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Secondary depression in severe anxiety disorders: a population-based cohort study in Denmark

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Summary

Background—Depression and anxiety disorders are highly comorbid conditions and a worldwide disease burden; however, large-scale studies delineating their association are scarce. In this retrospective study, we aimed to assess the effect of severe anxiety disorders on the risk and course of depression.

Methods—We did a population-based cohort study with prospectively gathered data in Denmark using data from three Danish population registers: The Danish Civil Registration System, the Danish Psychiatric Central Register, and the Danish National Hospital Registry. We selected the cohort from people born in Denmark between Jan 1, 1955, and Dec 31, 2002, who we followed up from Jan 1, 1994, to Dec 31, 2012. The cohort was restricted to individuals with known parents. First, we investigated the effect of specific anxiety diagnoses on risk of single depressive episodes and recurrent depressive disorder. Second, we investigated the effect of comorbid anxiety on risk of readmission for depression, adjusting for sex, age, calendar year, parental age, place at residence at time of birth, and the interaction of age with sex.

Findings—We included 3 380 059 individuals in our study cohort. The adjusted incidence rate ratio (IRR) for single depressive episodes was 3·0 (95% CI 2·8–3·1, $p<0\cdot0001$) and for recurrent depressive disorder was 5·0 (4·8–5·2) in patients with severe anxiety disorders compared with the general population. Compared with control individuals, the offspring of parents with anxiety disorders were more likely to be diagnosed with single depressive episodes (1·9, 1·8–2·0) or recurrent depressive disorder (2·1, 1·9–2·2). Comorbid anxiety increased the readmission rates in both patients with single depressive episodes and patients with recurrent depressive disorder.

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Contributors

SMM, MM, PBM, and TML contributed to the conception and the design of the study. SMM, LP, MM, OM, PBM, and TML were involved in the analysis and interpretation of the data. PBM and TML supervised the study. SMM wrote the manuscript. All authors critically revised the manuscript and approved submission. SMM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Interpretation—Severe anxiety constitutes a significant risk factor for depression. Focusing on specific anxiety disorders might help to identify individuals at risk of depression, thereby providing new insights for prevention and treatment.

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Introduction

Depression and anxiety disorders are the most prevalent mental disorders worldwide; together they make up 50% of the international disease burden attributable to psychiatric and substance use disorders.¹ Data from epidemiological studies² suggests that more than 20% of the general population have at least one of these disorders during their lifetime. Comorbidity is common with depression and anxiety disorders. Many patients have both disorders and at least half of all patients with depression are diagnosed with a co-occurring anxiety disorder.³ This preponderance of depression and anxiety disorders underscores the importance of delineating their association to improve early identification and care. This delineation seems especially important because compared with patients with depression alone, patients with comorbid anxiety have increased symptom severity,^{3,4} earlier age at onset,³ and increased general distress and suicide risk.⁴ The onset of anxiety disorders precedes the onset of depression in community and clinical populations of children, adolescents, and adults.^{5–7} Therefore, previous anxiety often constitutes an accurate predictor of subsequent depression,⁸ with great value for prevention in clinical practice. However, the clinical diagnoses of anxiety disorders and depression are quite heterogeneous. Therefore, whether all specific anxiety disorders are equally associated with different types of depression⁹ remains unclear. Large-scale prospective studies exploring such associations are still scarce. Whether the predictive value of specific anxiety disorders on the course of disorder differs across clinical stages of depression has not yet been examined.

To address these uncertainties, we have comprehensively assessed the risk of developing depression in patients with different specific anxiety disorders who had contact with clinics and psychiatric outpatient services. As mood and anxiety disorders tend to cosegregate over generations,^{10,11} we studied which parental anxiety disorders increased the offspring's risk of depression. In view of the varying trajectories of depression, we were especially interested in whether the specific anxiety disorders associated with an increased risk of single depressive episodes differed from those associated with an increased risk of recurrent depressive disorder. Additionally, we aimed to explore how co-morbid anxiety related to the course and outcome of depression. The presence of specific anxiety disorders, if identified as clear markers of risk and prognosis, might provide implications for prevention and treatment.

Methods

Study design and participants

In this population-based cohort study with prospectively gathered data, we linked data from three longitudinal nationwide Danish population registers: The Danish Civil Registration System, the Danish Psychiatric Central Register, and the Danish National Hospital Registry.

All residents of Denmark, including immigrants, have a unique personal identification number that is used in all national registers, which enables data to be linked across these registers. The Danish Civil Registration System was computerised in 1968 and has information about the sex, date of birth, and vital status (continuously updated) of all people living in Denmark.¹² From this register, we selected the cohort from people born in Denmark between Jan 1, 1955, and Dec 31, 2002, who we followed up from Jan 1, 1994, to Dec 31, 2012. The cohort was restricted to individuals with known parents. We identified all people who had been discharged from hospitals between 1994 and 2012 and diagnosed with single depressive episodes or recurrent depressive disorder. We identified the parents of these patients using the Danish Civil Registration System. This study was approved by the Danish Data Protection Agency. The investigators were masked to the identity of study members and because the study did not result in any contact with the participants, no written informed consent was needed.

Procedures

The Danish Psychiatric Central Register includes data for all people admitted to any hospital for assessment, treatment, or both in Denmark from 1969 onwards or people who had appointments with psychiatric outpatient services from 1995 onwards.¹³ In the Danish National Hospital Registry, all inpatient treatments at non-psychiatric facilities are recorded from 1977 onwards, whereas outpatient and emergency room contacts are recorded from 1995 onwards.¹⁴ Diagnoses of diseases are based on the International Classification of Diseases, versions eight (ICD-8) and ten (ICD-10). We used the register to identify all patients diagnosed with single depressive episodes (ICD-10 code: F32.00–F32.9, F34.10–F34.90, and F38.00–F39.99) and recurrent depressive disorder (ICD-10: F33.00–F33.99). Next, we singled out individual and parental diagnoses of severe anxiety disorders needing treatment in inpatient and outpatient facilities (ICD-10: F40.00–F40.20, F41.00–F41.10, and F42.00–F43.10), covering acute stress reaction, agoraphobia, generalised anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, specific phobia, and social phobia. Additionally, we established the parental and individual psychiatric history of participants, particularly whether they had been admitted to a psychiatric hospital or had been in outpatient care for any psychiatric disorders (ICD-8 codes: 290–315; ICD-10 codes: F00–F99). Parental diagnoses (in either one of the parents) were categorised hierarchically as parental anxiety disorder (ICD-10: F40.00–F40.20, F41.00–F41.10, and F42.00–F43.10); parental depression (ICD-8: 296.09, 296.29, 298.09, 300.49, and 301.19; ICD-10: F32.00–F32.9, F33.00–F33.99, F34.10–F34.90, and F38.00–F39.99); and any other parental psychiatric disorder (ICD-8: 290–315; ICD-10: F00–F99, excluding depression and anxiety disorders). As the ICD-8 and ICD-10 differ substantially with regard to the classification of anxiety disorders and the ICD-10 enables a finer subclassification of anxiety disorders, we restricted our analyses of parental anxiety disorders to ICD-10 diagnoses. However, the definition of parental depression and other psychiatric disorders included ICD-8 and ICD-10 diagnoses; we therefore assessed using sensitivity analysis whether restriction of all parental diagnosis to ICD-10 altered results. Depressive episodes in patients with bipolar disorders were excluded from the analyses because the focus was on unipolar depression. Furthermore, we excluded all diagnoses referring to mixed states of depression and anxiety because, in these cases, the temporal

order in the occurrence of depression and anxiety disorders was unclear, which might affect the accuracy of the results.

Outcomes

Study outcomes were the effect of specific anxiety diagnoses on the risk of single depressive episodes and recurrent depressive disorders and the effect of comorbid anxiety on risk of hospital readmission for recurrent depressive disorder, after adjustment for sex, age, calendar year, parental age, place at residence at time of birth, and the interaction of age with sex.

Statistical analysis

Cohort participants were followed up from their tenth birthday or Jan 1, 1994, until the onset of depression, date of death, date of emigration from Denmark, or Dec 31, 2012, whichever occurred first. In analyses of participant's first hospital admission, we established the risks of single depressive episodes and recurrent depressive disorder in patients with severe anxiety disorders compared with the general population using a log linear Poisson regression model, adjusted for calendar year, age, maternal and paternal age, sex, psychiatric family history, place of residence at time of birth (as described elsewhere¹⁵), and the interaction of age with sex. We included an adjustment for the first hospital contact due to any other psychiatric disorder because we aimed to examine the specific effect of a previous anxiety diagnosis relative to the effect of any other psychiatric diagnosis in the case history. All specific anxiety disorders were simultaneously taken into account. Finally, we intended to assess whether the incidence rate ratios (IRRs) of single depressive episodes and recurrent depressive disorder were higher for specific anxiety disorders than for anxiety disorders generally, therefore adjusting for the first hospital contact due to any specific anxiety disorder. In view of the fact that cohort participants could have several anxiety disorders, we explored how the number of comorbid anxiety disorders affects disease risk. The effect of parental anxiety disorders was analysed with a hierarchical model simultaneously adjusting for calendar year, age, maternal and paternal age at birth, sex, place of residence at time of birth, and the interaction of age with sex. Additionally, we assessed interactive effects of parental and individual psychopathology on depression risk.

For the analyses of the course of the disorder, we focused on two types of outcomes, transition to recurrent depressive disorder and readmission for recurrent depressive disorder. Transition to recurrent depressive disorder was defined as patients initially diagnosed with single depressive episodes who were readmitted to clinics and outpatient services with a diagnosis of recurrent depression. Cohort participants were followed up from their first contact due to a single depressive episode or Jan 1, 1994, until first admission for recurrent depressive disorder, date of death, date of emigration from Denmark, or Dec 31, 2012, whichever occurred first. Readmission for recurrent depressive disorder was defined as patients with recurrent depressive disorder, who were readmitted with recurrent depressive disorder. Cohort participants were followed up from their first contact due to recurrent depressive disorder or Jan 1, 1994, until readmission for recurrent depressive disorder, date of death, date of emigration from Denmark, or Dec 31, 2012, whichever occurred first. To establish the specificity of anxiety disorders on readmission, we compared the readmission and transition rates after a previous diagnosis of anxiety disorders to the

rates after a previous diagnosis of other psychiatric diagnoses, such as attention deficit hyperactivity disorder, autism, schizophrenia, and anorexia nervosa (appendix). The analyses underwent the same adjustment procedure as the analyses of first admission; however, the covariates time since first depression diagnosis and the interaction of time since first depression diagnosis with sex were added.

For our sensitivity analyses, we studied differences by diagnostic codes (ICD-8 vs ICD-10), settings (inpatient and outpatient), and time since anxiety diagnosis (during the first year vs after the first year). Finally, we stratified odds of first admission and readmission by age at diagnosis (younger than 40 years or older than 40 years). All analyses were done with SAS, version 9.3 (SAS Institute, NC, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, patient recruitment, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

We assessed data for 3 380 059 cohort participants from Jan 1, 1994 to Dec 31, 2012. Of these, 57 570 were admitted with a single depressive episode during the 44 910 072 person-years at risk. This admission rate corresponds to a crude incidence rate of 12.8 per 10 000 person-years. Of those 57 570 participants, 3360 (5.8%) were previously diagnosed with an anxiety disorder. During the study period, the adjusted IRR of single depressive episodes for patients with severe anxiety disorders needing treatment compared with the general population was 3.0 (95% CI 2.8–3.1). The risk did not differ across age groups, but we noted a difference in risk for time since first anxiety diagnosis (first year IRR 9.88, 95% CI 9.4–10.4 vs after first year 1.9, 1.8–2.0). The specific effect of severe anxiety disorders, in addition to the effect of any other psychiatric contact, was estimated to be 2.9 (2.8–3.0). All specific anxiety disorders individually increased the risk of single depressive episodes, with acute stress reaction and post-traumatic stress disorder increasing the risk more than anxiety disorders in general (table 1). Patients with several anxiety disorders did not have a higher risk of development of a single depressive episode than patients with a single anxiety disorder (appendix).

The parents of 1453 patients with single depressive episodes had been admitted to hospital with a diagnosis of a specific anxiety disorder. During the study period, the adjusted IRR of single depressive episodes in offspring of patients with anxiety disorders compared with the general population was 1.9 (95% CI 1.8–2.0). The risk associated with parental anxiety disorders was significantly higher than the risk associated with a parental diagnosis of any psychiatric disorder (IRR 1.7, 1.6–1.7) other than depression (2.1, 2.0–2.1; figure). Parental acute stress reaction, agoraphobia, panic disorder, and social phobia were the specific anxiety disorders increasing the risk of single depressive disorders more than any other parental psychiatric disorders (table 2). The interaction of parental and individual psychopathology was significant, with the highest risk for single depressive episodes

reported in patients with anxiety disorders and a family history of psychiatric disorders (4.1, 3.8–4.3).

From Jan 1, 1994 to Dec 31, 2012, 30 763 cohort participants were admitted to psychiatric inpatient and outpatient services with a diagnosis of recurrent depressive disorder during the 45 171 674 person-years at risk, corresponding to a crude incidence rate of 6.8 per 10 000 person-years. Of those 30 763 patients, 3358 (10.9%) were previously diagnosed with an anxiety disorder. During the study period, the adjusted IRR of recurrent depressive disorder for patients with severe anxiety disorders compared with the general population was 5.0 (95% CI 4.8–5.2). The risk did not differ across age groups, whereas it differed for time since first anxiety diagnosis (first year IRR 12.6, 95% CI 11.8–13.5 vs after first year 4.0, 3.9–4.2). The specific effect of anxiety disorders, in addition to the effect of any other psychiatric contact, was estimated to be 3.9 (3.8–4.1). All specific anxiety disorders individually increased the risk of recurrent depressive disorder, with generalised anxiety disorder, obsessive-compulsive disorder, panic disorder, and social phobia increasing the risk more than anxiety disorders in general (table 1). Patients with two or more anxiety disorders were at a significantly higher risk of development of recurrent depressive disorder than patients with a single anxiety disorder (appendix).

The parents of 717 patients with recurrent depressive disorder had been admitted with a diagnosis of a specific anxiety disorder. During the study period, the adjusted IRR of recurrent depressive disorder in offspring of patients with anxiety disorders compared with the general population was 2.1 (95% CI 1.9–2.2). The risk associated with parental anxiety disorders was significantly higher than the risk associated with a parental diagnosis of any psychiatric disorder (1.6, 1.6–1.7) other than depression (2.2, 2.2–2.3; figure). Parental acute stress reaction, agoraphobia, generalised anxiety disorder, obsessive-compulsive disorder, panic disorder, and social phobia were the specific anxiety disorders associated with a higher risk than any other parental psychiatric disorder (table 2). The interaction of parental and individual psychopathology was significant, with the highest risk for recurrent depressive disorder reported in patients with anxiety disorders and a family history of psychiatric disorders (6.5, 5.5–7.7).

10670 (18.5%) of the patients initially diagnosed with a single depressive episode transitioned to recurrent depressive disorder during the 382 145 person-years at risk, corresponding to a crude incidence rate of 279 per 10 000 person-years. Of those patients, 1621 (15%) had previously been diagnosed with an anxiety disorder. The adjusted transition rate ratio of recurrent depressive disorder for patients with severe anxiety disorders compared with the general population was 1.1 (95% CI 1.1–1.2). The specific effect of anxiety disorders, in addition to the effect of any other psychiatric contact, was estimated to be 1.1 (1.0–1.1). Several specific anxiety disorders individually increased the transition risk to recurrent depressive disorder, with generalised anxiety disorder and panic disorder increasing the rate more than anxiety disorders in general (table 1). The transition rate ratio was significantly increased in patients with three or more anxiety disorders compared with patients with a single anxiety disorder (appendix). Neither a previous diagnosis of attention deficit hyperactivity disorder, autism, schizophrenia, nor anorexia nervosa increased the transition risk. Parental depression (1.2, 1.2–1.3) and parental obsessive-compulsive disorder

(1.5, 1.0–2.2), but not anxiety disorders in general (1.0, 0.9–1.2), increased the offspring's transition risk. No interaction of parental and individual psychopathology was reported.

7157 (23%) of patients diagnosed with recurrent depressive disorder were readmitted with the same diagnosis during the 150 218 person-years at risk, corresponding to a crude incidence rate of 476 per 10 000 person-years. Of those patients, 1374 (19.2%) had previously been diagnosed with an anxiety disorder. The adjusted readmission rate ratio of recurrent depressive disorder for patients with severe anxiety disorders compared with the general population was 1.1 (95% CI 1.0–1.2). The specific effect of anxiety disorders, in addition to the effect of any other psychiatric contact, was estimated to be 1.1 (1.0–1.1). Several specific anxiety disorders individually increased the readmission risk for recurrent depressive disorder, with acute stress reaction and generalised anxiety disorder increasing the risk more than anxiety disorders in general (table 1). The readmission rate ratio did not differ between patients with a single anxiety disorder and patients with several anxiety disorders (appendix). Neither a previous diagnosis of attention deficit hyperactivity disorder, autism, schizophrenia, nor anorexia nervosa increased the readmission risk. Parental depression (1.1, 1.1–1.2) and parental anxiety disorders (1.2, 1.1–1.4) increased the offspring's risk of readmission with recurrent depressive disorder, with the highest risk reported in offspring of parents with agoraphobia (1.7, 1.1–2.4) and panic disorder (1.5, 1.1–2.0). We noted no interaction between parental and individual psychopathology.

In our sensitivity analyses, we identified no significant differences in odds of first admission and readmission between patients diagnosed on the basis of ICD-8 and ICD-10 and inpatients and outpatients. Descriptive statistics for all the samples included are presented in the appendix.

Discussion

In this study, we analysed the risk of first admission and readmission for depressive disorders in patients with severe anxiety. Our results suggest a high risk of depression and adverse course of depression in patients with severe anxiety. Although a direct causal interpretation is not possible, these associations might have important implications for clinical practice. The first and main such implication is that secondary prevention in severe anxiety disorders could have beneficial effects on the clinical management of depression.

We report three main findings. First, the adjusted IRR for single depressive episodes was 3.0 (95% CI 2.8–3.1) and for recurrent depressive disorder was 5.0 (4.8–5.2) in patients with severe anxiety compared with the general population. Consistent with previous studies,¹⁶ we identified evidence that rate ratio in patients with severe anxiety was higher for recurrent depressive disorder than for single depressive episodes. Second, we noted that anxiety disorders increased the risk of readmission for depression, which is in line with previous results.¹⁷ Comorbid conditions are widely acknowledged to worsen the course of depression. In this study, we showed that the worsening of depression seemed specific to comorbid anxiety disorders because comorbidity with other psychiatric disorders, such as attention deficit hyperactivity disorder, autism, schizophrenia, or anorexia nervosa, did not increase the transition and readmission risk. Third, with the exception of specific phobia, the

offspring's risk of development of depression was increased for parents with anxiety disorders.

To account for the heterogeneity of anxiety disorders, we individually assessed the effect of eight specific anxiety disorders on risk of first admission and readmission for depression. We noted a difference in the specific anxiety disorders increasing the risk of single depressive episodes and recurrent depressive disorder. Although stress-related anxiety disorders, such as post-traumatic stress disorder and acute stress reaction, increased the risk of single depressive episodes more than anxiety disorders in general, panic disorder, social phobia, generalised anxiety disorder, and obsessive-compulsive disorder increased the risk of recurrent depressive disorder. Specific anxiety disorders were further identified to have different effects on the course of depression. Generalised anxiety disorder was the specific anxiety disorder consistently associated with an adverse course of depression; beside panic disorder, generalised anxiety disorder increased the transition risk more than anxiety disorders in general and it also increased the readmission risk of patients with recurrent depressive disorder. In line with our findings, generalised anxiety disorder has previously been reported to be associated with increased persistence or recurrence of depression.¹⁸

In this study, we further explored effects of multi-comorbidity of anxiety disorders. Patients with several anxiety disorders were identified to be at an increased risk of recurrent depressive disorder and transition to recurrent depressive disorder compared with patients with a single anxiety diagnosis; however, their risk of development of a single depressive episode or of readmission with recurrent depressive disorder was not increased. Several anxiety disorders might accordingly serve as a marker for the subsequent development of recurrent depressive disorder. The results are likely to show the higher comorbidity rates reported in recurrent long-term depression.^{19,20}

Our results support a clinical staging model in which depressive symptoms might increase over time and eventually result in episodic or recurrent forms of depression, with specific anxiety disorders distinctively affecting this staging progress. On the basis of the current clinical stage (single depressive episode or recurrent depressive disorder), different specific anxiety disorders were identified to be indicative of a worsening course of depression. Although more research is needed to unravel the underlying mechanisms, our findings are intriguing because they suggest that the effect of specific anxiety disorders depends on the stage of depression. This theory underlines the importance of staging models for clinical practice because it suggests that taking the actual clinical state of patients into account can optimise prognosis.

In cross-generational analyses, the adjusted IRRs of single depressive episodes and recurrent depressive disorder in offspring of patients with severe anxiety disorders compared with the general population were 1.9 (95% CI 1.8–2.0) and 2.1 (1.9–2.2). A broad range of specific anxiety disorders was associated with an increased risk of depression in offspring. Parental specific anxiety disorders were identified to increase the offspring's transition and readmission risk. In line with previous studies,^{9,21–23} these results provide further evidence for a shared genetic susceptibility of depression and a wide spectrum of anxiety disorders.

Additionally, we noted a significant interaction of individual and parental psychopathology with the risk of single depressive episodes and recurrent depressive disorder. Patients with severe anxiety disorders and a family history of psychiatric disorders were identified to be at lower risk of depression than what would have been expected by multiplying the main effects. This negative interaction might be explained by the fact that both factors increase the risk by common pathological mechanisms, such as genetic susceptibility. However, a study²⁴ showed that children of mothers with depression in child care were identified to have fewer internalisation problems (eg, emotional problems, separation anxiety, and social withdrawal) than children of mothers with depression in maternal care, suggesting effects beyond pure genetics. Several studies suggest shared environmental risk factors of depression and anxiety disorders such as stress,^{25,26} traumatic events,^{26,27} and parental loss and divorce.^{26,27} Patients with anxiety disorders and depression were further reported to share personality traits, such as neuroticism, worry sensitivity, and rumination.^{25,28}

The different effects of specific anxiety disorders on the risk of depression and the course of the disorder could allow the identification of individuals at high risk of depression who might benefit from closer monitoring, consultation with liaison psychiatrists, and more intensive treatments. Anxious depression has previously been reported to be associated with poorer outcomes after antidepressant treatment,²⁹ which marks the need for treatment more specifically tailored to target this challenging form of depression.³⁰ Our results also underline the potential of prevention in patients with anxiety disorders, which has scarcely been emphasised so far.

Our study benefits from a longitudinal design and use of population-based nationwide registers in Denmark. Register linkage enabled us to minimise probable selection or recall bias effects as all exposures were recorded independently of the outcome. This study has two main limitations. First, we used patient registers to identify inpatients and outpatients with depression and anxiety. Although the prevalence of depression on the basis of Danish registers² is similar to other population-based studies³¹ and the diagnoses are of sufficient precision (>75%),³² the validity of the diagnoses is highest for severe and moderate types of depression and decreases for mild depression.³² Before our study, we aimed to validate the register-based anxiety diagnoses using familiarity as an indicator of nosology. The familial risk reported for the register-based anxiety diagnoses was very similar to that of other studies, including community-based and clinical samples^{33–40} (appendix). The accuracy of specific anxiety disorders in the Danish Register can therefore be assumed to be satisfactory. However both register-based anxiety and depression diagnoses are likely to echo the fact that the patient registers record contacts with clinics and psychiatric outpatient services, but not contacts with general practitioners. We might be missing a proportion of patients with milder symptoms who do not present to secondary care. Thus, the generalisability to milder forms of depression and anxiety is uncertain. Furthermore, many patients with anxiety disorders and depression tend not to contact the health-care sector, particularly psychiatric services. However, the sample identified in the study contains individuals who access services and, therefore, those to whom interventions could potentially be provided. The design further enabled us to study rare cases of severe anxiety needing inpatient treatment. Another major limitation is that when treatment contact occurs—if at all—it is often delayed in most affected individuals. Individuals not yet diagnosed with depression might have displayed

non-specific psychiatric symptoms, resulting in probable misclassification, which might have caused bias. Similar to what we identified, an increase in the risk of developing depression, even many years after being diagnosed with a specific anxiety disorder, is unlikely to be due to coexisting undetected depression alone.

The diagnostic classification of anxiety disorders has endured several substantial modifications in the past decades. To ensure the homogeneity of the diagnoses, we decided to focus on anxiety disorders coded according to the ICD-10, which only allowed us to capture anxiety disorders diagnosed since 1994. This might have affected the estimates' accuracy; however, restriction of all parental diagnoses to ICD-10 did not alter results. Overall, parental diagnoses are not wholly captured because psychiatric diagnoses have only been registered since 1970. Finally, the control participants in our sample might include people with other mental health problems but no diagnoses of specific anxiety disorders. Therefore, our findings might be conservative estimates because other mental disorders are associated with depression.

In summary, severe anxiety disorders are associated with a substantially increased risk of single depressive episodes, recurrent depressive disorder, and adverse course of depression. The effect of comorbid anxiety on the course of depression was identified to depend on the specific anxiety diagnosis and the clinical stage of depression. These findings could allow the identification of patients at high risk of depression but also suggest that people at high risk of developing depression could benefit from interventions that reduce anxiety. Additional research is needed to identify the mechanisms whereby severe anxiety increases the risk of depression and whether specific prevention efforts are possible to block the emergence of depression in those at increased risk (panel).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Panel: Research in context**Systematic review**

The risk of subsequent depression in patients with anxiety disorders is high. However, to what extent specific anxiety disorders distinctively affect the manifestation and outcome of depression is not clear. We searched PubMed for published articles, using combinations of terms that included “depressi*”, “prognosis”, and “outcome”. We did not use any language or date restrictions. We identified that most previous studies of the continuity of anxiety to depressive disorders have been based on the recall of patients diagnosed with depression. A few prospective studies assessed the risk of depression and adverse outcome in patients with anxiety disorders but did not specifically assess the distinctive effect of specific anxiety diagnoses.^{5,6,9,17,18,41–43} How the risk further depends on the current stage of depression, parental psychopathology, and multicomorbidity of anxiety disorders has been largely neglected.

Interpretation

Our study confirms that patients with severe anxiety disorders are at an increased risk of depression. An increased risk of depression and adverse outcomes was reported across generations in offspring of patients with severe anxiety disorders. Individual specific anxiety disorders were identified to differentially increase the risk to single depressive episodes, recurrent depressive disorder, and adverse course of depression, whereas the effect of specific anxiety disorders was identified to depend on the clinical stage of depression. Generalised anxiety disorder, panic disorder, and acute stress reaction specifically increased the transition and readmission risk of recurrent depressive disorder. Patients with several anxiety disorders were at an increased risk of recurrent depressive disorder and transition to recurrent depressive disorder compared with patients with a single anxiety diagnosis but not at an increased risk of single depressive episodes or of readmission with recurrent depressive disorder. The effects of individual psychopathology on depression susceptibility were moderated by parental factors, with the highest risk reported in patients diagnosed with anxiety disorders and a family history of psychiatric disorders. These findings raise the possibility of identification of individuals at high risk of depression and adverse outcomes who might benefit from closer monitoring, consultation with liaison psychiatry, and more intensive treatments.

Figure.

Incidence rate ratios with 95% CIs (error bars) of single depressive episodes and recurrent depressive disorder in offspring of parents with different diagnoses in a cohort restricted to parents born in Denmark between 1994 and 2012

Table 1
Incidence rate ratios of single and recurrent depressive episodes associated with anxiety diagnoses (1994–2012)

Cases	First adjustment [*]		Second adjustment [†]		Third adjustment [‡]	
	Incidence rate ratio	p value	Incidence rate ratio	p value	Incidence rate ratio	p value
Single depressive episodes associated with anxiety diagnoses						
Acute stress reaction	1160	3.5 (3.3–3.7) [§]	<0.0001	3.4 (3.1–3.5) [§]	<0.0001	1.4 (1.3–1.5) [§]
Agoraphobia	180	2.1 (1.8–2.4)	<0.0001	1.2 (1.0–1.4) [§]	0.0218	0.8 (0.7–0.9)
Generalised anxiety disorder	387	2.8 (2.6–3.1) [§]	<0.0001	1.8 (1.6–2.0) [§]	<0.0001	1.1 (1.0–1.2)
Obsessive–compulsive disorder	589	2.2 (2.1–2.4) [§]	<0.0001	2.1 (1.9–2.2) [§]	<0.0001	0.8 (0.7–0.9)
Panic disorder	670	2.9 (2.7–3.1) [§]	<0.0001	2.2 (2.1–2.4) [§]	<0.0001	1.1 (1.0–1.2)
Post-traumatic stress disorder	376	3.3 (3.0–3.6) [§]	<0.0001	2.5 (2.3–2.8) [§]	<0.0001	1.2 (1.1–1.4) [§]
Social phobias	322	2.1 (1.9–2.4) [§]	<0.0001	1.5 (1.4–1.7) [§]	<0.0001	0.8 (0.7–0.9)
Specific phobias	112	1.6 (1.3–1.9) [§]	<0.0001	1.2 (1.0–1.4)	0.0609	0.6 (0.5–0.7)
Recurrent depressive disorder associated with anxiety diagnoses						
Acute stress reaction	896	4.0 (3.7–4.3) [§]	<0.0001	3.2 (3.0–3.4) [§]	<0.0001	0.9 (0.9–1.0)
Agoraphobia	269	4.2 (3.7–4.7) [§]	<0.0001	1.6 (1.4–1.8) [§]	<0.0001	1.1 (0.9–1.2)
Generalised anxiety disorder	537	5.2 (4.8–5.7) [§]	<0.0001	2.2 (2.0–2.4) [§]	<0.0001	1.3 (1.2–1.5) [§]
Obsessive–compulsive disorder	629	4.4 (4.1–4.8) [§]	<0.0001	3.0 (2.8–3.2) [§]	<0.0001	1.1 (1.0–1.2)
Panic disorder	770	4.6 (4.2–4.9) [§]	<0.0001	2.4 (2.2–2.6) [§]	<0.0001	1.1 (1.0–1.2) [§]
Post-traumatic stress disorder	330	4.0 (3.6–4.4) [§]	<0.0001	2.3 (2.0–2.6) [§]	<0.0001	1.0 (0.9–1.1)
Social phobias	539	5.4 (4.9–5.9) [§]	<0.0001	2.7 (2.4–2.9) [§]	<0.0001	1.4 (1.3–1.5) [§]
Specific phobias	135	2.7 (2.3–3.2) [§]	<0.0001	1.5 (1.3–1.8) [§]	<0.0001	0.6 (0.5–0.8)
Transition to recurrent depressive disorder associated with anxiety diagnoses						
Acute stress reaction	432	1.2 (1.1–1.3) [§]	0.0002	1.2 (1.1–1.3) [§]	0.0015	1.1 (1.0–1.2)
Agoraphobia	147	1.2 (1.0–1.4)	0.0344	1.1 (0.9–1.3)	0.4073	1.1 (0.9–1.3)

Cases	First adjustment [*]		Second adjustment [†]		Third adjustment [‡]	
	Incidence rate ratio	p value	Incidence rate ratio	p value	Incidence rate ratio	p value
Generalised anxiety disorder	282 1.3 (1.1–1.5) [§]	<0.0001	1.2 (1.1–1.4) [§]	0.0007	1.2 (1.1–1.4) [§]	0.0014
Obsessive compulsive disorder	298 1.2 (1.0–1.3)	0.0599	1.1 (1.0–1.2)	0.3033	1.1 (0.9–1.2)	0.9821
Panic disorder	401 1.2 (1.1–1.4) [§]	<0.0001	1.2 (1.1–1.3) [§]	0.0027	1.1 (1.0–1.3) [§]	0.0058
Post-traumatic stress disorder	173 0.9 (0.8–1.1)	0.5085	0.9 (0.8–1.1)	0.2006	0.8 (0.7–1.0)	0.0234
Social phobias	263 1.1 (1.0–1.3)	0.0238	1.1 (0.9–1.2)	0.3194	1.1 (0.9–1.2)	0.5670
Specific phobias	60 1.3 (1.0–1.6)	0.0752	1.2 (0.9–1.5)	0.2570	1.1 (0.9–1.5)	0.3156
Readmission for recurrent depressive disorder associated with anxiety diagnoses						
Acute stress reaction	331 1.2 (1.1–1.4) [§]	0.0010	1.2 (1.0–1.3) [§]	0.0053	1.2 (1.0–1.3)	0.0138
Agoraphobia	126 0.9 (0.8–1.1)	0.2526	0.8 (0.7–1.0)	0.0590	0.8 (0.7–1.0)	0.0515
Generalised anxiety disorder	294 1.2 (1.1–1.4) [§]	0.0027	1.2 (1.0–1.3) [§]	0.0057	1.2 (1.0–1.3)	0.0328
Obsessive compulsive disorder	236 1.0 (0.9–1.1)	0.9585	1.0 (0.8–1.1)	0.5991	0.9 (0.8–1.1)	0.3205
Panic disorder	330 1.0 (0.9–1.2)	0.4678	1.0 (0.9–1.1)	0.9060	1.0 (0.9–1.1)	0.6388
Post-traumatic stress disorder	144 1.1 (0.9–1.3)	0.3155	1.0 (0.9–1.2)	0.5231	1.0 (0.9–1.2)	0.7743
Social phobias	266 1.0 (0.9–1.2)	0.4795	1.0 (0.9–1.2)	0.6493	1.0 (0.9–1.1)	0.7420
Specific phobias	52 1.0 (0.7–1.4)	0.7933	1.0 (0.8–1.3)	0.9967	1.0 (0.7–1.3)	0.8567

Data are incidence rate ratio (95% CI).

^{*} Incidence rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, psychiatric family history, place of residence at time of birth, and the interaction of age with sex.

[†] Incidence rate ratios were derived from multivariate analysis and adjusted for calendar year, age, maternal and paternal age, sex, psychiatric family history, first hospital contact due to any other psychiatric disorder, place of residence at time of birth, and the interaction of age with sex.

[‡] Incidence rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, psychiatric family history, first psychiatric hospital contact due to any specific anxiety disorder, place of residence at time of birth, and the interaction of age with sex.

[§] Significant after Bonferroni correction.

Incidence rate ratio of single depressive episodes and recurrent depressive disorder in off spring of parents with various psychiatric diagnoses (1994–2012)

Table 2

	Single depressive episodes			Recurrent depressive disorder		
	Cases	Incidence rate ratio	p value	Cases	Incidence rate ratio	p value
Acute stress reaction						
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..
Maternal	314	1.9 (1.7–2.1)*	<0.0001	146	1.9 (1.6–2.2)*	<0.0001
Paternal	178	1.6 (1.4–1.9)*	<0.0001	89	1.8 (1.5–2.2)*	<0.0001
Parental	490	2.0 (1.8–2.2)*	<0.0001	230	2.0 (1.7–2.3)*	<0.0001
Agoraphobia						
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..
Maternal	136	2.5 (2.1–2.9)*	<0.0001	65	2.5 (2.0–3.2)*	<0.0001
Paternal	33	2.5 (1.7–3.4)*	<0.0001	34	2.6 (1.5–4.1)*	0.0009
Parental	169	2.6 (2.2–3.0)*	<0.0001	99	2.7 (2.2–3.4)*	<0.0001
Generalised anxiety disorder						
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..
Maternal	191	1.8 (1.5–2.0)*	<0.0001	114	2.0 (1.7–2.4)*	<0.0001
Paternal	74	1.9 (1.5–2.4)*	<0.0001	49	2.5 (1.9–3.3)*	<0.0001
Parental	264	1.9 (1.7–2.1)*	<0.0001	163	2.3 (2.0–2.7)*	<0.0001
Obsessive-compulsive disorder						
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..
Maternal	65	1.9 (1.5–2.4)*	<0.0001	35	2.3 (1.6–3.1)*	0.0002
Paternal	29	1.8 (1.2–2.5)*	0.0044	18	2.4 (1.5–3.7)*	0.0011
Parental	94	2.0 (1.6–2.4)*	<0.0001	53	2.5 (1.9–3.2)*	<0.0001

Single depressive episodes				Recurrent depressive disorder			
Cases	Incidence rate ratio	p value		Cases	Incidence rate ratio	p value	
Panic disorder							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	259	1.9 (1.7–2.2) *	<0.0001	125	2.0 (1.6–2.3) *	<0.0001	
Paternal	111	2.0 (1.7–2.4) *	<0.0001	45	1.8 (1.3–2.4) *	0.0003	
Parental	368	2.1 (1.9–2.3) *	<0.0001	170	2.1 (1.8–2.4) *	<0.0001	
Post-traumatic stress disorder							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	132	1.7 (1.4–2.0) *	<0.0001	72	2.0 (1.6–2.5) *	<0.0001	
Paternal	89	1.5 (1.2–1.8) *	0.0008	26	1.4 (1.0–1.9)	0.0681	
Parental	219	1.7 (1.5–1.9) *	<0.0001	88	1.9 (1.6–2.3) *	<0.0001	
Social phobia							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	100	2.4 (2.0–2.9) *	<0.0001	54	2.8 (2.1–3.6) *	<0.0001	
Paternal	32	1.5 (1.0–2.1)	0.0303	15	1.6 (0.9–2.5)	0.1042	
Parental	132	2.2 (1.9–2.6) *	<0.0001	69	2.6 (2.0–3.2) *	<0.0001	
Specific phobia							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	36	1.1 (0.8–1.5)	0.5784	10	0.9 (0.4–1.6)	0.7119	
Paternal	9	1.4 (0.7–2.5)	0.3546	7	2.2 (0.9–4.2)	0.0682	
Parental	45	1.2 (0.9–1.6)	0.2221	17	1.2 (0.7–1.9)	0.3560	
Anxiety disorder							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	1010	1.8 (1.7–1.9) *	<0.0001	499	1.9 (1.8–2.1) *	<0.0001	

Single depressive episodes				Recurrent depressive disorder			
	Cases	Incidence rate ratio	p value	Cases	Incidence rate ratio	p value	
Paternal	473	1.7 (1.5–1.8) *	<0.0001	232	1.9 (1.6–2.1) *	<0.0001	
Parental	1453	1.9 (1.8–2.0) *	<0.0001	717	2.1 (1.9–2.2) *	<0.0001	
Depression							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	3764	2.0 (2.0–2.0) *	<0.0001	2331	2.1 (2.0–2.2) *	<0.0001	
Paternal	2408	1.9 (1.8–2.0) *	<0.0001	1556	2.1 (2.0–2.2) *	<0.0001	
Parental	5742	2.1 (2.0–2.1) *	<0.0001	3620	2.2 (2.2–2.3) *	<0.0001	
Other psychiatric diagnosis							
None	42 086	1.0 (reference)	..	21 885	1.0 (reference)	..	
Maternal	5379	1.7 (1.6–1.7) *	<0.0001	2900	1.6 (1.6–1.7) *	<0.0001	
Paternal	5038	1.6 (1.5–1.6) *	<0.0001	2739	1.6 (1.5–1.6) *	<0.0001	
Parental	8289	1.7 (1.6–1.7) *	<0.0001	4541	1.6 (1.6–1.7) *	<0.0001	

Data are incidence rate ratio (95% CI). Maternal or paternal diagnoses were categorised hierarchically as having a history of specific anxiety disorders, depression, or other psychiatric disorders. Incidence rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, and the interaction of age with sex.

* Significant after Bonferroni correction. The number of parental cases might be slightly lower than the sum of maternal and paternal cases because if both parents had an anxiety disorder, this was recorded only once in the parental category.