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Research paper

Mood and neurotic disorders among youth with prenatal substance exposure: A longitudinal register-based cohort study

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ABSTRACT

Background: Prenatal substance exposure is associated with mood and neurotic disorders but this association is complex and understudied. This study investigated the recorded use of specialised healthcare services for mood and neurotic disorders among youth with prenatal substance exposure in comparison with an unexposed matched cohort. Furthermore, the influence of adverse maternal characteristics and out-of-home care (OHC) is investigated.

Methods: This longitudinal register-based matched cohort study included 594 exposed and 1735 unexposed youth. Cox proportional hazard regression models were applied to study the first episode of mood and neurotic disorders in specialised healthcare from 13 years of age, and the influence of adverse maternal characteristics and OHC. Mediation analysis was applied to study the mediating effect of OHC on the association between prenatal substance exposure and the disorders.

Results: The exposed cohort had a two-fold higher likelihood of being treated at specialised healthcare for mood and neurotic disorders compared with the unexposed cohort (HR 2.34, 95% CI 1.86–2.95), but this difference was attenuated to non-significant levels (AHR 1.29, 95% CI 0.92–1.81) following adjustments with adverse maternal characteristics and OHC. OHC mediated 61% (95% CI 0.41–0.94) of the association between prenatal substance exposure and youth's mood and neurotic disorders.

Limitations: Register data likely include more severe cases of disorders, and as an observational study, causality cannot be assessed.

Conclusion: Mood and neurotic disorders are more common following prenatal exposure to substances and interlinked with significant adversities in the postnatal caregiving environment and OHC.

1. Introduction

Mood disorders (e.g. depressive disorders) and neurotic disorders (e.g. anxiety), often referred to as internalizing disorders, are common and often comorbid mental health disorders occurring throughout the life-course. Often these disorders become evident in childhood or adolescence and can persist into adulthood (Kessler et al., 2007; Patel et al., 2007). These disorders contribute to functional impairments, and health and developmental concerns which may influence educational achievements, peer relationships and substance abuse behaviours (Patel

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et al., 2007).

Several factors can increase the risk of mood and neurotic disorders over time, and often these disorders are more common among females (Kuehner, 2003; Rapee et al., 2009). Other factors include problems in the prenatal period (e.g. alcohol exposure) and early life adversities (e.g. financial difficulties in the family, parental psychiatric morbidity, parental substance abuse, death of a family member) (Basu and Banerjee, 2020; Essex et al., 2006; Rapee et al., 2009; Su et al., 2021). These risk factors can negatively influence parenting behavior and parent-child interaction, and subsequent mental health outcomes in children (Brumariu and Kerns, 2010; Rapee et al., 2009; Reising et al., 2013; Staton-Tindall et al., 2013). Furthermore, often these factors are indications for child protective services during early childhood (Kestilä et al., 2012; Sarkola et al., 2007). Mental health disorders, including mood and neurotic disorders, are highly overrepresented among children in out-of-home care or foster care in many studies (Bronsard et al., 2016; Egelund and Lausten, 2009; Lehmann et al., 2013).

Prenatal alcohol exposure is linked with neurodevelopmental disorders in children (Stein and Donald, 2018). Associations with mood and neurotic disorders seem more complex and less studied (Carta et al., 2001; O'Connor, 2014). Prior research has typically included small or clinically referred samples and parental assessment of a child's symptomatology. These studies have investigated depression and anxiety symptoms among exposed children or children with Foetal Alcohol Spectrum Disorders (FASD), and show an increased prevalence of symptoms among the exposed children compared with healthy controls (Fryer et al., 2007; Roebuck et al., 1999; Walthall et al., 2008; Weyrauch et al., 2017). To date, few studies have shown elevated rates of depressive or anxiety disorders (Famy et al., 1998) among youth or young adults with FASD (Famy et al., 1998; Streissguth, 1996). Prior studies, however, indicate that the mood and neurotic disorders in childhood have been likely influenced by factors within the postnatal caregiving environment and parenting domains (O'Connor and Paley, 2006; Walthall et al., 2008; Weyrauch et al., 2017).

Prenatal exposure to other substances (e.g. marijuana, cocaine, opiates, amphetamine) may also disrupt foetal neurodevelopment and can influence subsequent cognitive processing and behavior (Behnke et al., 2013; Morie et al., 2019; Nygaard et al., 2016). Research on mood and neurotic disorders among children and youth is, however, scarce and suggests an association between prenatal marijuana, opioid or polysubstance exposure and depressive symptoms in children (Gray et al., 2005) and youth (Nygaard et al., 2020).

Prenatal exposure to alcohol and/or other substances (prenatal substance exposure hereafter) is often linked with early life stressors such as maternal socioeconomic factors (e.g. low educational level, financial difficulties), maternal mental health problems and polysubstance use (Esper and Furtado, 2014; Flannigan et al., 2021; Jääskeläinen et al., 2016). A high proportion of these children need child protective services after birth, and they are placed in out-of-home care in early childhood due to significant risks in the caregiving environment (Lange et al., 2013; Sarkola et al., 2007). The increased likelihood of mood and neurotic disorders among individuals with prenatal substance exposure can, therefore, reflect this instability in care and exposure to early life adversities (Basu and Banerjee, 2020; Bronsard et al., 2016; Essex et al., 2006).

This study uses longitudinal comprehensive register data to study recorded use of specialised health care services covering inpatient and outpatient hospital care for mood and neurotic disorders among youth prenatally exposed to substances compared with a matched unexposed cohort. In addition, the study investigates the influence of offspring and maternal characteristics as well as out-of-home care on these disorders. The specific objectives were:

1. To study the specialised healthcare utilisation for mood and neurotic disorders among youth prenatally exposed to substances from 13 years of age in comparison to a matched unexposed cohort.
2. To study the influence of offspring and maternal characteristics and OHC on specialised healthcare utilisation for mood or neurotic disorders in relation to prenatal exposure.
3. To study the mediating effect of OHC on the association between prenatal substance exposure and mood and neurotic disorders.

2. Methods

2.1. Study design and population

The data used in this study are from a longitudinal register-based matched cohort study which has been described earlier (Koponen et al., 2020; Sarkola et al., 2007). The study population consisted of 615 youth with prenatal substance exposure (i.e. the exposed cohort) and a matched unexposed cohort ($n = 1787$). Offspring who died before the age of 13 (7 of the exposed, 15 of the unexposed) or were lost to follow-up before the age of 13 (1 of the exposed, 22 of the unexposed) were excluded from the final study population. In addition, offspring who had received a diagnosis for an intellectual disability following the International Classification of Diseases ICD-9 code 317–319 and ICD-10 code F70-F79 (13 of the exposed, 15 of the unexposed) were excluded due to the complexity of mood and neurotic disorders and the diagnosis of these disorders in this group (Rojahn and Meier, 2009). Therefore, the final study population comprised 594 exposed and 1735 unexposed youth (Fig. 1). None of those who died or were lost to follow-up before the age of 13 years was diagnosed with mood and neurotic disorders.

The exposed cohort represents offspring born in 1992–2001 to women with an antenatal follow-up at special outpatient clinics for women with substance use during pregnancy. The mothers were followed up every 2 to 4 weeks with information on substance use (i.e. alcohol, amphetamine, heroin, buprenorphine, non-medical use of central nervous system medication and other drugs) documented by self-reported use, voluntary urine toxicology screenings and conventional blood tests reflecting alcohol consumption at each follow-up visit and documented in hospital medical records (Sarkola et al., 2000). Information on tobacco smoking during pregnancy was collected from the Medical Birth Register.

The unexposed cohort was obtained from the Medical Birth Register and represent offspring born in 1992–2001 to women with no registered evidence of substance use one year prior to or at the time of the offspring's birth. The cohorts were matched for five maternal characteristics: maternal age, parity, number of foetuses, the month of birth, and delivery hospital of the index child. Register data were collected identically for the matched exposed and unexposed mother-offspring pairs (Supplementary material 1).

The local ethical committee of The Hospital District of Helsinki and Uusimaa has approved the study, and permission for data linkages was obtained from all the authorities maintaining the registers. The Finnish Institute for Health and Welfare performed the register linkages and pseudonymised the data prior to analyses. No study subjects were contacted and the data are considered highly confidential.

2.2. Study variables

2.2.1. Outcome variables

Data on all the offspring's mood disorder (ICD-10 codes F30-F39) and neurotic disorder (ICD-10 codes F40-F48) diagnoses were collected from birth, but as these disorders typically evolve in adolescence (Kessler et al., 2007), we focused on episodes from 13 years of age until the end of 2016 when participants were 15–24 years old. The onset age of mood and neurotic disorders was based on the first diagnoses in specialised healthcare (i.e. outpatient or inpatient hospital care) after the 13th birthday in the Care Register for Health Care maintained by the Finnish Institute for Health and Welfare. Data on all inpatient care episodes are available from 1992 to 2016 and outpatient care episodes in public hospitals from 1998 to 2016.

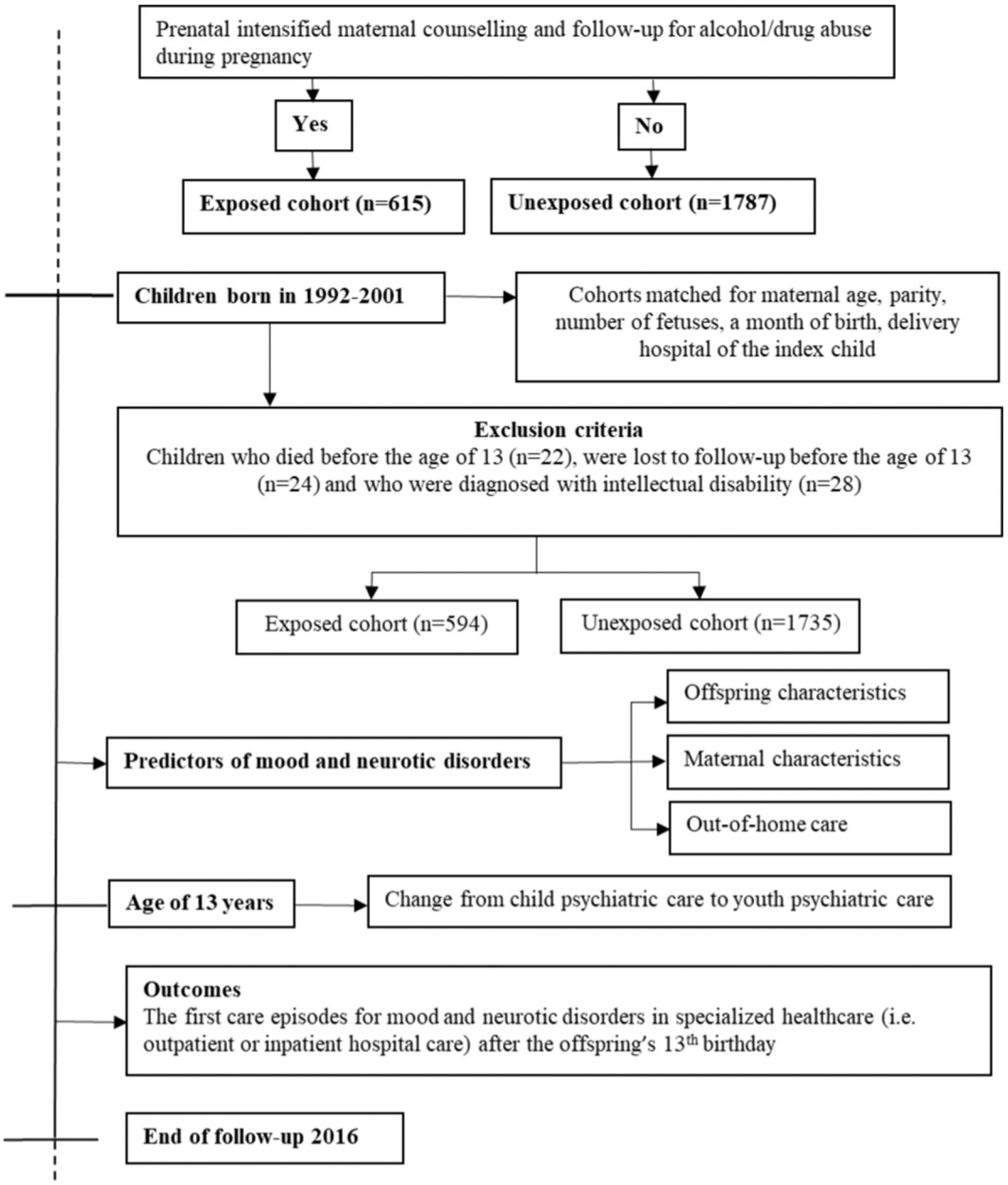

Fig. 1. Study outline.

2.2.2. Covariates

The selection of covariates was based on data availability and prior research demonstrating associations with mood and neurotic disorders (Basu and Banerjee, 2020; Bronsard et al., 2016; Essex et al., 2006). The selected covariates are described in detail in Supplementary material 1.

The studied offspring characteristics included sex, gestational age at birth, birth weight, prenatal exposure to tobacco smoking, and diagnosis within the FASD spectrum for exposed offspring. The variables describing adversities in the postnatal caregiving environment and potential confounders linked with offspring's mood and neurotic disorders were based on maternal characteristics. These included maternal age at the time of offspring's birth, maternal socioeconomic status, measured as maternal occupation during pregnancy, and marital status at the time of offspring's birth. Often childhood adversities co-occur (Carta et al., 2001), and therefore, a cumulative childhood adversity score including 0, 1, 2, or 3 to 5 adversities was constructed based on data before offspring's 13th birthday. This score included maternal mental or behavioural disorder, maternal substance misuse, maternal long-term financial social assistance, maternal criminality and death of the mother (Supplementary material 1).

Taking a child into care is considered as the last resort of child protective service in the Finnish child welfare system. Out-of-home care (OHC) generally refers to significant neglect in a child's care due to parental mental health problems, substance misuse or family violence. A child can be taken into care also if the child's behavior endangers the child's health or development. In this study, OHC was analysed in three categories: no OHC episodes, first OHC episode prior to offspring's 13th birthday, and first OHC episode at 13 years of age or later. We also included information on the median age at the first OHC episode and the cumulative number of years in OHC (Supplementary material 1).

2.2.3. Data analysis

The characteristics of the exposed and unexposed cohorts were compared using the Chi-squared test (χ^2) for categorical variables and the Mann-Whitney *U* test or independent samples *t*-test for continuous variables, as appropriate. Univariate Cox proportional hazard regression analyses were performed to investigate the associations between the covariates and specialised healthcare for mood and neurotic disorders separately for the exposed and unexposed.

Five multivariable Cox regression models were computed to study the association between prenatal substance exposure and mood and neurotic disorders and the influence of selected covariates. The selection of covariates for multivariable models was based on the results from the univariate analyses, prior research evidence indicating associations with youth's mood and neurotic disorders (Basu and Banerjee, 2020; Su et al., 2021), and data availability. Adjustments were not made for maternal marital status and gestational exposure to tobacco smoking due to substantial statistical multicollinearity with prenatal substance exposure. Maternal age at the time of offspring's birth was not included in the analyses as it was one of the matching criteria for the cohorts.

The crude association between prenatal substance exposure and mood and neurotic disorders was studied in the first multivariable Cox regression model. In model 2, adjustments were made for offspring's sex. In model 3, the influence of maternal characteristics was analysed, and adjustments were made for offspring's sex and cumulative childhood adversity score. The influence of OHC was studied in model 4, and adjustments were made for offspring's sex and OHC. In model 5, all covariates were included simultaneously. In the multivariable Cox regression models, the follow-up started at the offspring's 13th birthday and continued until the first record of diagnoses for mood and neurotic disorders in specialised healthcare, death or end of follow-up in 2016. Hazard ratios (HR) and adjusted hazard ratios (AHR) with a 95% Confidence Interval (CI) are reported.

Mediation analysis was applied to estimate the total effect of prenatal substance exposure on mood and neurotic disorders and the mediating effect of OHC. We begin by defining the direct association (c′) between prenatal substance exposure (X) and youth's mood and neurotic disorders (Y). Second, the association (a) between prenatal substance exposure (X) and the mediator (M) was defined. Next, we defined the association (b) between mediator (M) and youth's mood and neurotic disorders (Y) while controlling for the effect of prenatal substance exposure (X). Fourth, the indirect association (ab) indicating the path from prenatal substance exposure (X) to youth's mood and neurotic disorders (Y) through the mediator (M) was defined, following the definition of the total effect (c), which indicates the sum of the direct effect and indirect effect. Lastly, we defined the proportion mediated, which indicates the proportion of the effect of prenatal substance exposure (X) on youth's mood and neurotic disorders (Y) that is explained by the mediator (M). Parameter estimates (*b*) with standard errors (SE), 95% CIs and *p*-values are reported.

The statistical significance was set to $p < 0.05$. The descriptive analyses and Cox regression analyses were performed using IBM SPSS Statistics 28. The mediation analyses were done following a bootstrapping method including thousand simulations and performed with the mediation package for R (Tingley et al., 2014).

3. Results

Characteristics of the study population and a comparison between the cohorts are presented in Table 1. Significant differences between the exposed and unexposed cohorts were found in all of the offspring characteristics, except for sex and gestational age at birth (Table 1). Significant differences between the cohorts were also found for all maternal characteristics, except for maternal age at the time of offspring's birth, which was a matching criterion for the cohorts. Exposed youths' mothers were more often unmarried, from the lower socioeconomic status, and more likely to have mental or behavioural disorders, substance misuse, financial social assistance needs and criminal convictions. Also, a higher proportion of the exposed youth's mothers had died during the follow-up compared with unexposed. The cumulative childhood adversity score indicated that a higher proportion of the exposed youth had been exposed to multiple adversities compared with unexposed. The exposed and unexposed cohorts differed also with respect to OHC, and a higher percentage of the exposed had been placed in OHC during childhood and youth, at a younger age and for a longer cumulative period compared with the unexposed (Table 1).

Outpatient and inpatient hospital care for mood and neurotic disorders was more common among the exposed youth than the unexposed (Table 2). The number of outpatient care episodes (210.4 vs. 95.1 per 1000 people, $p < 0.001$) and the number of inpatient care episodes (60.6 vs. 16.7 per 1000 people, $p < 0.001$) were significantly higher among the exposed compared with the unexposed during the follow-up period. Statistically significant differences in the median age at the first care episode for the disorders in outpatient (14.5 vs. 15.1, $p = 0.112$) or inpatient hospital care (15.6 vs. 16.5, $p = 0.173$) were not found between the exposed and unexposed cohorts. Neither was the cumulative number of care episodes at outpatient or inpatient hospital care statistically significantly different (Table 2). Due to the low number of inpatient hospital care episodes for mood and neurotic disorders from 13 years of age, the outcome variable in the Cox regression analyses was the first record of the diagnoses for mood and neurotic disorders either in inpatient or outpatient hospital care (i.e. specialised healthcare). Of the exposed, 20.9% had been in specialised healthcare for the disorders ≥13 years of age compared with 9.6% among unexposed. The number of care episodes in specialised healthcare for the disorders was significantly higher among exposed compared with unexposed during the follow-up period (208.8 vs. 95.7 per 1000 people, $p < 0.001$) (Table 2).

The results from the univariate Cox regression analysis for the covariates in relation to mood and neurotic disorders are presented in Fig. 2 for the exposed and in Fig. 3 for the unexposed. Among the exposed, only female sex and first OHC episode ≥13 years of age were associated with youth's mood and neurotic disorders (Fig. 2). Among the unexposed, all the studied covariates except for low birth weight were associated with youth's mood and neurotic disorders (Fig. 3).

Table 3 present the results from the multivariable Cox regression analysis. The crude model (model 1) indicated that the exposed were twice more likely to have been in specialised healthcare for mood and neurotic disorders compared with the unexposed (HR 2.34, 95% CI 1.86–2.95). The further adjustments made for offspring's sex in model 2 yielded similar significant results on the association between the exposure and mood and neurotic disorders (AHR 2.34, 95% CI 1.85–2.95). In model 3, the association between the exposure and specialised healthcare for mood or neurotic disorders was diminished and statistically insignificant (AHR 1.30, 95% CI 0.96–1.77) following adjustments for cumulative childhood adversity score. In model 4, the influence of OHC was studied, and the association between the exposure and mood and neurotic disorders remained insignificant (AHR 1.36, 95% CI 0.99–1.85) after adjusting the model for offspring's sex and OHC. The results of model 5 in which all covariates were included simultaneously yielded insignificant results on the association between the exposure and specialised healthcare for mood and neurotic disorders (AHR 1.08, 95% CI 0.78–1.49). The results of model 5 indicated that female sex (AHR 2.44, 95% CI 1.90–3.12), cumulative childhood adversity score and OHC were

Table 1
Descriptive statistics and comparison between the exposed and unexposed cohorts.

	Exposed $n = 594$	Unexposed $n = 1735$	p-value
Follow-up time in years (median, IQR)	18.8 (16.7; 21.0)	18.6 (16.7; 20.9)	0.713
Offspring characteristics, *n* (%)			
Sex			0.475
Male	296 (49.8)	894 (51.5)	
Female	298 (50.2)	841 (48.5)	
Gestational age at birth			0.790
<37 weeks	48 (8.1)	148 (8.5)	
≥37 weeks	538 (90.6)	1584 (91.3)	
Missing data	8 (1.3)	3 (0.2)	
Gestational exposure to tobacco smoking			<0.001
No	138 (23.2)	1400 (80.7)	
Yes	456 (76.8)	335 (19.3)	
Birth weight			<0.001
<2500 g	70 (11.8)	109 (6.3)	
≥2500 g	524 (88.2)	1624 (93.6)	
Missing data	- (0.0)	2 (0.1)	
A diagnosis within the FASD spectrum			<0.001
No	553 (93.1)	- (0.0)	
Yes	41 (6.9)	- (0.0)	
Maternal characteristics, *n* (%)			
Maternal age at the time of offspring's birth			0.612
<25 years	225 (37.9)	637 (36.7)	
≥25 years	369 (62.1)	1098 (63.3)	
Maternal age at the time of offspring's birth (mean, SD)	27.3 (6.5)	27.6 (6.5)	0.449
Maternal marital status			<0.001
Unmarried (single/widowed/divorced)	474 (79.8)	705 (40.6)	
Married	120 (20.2)	1030 (59.4)	
Maternal socioeconomic status			<0.001
Low (manual workers/students/pensioners/others)	409 (68.9)	789 (45.5)	
High	185 (31.1)	946 (54.5)	
Maternal mental or behavioural disorder*			<0.001
No	318 (53.5)	1491 (85.9)	
Yes	276 (46.5)	244 (14.1)	
Maternal substance misuse*			<0.001
No	300 (50.5)	1701 (98.0)	
Yes	294 (49.5)	34 (2.0)	
Maternal recipiency of financial social assistance*			<0.001
No	65 (10.9)	1207 (69.6)	
Short-term (1–9 months during a calendar year)	140 (23.6)	322 (18.6)	
Long-term (10–12 months during a calendar year)	389 (65.5)	206 (11.9)	
Maternal criminality*			<0.001
No	549 (92.4)	1727 (99.5)	
Yes	45 (7.6)	8 (0.5)	
Death of mother*			<0.001
No	542 (91.2)	1729 (99.7)	
Yes	52 (8.8)	6 (0.3)	
Childhood adversity score*			<0.001
0	90 (15.2)	1353 (78.0)	
1 adversity	161 (27.1)	289 (16.7)	
2 adversities	173 (29.1)	73 (4.2)	
3 to 5 adversities	170 (28.6)	20 (1.2)	
Out-of-home care			
First OHC episode, n (%)			<0.001
No OHC episodes	213 (35.9)	1594 (91.9)	
Yes, <13 years of age	344 (57.9)	86 (5.0)	
Yes, ≥13 years of age	37 (6.2)	55 (3.2)	
Age in years at the first OHC episode (median, IQR)	2.9 (1.0; 6.9)	10.8 (5.3; 14.3)	<0.001
Cumulative length of OHC episodes in years (median, IQR)	9.2 (2.1; 15.0)	1.1 (0.2; 4.1)	<0.001

Note: p-values based on χ^2 test for categorical variables and Mann-Whitney U test or independent samples t-test for continuous variables, SD: Standard Deviation, IQR: Interquartile Range, FASD: Fetal Alcohol Spectrum Disorders, *occurred prior to the offspring's 13th birthday, Childhood adversity score includes the occurrence of maternal mental and/or behavioural disorder, maternal substance misuse, maternal long-term financial social assistance, maternal criminality, and death of the mother.

increasingly associated with mood and neurotic disorders. Regarding the cumulative childhood adversity score, the likelihood of mood and neurotic disorders was nearly similar across the categories and AHR spanned from 1.83 (1.33–2.51) for 1 adversity, AHR 1.90 (1.25–2.87) for 2 adversities to AHR 2.00 (1.24–3.22) for 3 to five adversities. With respect to OHC, the likelihood of the disorders differed between the categories, AHR spanning from 1.77 (95% CI 1.22–2.55) for first OHC episode <13 years of age to AHR 5.12 (95% CI 3.53–7.43) for first OHC episode ≥13 years of age (Table 3).

In the mediation analyses, we studied the mediating effect of OHC on the association between prenatal substance exposure and mood and neurotic disorders during youth. Although prenatal substance exposure showed a minor direct effect on mood and neurotic disorders ($b = 0.04$, 95% CI 0.01–0.08), the mediating effect of OHC was strong (indirect effect $b = 0.07$, 95% CI 0.05–0.08). The results indicated that OHC mediated 61% (95% CI 0.41–0.94) of the association between prenatal substance exposure and mood and neurotic disorders (Table 4, Fig. 4).

Table 2
Specialised healthcare for mood and neurotic disorders among the exposed and unexposed.

	Exposed (n = 594)	Unexposed (n = 1735)	p-value
Outpatient hospital care			
Care episodes (≥13 years of age) per 1000 people	210.4	95.1	<0.001
First care episode by age, n (%)			<0.001
No care episodes	431 (72.6)	1529 (88.1)	
<13 years of age	38 (6.4)	41 (2.4)	
≥13 years of age	125 (21.0)	165 (9.5)	
Age at the first care episode (median, IQR)	14.5 (13.3; 16.7)	15.1 (13.5; 16.8)	0.112
Cumulative number of care episodes ≥13 years of age (median, IQR)	14.0 (5.0; 32.0)	13.0 (2.0; 35.0)	0.386
Inpatient hospital care			
Care episodes (≥13 years of age) per 1000 people	60.6	16.7	<0.001
First care episode by age, n (%)			<0.001
No care episodes	548 (92.3)	1700 (98.0)	
<13 years of age	10 (1.7)	6 (0.3)	
≥13 years of age	36 (6.1)	29 (1.7)	
Age at the first care episode (median, IQR)	15.6 (13.2; 17.1)	16.5 (14.6; 17.9)	0.173
Cumulative number of days spent in inpatient hospital care ≥13 years of age (median, IQR)	12.0 (3.0; 28.0)	12.0 (3.5; 22.5)	0.861
Outpatient or inpatient hospital care			
Care episodes (≥13 years of age) per 1000 people	208.8	95.7	<0.001
First care episode by age, n (%)			<0.001
No care episodes	429 (72.2)	1525 (87.9)	
<13 years of age	41 (6.9)	44 (2.5)	
≥13 years of age	124 (20.9)	166 (9.6)	

Note: Mood and neurotic disorders based on ICD-10 categories F30-F39 and F40-F48; Comparison between exposed and unexposed based on χ^2 test for categorical variables and Mann-Whitney U test for continuous variables, IQR; Interquartile Range.

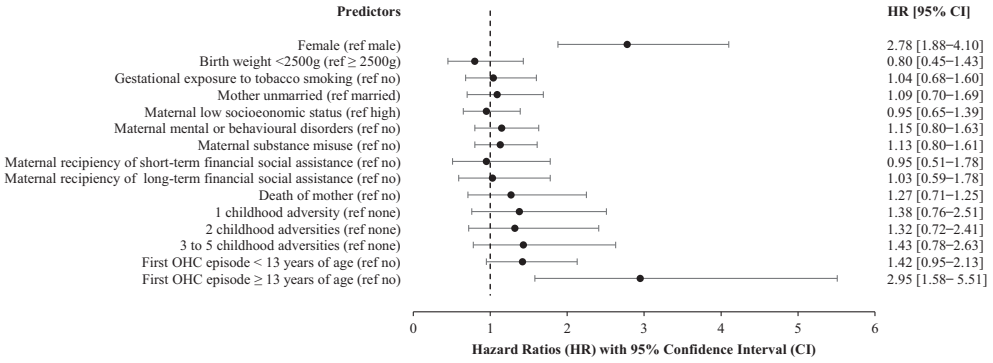

Fig. 2. Hazard ratios (HR) with 95% Confidence Intervals (CI) for predictors in relation to mood and neurotic disorders for exposed offspring. Follow-up starts from the 13th birthday and continues until the first episode in specialised healthcare (≥13 years of age), death or end of follow-up 2016 (n = 594).

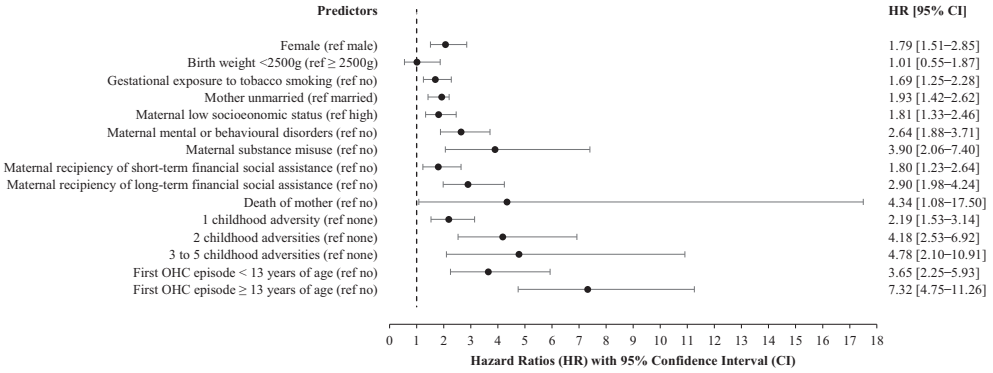

Fig. 3. Hazard ratios (HR) with 95% Confidence Intervals (CI) for predictors in relation to mood and neurotic disorders for unexposed offspring. Follow-up starts from the 13th birthday and continues until the first episode in specialised healthcare (≥13 years of age), death or end of follow-up 2016 (n = 1735).

Table 3
Cox proportional hazard regression analysis with crude Hazard Ratio (HR) and adjusted Hazard Ratios (AHR) with 95% Confidence Intervals (CI) for specialised healthcare for mood or neurotic disorders. Follow-up starts from the 13th birthday and continues until the first episode in specialised healthcare, death or end of follow-up 2016 ($N = 2329$).

	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
Offspring characteristics										
Prenatal substance exposure										
Unexposed (ref)	1		1		1		1		1	
Exposed	2.34 (1.86–2.95)	<0.001	2.34 (1.85–2.95)	<0.001	1.30 (0.96–1.77)	0.095	1.36 (0.99–1.85)	0.055	1.08 (0.78–1.49)	0.648
Sex										
Male (ref)			1		1		1		1	
Female			2.35 (1.83–3.00)	<0.001	2.34 (1.83–2.99)	<0.001	2.44 (1.91–3.13)	<0.001	2.44 (1.90–3.12)	<0.001
Maternal characteristics										
Cumulative childhood adversity score*										
No (ref)					1				1	
1 adversity					2.17 (1.60–2.96)	<0.001			1.83 (1.33–2.51)	0.067
2 adversities					2.60 (1.76–3.83)	<0.001			1.90 (1.25–2.87)	0.002
3 to 5 adversities					2.66 (1.71–4.15)	<0.001			2.00 (1.24–3.22)	0.005
Out-of-home care										
First OHC episode										
No OHC episodes							1		1	
Yes, <13 years of age							2.34 (1.66–3.29)	<0.001	1.77 (1.22–2.55)	0.002
Yes, ≥13 years of age							5.97 (4.14–8.60)	<0.001	5.12 (3.53–7.43)	<0.001

Note: Childhood adversity score includes the occurrence of maternal mental or behavioural disorder, maternal substance misuse, maternal recipiency of long-term financial social assistance, maternal criminality, and death of the mother prior to offspring's 13th birthday.

Table 4
The effect of out-of-home care (OHC) on the association between prenatal substance exposure and youth's mood and neurotic disorders. Parameter estimates (*b*) with standard error (SE), 95% Confidence Interval (CI) and *p*-value.

	Out-of-home care			
	b	SE	95% CI	p-Value
Prenatal substance exposure and mediator (a)	0.59	0.02		<0.001
Mediator and youth's mood and neurotic disorder (b)	0.94	0.11		<0.001
Indirect effect (ab)	0.07		0.05–0.08	<0.001
Direct effect (c′)	0.04		0.01–0.08	0.028
Proportion mediated (ab / (ab + c′))	0.61		0.41–0.94	<0.001
Total effect (c)	0.11		0.07–0.14	<0.001

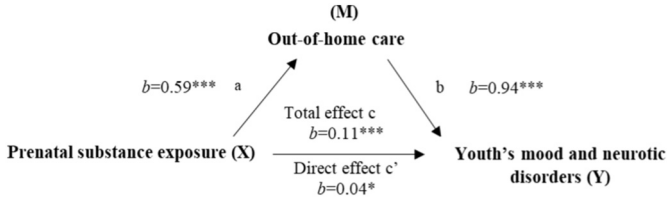

Fig. 4. The mediating effect of out-of-home care (M) on the association between prenatal substance exposure (X) and youth's mood and neurotic disorders (Y). Parameter estimates (*b*) with *p*-value ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

4. Discussion

This study shows a two-fold higher likelihood of specialised healthcare episode for mood and neurotic disorder among youth with prenatal substance exposure compared with matched unexposed youth. The study shows that mood and neurotic disorders are influenced by female sex, adversities in the postnatal caregiving environment and out-of-home care (OHC), and the association between prenatal substance exposure and mood and neurotic disorders is mediated by OHC.

Prior research has mainly studied specific mood or neurotic disorders among small samples of children and youth exposed to alcohol or other substances during pregnancy, and the information on symptomatology has mainly been based on parental assessment (Fryer et al., 2007; Gray et al., 2005; Nygaard et al., 2020; Roebuck et al., 1999; Walthall et al., 2008; Weyrauch et al., 2017). Despite these methodological differences, our results are in line with prior evidence indicating a higher prevalence of mood and neurotic disorders among prenatally exposed youth.

Earlier studies among children with FASD (Famy et al., 1998; Fryer et al., 2007; Walthall et al., 2008; Weyrauch et al., 2017), and children and youth with prenatal exposure to other substances (Gray et al., 2005; Nygaard et al., 2020) show, similar to the present study, the association between mood and neurotic disorders and caregiving adversities. Mood and neurotic disorders are, thus, multifaceted in these populations, and involve both adverse prenatal and postnatal conditions. In line with prior studies (Kuehner, 2003; Rapee et al., 2009), the study also shows that mood and neurotic disorders are more common among female youth.

A strength of our study was the ability to address the influence of multiple types of postnatal risk factors in our analyses. Our results are in line with earlier studies showing that maternal substance use during pregnancy is associated with other, often co-occurring risk factors in the postnatal caregiving environment including single parenthood, maternal mental health disorders, substance misuse, financial difficulties and challenges in the parenting domain (Esper and Furtado, 2014; Jääskeläinen et al., 2016). Our results showed that the exposure to a cumulative number of adversities in the postnatal caregiving environment was associated with an increased likelihood of mood and neurotic disorders. The significant influence of early life adversities on youth's mental health outcomes has been identified also in earlier studies (Basu and Banerjee, 2020; Essex et al., 2006). Exposure to adversities in the postnatal caregiving environment can be associated with the stress of the child and this can cause physiological and anatomical

alternations in the brain (Danese and McEwen, 2012; Shonkoff and Garner, 2012; Su et al., 2021), potentially affecting child's mental health outcomes. Adversities in childhood can also negatively influence parenting behaviours and parent-child interaction, and thus, indirectly increase the likelihood of a child's symptomatology of mood and neurotic disorders (Brumariu and Kerns, 2010; Rapee et al., 2009; Reising et al., 2013; Staton-Tindall et al., 2013).

The adversities in the postnatal caregiving environment and instability in care are also common indications for child protection services and a high proportion of prenatally exposed children need OHC during early childhood (Flannigan et al., 2021; Sarkola et al., 2007). Also, our results show that a high proportion of the exposed youth had been placed in OHC in childhood. Previous studies also show that multiple types of childhood adversities (Basu and Banerjee, 2020; Björkenstam et al., 2017; Essex et al., 2006) and OHC predict mood and neurotic disorders in childhood (Bronsard et al., 2016; Sarkola et al., 2011). In line with prior studies, also the mediation analyses indicated a significant influence of OHC on mood and neurotic disorders and showed that 61% of the association between prenatal substance exposure and youth's mood and neurotic disorders was explained by the influence of OHC. OHC typically refers to significant problems in the postnatal caregiving environment and parenting domains, which can negatively influence a child's mental health. However, it was not in the scope of this study to investigate the role of OHC in more detail, and therefore, more studies investigating the influence of OHC are needed. The influence of OHC likely differs between the cohorts considering the timing of the first OHC episode and the duration, potentially reflecting different reasons for OHC placement among the exposed and unexposed. However, having to be separated from biological parents is a traumatic experience as such and underlying capacity and resilience to cope with this experience may also differ between the exposed and unexposed children.

Youth is a period for education completion, finding a job and establishing relationships. Mood and neurotic disorders commonly evolve in youth, and the high prevalence of these disorders among exposed youth may contribute to functional impairments and challenge the accomplishment of these activities (Patel et al., 2007). The disorders may, therefore, have a substantial impact on economic and social outcomes extending into adulthood. With a view to the prevention of these disorders and related problems, the optimisation of postnatal parenting and caregiving among prenatally exposed children and youth seems important. Early preventative interventions aiming to reduce the long-term consequences of prenatal substance exposure should focus on reducing postnatal childhood adversities and potential adverse effects of OHC.

4.1. Strengths and limitations

A strength of this study is the use of national health and social care registers with high completeness and validity (Aro et al., 1990; Gissler and Haukka, 2004). By using national mandatory health and social care register data on specific types of childhood adversities, we were able to avoid the risk of recall bias or under-reporting of adverse events. In addition, we included data on specialised healthcare episodes for mood and neurotic disorders and thus were able to avoid data collection inaccuracies related to retrospectively reported information on youth symptomatology only. However, specialised healthcare data likely include more severe cases of youth with mood and neurotic disorders, and we may have missed milder forms of the studied psychiatric disorders.

Although the delivery of out-of-home care generally indicates significant problems in the caregiving environment or the parenting domain, we acknowledge the limitations related to the indicators of childhood adversities and the possibility of missed information on specific indicators (e.g. neglect, abuse, witnessing domestic violence, parent-child interaction, and paternal influences) that could be linked with mood and neurotic disorders.

In addition, we acknowledge the lack of specific information on the type, timing and severity of maternal alcohol and/or other substance use during the pregnancy. Self-reported information on substance use in the clinic setting is inevitably inaccurate and the data precludes meaningful analyses on independent associations with a specific type of substance. Therefore, exposed vs. unexposed categorisation was applied in the analyses. Our exposed cohort, however, represent children born to women with significant substance misuse during pregnancy, and thus excludes children born to mothers with low or moderate substance use. Furthermore, the unexposed cohort may also include cases with low prenatal substance exposure. All efforts were made to exclude from the unexposed group youth with registered information on maternal substance misuse related primary or secondary diagnoses or external causes in specialised healthcare one year before delivery or at the time of delivery. Substance use is also commonly linked with significant psychiatric comorbidity as shown among mothers in our exposed cohort. Our data did not, however, allow us to separately delineate contributions of maternal postnatal substance use and psychiatric comorbidities on youth outcomes. Lastly, as this is an observational study, causal links are difficult to prove.

5. Conclusions

Mood and neurotic disorders are more common following prenatal substance exposure and are interlinked with significant postnatal caregiving adversities and OHC. These disorders could potentially be prevented with efforts focused not only on preventing prenatal substance exposure but also on improving the postnatal caregiving environment and optimising child protection services.

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Author contributions

NMN merged the data, conducted the statistical analyses and drafted the manuscript and revised the later versions. MG participated in data collection design, anonymised the original data, advised with statistical analyses and reviewed and revised the manuscript. TS, IAR, and HK participated in data collection design and reviewed and revised the manuscript. AK acquired funding for the research, designed the data collection and reviewed and revised the manuscript. All the authors approved the final version and consented to its publication.

Data availability

The data are not publicly available due to data confidentiality. The authors do not have permission to share the data, but similar data can be applied for from Findata, the Finnish Social and Health Data Permit Authority: (https://findata.fi/en/).

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Conflict of interest

The authors have no conflicts of interest to declare.

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