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Maternal prenatal psychological distress associates with offspring early-life wheezing – FinnBrain Birth Cohort

Emma Puosi[1,2,3] | Laura S. Korhonen[1,2,3] | Linnea Karlsson[1,3,4] | Eeva-Leena Kataja[1,3,5] | Heikki Lukkarinen[1,2] | Hasse Karlsson[1,3,4] | Minna Lukkarinen[1,2,3]

[1]Department of Clinical Medicine, FinnBrain Birth Cohort Study, Turku Brain and Mind Center, University of Turku, Turku, Finland

[2]The Department of Pediatrics and Adolescent Medicine, University of Turku, and Turku University Hospital, Turku, Finland

[3]Centre for Population Health Research, University of Turku, and Turku University Hospital, Turku, Finland

[4]The Department of Psychiatry, University of Turku, and Turku University Hospital, Turku, Finland

[5]The Department of Psychology, University of Turku, Turku, Finland

Correspondence
Emma Puosi, FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, 20520 Turun yliopisto, Finland.
Email: emmapu@utu.fi

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Abstract

Background: Exposure to prenatal maternal psychological distress may contribute to the development of childhood atopic disorders. Little is known about the importance of distress severity and its duration for the risk. Our aim was to investigate how chronic maternal depressive and anxiety symptoms across gestation influence the risk of wheezing and eczema at child age 24 months.

Methods: The study population was drawn from the FinnBrain Birth Cohort Study, including 1305 mother-infant dyads followed across gestation until the child age of 24 months when the outcomes were mother-reported wheezing ever and doctor-diagnosed eczema. To investigate the risk of wheezing phenotypes, wheezing with and without eczema was separated. Maternal distress was assessed with the Edinburgh Postnatal Depression Scale for depressive and the Symptom Checklist-90 for anxiety symptoms three times during pregnancy, and the chronicity was demonstrated using symptom trajectories composed by latent growth mixture modeling.

Results: Of the children, 219/1305 (17%) had wheezing ever and 285/1276 (22%) had eczema. Risk of wheezing ever was elevated with maternal consistently high depressive symptoms (adjusted odds ratio 2.74; 95% confidence interval 1.37–5.50) or moderate and increasing anxiety symptoms (1.94; 1.06–3.54, respectively). Similarly, wheezing without eczema was associated with consistently high depressive (3.60; 1.63–7.94, respectively) and moderate and increasing anxiety symptoms (2.43; 1.21–4.91, respectively).

Conclusions: Maternal chronic psychological distress across gestation was associated with toddler wheezing and especially wheezing without other atopic features

Abbreviations: CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwk, gestational week; IQR, interquartile range; ISAAC, The International Study of Asthma and Allergies in Childhood; OR, odds ratio; PD, psychological distress; SCL-90, Symptom Checklist-90, anxiety subscale; SD, standard deviation.

(eczema). This finding supports the theory of intrauterine programming effect by maternal psychological distress on offspring immune system and respiratory morbidity.

KEYWORDS
allergy, anxiety, atopy, child, depression, eczema, prenatal, psychological distress, wheezing

1 | INTRODUCTION

Wheezing respiratory illness in early childhood is an expiratory breathing difficulty with multifactorial background, and it may indicate the development of asthma when occurring recurrently.[1] The incidence of childhood asthma has increased during the last decades, and the subsequent socioeconomic burden is considerable.[1] While multiple contributors, for example, hygiene hypothesis have been discovered, much of the increased incidence remains unexplained.[1] Current asthma research in children has mainly focused on postnatal exposures even though factors during gestation such as maternal psychological distress (PD) symptoms during gestation have recently been associated with elevated risk of offspring atopic diseases.[2-12] This association could result from the programming effect of maternal PD predisposing the offspring to aberrant immune responses and altered lung development by interfering with immune functions alongside other integrated systems.[13] Animal studies have shown that chronic prenatal PD exposes the offspring to immune system changes,[5] while only little is known how chronic maternal PD symptoms affect the immune system in human fetuses/infants.[14] Majority of previous prospective birth cohort studies on maternal PD during gestation and later risk of offspring wheezing and asthma included only one timepoint during gestation, and only two investigated stress separately in two trim esters.[6-8,10,12,15-19] It is suggested that exposure to maternal PD during end-gestation, rather than mid-gestation, predisposes older children to atopic diseases, which could be the effect of a sensitive window but also the cumulating effect of chronic PD symptoms.[2] However, our recently published study indicated that chronic PD symptoms across gestation increase the risk for food allergy at the age of 6 months suggesting an early programming effect and altered immune responses14. Other previous studies have not used standardized analyses on severity and duration of maternal PD symptoms covering the entire gestation.14 Based on this study, we hypothesized that chronic maternal PD symptoms (depression or anxiety) also influence the offspring risk for later wheezing and eczema.[2,6] We aimed to investigate how chronic PD symptoms associate with (1) wheezing ever or doctor-diagnosed eczema at the age of 24 months and further with (2) with atopic and non-atopic wheezing subtypes, which may serve as indicators for later childhood asthma phenotypes.

Key message

Maternal prenatal chronically elevated psychological distress symptoms were associated with offspring wheezing and eczema at child age 24 months, suggesting altered immunology and increased risk of atopic diseases.

2 | METHODS

2.1 | Study subjects and design

The FinnBrain Birth Cohort Study is population-based, prospective pregnancy cohort investigating the long-term effects of prenatal and early-life exposures on child health outcomes.[20] Originally, the cohort consists of 3808 mothers, 2623 fathers, and 3837 children. The families were recruited by research nurses when attending the free-of-charge ultrasounds at gestational weeks (gwks) 12 in three maternity welfare clinics in the Southwestern Hospital District and Åland Islands in Finland 12/2011–04/2015. To this study, 1368 mother-infant dyads with available primary outcome data at the child age of 24 months were eligible (Figure S1). Of these, the children born preterm (gwks <37) were excluded since the preterm delivery is a risk factor for wheezing (Figure S1).[21] The study conforms to the Declaration of Helsinki, was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK:57/180/2011), and commenced only after obtaining written informed consent from the guardians.

2.2 | Exposures

At gwks 14, 24, 34, and at child age 24 months, the maternal PD symptom scores were assessed using the Edinburgh Postnatal Depression Scale (EPDS, range 0–30 points) for the depressive and the Symptom Checklist-90, anxiety scale (SCL-90, range 0–40 points) for the anxiety symptoms.[20,22] Prenatal symptom chronicity and severity assessment was based on the EPDS and SCL-90 scores during entire gestation and modeled as symptom trajectories using latent growth mixture modeling with imputed missing data in Mplus 6.0 (StatModel).[23,24] Five latent curves of

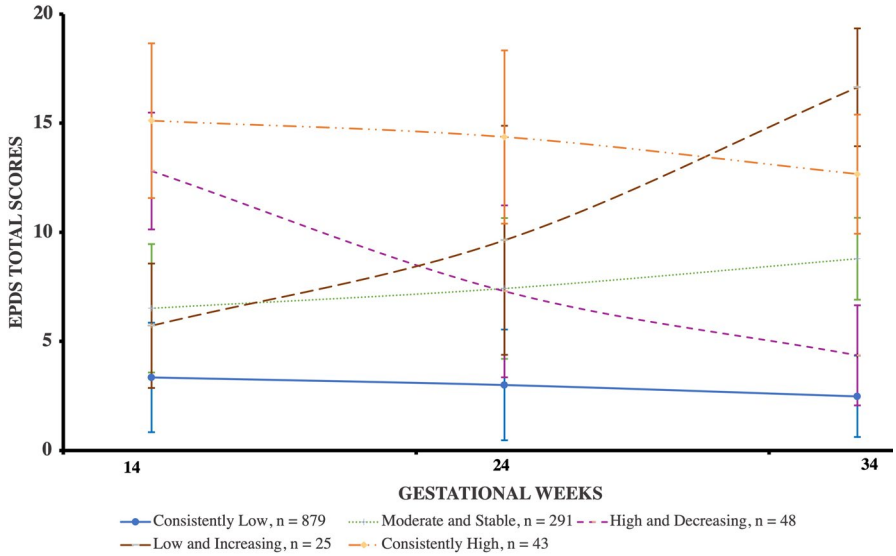

FIGURE 1 Five latent growth curve trajectories of depressive symptoms illustrate the chronicity and severity of the maternal psychological distress symptoms during entire gestation. The depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS, range 0–30 points)

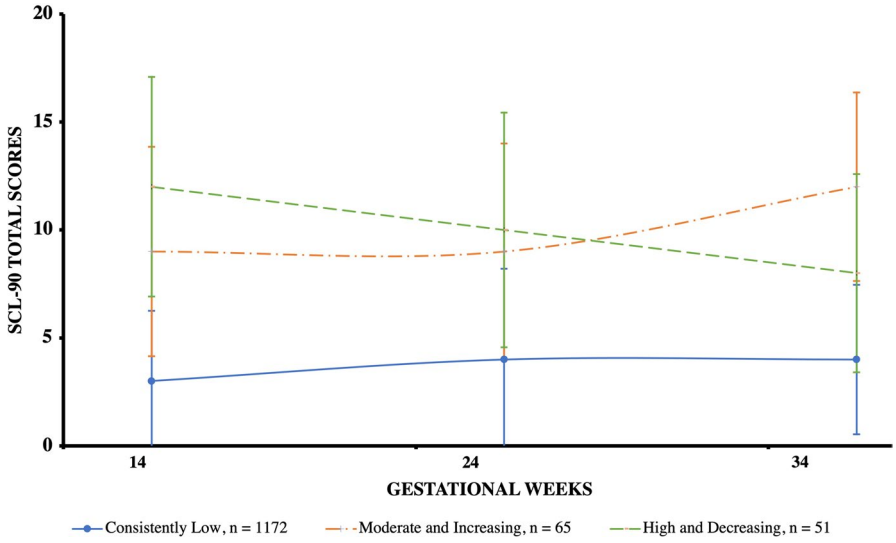

FIGURE 2 Three latent curves of anxiety symptoms illustrate the chronicity and severity of the maternal psychological distress symptoms during entire gestation. The anxiety symptoms with the Symptom Checklist-90, anxiety scale (SCL-90, range 0–40 points)

depressive symptoms and three of anxiety symptoms were chosen for analyses based on the inspection of Akaike's information criterion and Bayesian's information criterion and entropy value (Figures 1 and 2, Table S6). Data for maternal body mass index, smoking, and delivery were derived from the Finnish Medical Birth Register and other data from the parental questionnaires (Table 1). Parental education level was used as the indicator of socioeconomical status. It was divided into three groups (low: ≤12, mid: 12–15, and high: >15 years).[20] Atopic diseases were identified from the question "Have you or at least one of your children had allergies, allergic rhinitis and/or eczema?" (yes/no).

2.3 | Outcomes

The primary outcomes were the maternal report of wheezing ever and doctor-diagnosed eczema at the child age of 24 months according to the standardized questionnaire of The International Study of Asthma and Allergies in Childhood (ISAAC).[25] To demonstrate the susceptibility to diverged immunology after prenatal PD exposure, we categorized the wheezing ever into atopic and non-atopic wheezing subtypes by adding the information of existing doctor-diagnosed eczema. For this purpose, we formed the four-class combination outcome: "wheezing with eczema," "wheezing without eczema," "eczema without wheezing," and "neither wheezing nor eczema."

2.4 | Statistics

Characteristics and subgroup comparisons were done using the *t* test, Mann-Whitney *U* test, or the Pearson chi-square (Tables 1-3). In the primary analyses, the risk for wheezing ever or doctor-diagnosed eczema ever was assessed with the binary logistic regression, first in univariable and then in multivariable analyses. The multivariable analyses were adjusted for known risk factors; for wheezing, prenatal maternal smoking, parental education level, child's sex, and maternal history of asthma[1]; whereas for eczema, child's sex, maternal history of atopic diseases, and parental education level.[26] The

TABLE 1 Population characteristics and attrition analysis

Exposures	Cohort *N* = 3837	Included *N* = 1305	Excluded *N* = 2532	*p*[a]
Maternal characteristics during gestation				
Maternal age at birth, years (SD)	31 (4.5) *n* = 3684	31 (4.4) *n* = 1305	30 (4.8) *n* = 2532	<.001
Maternal pre-pregnancy body mass index, kg/m^2 median (IQR)	24 (22:27) *n* = 3684	23 (21:27) *n* = 1287	24 (21:27) *n* = 2297	.16
Maternal smoking, nr (%)				
Quit in early pregnancy	274/3748 (7.1)	65/1285 (5.1)	209/2396 (8.7)	<.001
Through pregnancy	207/3748 (5.4)	37/1285 (2.9)	170/2396 (7.1)	
Maternal asthma	287/3096 (7.4)	108/1249 (8.6)	179/1847 (9.7)	.33
Maternal atopic diseases	1299/3096 (34)	537/1249 (43)	762/1847 (41)	.34
Maternal asthma and/or atopic diseases	1354/3096 (44)	558/1249 (45)	796/1847 (43)	.39
Maternal use of inhaled or oral corticosteroids, nr (%)	134/3690 (3.5)	20/1287 (1.6)	114/2403 (4.7)	<.001
Parental education level				
Up to 12 years	1070/3163 (34)	303/1259 (24)	767/1904 (40)	<.001
Between 13 and 15 years	1077/3163 (43)	446/1259 (35)	631/1904 (33)	
Over 15 years	1016/3163 (32)	510/1259 (41)	506/1904 (27)	
EPDS trajectories				
"Moderate and Stable"	N/A	292/1293 (23)	N/A	
"Low and Increasing"		29/1292 (2.2)		
"Consistently High"		43/1292 (3.3)		
"High and Decreasing"		50/1292 (3.9)		
"Consistently Low"		872/1292 (68)		
SCL-90 trajectories				
"High and Decreasing"	N/A	53/1292 (4.1)	N/A	
"Moderate and Increasing"		67/1292 (5.2)		
"Consistently Low"		1172/1292 (91)		
Infant characteristics at birth				
Gestational age, weeks median (IQR)	40 (39:41) *n* = 3762	40 (39:41) *n* = 1305	40 (39:41) *n* = 2353	<.001
Birthweight, g (SD)/length, cm (SD)	3500 (540)/51 (2.4) *n* = 3684/*n* = 3687	3600 (480)/51 (2.0) *n* = 1288/*n* = 1280	3500 (590)/50 (2.7) *n* = 2408/*n* = 2396	<.001/<.001
Male sex, nr (%)	1961/3748 (51)	698/1305 (54)	1263/2443 (52)	.30
One or more older siblings (%)	975/2254 (43)	606/1305 (46)	1952/2532 (77)	<.001
Older siblings with mother-reported atopic diseases	444/3096 (12)	180/1249 (14)	264/1847 (14)	.93
Older siblings with mother-reported asthma	97/3096 (2.5)	36/1249 (2.9)	61/1847 (3.3)	.51
Delivery with cesarean section	298/3690 (3.5)	98/1287 (7.6)	200/2403 (8.3)	.45
Doctor visit at age 12 months	302/3837 (7.9)	193/1113 (15)	109/525 (21)	.056
Maternal characteristics at child age 24 months				
EPDS point medians (range 0–30) (IQR)	4.0 (1.0–7.0) *n* = 1366	4.0 (1.0–7.0) *n* = 1291	4.0 (2.0–8.0) *n* = 78	.31
SCL point medians (range 0–40) (IQR)	1.1 (0.0–4.0) *n* = 1366	1.1 (0.0–4.0) *n* = 1292	2.0 (0.0–5.0) *n* = 77	.67

Abbreviations: BMI, body mass index; CI, confidence interval; EPDS, The Edinburgh Postnatal Depression Scale; gwks, gestational weeks; IQR, interquartile range; N/A, not applicable; OR, odds ratio; SCL-90, The Symptom Checklist-90, anxiety scale; SD, standard deviation.

[a]Indicates the comparisons with "excluded" as a reference group.

TABLE 2 Population characteristics of the included at 24 months

Exposures	No wheezing ($n = 1086$)	Wheezing ever ($n = 219$)	p^a	No eczema ($n = 991$)	Doctor-diagnosed eczema ($n = 285$)	p^a
Maternal characteristics during gestation						
Maternal age at birth, years (SD)	31 (4.4) $n = 912$	31 (4.2) $n = 183$	.42	31 (4.3) $n = 991$	31 (4.4) $n = 285$	.10
Maternal pre-pregnancy body mass index, kg/m^2 median (IQR)	23 (21:26) $n = 1070$	24 (21:28) $n = 217$	.21	23 (21:26) $n = 977$	24 (21:27) $n = 283$	.86
Maternal smoking, nr (%)						
Quit in early pregnancy	52/1068 (4.9)	13/217 (6.0)	.79	50/975 (5.1)	15/283 (5.3)	.93
Through pregnancy	31/1068 (2.9)	6/217 (2.8)		27/975 (2.8)	9/283 (3.2)	
Maternal asthma[b]	78/1042 (7.5)	30/207 (15)	**.001**	76/950 (8.0)	10/272 (9.2)	.53
Maternal atopic diseases [c]	435/1042 (42)	102/207 (49)	**.046**	379/950 (40)	148/272 (54)	**<.001**
Maternal asthma and/or atopic diseases	471/1082 (44)	115/223 (52)	**.032**	414/990 (42)	160/286 (56)	**<.001**
Maternal use of inhaled or oral corticosteroids, nr (%)	17/1070 (1.6)	3/217 (1.4)	.82	13/977 (1.3)	6/283 (2.1)	.34
Parental education level						
Up to 12 years	249/1050 (24)	54/209 (26)	**.014**	221/952 (23)	72/271 (27)	.053
Between 13 and 15 years	373/1050 (36)	73/209 (35)		331/952 (35)	104/271 (38)	
Over 15 years	428/1050 (41)	82/209 (39)		400/952 (42)	95/271 (35)	
EPDS trajectories nr (%)						
"Moderate and Stable"	246/1077 (23)	52/215 (24)	**.02**	218/973 (22)	73/282 (26)	.64
"Low and Increasing"	24/1077 (2.2)	5/215 (2.3)		22/973 (2.3)	7/282 (2.5)	
"Consistently High"	28/1077 (2.6)	15/215 (7.0)		32/973 (3.3)	8/282 (2.8)	
"High and Decreasing"	42/1077 (3.9)	8/215 (3.7)		35/973 (3.6)	13/282 (4.6)	
"Consistently Low"	737/1077 (68)	135/215 (64)		666/973 (68)	181/282 (64)	
SCL-90 trajectories, nr (%)						
"High and Decreasing"	43/1077 (4.0)	10/215 (4.7)	.12	33/973 (3.4)	16/282 (5.7)	**.049**
"Moderate and Increasing"	50/1077 (4.6)	17/215 (7.9)		45/973 (4.6)	20/282 (7.1)	
"Consistently Low"	984/1077 (91)	188/215 (87)		895/973 (92)	246 (87)	
Infant characteristics at birth						
Gestational age, weeks (SD)	40 (1.2) $n = 1086$	40 (1.3) $n = 219$	**.04**	40.0 (1.2)	39.9 (1.2)	.56
Birthweight, g (SD)/length, cm (SD)	3600 (470)/51 (2.0) $n = 1070/n = 1062$	3600 (490)/51 (2.0) $n = 218/n = 218$	.72/.67	3600 (470)/51 (2.1) $n = 970/n = 966$	3600 (470)/51 (1.9) $n = 282/n = 280$	.58/.97
Male sex, nr (%)	553/1086 (51)	145/219 (66)	**<.001**	521/991 (53)	159/285 (56)	.34
One or more older siblings (%)	496/1086 (46)	110/219 (50)	.12	463/983 (47)	126/284 (44)	.42

(Continues)

TABLE 2 (Continued)

Exposures	No wheezing (n = 1086)	Wheezing ever (n = 219)	p^a	No eczema (n = 991)	Doctor-diagnosed eczema (n = 285)	p^a
Older siblings with mother-reported asthma [b]	24/1042 (2.3)	12/207 (5.8)	**.006**	28/950 (2.9)	7/272 (2.6)	.74
Older siblings with mother-reported atopic diseases [c]	145/1042 (14)	35/207 (17)	.26	118/950 (12)	59/272 (22)	**<.001**
Delivery with cesarean section, nr (%)	83/1070 (7.8)	15/217 (6.9)	.67	71/977 (7.3)	23/283 (8.1)	.63
Doctor visit at age 12 months	140/930 (13)	53/183 (24)	**<.001**	132/854 (16)	52/227 (23)	**.008**
Maternal characteristics at child age 24 months						
EPDS point medians (range 0–30) (IQR)	3.0 (1.0–7.0) n = 1074	4.0 (2.0–8.0) n = 217	**.003**	3.0 (1.0–7.0) n = 983	4.0 (1.0–8.0) n = 282	**.04**
SCL point medians (range 0–40) (IQR)	1.0 (0.0–4.0) n = 1075	2.0 (0.0–5.0) n = 217	**.002**	1.0 (0.0–4.0) n = 983	2.0 (0.0–5.0) n = 282	.12

Abbreviations: BMI, body mass index; CI, confidence interval; EPDS, The Edinburgh Postnatal Depression Scale; gwks, gestational weeks; IQR, interquartile range; N/A, not applicable; OR, odds ratio; SCL-90, The Symptom Checklist-90, anxiety scale; SD, standard deviation. Bold values indicate significance of $P < .05$.

[a]Indicates the group comparisons.

[b]The correlation between maternal and sibling asthma in the cohort, $p = .003$

[c]The correlation between maternal and sibling atopic diseases in the cohort, $p < .001$.

impact of chronic depressive and anxiety symptoms on the outcomes was analyzed using symptom trajectories with multinomial logistic regression, where the trajectory of consistently low symptoms was the reference group (Table 4, Figures 1 and 2). In the secondary analyses, the risk for the four-class combination outcome was assessed using the multinomial logistic regression, where the "neither wheezing nor eczema" was the reference group (Table S3). These analyses were adjusted for parental education level, child's sex, maternal prenatal smoking, and history of asthma and/or atopic diseases as a combined variable. In the supplementary analyses, distress symptom scores were studied as continuous variables at each timepoint to illustrate the role of distress exposure separately in each trimester (Table S2). Correlation analysis of perinatal maternal PD symptom scores was performed (Table S4) following the inclusion of maternal PD symptoms at the child age of 24 months as a potential confounder of reporting bias for the pediatric outcomes (Table S5).[27] The p value <.05 was regarded as significant, and 95% confidence interval (CI) was used. Analyses were performed using the IBM SPSS 27.0 software (SPSS Inc.).

3 | RESULTS

3.1 | Study population and characteristics

At the child age of 24 months, maternal questionnaires including data for wheezing were available from 1368/3837 (36%) and for eczema from 1335/3837 (35%) of the cohort children (Figure S1). Children whose mothers did not return the 24-month questionnaire were excluded. The non-responding mothers were younger, had higher total sum scores in the EPDS and SCL-90 questionnaires, and smoked more during gestation (Table 1, Table S1, and Figure S1). Additionally, children born preterm (gwks <37) were excluded, and from them, 63/1368 (5%) had available data on wheezing ever and 59/1335 (4%) on doctor-diagnosed eczema. Finally, 1305/3837 (34%) full-term children with available outcome data were included (Figure S1). From these 1305 children, the number of children whose mothers had reported wheezing ever was 219 (17%) and doctor-diagnosed eczema 285 (22%) (Table 2 and Figure S1). Based on the four-class combination outcome, the number of children with wheezing with eczema was 53 (4%), wheezing without eczema 154 (12%), eczema without wheezing 231 (18%), or neither wheezing nor eczema 829 (66%) (Table 3).

The children with wheezing ever had more family atopy than non-wheezing children: maternal asthma (15% vs. 8%; $p = .001$) and atopic diseases (49% vs. 42%; $p = .046$), and older siblings with mother-reported asthma (6% vs. 2%; $p = .006$), which correlated with maternal asthma ($p < .001$) (Table 2). The children with eczema had more maternal atopic diseases than children without eczema (54% vs. 40%; $p < .001$) (Table 2). Male sex dominated among children with wheezing (66%; $p < .001$). No differences were found regarding maternal smoking during gestation or delivery type (Table 2).

TABLE 3 Population characteristics of the included at 24 months

Exposures	Wheezing with eczema (*n* = 53)	Wheezing without eczema (*n* = 154)	Eczema without wheezing (*n* = 231)	Neither wheezing nor eczema (*n* = 829)	*p*[a]
Maternal characteristics during gestation					
Maternal age at birth, years (SD)	31 (3.4) *n* = 53	32 (4.4) *n* = 154	32 (4.4) *n* = 231	32 (4.4) *n* = 829	.27
Maternal pre-pregnancy body mass index, kg/m^2 median (IQR)	24 (21:29) *n* = 53	24 (21:27) *n* = 152	24 (21:27) *n* = 229	23 (21:26) *n* = 817	.63
Maternal smoking, nr (%)					
Quit in early pregnancy	4/53 (7.5)	8/152 (5.3)	11/229 (4.8)	41/815 (5.0)	.71
Through pregnancy	3/53 (5.7)	2/152 (1.3)	6/229 (2.6)	25/815 (3.1)	
Maternal asthma[b]	7/48 (15)	18/147 (12)	18/223 (8.1)	58/795 (7.3)	.090
Maternal atopic diseases[c]	25/48 (52)	68/147 (46)	122/223 (54.7)	306/795 (39)	**<.001**
Maternal asthma and/or atopic diseases	29/52 (56)	76/158 (48)	130/233 (55.8)	334/824 (41)	**<.001**
Maternal use of inhaled or oral corticosteroids, nr (%)	1/53 (1.9)	1/152 (0.66)	5/229 (2.2)	12/817 (1.5)	.68
Parental education level					
Up to 12 years	14/48 (29)	*35/149 (24)*	*58/223 (26)*	*186/803 (23)*	***.039***
Between 13 and 15 years	*17/48 (35)*	*52/149 (35)*	*87/223 (39)*	*279/803 (35)*	
Over 15 years	*17/48 (35)*	*62/149 (42)*	*78/223 (35)*	*338/803 (42)*	
EPDS trajectories nr (%)					
"Moderate and Stable"	13/51 (26)	37/152 (24)	60/231 (26)	181/821 (22)	.10
"Low and Increasing"	2/51 (3.9)	3/152 (2.0)	5/231 (2.2)	19/821 (2.3)	
"Consistently High"	1/51 (2.0)	12/152 (7.9)	7/231 (3.0)	20/821 (2.4)	
"High and Decreasing"	1/51 (2.0)	7/152 (4.6)	12/231 (5.2)	28/821 (3.4)	
"Consistently Low"	34/51 (67)	93/152 (61)	147/231 (64)	573/821 (70)	
SCL-90 trajectories, nr (%)					
"High and Decreasing"	1/51 (2.0)	7/152 (4.6)	15/231 (6.5)	26/821 (3.2)	**.03**
"Moderate and Increasing"	5/51 (9.8)	12/152 (7.9)	15/231 (6.5)	33/821 (3.2)	
"Consistently Low"	45/51 (89)	133/152 (88)	201/231 (87)	762/821 (93)	
Infant characteristics at birth					
Gestational age, weeks (SD)	39.6 (1.3) *n* = 53	39.9 (1.3) *n* = 154	40.0 (1.2) *n* = 231	40.0 (1.2) *n* = 829	.10
Birthweight, g (SD)/length, cm (SD)	3600 (500)/51 (2.0) *n* = 53/*n* = 63	3600 (490)/51 (2.0) *n* = 153/*n* = 153	3600 (460)/51 (1.9) *n* = 229/*n* = 227	3600 (470)/51 (2.1) *n* = 817/*n* = 813	.92/.98
Male sex, nr (%)	42/52 (79)	95/154 (61)	116/231 (50)	423/829 (51)	**<.001**
One or more older siblings (%)	27/52 (51)	79/154 (51)	99/231 (43)	384/829 (46)	.38
Older siblings with mother-reported asthma[b]	2/48 (4.2)	9/147 (6.1)	5/233 (2.2)	19/795 (2.4)	**.08**
Older siblings with mother-reported atopic diseases[c]	10/48 (21)	24/147 (16)	49/223 (22)	94/795 (12)	**.001**
Delivery with cesarean section, nr (%)	3/53 (5.7)	11/152 (7.2)	20/229 (8.7)	60/817 (7.3)	.85
Doctor visit at age 12 months	15/40 (38)	34/133 (26)	37/187 (20)	98/721 (14)	**<.001**
Maternal characteristics at child age 24 months					
EPDS point medians (range 0–30) (IQR)	5.0 (2.0–8.8) *n* = 52	4.0 (2.0–7.0) *n* = 153	4.0 (1.0–8.0) *n* = 229	3.0 (1.0–7.0) *n* = 822	**.009**
SCL point medians (range 0–40) (IQR)	2.5 (1.0–7.0) *n* = 52	2.0 (0.0–5.0) *n* = 153	2.0 (0.0–5.0) *n* = 229	1.0 (0.0–4.0) *n* = 822	**.01**

Abbreviations: BMI, body mass index; CI, confidence interval; EPDS, The Edinburgh Postnatal Depression Scale; gwks, gestational weeks; IQR, interquartile range; N/A, not applicable; OR, odds ratio; SCL-90, The Symptom Checklist-90, anxiety scale; SD, standard deviation. Bold values indicate significance of $P < .05$.

[a]Indicates the comparisons with "Neither wheezing nor eczema" as the reference group.

[b]The correlation between maternal and sibling asthma in the cohort, $p = .003$

[c]The correlation between maternal and sibling atopic diseases in the cohort, $p < .001$

TABLE 4 Risk of wheezing or doctor-diagnosed atopic eczema at 24 months

Maternal reported exposures during gestation	Wheezing ever			Doctor-diagnosed eczema		
	OR	95% CI	p^a	OR	95% CI	p^a
Unadjusted analyses						
Maternal atopic diseases	1.4	1.0–1.8	**.046**	1.8	1.4–2.4	**<.001**
Maternal asthma	2.1	1.3–3.3	**.001**	1.2	0.73–1.9	.53
Maternal smoking during pregnancy						
Quit in early pregnancy[a]	1.2	0.67–2.3	.50	1.0	0.57–1.9	.90
Through pregnancy[a]	0.96	0.40–2.3	.93	1.2	0.54–2.49	.71
Older children with mother-reported atopic diseases	1.3	0.84–1.9	.26	2.0	1.4–2.8	**<.001**
Older children with mother-reported asthma	2.6	1.3–5.3	**.008**	0.87	0.38–2.0	.75
Male sex vs. female sex	1.9	1.4–2.6	**<.001**	1.1	0.87–1.5	.34
Parental education level						
Up to 12 years[a]	2.6	1.4–4.7	**.002**	1.4	0.95–1.9	.090
Between 13 and 15 years[a]	1.8	1.1–3.0	**.032**	1.3	0.95–1.8	.11
Over 15 years[a]	1.0			1.0		
EPDS trajectories with "Consistently Low" as reference						
"Moderate and Stable"	1.15	0.81–1.64	.42	1.23	0.90–1.68	.19
"Low and Increasing"	1.14	0.43–3.03	.80	1.17	0.49–2.78	.72
"Consistently High"	2.93	1.52–5.62	**.001**	0.92	0.42–2.03	.84
"High and Decreasing"	1.04	0.48–2.26	.92	1.37	0.71–2.64	.35
SCL-90 trajectories with "Consistently Low" as reference						
"High and Decreasing"	1.22	0.60–2.47	.59	1.76	0.96–3.26	.070
"Moderate and Increasing"	1.78	1.00–3.15	**.048**	1.62	0.94–2.79	.084
Adjusted analyses						
EPDS trajectories with "Consistently Low" as the reference						
"Moderate and Stable"	1.07	0.74–1.55	.74	1.25	0.91–1.73	.17
"Low and Increasing	1.64	0.60–4.51	.34	1.15	0.45–3.00	.77
"Consistently High"	2.74	1.37–5.50	**.005**	0.93	0.41–2.09	.86
"High and Decreasing"	0.99	0.45–2.20	.98	1.52	0.78–3.00	.22
Maternal atopic diseases	N/A			1.8	1.4–2.4	**<.001**
Maternal asthma	2.2	1.4–3.5	**<.001**	N/A		
Maternal asthma and/or atopic diseases	N/A					
Male sex vs. female sex	1.8	1.3–2.5	**<.001**	1.1	0.84–1.5	.48
Maternal smoking during pregnancy	1.0	0.42–2.2	.95			
Parental education level						
Up to 12 years[a]	1.1	0.71–1.6	.78	1.3	0.92–1.9	.13
Between 13 and 15 years[a]	1.1	0.74–1.5	.77	1.4	1.0–1.9	**.037**
Over 15 years[a]	1.0			1.0		
SCL-90 trajectories with "Consistently Low" as the reference						
"High and Decreasing"	1.27	0.61–2.6	.52	1.89	1.00–3.55	**.049**
"Moderate and Increasing"	1.94	1.1–3.5	**.032**	1.48	0.83–2.63	.18
"Maternal atopic diseases	N/A			1.8	1.37–2.38	**<.001**
Maternal asthma	2.2	1.4–3.5	**<.001**	N/A		

TABLE 4 (Continued)

Maternal reported exposures during gestation	Wheezing ever			Doctor-diagnosed eczema		
	OR	95% CI	p^a	OR	95% CI	p^a
Maternal asthma and/or atopic diseases	N/A					
Male vs. female sex	1.9	1.4–2.5	**<.001**	1.1	0.84–1.5	.45
Maternal smoking during pregnancy	1.0	0.44–2.3	.99	N/A		
Parental education level						
Up to 12 years[a]	1.1	0.73–1.6	.66	1.3	0.92–1.9	.13
Between 13 and 15 years[a]	1.1	0.74–1.5	.79	1.4	1.0–1.9	**.043**
Over 15 years[a]	1.0			1.0		

Abbreviations: BMI, body mass index; CI, confidence interval; EPDS, The Edinburgh Postnatal Depression Scale; gwks, gestational weeks; IQR, interquartile range; N/A, not applicable; OR, odds ratio; SD, standard deviation; SCL-90, The Symptom Checklist-90, anxiety scale. Bold values indicate significance of $P < .05$.

[a]Indicates the comparison with "No wheezing" or "No eczema" as the reference groups.

3.2 | The primary analysis

3.2.1 | Risk of wheezing at age 24 months

In the unadjusted analyses, wheezing ever associated with maternal asthma and atopic diseases, gestational weeks at delivery, male sex, mother-reported asthma in older siblings, and parental education level (Tables 2 and 3). In the EPDS trajectory model, the risk was elevated with the "Consistently High" trajectory (odds ratio [OR] 2.74; 95% CI 1.37–5.50; $p = .004$) (Table 3, Figures 1 and 2). Likewise, SCL-90 trajectory of "Moderate and Increasing" symptoms was associated with increased risk of wheezing (Table 4, Figures 1 and 2). In the adjusted analyses, the results remained unchanged for both depressive and anxiety symptom trajectories (Table 4).

3.2.2 | Risk of eczema at 24 months

In the unadjusted analysis, doctor-diagnosed eczema at 24 months associated with atopic diseases of mothers and older siblings (Table 3). Prenatal maternal depressive or anxiety symptom trajectories did not associate with doctor-diagnosed eczema (Table 3, Figures 1 and 2). After adjustments, the "High and Decreasing" SCL trajectory was associated with increased risk for eczema (OR 1.89; 95% CI 1.00–3.55; $p = .049$) (Table 4).

3.3 | The secondary analysis

3.3.1 | Risk in four-class combination outcome

In the unadjusted analysis, the risk for wheezing without eczema was elevated with the EPDS trajectory of "Consistently High" (OR 3.40; 95% CI 1.75–7.81; $p = .001$) and SCL-90 trajectory of "Moderate and Increasing" (2.08; 1.05–4.14; $p = .036$, respectively). The risk for eczema without wheezing was elevated with the SCL-90 trajectory of "High and Decreasing" (2.19; 1.14–4.21; $p = .019$) (Table S3). Adjustments did not change the results (Table S3). In all trajectory analyses, the "neither wheezing nor eczema" was the reference group.

3.4 | The supplementary analyses

The PD symptom scores were studied as continuous variables at each timepoint to illustrate the role of distress exposure separately in each trimester. The risk of wheezing ever was increased in the first and last trimesters when using the continuous EPDS scores and in the second and last trimesters when using the continuous SCL-90 scores (Table S2).

The chronic nature of maternal PD symptoms is illustrated with correlation analysis between PD symptoms during gestation and at 24 months (Table S4). The associations between EPDS trajectories during gestation and wheezing remained unchanged after adjusting for maternal PD symptoms at the child age of 24 months, but not between SCL-90 trajectories (Table S5). However, the associations remained unchanged when the risk of wheezing and eczema was examined in the four-class combination outcome of "Wheezing without eczema" and "Eczema without wheezing" (Table S5).

4 | DISCUSSION

In keeping with earlier studies, we demonstrate that maternal PD during gestation associates with atopic disorders in offspring.[3,7,8,11,16,18,19] Furthermore, we found that mother-experienced PD symptoms that are chronically elevated across gestation, assessed in three timepoints, associated with offspring wheezing and eczema at the age of 24 months. This is the first study on early childhood asthma which observed maternal PD across gestation and

applied latent growth curve modeling in composing the trajectories for chronicity/severity of the PD symptoms.[14] Our finding is in line with our previous study where maternal chronic PD associated with offspring food allergy at the infant age of 6 months.[14] Our study also sheds new light into the effects of chronic maternal PD resulting in varied risk for different wheezing subtypes.[2]

The novelty of our study was the creation of PD symptom trajectories enabling the investigation of symptom severity and chronicity on the outcomes. In previous studies on prenatal PD and atopic diseases, the questionnaires and distress types and timing have been heterogenous.[2] The studies to date have used different validated questionnaires of depressive and anxiety symptoms[3,7,9] but also self-reported negative life events or other stressful situations.[8,12,18,19] The timing of these exposures during gestation has varied between studies,[2] but also inside studies, a single time point at any time during gestation,[8] at one trimester,[7,10-12,18,19] at two trimesters (2nd and 3rd),[4] or before and after gwks 18.[3] Derived from previous studies the third trimester may be the most vulnerable time regarding PD exposure.[2] However, our study shows that chronic depressive and anxiety symptoms may be risk factor for wheezing and eczema and this finding is endorsed by the aligned results of PD symptoms per the time point assessment. We adjusted analyses for maternal atopic diseases or asthma since the correlation between mother/sibling atopic diseases and asthma was significant. Male sex associated with wheezing, as expected.[21] Possible reporting bias because of maternal distress symptoms was acknowledged, and therefore, we also adjusted for the PD symptoms at 24 months.[27] Also, we acknowledge that the attrition could affect the generalizability of the results particularly in the population with accumulated risk factors as maternal PD and lower socioeconomic status were related to attrition. The potential bias resulting from these characteristics in the attrition may dilute the observed associations as the subjects with higher PD symptoms were underrepresented.

To provide new insights into underlying aberrant immune system of different early childhood wheezing subtypes, a four-class combination outcome was applicated. For this, we combined wheezing ever and doctor-diagnosed eczema to model the simplified outcomes of "wheezing with eczema," "wheezing without eczema," "eczema without wheezing," and "neither wheezing nor eczema." They were intended to anticipate the atopic/non-atopic wheezing subtypes, and further, the early phenotypes of atopic/non-atopic asthma. Noteworthy is that exposure to prenatal chronic PD was associated with wheezing without eczema, but not with wheezing with eczema or eczema without wheezing, suggesting that prenatal chronic PD predisposes the offspring toward non-atopic wheezing subtype. However, we acknowledge the statistical power issue caused by relatively small cell sizes, and therefore, conclusions should be made with caution. We hope that these preliminary findings inspire future research as they support the previous studies showing that the susceptibility to diverged immune responses leading to school-age atopic or non-atopic asthma can been seen during the first year of life implying that asthma programming occurs prenatally because of genetic predisposition and environmental exposures.[2,5,28,29] In addition, previously has been shown that school-age atopic and non-atopic asthma have different early-life risk factors; that is, atopic asthma has concomitant sensitization and/or eczema in infancy whereas maternal smoking during gestation has associated with non-atopic asthma.[28,29] In current study, maternal prenatal smoking did not associate with wheezing ever or wheezing without eczema, and importantly, maternal depressive and anxiety symptoms did not associate with smoking either. This underlines the notion that prenatal PD may be an independent risk factor for offspring non-atopic wheezing subtype. Prenatal exposures may partly explain the non-genetic variability seen in childhood asthma phenotypes interfering with the immune system and inducing the shift toward Th2-dominant predisposition. The allergen-specific immunoglobulin E was not tested here since sensitization to aeroallergens develops later in general population and its value indicating asthma risk in early life is decreased.[30] Possible simultaneously mediating mechanisms might include the elevated levels of maternal glucocorticoids and/or cytokines resulting in placental dysregulation, impaired fetal maturation of HPA axis, and altered glucocorticoid levels.[2,5]

The strengths include the large and non-selected sample of 1305 mother-infant dyads from prospective, population-based pregnancy cohort without major exclusion criteria. It can be perceived as an unselected sample of the general population and therefore represents the maternal and paternal prenatal period of depressive and anxiety symptoms adequately. In general population, the prevalence of wheezing ever before the child age of three years is approximately 20% and for childhood eczema approximately 20%.[26,31] In current study, the prevalence of wheezing ever and eczema was within expected. The outcomes were based on the structured and widely used ISAAC questionnaire which makes comparison between studies feasible.[25] In earlier studies on prenatal PD exposure, the outcomes have varied greatly including mother-reported wheezing,[10] mother-reported doctor-diagnosed wheeze and asthma,[3,7] mother-reported doctor-diagnosed eczema,[8,9,11] only mother-reported,[4,12] and ISAAC-based eczema,[11] ranging between 1 and 14 years.[2] The use of mother-reported questionnaires poses a possible reporting bias, also in our study. The review of medical charts would have provided more accurate outcomes, but as our study population originates from large birth cohort with multiple simultaneous multi-disciplined sub-studies, the number of questions were restricted. We would have benefitted from the wheezing severity or number of wheezing episodes, but it was unachievable to examine children during every wheezing episode.

In conclusion, mother-experienced chronic PD symptoms during gestation were associated with elevated risk of offspring wheezing and non-atopic type of wheezing during the first two years of life. The findings highlight the influence of prenatal PD exposure on immune system and support the theory of intrauterine programming effect of maternal PD leading to atopic diseases and respiratory morbidity.[2]

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Emma Puosi: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (supporting); Investigation (lead); Methodology (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (equal). **Laura S. Korhonen:** Data curation (supporting); Investigation (supporting); Methodology (supporting); Resources (supporting); Writing – original draft (supporting); Writing – review & editing (equal). **Linnea Karlsson:** Conceptualization (supporting); Funding acquisition (supporting); Project administration (lead); Resources (supporting); Writing – review & editing (equal). **Eeva-Leena Kataja:** Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Visualization (supporting); Writing – original draft (supporting); Writing – review & editing (equal). **Heikki Lukkarinen:** Conceptualization (lead); Investigation (supporting); Methodology (equal); Supervision (equal); Writing – review & editing (equal). **Hasse Karlsson:** Conceptualization (supporting); Funding acquisition (supporting); Project administration (lead); Resources (supporting); Writing – review & editing (equal). **Minna Lukkarinen:** Conceptualization (lead); Data curation (equal); Funding acquisition (supporting); Methodology (lead); Supervision (lead); Writing – original draft (supporting); Writing – review & editing (lead).

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ORCID

Emma Puosi https://orcid.org/0000-0002-6301-9353
Minna Lukkarinen https://orcid.org/0000-0001-6826-5505

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