Received: 24 March 2022 | Revised: 20 April 2022 | Accepted: 27 April 2022

DOI: 10.1111/apa.16377

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Preterm birth, poor foetal growth and anxiety disorders in a Finnish nationwide register sample

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Funding information
Dr. Sourander received funding from the Academy of Finland Flagship Programme (decision number 320162), the Strategic Research Council at the Academy of Finland (decision number 303581), the Academy of Finland Health from Cohorts and Biobanks Programme (decision number 308552). Dr. Sucksdorff received funding from the State Research Funding of the Turku University Hospital, the Finnish Medical Foundation and the Päivikki and Sakari Sohlberg Foundation. The funders played no role in any aspect of the study or manuscript

Abstract

Aim: We examined the associations between preterm birth, poor foetal growth and anxiety disorders among children and adolescents. Additionally, we examined the impact of common comorbidities and specific anxiety disorders separately.

Methods: Three Finnish registers provided data on a nationwide birth cohort of 22,181 cases with anxiety disorders and 74,726 controls. Conditional logistic regression was used to examine the associations.

Results: Extremely very preterm birth and moderate-late preterm birth were associated with increased adjusted odds ratios (aOR) for anxiety disorders (aOR 1.39, 95% CI 1.11–1.75 and aOR 1.13, 95% CI 1.03–1.23, respectively). Weight for gestational age of less than −2SD (aOR 1.29, 95% CI 1.17–1.42) and −2SD to −1SD (aOR 1.08, 95% CI 1.03–1.14) were associated with increased odds ratios for anxiety disorders. When comorbidities were considered, the associations became statistically insignificant for pure anxiety disorders, but remained significant in the groups with comorbid depressive or neurodevelopmental disorders.

Conclusion: Preterm birth and poor foetal growth increased the odds for anxiety disorders. However, the associations seem to be explained by the conditions of comorbid depressive and neurodevelopmental disorders. Comorbidities should be considered when examining and treating child and adolescent anxiety disorders.

KEYWORDS
anxiety disorders, epidemiology, fatal growth, gestational age, preterm birth

1 | INTRODUCTION

Anxiety disorders are among the most common psychiatric disorders, with an estimated worldwide pooled prevalence of 6.5% in children and adolescents.[1] They tend to impair many areas of life and may lead to secondary psychopathology.[2,3] The aetiology is complex, as it involves genetics, temperamental factors, sociodemographic factors and childhood adversities.[4] Being born preterm or with poor foetal growth, defined as being born small for gestational age (SGA), have been associated with various psychiatric disorders.[5–10] The rates for preterm births vary globally, but the overall worldwide estimate is 9.6%–11.1%.[11] In Finland, 5%–6% of children are born preterm,[12] before 37 weeks of gestation.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; GA, gestational age; ICD, international classification of diseases; OR, odds ratio; SD, standard deviation; SES, socio-economic status; SGA, small for gestational age; WGA, weight for gestational age.

A limited number of studies have examined the role of preterm birth and poor foetal growth in the development of anxiety disorders in children and adolescents. These have mainly been cohort studies, with less than 100 cases. Register-studies enable researchers to examine large samples and to obtain reliable data on perinatal events. Seven register-based studies that examined preterm birth, birth weight or SGA and anxiety disorders were identified.[5–8,13–15] Only two of these specifically reported results on anxiety disorders among children and adolescents.[13,14] One Canadian register study of 7,800 children and adolescents with anxiety disorders reported that being born late preterm or early term increased the odds for anxiety disorders.[13] Another Canadian register study of 590 children as young as five years of age found that preterm birth decreased the odds.[14] The other five register studies focused on mixed age groups and broader diagnostic outcomes and also produced contradictory results.[5–8,15] No significant associations have been observed between SGA and anxiety disorders just among children and adolescents.[13,14,16] However, three of the register studies that included adults found associations between being born SGA and anxiety-related disorders.[5–7]

It should be noted that these previous register-based studies had their limitations. None of these register-based studies examined specific anxiety disorders separately and none of them studied the effects of comorbidities on the associations between gestational age (GA) or weight for gestational age (WGA) and anxiety disorders. Comorbidity means the co-occurrence of two or more disorders, although the temporal relationship can be defined broadly.[17] Comorbidities are highly common with youth anxiety disorders, especially depression and neuropsychiatric disorders.[2,18]

The main aim of this register-based study was to examine the associations between preterm birth, poor foetal growth and later anxiety disorders in children and adolescents, using a nested case-control design. GA and WGA were examined as categorical, as well as continuous variables. The aim was to examine whether the associations remained the same when common comorbidities were considered, and whether GA or WGA had a unique impact on the different types of anxiety disorders. Our hypothesis was that preterm birth and poor foetal growth would be associated with increased odds for anxiety disorders.

Key Notes

- This was the largest study to date examining the associations between preterm birth, poor foetal growth and child and adolescent anxiety disorders.
- Preterm birth and poor foetal growth associated linearly with increased odds for child and adolescent anxiety disorders.
- Conditions of comorbid depressive and neurodevelopmental disorders accounted for these associations.

2 | METHODS

2.1 | The registers

This study was part of the Finnish Prenatal Study of Anxiety (FIPS-Anx), which is an ongoing nationwide birth cohort study with a nested case-control study design. Cases with anxiety disorders were identified within the birth cohort and each case was matched with controls. Controls were selected from the same risk-set at each time of an incident case. The data for this study has been extracted from three national registers. Each resident in Finland receives a personal identification code and that code enabled researchers to link the information from all the national registers. The Data Protection Ombudsman approved the use and linkage of the register data. The national registers used in this study were the Finnish Care Register for Health Care (providing data on in- and out-patient diagnoses and treatment in specialised services), the Finnish Medical Birth Register (providing data on prenatal and perinatal variables) and the Finnish Population Register Centre (providing data on residency, immigrant status and paternal age) (Figure S1). Ethical approval was obtained from the Ethics Committee of the Hospital District of Southwest Finland.

2.2 | The sample

This study was based on a nationwide birth cohort of all singletons born in Finland between January 1st 1992 and December 31st 2006 and followed up until 2016. We focused on the 22,181 subjects who had received an anxiety disorder diagnosis between 1998 and 2012 and had the required data on GA and WGA recorded. Each case was matched with four controls by sex and date of birth (±30 days). The diagnoses were obtained from the Care Register for Health Care, and the clinician made diagnoses included the following International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes: F40, F41, F93 and F94.0. Cases who were diagnosed only before the year of their sixth birthday were excluded. Subjects with severe or profound intellectual disabilities were excluded from both the cases and the controls. In addition, those who received an anxiety disorder diagnosis during the follow-up period, to 2016, were excluded from the controls. This means that there were 74,726 controls.

2.3 | Comorbidities

The cases were stratified by comorbidity status (Table S1). Comorbid depressive (ICD-10: F32–F39) and neurodevelopmental disorders (ICD-10: F70–F71, F78–F84, F90, F95) were chosen, and these diagnoses were given at any time during the study period. These comorbidities have been reported to be common

among children and adolescents with anxiety disorders,[2,18] and they have been associated with preterm birth or poor foetal growth.[9,10,19,20] The group of pure anxiety disorders comprised of those cases, who had no other psychiatric disorder diagnoses during the study period.

2.4 | Specific anxiety disorders

The subtypes of anxiety disorders were also examined: generalised anxiety disorder (ICD-10: F41.1 and F93.80) (n = 2,115), panic disorder and/or agoraphobia (F40.00, F40.01, F41.00, F41.01, F41.08, F41.09) (n = 1,939), separation anxiety disorder (F93.0) (n = 655), social phobia (F40.1 and F93.2) (n = 1,921) and specific phobia (F40.2 and F93.1) (n = 2,567).

2.5 | Exposures

Gestational age was classified according to the World Health Organization categories: extremely and very preterm (less than 32 gestational weeks), moderate to late preterm (32–36 gestational weeks), term (37–41 gestational weeks) and post term (42 or more gestational weeks), with term as the reference category. Weekly categorisation of GA enables to indicate certain weeks of vulnerability, whereas continuous analyses are able to show whether the examined associations are linear or quadratic by nature. We analysed GA weekly and as a continuous variable, with week 40 as the reference category. GA was calculated based on a first trimester ultrasound. WGA was calculated according to national gender-specific birth weight distribution standards for a given gestational age. WGA was categorised into five categories: less than −2 SD, from −2SD to −1SD, from −1 SD to +1SD (reference category), from +1SD to +2SD, more than +2 SD. We also analysed WGA as a continuous variable.

We excluded 1,614 subjects, of which 207 (12.8%) were cases, from the original pool of cases and controls, because the information on GA or birth weight was not available and a further three because the WGA value was incorrect (>±10SD).

2.6 | Covariates

Table 1 presents the confounders included in this study: parental age, number of previous births, one-minute Apgar score, maternal smoking during pregnancy, marital status at birth, maternal socioeconomic status (SES), urbanicity, maternal immigrant status, maternal substance use disorders (ICD-8: 291, 303, 304; ICD-9: 291, 292, 303, 304, 305; ICD-10: F10–F19) and parental psychopathology (ICD-8: 291–308; ICD-9: 291–316; ICD-10: F10–F99, maternal substance use disorders excluded). The paternal factors were missing for 1,144 children, which was 1.2% of the whole cohort of cases and controls. Comorbid depressive (ICD-10: F32–F39) and neurodevelopmental disorders (ICD-10: F70–F71, F78–F84, F90, F95) were examined as confounders for specific anxiety disorders. Comorbidities were diagnosed at any point of time during the study period.

2.7 | Statistical methods

We used conditional logistic regression to estimate the unadjusted odds ratios (ORs) and two-sided 95% confidence intervals (CI) for the case-control model, namely anxiety disorders by GA and by WGA. The adjusted model was developed in three phases. First, we evaluated the association between each potential confounder and GA and WGA, using Pearson's chi-square for the general population controls. Second, we used conditional logistic regression to test for the association between each covariate and diagnosed anxiety disorder in the case-control design. Finally, covariates were considered as confounders in the final multivariate model if steps one and two indicated statistical significance. In order to detect possible multicollinearity, Spearman's correlation was calculated between depressive and neurodevelopmental disorders, as well as between maternal SES, marital status and smoking variables. In addition, the possible clustering of the missing values of these three maternal variables were examined. GA and WGA were examined as categorical and continuous variables. The model fit in the linear and quadratic models were tested and the linear model was chosen based on the Akaike information criterion. Two-sided $p < 0.05$ was considered statistically significant. The statistical analyses were carried out using the SAS software, version 9.4 (SAS Institute, Inc.).

3 | RESULTS

The total study population consisted of 22,181 cases and of 74,726 controls and 55.4% were female. The mean age at the time of an anxiety disorder diagnosis was 12.7 ± 3.7 years (range 5–20 years). Among the sample, 19,110 cases (86.2%) and 67,698 controls (90.6%) had all the requisite data available and these subjects were used in the adjusted analyses. All the covariates, except for paternal psychiatric history, were associated with GA, and they were all associated with WGA and offspring anxiety disorders. The frequencies of demographic and perinatal variables among the cases and controls can be seen in Table 1.

Table 2 shows the results of the unadjusted and adjusted models for categorised GA and WGA. Extremely to very and moderate to late preterm birth were significantly associated with an increased odds ratio for anxiety disorders in both the unadjusted and adjusted models (aOR 1.39, 95% CI 1.11–1.75 and aOR 1.13, 95% CI 1.03–1.23, respectively). Figure 1 shows the observed linear association between continuous GA and anxiety disorders ($p < 0.001$). The results for the weekly categorisation are presented in Table S2 and Figure S2.

TABLE 1 Confounders and their associations with exposures and outcome

Covariate	Cases total *n* (%) *N* = 22,181	Controls total *n* (%) *N* = 74,726	Association with gestational age/*weight for gestational age*	Association with any anxiety disorder
Maternal age at birth				
≤19	1,032 (4.65)	1,879 (2.51)	$p < 0.001$/ $p < 0.001$	$p < 0.001$
20–29	11,587 (52.24)	38,743 (51.85)		
30–39	8,775 (39.56)	32,056 (42.90)		
≥40	787 (3.55)	2,048 (2.74)		
Paternal age at birth				
≤19	321 (1.48)	482 (0.65)	$p < 0.001$/ $p < 0.001$	$p < 0.001$
20–29	8,704 (40.16)	28,675 (38.70)		
30–39	10,170 (46.92)	37,940 (51.21)		
≥40	2,478 (11.43)	6,993 (9.44)		
Missing	508	636		
Number of mothers' previous births				
0	9,548 (43.08)	29,692 (39.76)	$p < 0.001$/ $p < 0.001$	$p < 0.001$
≥1	12,614 (56.92)	44,987 (60.24)		
Missing	19	47		
The one-minute Apgar score				
<7	928 (4.18)	2,873 (3.84)	$p < 0.001$/ $p < 0.001$	$p = 0.02$
≥7	21,253 (95.82)	71,853 (96.16)		
Maternal smoking during pregnancy[a]				
Yes	5,481 (25.27)	11,064 (15.13)	$p < 0.001$/ $p < 0.001$	$p < 0.001$
No	16,208 (74.73)	62,044 (84.87)		
Missing	492	1,618		
Maternal substance abuse disorders				
Yes	1,878 (8.47)	1,890 (2.53)	$p = 0.002$/ $p < 0.001$	$p < 0.001$
No	20,303 (91.53)	72,836 (97.47)		
Maternal psychiatric disorders				
Yes	7,615 (34.33)	10,627 (14.22)	$p < 0.001$/ $p < 0.001$	$p < 0.001$
No	14,566 (65.67)	64,099 (85.78)		
Paternal psychiatric disorders				
Yes	6,108 (28.18)	10,613 (14.32)	$p = 0.51$/ $p < 0.001$	$p < 0.001$
No	15,565 (71.82)	63,477 (85.68)		
Missing	508	636		
Maternal marital status at time of birth[a]				
Married/in a relationship	18,638 (93.84)	67,620 (97.14)	$p < 0.001$/ $p < 0.001$	$p < 0.001$
Single	1,224 (6.16)	1,994 (2.86)		
Missing	2,319	5,112		
Maternal SES at time of birth[a]				
Upper white-collar worker	2,700 (12.17)	11,516 (15.41)	$p = 0.002$/ $p < 0.001$	$p < 0.001$
Lower white-collar worker	8,957 (40.38)	33,667 (45.05)		
Blue-collar worker	4,712 (21.24)	13,817 (18.49)		
Others	4,523 (20.39)	12,374 (16.56)		
Missing	1,289 (5.81)	3,352 (4.49)		
Region of birth				
Rural	3,857 (17.39)	16,176 (21.65)	$p = 0.001$/ $p < 0.001$	$p < 0.001$
Semi-urban	3,240 (14.61)	13,016 (17.42)		
Urban	15,078 (68.00)	45,509 (60.92)		
Missing	6	25		

TABLE 1 (Continued)

Covariate	Cases total *n* (%) *N* = 22,181	Controls total *n* (%) *N* = 74,726	Association with gestational age/*weight for gestational age*	Association with any anxiety disorder
Maternal immigrant status				
Immigrant	520 (2.34)	1,980 (2.65)	$p = 0.02$/ $p < 0.001$	$p = 0.01$
Not immigrant	21,661 (97.66)	72,746 (97.35)		

Abbreviation: SES, socio-economic status.

[a] Spearman's correlation values between maternal SES, marital status and smoking were small (0.1 – 0.15) indicating there was no multicollinearity. The information on all of these three covariates was missing from 0.03% of the sample and there was missing information for two of these covariates from 1% of the sample.

TABLE 2 Frequencies for cases with anxiety disorders, their matched controls and the associations between gestational age, weight for gestational age and anxiety disorders in the unadjusted and adjusted models

Gestational age, weeks [a]	Cases (%) *N* = 22,181	Controls (%) *N* = 74,726	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
<32	160 (0.72)	358 (0.48)	**1.52 (1.26–1.84)**	**<0.001**	**1.39 (1.11–1.75)**	**0.005**
32–36	965 (4.35)	2,756 (3.69)	**1.20 (1.11–1.29)**	**<0.001**	**1.13 (1.03–1.23)**	**0.007**
37–41	19,978 (90.07)	68,194 (91.26)	Reference		Reference	
≥42	1,078 (4.86)	3,418 (4.57)	**1.08 (1.00–1.16)**	**0.04**	1.03 (0.95–1.12)	0.45
Weight for gestational age[b]						
<−2SD	873 (3.94)	2,087 (2.79)	**1.45 (1.33–1.57)**	**<0.001**	**1.29 (1.17–1.42)**	**<0.001**
−2SD to −1SD	3,700 (16.68)	10,697 (14.31)	**1.20 (1.15–1.26)**	**<0.001**	**1.08 (1.03–1.14)**	**0.002**
−1SD to +1SD	14,235 (64.18)	49,523 (66.27)	Reference		Reference	
+1SD to +2SD	2,635 (11.88)	9,695 (12.97)	**0.95 (0.90–0.99)**	**0.02**	0.98 (0.92–1.03)	0.35
>+2SD	738 (3.33)	2,724 (3.65)	0.95 (0.87–1.03)	0.19	0.98 (0.89–1.08)	0.73

The bolded values are statistically significant (p<0.05).

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

[a] Adjusted for maternal age, paternal age, number of previous births, 1-minute Apgar score, maternal smoking, maternal substance use disorders, maternal psychiatric disorders, maternal marital status, maternal SES, region of birth and maternal immigrant status.

[b] Adjusted for maternal age, paternal age, number of previous births, 1-minute Apgar score, maternal smoking, maternal substance use disorders, maternal psychiatric disorders, paternal psychiatric disorders, maternal marital status, maternal SES, region of birth and maternal immigrant status.

Weight for gestational age of <−2SD and WGA of −2SD to −1SD were significantly associated with an increased odds ratio for anxiety disorders in both the unadjusted and adjusted models (aOR 1.29, 95% CI 1.17–1.42 and aOR 1.08, 95% CI 1.03–1.14, respectively) (Table 2). The linear association found between continuous WGA and anxiety disorders ($p < 0.001$) is presented in Figure 2.

3.1 | Comorbidities

Only 21.6% of the cases were in the pure anxiety disorder group. It was found that 42.1% of the cases had comorbid depressive and 30.3% had comorbid neurodevelopmental disorders.

Surprisingly, the associations between preterm birth, poor foetal growth and pure anxiety disorders were not significant after the study subjects were stratified into the comorbidity groups. Nevertheless, the associations between preterm birth, poor foetal growth and anxiety disorders remained significant in the groups of comorbid depressive or neurodevelopmental disorders. These results are presented in detail in Table 3. In the comorbid depressive disorders group, extreme to very preterm birth (aOR 1.71, 95% CI 1.19–2.45), WGA less than −2SD (aOR 1.19, 95% CI 1.02–1.39) and WGA −2SD to −1SD (aOR 1.09, 95% CI 1.01–1.18) were significantly associated with an increased odds ratio for anxiety disorders. In the neurodevelopmental comorbidity group, the odds ratios indicated even more increased odds for anxiety disorders. There were significant associations with extremely to very preterm birth (aOR 2.91, 95% CI 2.04–4.15) and moderate to late preterm birth (aOR 1.36, 95% CI 1.17–1.59), WGA of less than −2SD (aOR 1.81, 95% CI 1.53–2.14) and WGA −2SD to −1SD (aOR 1.14, 95% CI 1.04–1.24) and anxiety disorders.

3.2 | Specific anxiety disorders

The mean age in years (SD) for each specific anxiety disorder was 12.2 (3.7) for generalised anxiety disorder; 15.3 (2.6) for panic disorder/agoraphobia; 9.8 (2.7) for separation anxiety disorder; 14.5 (3.1) for social phobia; and 9.9 (3.0) for specific phobia. The age range was 5–20 years for all. Moderate to late preterm birth was significantly

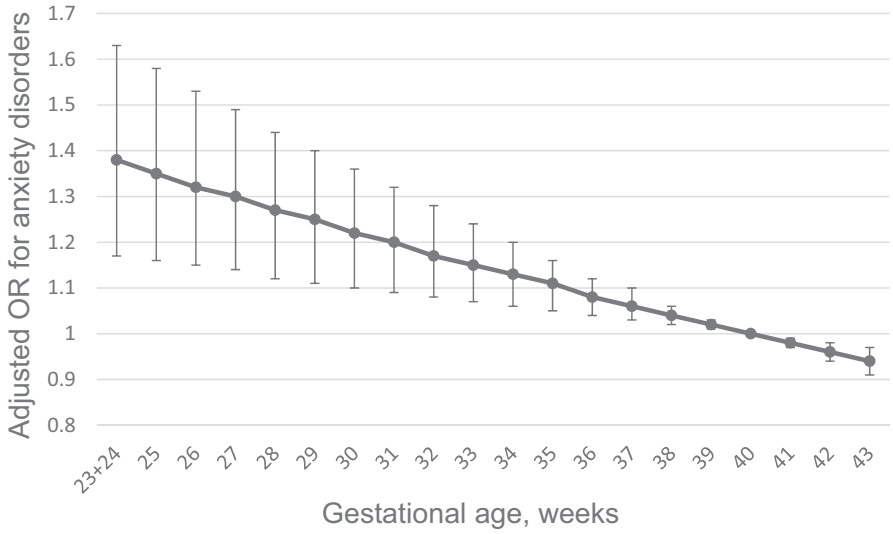

FIGURE 1 Adjusted linear association between gestational age and anxiety disorders. OR, odds ratio. Adjusted for maternal age, paternal age, number of previous births, 1-minute Apgar score, maternal smoking, maternal substance use disorders, maternal psychiatric disorders, maternal marital status, maternal SES, region of birth and maternal immigrant status

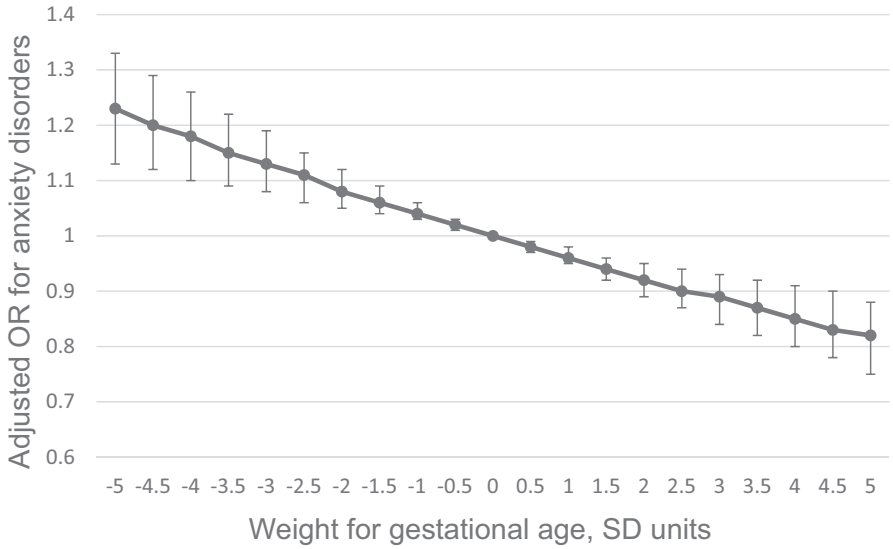

FIGURE 2 Adjusted linear association between weight for gestational age and anxiety disorders. OR, odds ratio; SD, standard deviation. Adjusted for maternal age, paternal age, number of previous births, 1-minute Apgar score, maternal smoking, maternal substance use disorders, maternal psychiatric disorders, paternal psychiatric disorders, maternal marital status, maternal SES, region of birth and maternal immigrant status

associated with an increased odds ratio for generalised anxiety disorder (aOR 1.72, 95% CI 1.22–2.43), post term birth with a decreased odds ratio for separation anxiety disorder (aOR 0.46, 95% CI 0.21–0.98) and WGA of less than −2SD with an increased odds ratio for specific phobia (aOR 1.58, 95% CI 1.18–2.13) (Tables S3–S4). A significant inverse linear association was observed in the continuous model between preterm birth and specific phobia in both, the unadjusted and adjusted models, (weeks 23 and 24: aOR 2.34, 95% CI 1.38–3.98). No significant associations were found for the other specific anxiety disorders in the adjusted continuous models (Table S5).

4 | DISCUSSION

This was the largest study to date to examine the associations between preterm birth, poor foetal growth and anxiety disorders among children and adolescents. Both preterm birth and poor foetal growth were associated with an increased odds for anxiety disorders when the data were controlled for potential confounders. When the sample was stratified into three groups, based on comorbidities, it was found that preterm birth and poor foetal growth were associated with anxiety disorders with comorbid depressive disorders and comorbid neurodevelopmental disorders. However, the group with pure anxiety disorders was not associated with preterm birth or poor foetal growth.

Previous register-based studies have reported inconsistent findings between preterm birth, poor foetal growth and anxiety disorders, both in children and adults.[5–8,13–15] The inconsistencies could be explained by the differences in the study designs as well by the limitations of the studies. The age ranges varied from young children to older adults and the outcome diagnoses and exposures varied substantially. Paternal confounders were poorly taken into account, as paternal age and psychopathology only included in one study each.[7,8] Most of all, none of the previous studies examined the impact that comorbidities had on the associations between GA, WGA and anxiety disorders. Including possible comorbidities in the analyses was of major importance, as preterm birth and poor foetal

TABLE 3 Frequencies for cases with anxiety disorders, their matched controls and the associations between gestational age, weight for gestational age and pure anxiety disorders, anxiety with comorbid depressive disorders or anxiety with comorbid neurodevelopmental disorders in the unadjusted and adjusted models

Gestational age, weeks [a]	Cases in pure anxiety group *n* (%) *N* = 4,789	Controls in pure anxiety group *n* (%) *N* = 16,098	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
<32	21 (0.44)	81 (0.50)	0.89 (0.55–1.44)	0.62	0.91 (0.52–1.59)	0.75
32–36	208 (4.34)	604 (3.75)	1.15 (0.98–1.35)	0.10	1.12 (0.93–1.35)	0.23
37–41	4,370 (91.25)	14,691 (91.26)	Reference		Reference	
≥42	190 (3.97)	722 (4.49)	0.89 (0.75–1.05)	0.16	0.88 (0.73–1.06)	0.17
Weight for gestational age [b]						
<−2SD	142 (2.97)	438 (2.72)	1.11 (0.91–1.35)	0.29	1.08 (0.87–1.35)	0.49
−2SD to −1SD	716 (14.95)	2,284 (14.19)	1.06 (0.97–1.17)	0.20	0.99 (0.89–1.10)	0.88
−1SD to +1SD	3,144 (65.65)	10,650 (66.16)	Reference		Reference	
+1SD to +2SD	612 (12.78)	2,169 (13.47)	0.95 (0.86–1.05)	0.33	0.95 (0.85–1.06)	0.35
>+2SD	175 (3.65)	557 (3.46)	1.08 (0.91–1.29)	0.38	1.14 (0.94–1.38)	0.20
Gestational age, weeks [a]	**Cases in comorbid depressive disorders group *n* (%) *N* = 9,337**	**Controls in comorbid depressive disorders group *n* (%) *N* = 31,238**	**Unadjusted OR (95% CI)**	***p*-Value**	**Adjusted OR (95% CI)**	***p*-Value**
<32	65 (0.70)	145 (0.46)	**1.51 (1.12–2.02)**	**0.007**	**1.71 (1.19–2.45)**	**0.004**
32–36	362 (3.88)	1,126 (3.60)	1.09 (0.97–1.23)	0.16	0.99 (0.86–1.14)	0.85
37–41	8,444 (90.44)	28,538 (91.36)	Reference		Reference	
≥42	466 (4.99)	1,429 (4.57)	1.10 (0.99–1.22)	0.09	1.07 (0.94–1.21)	0.31
Weight for gestational age [b]						
<−2SD	340 (3.64)	860 (2.75)	**1.35 (1.19–1.54)**	**<0.001**	**1.19 (1.02–1.39)**	**0.03**
−2SD to −1SD	1,549 (16.59)	4,425 (14.17)	**1.21 (1.13–1.29)**	**<0.001**	**1.09 (1.01–1.18)**	**0.02**
−1SD to +1SD	6,005 (64.31)	20,728 (66.36)	Reference		Reference	
+1SD to +2SD	1,135 (12.16)	4,057 (12.99)	0.97 (0.90–1.04)	0.34	0.99 (0.91–1.08)	0.88
>+2SD	308 (3.30)	1,168 (3.74)	0.90 (0.79–1.03)	0.12	0.93 (0.80–1.07)	0.31
Gestational age, weeks [a]	**Cases in comorbid neurodevelopmental disorder group *n* (%) *N* = 6,714**	**Controls in comorbid neurodevelopmental disorder group *n* (%) *N* = 22,930**	**Unadjusted OR (95% CI)**	***p*-Value**	**Adjusted OR (95% CI)**	***p*-Value**
<32	96 (1.43)	111 (0.48)	**3.03 (2.30–3.99)**	**<0.001**	**2.91 (2.04–4.15)**	**<0.001**
32–36	356 (5.30)	881 (3.84)	**1.43 (1.25–1.62)**	**<0.001**	**1.36 (1.17–1.59)**	**<0.001**
37–41	5,906 (87.97)	20,887 (91.09)	Reference		Reference	
≥42	356 (5.30)	1,051 (4.58)	**1.20 (1.06–1.35)**	**0.005**	1.14 (0.98–1.32)	0.09

(Continues)

TABLE 3 (Continued)

Gestational age, weeks [a]	Cases in comorbid neurodevelopmental disorder group *n* (%) *N* = 6,714	Controls in comorbid neurodevelopmental disorder group *n* (%) *N* = 22,930	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
Weight for gestational age [b]						
<−2SD	361 (5.38)	648 (2.83)	**2.03 (1.78–2.32)**	**<0.001**	**1.81 (1.53–2.14)**	**<0.001**
−2SD to −1SD	1,196 (17.81)	3,374 (14.71)	**1.29 (1.20 to 1.39)**	**<0.001**	**1.14 (1.04–1.24)**	**0.006**
−1SD to +1SD	4,193 (62.45)	15,210 (66.33)	Reference		Reference	
+1SD to +2SD	749 (11.16)	2,891 (12.61)	0.94 (0.86–1.03)	0.18	1.03 (0.93–1.14)	0.57
>+2SD	215 (3.20)	807 (3.52)	0.98 (0.84–1.14)	0.75	1.02 (0.85–1.22)	0.88

The bolded values are statistically significant (p<0.05).

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

[a] Adjusted for maternal age, paternal age, number of previous births, 1-minute Apgar score, maternal smoking, maternal substance use disorders, maternal psychiatric disorders, maternal marital status, maternal SES, region of birth and maternal immigrant status.

[b] Adjusted for maternal age, paternal age, number of previous births, 1-minute Apgar score, maternal smoking, maternal substance use disorders, maternal psychiatric disorders, paternal psychiatric disorders, maternal marital status, maternal SES, region of birth and maternal immigrant status.

growth associated with various psychiatric disorders,[5–10] and comorbidity rates in children and adolescents with anxiety disorders are known to be high, notably depressive and neurodevelopmental disorders.[2,18] The inconsistencies in previous studies may well have been affected by the presence or lack of comorbidities.

Various mechanisms have been suggested to explain the associations between preterm birth, poor foetal growth and later psychiatric disorders. Preterm and SGA born individuals may encounter abnormal environments, both prenatally and postnatally, and this means that multiple mechanisms can occur at different perinatal stages.[11,21] Alterations in brain development[22] and the hypothalamus-pituitary-adrenal axis function[23] have been observed in preterm born individuals. Brain development is rapid during the last weeks of pregnancy and it has been observed that preterm brain can be extremely vulnerable to disturbances.[24] Altered brain development also associates with poor foetal growth, and it is explained by placental insufficiency.[25] Postnatal stress due to neonatal hospitalisation and treatment procedures has been linked to alterations in the central nervous system.[26] In addition, postnatal parental stress about their preterm children may have an impact on the development of psychopathology, via parental attachment and behaviour.[27] These mechanisms are not specific to anxiety disorders, but explanatory theories for a wide range of psychiatric disorders.

This study examined the effects of comorbidities in order to gain knowledge on the specific risk factors and mechanisms of anxiety disorders. However, the concept of comorbidities is complex.[3,17] The differences observed between the comorbidity groups in this study can be explained by a number of hypothetical theories.

First, it is possible that anxiety disorders are not impacted by preterm birth or poor foetal growth and all the associations are caused by comorbid disorders. This would highlight the etiological differences between anxiety disorders and depressive or neurodevelopmental disorders. It was not possible to compare pure depressive or pure neurodevelopmental disorders in the study, as the sample was comprised of anxiety disorder cases. It is also important to note that we did not examine whether comorbidities were the primary diagnoses or given after the anxiety disorder diagnosis. The results in our study could be different if primary and secondary comorbidities were separated, as the etiological processes might differ depending in which order the comorbidity appears. The primary disorder might serve as a risk factor for the secondary disorder or they might stem from shared etiological factors.[3]

The second hypothetical explanation for our findings is that comorbidities could have indicated more severe cases of anxiety disorders. That would highlight the importance of perinatal factors in the development of severe anxiety disorders. There was no information on the severity of the disorders in this sample. Third, it is possible that when anxiety disorders were combined with comorbidities, they formed somewhat different disorder entities than pure anxiety disorders alone and that this could explain the etiological differences that were observed. Bias in the diagnostic categorisation is also possible, all disease entities might not be valid in the psychiatric nosology.[17]

Fourth, there might be some common etiological factors for anxiety disorders and depressive and neurodevelopmental disorders that potentiate the impact of risk factors, namely preterm birth and poor foetal growth. For example, other perinatal factors that could have a potentiating impact may exist and genetic interference is also a possibility. The genetic effect could be further examined within a sibling model. All these theories provide possible explanations for the findings that we observed, but they remain hypothetical and need further examination.

Hypothetical theories can also be derived from the findings between preterm birth, poor foetal growth and specific anxiety disorders. We found differences between the specific anxiety disorders, although there were only a few significant findings. Preterm birth or SGA was only associated with increased rates of generalised anxiety disorders and specific phobias. These findings were somewhat similar to a meta-analysis by Fitzallen et al.[28]; the authors reported significant associations between preterm born children and increased risks for unspecified anxiety disorders, generalised anxiety disorders and specific phobias. Etiological differences in different anxiety disorders have previously been observed with regard to environmental factors.[29] Our study indicates that etiological differences may be also found in preterm birth and poor foetal growth.

There are certain limitations that must be considered when interpreting the findings of this study. The diagnoses in the Finnish Care Register for Health Care were made by specialised services and this means that milder anxiety disorders were not included. We were unable to validate the anxiety disorder diagnoses in the register. However, mental disorder diagnoses in the Finnish Care Register for Health Care have previously been rated from satisfactory to very good.[30] The numbers of the specific anxiety disorders were small and the results related to these should be carefully interpreted. The power of these analyses was only moderate and no diagnostic validation was carried out. In addition, we do not know, whether any of the controls received an anxiety disorder diagnosis after the follow-up period. We did not include multiple births, which might impact on the generalisation of the results. Finally, the subjects in this study received their diagnoses between the ages of six and 20 and that means that our findings cannot be generalised outside that age range.

5 | CONCLUSION

Preterm birth and poor foetal growth are risk factors for various psychiatric disorders. The associations with anxiety disorders among children and adolescents were better explained by their comorbid occurrence with depressive and neurodevelopmental disorders, but the actual weight of the effect that comorbidities had remains unknown. The high levels of comorbidities, and their possible contributions, should be considered when treating children and adolescents with anxiety disorders and when examining the risk factors for anxiety disorders. Future research areas include even larger sample sizes, comparisons between different disorder groups and sibling studies.

ACKNOWLEDGEMENT

The study was supported by the INVEST Research Flagship, APEX Research Consortium and PSYCOHORTS consortium and was conducted at the University of Turku, Finland. We thank the investigators and staff at the medical centres involved in this research.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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How to cite this article: Ståhlberg T, Upadhyaya S, Khanal P, et al. Preterm birth, poor foetal growth and anxiety disorders in a Finnish nationwide register sample. Acta Paediatr. 2022;00:1–10. doi:10.1111/apa.16377