Breaking the cycle?

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Doomed for disorder? High incidence of mood and anxiety disorders in offspring of depressed and anxious patients: a prospective cohort study

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ABSTRACT

Objective

Early recognition of individuals at risk for depressive and anxiety disorders is key in influencing onset and course of these disorders. Parental history is a potent risk factor for the development of these disorders in offspring. However, knowledge about the magnitude of this risk is limited as large scale longitudinal studies with a follow-up into adulthood are scarce. Those offspring at highest risk may possibly be identified by easy-to-determine parental psychiatric characteristics, family context, and offspring characteristics.

Method

From 2000-2002 we recruited 523 offspring (age 13-25 years) of 366 patients who had received specialized treatment for depressive and/or anxiety disorder. Offspring DSM-IV mood (major depressive disorder, dysthymia, and bipolar disorder) and anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, and agoraphobia) were assessed at baseline and at 4-, 6-, 8- and 10- year follow-up.

Results

Kaplan-Meier analysis showed that the cumulative incidence of mood and/or anxiety disorders was 38.0% at age 20 years and 64.7% at age 35 years. Parental early disorder onset (hazard ratio [HR]=1.33, 95%CI=1.00-1.77), having two affected parents (HR=1.58, 95%CI=1.10-2.27), and offspring female gender (HR=2.34, 95%CI=1.74-3.15) were independent predictors of offspring mood and/or anxiety disorder. Balanced family functioning (HR=0.73, 95%CI=0.56-0.96) was found to be protective against offspring risk.

Conclusion

Offspring of depressed and anxious patients are at very high risk of a mood and/or anxiety disorder themselves. Parental early onset, having two affected parents, female gender, and family functioning are important additional markers that can be used in clinical practice to identify those offspring at greatest risk.

INTRODUCTION

Despite the fact that depressive and anxiety disorders are highly prevalent and responsible for a substantial burden on both the individual and society at large,[1] substantial underrecognition and under-treatment still exis.[2,3] Early recognition of individuals at risk for these disorders is key in influencing onset and course of these disorders. Due to a combination of genetic and environmental risk factors,[4,5] offspring of depressed or anxious patients are at increased risk of developing a disorder themselves[6,7] and also of having a poor prognosis.[8-10] These offspring could, therefore, be an important target for prevention strategies.

To determine health service needs and guide policy decision-making, accurate information on the incidence of depressive and anxiety disorders in these offspring is necessary. Unfortunately, reported lifetime prevalence rates vary widely across studies. Studies in high-risk offspring populations reported cumulative incidence of around 10 to 50%.[11-16] These percentages could be underestimates due to recall failure,[17] as these studies were cross-sectional or had two assessment waves and, thus, mainly relied on retrospective data. Therefore, long-term follow-up studies are needed, with, importantly, a follow-up into adulthood since adolescence and young adulthood are core risk periods for disorder onset.[18,19] However such studies are scarce[6,7] and additional studies with a follow-up into adulthood are needed to obtain accurate estimates of offspring risk.

A first and crucial step in prevention is to identify offspring at the highest risk of developing a disorder and to do so as early as possible in order to monitor and possibly treat early symptoms. Within this vulnerable group, the magnitude of offspring's risk quite likely differs and may depend on parental psychiatric characteristics, the family context, and offspring characteristics. Easy-to-determine parental, family, and offspring characteristics may be used in every day clinical practice to obtain a quick indication of individual risk. This information can be valuable in making decisions regarding monitoring of offspring, or prevention and intervention strategies. Previous studies have indicated that parental psychiatric characteristics, such as parental early onset of disorder[20,21] and comorbidity[22,23] as well as having two affected parents[24,25], are associated with increased offspring risk. In addition, offspring with parental mental illness more often grow up in a less favorable family context[5,26], such as financial hardship or family discord, which may also contribute to increased offspring risk. Finally, risk very likely depends on offspring characteristics like gender, self-esteem and cognitive skills.[4,27,28] Although several studies have evaluated some of these potential predictors, none has determined their independent and long-term effects. To be able to delineate those offspring at highest risk, the impact of parental psychiatric characteristics, family context and offspring characteristics on offspring risk need to be evaluated simultaneously, such that their inter-relatedness can be accounted for. Furthermore, this evaluation needs to be done particularly in prospective studies with a follow-up into adulthood at which point in development offspring have passed through the major risk period for depressive and anxiety disorders.

Here, we report one of the few long-term follow-up studies in offspring (N=523) of depressed or anxious patients who were followed into adulthood (i.e., mean age at 10-year follow-up was 28.5 years). Our aims were 1) to determine the cumulative incidence of mood and anxiety disorders in these offspring and 2) to determine how offspring risk varies by parental psychiatric characteristics (i.e. age of disorder onset, comorbidity, hospitalization, having two affected parents), the family context (i.e. socioeconomic status, family functioning, parentification, parental divorce, parental medical illness) and offspring characteristics (i.e. gender, intelligence quotient [IQ], severe medical illness, childhood trauma) adjusting for their interrelatedness. Stratification by these easy-to-determine characteristics in this well-established high-risk group may aid substantially in identifying those offspring who very likely need (future) help.

METHOD

Design and recruitment

Data were from the ARIADNE cohort (Adolescents at Risk of Anxiety and Depression: a Neurobiological and Epidemiological approach; starting in 2000).[29] This prospective cohort study included 523 offspring (baseline age, 13-25 years; recruited form 2000-2002) of 366 patients who had received specialized treatment for depressive (i.e. major depressive disorder, dysthymia) and/or anxiety disorder (i.e. panic disorder with or without agoraphobia, obsessive compulsive disorder) at 1 of 16 psychiatric services in the north of the Netherlands. Of the index-parents, 320 had a depressive disorder (87.4%; of which 43.1% had a pure depressive disorder and 56.9% had a comorbid anxiety disorder) and 207 had an anxiety disorder (56.6%; of which 12.1% had a pure anxiety disorder and 87.9 % had a comorbid depressive disorder) as established with the Composite International Diagnostic Interview (CIDI).[30] No formal CIDI diagnosis was present in 5.5% of the index-parents. All but one of these parents passed the CIDI screener questions indicating the presence of subclinical depressive and/or anxiety symptoms. For one parent, there was no CIDI information available. Patients and their offspring were not eligible to participate if the parent had a history of a schizophrenia or post-traumatic stress disorder.

Face-to-face assessments, including a psychiatric diagnostic interview, were conducted at baseline with the recruited patients (also referred to as index-parents) and their offspring, after which offspring were followed-up at one, two and four years by means of self-report questionnaires. Further follow-up of this offspring cohort took place within the context of the Netherlands Study of Depression and Anxiety (NESDA; starting in 2005), an ongoing cohort study with face-to-face assessments, including the same diagnostic interview, with two-year intervals. The ARIADNE and NESDA study protocols were approved by the Medical Ethics Committee of the University Medical Center Groningen, Groningen, The Netherlands, and, for both studies, written informed consent was obtained. Figure 1 presents an overview of the study design and a detailed description of the recruitment procedures and methods is provided by Landman-Peeters et al[29] and Penninx et al.[31]

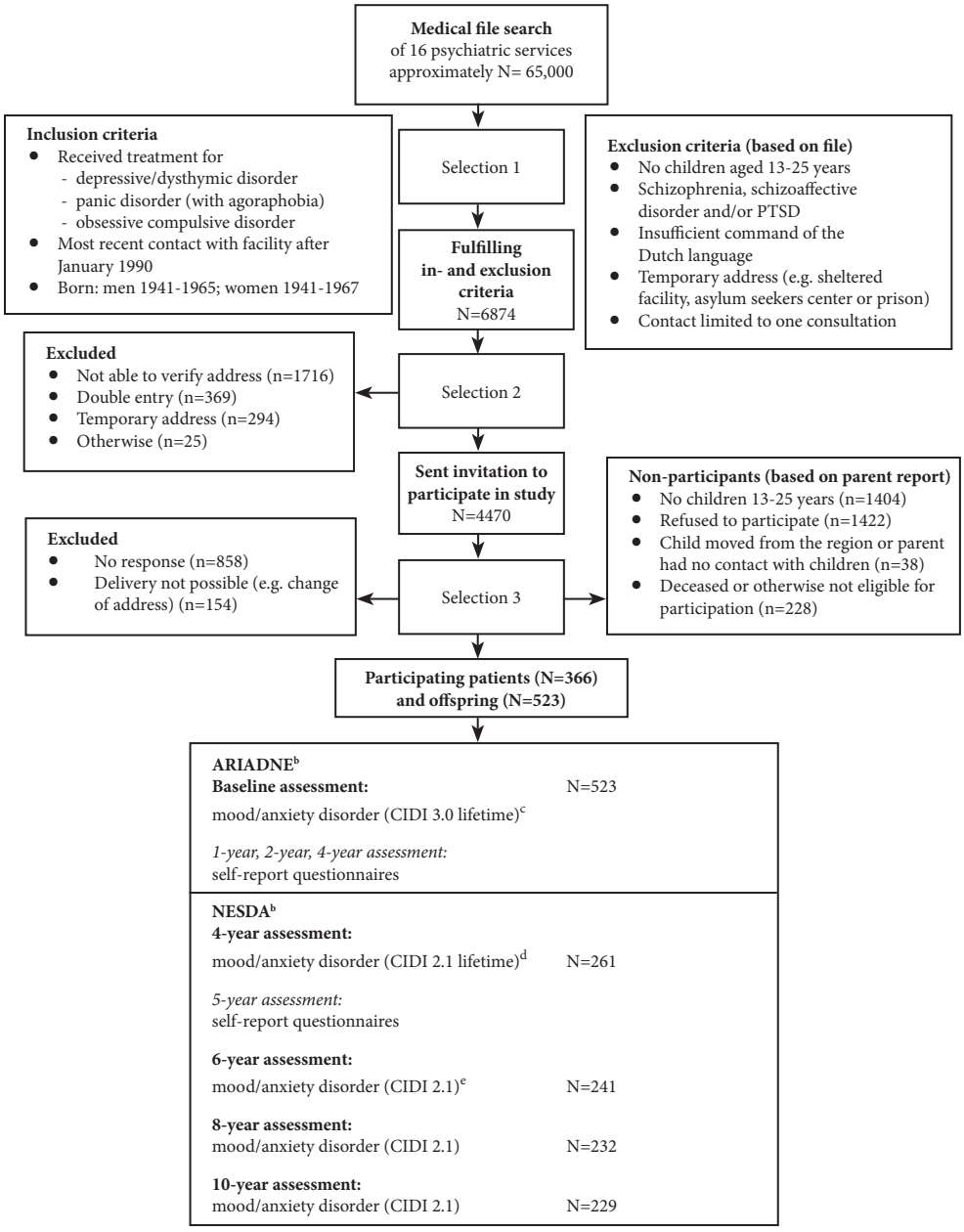


Figure 1. Flowchart of study design[a]

a Adapted from Landman-Peeters[69]
b Only those waves that contained CIDI interviews were used in the present study; self-report questionnaires were filled in at each of the 8 waves.
c CIDI version 1.1 was used to assess bipolar disorder because this section was not included in the CIDI 3.0 version.
d Bipolar disorder was not assessed at the 4-year interview.
e Because bipolar disorder was not assessed at the 4-year interview, lifetime diagnosis was established.
Abbreviations: ARIADNE = Adolescents at Risk of Anxiety and Depression: a Neurobiological and Epidemiologic approach, CIDI = Composite International
Diagnostic Interview, NESDA = Netherlands Study of Depression and Anxiety, PTSD = posttraumatic stress disorder.

For the present study, the baseline assessment of ARIADNE and four assessments of NESDA were combined, covering a period of 10 years of prospective data. In combination with the retrospective data derived from the ARIADNE baseline assessment, the mean follow-up duration of offspring (i.e. age at last interview) was 23.0 years (standard deviation [SD]=6.0, range 13-37 years). Four characteristics were associated with follow-up duration: offspring gender (female: odds ratio [OR]=1.04, p=.015), occupational level (skilled: OR=1.06, p=.001), educational attainment (medium: OR= 1.06, p=.032; high: OR=1.10, p=<.001) and IQ (β=0.29, p<.001). All analyses were corrected for baseline age. The other characteristics were not related to follow-up duration (p≥0.09). In total, 43.8% of offspring (n=229) participated in the final 10-year follow-up assessment (age: mean [SD] =28.5 [3.1]; range, 23-37 years).

Measures

Outcome measures

Offspring onset of mood and anxiety disorders. To assess offspring DSM-IV diagnoses of mood disorder (major depressive disorder, dysthymia, and bipolar disorder) and anxiety disorder (generalized anxiety disorder, social phobia, panic disorder, and agoraphobia) the CIDI[30] was administered at baseline (CIDI, version 3.0) and at 4-year, 6-year, 8-year, and 10-year follow-up (CIDI, version 2.1). The CIDI has been shown to be reliable and valid in assessing psychiatric disorders according to DSM-IV criteria.[32] Kappa coefficients for inter-rater reliability ranged from 0.92 to 0.99[32] for the CIDI sections that we used for our offspring. Offspring were interviewed at home or at the Department of Psychiatry by intensively trained and monitored interviewers with various backgrounds; the Department of Psychiatry of the University Medical Center Groningen is an Expert Training Center for the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI), indicating high training quality of our interviewers. To ensure blindness to parental diagnoses, offspring and parents were interviewed separately by different interviewers. For all diagnoses, age-at-onset were obtained by standard CIDI age-at-onset questions. When multiple diagnoses were present, the first age-of-onset was incorporated in the analyses.

Potential predictors

<u>Parental psychiatric characteristics</u>

Index-parents' lifetime diagnoses of depressive disorder (major depressive disorder, dysthymia) and anxiety disorder (panic disorder with or without agoraphobia, obsessive-compulsive disorder) were assessed at baseline using the CIDI, version 3.0.[30] Kappa coefficients for inter-rater reliability were 0.94 and 0.95 for the CIDI sections that we used for our index parents.[32] Like their offspring, parents were interviewed at home or at the Department of Psychiatry by the highly skilled interviewers. Information regarding psychiatric history of the other biological parent was gathered using the Family History Research Diagnostic Criteria method.[33] Index-parents were asked about the history of depressive or anxiety disorder of the other biological parent using case vignettes describing the main DSM-IV characteristics

of the disorder under investigation, followed by a series of questions assessing lifetime occurrence, professional treatment and, medication use (see Ormel[34] et al for more details on this method). The other biological parent was classified as "affected" if he or she had received treatment for depressive or anxiety disorder. This criterion served as a proxy measure of equal "illness severity" for the two affected parents.[35] Based on this information, the following parental psychiatric characteristics were defined:

Comorbidity. Comorbidity was present when at least one parent had both depressive and anxiety disorder.

Early onset of disorder. Parental early onset was defined as having at least one parent with an age-at-onset before 20 years.

Number of affected parents. The number of affected parents was based on information on whether only the index-parent or also the other biological parent had received treatment for depressive and/or anxiety disorder.

Hospitalization. Hospitalization was based on a single question posed to the index-parents as to whether one of the parents had been hospitalized for psychiatric problems.

Characteristic of the family context

Socioeconomic status. Three dimensions of parental socioeconomic status (SES) were measured at baseline: educational attainment (low, medium, high), occupational level (semiskilled/ unskilled or skilled) and income level (below average or above average). The variables are based on the highest level for parents or caregivers in the household in which the child lived the largest part of his or her life.

Family functioning. Family functioning was assessed in offspring at baseline with the Cohesion and Adaptability scales of the Dutch Family Dimension Scales (FDS).[36] The FDS is based on the Family Adaptability and Cohesion Evaluation Scales (FACES).[37] Four levels of family adaptability (rigid, structured, flexible, and chaotic) and four levels of family cohesion (disengaged, separated, connected, and enmeshed) were distinguished. For both scales, the two central levels were considered to be balanced levels of functioning. 'Balanced' family functioning was defined as having balanced levels of both family cohesion and family adaptation.[36] Remaining scores were categorized as 'unbalanced'.

Parentification. Index-parents were asked whether their child had taken on parental duties or tasks before the age of 16 years. This yes/no index was aggregated from took over care for siblings, for parents, for family income and/or for housekeeping.

Parental chronic, medical illness. Index-parents were asked whether their child had experienced a chronic medical illness in one of the co-resident parents.

Parental divorce. Index-parents were asked whether their child had experienced separation or divorce of co-resident parents.

Offspring characteristics

Gender. Gender was included as potential predictor.

Intelligence. Intelligence was assessed at baseline using the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS).[38] A full scale IQ was estimated using the formula described by Sattler.[39] As the average IQ score has been shown to increase about 3 points per decade[40] (i.e. the Flynn effect), we corrected the full-scale IQ scores by subtracting 9 points (test was standardized in the Netherlands in 1970 and performed by our participants in 2000).

Severe medical illness. Index-parents were asked whether their child had a severe medical illness.

Childhood trauma. The post-traumatic stress disorder section of the CIDI was used to assess traumatic experiences in childhood (age <=12 years).

Statistical analyses

First, the Kaplan-Meier method was performed to estimate the cumulative incidence of mood and/or anxiety disorder using data of all 523 offspring. We used survival analyses to analyze our data as our outcome of interest was the time to offspring's first onset of a mood or anxiety disorder. Apart from this, another major additional advantage of this method is that it takes into account the follow-up time of each person being followed and, thus, takes into account all available data. As we aim to determine offspring's first onset of mood and/or anxiety disorder we used data of the baseline assessments (i.e. retrospective reports) as well as the follow-up assessments (i.e. prospective reports) to estimate cumulative incidence. Then, Cox regression analyses were performed to examine whether potential predictors (i.e., parental psychiatric characteristics, the family context and, offspring characteristics) were related to the onset of mood and/or anxiety disorder. These analyses were performed in 522 offspring as one case was excluded because no CIDI information and no SES information were available from from the parent. To investigate whether associations were consistent for males and females, gender-interaction terms were added to the regression models. To determine independent effects, multivariable Cox regression analysis was performed including all variables with a $p<.10$ in the univariable analyses. Additional analyses were performed to test if associations were similar for mood versus anxiety disorder. Analyses were conducted using Stata version 13.0 (StataCorp) and adjusted for familial clustering.

RESULTS

Sample characteristics

Our sample included 523 offspring. Mean (SD) age of offspring participating in the final 10-year follow-up assessment was 28.5 (3.1) years (range, 23-37 years). Table 1 presents the baseline characteristics of offspring.

Cumulative incidence of mood and/or anxiety disorder

Figure 2 shows the cumulative incidence of mood and/or anxiety disorders in offspring and illustrates that the incidence starts to increase at the age of 10 years (cumulative incidence: 7.5%) and continues to be high during adolescence (cumulative incidence at age 20 years: 38.0%) and young adulthood (cumulative incidence at age 35 years: 64.7%). In general, the incidence rate of any mood and/or anxiety disorder was 21.9 onsets per 1000 person-years; more specifically, these rates were 16.3 for major depressive disorder, 7.8 for panic disorder and/or agoraphobia, 6.4 for social phobia, 6.2 for generalized anxiety disorder, 3.1 for dysthymia, and 1.7 for bipolar disorder. Of the 215 offspring who had developed a disorder (retrospective reports, n=145; prospective reports, n=70), 63 (29.3%) had a mood disorder, 39 (18.1%) had an anxiety disorder, and 113 (52.6%) had a comorbid mood and anxiety disorder. In these comorbid cases, 24.8% had a primary anxiety disorder (anxiety disorder preceded mood disorder), 31.0% had a primary mood disorder, and 44.2% had a simultaneous onset within two years. Additional analysis indicated that offspring risk did not differ by parental disorder type (i.e. pure depressive disorder, pure anxiety disorder, or comorbid depressive and anxiety disorder yielded highly similar hazard ration [HRs] and overlapping 95% confidence intervals). In addition, similar associations were found for both maternal disorder type and paternal disorder type (tables available on request).

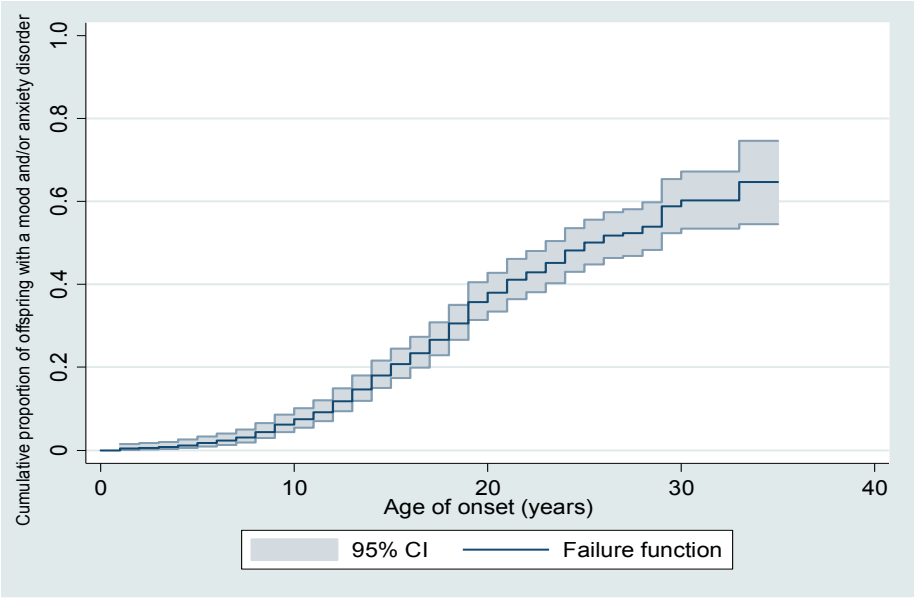


Figure 2. Cumulative incidence of mood and/or anxiety disorder in offspring of depressed and/or anxious patients (kaplan-meier failure estimate)

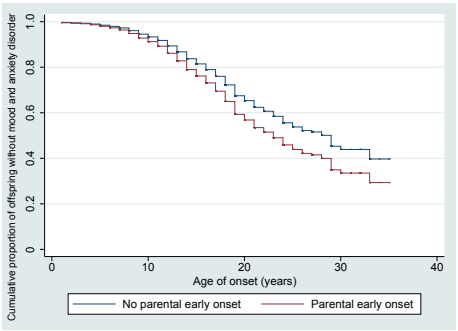
Table 1. Sample characteristics and predictors of offspring onset of mood and/or anxiety disorder

	Offspring (N=522)	Offspring onset of mood/anxiety disorder Univariable[a]			Offspring onset of mood/anxiety disorder Multivariable[b]		
Baseline predictor	n(%)/ mean (sd)	HR	95% CI	p	HR	95% CI	p
Parental psychiatric characteristics							
Early onset of disorder	202 (38.7)	1.33	1.00-1.76	.050	1.33	1.00-1.77	.048
Comorbidity	271 (51.9)	1.27	0.96-1.69	.098	1.19	0.89-1.60	.247
Hospitalized	166 (31.8)	1.12	0.82-1.54	.469	-	-	-
Two affected parents	101 (19.3)	1.52	1.08-2.16	.018	1.58	1.10-2.27	.014
Family context							
Socioeconomic status							
Educational attainment							
High	197 (37.7)		reference		-	-	-
Medium	178 (34.1)	1.09	0.78-1.51	.611	-	-	-
Low	147 (28.2)	1.00	0.70-1.42	.992	-	-	-
Occupational level (semi- or unskilled)	238 (45.6)	1.06	0.80-1.41	.677	-	-	-
Income level (below or at average)	261 (50.0)	1.06	0.79-1.41	.695	-	-	-
Balanced family functioning	258 (49.4)	0.72	0.55-0.94	.016	0.73	0.56-0.96	.025
Parentification	66 (12.6)	1.33	0.90-1.96	.153	-	-	-
Parent with chronic, medical disease	98 (18.8)	1.09	0.76-1.56	.651	-	-	-
Parental divorce	101 (19.3)	1.27	0.91-1.77	.156	-	-	-
Offspring characteristic							
Female gender	299 (57.3)	2.20	1.65-2.95	<.001	2.34	1.74-3.15	<.001
IQ	105.1 12.8)	1.01	1.00-1.02	.118	-	-	-
Severe medical illness	163 (31.2)	1.03	0.78-1.37	.835	-	-	-
Childhood trauma	141 (27.0)	1.28	0.95-1.72	.109	-	-	-

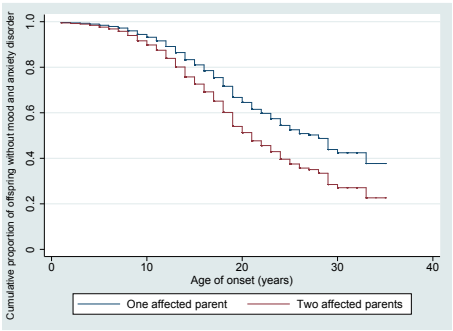
a = Based on univariable Cox regression analyses
b = Based on multivariable Cox regression analysis, including all variables that had a p<.10 in the univariable analyses
Abbreviations: CI=confidence interval, HR=hazard ratio, IQ=intelligence quotient, SD=standard deviation.

Predictors of onset

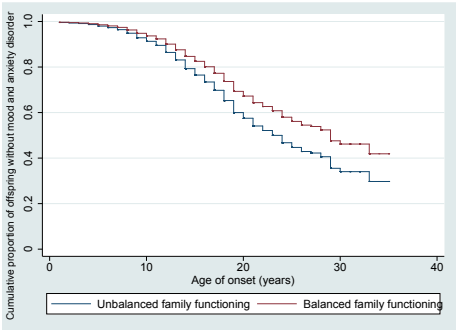
Table 1 depicts the results of the univariable Cox regression relating potential predictors to the onset of mood and/or anxiety disorders in offspring. Parental early onset (HR=1.33, 95%CI=1.00-1.76; Figure 3a) and having two affected parents (HR=1.52, 95%CI=1.08-2.16; Figure 3b) were significantly associated with increased hazard of offspring mood and/or anxiety disorder. None of the other parental psychiatric characteristics showed a significant association. Of the family context variables, balanced family functioning (HR=0.72, 95%CI=0.55-0.94; Figure 3c) was associated with decreased hazard of offspring risk, whereas none of the other family context variables showed a significant association. Offspring female gender (HR=2.20, 95%CI=1.65-2.95; Figure 3d) was significantly associated with increased hazard of offspring mood and/or anxiety disorder. The other offspring characteristics did not show a significant association. Parental early onset (HR=1.33, 95%CI=1.00-1.77), having two affected parents (HR=1.58, 95%CI=1.10-2.27), balanced family functioning (HR=0.73, 95%CI=0.56-0.96) and offspring female gender (HR=2.34, 95%CI=1.74-3.15) remained significant predictors in multivariable Cox regression analysis. Additional analyses showed



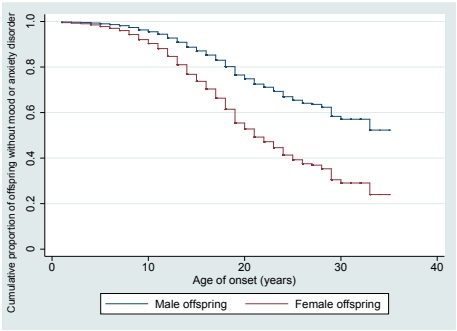
A. Offspring with and without parental early onset of disorder (<20 years)



B. Offspring with 1 and 2 affected parents



C. Offspring with balanced and unbalanced family functioning



D. Male and female offspring

Figure 3. Predictors of onset of mood and/or anxiety disorder in offspring

that the aforementioned associations were rather similar for mood versus anxiety disorders (Appendix Tables 1 and 2). Childhood trauma was an exception, showing different associations with offspring onset of mood (HR=1.50, 95%CI=1.08-2.08) and anxiety disorders (HR=0.99, 95%CI=0.68-1.42). In addition, offspring gender did not show a significant interaction with any of the characteristics in predicting the onset of mood and/or anxiety disorder (p≥.13), indicating that associations were consistent for boys and girls.

DISCUSSION

Principal findings

This study shows, first, that the majority of offspring of depressed and anxious patients develop a mood or anxiety disorder themselves. The cumulative incidence is already 38% at the age of 20 years and is as high as 65% at the age of 35 years. This risk is, consequently, 2-3 times higher in these offspring than reported in a highly similar Dutch community sample of persons aged 25-44 years using the same diagnostic interview,[41] or in other international community studies.[42,43] This study shows, second, that parental early onset, having two affected parents

and female gender increase offspring risk, as they had additive effects on the onset of mood or anxiety disorders. In addition, we found balanced family functioning to be protective against offspring risk. These findings indicate that relatively basic information is sufficient to identify children and young adults who have a major risk of psychopathology and who could be an important target for prevention strategies. Parental comorbidity, hospitalization or divorce, socioeconomic status, parentification, parental or offspring medical illness, and offspring IQ were not significant independent predictors. Childhood trauma significantly increased offspring risk for mood disorders (but not anxiety) which is in line with previous research findings.[44,45]

Strengths and limitations

Major strengths of our study are the large sample size, the prospective design with a 10-year follow-up into adulthood, the rigorous clinical assessment of offspring and index-parents, the information on the lifetime history of depressive and/or anxiety disorder of both parents and the inclusion of a broad range of parental psychiatric characteristics, family context and offspring characteristics as predictors of offspring risk. However, some limitations need to be pointed out as well. First, we did not succeed in following the complete cohort for the entire follow-up period of 10 years. This was mainly due to the Medical Ethical Committee's decision to officially close ARIADNE before requesting offspring to participate in NESDA, which then resulted in a considerable dropout rate (i.e., 50.1%) in the process between the studies. Second, the relatively low rates of participation among eligible parents may have affected the representativeness of the sample. It should be noted, however, that this population is very difficult to engage in research (for example, parents do not want to burden their offspring with their "at risk" status) and that the number of parents and children that eventually were recruited for the study is high, relative to previous studies. Third, although our study had a prospective design with regular diagnostic assessments, baseline information relied on retrospective reports and this may have affected our findings. Failure to recall past mood or anxiety episodes may, for example, have resulted in underestimates of the already impressive incidence rates. In addition, age-at-onset recall may be less accurate, but we attempted to reduce bias by using a sequence of questions designed to improve the reliability of retrospective estimates of age-at-onset.[46] Recall bias could have been avoided if assessments would have started in early childhood, which would result in a higher number of offspring having a mood/or anxiety onset during the study. This is, however, costly and difficult to achieve due to the follow-up time required to catch the majority of incidences in late adolescence and young adulthood. Furthermore, with regard to parental anxiety disorders, recruitment involved patients with panic disorder with or without agoraphobia and obsessive compulsive disorder, which may have limited the generalizability of our findings. It should be noted, however, that other anxiety disorders like social phobia and generalized anxiety disorder, are probably present in a large number of parents as the comorbidity of these anxiety disorders with depression as well as with other anxiety disorders is found to be extensive.[e.g.47,48] Based on the CIDI screening

questions (only the screening sections were administered), 55.2%, 91.3%, and 75.1% of the index-parents screened positive for social anxiety, generalized anxiety disorder, and specific phobia, respectively, confirming this. Likewise, the most prevalent anxiety disorders were assessed in offspring. The term anxiety disorder in the current article therefore refers to generalized anxiety disorder, social phobia, panic disorder, and agoraphobia. Post-traumatic stress disorder, for instance, was not included. Consequently, offspring risk may be somewhat higher than presented. In addition, clinical information of both parents was based on one informant, as only the index-parent was interviewed, yet, this is an important improvement compared to studies taking into account index-parents' psychopathology alone. Future work may try to diagnostically assess both parents. Finally, we could not take a developmental perspective on our research question because, as in previous studies[e.g.10,11], our offspring sample had a broad age range. It should be noted that recruitment difficulties are a major problem in offspring studies given the low participation rates among approached families.[e.g.49-51] At this moment, it does not seem to be feasible with current recruitment strategies to recruit, within a reasonable budget, a group of high-risk offspring of similar ages that is sufficiently large to guarantee adequate statistical power. Improved recruitment strategies should, therefore, first be developed and assessed before such samples can be recruited.

Comparison with previous studies

We showed that offspring of depressed and anxious patients constitute a group at substantial risk for mood and anxiety disorders with estimates in line with two other longitudinal high-risk studies that also reported impressive incidence rates.[6,7] Our estimates were somewhat lower compared to a 20-year follow-up study,[6] but confirm the bleak picture of the extent of offspring risk. Our finding that parental early onset and having two affected parents increased offspring risk was consistent with two other longitudinal studies.[e.g.21,25] The likely mechanisms behind this increased risk are the higher genetic loading associated with these characteristics, environmental risk, as well as their interplay.[52-54] Parental early onset may affect offspring at a younger age or for a greater part of their life. The presence of two affected parents will certainly limit compensation by the second parent as compared to families with one affected parent as well as enhance chances of an unsupportive home environment.

We found that offspring who evaluated their family functioning to be balanced had a decreased risk for mood and/or anxiety disorder, which is in line with a 20-year follow-up study in a similar sample of offspring of treatment-seeking depressed patients (i.e. a marginally significant association was found between low family cohesion and offspring major depressive disorder).[55] Our finding that offspring risk varies by parental psychiatric characteristics while most family factors had no impact on offspring risk may indicate that biological factors play an important role in the intergenerational transmission of psychopathology. However, as shown, this does not hold for the protective effect of healthy family functioning. This finding is more in line with the interpretation that environmental protective factors may dilute biological risk.

Offspring gender was an additional independent predictor, and, as in the general

population[42,43,56], girls had a 2-fold increased risk of mood or anxiety disorder compared to boys. Thus, gender remains a strong predictor regardless of parental psychopathology. The exact mechanisms behind this are still unclear, but biological, psychological and social factors have been suggested to explain this preponderance to depression and anxiety in females. Studies for instance note the importance of differences in pubertal development, coping styles, social roles, and childhood adversity.[e.g.57,58] Our finding of a similar sex ratio in high-risk offspring suggests that these mechanisms may not be different in high-risk offspring.

We found no indications of differential risk to offspring by parental disorder type (i.e. pure depressive disorder, pure anxiety disorder or comorbid depressive and anxiety disorder), which is in line with a meta-analysis.[59] It should be noted that knowledge on offspring of patients with pure anxiety disorder is fairly limited. Many studies on children of anxious parents did not exclude parents with comorbid mood disorders and the few studies that did include parents with an anxiety disorder alone, were, like ours, limited by a small sample size. Recruiting larger samples seems to be quite a challenge as pure anxiety disorders only seldom occur in pure and isolated form.

Practical implications

In light of the high prevalence of mood and anxiety disorders, very large numbers of children grow up in a family with an affected parent. Estimates in the United States, for example, suggest that this is the case in at least 15 million children (i.e., about one in five).[60] A substantial part of all incident mood and anxiety disorders will develop in this well-delineated risk group. Systematic preventive efforts that reduce offspring's risk would therefore have large individual and public mental health consequences.

A first and crucial step in prevention is to identify persons at high risk for mood and/or anxiety disorder. The general practitioner may be the first point of contact for mental health problems and is well positioned to identify and monitor not only the affected parent but also their offspring. Second, professionals working with depressed or anxious adults (e.g., psychiatrist, psychologist, social worker) would be in such a position. Third, professionals working with children and adolescents (e.g., youth care professionals, teachers) could take into account parental mental health to delineate these high-risk offspring. It is important to note in this context that particularly during childhood, referral may take place for other complaints that predate and perhaps forebode an adolescent onset of a depressive or anxiety disorder. Although this may seem a simple advice, it is our experience that, in practice, screening for depression and anxiety in offspring is certainly not a structural part of the intake process in every facility and for every clinician. Simple markers such as parental psychiatric characteristics, the family context, and offspring characteristics may be valuable for identifying those offspring at greatest risk and could be routinely assessed by professionals working with parents as well as professionals working with their offspring.

In addition to the identification of children at risk, several intervention types have been developed to reduce symptoms and prevent the onset of mood and/or anxiety disorder.

These interventions could be used in vulnerable offspring. For example, indicated preventive interventions may be effective in individuals already experiencing depressive and anxiety symptoms.[61-63] Second, specific child-focused as well as parent-focused and family-intervention programs for offspring and/or their parents indicate positive results.[64] As offspring of depressed and/or anxious patients are at such a very high risk of mood and anxiety disorders, selective prevention strategies targeting all these offspring could, despite ethical concerns that have also been raised by parents,[62,65] also be promising. These intervention strategies may include psycho-education aimed at increasing offspring's awareness and knowledge of signs and symptoms of psychiatric disorders, low-threshold positive psychology interventions[66] or self-help interventions for the management of negative emotions (e.g., MoodGYM).[67] Importantly, effective treatment of the depressed or anxious parent can also have a positive impact on offspring's mental health.[68] An approach targeting both parents and offspring may, therefore, have the highest chance of influencing both onset and early course of mood and anxiety disorders in offspring.

Although such recognition and intervention strategies may be promising, more research is needed to establish their benefits in daily practice. For example, future studies should examine whether systematic identification of high-risk offspring by general practitioners or mental health providers is feasible. In addition, further efforts are needed to assess the long-term impact of interventions to see whether they can prevent the onset of mood and anxiety disorders in these offspring. Finally, prospective research is needed to understand why some offspring thrive, even in the most difficult circumstances, while others become depressed or anxious even though parents were less severely affected and able to provide adequate care. Improved knowledge on mechanisms of transmission will ultimately give us more precise knowledge on ways to enhance resilience in these offspring.

Conclusion

This study showed that two-thirds of offspring of depressed or anxious patients develop a similar condition before the age of 35 years. Parental early onset, having two affected parents and female gender increase offspring risk even further, while balanced family functioning decreases offspring risk. These relatively basic characteristics can aid substantially in identifying those offspring at greatest risk. A comprehensive prevention strategy is recommended that focuses on both identifying these offspring and providing timely monitoring and effective interventions.

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