

**Prenatal stress as a risk factor for depression and commonly comorbid anxiety symptoms
in offspring of depressed and/or anxious patients**

Abstract

Depression is among the top ten diseases for disease burden worldwide. A multitude of risk factors are implicated in its etiology, with having a depressed and/or anxious parent being a substantial one. Mounting evidence demonstrates that certain risk factors are differentially linked to individual depressive symptoms. Maternal prenatal stress is one established risk factor for offspring depression which has not been studied in this context. The current cross-sectional study examines whether offspring differ in number of reported depressive and commonly comorbid anxiety symptoms and in particular reported symptoms, based on the presence of maternal prenatal stress (life stressors) and gender. A high-risk sample of offspring ($n = 510$; age: 16-25 years) of patients who had received specialized treatment for depression and/or anxiety was used. Kruskal-Wallis tests showed that prenatal stress was not significantly linked to symptom count ($p = .11$). Binary logistic regressions indicated that the presence of prenatal stress was significantly associated with early night insomnia (OR = 1.94, 95% CI 1.03 – 3.63). The associations with the remaining symptoms did not reach significance but varied markedly in terms of magnitude (ranging from OR = 0.59 to OR = 1.94). All results were consistent across boys and girls. The current study showed that prenatal life stressors do not contribute to the risk of depression and anxiety in a highly vulnerable sample of offspring of depressed/anxious parents. Preliminary evidence for differential associations between prenatal stress and individual symptoms calls for more prospective investigations and a symptom-specific approach in research.

Introduction

Major depression is a serious mental disorder that may negatively affect an individual's emotional, neurovegetative and neurocognitive functioning (Malhi & Mann, 2018). It ranks among the most common forms of psychopathology, with a lifetime risk of about 15-18% (Bromet et al., 2011). Depression is highly recurrent, as an alarming 50% of individuals relapse after an initial episode (Eaton et al., 1997; Eaton et al., 2008). The mean number of depression episodes per affected individual are four, lasting between 14 and 23 weeks depending on the episode's severity (Kessler et al., 2003). Notably, nearly 40% of first episodes occur before sufferers have turned 20 years (Moffitt et al., 2010). Despite this, depression often remains undiagnosed in adolescence and the longer it goes untreated, the less favorable its clinical course is (Fletcher, 2008). Globally, depression was among the top ten diseases for disease burden at the beginning of the decade (Lopez et al., 2006) and the World Health Organization (WHO) predicted that it would rank first in the list by 2030 (World Health Organization [WHO], 2008, p.50). These findings emphasize depression's deleterious effects and call for a nuanced understanding of etiological mechanisms and risk factors that would inform clinical practice as well as efficient and timely preventive strategies.

Intergenerational transmission of depression

A substantial risk factor for depression is being the child of a depressed and/or anxious parent. A recent paper, using data from the prospective cohort study ARIADNE (Adolescents at Risk of Anxiety and Depression; A combined Neurobiological and Epidemiological approach), reported that 60-70% of offspring of Dutch patients in treatment for depression and anxiety developed depression and/or an anxiety disorder at some point in their life - a percentage that is two to three times higher compared to the offspring of non-depressed/anxious individuals (Havinga et al., 2017). The risk of becoming depressed remains high in a sample of depressed parents' offspring that were followed up for up to 38 years (Weissman et al., 2021). Furthermore, children

of depressed patients are more likely to become depressed at an earlier age and have a worse prognosis of the disease than peers whose parents have not been depressed (Hirshfeld-Becker et al., 2012; Weissman et al., 2016). Family history of major depression is also associated with younger age of onset among individuals with recurrent depressive episodes (Tozzi et al., 2008). Recent research has demonstrated that the magnitude of offspring's risk of becoming depressed differs across individuals based on factors such as parental psychiatric characteristics, offspring's gender, and family functioning (Havenga et al., 2017). Knowledge that such risk factors are present can point to affected individuals as targets for prevention.

Maternal prenatal stress and risk for offspring depression

Maternal prenatal stress is a well-known risk factor for various unfavorable developmental outcomes for offspring of prenatally stressed mothers, with mounting evidence pointing at depression as one such outcome (e.g. Huizink & Rooij, 2018; Betts et al., 2015; Pawlby et al., 2009). Prenatal stress is defined as maternal exposure to events that cause feelings of stress or physiological stress responses during pregnancy (Huizink & Rooij, 2018). In research concerning the relationship between prenatal stress and affective disorders, this definition encompasses exposure to a broad array of distressing events, such as war (Kleinhaus et al., 2013), bereavement (Khashan et al., 2011), under- or malnutrition, maternal exposure to toxins, psychological distress (Braithwaite, Murphy & Ramchandani, 2014), maternal depression (e.g. Pawlby et al., 2009; Pearson et al., 2013; Betts et al., 2015), life stressors (Khashan et al., 2011; Kingsbury et al., 2016; Maxwell et al., 2018), and more. In addition, there is evidence on a relationship between prenatal stress and childhood outcomes linked to or preceding depression. For instance, maternal anxiety and depression during pregnancy were associated with increased emotional and behavioral problems in early childhood (O'Connor et al., 2002). Additionally, maternal depressive, anxious and stress symptoms predicted internalizing behavior problems in offspring in adolescence and

adulthood (Betts et al., 2014; Betts et al., 2015). Furthermore, there is a well-documented relationship between prenatal stress and offspring temperamental traits and constellations, such as inhibited temperament, fearful temperament, and negative affectivity and difficult temperament (Talge et al., 2007; Sandman et al., 2013; Van den Bergh, 2020). Notably, recent research has demonstrated that temperament is predictive of an elevated frequency of major depression episodes and that parental depression is a moderator of the relationship between offspring temperament and severity of the depression episodes (Sherman et al., 2016). The aforementioned findings predominantly come from community-based birth cohort studies and research exploring these relationships in high-risk samples, such as the offspring of depressed parents, is lacking.

Variability in clinical presentations of depression and associated risk factors

Another line of scientific investigation links the presence of some risk factors to the etiology of particular phenotypes of depression. Increasing evidence reveals significant interpersonal variability in clinical presentations of common disorders like depression (Nandi, Beard, & Galea, 2009). In one study, authors identified 1030 symptom profiles of depression among 3703 diagnosed individuals, with the most common symptom profile being attributable to less than 2% of all individuals (Fried & Nesse, 2015a). Research exploring the sources of this variability pin points that individual symptoms of depression are differentially related to a variety of clinical validators (Fried & Nesse, 2015b). Correspondingly, a study demonstrated that depressed adolescents differed in their symptoms, based on the type of childhood abuse they had experienced (Danielson et al., 2005). Distinct patterns of depressive symptoms were also linked to the experience of different kinds of challenging life events (Keller & Nesse, 2006; Keller, Neale & Kendler, 2007). Other authors discovered varying relationships of individual depressive symptoms with demographic factors, comorbid disorders, features of the depressive episode and personality traits, with part of the variability explained by the distinction between cognitive and neurovegetative symptoms (Lux

& Kendler, 2010). Furthermore, depression history, gender, number of stressful life events and childhood stress were found to predict increases in specific depressive symptoms (Fried et al., 2014). This line of research is still in its infancy and many known risk factors for depression are yet to be investigated in this context, prenatal stress being one of them.

Collectively, the foregoing findings can be the basis for exploring a putative relationship between the experience of prenatal stress and particular patterns of predisposing factors or symptoms of depression. Since the presence of particular depressive symptoms can be used to inform treatment choice and predict treatment response, further elucidating which risk factors are linked to which phenotypes can bear immense practical significance (Fried et al., 2014). Prenatal stress is a risk factor which has not yet been studied in relation to individual depressive symptoms, however, it has been linked to factors that can be implicated in individuals' susceptibility to depression, and in the course and severity of depression. Additionally, information about maternal antenatal experiences of life stressors, namely emotional and interpersonal problems like unwanted pregnancy, divorce, family environment, problems at work, can be easy to obtain in everyday clinical practice and as such, can support early recognition of vulnerable individuals with the goal of providing subsequent appropriate prevention. Notably, studying the potential relationship between prenatal stressors and depression and prenatal stressors and patterns of depressive symptoms in a high-risk sample, such as the offspring of depressed parents, is of value for several reasons. Firstly, no previous studies have thus far explored whether prenatal stressors are associated with depression in offspring exposed to the prominent risk factor of parental depression. Second, these offspring are a vulnerable population and moreover, one that can be readily identified by mental health professionals treating the depressed parent(s). Therefore, this offspring group undoubtedly represents an important and accessible target for prevention programs. Lastly, exploring putative mechanisms in a high-risk sample offers methodological advantages such as a

higher prevalence of affected individuals as well as more variation in risk factors, severity and clinical presentations of depression than could be expected in general population samples.

Present study aims and hypotheses

To the end of examining the association between maternal prenatal stress and clinical presentations of depression, a cross-sectional investigation was conducted using data from the ARIADNE project. ARIADNE is an observational cohort study including 522 offspring of parents who had been treated for depressive and/or anxiety disorders in psychiatric services in the Northern Netherlands. Given the substantial overlap between depression and anxiety in general (e.g., Jacobi et al., 2004; Lamers et al., 2011), and in this particular sample (Landman-Peeters, 2007), we decided to include three prominent anxiety symptoms next to 12 depression symptoms. Thus, the following research questions were addressed: 1) is prenatal stress, in the form of emotional and interpersonal stressors, associated with the number of reported depressive and commonly comorbid anxiety symptoms in the offspring of affected mothers, 2) is the presence of emotional and interpersonal stressors during the antenatal period linked to specific symptoms of depression and anxiety? It was hypothesized that 1) the presence of prenatal stress is associated with an increased number of symptoms and that 2) prenatal stress is differentially related to individual symptoms. Given that there are established gender differences in susceptibility to prenatal stress (Sandman et al. 2013), it was also explored whether prenatal stress' associations with symptom count and individual symptoms differed between girls and boys.

Methods

Design and Participants

Data were derived from the baseline assessment of the ARIADNE study (recruitment: 2000-2002), an observational cohort study that included 522 native Dutch offspring (57.3% girls; age range: 16-25 years) of 366 depressed and/or anxious patients. All patients had received

treatment for a depressive (dysthymia, major depressive disorder) and/or an anxiety disorder (obsessive-compulsive disorder, panic disorder with or without agoraphobia) at one of 16 psychiatric services in the north of the Netherlands. Parental diagnoses were established using the Composite International Diagnostic Interview (CIDI) (Kessler & Üstün, 2004). In total, 320 parents had a lifetime depressive disorder (87.4%; 138 with a pure depressive disorder and 182 with a comorbid anxiety disorder) and 207 had a lifetime anxiety disorder (56.6%; 25 with a pure anxiety disorder and 182 with a comorbid depressive disorder). No formal diagnosis was present for 5.5% of the parents. One parent did not meet the CIDI criteria for subclinical depressive and/or anxiety symptoms and for another parent, CIDI information was missing. Parents with a history of schizophrenia, schizoaffective disorder and/or post-traumatic stress disorder were excluded from this study. More information on ARIADNE's design and recruitment procedure are presented in Figure 1, adapted from Landman-Peeters (2007).

Comprehensive face-to-face assessments, including the CIDI, were conducted for parents and their offspring. Parents were administered self-report questionnaires collecting data on demographics, pregnancy and birth, events and behavior in the different stages of life of offspring, offspring health history, and offspring symptoms and dispositions. Offspring completed self-report questionnaires assessing a range of DSM-IV symptoms, temperament, social support, coping, family functioning and parent-adolescent communication, as well as the DSM-IV Questionnaire (Hartman et al., 2001). The current study selected those offspring with complete baseline data on key variables (N = 510) and focused on the cross-sectional association of prenatal stress (independent variable) with the number of reported depressive symptoms in offspring (dependent variable). Next, in a set of exploratory analyses, it is also tested whether the presence of prenatal stress (independent variable) is differentially related to individual depressive symptoms (dependent variables).

Ethical approval

ARIADNE received ethical approval by the Medical Ethics Committee of the University Medical Center Groningen. Participants provided written informed consent before participating in the study.

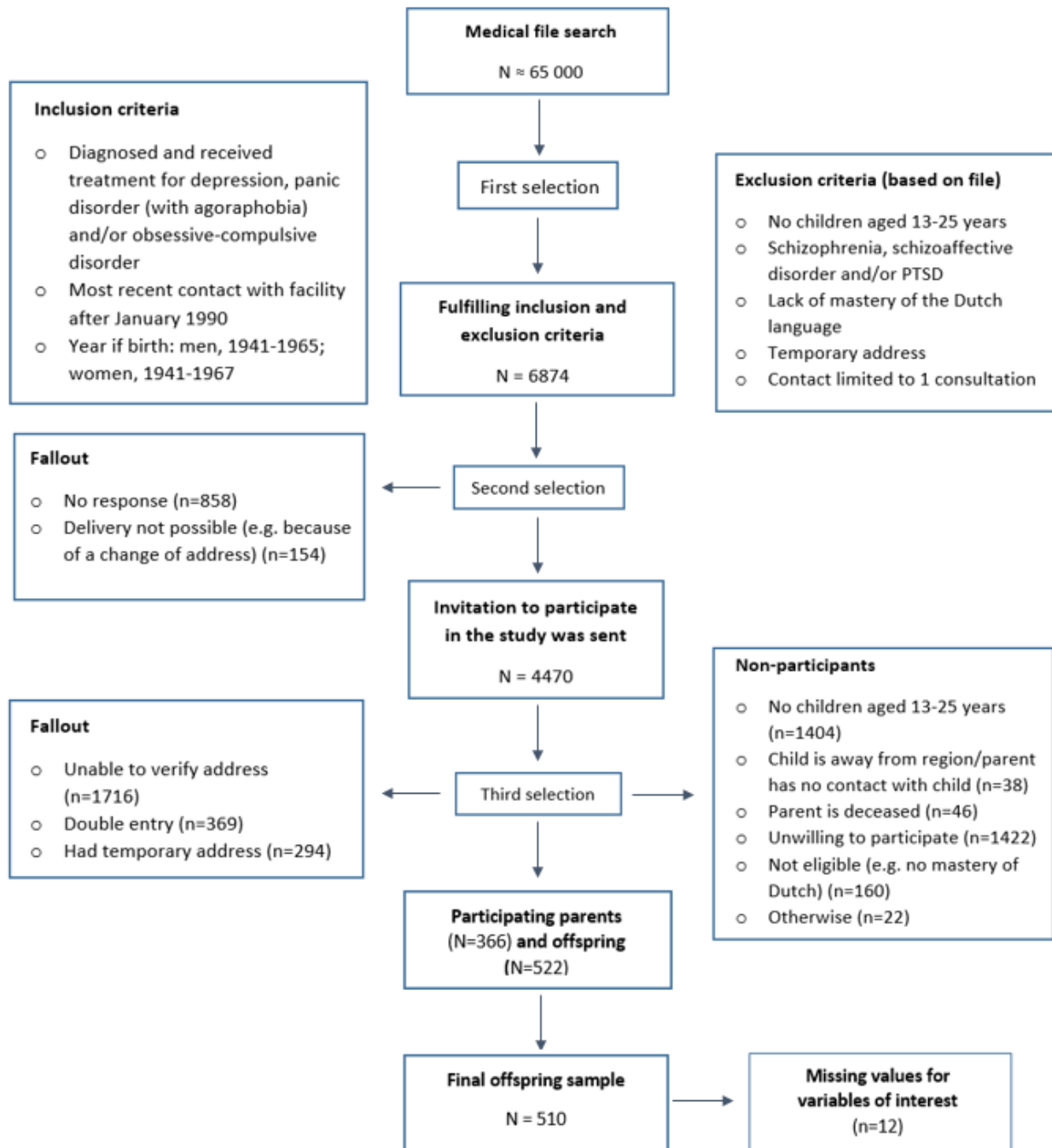


Figure 1 Flowchart of study design and participant selection

Measures

Outcome measures. *Depressive and anxiety symptoms.* Depressive and anxiety symptoms were considered as two different types of measures: a continuous measure indicating the number of reported symptoms (range 0-15) and 15 dichotomous measures, indicating the presence or absence of each individual symptom. The symptoms were measured using the DSM-IV Questionnaire. The depression scale in this questionnaire consists of 14 items, such as “I am often unhappy”, “Even if I didn't like someone, I would feel guilty if I had hurt them”, “I often feel tired”, etc. Three symptoms from the anxiety subset of the questionnaire were also included. Participants used a 4-point Likert-scale to rate to what extent the descriptions in the items applied to their behavior in the preceding 12 months and at the time of measurement, and their answers were subsequently dichotomized into the categories “present” and “absent”. The 15 individual symptoms measured by the DSM-IV Questionnaire were: 1) feeling sad, 2) feeling hopeless, 3) feeling worthless, 4) feeling guilty, 5) lack of energy or tiredness, 6) anhedonia, 7) psychomotor retardation, 8) suicidality, 9) early night insomnia, 10) late night insomnia, 11) sleep disturbance, 12) excessive worry, 13) feeling tense, 14) panic, and 15) indecisiveness. The DSM-IV Questionnaire has acceptable psychometric properties (Hartman et al., 2001), which was also confirmed in the present sample by a good Cronbach’s alpha ($\alpha = .86$). It also has the advantage of capturing clinical as well as subclinical levels of symptomatology.

Exposure variables. *Gender.* Gender of offspring was included in the analyses as female offspring have been shown to be more vulnerable to depression by previous research on the ARIADNE sample (Havinga et al., 2017).

Maternal prenatal stress. Maternal prenatal stress was measured by asking the index parent the question “Were there important stressful life events during pregnancy?”. There were two answer possibilities: “no” and “yes”, with “yes” followed by the options: 1) relationship problems,

2) divorce, 3) unwanted pregnancy, 4) problems with living situation, 5) moving houses, 6) financial problems, 7) work problems, 8) problems with family, 9) death of a family member and/or friend, and 10) a blank option to fill in “other” events that have occurred. Prenatal stress was used as a binary variable in all analyses.

Statistical analyses

The IBM SPSS Statistics software, version 28 was used. Initially, the data set was inspected for missing values and outliers, and those were removed. All statistical analyses were performed solely for offspring for whom full and valid responses to all relevant questions were provided. Next, data were explored to determine whether the core assumptions required for the performance of each selected analysis were met.

Initially, 2-way ANOVA with prenatal stress and gender as independent variables and the number of depressive and anxiety symptoms as the dependent variable was selected. However, data on number of reported symptoms did not meet the assumption of normality required for conducting 2-way ANOVA, as indicated by Shapiro-Wilk tests performed for the two independent variables offspring gender, $W(216) = 0.96, p < .001$, and prenatal stress, $W(373) = 0.94, p < .001$. Owing to this violated assumption, three Kruskal-Wallis tests were used to examine the relationship of prenatal stress with number of depressive and anxiety symptoms. First, the association was tested in the entire sample and next, two tests were performed in the subsamples of girls and boys.

Second, 15 binary logistic regressions were carried out to explore the associations of prenatal stress with individual depressive and anxiety symptoms. Prenatal stress was the independent variable and each of the symptoms were the dependent variables. Gender-interaction terms were added to the 15 regression analyses to determine whether the associations differed between girls and boys.

Results

Sample characteristics

Table 1 summarizes baseline characteristics of the 510 included offspring, of whom 68.6% had a mother receiving treatment for depression and/or anxiety (i.e., index parent in ARIADNE). Presence of any prenatal stressor was reported for mothers of 26.9% offspring, of which relationship problems (6.1%), moving houses (6.3%) and the answer “other” (8.7%) were the most commonly reported stressors. The majority of offspring (91.4%) reported at least one depressive or anxiety symptom, and the most common symptoms were excessive worry (75.1%), and feeling guilty (57.6%).

Association of prenatal stress with the number of symptoms

Table 2 depicts the results of the Kruskal-Wallis tests relating prenatal stress to the number of reported depression and anxiety symptoms in offspring. The analysis revealed a trend for offspring affected by prenatal stress to report more depression and anxiety symptoms, $Mdn = 6$, than those who had not been affected, $Mdn = 5$. However, contrary to our expectations, the association did not reach significance, $H(1) = 2.53, p = .11$. With offspring stratified by gender, the Kruskal-Wallis tests showed that prenatal stress was not significantly associated with the number of reported symptoms in girls, $H(1) = 2.01, p = .16$, nor boys, $H(1) = .55, p = .46$. Thus, there was no interaction effect between prenatal stress and gender.

Table 1 Descriptive statistics

	Mean (SD) / N (%)
Offspring sociodemographics	
Female gender	294 (57.6%)
Age in years	18.0 (3.2)
Prenatal stressors	
Presence of any prenatal stressor	137 (26.9%)
- Relationship problems	31 (6.1%)
- Divorce	1 (0.2%)
- Unwanted pregnancy	3 (0.6%)
- Living situation problems	9 (1.8%)
- Moving houses	32 (6.3%)
- Financial problems	12 (2.4%)
- Work problems	2 (0.4%)
- Family problems	24 (4.7%)
- Death of a loved one	23 (4.5%)
- Other stressors	45 (8.8%)
Depression/anxiety symptoms in offspring	
Number of depression/anxiety symptoms	5.8 (4.1)
- Feeling sad	246 (48.2%)
- Feeling hopeless	155 (30.4%)
- Feeling worthless	179 (35.1%)
- Feeling guilty	294 (57.6%)
- Lack of energy	248 (48.6%)
- Anhedonia	140 (27.5%)
- Psychomotor retardation	186 (36.5%)
- Suicidal thoughts	82 (16.1%)
- Early night insomnia	203 (39.8%)
- Middle night insomnia	107 (21%)
- Sleep disturbances	171 (33.5%)
- Excessive worry	383 (75.1%)
- Feeling tense	179 (35.1%)
- Panic	127 (24.9%)
- Indecisiveness	263 (51.6%)

Note.— SD – Standard deviation

Table 2 Descriptive Statistics for Number of Symptoms per PS group and Gender x PS group				
Group	n	Mean	SD	Mean Rank
Whole sample				
PS	137	6.2	4.0	273
No PS	373	5.7	4.1	249
Females				
PS	81	7.3	4.1	158
No PS	213	6.6	4.2	143
Males				
PS	56	4.7	3.4	114
No PS	160	4.4	3.7	107

Note.— SD = Standard deviation, PS = Prenatal Stress

Association of prenatal stress with specific symptoms of depression and anxiety

The outcomes of the 15 binary logistic regression tests relating prenatal stress to individual symptoms of depression and anxiety are summarized in Figure 2. Prenatal stress was significantly related to an increased risk of one of the symptoms, namely early night insomnia, $Wald = 4.282, p = .04$, with offspring in the prenatal stress group being almost two times more likely to report this symptom, $OR = 1.94$ (95% CI 1.03 – 3.63). The remaining associations between prenatal stress and individual symptoms were insignificant but differed substantially in terms of magnitude. The strongest positive associations were found for feeling guilty, feeling tense and indecisiveness ($OR = 1.52$, $OR = 1.56$ and $OR = 1.64$, respectively), and the strongest negative associations were found for feeling hopeless and feeling sad ($OR = 0.59$ and $OR = 0.77$, respectively). Separate analyses showed that gender-interactions were not significant for any of the symptoms (all p -values $> .05$), indicating that prenatal distress' associations to individual symptoms did not differ between girls and boys.

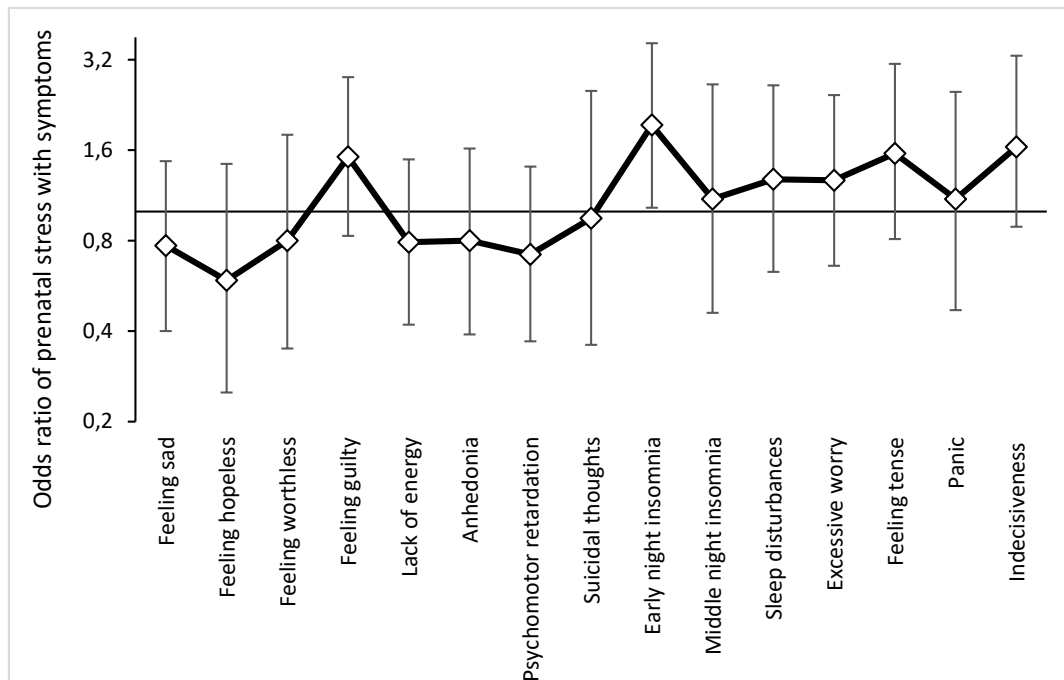


Figure 2 Relationships of prenatal stress with individual symptoms

Discussion

Main findings

The present cross-sectional study was the first to explore whether maternal experience of psychological and interpersonal life stressors during pregnancy was associated with depression and commonly comorbid anxiety symptoms in offspring of depressed and/or anxious parents. Offspring whose mothers had experienced prenatal stress reported more depression and anxiety symptoms than offspring whose mothers had not experienced prenatal stress but, in contrast to our hypothesis, this tendency was not statistically significant. In addition, prenatal stress was not related to any of the individual symptoms of depression and anxiety in offspring, with the exception of one significant but small association with early night insomnia. All findings were consistent in girls and boys.

Comparison with previous studies

Prenatal stress and depression. The current results stand in contrast with the body of literature pinpointing maternal psychological stress during pregnancy as a risk factor for depression in offspring. Most research on prenatal stress and offspring depression applies the concept of prenatal stress to maternal depression and anxiety, or symptoms thereof (e.g., Pawlby et al., 2009; Pearson et al., 2013; Betts et al., 2015). Contrastingly, the present study focused on the experience of life stressors, particularly emotional and interpersonal problems, as a putative risk factor. Few previous studies have examined the influence of life stressors on offspring depression, however, recent well-conducted prospective investigations present findings supporting the existence of such an influence (Khashan et al., 2011; Kingsbury et al., 2016; Maxwell et al., 2018). The question of why no association was revealed by the current investigation arises.

What markedly differentiates the present study from the aforementioned ones is the selected sample. While Khashan et al. (2011), Kingsbury et al. (2016) and Maxwell et al. (2018) found significant effects studying large community-based samples, the current investigation used a comparably smaller and very high-risk sample of offspring whose parents had been treated for anxiety and/or depression. Markers of severity among the participants in the current investigation were considerably elevated, with a mean number of reported depression and anxiety symptoms of 5.8, and nearly all symptoms being reported by at least a third of the participants. Notably, the least frequently reported symptom, namely suicide ideation, was reported by 16.1% of offspring which is about 4 times higher compared to general population rates of 4%-5.6% (Ivey-Stephenson et al., 2022; Kuo, Gallo, & Tien, 2001). It is highly likely that this substantial vulnerability to symptoms is mainly attributable to parental depression and anxiety. It could, thus, be that, life stressors do not confer additional risk in this sample but would in samples where prominent risk factors such as parental depression and anxiety are not present, as shown by previous research (Khashan et al., 2011; Kingsbury et al., 2016; Maxwell et al., 2018).

Furthermore, maternal depression and anxiety in the antenatal period specifically were not accounted for in the current study. Nevertheless, they may have been significant risk factors given the fact that many of the studied offspring's mothers had been treated for these disorders and in the light of research findings (Pawlby et al., 2009; Pearson et al., 2013; Betts et al., 2015). In this sense, prenatal stress could have contributed to an increased risk but in another form, namely as maternal prenatal depression and/or anxiety.

It is also highly plausible that prenatal stressors and maternal prenatal depression and anxiety are related themselves. On one hand, it is conceivable that mothers' assessments of their stress levels during pregnancy would be influenced by factors such as concurrent depression and anxiety (e.g. Hammen, 2006). In the current study, a substantial number, i.e. nearly a third, of depressed and/or anxious index parents reported maternal experience of at least one prenatal stressor. A possibility could be that depression and anxiety during pregnancy increase the chance of a mother experiencing common stressors or increase the mother's susceptibility to these stressors (Hammen, 2006). On the other hand, stress contributes to the onset of psychopathology, such as depression and anxiety (Grant et al., 2014) and research in animals has demonstrated that prenatal stressors in particular predispose mothers to depression and anxiety (Maccari et al., 2003). These links may constitute another pathway via which prenatal stressors, maternal depression and anxiety and offspring depressive and anxiety symptoms are related. The foregoing considerations would be important topics of future investigations.

Prenatal stressors and individual depression and anxiety symptoms. The present study was an initial attempt at testing whether maternal experience of psychological and interpersonal stressors during pregnancy are related to specific symptoms of depression and anxiety. Early night insomnia was the only symptom which prenatal stress was significantly associated with. This finding could be noteworthy given that insomnia and its symptom "difficulty initiating sleep",

especially if experienced at the beginning of the night, are independent prospective predictors of first-onset major depression disorder (Taylor et al., 2005; Boshcloo et al., 2016; Blanken, 2020). Notwithstanding, the finding challenging to interpret in the light of the dearth of literature on maternal prenatal stress and offspring insomnia and sleep overall. Evidence on this topic primarily comes from animal studies, which have been pointing at a cascade of neurological alterations, implicated in circadian rhythms and sleep quality disturbances, in offspring of prenatally stressed mothers (Palagini, Biber, & Riemann, 2014). In humans, one study has found a link between minor psychological stress experienced antenatally and offspring sleep disturbance, independent from postnatal depression (Baird et al., 2009). However, offspring in this study were only followed until infancy. Although studies in mice have suggested that prenatal stress has long term effects on offspring sleep, persisting in adulthood (Yun, Lee, & Choe, 2020), no conclusions can be drawn for humans based on these limited findings. With this in mind, the results of the present study could be interpreted as provisional support for the suggested link between prenatal stress and offspring sleep disturbances, regardless of parental depression and/or anxiety. Much more research in humans is necessary to elucidate which types of prenatal stress influence which types of sleep disturbances, through what mechanisms and what relevance these relationships carry with regards to offspring depression.

The insignificance of the associations between prenatal stress and the remaining symptoms should not serve to discourage future scientific endeavors in the same direction, as a multitude of investigations have demonstrated the importance of a symptom-specific approach in studying and treating depression (Fried & Nesse, 2015b; Boschloo et al., 2016; Bekhuis et al., 2018). The statistical insignificance of the current findings may be referable to the fact that prenatally experienced life stressors were not related to number of symptoms in the present study's high-risk sample. Nevertheless, the observed associations fluctuated notably in terms of strength, with odd

ratios ranging from 0.59 to 1.94. These substantial fluctuations bear practical relevance and tentatively attest to our hypothesis that prenatal stress is differentially linked to depressive/anxiety symptoms.

Suggestions for future research

The current findings highlight the importance of a symptom-specific approach in research (Fried & Nesse, 2015b) and reveal possibilities for subsequent investigation. Future research should undoubtedly detect whether significant associations between life stressors and individual symptoms would emerge in general population samples. Next, it would be important for future studies to examine prenatal stressors and maternal prenatal depression and anxiety prospectively within the same model to explore the relationship between these factors and to disentangle their individual contributions to offspring vulnerability to depression and anxiety as well as to individual depressive and anxiety symptoms. Lastly, among previous prospective studies on the relationship between prenatal life stressors and depression, some highlight particular stressors, e.g. unwanted pregnancy (Maxwell et al., 2018) and bereavement (Khashan et al., 2011) as more influential, whether others consider mothers' sum scores on a life stressor scale (Kingsbury et al., 2016). In this sense, it could be noteworthy to examine the influence both of individual life stressors and of the overall presence of stressors experienced prenatally more extensively in relation to individual symptoms.

Clinical implications

Although statistically insignificant in their majority, the results of this study showed that prenatal stress' relationships to individual symptoms varied substantially in their strength, preliminarily suggesting that prenatal stress is a risk factor which may be linked to certain manifestations of depression more strongly than to others. These findings could hopefully serve mental health professionals as yet another confirmation that depression is not a homogeneous

disorder but that it rather has various clinical presentations linked to the unique cascade of clinical validators relevant for an individual (e.g. Fried & Nesse, 2015b). This information calls for an individualized treatment approach for depressed clients.

Strengths and limitations

Major strengths of this study are the rather large sample size and the sound diagnostic tools used to measure offspring symptoms. However, the study ought to be considered in the light of some important limitations too. First, the current results were obtained using multiple testing and no statistical correction was employed to account for this limitation. It is, therefore, possible that the presented results are a methodological artefact. Second, the cross-sectional design carries downsides. This study was not able to monitor the associations of interest across time and thus, no inferences for causality between prenatal stress and early night insomnia can be made. Also, no insight into potential differences in the associations across offspring developmental periods could be gained. Third, information on prenatal stress relied on retrospective reports which may have potentially produced underestimates in terms of the number of mothers who have experienced prenatal stressors and the experienced stressor count per mother. Furthermore, these data were collected from one of the participating parents, and 31.4% of parents were the fathers. It is highly likely that fathers did not recall or were not acquainted with mothers' experiences fully accurately.

Conclusion

In contrast with previous research, this study offered no evidence for a significant association between maternal experience of life stressors during pregnancy and the number of experienced depression and commonly comorbid anxiety symptoms in the offspring of affected mothers. In addition, prenatal stress was differentially related to one of the individual symptoms, namely early night insomnia. Although there is room for the possibility that this form of prenatal stress is not differentially linked to individual symptoms, prenatal stress' symptom-specific

associations varied widely in their strength and future studies in general population samples are needed. In view of the severe global impact and marked heterogeneity of depression, detailed understanding of risk factors of overall vulnerability and vulnerability to individual symptoms is crucial for appropriately detecting at-risk individuals and intervening in a timely and symptom-specific manner.

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