings for any depressive disorder (vs. 18.9% of the Dutch population; ~2.1 times higher) and in 31.1% of siblings for any anxiety disorder (vs. 15.1% of the Dutch population; ~2.1 times higher). The risk for specific diagnoses was between ~1.6 (15.3% vs. 9.3% of the Dutch population; lifetime social phobia) and ~3.3 times higher (12.6% vs. 3.8% of the Dutch population; lifetime panic disorder); the risk of current panic disorder, current and lifetime agoraphobia, and lifetime dysthymia appeared to be substantially higher (6.6% vs. 1.2% to 3.7% vs. 0.4%; ~5.7 to ~9.3 times higher) but was based on relatively low numbers of cases (*N*=14 to *N*=34). Affected siblings were more often diagnosed with current social phobia as compared to probands (*p*=.005), but did not differ in prevalence of other current anxiety or depressive disorders (all *p*>.06; results not shown). Overall, as indicated in the Methods section, the NEMESIS sample slightly differs from NESDA, which has slightly older participants and more females. We know from previous research that females have a higher rate of depression and anxiety and that the chance of a lifetime depression increases with age, which might have resulted in slightly more diagnoses in the sibling sample.

When comparing the affected targets with the affected siblings on diagnoses, results showed that 59% of targets had a lifetime comorbid diagnosis (versus 30% of affected siblings), 16% of targets had a lifetime pure anxiety disorder (versus 23% of affected siblings), and 24% of targets had a lifetime pure depressive disorder (versus 38% of affected siblings). These results indicate that siblings more often suffered from lifetime pure diagnoses, whereas the targets suffer more from comorbid diagnoses

3.3. Proband-sibling resemblance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality

Fig. 1 shows the standardized covariate-adjusted ICCs of the 15 mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits, reflecting the degree of proband-sibling

Table 2
Socio-demographics, mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality for healthy control, sibling, and proband groups.

	Healthy controls N=293		Unaffected siblings N=189		Affected siblings N=191		Probands N=256	
	M	SD	M	SD	M	SD	M	SD
Socio demographics								
Female (N; %)	178	60.8	85	45.0	124	64.9	188	73.4
Age	52.60	13.68	50.66	13.57	50.27	12.96	48.52	13.10
Years of education	13.07	3.28	13.30	3.36	13.04	3.08	13.42	2.99
Mental health symptoms								
Depressive symptoms	7.33	6.63	8.36	6.44	18.05	10.55	16.49	10.61
Panic symptoms	0.88	1.71	0.80	1.37	3.13	3.61	3.00	3.31
Phobia symptoms	7.99	10.46	8.67	9.26	18.53	15.26	17.81	15.23
Social vulnerabilities								
Poor interpersonal functioning	17.34	14.30	22.06	13.12	35.79	17.99	33.91	18.05
Past-year negative life events – Independent	0.30	0.55	0.49	0.71	0.41	0.63	0.30	0.60
Past-year negative life events – Dependent	0.13	0.39	0.27	0.60	0.28	0.57	0.21	0.54
Childhood trauma	32.61	8.82	34.14	7.54	40.46	11.08	38.75	11.36
Cognitive vulnerabilities								
Worry	18.12	8.02	19.81	7.31	29.19	10.61	28.12	11.10
Hopelessness	1.12	2.05	1.42	1.90	3.58	4.06	3.70	3.56
Rumination	3.04	3.70	4.42	3.47	8.17	4.63	7.84	4.53
Anxiety sensitivity – Physical concerns	2.72	3.64	3.21	3.76	5.95	5.42	5.91	6.04
Anxiety sensitivity – Social-cognitive concerns	3.38	2.63	4.04	2.68	5.78	3.87	5.76	3.71
Personality								
Neuroticism	25.74	7.24	25.98	7.24	34.45	8.38	38.18	8.02
Introversion	29.85	6.43	30.93	6.72	34.38	7.06	35.37	6.99
External locus of control	8.19	3.57	8.89	3.59	12.07	4.37	11.20	4.26

Note. Sample sizes vary slightly due to marginally missing data on mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (see *Table S1* in the supplementary materials). *M* = mean; *SD* = standard deviation.

Table 3
Current (12-month) and lifetime prevalence of depressive and anxiety disorders in siblings of lifetime depressed and/or anxious probands as compared to population-based estimates as assessed by the national representative and large-scale Netherlands Mental Health Survey and Incidence Study (NEMESIS; De Graaf et al., 2012).

	Current (12-month) prevalence		Lifetime prevalence	
	At-risk siblings *N*=380	General population[a] *N*=6,646	At-risk siblings *N*=380	General population[a] *N*=6,646
Diagnosis	%	%	%	%
Any depressive disorder	13.2	5.3	38.9	18.9
Major depressive disorder	12.4	5.2	38.2	18.7
Dysthymia	2.4	0.9	8.9	1.3
Any anxiety disorder	19.5	6.3	31.1	15.1
Generalized anxiety disorder	4.5	1.7	9.2	4.5
Panic disorder with or without agoraphobia	6.8	1.2	12.6	3.8
Social phobia	9.7	3.8	15.3	9.3
Agoraphobia only	3.7	0.4	7.1	0.9
Any depressive and/or anxiety disorder	26.8	10.0	50.3	26.9

Note. Permission to replicate (part of) the original table from the NEMESIS study has been given to the authors by M. Ten Have on April 22, 2020. No statistical testing was used for this comparison.
[a] Weighted figures. NEMESIS participants were aged 18-64 years.

resemblance in these features. Higher values indicate stronger resemblance among probands and siblings from the same family. The majority of features consistently showed some degree of proband-sibling resemblance (all *ps*<.05), with comparable ranges of small to medium ICCs (mental health symptoms: range 0.10-0.19; social vulnerabilities: range 0.10-0.32; cognitive vulnerabilities: range 0.06-0.21; personality: range 0.06-0.19). Thus, 6-32% of the variance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality was explained by the family. The highest proband-sibling resemblance was found for childhood trauma (ρ=0.32, p<.001). ICCs of anxiety sensitivity – social-cognitive concerns (ρ=0.06, p=.116) and neuroticism (ρ=0.06, p=.116) were small and not significantly different from zero, indicating that probands and siblings from the same family do not resemble each other more in their reports of these vulnerabilities as compared to randomly chosen other persons in the analytic sample.

3.4. Group differences in mental health symptoms, social vulnerabilities cognitive vulnerabilities, and personality

Table 4 displays the standardized effects sizes of multilevel regression analyses that were computed to test for differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality between unaffected siblings of lifetime depressed and/or anxious probands and healthy controls. Unaffected siblings reported poorer interpersonal functioning (γ=0.41, p<.001), more independent (γ=0.29, p=.027) and dependent past-year negative life events (γ=0.27, p=.031), childhood trauma (γ=0.28, p=.030), and rumination (γ=0.37, p<.001), as compared to healthy controls. No significant differences were found between unaffected siblings and healthy controls on other measures of cognitive vulnerability, nor on any measures of the mental health symptom or personality domains. As expected, unaffected siblings reported significantly lower levels on most measures (all *ps*<.001, except for reporting more independent past-year negative life events [p=.018] and no difference in dependent past-year negative life events [p=.396]), as compared to their affected siblings (including probands; see *Table 5*).

4. Discussion

The present study showed that siblings of probands with depressive and/or anxiety disorders are at higher risk for the same psychopathology: lifetime disorders were present in 50.3% of siblings, which is higher than the lifetime population prevalence of 26.9% in the Netherlands (De Graaf et al., 2012). We consistently found small to medium proband-sibling resemblance across the majority of mental health

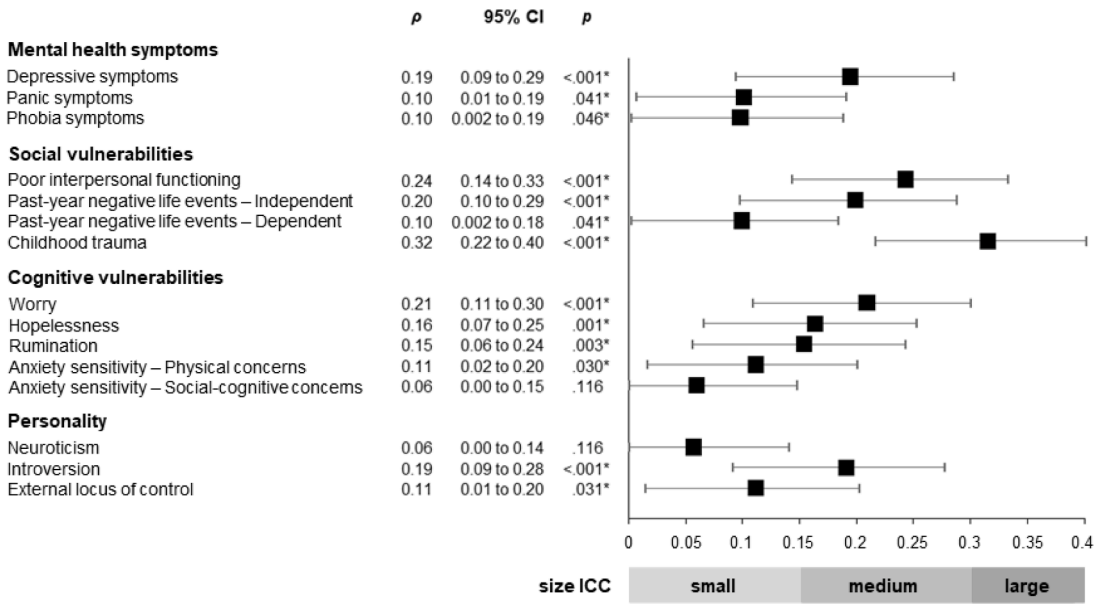

Fig. 1. Estimates (ρ) of standardized covariate adjusted intraclass correlations (ICC), reflecting the degree of proband-sibling resemblance for measures of mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality, with higher values indicating a higher degree of resemblance among probands and siblings from the same family ('small': $\rho<0.15$, 'medium': $0.15\leq\rho<0.3$, and 'large': $\rho\geq0.3$; Bliese, 2000; James, 1982). ICCs were calculated by dividing the between-family variance of an outcome measure by the total family variance of that measure. Family variance components were obtained from unconditional means models, controlled for covariates age, gender, and years of education to reduce residual error (Shoukri et al., 2013). 95% confidence intervals (CI) were obtained with bootstrapping for mixed models using 5000 bootstrap samples. *p*-values were derived from the bootstrapped 95%CIs according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within this research aim to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values are reported. Sample sizes vary slightly due to marginally missing data on the 15 outcome measures (see *Table S1* in the supplementary materials).
Note that these analyses included all siblings, irrespective of their diagnosis ($N = 256$ targets, $N = 380$ siblings).
* Significantly different from zero after correction for multiple testing with FDR<.05.

symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits, with highest resemblance in childhood trauma. Unaffected siblings showed poorer interpersonal functioning, more past-year negative life events, and higher levels of childhood trauma and rumination, as compared to healthy controls, but did not significantly differ in mental health symptoms, (most) cognitive vulnerabilities, and personality traits. Our findings implicate that siblings of lifetime depressed and/or anxious probands may (have) experience(d) similar adversities, but that substantial individual differences exist between siblings from the same family. Despite their familial disposition and enhanced social and cognitive vulnerability, half of the siblings were unaffected, which can teach us important insights into resilience.

4.1. *Prevalence of depressive and anxiety disorders in siblings*

The prevalence of current (26.8%) and lifetime (50.3%) depressive and/or anxiety disorders in siblings of lifetime depressed and/or anxious probands was substantial, and higher as compared to population frequencies in the Netherlands (10.0%, ~2.7 times higher and 26.9%, ~1.9 times higher respectively; NEMESIS; De Graaf et al., 2012). Our findings are comparable to the two- to three-fold increased risk found in previous sibling (Li et al., 2011, 2008) and family studies (Steinhausen et al., 2009). Furthermore, in line with previous studies (Li et al., 2011, 2008; Steinhausen et al., 2009), prevalence in siblings was higher to a similar extent for any depressive (current ~ 2.5 times higher; lifetime ~2.1 times higher) and any anxiety disorder (current: ~ 3.1 times higher; lifetime: ~2.1 times higher). Overall, given that our study is one of the few relatively large studies that thoroughly investigated multiple affected and unaffected siblings per family, our findings are important as they provide detailed insight into the risk for (specific) depressive and/or anxiety disorders in an at-risk group of siblings of lifetime depressed and/or anxious probands.

4.2. *Proband-sibling resemblance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality*

Our findings show that, to a certain extent, mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits pose a family-wide problem. The consistent small to medium proband-sibling resemblance across features indicates that siblings of lifetime depressed and/or anxious probands may (have) experience(d) similar adversities, without a clear distinction in the degree of resemblance between domains, but that substantial individual differences exist between siblings from the same family.

The overall modest resemblance among probands and siblings is consistent with evidence from behavioral-genetic research suggesting an increased role across the lifespan for individual environments and unique risk and protective factors (Plomin, 2011; Plomin et al., 2001; Plomin and Daniels, 2011, 1987) in shaping behavioral, psychological, and personality features. This is corroborated by longitudinal twin studies that found increases in phenotypic variance in personality (Kandler et al., 2010; Laceulle et al., 2013; Viken et al., 1994) and depressive/anxiety symptoms (Kendler et al., 2011; Nivard et al., 2015) as a result of increasing nonshared environmental effects across the lifespan. It is therefore conceivable that the magnitude of proband-sibling resemblance in the features measured in the present study, in which participants were aged on the upper end of the age-range in which most first onsets appear (De Graaf et al., 2012), may vary over the course of the lifetime, with a higher degree of resemblance when estimated at younger age. Indeed, previous studies in younger samples have reported generally higher estimates of proband-sibling resemblance for depressive/panic/phobia symptoms, worry, hopelessness (Moskvina et al., 2008), subtypes of childhood trauma (Hines et al., 2006; MacMillan et al., 2013), neuroticism, and introversion (Farmer et al., 2002).

Table 4
Differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality between unaffected siblings and healthy controls.

	Unaffected siblings (*N*=189) vs. Healthy controls (*N*=293)		
	Estimate	95% CI	*p*
Mental health symptoms			
Depressive symptoms	0.20	0.003 to 0.40	.072
Panic symptoms	-0.02	-0.21 to 0.16	1.000
Phobia symptoms	0.14	-0.04 to 0.33	.155
Social vulnerabilities			
Poor interpersonal functioning	0.41	0.20 to 0.61	<.001*
Past-year negative life events – Independent	0.29	0.09 to 0.50	.027*
Past-year negative life events – Dependent	0.27	0.06 to 0.48	.031*
Childhood trauma	0.28	0.07 to 0.49	.030*
Cognitive vulnerabilities			
Worry	0.22	0.03 to 0.40	.051
Hopelessness	0.21	0.02 to 0.39	.052
Rumination	0.37	0.18 to 0.55	<.001*
Anxiety sensitivity – Physical concerns	0.14	-0.06 to 0.35	.184
Anxiety sensitivity – Social-cognitive concerns	0.22	0.03 to 0.42	.051
Personality			
Neuroticism	0.07	-0.12 to 0.26	.517
Introversion	0.19	-0.003 to 0.38	.072
External locus of control	0.20	0.01 to 0.39	.062

Note. Sample sizes vary slightly due to marginally missing data on mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (see *Table S1* in the supplementary materials). Standardized estimates and 95% confidence intervals (CI) were retrieved from multilevel regression models fitted with clustered bootstrapping using 5000 bootstrap samples, with a random intercept of family ID and age, gender, and years of education added as covariates. *p*-values were derived from bootstrapped 95%CIs according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within this research aim to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values are reported. CI=confidence interval.
* Significant after correction for multiple testing with FDR<.05.

Table 5
Differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality between unaffected siblings and affected siblings (i.e., including probands).

	Unaffected siblings (*N*=189) vs. Affected siblings (including probands; *N*=447)		
	Estimate	95%CI	*p*
Mental health symptoms			
Depressive symptoms	-0.85	-0.99 to -0.72	<.001*
Panic symptoms	-0.73	-0.85 to -0.61	<.001*
Phobia symptoms	-0.62	-0.77 to -0.48	<.001*
Social vulnerabilities			
Poor interpersonal functioning	-0.77	-0.92 to -0.61	<.001*
Past-year negative life events – Independent	0.22	0.04 to 0.39	.018*
Past-year negative life events – Dependent	0.08	-0.10 to 0.27	.396
Childhood trauma	-0.50	-0.64 to -0.37	<.001*
Cognitive vulnerabilities			
Worry	-0.82	-0.96 to -0.68	<.001*
Hopelessness	-0.62	-0.75 to -0.47	<.001*
Rumination	-0.76	-0.90 to -0.61	<.001*
Anxiety sensitivity – Physical concerns	-0.49	-0.64 to -0.33	<.001*
Anxiety sensitivity – Social-cognitive concerns	-0.50	-0.66 to -0.34	<.001*
Personality			
Neuroticism	-1.08	-1.22 to -0.93	<.001*
Introversion	-0.64	-0.81 to -0.46	<.001*
External locus of control	-0.61	-0.77 to -0.45	<.001*

Note. Sample sizes vary slightly due to marginally missing data on mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (see *Table S1* in the supplementary materials). Standardized estimates and 95% confidence intervals (CI) were retrieved from multilevel regression models fitted with clustered bootstrapping using 5000 bootstrap samples, with a random intercept of family ID and age, gender, and years of education added as covariates. *p*-values were derived from bootstrapped 95%CIs according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within this research aim to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values are reported. CI=confidence interval.
* Significant after correction for multiple testing with FDR<.05.

Nonetheless, even though estimates were small to medium in size, we add to the existing literature by showing proband-sibling resemblance in poor interpersonal functioning, past-year negative life events, rumination, anxiety sensitivity – physical concerns, and external locus of control. Particularly in the case of childhood trauma, probands and siblings likely experienced similar adversity as reflected by a large ICC ($\rho \geq 0.3$; Bliese, 2000; James, 1982). This is in line with earlier findings from our (Kullberg et al., 2020) and other studies (Hines et al., 2006; MacMillan et al., 2013), finding medium to high proband-sibling resemblance in the most prevalent subtypes of childhood trauma, emotional maltreatment and physical abuse. Childhood trauma, which does not change beyond childhood/adolescence, has strong long-term effects (Cloitre and Beck, 2017) and often occurs within a family context (i.e. parents account for 80% of the identified perpetrators in case of emotional maltreatment and physical abuse; Hovens et al., 2010), thereby increasing risk of childhood trauma for all siblings within the family (Hamilton-Giachritsis and Browne, 2005; Witte et al., 2018). This may explain the larger proband-sibling resemblance in childhood trauma as compared to the other tested features.

4.3. Group differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality

On top of poor interpersonal functioning and childhood trauma, already identified in a previous family study (Watters et al., 2013), we identified two additional features that were elevated in unaffected siblings as compared to healthy controls – (independent and dependent) past-year negative life events and rumination. These features may represent important vulnerabilities determining the increased risk of developing depressive and/or anxiety disorders in siblings of affected probands. It is interesting that the difference between unaffected siblings and healthy controls were so large for rumination, indicating that rumination might be one factor that is highly shared between siblings, even if they are not both affected. It has been shown that rumination is moderately heritable (Johnson et al., 2014). It might be that due to this genetic influence, siblings might also report higher rumination, but these might not lead to increased depressive symptoms due to other protective factors (e.g., the use of other more adaptive emotion regulation strategies).

On the other hand, in contrast to some previous family and sibling studies in younger samples (Lauer et al., 1997; Modell et al., 2003; Watters et al., 2013; although see Farmer et al., 2002; Lauer et al., 1997; Modell et al., 2003; Ouimette et al., 1996).,the majority of mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits were, in fact, not elevated in unaffected siblings as compared to healthy controls and were lower in unaffected siblings as compared to affected siblings (including probands). This suggests a potential degree

of individual resilience against the risk of developing depressive and anxiety disorders. The found differences suggest potential protective candidate factors that should be tested in future interventions studies aimed at preventing the onset of psychiatric disorders in siblings of affected patients. For instance, preventive interventions for children of parents with mood and/or anxiety disorders, which also have a higher chance to develop a mood/anxiety disorder, focus on, amongst other things, cognitive restructuring, likely improving rumination, and strengthening social support, likely improving interpersonal functioning. These programs have been shown to be effective in preventing the onset of anxiety/depressive disorders and reducing subthreshold symptoms (Havinga et al., 2021). While multiple observational studies stress the need for targeting siblings of affected individuals for preventive interventions (for a review see Ma et al., 2020), we are not aware of any randomized controlled trial that has studied the effect of an intervention or prevention targeting the identified vulnerabilities in our studies in this particular population. The fact that, in our study, we did not find that unaffected siblings differed from healthy controls on mental health symptoms, (most) cognitive vulnerabilities, and personality, suggests that these may be a direct result of the disorders, rather than prodromal indicators.

4.4. Strengths and limitations

Strengths of this study include the relatively large sample, consisting of lifetime depressed and/or anxious probands, their affected and unaffected siblings, and healthy controls, which contributes to the understanding of how mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits manifest themselves within at-risk families; the sibling structure of the data, which has the advantage that sibling relationships contain a higher shared proportion of (early) environmental factors as compared to parent-offspring relationships; the relatively older age of the sample, which allows for the examination of more definite clinical profiles in siblings and individual differences that emerged across the lifespan; the wide variety of assessed mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits; and the adequate correction for multiple testing.

Some limitations should be noted as well when interpreting the results. First, the present study only used cross-sectional data. Prospective longitudinal studies are needed to confirm the suggested psychopathology-related features potentially associated with the familial transmission of depressive and anxiety disorders. Second, no information was collected on siblings of healthy controls. We were therefore unable to investigate whether the proband-sibling resemblance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits is different (and potentially higher) in at-risk families as compared to families without affected persons (Wickramaratne, 1995). Third, the proband group exclusively consisted of persons that received a depressive and/or anxiety disorder diagnosis on at least two NESDA waves, which limits generalizability to at-risk families of lifetime affected persons with more severe problems.

One explanation for the null-findings of neuroticism is that the reliability of the neuroticism measure was relatively low in our subsample. However, previous NESDA papers have shown that neuroticism has a good predictive validity in the overall sample (e.g., Lamers et al., 2011; Renner et al., 2013). Moreover, while some research indicates that there are mean level changes in personality across the life-span with increases in neuroticism and decreases in extraversion (Graham et al., 2020), a paper using NESDA data showed the temporal stability of neuroticism and extraversion is moderate to strong and diminishes only slightly over time, suggesting that these indicators are rather traits than states (Struijs et al., 2020). Thus, we do not think that the latter might have influenced the results.

Additionally, there were some differences between the included and excluded group, which might limit the representativeness of the sample of included affected targets compared to the whole NESDA sample of affected targets. However, the differences were not large and we controlled for those demographic factors in all our analyses.

Lastly, an analytical choice that could have influence our results is controlling for years of education in our analyses, although this could potentially also be an outcome of psychopathology and not only an indicator and might thus remove variance that should be attributed to depression. However, when re-running the models without education as a covariate results were virtually the same.

4.5. Implications, conclusions, and future research

Siblings of probands with depressive and/or anxiety disorders are at higher risk to also be diagnosed with a depressive and/or anxiety disorder: about 50% of all siblings of affected probands in our study had a lifetime depressive and/or anxiety disorder themselves. However, our study did not examine concordance within siblings pairs, thus we can only draw conclusions about general prevalence rates of probands and siblings.. Despite this, resemblance among probands and siblings in features commonly associated with the development of the disorders such as mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits was only mild to moderate. While our findings illustrate that the majority of these features, in part, pose a family-wide problem as probands' siblings may (have) experience(d) similar adversities, they also suggest substantial individual differences between siblings from the same family. Moreover, although probands' unaffected siblings showed some enhanced vulnerability as compared to healthy controls without affected relatives, they did not differ in mental health symptoms, (most) cognitive vulnerabilities, and personality traits which may indicate their underlying resilience. This underscores the importance for future studies to identify in siblings from at-risk families the exact mechanisms that determine divergent clinical trajectories across the lifespan. Such identification may give important clues about strategies to improve resilience in subjects with familial risk.

Moreover, while the current paper gives a better indication of familial resemblance of mental health symptoms and a large variety of vulnerabilities, we did not study the concordance of these factors within sibling pairs. Future studies should examine the overlap of diagnoses in sibling pairs to determine homotypic and heterotypic con- and discordance (e.g., do sibs of adults with depression have increased rates of anxiety disorders?). Moreover, studying whether certain factors (e.g., sociodemographic, social-environmental, lifestyle factors) can explain proband-sibling (dis)similarity in lifetime diagnosis and current symptoms of depression and anxiety would help to identify mechanisms that determine convergent/divergent clinical trajectories in probands and siblings from the same families.

5. Contributors

B.W.J.H.P. developed the NESDA study concept and design. Together with B.W.J.H.P., B.M.E. and A.M.v.H. were closely involved in the design of the family study of NESDA. E.D.v.S. and M.K. prepared the data for the analyses. E.D.v.S. performed the data analysis and interpretation under the supervision of D.F.M., Y.M., M.X.H., and B.W.J.H.P. E.D.v.S. drafted the manuscript, and B.W.J.H.P., D.F.M., Y.M., M.K., M. X.H., C.A.H., B.M.E., and A.M.v.H. provided critical revisions. All authors approved the final version of the paper for submission.

Declaration of Competing Interests

None.

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Data statement

The data that support the findings of this study are available via the website of NESDA (https://www.nesda.nl/pro-index/), which will be provided after handing in a data request. This paper and the R code for the analyses were pre-registered on the Open Science Framework (https://osf.io/9vn68/?view_only=fc54de1af6d94e6eb8bd50244fdaa291).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.06.072.

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