

Prenatal Exposures

Pre-eclampsia and risk of early-childhood asthma: a register study with sibling comparison and an exploration of intermediate variables

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Abstract

Background: We aimed to study whether pre-eclampsia is associated with childhood asthma, allergic and non-allergic asthma, accounting for family factors and intermediate variables.

Methods: The study population comprised 779 711 children born in 2005–2012, identified from Swedish national health registers ($n = 14\ 823/7410$ exposed to mild/moderate and severe pre-eclampsia, respectively). We used Cox regression to estimate the associations of mild/moderate and severe pre-eclampsia with incident asthma, before and after age 2 years. Cox regressions were controlled for familial factors using sibling comparisons, then stratified on high and low risk for intermediate variables: caesarean section, prematurity and small for gestational age. We used logistic regression for allergic and non-allergic prevalent asthma at 6 years as a measure of more established asthma.

Results: The incidence of asthma in children was 7.7% ($n = 60\ 239$). The associations varied from adjusted hazard ratio (adjHR) 1.11, 95% confidence interval (CI): 1.00, 1.24 for mild/moderate pre-eclampsia and asthma at >2 years age, to adjHR 1.78, 95% CI: 1.64, 1.95 for severe pre-eclampsia and asthma at <2 years age. Sibling comparisons attenuated most estimates except for the association between severe pre-eclampsia and asthma at <2 years age (adjHR 1.45, 95% CI: 1.10, 1.90), which also remained when stratifying for the risk of intermediates. Mild/moderate and severe pre-eclampsia were associated with prevalent non-allergic (but not allergic) asthma at 6 years, with adjusted odds ratio (adjOR) 1.17, 95% CI: 1.00, 1.36 and adjOR 1.51, 95% CI: 1.23, 1.84, respectively.

Conclusions: We found evidence that severe, but not mild/moderate, pre-eclampsia is associated with asthma regardless of familial factors and confounders.

Key words: Asthma, caesarean section, child, epidemiology, intermediate, pre-eclampsia, prematurity, registers, sibling, small for gestational age

Key Messages

- Severe pre-eclampsia exposure is associated with childhood early-onset asthma (<2 years of age) and the association cannot be explained by familial confounding, mode of delivery, gestational age or birthweight.
- Severe pre-eclampsia exposure is associated with prevalent non-allergic asthma at age 6 years but we cannot rule out confounding by familial factors.
- Associations between mild pre-eclampsia and asthma show evidence of familial confounding that should be considered in other similar studies.

Introduction

Asthma is the most common chronic childhood disease worldwide, with a prevalence of 6–9%, thus creating a significant burden on families and healthcare services.¹ Studies have indicated the importance of early-life programming for the risk of asthma.² One condition possibly impacting early-life programming is pre-eclampsia—a potentially serious complication in the second half of pregnancy characterized by increased blood pressure and proteinuria, and increased risk of morbidity and mortality in both mother and child.³ Of importance, pre-eclampsia has increased in prevalence from 2–4% to 4–8% during the last two decades.⁴

Pre-eclampsia, especially in its severe form, is characterized by an increase in circulating cytokines, which may influence the offspring's development towards inflammatory conditions like asthma.^{5,6}

An association between pre-eclampsia exposure *in utero* and subsequent asthma has been found in large studies but is not supported by smaller studies, and the question of causality remains unresolved.^{7–12} Although the largest studies have differentiated between onset and duration of pre-eclampsia, few have explored severity.^{13–15} Furthermore, previous studies on the association between pre-eclampsia and asthma have not differentiated allergic from non-allergic asthma. A sibling study of nearly 150 000 Danish children suggested that any association between pre-eclampsia and asthma may be confounded by shared familial (genetic and environmental) factors that are not always measurable.⁸ However, this finding requires verification and it is unknown whether familial factors could also explain associations between severe pre-eclampsia and asthma phenotypes.

Aside from possible familial confounding, there are other explanatory pathways to explore in the pre-eclampsia–asthma association. The variables mode of delivery,

gestational age and birthweight are on the causal pathway between pre-eclampsia and asthma, and therefore may mediate the association.^{2,16} However, bias may arise when conditioning on these intermediate variables^{17,18} due to unknown or unmeasured confounders between these intermediate variables and the outcome, thereby introducing collider bias.¹⁹ Methods for indirectly conditioning on intermediate variables exist but have not previously been used in studies on pre-eclampsia and asthma and it is possible that collider bias due to incorrect conditioning on intermediate variables has influenced previous studies.¹⁸

The overall aim is to study whether pre-eclampsia exposure *in utero* is associated with subsequent asthma in children. The objectives are to study whether pre-eclampsia exposure by severity is associated with childhood 'incident asthma' and 'allergic' or 'non-allergic prevalent asthma' at age 6 years, and to explore whether the association between pre-eclampsia and asthma is independent of familial factors, mode of delivery, gestational age and birthweight.

Methods

Study design

To create the cohort, we used information from the following national health and socio-demographic registers held by the National Board of Health and Welfare and Statistics Sweden, and linked by the Swedish Personal Identity number:²⁰ the Medical Birth Register (MBR), which includes data on >98% of all births in Sweden; the National Patient Register (NPR, using in- and specialist outpatient diagnoses); the Prescribed Drug Register (PDR, using dispensed medication based on the Anatomical Therapeutic Chemical classification system, ATC); the Multi-Generation Register (MGR) with links between parents

and siblings; and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA).

Participants

Based on the MBR, we identified 805 535 children born in Sweden between July 2005 and 31 December 2012. In total, 780 118 were singletons and live-born, and 779 711 survived beyond the first day of life, making up our study population.

Asthma outcomes

‘Incident asthma’ was assessed until 31 December 2013 for the entire follow-up (until 8 years old) for the cohort and defined in children according to diagnoses and/or medications from the NPR and PDR based on a previously validated algorithm.²¹ Please see [Supplementary Methods](#) (available as [Supplementary data](#) at *IJE* online) for more detail.

‘Prevalent asthma’ at age 6 years was defined as ‘incident asthma’ combined with at least one dispense of any asthma medication ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online) and/or an asthma diagnosis in the NPR during the sixth year for a subgroup born between 1 July 2005 and 31 December 2007 alive and residing in Sweden until the sixth birthday.

‘Prevalent allergic asthma’ at age 6 years was defined as ‘prevalent asthma’ at age 6 years combined with ‘allergic rhinitis’, using an algorithm for allergic rhinitis based on medication and/or diagnosis from the NPR and PDR ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online).²²

‘Prevalent non-allergic asthma’ at age 6 years was defined as ‘prevalent asthma’ at age 6 years without ‘allergic rhinitis’.

Exposure

Pre-eclampsia was divided into mild/moderate and severe forms (based on International Classification of Diseases, ICD-10 diagnoses from the NPR).²³ The mild/moderate forms included ‘Mild to moderate preeclampsia’ (O14.0), ‘Unspecified preeclampsia’ (O14.9) and ‘Preeclampsia with preexisting hypertension’ (O11.9). The severe forms included ‘Severe preeclampsia’ (O14.1), ‘Hemolysis, Elevated Liver enzymes, and Low Platelet count (HELLP)’ (O14.2) and ‘Eclampsia’ (O15.0, O15.1, O15.2 and O15.9). The Swedish guidelines for the ICD-10 pre-eclampsia diagnosis codes from the Swedish Association for Obstetrics and Gynaecology are equivalent to the

British National Institute for Health and Care Excellence guidelines, which are widely used in Europe.^{24,25}

Potential confounders

Child characteristics (MBR): ‘Gender’ and ‘birth order’.

Maternal characteristics (MBR): ‘Maternal smoking’ and ‘Swedish oral snuff’,²⁶ ‘maternal age’, ‘maternal body mass index’ (BMI) (recoded according to the World Health Organization BMI classification categories).²⁷ ‘Maternal asthma’ was defined as ‘asthma ever’ until the delivery in question (MBR, NPR or PDR).²⁸ LISA: ‘Mother’s education’ and ‘family income’, where the latter was the disposable income at the household level, represented as 2005-currency equivalents and log-transformed. MGR: ‘Mother’s birth country’.

Statistics

‘The association between pre-eclampsia according to severity and incident asthma’: Cox proportional-hazards regression analyses were used with attained age as the underlying timescale. The exit date was defined as death, emigration, asthma or 31 December 2013, whichever came first. We tested the assumption of proportional hazards based on Schoenfeld residuals, which indicated that the hazards were non-proportional. We therefore allowed for time-varying effects of the exposure before and after 2 years of age ([Supplementary Table S1](#), available as [Supplementary data](#) at *IJE* online). Analyses were adjusted for potential confounders (child: gender and birth order; maternal: age, smoking, Swedish oral snuff, education, asthma, BMI, ethnicity and family income) as shown in a directed acyclic graph (DAG) ([Figure 1](#)).²⁹

‘The association between pre-eclampsia according to severity and prevalent asthma’ at age 6 years: Logistic-regression models for the outcomes ‘prevalent non-allergic asthma’ and ‘prevalent allergic asthma’ were applied, first unadjusted, then adjusted for potential confounders according to the DAG.

‘Sibling comparisons’: If associations were found in the adjusted analyses, we then applied sibling comparisons to explore the role of familial confounding. Based on the MGR, we identified all possible sibling pairs with complete data within the cohort. Next, we identified sibling pairs discordant on pre-eclampsia exposure. Third, we used stratified Cox regression and conditional logistic regression, stratified or conditioned on the discordant sibling pairs, respectively. Thereby we accounted for all confounders and mediators that are shared within the pair, both measured and unmeasured, recently discussed in a methods publication.³⁰ In the sibling comparisons, we adjusted for

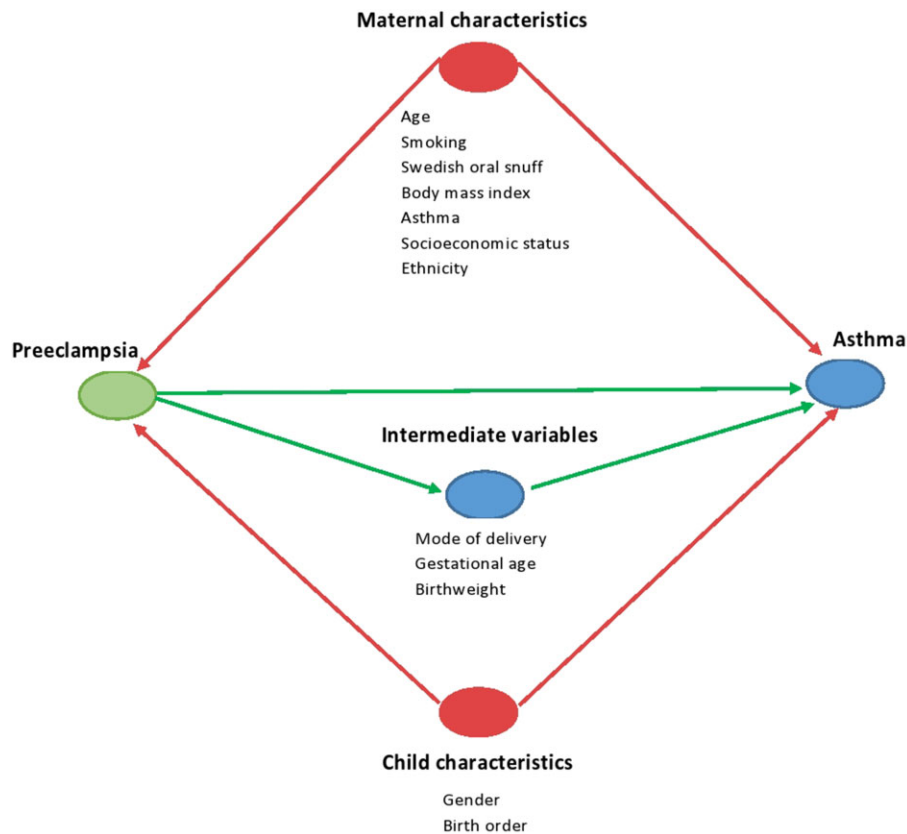


Figure 1 Directed acyclic graph showing the exposure, outcome variable, potential confounders and intermediate variables in the study

all the potential confounders not shared between siblings (child: gender and birth order; maternal: smoking, Swedish oral snuff, age and BMI).

‘Conditioning on the risk of intermediate variables: caesarean section, prematurity and small for gestational age’ (SGA): If the sibling comparisons indicated a potential causal effect, we explored the role of the potential intermediate variables. To avoid collider bias from adjusting directly for the intermediate variables, we used baseline covariates ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online) to determine the risk of each of the intermediate variables stratified into high and low risk above and below the 95th percentile of the estimated risk, respectively ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online). We then estimated the adjusted hazard ratios (HRs) in the low- and high-risk groups of these intermediate covariates, as suggested by VanderWeele *et al.*, to estimate the direct effect, not mediated through those factors, of pre-eclampsia on asthma ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online).¹⁸ Finally, to test the difference between high- and low-risk groups, we analysed high- and low-risk groups together and tested for interactions with pre-eclampsia. The risk predictions compared

with the actual potential intermediate variables are shown in [Supplementary 2×2 Tables](#) (available as [Supplementary data](#) at *IJE* online).

In all analyses, we used the sandwich estimator for the standard errors to account for clustering within the same family.

We present the results of Cox- and logistic-regression analyses as HR and odds ratios (ORs), respectively, with 95% confidence intervals (CIs).

We used Stata Statistical Software release 16 for all statistical analyses.

Results

In the study population of 780 118 children, 14 823 (1.9%) were exposed to ‘mild/moderate pre-eclampsia’ and 7410 (0.9%) were exposed to ‘severe pre-eclampsia’ ([Table 1](#)). The incidence of asthma was 23 cases per 1000 person-years or 7.7% ($n = 60\ 239$) of all children. The mean follow-up time was 3.3 years. For the analysis of ‘prevalent asthma’ at age 6 years, 242 117 children were available for analysis; 10 628 (4.4%) had ‘prevalent non-allergic asthma’ and 5582 (2.3%) had ‘prevalent allergic asthma’. [Table 1](#) shows the background characteristics

Table 1 Background characteristics of the study population of 780 118 children born in Sweden in 2005–2012 according to pre-eclampsia-exposure severity

	Pre-eclampsia categories		
	None <i>n</i> = 757 885 (97.1)	Mild/moderate <i>n</i> = 14 823 (1.9)	Severe <i>n</i> = 7410 (0.9)
Gender			
Male	389 290 (51.4)	7813 (52.7)	3835 (51.7)
Firstborn			
Yes	334 790 (44.2)	9732 (65.6)	5318 (71.8)
Prematurity			
Yes	32 467 (4.3)	1452 (9.8)	3465 (46.8)
Small for gestational age			
Yes	14 584 (1.9)	1234 (8.3)	1514 (20.4)
Missing	1250 (0.2)	18 (0.1)	17 (0.2)
Delivery by caesarean section			
Yes	122 078 (16.1)	4362 (29.4)	4487 (60.5)
Maternal smoking at first antenatal visit			
Yes	49 502 (6.5)	786 (5.3)	293 (3.9)
Missing	33 659 (4.4)	610 (4.1)	427 (5.8)
Maternal Swedish oral snuff at first antenatal visit			
Yes	8739 (1.1)	205 (1.4)	90 (1.21)
Missing	33 678 (4.4)	615 (4.1)	427 (5.8)
Maternal education (years)			
<10	82 164 (10.8)	1553 (10.5)	752 (10.1)
10–12	286 529 (37.8)	6256 (42.2)	2944 (39.7)
>12	371 057 (49.0)	6762 (45.6)	3526 (47.6)
Missing	18 135 (2.4)	252 (1.7)	188 (2.5)
Maternal asthma			
Yes	92 002 (12.1)	2250 (15.2)	1113 (15.0)
Maternal birth country			
Sweden	587 124 (77.5)	12 388 (83.6)	5955 (80.4)
Other Nordic countries	11 556 (1.5)	228 (1.5)	122 (1.6)
Other European countries ^a , North America, Oceania	26 943 (3.6)	404 (2.7)	189 (2.5)
Rest of the world	132 164 (17.4)	1802 (12.2)	1144 (15.4)
Missing	98 (0.0)	1 (0.0)	0 (0.0)
Maternal body mass index (kg/m ²)			
<18.5	17 186 (2.3)	171 (1.1)	113 (1.5)
18.5–25	423 947 (55.9)	5783 (39.0)	3357 (45.3)
25–30	172 759 (22.8)	4034 (27.2)	1826 (24.6)
>30	81 428 (10.7)	3617 (24.4)	1429 (19.3)
Missing	62 565 (8.3)	1.218 (8.2)	685 (9.2)
Family income (×1000 Swedish kroner equivalent to 2005)			
Median (interquartile range)	407 (227)	401 (212)	396 (228)
Maternal age at delivery (years)			
Median (interquartile range)	31 (8)	31 (8)	31 (8)

Values unless specified otherwise are *n* (%).^aIncluding the Soviet Union.

Table 2 Hazard ratios of incident asthma in the study population of 779 711 children born in Sweden in 2005–2012 according to pre-eclampsia exposure *in utero*

	Mean follow-up time (years)	Incident asthma [n (%)]	Incidence rate of asthma ^c	Crude (n = 779 711) HR (95% CI)	Adjusted ^a (n = 656 112) HR (95% CI)	Sibling analysis ^b (n = 16 460) HR (95% CI)
No pre-eclampsia		58 029 (7.7)		Reference	Reference	Reference
Asthma onset:						
0–2 years of age	1.6		32			
>2 years of age	2.6		14			
Mild/moderate pre-eclampsia		1327 (9.0)				
Asthma onset:						
0–2 years of age	1.6		37	1.15 (1.08, 1.23)	1.13 (1.05, 1.21)	0.94 (0.78, 1.14)
>2 years of age	2.5		18	1.30 (1.18, 1.43)	1.11 (1.00, 1.24)	0.70 (0.45, 1.08)
Severe pre-eclampsia		883 (11.9)				
Asthma onset:						
0–2 years of age	1.6		55	1.71 (1.58, 1.85)	1.78 (1.64, 1.95)	1.45 (1.10, 1.90)
>2 years of age	2.6		19	1.39 (1.22, 1.59)	1.26 (1.08, 1.46)	0.68 (0.38, 1.21)

No pre-eclampsia is the reference value.

The age indicated under the pre-eclampsia severities reflects the age of asthma diagnosis.

n, number of participants; HR, hazard ratio; CI, confidence interval.

^aAdjusted for maternal: age, smoking, Swedish oral snuff, education, asthma, birth country, body mass index; child: gender, firstborn; and family disposable income.

^bConditioned on sibling pairs and adjusted for maternal: age, smoking, Swedish oral snuff, body mass index; and child: gender, firstborn. The analysis was not applicable if the estimates in the adjusted analysis was close to null. N, number of individuals in the sibling pairs discordant for the exposure to pre-eclampsia.

^cPer 1000 person-years.

according to pre-eclampsia exposure. In total, 1022 sibling pairs ($n=2044$) were discordant for exposure to pre-eclampsia and ‘incident asthma’.

The association between pre-eclampsia and ‘incident asthma’

We found positive associations between ‘mild/moderate pre-eclampsia’ and asthma with onset before 2 years of age [adjusted (adj)HR 1.13, 95% CI: 1.05, 1.21] and after two years of age (adjHR 1.11, 95% CI: 1.00, 1.24) (Table 2). Further, we found positive associations between ‘severe pre-eclampsia’ and asthma with onset before 2 years of age (adjHR 1.78, 95% CI: 1.64, 1.95) and after 2 years of age (adjHR 1.26, 95% CI: 1.08, 1.46). In sibling comparisons, all associations were attenuated with adjHRs ranging from 0.68 to 0.94 and the 95% CIs ranging from 0.38 to 1.21, except for the association between ‘severe pre-eclampsia’ and asthma onset before 2 years of age (adjHR 1.45, 95% CI: 1.10, 1.90).

The association between pre-eclampsia and prevalent asthma at age 6 years

We found positive associations between ‘mild/moderate pre-eclampsia’, ‘severe pre-eclampsia’ and ‘prevalent non-allergic

asthma’ (adjOR 1.17, 95% CI: 1.00, 1.36; adjOR 1.51, 95% CI: 1.23, 1.84), respectively (Table 3). We did not find an association between ‘mild/moderate pre-eclampsia’ and ‘prevalent allergic asthma’ (adjOR 0.91, 95% CI: 0.72, 1.15), although we did find a possible positive association between ‘severe pre-eclampsia’ and ‘prevalent allergic asthma’ (adjOR 1.31, 95% CI: 0.98, 1.74). Owing to very few discordant sibling pairs available for analysis ($n=37$), we did not perform sibling comparisons for the outcomes of ‘prevalent allergic’ and ‘non-allergic asthma’. Similarly to asthma with onset after 2 years of life, the association between pre-eclampsia and ‘prevalent asthma’ could also be confounded by familial factors, and therefore we did not proceed with conditioning on intermediate variables.

The association between pre-eclampsia and ‘incident asthma’ conditioning on the risk for intermediate variables

As all associations with incident asthma from the sibling analyses were clearly attenuated except between ‘severe pre-eclampsia’ and ‘incident asthma’ before 2 years of age, this was the only association for which we estimated associations stratified on the high and low risk of intermediates. The associations were similar to the original adjusted HRs for all low- and high-risk intermediate groups

Table 3 Odds ratios of prevalent asthma at age 6 years in the study population of 242 117 children born in Sweden in July 2005–December 2007 according to pre-eclampsia exposure *in utero*

Pre-eclampsia	Prevalent non-allergic asthma (<i>n</i> = 236 535)			Prevalent allergic asthma (<i>n</i> = 231 489)		
	Prevalence	Crude (<i>n</i> = 236 535) OR (95% CI)	Adjusted ^a (<i>n</i> = 165 987) OR (95% CI)	Prevalence	Crude (<i>n</i> = 231 489) OR (95% CI)	Adjusted ^a (<i>n</i> = 162 225) OR (95% CI)
None (235 296)	10 224/229 910 (4.4%)	Reference	Reference	5386/225 072 (2.4%)	Reference	Reference
Mild/moderate (4508)	257/4389 (5.9%)	1.34 (1.18, 1.52)	1.17 (1.00, 1.36)	119/4251 (2.8%)	1.17 (0.98, 1.41)	0.91 (0.72, 1.15)
Severe (2313)	147/2236 (6.6%)	1.51 (1.28, 1.79)	1.51 (1.23, 1.84)	77/2 166 (3.5%)	1.50 (1.20, 1.89)	1.31 (0.98, 1.74)

No pre-eclampsia is the reference category.

n, number of participants; OR, odds ratio; CI, confidence interval.

^aAdjusted for maternal: age, smoking, Swedish oral snuff, education, asthma, birth country, body mass index; child: gender, firstborn; and family disposable income.

(caesarean section, prematurity, SGA) with HRs ranging from 1.63 to 1.79. We did not find any differences in HRs between the high- and low-risk groups for any of the intermediates, with *p*-values for interactions ranging from 0.70 to 1.00 (Table 4).

Discussion

In this population-based study, we found positive associations between pre-eclampsia and ‘incident asthma’ of all ages. However, only the association between ‘severe pre-eclampsia’ and asthma onset before 2 years of age remained in sibling comparison, and it remained when conditioning on the risk of the potential intermediate variables of caesarean section, prematurity and SGA, supporting a direct causal interpretation. We found a positive association between ‘severe pre-eclampsia’ and ‘prevalent non-allergic asthma’ at age 6 years, although we lacked the power to evaluate a possible influence of familial factors, and therefore we did not proceed with conditioning on the risk of potential intermediate variables.

Comparison with previous studies

To our knowledge, this is the first large study on the association between pre-eclampsia and asthma dividing asthma into allergic and non-allergic phenotypes, and conditioning on important potential intermediates by stratifying on the risk of intermediates, rather than the intermediates themselves, to avoid collider bias due to unknown confounders for the association between the intermediates and the outcome. Differences in design, power, familial confounding or collider bias may explain the inconsistency between previous studies on the association between pre-eclampsia and asthma.^{7–12,18,31–34} Our results for pre-eclampsia and

asthma onset before 2 years of age support previous research. First, in a population-based cohort of 13 758 children, pre-eclampsia was associated with wheezing at 18 months of age (adjOR 1.31, 95% CI: 0.94, 1.82) but not asthma at 7 years of age.¹² Second, in a pooled analysis of 14 European cohorts of 85 509 children in total, pre-eclampsia was associated with wheezing until 24 months of age [adj relative risk (RR) 1.04, 95% CI: 0.97, 1.13].³⁴ Further, in a Danish case-sibling study of 147 312 children based on a nested case-control study of 923 533 children, an association between early-onset pre-eclampsia and asthma was found (incidence rate ratio 1.15, 95% CI: 1.02, 1.29).⁸ This was similar to our results in the sibling comparison, as early-onset pre-eclampsia (the exposure variable in the Danish study) comprises mostly severe cases of pre-eclampsia (the exposure variable in our study).³ Regarding later childhood, a Norwegian register study of 406 907 children found an association between pre-eclampsia and asthma at 7 years of age (adjRR 1.31, 95% CI: 1.22, 1.41).¹⁰ This study did not differentiate pre-eclampsia by severity or asthma by phenotype, but was still similar to our results showing positive associations between ‘severe pre-eclampsia’ and ‘prevalent non-allergic asthma’ at age 6 years. Finally, four studies with adjustments for mode of delivery, birthweight and gestational age found positive associations between pre-eclampsia and asthma/wheeze that were similar to our results for the association between ‘severe pre-eclampsia’ and asthma onset before 2 years of age when conditioning on the risk of caesarean section, prematurity and SGA.^{7,12,15,31}

Potential underlying mechanisms

The associations between ‘mild/moderate pre-eclampsia’ and asthma, and ‘severe pre-eclampsia’ and asthma onset

Table 4 Hazard ratios of incident asthma in the study population of 779 711 children born in Sweden in 2005–2012 according to severe pre-eclampsia exposure *in utero* and adjusted for the risk of intermediate variables

	Caesarean section ^{a,b}			Prematurity ^{a,b}			SGA ^{a,b}		
	Low risk (n = 623 310)	High risk (n = 32 802)	Interaction	Low risk (n = 619 688)	High risk (n = 32 598)	Interaction	Low risk (n = 619 714)	High risk (n = 32 572)	Interaction
	HR (95% CI)	HR (95% CI)	p	HR (95% CI)	HR (95% CI)	p	HR (95% CI)	HR (95% CI)	p
Severe pre-eclampsia	1.78 (1.63, 1.95)	1.72 (1.28, 2.30)	0.72	1.75 (1.59, 1.92)	1.75 (1.39, 2.19)	1.00	1.79 (1.63, 1.95)	1.63 (1.13, 2.33)	0.70
0–2 years of age									

No pre-eclampsia is the reference value.

The age indicated under the pre-eclampsia severities reflects the age of asthma diagnosis.

No association between severe pre-eclampsia and incident asthma above 2 years of age was found in the adjusted analysis, so we did not perform stratified analyses for intermediate variables for this predictor.

n, number of participants; HR, hazard ratio; CI, confidence interval; SGA, small for gestational age; p = p-value for testing differences in HRs between the high- and low-risk groups.

^aAdjusted for maternal: age, smoking, Swedish oral snuff, education, asthma, birth country, body mass index; child: gender, firstborn; and family disposable income.

^bBased on baseline covariates, the risk for the variable is calculated and stratified according to high or low risk for the intermediate variables to occur: caesarean section, prematurity or SGA.

after 2 years of age were attenuated in sibling comparisons, suggesting the association was at least partly explained by confounding factors shared by siblings. These factors may be genes, maternal factors and shared family environments. However, the association between ‘severe pre-eclampsia’ and asthma onset before 2 years of age persisted in the sibling comparison and in both the high- and low-risk groups of caesarean section, prematurity and SGA, strengthening the possibility of a direct causal link, which could be explained by *in utero* inflammation causing immune dysregulation in the affected children.^{5,6} The explanation for an association between pre-eclampsia and non-allergic asthma may be an increase in pro-inflammatory cytokines that are also involved in the development of a non-eosinophilic inflammation of the airways, as found in non-allergic asthma.^{6,35} Furthermore, pre-eclampsia may give rise to epigenetic changes in the offspring, especially immunological ones, as shown in a study in which Herzog *et al.* found an association between pre-eclampsia and a derangement in fetal haematopoiesis.³⁶ Finally, early wheezing after exposure to pre-eclampsia may be related to an antiangiogenic maternal and fetal environment affecting the fetal lungs,³⁷ supported by one prospective cohort in which analysis of the neonate cord blood reflected the maternal antiangiogenic status.³⁸

Strengths and limitations

This study has several strengths. First, it is a large register-based study with >700 000 participants, allowing us to meaningfully differentiate between the severities of the exposure pre-eclampsia and the two phenotypes of asthma. Second, we used a validated definition of asthma, thereby reducing the likelihood of early transient wheeze caused by infectious agents. Third, instead of adjusting directly for the intermediate variables on the pathway between pre-eclampsia and asthma, which may cause bias, we used baseline covariates to estimate the risk of these and stratified on risk groups. A disadvantage of this method is if the risk groups have low predictive value. The positive highest predictive value for the high-risk group was found for caesarean section, suggesting those results are the most reliable (Supplementary 2 × 2 Tables, available as [Supplementary data](#) at *IJE* online). Another issue is that it is not fully known whether hypertension in pregnancy may be a precursor of pre-eclampsia or a similar condition. In our study, we only aimed to study the association between pre-eclampsia diagnoses and not hypertension diagnoses with asthma, thus the diagnosis ‘pre-eclampsia with pre-existing hypertension’ was the only hypertension diagnosis included in the group of ‘mild/moderate pre-eclampsia’. In some studies, all hypertensive disorders, including

pre-eclampsia, were combined to study the association with offspring asthma.^{12,31} From this aspect, hypertension could be regarded as the exposure and not pre-eclampsia per se, which would be a different aim than we had in our study.

Conclusion

The results suggest that ‘severe pre-eclampsia’ is associated with childhood early-onset asthma, regardless of family factors, mode of delivery, gestational age or birthweight. Further, ‘severe pre-eclampsia’ is also associated with ‘prevalent non-allergic asthma’ at age 6 years but we cannot rule out confounding by familial factors. Finally, associations found between ‘mild/moderate pre-eclampsia’ and asthma show evidence of familial confounding.

Our results contribute to the understanding of early-life risks for asthma, but further research should be powered to perform sibling comparisons on asthma phenotypes to differentiate the type of wheeze/asthma that is associated with ‘severe pre-eclampsia’.

Supplementary data

Supplementary data are available at *IJE* online.

Ethics approval

Ethical approval was obtained from the Regional Ethical Review Board in Stockholm, Sweden (reference 2013/862–31/5).

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Data availability

The data underlying this article cannot be shared publicly owing to Swedish data-storage laws. The data may be accessed by researchers who obtain ethical approval from a regional ethical review board and thereafter ask the Swedish National Board of Health and Welfare and Statistics Sweden for the original data.

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Author contributions

All authors conceptualized and designed the study, K.K.B. drafted the manuscript and made final revisions, and all authors critically revised, read and approved the final manuscript.

Conflict of interest

None declared.

References

1. Asher MI, Montefort S, Bjorksten B *et al.*; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–43.
2. Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedon JC. Risk and protective factors for childhood asthma: what is the evidence? *J Allergy Clin Immunol Pract* 2016;**4**:1111–22.
3. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;**376**:631–44.
4. Auger N, Luo ZC, Nuyt AM *et al.* Secular trends in preeclampsia incidence and outcomes in a large Canada database: a longitudinal study over 24 years. *Can J Cardiol* 2016;**32**:987.e15–23.
5. Herberth G, Hinz D, Roder S *et al.* Maternal immune status in pregnancy is related to offspring’s immune responses and atopy risk. *Allergy* 2011;**66**:1065–74.
6. Spence T, Allsopp PJ, Yeates AJ, Mulhern MS, Strain JJ, McSorley EM. Maternal serum cytokine concentrations in healthy pregnancy and preeclampsia. *J Pregnancy* 2021;**2021**:6649608.
7. Stokholm J, Sevelsted A, Anderson UD, Bisgaard H. Preeclampsia associates with asthma, allergy, and eczema in childhood. *Am J Respir Crit Care Med* 2017;**195**:614–21.
8. Liu X, Olsen J, Agerbo E, Yuan W, Wu CS, Li J. Maternal pre-eclampsia and childhood asthma in the offspring. *Pediatr Allergy Immunol* 2015;**26**:181–85.
9. Byberg KK, Oglund B, Eide GE, Oymar K. Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study. *BMC Pediatr* 2014;**14**:101.
10. Magnus MC, Haberg SE, Magnus P *et al.* Pre-eclampsia and childhood asthma. *Eur Respir J* 2016;**48**:1622–30.
11. Mirzakhani H, Carey VJ, McElrath TF *et al.* Impact of pre-eclampsia on the relationship between maternal asthma and offspring asthma. an observation from the VDAART clinical trial. *Am J Respir Crit Care Med* 2019;**199**:32–42.
12. Shaheen SO, Macdonald-Wallis C, Lawlor DA, Henderson AJ. Hypertensive disorders of pregnancy, respiratory outcomes and atopy in childhood. *Eur Respir J* 2016;**47**:156–65.
13. Vatten LJ, Skjaerven R. Is pre-eclampsia more than one disease? *BJOG* 2004;**111**:298–302.

14. Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol* 2009;**201**: 269.e1–10.
15. Nahum Sacks K, Friger M, Shoham-Vardi I, Sergienko R, Landau D, Sheiner E. In utero exposure to pre-eclampsia as an independent risk factor for long-term respiratory disease. *Pediatr Pulmonol* 2020;**55**:723–28.
16. Ortqvist AK, Lundholm C, Carlstrom E, Lichtenstein P, Cnattingius S, Almqvist C. Familial factors do not confound the association between birth weight and childhood asthma. *Pediatrics* 2009;**124**:e737–43.
17. Lederer DJ, Bell SC, Branson RD *et al.* Control of confounding and reporting of results in causal inference studies: guidance for authors from editors of Respiratory, Sleep, and Critical Care Journals. *Ann Am Thorac Soc* 2019;**16**:22–28.
18. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology* 2012; **23**:1–9.
19. Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am J Epidemiol* 2011;**174**:1062–68.
20. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**: 659–67.
21. Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf* 2013;**22**:850–60.
22. Henriksen L, Simonsen J, Haerskjold A *et al.* Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 2015;**136**: 360–66.e2.
23. National Collaborating Centre for Women's and Children's Health. *National Institute for Health and Clinical Excellence: Guidance. Hypertension in Pregnancy: The Management of Hypertensive Disorders during Pregnancy*. London: RCOG Press, Royal College of Obstetricians and Gynaecologists, 2010.
24. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC; Guideline Committee. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. *BMJ* 2019;**366**:l5119.
25. Andolf E, Bremme K, Bruss C, *et al.*; Swedish Association for Obstetrics and Gynecology, Work and Reference Group for Perinatology. Preeclampsia. 2014. https://www.sfog.se/natup-plaga/ARG72_komplett_LRbf4f5598-2309-4013-8dea-3cbb534708ee.pdf (9 September 2021, date last accessed).
26. Gunnerbeck A, Edstedt Bonamy A-K, Wikström A-K, Granath F, Wickström R, Cnattingius S. Maternal snuff use and smoking and the risk of oral cleft malformations: a population-based cohort study. *PLoS One* 2014;**9**:e84715.
27. Ferro-Luzzi A, Garza C, Haas J *et al.* Physical status: the use and interpretation of anthropometry: report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;**854**: 1–452.
28. Rejnö G, Lundholm C, Larsson K *et al.* Adverse pregnancy outcomes in asthmatic women: a population-based family design study. *J Allergy Clin Immunol Pract* 2018;**6**:916–22.e6.
29. Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. *Respirology* 2014;**19**:303–11.
30. Petersen AH, Lange T. What is the causal interpretation of sibling comparison designs? *Epidemiology* 2020;**31**:75–81.
31. Wilmink FA, den Dekker HT, de Jongste JC *et al.* Maternal blood pressure and hypertensive disorders during pregnancy and childhood respiratory morbidity: the Generation R Study. *Eur Respir J* 2018;**52**.
32. Nafstad P, Magnus P, Jaakkola JJ. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *J Allergy Clin Immunol* 2000;**106**:867–73.
33. Nafstad P, Samuelson SO, Irgens LM, Bjerkedal T. Pregnancy complications and the risk of asthma among Norwegians born between 1967 and 1993. *Eur J Epidemiol* 2003;**18**:755–61.
34. Zugna D, Galassi C, Annesi-Maesano I *et al.* Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. *Int J Epidemiol* 2015;**44**:199–208.
35. Szeffler SJ, Chmiel JF, Fitzpatrick AM *et al.* Asthma across the ages: knowledge gaps in childhood asthma. *J Allergy Clin Immunol* 2014;**133**:3–14.
36. Herzog EM, Eggink AJ, van der Zee M *et al.* The impact of early- and late-onset preeclampsia on umbilical cord blood cell populations. *J Reprod Immunol* 2016;**116**:81–85.
37. Tang JR, Karumanchi SA, Seedorf G, Markham N, Abman SH. Excess soluble vascular endothelial growth factor receptor-1 in amniotic fluid impairs lung growth in rats: linking preeclampsia with bronchopulmonary dysplasia. *Am J Physiol Lung Cell Mol Physiol* 2012;**302**:L36–46.
38. Herzog EM, Eggink AJ, Willemsen SP *et al.* Early- and late-onset preeclampsia and the tissue-specific epigenome of the placenta and newborn. *Placenta* 2017;**58**:122–32.