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PSYCHIATRIC DISORDERS IN THE OFFSPRING OF MOTHERS WITH ANTENATAL FATIGUE AND STRESS

ABSTRACT

Maternal stress during pregnancy is commonly associated with adverse obstetric outcomes, but long-term psychiatric outcomes of antenatal fatigue in the offspring remain unknown. The aim of this study is to identify potential associations between maternal antenatal fatigue and stress, and offspring psychiatric diagnoses. This study is based on the Northern Finland Birth Cohort 1986 (n=9432 children). Maternal fatigue was assessed with a one-item self-reported question and antenatal stress by elevated blood pressure, blood glucose and hsCRP levels. Cohort members with psychiatric diagnoses were identified using the Finnish Care Register for Health Care. To study associations between maternal stress and fatigue and offspring psychiatric diagnoses, chi-square tests and Cox proportional hazard regression models were conducted utilizing gestational smoking, alcohol use, marital status, maternal education and parental psychiatric diagnoses as confounders. Female offspring whose mothers had fatigue and/or stress had more borderline personality disorders, while male offspring had more mental disorders related to alcohol use and mood disorders, compared to participants without maternal antenatal fatigue or stress. Results suggest maternal antenatal fatigue and stress may have associations with offspring psychiatric disorders, but clinical implications are uncertain. Considering the prevalence of fatigue and stress among pregnant mothers, preventive and supportive interventions could be favourable for offspring.

KEYWORDS: MATERNAL ANTENATAL STRESS, MATERNAL ANTENATAL FATIGUE, PSYCHIATRIC DISORDERS, NORTHERN FINLAND 1986 BIRTH COHORT

INTRODUCTION

Pregnancy is a demanding state in which the mother undergoes physical, physiological, mental and social changes. These changes can increase the risk for the expecting mother to become depressed, anxious, stressed, and, most commonly, fatigued during pregnancy (1–3). Antenatal fatigue is a state of persistent and unrelievable exhaustion which includes physical and mental fatigue (4). Fatigue during pregnancy decreases the quality of life in the form of tiredness, lack of motivation and decreased ability to restore sleep. Studies suggest that 44.4% to over half of expecting mothers experience fatigue during their pregnancy (1,3). Maternal fatigue is suggested to be linked to foetal growth retardation and maternal sleep disturbances, and fatigue may be related to poorer cognitive performance in toddlers at 24 to 36 months (5,6). However, little of maternal fatigue and its long-term effects on offspring are known.

Maternal antenatal stress includes physical, psychological and emotional stressors (7). It is a state that approximately 25 per cent of pregnant women report to suffer from during their pregnancies (8). It seems to be associated with lengthened and premature birth, as well as decreased birthweight in infants and adverse neurodevelopmental outcomes, all of which can have negative long-lasting effects on the offspring (9–12). The effects of maternal stress on the foetus appear to be based on the persistence, duration and time frame of the experienced stress during pregnancy (2,10,13–15). Women suffering from stress during pregnancy show elevated levels of cortisol and untypical production of placental corticotropin-releasing hormone (16,17). Maternal cortisol during pregnancy is mostly inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Maternal antenatal stress is linked to the 11β-HSD2 inhibition leading to elevated cortisol levels in the foetus. Elevated foetal cortisol levels may have adverse effects

on neurodevelopment (2,18,19). Offspring of women suffering from antenatal stress appear to have altered hypothalamic-pituitary-adrenal (HPA) axis reactivity which may leave them vulnerable to behaviour and mental health problems (10).

In Finland, mental disorders are a growing public health concern even though general quality of life and wellbeing have both increased over the years. In the Organisation for Economic Co-operation and Development's (OECD) 2018 report, Finland was leading the charts in the mental illness category, and its cost was reported as 5.3 per cent of gross domestic product (GDP) (€11 billion yearly) (20). In previous years, mental health problems have been the most common reason (around 50 per cent) for disability pension (21). OECD publication from 2022 reports elevated prevalence of mental health problems and anxiety, especially among youth, and an increase in depression among adults between years 2020 and 2022 (22).

Complete mechanisms of maternal stress and the extent of long-term effects on foetus are unclear, yet studies are increasingly recognizing antenatal maternal stress as a significant factor to potential adverse outcomes in offspring (16,23,24). Understanding these potential links between fatigue, maternal stress and psychiatric disorders in offspring could offer us new ways to combat them. The purpose of this study was to examine whether maternal antenatal fatigue and stress either together or separately are associated with offspring lifetime severe psychiatric disorders in a large population-based sample.

METHODS

STUDY COHORT, STUDY DESIGN AND DATA SOURCES

This study examined associations between antenatal maternal fatigue and/or stress and offspring mental disorders in The Northern Finland Birth Cohort 1986 (NFBC1986). NFBC1986 is a prospective Finnish birth cohort study of University of Oulu, from an unselected population in the two northernmost provinces of Finland, that longitudinally observes and studies the cohort members for their health and wellbeing since the foetal period. The cohort consists of 9432 children who were born alive between July 1985 and June 1986 and 9362 mothers. Follow-ups to the cohort members have been regularly conducted, with the latest of them being done between ages 33 and 35 (25).

The collection of cohort data started in antenatal period using two questionnaires, one at early pregnancy and another at third trimester or early postpartum, and by clinical examinations at the antenatal clinics. The antenatal questionnaires were divided by topics, one for background questions such as socioeconomic status, family structure, previous pregnancies and contraceptive use, and another for the mother's current pregnancy (25,26).

MATERNAL STRESS AND FATIGUE (EXPOSURE)

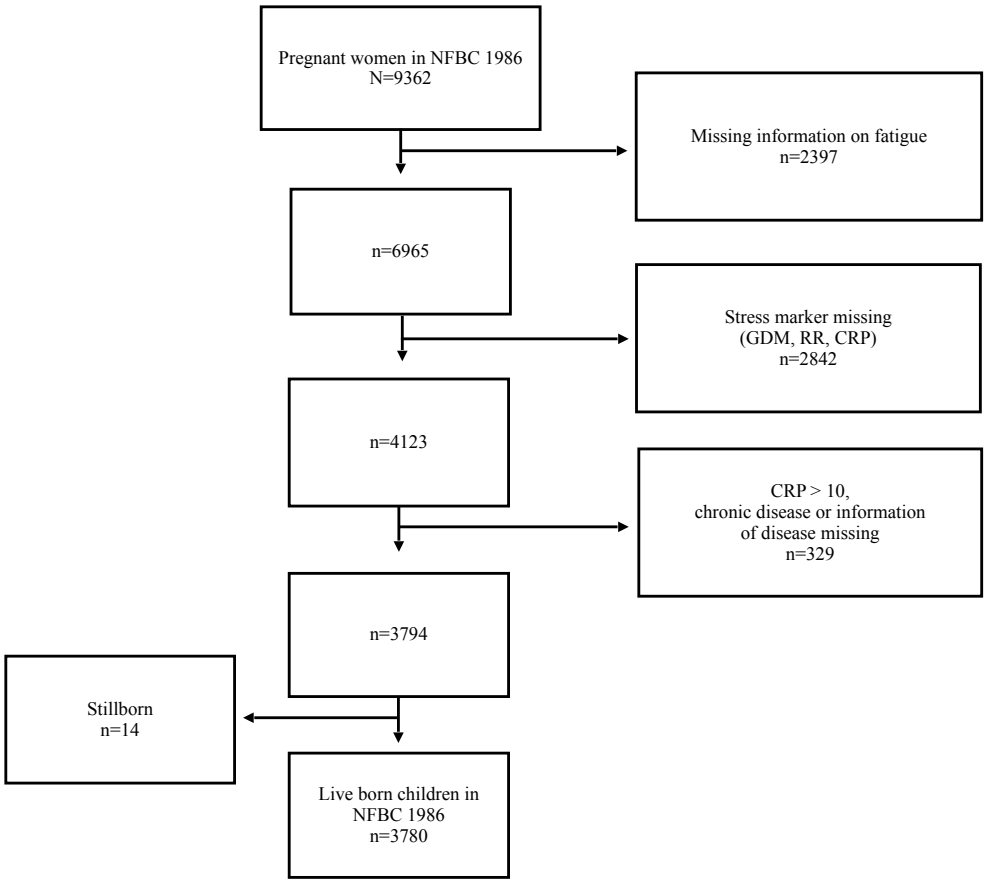
In this study, we used data of mothers (n=3780) from NFBC1986 to measure maternal stress and fatigue during pregnancy as exposure variables (Figure 1). Antenatal fatigue was self-reported with a questionnaire by cohort members' mothers during their last maternity clinic visit or during their postpartum check-up. In the questionnaire the mothers were asked: "How have you felt during this pregnancy?" It was categorized as: 'tired', 'nearly normal' or 'on top of the world'. Mothers who rated themselves as 'tired' were considered as having antenatal fatigue in this study.

Antenatal physical stress was analysed as a sum factor using clinical examination data as well as maternal sera. Maternal antenatal stress was determined by elevated high-sensitivity C-Reactive Protein (hsCRP) levels (3-10), elevated systolic or diastolic blood pressure (sRR>135mmHg or dRR>85mmHg in any measurement) or if the mother had developed gestational diabetes. Clinical examination data was reported on the questionnaire which included blood pressure and blood sugar. Blood pressure was measured on multiple occasions, and if it had been elevated once, it was accounted as a stress marker. Gestational diabetes was determined by elevated glucose levels during oral glucose tolerance test. Maternal sera were taken once from each mother during the first or early second trimester. These samples were available in the Finnish Maternity Cohort of Northern Finland Biobank Borealis. The sera samples included information regarding prenatal hsCRP, thyroid hormones (TSH, T4-V, T3-V) and thyroid antibodies (TPO-Ab).

Final study groups of our study were as following: only fatigue, only stress, both and control group. Mothers who self-reported 'tired' but expressed no antenatal stress markers were labelled 'only fatigue' (n=331), and mothers who did not report 'tired' on the questionnaire but presented elevated levels of any of the stress markers were categorized as 'only stress' (n=1672). Lastly, mothers who reported 'tired' on the questionnaire and expressed stress markers were categorized into a group labelled 'both' (n=446). The control group (n=1331) consists of cohort mothers who didn't qualify as fatigued or stressed. Cohort members' mothers who had missing information on fatigue, had their CRP level above 10 (measured once during pregnancy), had missing information on gestational diabetes or blood pressure were excluded from this study's population

(*Figure 1*). Mothers who had missing information on chronic diseases or suffered from one were also excluded from data analysis to reduce potential confounding.

Figure 1. Participant flow chart of mothers of NFBC1986's cohort members. Flow chart excludes pregnant mothers with chronic diseases or missing information of chronic diseases. Other exclusions happen during or after pregnancy, such as cohort members whose mothers had missing information on stress markers (CRP, blood pressure and blood glucose levels) and withdrawn consent of data use after its collection. Stillborn cohort members, live born twins and triplets have also been excluded



PSYCHIATRIC DISORDERS IN THE OFFSPRING (OUTCOMES)

To examine offspring psychiatric disorders as outcomes, we identified psychiatric diagnoses of cohort members from the Finnish Care Register for Health Care (CRHC). The CRHC (27) provides data on inpatient treatments dating back from 1969 and on specialized outpatient care since 1994 based on International Classification of Diseases (ICD-8-10). The CRHC data was obtained from Findata, the Finnish Social and Health Data Permit Authority, with data permit THL/4442/14.02.00/2023. Findata was responsible for the pseudonymization of the data and ensuring the anonymity of the final results. This data was used to identify offspring mental disorders treated in specialized care from birth up to age 34 (covering the years 1985-2020). The psychiatric disorders were considered severe, as they were treated in specialized care. Because previous research suggests that prenatal exposures may have sex-specific effects (28), we examined psychiatric diagnoses separately by sex.

Psychiatric diagnoses of NFBC1986 members were categorized into main groups. There were seven main diagnostic groups categorized using ICD-10 and corresponding ICD-9 standards. These diagnostic main groups include any psychiatric disorder (F1-F5, F60-F63, F68-F69, F7-F9), disorders diagnosed in childhood or in adolescence (F80-F84, F88-F95, F98), mental

disorders due to psychoactive substance use (F1) (with alcohol and other substances categorized as their own subgroups), mood disorders (F3) (depression-related diagnoses as their own subgroup), neurotic, stress-related and somatoform disorders (F4) (anxiety-related diagnoses as their own subgroup), behavioural syndromes associated with eating, sleep or puerperium (F50, F51, F53), and disorders of adult personality as a main group (F60, F61, F62) and borderline personality disorder as its subgroup. ICD codes used are listed in a *Supplementary Table*. The number of participants with a diagnosis of psychotic and neurodevelopmental disorders was too low (n<5) to be included in the statistical analyses.

CONFOUNDERS

Our confounders for cohort members' parents consisted of self-reported questionnaire data regarding mothers' smoking during pregnancy (yes or no), mothers' alcohol use during pregnancy (yes or no), mothers' marital status (married/cohabiting or other), mothers' education level (basic, secondary or higher) as well as confounders separately for mothers' or fathers' psychiatric diagnosis (yes or no) from CRHC. Parental psychiatric diagnoses included all psychiatric and neurodevelopmental disorder diagnoses recorded in the CRHC between 1972 and 2020. These confounders were chosen due to previous research literature linking antenatal mental health issues to adverse outcomes in offspring (29). They are listed as their own table (*Table 1*).

Table 1. Background characteristics of the study sample

Confounders for both sexes	Control	Only fatigue		Only stress		Both	
	n (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value
n (mothers)	1331	331		1672		446	
Sex of offspring (cohort member)							
Female	634 (47.6)	165 (49.8)	0.509	819 (49.0)	0.485	211 (47.3)	0.949
Male	697 (52.4)	166 (50.2)		853 (51.0)		235 (52.7)	
Mother's smoking during pregnancy							
No	1028 (77.4)	237 (71.8)		1339 (80.1)	0.076	341 (76.5)	0.746
Yes	301 (22.6)	93 (28.2)		333 (19.9)		105 (23.5)	
Mother's alcohol use during pregnancy							
No	1133 (87.5)	276 (85.4)	0.376	1451 (89.0)	0.240	365 (85.5)	0.323
Yes	162 (12.5)	47 (14.6)		180 (11.0)		62 (14.5)	
Mother's marital status							
Married/Cohabiting	1255 (94.3)	320 (96.7)	0.108	1584 (94.7)	0.649	432 (96.9)	0.044*
Other	76 (5.7)	11 (3.3)		88 (5.3)		14 (3.1)	
Mother's education level							
Basic	253 (20.6)	91 (30.1)	<0.001*	389 (25.5)		111 (27.2)	0.016*
Higher	91 (7.4)	12 (4.0)		107 (7.0)		23 (5.6)	
Secondary	882 (71.9)	199 (65.9)		1030 (67.5)		274 (67.2)	

Confounders for both sexes	Control	Only fatigue		Only stress		Both	
	n (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value
Parent's psychiatric diagnosis							
Father							
No	1178 (88.5)	300 (90.6)	0.314	1501 (89.8)	0.292	388 (87.0)	0.442
Yes	153 (11.5)	31 (9.4)		171 (10.2)		58 (13.0)	
Mother							
No	1225 (92.0)	291 (87.9)		1539 (92.0)	1.000	394 (88.3)	0.023*
Yes	106 (8.0)	40 (12.1)		133 (8.0)		52 (11.7)	

DATA ANALYSIS

Chi-squared tests were used in cross-tabulations to compare maternal stress and fatigue across background characteristics, which were considered as potential confounders. To analyse the association between maternal stress and fatigue and offspring psychiatric disorders, both descriptive statistics and Cox proportional hazards regression models were applied. The incidence of psychiatric disorders from birth to age 34 was reported and compared between the control group and the three study groups using chi-squared tests. To investigate longitudinal associations, Cox proportional hazards regression models were fitted and stratified by sex to provide separate estimates for men and women. The proportional hazards assumption was formally assessed using scaled Schoenfeld residuals, with no evidence of violation in the global tests.

Both crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) are reported. The adjusted regression models were adjusted for maternal smoking during pregnancy, maternal alcohol use during pregnancy, maternal marital status, maternal education level, maternal diagnosed psychiatric disorder and paternal diagnosed psychiatric disorder. In the regression analyses, emigration or death during follow-up were treated as censoring events. To account for multiple testing across the diagnostic outcomes, p-values from the fully adjusted models were adjusted using the Benjamini-Hochberg procedure to control the false discovery rate (FDR). The correction was performed separately for each exposure category (only fatigue, only stress and both fatigue and stress).

Cumulative incidence functions were generated to provide a visual representation of the development of psychiatric disorders over the follow-up period by sex. The cumulative incidence curves are shown in *Figure 2*. All statistical analyses were performed using R software (version 4.3.1).

In addition, potential selection due to attrition was assessed by comparing participants included in the analytical sample (n=3780) with live-born cohort members not included in the analyses (n=5291) with respect to the study exposures, diagnostic outcomes and potential confounders using cross-tabulations and chi-squared tests.

RESULTS

Our data comprised cohort members of NFBC1986 (n=3780) and their mothers. Of the female offspring, 165 (49.8%) were born to mothers in 'only fatigue' group, 819 (49.0%) to 'only stress' study group and 211 (47.3%) to 'both' study group. Of the male offspring, 166 (50.2%) were in 'only fatigue' study group, 853 (51.0%) in 'only stress' and 235 (52.7%) in 'both' study group.

The descriptive statistics of the study sample are presented in *Table 1*. Mothers who reported only fatigue were less educated compared to other study groups (p<.001) and reported to have smoked more than other study groups during their pregnancies (p=0.041) (*Table 1*). Mothers who suffered from antenatal fatigue and mothers who suffered from both antenatal fatigue and stress were more likely to have received a psychiatric or neurodevelopmental diagnosis compared to other study groups (p=0.024, p=0.023).

Participants included in the analytical sample were generally similar to those not included with respect to the examined characteristics, although mothers of offspring in the non-analytical sample had lower educational attainment and higher levels of fatigue (*Supplementary Table 1*).

MENTAL DISORDERS IN FEMALE OFFSPRING

Female offspring of mothers who had antenatal fatigue presented more borderline personality disorders (BPD) (4.2%) in both crude and adjusted models when compared to female offspring of mothers without antenatal fatigue or stress (1.3%) (HR=4.02, 95% CI 1.40-11.56) (*Table 2*). Female offspring of mothers who suffered from antenatal fatigue and stress also presented BPD more often than control group (3.3%). Adjusted models utilizing potential confounders for female offspring resulted in similar results compared to crude models. A small but statistically significant increase in risk for disorders in adult personality in female offspring of mothers suffering from antenatal fatigue was found in adjusted model (HR=2.29, 95% CI 1.00-5.26). Personality disorders other than BPD were not included due to small study group sizes (n<5). Female offspring whose mothers suffered from antenatal fatigue received more disorders diagnosed in childhood or in adolescence when compared to other study groups. However, the statistically significant finding in crude model lost relevance in adjusted model (HR=1.98, 95% CI 0.96-4.11). After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05.

MENTAL DISORDERS IN MALE OFFSPRING

Mental disorders due to alcohol use occurred more often in male offspring whose mothers suffered from both maternal stress and fatigue during their pregnancies compared to control group (7.2% and 4.3% respectively) (HR=1.90, 95% CI 1.03-3.50, adjusted model) (*Table 3*). Mental disorders related to use of other substances were more prevalent in male offspring of mothers who suffered from fatigue (5.4% compared to control 1.7%), with crude model reporting statistically significant finding that lost relevance in adjusted model (HR=2.51, 95% CI 0.96-6.55). Mood disorders in male offspring were most prevalent in 'both' group (10.2%, with control group reporting 6.2%) with both crude and adjusted model having a slight but statistically significant relevance (HR=1.70, 95% CI 1.00-2.88, adjusted model). After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05.

Figure 2 represents the cumulative incidence of any psychiatric disorder over the entire follow-up period (ages 0–34 years) by sex. No statistically significant differences between the maternal fatigue and stress groups compared with the control group were observed. The age at onset was earlier in females, but the total cumulative incidences during the whole follow-up were similar between sexes.

Table 2. Associations of cumulative incidences of psychiatric diagnoses and maternal antenatal stress and fatigue in female cohort members

Confounders for both sexes		**Control**	**Only fatigue**		**Only stress**		**Both**	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Any psychiatric or neurodevelopmental disorder	crude adjusted	141 (22.2)	38 (23.0)	1.07 (0.75-1.53) 1.08 (0.75-1.57)	166 (20.3)	0.89 (0.71-1.11) 0.87 (0.69-1.10)	51 (24.2)	1.09 (0.79-1.50) 1.06 (0.75-1.49)
Disorders diagnosed in childhood or in adolescence	crude adjusted	23 (3.6)	12 (7.3)	2.07 (1.03-4.16)* 1.98 (0.96-4.11)	23 (2.8)	0.77 (0.43-1.37) 0.71 (0.39-1.30)	5 (2.4)	0.64 (0.25-1.70) 0.64 (0.24-1.69)
Mental disorders due to psychoactive substance use	crude adjusted	17 (2.7)	7 (4.2)	1.61 (0.67-3.89) 1.60 (0.66-3.87)	30 (3.7)	1.36 (0.75-2.47) 1.23 (0.66-2.28)	5 (2.4)	0.88 (0.32-2.38) 0.85 (0.31-2.32)
Alcohol	crude adjusted	14 (2.2)	6 (3.6)	1.67 (0.64-4.35) 1.70 (0.65-4.45)	20 (2.4)	1.10 (0.56-2.18) 0.96 (0.47-1.97)	5 (2.4)	1.07 (0.38-2.96) 1.06 (0.38-2.95)
Mood disorders	crude adjusted	89 (14.0)	25 (15.2)	1.11 (0.72-1.74) 1.10 (0.70-1.73)	98 (12.0)	0.83 (0.62-1.11) 0.78 (0.58-1.05)	34 (16.1)	1.15 (0.78-1.71) 1.07 (0.71-1.63)
Depression	crude adjusted	81 (12.8)	23 (13.9)	1.12 (0.71-1.79) 1.09 (0.68-1.76)	93 (11.4)	0.87 (0.65-1.17) 0.80 (0.59-1.10)	30 (14.2)	1.11 (0.73-1.69) 1.01 (0.65-1.58)
Neurotic, stress-related and somatoform diseases	crude adjusted	76 (12.0)	20 (12.1)	1.02 (0.63-1.68) 1.01 (0.61-1.68)	92 (11.2)	0.92 (0.68-1.24) 0.89 (0.65-1.23)	26 (12.3)	1.01 (0.65-1.58) 0.98 (0.61-1.57)

Confounders for both sexes		Control	Only fatigue		Only stress		Both	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Anxiety disorders	crude adjusted	43 (6.8)	9 (5.5)	0.81 (0.40-1.66) 0.86 (0.42-1.78)	42 (5.1)	0.74 (0.48-1.13) 0.74 (0.47-1.16)	13 (6.2)	0.89 (0.48-1.66) 0.83 (0.43-1.63)
Behavioural syndromes associated with eating, sleep or puerperium	crude adjusted	19 (3.0)	6 (3.6)	1.22 (0.49-3.06) 1.42 (0.55-3.65)	22 (2.7)	0.89 (0.48-1.64) 0.85 (0.43-1.68)	5 (2.4)	0.78 (0.29-2.09) 0.76 (0.25-2.27)
Disorders of adult personality	crude adjusted	16 (2.5)	9 (5.5)	2.21 (0.98-5.01) 2.29 (1.00-5.26)*	22 (2.7)	1.06 (0.55-2.01) 1.07 (0.55-2.10)	9 (4.3)	1.69 (0.75-3.82) 1.61 (0.68-3.81)
Borderline personality disorder	crude adjusted	8 (1.3)	7 (4.2)*	3.44 (1.25-9.48)* 4.02 (1.40-11.56)*	9 (1.1)	0.86 (0.33-2.24) 1.04 (0.39-2.82)	7 (3.3)	2.62 (0.95-7.24) 3.07 (1.07-8.78)*

Incidences of psychiatric diagnoses of female cohort members of NFBC1986 from the Finnish Care Register for Health Care (CRHC). Psychiatric diagnoses were categorized into main groups using ICD-10 classification. Subgroups are listed below main groups
Adjusted model: adjusted with mother's smoking during pregnancy, mother's use of alcohol during pregnancy, mother's marital status, mother's education level, mother's diagnosed psychiatric disorder and father's diagnosed psychiatric disorder
HR=hazard ratio, CI=confidence interval
*p-value <0.05
After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05

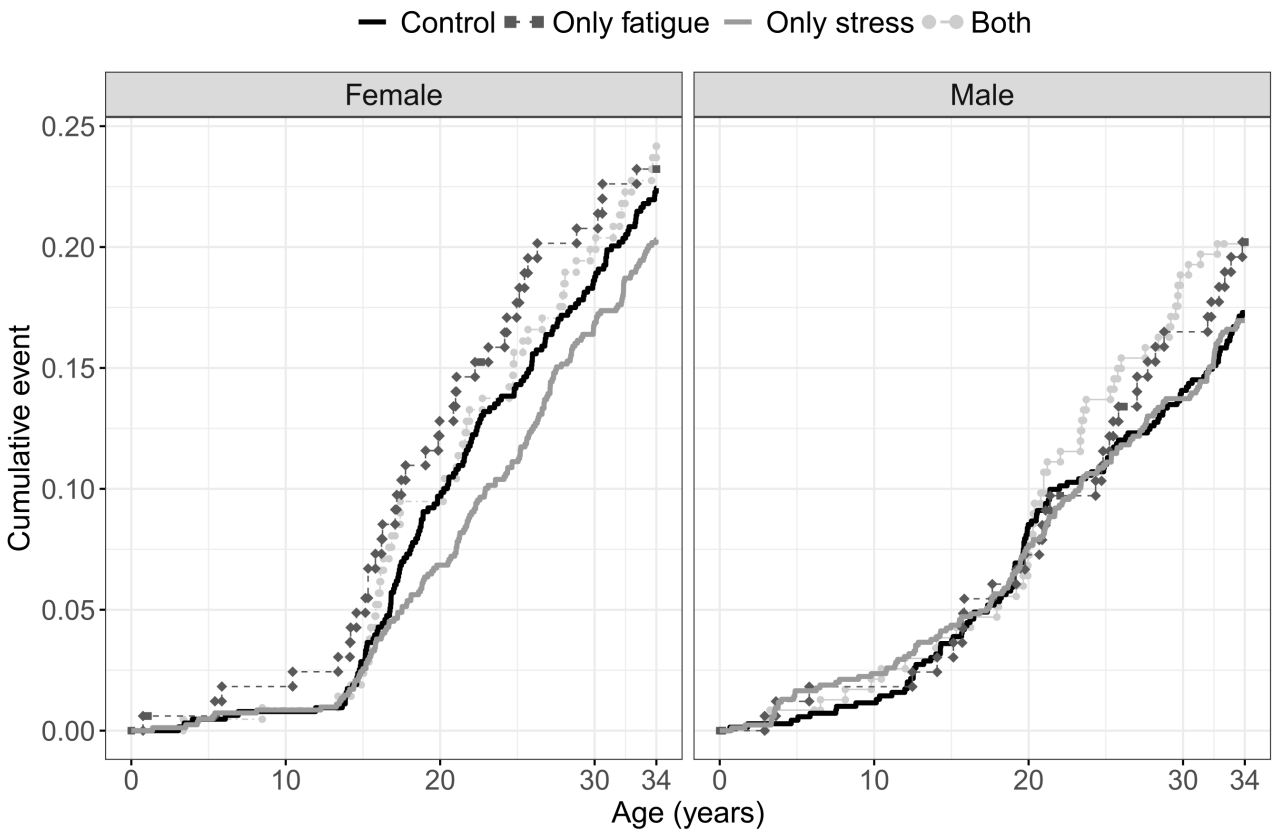
Table 3. Associations of cumulative incidences of psychiatric diagnoses and maternal antenatal stress and fatigue in male cohort members

Confounders for both sexes		Control	Only fatigue		Only stress		Both	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Any psychiatric or neurodevelopmental disorder	crude adjusted	119 (17.1)	33 (19.9)	1.18 (0.80-1.73) 1.13 (0.75-1.70)	143 (16.8)	0.98 (0.77-1.25) 1.00 (0.77-1.30)	47 (20.0)	1.19 (0.85-1.66) 1.27 (0.89-1.81)
Disorders diagnosed in childhood or in adolescence	crude adjusted	26 (3.7)	8 (4.8)	1.28 (0.58-2.84) 1.29 (0.55-3.04)	30 (3.5)	0.94 (0.56-1.59) 0.91 (0.51-1.63)	10 (4.3)	1.14 (0.55-2.36) 1.36 (0.64-2.88)
Mental disorders due to psychoactive substance use	crude adjusted	35 (5.0)	14 (8.4)	1.73 (0.93-3.21) 1.50 (0.77-2.94)	58 (6.8)	1.35 (0.89-2.06) 1.35 (0.87-2.10)	19 (8.1)	1.62 (0.93-2.83) 1.71 (0.95-3.05)
Substance (other)	crude adjusted	12 (1.7)	9 (5.4)*	3.24 (1.37-7.69)* 2.51 (0.96-6.55)	26 (3.0)	1.77 (0.89-3.50) 1.67 (0.81-3.44)	8 (3.4)	1.97 (0.81-4.83) 1.93 (0.75-5.01)
Alcohol	crude adjusted	30 (4.3)	11 (6.6)	1.57 (0.78-3.13) 1.32 (0.62-2.83)	47 (5.5)	1.28 (0.81-2.02) 1.26 (0.77-2.04)	17 (7.2)	1.68 (0.93-3.05) 1.90 (1.03-3.50)*
Mood disorders	crude adjusted	43 (6.2)	12 (7.2)	1.19 (0.63-2.25) 1.04 (0.51-2.09)	52 (6.1)	0.98 (0.65-1.46) 0.99 (0.64-1.53)	24 (10.2)	1.67 (1.02-2.76)* 1.70 (1.00-2.88)*
Depression	crude adjusted	40 (5.7)	10 (6.0)	1.05 (0.53-2.10) 0.86 (0.40-1.86)	51 (6.0)	1.03 (0.68-1.56) 1.03 (0.66-1.59)	18 (7.7)	1.34 (0.77-2.33) 1.46 (0.82-2.58)
Neurotic, stress-related and somatoform diseases	crude adjusted	58 (8.3)	14 (8.4)	1.01 (0.57-1.82) 0.93 (0.49-1.76)	58 (6.8)	0.81 (0.56-1.16) 0.83 (0.56-1.23)	15 (6.4)	0.75 (0.43-1.33) 0.79 (0.44-1.44)

Confounders for both sexes		Control	Only fatigue		Only stress		Both	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Anxiety disorders	crude adjusted	36 (5.2)	10 (6.0)	1.17 (0.58-2.36) 1.10 (0.50-2.44)	36 (4.2)	0.81 (0.51-1.29) 0.94 (0.56-1.56)	9 (3.8)	0.73 (0.35-1.51) 0.81 (0.37-1.79)
Disorders of adult personality	crude adjusted	10 (1.4)	5 (3.0)	2.12 (0.72-6.20) 1.52 (0.47-4.89)	17 (2.0)	1.39 (0.64-3.04) 1.16 (0.51-2.63)	5 (2.1)	1.48 (0.51-4.33) 1.40 (0.48-4.14)

Incidences of psychiatric diagnoses of male cohort members of NFBC1986 from the Finnish Care Register for Health Care (CRHC). Psychiatric diagnoses were categorized into main groups using ICD-10 classification. Subgroups are listed below main groups
Adjusted model: adjusted with mother's smoking during pregnancy, mother's use of alcohol during pregnancy, mother's marital status, mother's education level, mother's diagnosed psychiatric disorder and father's diagnosed psychiatric disorder
HR=hazard ratio, CI=confidence interval
*p-value <0.05
After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05

Figure 2. Cumulative incidence of psychiatric diagnoses of cohort members by sex. The graphic shows any psychiatric or neurodevelopmental disorder (F0-F5, F60-F63, F68-F69, F7-F9) variable categorized by study group



DISCUSSION

To the best of our knowledge, this article is the first analysing associations between maternal antenatal fatigue and stress, and offspring psychiatric diagnoses from childhood to adulthood. Our findings suggest that female offspring whose mothers had antenatal fatigue were at increased risk for personality disorders, especially borderline personality disorder compared to control group. The male offspring of mothers with both antenatal fatigue and stress were at increased risk for severe, specialized care-treated mood disorders and mental disorders related to alcohol use. On the other hand, the statistical significance of these findings was low due to low number of participants in the diagnostic groups and multiple testing.

Surprisingly, the offspring of mothers with only stress did not significantly differ from the control group in any of the diagnostic groups. This indicates that in this study setting, where mothers with chronic somatic illness were excluded, common pregnancy complications such as low-grade inflammation, hypertension and gestational diabetes would not be a risk factor for severe mental disorders in the offspring. This is opposite to many previous findings, based on Finnish population (30), and should be further studied.

There were no statistically significant differences between the four study groups regarding the cumulative incidences of mental disorders during the 34-year follow-up, indicating that antenatal fatigue or stress is not associated with different total prevalence or different age at onset for offspring mental disorders. As in earlier literature (30), female participants presented mental health problems at earlier stages of life compared to male participants, most noticeable after the age of 15 years, but the number of psychiatric diagnoses for both sexes remained similar, with male cohort members catching up to female participants after the age of 20 years.

Previous literature explores maternal stress and maternal depression and their correlations regarding offspring outcomes, whereas maternal fatigue and its long-term effects on offspring outcomes have remained less researched. Our study found increase in substance-related disorders in male participants whose mothers had experienced fatigue and stress during their pregnancies. This is in line with previous studies that antenatal stress may influence substance use in offspring, although the exact mechanisms behind these phenomena are not completely understood. Early maternal stress increases dysregulation of the hypothalamic-pituitary-adrenal axis and immune systems which may increase substance abuse and addiction risk, leaving offspring vulnerable later in life (31). Substance abuse later in life may also be indirectly influenced by offspring behaviour, especially externalizing problems (32). Our study also found slight increase in disorders diagnosed in childhood or in adolescence and in borderline personality disorder, particularly in women whose mothers had antenatal fatigue. Exposure to moderate or severe maternal stress appears to be a risk factor for developing a personality disorder later in life for offspring, and that it may act as a non-specific risk factor in mental health disorders generally (33). Fatigue, however, was not measured as an independent variable in these studies.

Previous literature also suggests that antenatal and postnatal depression increase the risk for offspring to suffer from anxiety and depression later in life (34,35). Antenatal depression also may elevate risk for male offspring to develop antisocial personality disorder (36). Previous literature suggests that antenatal stress is linked to offspring mood disorders, schizophrenia and anxiety (33), and our findings suggest that male offspring may be more vulnerable to mood disorders when exposed to maternal antenatal stress and fatigue. Our study, however, had modest results in other categories as there appeared no drastic differences between the study groups of exposure to maternal stress and fatigue. The differences in outcomes may partially be explained by differences in measurement methods, such as our use of questionnaires self-reported by mothers or due to low sample size.

Fatigue may also be described as non-specific symptom, and due to its high prevalence during pregnancy, associations with dramatic outcomes were not expected. In our findings, self-reported maternal fatigue, elevated blood pressure, gestational diabetes and low-grade inflammation did not appear to be strongly associated with serious mental health outcomes in offspring, but fatigue per se and combined with other pregnancy complications may be related to a modest increase in risk of psychiatric disorders.

STRENGTHS AND LIMITATIONS

This study has multiple strengths regarding the data setting and its utilization. Finland has a credible national registry for psychiatric diagnoses that covers the whole population, which makes it a valuable resource for research (37). Northern Finland Birth cohorts provide unique information of northernmost parts of Finland and its population. On the other hand, Finnish population in the 1980s was quite homogeneous and thus the findings of this study may not be generalizable to other populations. Some of the measures utilized during data collection are credible (stress markers such as CRP), and the wellbeing and maternal stress of mothers of the NFBC1986

during their pregnancies have been analysed with both objective and subjective measures. With this data we were able to research sexes separately and detect potential risks for both genders. We were also able to exclude the effects of several maternal chronic and gestational illnesses when evaluating the effects of antenatal fatigue on offspring outcomes.

There are some limitations to this study and its population sample regarding technical issues, collection of data as well as the size of the study sample. The variables regarding maternal psychological wellbeing and stress were limited in the data of NFBC1986 resulting in relatively crude exposure variables. The analytical sample comprised approximately 40% of the original cohort, which may have introduced selection bias and limited the generalizability of the findings. However, attrition analyses indicated that participants included in the analytical sample were generally similar to those not included across most examined characteristics. Differences were observed in maternal education and fatigue, with mothers of non-participants having lower educational attainment and higher levels of fatigue. Although modest statistically significant findings were observed, the low number of participants and statistical bias related to multiple testing decreased the statistical reliability of our findings. Unfortunately, the number of participants in this study was too low to include psychotic disorders in the analyses.

Other limiting factors are information regarding mother's mood and other mental health status during the antenatal period, except for the register-based psychiatric diagnoses. Maternal fatigue was self-reported only once in antenatal period and the question regarding tiredness, despite covering the full gestational period, was vague.

Confounding factors regarding parental psychiatric diagnoses may be incomplete as collection of outpatient records started in 1994 in Finland. Inpatient records go back to 1969, which may also leave information out from this study. Our data does not include outpatient mental health services from primary healthcare for cohort members, as we were only interested in severe mental disorders, assessed by specialized psychiatrist, which increases the validity of the outcome measures.

CLINICAL IMPLICATIONS

Our study has brought some new findings regarding maternal fatigue and stress during pregnancy and their potential effect on increased risk for personality disorders in women and alcohol use disorders and mood disorders in men. Currently, the scientific knowledge on maternal fatigue is limited, and in other study samples there may be other methods to study these associations better. Adequate and timely psychosocial support for pregnant women with fatigue could provide an opportunity to decrease the potential adverse effects of antenatal fatigue. Yet, in this study, common pregnancy complications such as fatigue, low-grade inflammation, gestational diabetes or hypertension were not very significant risk factors for subsequent mental disorders in the offspring, but these findings should be replicated in other studies before any assumptions can be drawn.

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Ethical Considerations

Cohort 1986 33y: Northern Ostrobothnia Hospital District Ethical Committee 108/2017 (15.1.2018)

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Supplementary Material

Supplementary data are available at Psychiatria Fennica online.

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