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ORIGINAL PAPER

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Age-specific familial risks of anxiety

A nation-wide epidemiological study from Sweden

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Abstract *Objective* Familial risks of anxiety have been assessed in small case-control studies, usually based on reported, but not medically verified, anxiety in family members; thus the degree of familial clustering of these diseases remains to be established. *Methods* The Multigeneration Register, in which all men (sons) and women (daughters) born in Sweden from 1932 onward are registered together with their parents, was linked to hospital admission data. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to the expected number of cases of men and women with mothers and/or fathers affected by anxiety, compared with men and women whose mothers and/or fathers were not affected by anxiety. *Results* A total of 55,642 and 57,196 cases of anxiety were recorded in offspring and parents, respectively. The overall significant SIRs among men and women with a mother, father or both parents hospitalized for anxiety varied between 1.90 and 5.10. Maternal transmission of anxiety was slightly higher than paternal and the highest SIRs were found in the youngest age groups and among those with both parents affected by anxiety. The degree of parental transmission of anxiety was similar for both men and women. *Conclusions* This study has provided the first data on age-specific familial clustering of anxiety, based on medically confirmed records. The risks were so high that hereditary factors were considered to be likely to contribute, possibly modified by environmental factors. Age-specific risks tables would be helpful for clinical counseling.

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Introduction

Anxiety is one of the most common psychological disorders in the general population and in various clinical settings. It is characterized by feelings of nervousness and unjustified fear that sometimes is accompanied by a variety of physical symptoms, sleep disorder and other functional problems. Severe anxiety can have a serious impact on daily life and reduce quality of life [3]. There is also a co-occurrence between depression, alcohol abuse and anxiety [1]. Prevalence estimates range from 10% to a maximum of 25% [2, 11, 20] with a higher prevalence among women [20]. The risk factors of anxiety are most likely a combination of biological, genetic, and environmental factors.

Current etiological models of anxiety disorders emphasize both internal risk factors and external stressors as important in the development and maintenance of clinical anxiety and considerable evidence suggests that personality, genetic, and environmental variables are important in these interactions [15].

The environmental impact on anxiety has been reported in previous studies. For example, there is an association between anxiety and socioeconomic factors at both the individual and neighbourhood level [12, 13, 22].

In one epidemiological meta-analysis, a 4–6-fold risk of anxiety was observed between first-degree relatives [8a]. A population-based sample of twins from Virginia showed a modest genetic influence of 23–36% for main types of anxiety [10]. Another study of twins recruited from psychiatric treatment centers demonstrated strong genetic influences on the development of general anxiety [14]. Results from family

and epidemiological studies have led to the suggestion that early-onset anxiety may be more strongly genetically influenced than adult-onset anxiety [5]. These findings have not been reported consistently [4, 16]. The influence of genetic factors has been reported to have significantly greater transmissibility of anxiety in women than in men [19]. The possible mechanisms of familial risk are complex and could include both genetic and environmental factors as well as genetic-environmental interactions. Consequently, there is a need for further research into the genetic etiology of anxiety with specific attention paid to age and sex effects.

Because of the limited amount of population-based data on familial clustering of anxiety, we examined age-specific familial risks for anxiety using the nationwide Swedish MigMed Research Database. The Swedish data on family relationships and anxiety were obtained from register sources with practically complete coverage. In addition, The Swedish family dataset, i.e., the Multigeneration Register, is a well-validated source that has been found to be reliable in the study of many familial diseases [6, 7, 23]. This study examined age-specific familial risks among men and women with a mother and/or father with anxiety after adjustment for several confounders.

Materials and methods

Migmed research database

Data used in this study were retrieved from the MigMed database, located at the Center for Family and Community Medicine at the Karolinska Institute in Stockholm. MigMed is a single, comprehensive database that has been constructed using several national Swedish data registers, including, but not limited to, the Total Population Register, the Multigeneration Register, and the Swedish Hospital Discharge Register (1987–2004) [17, 21, 24]. Information from the various registers in the database is linked at the individual level via the national registration number assigned to each person in Sweden for his or her lifetime. Prior to inclusion in the MigMed database, national registration numbers were replaced by serial numbers to ensure the anonymity of all individuals.

Since the database contains information from the Multigeneration Register, it is possible to link all individuals born in or after 1932 that were registered in Sweden at any time since 1961 with their biological parents.

Outcome variable

Anxiety was retrieved from hospital discharge records reported according to the 9th (1987–1996) and 10th (1997–2004) versions of the International Classification of Diseases. The following ICD codes were included for both parents and offspring: 300.0 to 300.3, 308 and 309 (ICD-9) and F40–F43 (ICD-10).

Individual variables

Gender: males and females

Age at diagnosis was categorized in 5-year groups, and the groups were merged as necessary.

Anxiety in father/mother was dichotomized into Yes and No.

Socioeconomic status was divided into six groups according to occupation: (1) Farmers; (2) Unskilled/Skilled workers; (3) White-collar workers; (4) Professionals; (5) Self-employed; and (6) All others.

Geographic region was divided into large cities (cities with a population of more than 200, 000, i.e., Stockholm, Gothenburg, and Malmö), Southern Sweden, and Northern Sweden. Geographic region was included as an individual variable to adjust for possible differences between geographic regions in Sweden with regard to hospital admissions for anxiety.

Other covariates that were included in the analysis were simultaneous hospitalization for mood disorders (ICD-9: 296, 298.0, 298.1, 300.4, 300.9, 301.1, and 311. ICD-10: F30–39) and simultaneous hospitalization for substance abuse (ICD-9: 291, 292, 303, 304, and 305. ICD-10: F10–F19).

Statistical analysis

Person-years were calculated from the start of follow-up on January 1, 1987, until the hospital diagnosis of anxiety, death, emigration, or the end of the study on December 31, 2004. Age-standardized incidence ratios were calculated for the whole follow-up period, divided into six 3-year periods (1987–1989, 1990–1992, 1993–1995, 1996–1998, 1999–2001, and 2002–2004). Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to the expected number of cases [18]. The expected number of cases was calculated as the actual number of cases in the reference group. The expected number of cases was calculated for age (in 5-year groups), sex, period (in 3-year groups), socioeconomic status (in six groups), and region (in three groups). Familial risks were calculated for men and women with mothers or fathers affected by anxiety, compared with men and women whose mothers or fathers were not affected by anxiety. Confidence intervals (95% CI) were calculated assuming a Poisson distribution. We considered it to be appropriate to use SIRs for the estimation of familial risk, which is in accordance with previous research [18].

Ethical considerations

Necessary permissions were obtained from the Swedish Data Inspection Board, the National Board of Health and Welfare, Statistics Sweden, and the Regional Ethical Committee of the Karolinska Institute, Stockholm, Sweden. It was thus possible to link individual-level clinical data to population registers.

Results

The database covered the years 1987–2004 in the Swedish Hospital Discharge Register and included 23,121 cases among men (sons) and 32,521 cases among women (daughters), in addition to 21,825 and 35,371 cases of anxiety among fathers and mothers, respectively (Table 1). In Fig. 1 the age-specific incidence is plotted by parental family history. The hospitalization rates of familial anxiety were higher than that of sporadic anxiety, with an upward bend between the ages 20–24 and 40–44 and after age 60.

Familial risks were calculated separately for anxiety in men (sons) and women (daughters) according to the presence of anxiety in fathers and mothers (Table 2). All the models are adjusted for all the explanatory variables simultaneously, i.e., age, socioeconomic status, period, region, simultaneous hospi-

Table 1 Number of cases of anxiety in men (sons) and women (daughters) and parents

Age at diagnosis	Men		Women		Fathers		Mothers	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
<20	1,760	7.6	4,005	12.3	297	1.4	1,272	3.6
20–29	5,325	23.0	7,781	23.9	2,683	12.3	5,186	14.7
30–39	6,349	27.5	8,013	24.6	5,361	24.6	8,067	22.8
40–49	5,820	25.2	7,354	22.6	5,789	26.5	7,920	22.4
50–59	3,094	13.4	4,206	12.9	3,639	16.7	4,992	14.1
60–69	754	3.3	1,112	3.4	1,754	8.0	2,915	8.2
70–79	19	0.1	50	0.2	1,445	6.6	3,047	8.6
≥80					857	3.9	1,972	5.6
All	23,121	100.0	32,521	100.0	21,825	100.0	35,371	100.0

Fig. 1 Age-specific incidence rate of anxiety in offspring of parents with and without anxiety

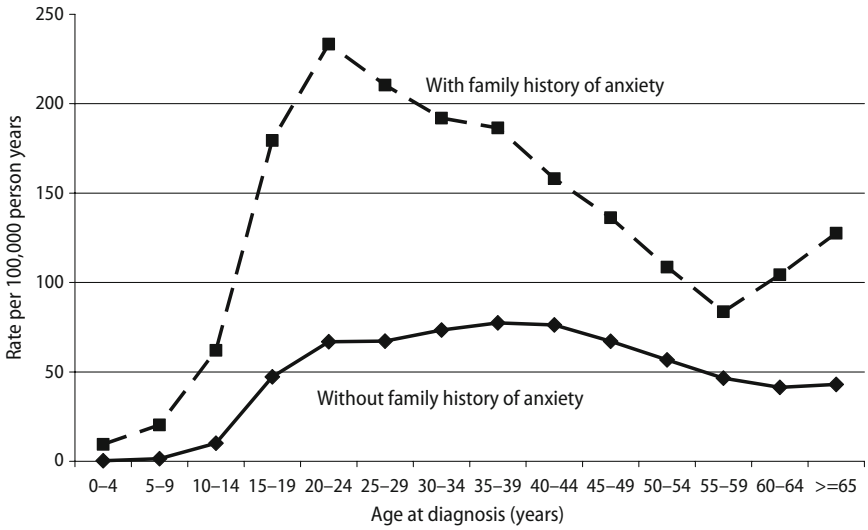

Table 2 SIRs for anxiety in offspring of fathers/mothers with anxiety

Age at diagnosis (years)	Men (sons)								Women (daughters)							
	Father with anxiety				Mother with anxiety				Father with anxiety				Mother with anxiety			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
0–9	19	**15.77**	**9.48**	**24.68**	29	**20.90**	**13.98**	**30.04**	18	**14.44**	**8.54**	**22.87**	26	**15.83**	**10.33**	**23.23**
10–19	60	**2.45**	**1.87**	**3.16**	153	**3.49**	**2.96**	**4.09**	123	**2.22**	**1.84**	**2.65**	231	**2.92**	**2.55**	**3.32**
20–29	121	**1.97**	**1.63**	**2.35**	226	**2.10**	**1.83**	**2.39**	159	**2.01**	**1.71**	**2.35**	337	**2.08**	**1.87**	**2.32**
30–39	61	**1.31**	**1.00**	**1.69**	146	**1.71**	**1.44**	**2.01**	89	**1.55**	**1.25**	**1.91**	215	**1.86**	**1.62**	**2.12**
40–49	35	**1.47**	**1.02**	**2.04**	84	**1.42**	**1.13**	**1.76**	42	1.28	0.93	1.74	107	**1.40**	**1.15**	**1.69**
≥50	14	**2.44**	**1.33**	**4.10**	26	1.34	0.87	1.97	20	**2.51**	**1.53**	**3.88**	54	1.31	0.99	1.71
All	310	**1.90**	**1.69**	**2.12**	664	**2.10**	**1.94**	**2.26**	451	**1.93**	**1.75**	**2.12**	970	**2.04**	**1.91**	**2.17**

Bold type: 95% CI does not include 1.00
O observed number of cases, *SIR* standardized incidence ratio, *CI* confidence interval

talization for mood disorders and simultaneous hospitalization for substance abuse. The overall SIRs were similar in men and women with a mother who had had anxiety (2.10, 95% CI, 1.94–2.26 and 2.04, 95% CI 1.91–2.17) and similar in men and women with a father who had had anxiety (1.90, 95% CI, 1.69–2.12 and 1.93, 95% CI 1.75–2.12). Maternal transmission of anxiety was slightly higher than paternal transmission. A gradient was found for both men and women, so that with increasing age the SIRs decreased but remained significant in most age groups.

Table 3 shows the SIRs for men and women according to parental anxiety. We combined fathers and mothers as family (parental) history. The overall risk was 2.00 (95% CI, 1.88–2.14) for men and 2.05 (95%CI, 1.94–2.16) for women. When both parents were affected by anxiety, the SIRs were even higher, i.e., 5.10 (95% CI, 3.51–7.18) for men and 4.78 (95%

Table 3 SIRs for anxiety in offspring of parents with anxiety

Age at diagnosis (years)	Men (sons)								Women (daughters)							
	Father or mother with anxiety				Both parents with anxiety				Father or mother with anxiety				Both parents with anxiety			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
0–9	35	**16.24**	**11.31**	**22.61**	13	**263.69**	**139.83**	**452.21**	35	**15.64**	**10.89**	**21.77**	9	**197.80**	**89.68**	**377.11**
10–19	202	**3.20**	**2.77**	**3.67**	11	**13.03**	**6.47**	**23.40**	333	**2.64**	**2.36**	**2.94**	21	**9.90**	**6.12**	**15.15**
20–29	339	**2.13**	**1.91**	**2.36**	8	2.31	0.99	4.57	490	**2.16**	**1.97**	**2.36**	6	2.41	0.87	5.28
30–39	206	**1.54**	**1.33**	**1.76**	1	0.54	0.00	3.09	300	**1.82**	**1.62**	**2.04**	4	1.16	0.30	3.01
40–49	119	**1.43**	**1.18**	**1.71**	0				149	**1.39**	**1.18**	**1.64**	0			
≥50	40	**1.47**	**1.05**	**2.01**	0				74	**1.57**	**1.23**	**1.97**	0			
All	941	**2.00**	**1.88**	**2.14**	33	**5.10**	**3.51**	**7.18**	1,381	**2.05**	**1.94**	**2.16**	40	**4.78**	**3.41**	**6.51**

Bold type: 95% CI does not include 1.00
O observed number of cases, *SIR* standardized incidence ratio, *CI* confidence interval

CI, 3.41–6.51) for women. The highest SIRs were found in the youngest age groups when both parents were affected with anxiety; i.e. the SIR was 263.69 (95%, CI, 139.83–452.21) for sons and 197.80 (95%, CI, 89.68–377.11) for daughters aged 0–9 years with two affected parents.

Discussion

Familial clustering of disease has been studied traditionally in the clinical setting where probands and their multiply affected relatives have been identified. This approach has also been very productive in terms of understanding the genetic factors. The disadvantages include difficulties in obtaining large numbers of cases and in securing unbiased risk estimates. These problems can be overcome in population datasets where anxiety data on cases and probands are unbiased by potential recall and self-report bias. The largest population-based dataset on familial anxiety is the Swedish familial anxiety database that was used in our present study, covering 10.2 million people and 57,196 cases of anxiety in the first generation and 55,642 cases of anxiety in the second generation.

A possible limitation of this study is that the mean age at diagnosis was higher among the parents than among the studied men and women because the Swedish Hospital Discharge Register began recording complete data on all discharges in Sweden only in 1986. We were unable to test for the validity of the anxiety diagnoses because our data were based on the entire population. However, we only used main diagnoses for anxiety recorded in the hospital registers, i.e., all patients were hospitalized mainly for anxiety, which increases the possibility that the diagnoses for anxiety are valid. Among the total number of hospitalized cases, 69% had anxiety as their only diagnosis. Among the 31% of the patients that also had at least one additional diagnosis, about one third was simultaneously hospitalized for mood disorders or substance abuse. We also investigated the number of subsequent hospitalizations for anxiety. Two or more admissions for anxiety were recorded in 26% of the cases, whereas 74% had one admission for anxiety. However, this bias is present in both the compared groups and we have no reason to believe that the magnitude of this bias differed between the two groups. We had no access to data on outpatient care, which is a limitation because many patients with anxiety are treated as outpatients. It is also likely that the probability of being hospitalized for anxiety could differ between regions, hospitals and over time. Moreover, applied diagnostic manuals also changed over time. We tried to minimize these biases by including region and time period as covariates in the analysis. Finally, we had no data on what kind of treatment that was given at the different hospitals.

This study also has a number of strengths. For example, the study population included a well-defined open cohort, the entire population of Sweden. Because of the national registration number assigned to each individual in Sweden, it was possible to track the records of every person for the whole follow-up period. The unique Swedish Population Registers are almost entirely complete with very little missing data. For example, data on occupational status were nearly 100% complete (99.2%), which enabled us to adjust our models for socioeconomic status. The use of a personal identification number made it possible to track each individual in different registers, e.g. the Migrant Register, which allowed calculation of exact risk time. In addition, the data in the Swedish Hospital Discharge Register is also nearly complete. In 2001, the main diagnosis was missing in only 0.9% of cases and the national registration number in 0.4% of hospitalizations [17]. Finally, the accuracy of the multigenerational part of the MigMed database is very high and it includes highly complete information about parents, children, siblings, and adoptions.

The present study provided evidence on age-specific familial risks of anxiety in the 0 to 72-year-old population. The risk magnitude was in line with earlier publications on familial anxiety [8]. Our results indicated that there was no gender difference in

the transmission of anxiety from mothers and fathers. In addition, the risk of anxiety was especially high for men and women with both parents affected by anxiety. Because of the large numbers, we were able to describe age-specific familial risks to some extent. In the offspring of affected parents, the highest risks were found in the youngest age groups. Previous studies have suggested that the etiology of anxiety in childhood and adolescence may differ from that of early-onset anxiety and may be more strongly genetically influenced than adult-onset anxiety [5].

Another feature of our study is that we were able to give gender-specific familial risk estimates. Although differences in the lifetime prevalence of anxiety in men and women are demonstrated consistently in epidemiological studies, we found no significant differences in familial risks of anxiety between the sexes, including transmission from father and mother, separately. This result is consistent with prior evidence [9, 14].

Conclusion

There was an age-specific familial risk of anxiety by parental proband. We showed an age-dependent familial risk for anxiety and an overall increased risk of anxiety among the ≤72-year-old offspring of parents with anxiety. Further progress in the understanding of the heritable basis of anxiety requires coordinated efforts in genetic epidemiology and molecular genetics.

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Declaration of interest There are no conflicts of interest.

References

1. Almeida-Filho N, Lessa I, Magalhaes L, Araujo MJ, Aquino E, de Jesus Mari J (2007) Co-occurrence patterns of anxiety, depression and alcohol use disorders. Eur Arch Psychiatry Clin Neurosci 257:423–431
2. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. (2004) Prevalence of mental disorders in Europe: results from the European study of the epidemiology of mental disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 420:21–27
3. Boelen PA, Prigerson HG (2007) The influence of symptoms of prolonged grief disorder, depression, and anxiety on quality of life among bereaved adults: a prospective study. Eur Arch Psychiatry Clin Neurosci 257:444–452
4. Eley TC, Stevenson J (1999) Exploring the covariation between anxiety and depression symptoms: a genetic analysis of the effects of age and sex. J Child Psychol Psychiatry 40:1273–1282
5. Goldstein RB, Wickramaratne PJ, Horwath E, Weissman MM (1997) Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. Arch Gen Psychiatry 54:271–278
6. Hemminki K, Li X, Johansson SE, Sundquist K, Sundquist J (2006a) Familial risks of aortic aneurysms among siblings in a nationwide Swedish study. Genet Med 8:43–49
7. Hemminki K, Sundquist K, Li X (2006b) Familial risks for main neurological diseases in siblings based on hospitalizations in Sweden. Twin Res Hum Genet 9:580–586
8. Hettema JM, Neale MC, Kendler KS (2001a) A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 158:1568–1578
9. Hettema JM, Prescott CA, Kendler KS (2001b) A population-based twin study of generalized anxiety disorder in men and women. J Nerv Ment Dis 189:413–420
10. Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS (2005) The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch Gen Psychiatry 62:182–189
11. Kadri N, Agoub M, El Gnaoui S, Berrada S, Moussaoui D (2007) Prevalence of anxiety disorders: a population-based epidemiological study in metropolitan area of Casablanca, Morocco. Ann Gen Psychiatry 6:6
12. Lewis G, Bebbington P, Brugha T, Farrell M, Gill B, Jenkins R, et al. (1998) Socioeconomic status, standard of living, and neurotic disorder. Lancet 352:605–609
13. Lofors J, Ramirez-Leon V, Sundquist K (2006) Neighbourhood income and anxiety: a study based on random samples of the Swedish population. Eur J Public Health 16:633–639
14. Middeldorp CM, Birley AJ, Cath DC, Gillespie NA, Willemsen G, Statham DJ, et al. (2005) Familial clustering of major depression and anxiety disorders in Australian and Dutch twins and siblings. Twin Res Hum Genet 8:609–615
15. Mineka S, Oehlberg K (2008) The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. Acta Psychol (Amst) 127:567–580
16. Rende R, Weissman M, Rutter M, Wickramaratne P, Harrington R, Pickles A (1997) Psychiatric disorders in the relatives of depressed probands. II. Familial loading for comorbid non-depressive disorders based upon proband age of onset. J Affect Disord 42:23–28
17. Rosen M, Hakulinen T (2005) Use of disease registers. In: Ahrens W, Pigeot I (eds) Handbook of epidemiology. Springer-Verlag, Berlin
18. Rothman KJ, Greenland S (1998) Modern epidemiology, 2nd ed. Lippincott-Raven, Philadelphia
19. Skre I, Onstad S, Edvardsen J, Torgersen S, Kringlen E (1994) A family study of anxiety disorders: familial transmission and relationship to mood disorder and psychoactive substance use disorder. Acta Psychiatr Scand 90:366–374
20. Somers JM, Goldner EM, Waraich P, Hsu L (2006) Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Can J Psychiatry 51:100–113
21. Statistics Sweden (2005) The Swedish multi generation register (1960–1990): http://www.scb.se/default_2154.asp (In Swedish: registret över totalbefolkningen/RTB).
22. Sundquist K, Frank G, Sundquist J (2004) Urbanisation and incidence of psychosis and depression: follow-up study of 4.4 million women and men in Sweden. Br J Psychiatry 184:293–298
23. Sundquist K, Li X, Hemminki K (2006) Familial risk of ischemic and hemorrhagic stroke. a large-scale study of the Swedish population. Stroke 37:1668–1673
24. The National Board of Health and Welfare (2004) The Swedish hospital discharge register and the cause of death register (1961–2001). http://www.socialstyrelsen.se/en/