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Pre-eclampsia and childhood asthma

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Abstract

Studies of pre-eclampsia and childhood asthma are conflicting, and none did a formal mediation analysis of preterm birth.

We examined the association between pre-eclampsia and asthma at 7 years using national registries, including all births in Norway from 1996 to 2006 (n=406,907), and a subsample of children in the Norwegian Mother and Child Cohort Study (MoBa) (n=45,028) using log-linear regression. We performed a mediation analysis of preterm birth, and a sibling comparison to evaluate unobserved confounding.

There was a positive association between pre-eclampsia and asthma in the registry study, with an adjusted RR of 1.31 (95% CI: 1.22, 1.41), but not MoBa, adjusted RR of 1.19 (95% CI: 0.99, 1.44). The odds ratio for the direct effect not mediated through preterm birth and the indirect effect in the registry linkage were 1.19 (95 % CI: 1.10, 1.29) and 1.12 (95% CI: 1.11, 1.14) respectively. The sibling comparison indicated no association between pre-eclampsia and asthma, adjusted OR 1.07 (95% CI: 0.87, 1.33).

In this large study, which used different datasets and analytic approaches, there was little evidence for an association between pre-eclampsia and childhood asthma. The association was weak and largely explained by pre-term birth and confounders shared by siblings.

Keywords: Asthma and pre-eclampsia

Introduction

Asthma is the most common chronic disease in children, and is characterized by reversible airway obstruction and inflammation [1]. There is a genetic predisposition in development of asthma [2]. However, despite decades of research, there are few established environmental causes, but pregnancy and early childhood are recognized as crucial time periods for the developing airways and immune system [3].

Pre-eclampsia is a characterized by pregnancy-induced hypertension, in combination with proteinuria, occurring in between 2% and 8% of pregnancies [4]. Early-onset pre-eclampsia may affect placental development, with a subsequent reduced blood flow to the fetus [5]. Furthermore, pre-eclampsia often results in an earlier delivery, as delivery is the only intervention that will reverse the condition completely. Both preterm birth and low birth weight are associated with childhood asthma [6-8].

A few studies have examined the association between pre-eclampsia and childhood asthma in school age or later [9-12], one of which reported a positive association [10]. Other studies have evaluated the association between pre-eclampsia and childhood wheezing phenotypes, both of which indicated a positive association [13, 14]. As far as we know, none of the previous studies conducted a formal mediation analysis to quantify the magnitude of the association between pre-eclampsia and childhood asthma mediated through preterm birth. Only one study performed a sibling comparison analysis [10] , in order to evaluate the potential role of unobserved confounding at sibling level [15]. Most previous studies had a relatively modest sample size, and therefore limited power to evaluate pre-eclampsia as a risk factor for asthma.

The heterogeneity and inconsistent results of previous studies indicate that we need to address this research question using different methodological approaches and carefully assess potential influence from confounding and mediating factors.

The objectives of the current study were 1) to examine the association between pre-eclampsia and childhood asthma, and 2) to evaluate whether preterm birth might mediate the association between pre-eclampsia and childhood asthma. We evaluated these objectives in both a national registry-based study and in a large prospective pregnancy cohort including detailed questionnaire information for additional potential confounding factors. The registry-based study included all births in Norway between January 1999 and July 2006, and the large number of children was the basis for using a sibling design.

Methods

Study subjects

The registry-based study included information from the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD) and the Norwegian Education Database. This linkage encompassed all children born in Norway and registered in the MBRN between January 1999 and July 2006 (n= 443,300). Only live-born singletons with a valid national identification number, a birth weight of 500 grams or more, a gestational age of 22 weeks or longer, and who were alive and living in Norway at their eight birthday were eligible for the current study (Figure 1). This left 406,907 children in the analysis.

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective pregnancy cohort administered by the Norwegian Institute of Public Health [16, 17]. MoBa recruited pregnant women between 1999 and 2008, at approximately 18 weeks gestation. The participation rate was 41%. Mothers could participate in the cohort with more than one pregnancy, resulting in a cohort of 95,000 mothers and 114,500 children. All participants gave a written informed consent. In this study, we included children with information from questionnaires administered at 18-and 30 gestational weeks, in addition to questionnaires administered when the child was 6 months, with a birth weight 500 grams or more, a gestational age of 22 weeks or longer, and had reached 7 years by April 1st 2013 (Figure 1). This left 45,028 children born between January 2000 and March 2006 in the analysis. Data from MoBa was linked to the MBRN and the NorPD.

The Norwegian Data Inspectorate and the Regional Committees for Medical and Health Research Ethics of South/East and West Norway approved this study.

Pre-eclampsia

In Norway, pregnant women carry a standardized chart to all antenatal examinations during pregnancy. At the time of delivery, the midwife transfers information from this chart to the MBRN notification form which is mandatory for all births. The MBRN has 5 checkoff boxes relevant to pre-eclampsia: (1) HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count); (2) eclampsia; (3) early pre-eclampsia (diagnosed before 34 weeks); (4) mild pre-eclampsia; and (5) severe pre-eclampsia. We defined pre-eclampsia (yes/no) as a registration of any of these conditions in the MBRN. We combined information on gestational age at birth with information on pre-eclampsia into four mutually exclusive categories (neither, pre-eclampsia only, preterm birth only and pre-eclampsia with preterm birth). Preterm birth was defined as a gestational age of less than 37 weeks.

Childhood asthma

The child's asthma status was defined by evaluating dispensed asthma medications as registered in the NorPD. The NorPD contains information on all dispensed prescriptions from all Norwegian pharmacies since January 2004. Asthma medications included inhaled short- and long-acting beta(2)-agonists (R03AC), inhaled corticosteroids (R03BA), fixed-dose combinations of inhaled beta(2)-agonists and corticosteroids (R03AK), and leukotriene antagonists (R03DC). A child was defined as having asthma at 7 years if there was at least one dispensed prescription for asthma medications in the past 12 months in addition to at least one second dispensed prescription within 12 months after the first. In a secondary analysis within the MoBa cohort, we defined children as having asthma if the mother in the questionnaire at age 7 had reported that the child was doctor diagnosed with asthma and also had either current symptoms or had used asthma medications in the past 12 months.

Covariates

We used information on characteristics that could potentially influence the association of interest. Child characteristics included sex (male/female). Maternal characteristics included age at delivery (entered as a continuous variable), parity (categorized into primiparous, 1, 2 and 3 or more), education (categorized into less than high school, high school, up to 4 years of college and 4 or more years of college), maternal asthma (categorized as yes/no) and smoking during pregnancy (categorized as yes/no). Additional information from questionnaires in MoBa included maternal pre-pregnancy body-mass index (BMI; entered as a continuous variable).

Statistical analysis

We did descriptive analyses showing the distribution of pre-eclampsia by the covariates. The further analysis was done in several steps. First, we used national registry data and evaluated the association between pre-eclampsia and the child's risk of asthma using log-binomial regression models, reporting relative risks (RR) and 95 % confidence intervals (CI), accounting for the dependency between siblings by using robust cluster variance estimation. The multivariable analyses adjusted for the maternal age, parity, education, maternal asthma and the child's gender. Additional adjustment for maternal smoking during pregnancy was explored among the 75% of children for whom this information was available in the registry. Secondly, we repeated the analysis in the subsample of children participating in the MoBa cohort. In the multivariable analyses using MoBa data we further adjusted for pre-pregnancy BMI in addition to the characteristics mentioned above. Thirdly, we conducted a secondary analysis in MoBa using a questionnaire based asthma definition as the outcome.

Fourth, we evaluated the independent and combined effect of preterm birth and pre-eclampsia on asthma development, and subsequently calculated the relative excess risk due to

interaction, before moving on to a formal mediation analysis. Figure 2 shows the theoretical framework underlying our mediation analysis. The mediation analysis was performed by a logistic decomposition of the total effects into indirect and direct effects using the ldecomp command in the Stata software [18]. We also explored conventional multivariable adjustment for preterm birth as an alternative approach to obtain an estimate of the direct effects of pre-eclampsia. Last, we used the national registry data and conducted an analysis of sibling pairs discordant for asthma using conditional logistic regression analysis, reporting odds ratios (OR) and 95% CI. This approach compares the distribution of pre-eclampsia between sibling pairs discordant for asthma.

The amount of missing covariate information was generally low (<2%). Nevertheless, we explored robustness of the results using multiple imputation by chained equations imputing a total of 20 datasets. The statistical significance level was 5%. The analysis was conducted using Stata version 14 (Statacorp, Texas).

Results

Distribution of pre-eclampsia by maternal and child characteristics

The prevalence of pre-eclampsia was 4%, while 5% of children had asthma at 7 years. The prevalence of pre-eclampsia decreased with maternal age, parity, educational level and smoking, while it increased with maternal pre-pregnancy BMI (table 1). Furthermore, there was a higher prevalence of pre-eclampsia among mothers with asthma and among mothers delivering preterm (table 1).

Pre-eclampsia and asthma at 7 years

There was a positive association between pre-eclampsia and asthma at 7 years in the registry study, with an adjusted RR of 1.31 (95 % CI: 1.22, 1.41), but not in MoBa, with an adjusted RR of 1.19 (95% CI: 0.99, 1.44) (table 2). The difference in the strength of the association in the registry study and the MoBa cohort was mostly explained by additional adjustment for maternal pre-pregnancy BMI in MoBa. The adjusted RR was 1.27 (95% CI: 1.06, 1.53) without adjustment for pre-pregnancy BMI. There was no change in the observed associations after exclusion of mothers with pre-existing hypertension before pregnancy (online supplementary table E1). The multiple imputation analysis also gave similar results (online supplementary table E2). Furthermore, there was no difference in the observed associations among primiparous and multiparous mothers (online supplementary table E3). In MoBa, the magnitude of the association between pre-eclampsia and asthma at 7 years was larger and only statistically significant when using maternal report of doctor diagnosed asthma at 7 years as an outcome (online supplementary table E4).

Combined effects of pre-eclampsia and preterm birth on asthma at 7 years

Around 4% of children were born preterm by mothers who did not have pre-eclampsia, 3% of children were born at term to mothers who had pre-eclampsia, while 1% of children were born preterm to mothers who had pre-eclampsia. There was a positive association between being born at term to mothers with pre-eclampsia and asthma at 7 years in the registry-based study, adjusted RR 1.21 (95% CI: 1.11, 1.32), but not in MoBa, adjusted RR 1.01 (95% CI: 0.80, 1.28) (table 2). There was some indication in MoBa that the association between pre-eclampsia and preterm birth in combination with asthma was greater than the independent associations seen for these two exposures (table 2 and table E4). However there was no statistically significant excess relative risk due to interaction.

The mediating effect of preterm birth on the association between pre-eclampsia and asthma at 7 years

Pre-eclampsia was around 6 times more prevalent among those born preterm (Table 1), and preterm birth was also a risk factor for asthma (table 2). We therefore evaluated the potential indirect effect of pre-eclampsia on asthma mediated through preterm birth. The results from the mediation analysis indicated a significant direct effect of pre-eclampsia on childhood asthma in the registry-based study, adjusted OR 1.19 (95% CI: 1.10, 1.29), while the indirect effect was 1.12 (95% CI: 1.11, 1.14) (table 3).There was no direct effect in MoBa, adjusted OR 1.11 (95 % CI: 0.89, 1.37) (table 3). When adjusting for preterm birth a covariate, the results yielded an adjusted RR of 1.17 (95% CI: 1.10, 1.27) in the registry linkage and 1.10 (95% CI: 0.91, 1.33) in MoBa. Secondary analyses evaluated the combined indirect effect of preterm birth, low birth weight and delivery by caesarean section (Table E5). The results of the direct effect not mediated through these three pregnancy outcomes was OR 1.11 (95% CI:1.04, 1.18) in the registry linkage and 1.03 (95 % CI: 0.83, 1.27) in MoBa.

Sibling pair analysis of pre-eclampsia and asthma at 7 years

There were a total of 5,923 sibling groups (of two or more children) with at least two siblings discordant for asthma. The sibling pair analysis indicated no significant association between pre-eclampsia and childhood asthma, adjusted OR 1.07 (95% CI: 0.87, 1.33) (table 4).

Discussion

In this large-scale prospective study, we observed a positive association between pre-eclampsia and school-age asthma. Our findings indicate that that this association could be largely explained by a mediating effect of preterm birth. Furthermore, we cannot exclude the possibility of unobserved confounding due to characteristics that are shared by siblings.

Strengths and limitations of the study

The different methodological approaches in this study have their strengths and limitations and when interpreting the results these should be taken into consideration. The overall analysis in the registry linkage had the best power, but is likely to be hampered by some unobserved confounding. We therefore explored the association in the sub-set of individuals participating in MoBa with more detailed information on potential confounding factors, and added a registry based sibling comparison analysis. Results from the MoBa analyses might be influenced by selection bias due to the participation rate [17], and the sibling comparison conducted within the registry linkage had limited power due to the modest number of discordant sibling pairs available for analysis. However, there was sufficient power to detect a significant association between preterm birth and asthma in the sibling pair analysis. Our study also has additional limitations. Using the MBRN to classify pre-eclampsia might have resulted in misclassification, as indicated by a validation study [19]. The prevalence of asthma at 7 years was similar when the asthma definition was based on the prescription registry (4.8%) or maternal report through questionnaires (5.8%), which strengthens the reliability of an asthma prevalence of around 5% at age 7. However, this is a lower prevalence than in some other European countries, but not all. For example, the estimated prevalence of asthma at approximately 7 years is 11% in the Avon Longitudinal Study of Parents and Children (ALSPAC) [20], while current asthma at 6 years was only

reported for 3% in Generation R [21]. It was also not possible to distinguish between full versus half siblings. The results of the sibling pair analysis might therefore not account for shared genetic predisposition to a full extent as would be expected based on a comparison of known full siblings. Although we did not know the ethnicity of the study participants, excellent Norwegian language skills were a requirement for participation in MoBa and the overwhelming majority of MoBa participants are assumed to be of European descent.

The mediation analysis conducted in this study assumes no residual or unobserved confounding for the association between pre-eclampsia and asthma, pre-eclampsia and preterm birth, in addition to the association between preterm birth and asthma. A mediation analysis may also cause a spurious association due to collider stratification bias [22]. We adjusted for a wide range of maternal characteristics, but we cannot exclude the possibility that our observed associations still may be influenced by residual confounding. The results should therefore be interpreted with caution. Furthermore, the direct effect is to be interpreted as the residual association not mediated through preterm birth.

Comparison with previous studies

Four previous studies have examined the association between pre-eclampsia and childhood asthma [9-12]. A large Danish registry based study observed an incidence rate ratio of 1.19 (95% CI: 1.15, 1.24) between pre-eclampsia and asthma [10]. In contrast, a Norwegian historical cohort study (n=617) indicated no association between pre-eclampsia and asthma at 10 years of age, odds ratio 0.72 (95% CI: 0.19, 2.77) for severe pre-eclampsia [9]. Similarly, findings from ALSPAC indicated no association between pre-eclampsia and asthma at 7 years, adjusted odds ratio 1.23 (95% CI: 0.80–1.88) [12]. A large Norwegian registry study of all live births 1967-1993 (n = 1,548,429), which linked the MBRN to the National Insurance Administration Register, indicated that pregnancy complications

(including pre-eclampsia) may represent risk factors for childhood asthma [11]. The current study further contributes information to these previous studies by conducting a formal mediation analysis of the indirect due to preterm birth.

Interpretation of findings

Our finding of a stronger association between pre-eclampsia leading to preterm birth is likely to reflect an underlying severity of pre-eclampsia. Of the three studies of pre-eclampsia and school-age asthma that adjusted for gestational age, one found no association even before adjustment [12], one indicated that the association was attenuated and became non-significant after multivariable adjustment for gestational age [10], while the third found no association after adjustment for a number of factors without specifically examining the influence of adjustment for gestational age [9]. Our study is therefore the first to attempt to quantify the indirect effects of pre-eclampsia on childhood asthma explained by preterm birth, and indicated evidence of a direct effect of pre-eclampsia on childhood asthma in the registry linkage [23]. As expected, the estimate of the combined indirect effect of preterm birth, low birth and delivery by caesarean section was larger than observed for preterm birth alone. However, a significant direct effect of preelampsia not mediated through these three pregnancy outcomes was still found in the registry analyses.

A potential explanation for a direct effect between pre-eclampsia and asthma not mediated through poor placental function leading to poor intra uterine growth and preterm birth, is an influence of immunological mechanisms. Maternal immune tolerance is important to ensure a healthy pregnancy outcome, and pre-eclampsia is hypothesized to be partly due to a maladaptation of this necessary immune tolerance during pregnancy [24-26]. Studies are beginning to unravel the potential interactions between the innate and the adaptive immune system that are required to maintain a healthy pregnancy [24]. One might speculate that the

failure of the necessary immunological adaptions during pregnancy also could have consequences for the offspring's development of immune-related diseases such as asthma.

The fact that we observed a direct effect of pre-eclampsia on asthma development not mediated through preterm birth in the registry linkage and not in MoBa could be explained by the additional adjustment for pre-pregnancy BMI in MoBa. Overweight and obesity is a well-known risk factor for pre-eclampsia [27, 28]. This might be explained by the systemic inflammation and subsequent immunological changes observed among those who are obese or overweight [29]. We have previously found maternal obesity during pregnancy to increase the risk of wheezing in infancy [30], and thus maternal BMI might confound the association between pre-eclampsia and childhood asthma.

A sibling comparison allows an evaluation of the likelihood that unobserved background characteristics shared by siblings are influencing the observed associations [15]. Only one previous study performed a sibling comparison when evaluating the association between pre-eclampsia and childhood asthma [10]. In line with our findings, this previous study indicated no association between pre-eclampsia and asthma, supporting the notion that the weak direct effect observed in the overall analysis in the registry-based study might be influenced by confounding due to unobserved background characteristics shared by siblings. However, it is important to acknowledge that any sibling comparison is more susceptible to confounding by unobserved background characteristics not shared by siblings [15].

Conclusion

In this large study, which used different datasets and analytic approaches, there was little evidence for an association between pre-eclampsia and childhood asthma. The association was weak and largely explained by pre-term birth and confounders shared by siblings.

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Proposed twitter feed:

Pre-eclampsia shows no strong evidence for an association with childhood asthma at 7 years.

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Figure legends

Figure 1 Illustration of sample selection

(a) Registry-based study

(b) The Norwegian Mother and Child Cohort Study

Figure 2 Theoretical framework

Maternal background characteristics include maternal age, parity, education, body-mass index, asthma and smoking during pregnancy.

Table 1 Distribution of pre-eclampsia by maternal and child characteristics

	Registry linkage (n=406,907)		**MoBa (n=45,028)**	
Characteristics	n	% pre-eclampsia	n	% pre-eclampsia
Pre-eclampsia				
No	390,578		43,281	
Yes	16,329	4.0	1,747	3.9
Maternal age at delivery, years				
<25	70,123	4.9	4,996	5.5
25-29	137,239	4.1	15,457	4.3
30-34	135,788	3.5	17,300	3.2
35+	63,757	3.9	7,275	3.4
Maternal parity				
Nulliparous	164,683	5.9	19,511	5.6
1	146,081	2.8	16,045	2.6
2	68,174	2.6	7,407	2.4
3+	27,969	2.7	2,065	3.0
Maternal education				
Less than high school	77,340	4.2	3,789	4.5
High school	148,773	4.4	14,479	4.4
Up to 4 years of college	137,854	3.9	18,387	3.6
More than 4 years of college	29,950	3.1	8,206	3.3
Missing	12,990	2.7	167	5.4
Maternal asthma				
No	389,995	4.0	43,199	3.8
Yes	16,912	5.3	1,829	5.2
Maternal smoking at start of pregnancy				
No	268,177	4.1	39,868	4.0
Yes	72,409	3.4	4,968	2.8
Missing	66,321	4.2	192	2.1
Maternal pre-pregnancy BMI				
Underweight (<18.5)	NA		1,253	2.4
Normal weight (18.5-24.9)	NA		28,421	2.7
Overweight (25-29.9)	NA		9,865	5.2
Obese (>=30)	NA		4,238	8.7
Missing	NA		1,251	4.6
Year of birth				
1999	55,155	4.3		
2000	54,974	4.2	1,102	4.5
2001	52,630	4.1	3,265	4.2
2002	51,643	4.3	6,878	4.3
2003	52,861	3.7	10,060	3.6
2004	53,459	3.7	10,632	3.9
2005	53,347	3.8	11,828	3.7

2006	32,838	3.9	1,263	3.6
Child gender				
Male	208,643	4.1	22,975	3.9
Female	198,264	4.0	22,053	3.8
Preterm birth				
No	385,458	3.2	42,997	3.1
Yes	21,449	18.0	2,031	19.5

There were significant differences in the distribution of pre-eclampsia by all maternal and child characteristics ($p<0.003$) except for child gender (p-value 0.109 in the registry linkage and in 0.639 MoBa).

Table 2 Relative risks of asthma at 7 years in children born to mothers with pre-eclampsia

Registry linkage (n=406,907)					
Pre-eclampsia	n	% asthma	Unadjusted RR(95% CI)	Adjusted RR (95 % CI) [a]	Adjusted RR (95 % CI)[a,b]
No	390,578	3.6	1	1	1
Yes	16,329	4.9	1.37 (1.28, 1.47)	1.31 (1.22, 1.41)	1.29 (1.19, 1.39)
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]	Adjusted RR (95 % CI)[a,b]
Neither	372,992	3.4	1	1	1
Preterm birth only	17,586	6.0	1.74 (1.64, 1.85)	1.66 (1.56, 1.76)	1.67 (1.56, 1.78)
Pre-eclampsia only	12,466	4.4	1.28 (1.17, 1.39)	1.21 (1.11, 1.32)	1.21 (1.10, 1.32)
Preeclampsia and preterm birth	3,863	6.4	1.87 (1.65, 2.11)	1.83 (1.62, 2.07)	1.75 (1.52, 2.01)
Relative excess risk due to interaction			-0.15 (-0.42, 0.12)	-0.04 (-0.30, 0.22)	-0.13 (-0.41, 0.16)
MoBa (n=45,028)					
Pre-eclampsia	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [c]	
No	43,281	4.8	1	1	
Yes	1,747	6.4	1.33 (1.11, 1.60)	1.19 (0.99, 1.44)	
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [c]	
Neither	41,645	4.7	1	1	
Preterm birth only	1,636	7.1	1.51 (1.26, 1.82)	1.39 (1.15, 1.67)	
Pre-eclampsia only	1,352	5.3	1.12 (0.89, 1.41)	1.01 (0.80, 1.28)	
Preeclampsia and preterm birth	395	10.1	2.16 (1.61, 2.91)	1.86 (1.38, 2.50)	
Relative excess risk due to interaction			0.53 (-0.21, 1.26)	0.46 (-0.19, 1.11)	

[a] Adjusted for maternal age, parity, education, asthma and child gender.
[b] Additional adjustment for maternal smoking during pregnancy available for 84% of the study population.
[c] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table 3 Logistic regression model of the direct and indirect effects through preterm birth of pre-eclampsia on asthma at 7 years

Registry linkage (n=406,907)		
Component	Adjusted Odds Ratio[a]	(95% CI)
Direct Effect	1.19	(1.10, 1.29)
Indirect Effect	1.12	(1.11, 1.14)
Total Effect	1.34	(1.25, 1.44)
MoBa (n=45,028)		
Component	Adjusted Odds Ratio[b]	(95% CI)
Direct Effect	1.11	(0.89, 1.37)
Indirect Effect	1.09	(1.05, 1.14)
Total Effect	1.21	(0.98, 1.49)

[a] Adjusted for maternal age, parity, education, asthma and child gender.
[b] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

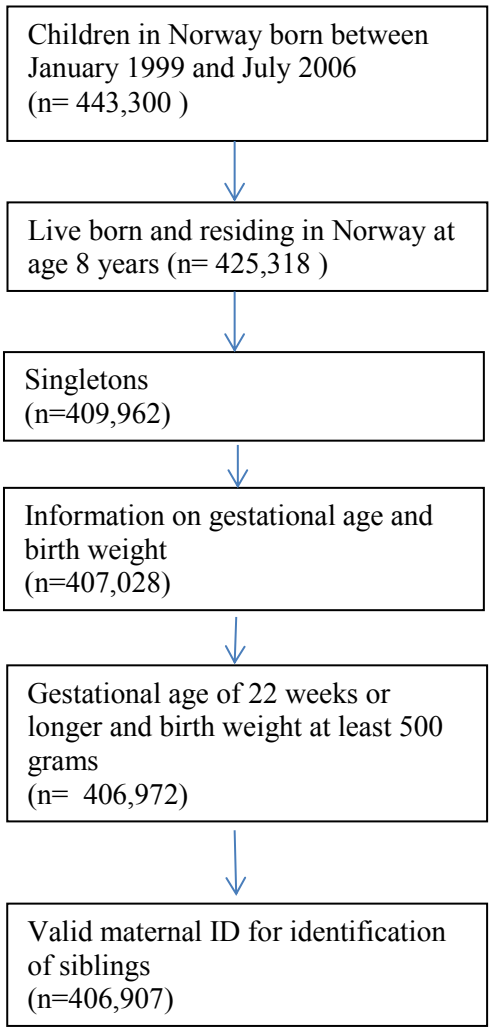
Table 4 Sibling pair analysis of associations between pre-eclampsia in combination with preterm birth with asthma at 7 years

(n= 5,923 discordant sibling groups)

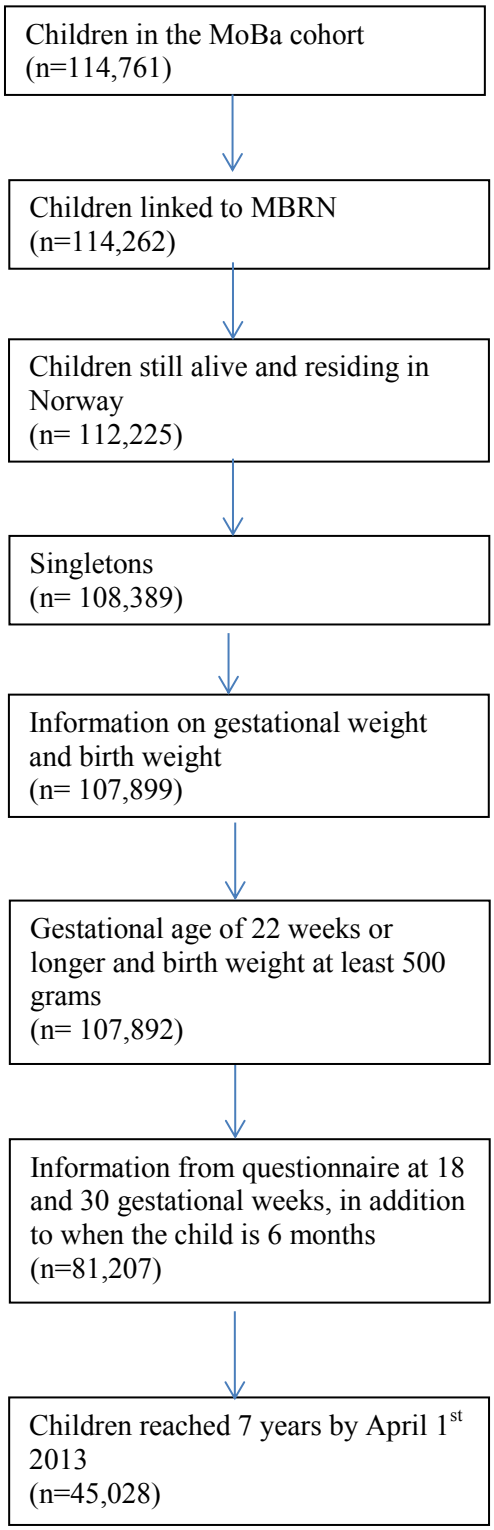
Pre-eclampsia	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]
No	1	1
Yes	1.16 (0.94, 1.42)	1.07 (0.87, 1.33)
Pre-eclampsia in combination with preterm birth	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]
Neither	1	1
Preterm birth only	1.57 (1.32, 1.88)	1.55 (1.28, 1.87)
Pre-eclampsia only	1.17 (0.94, 1.46)	1.09 (0.86, 1.38)
Preeclampsia and preterm birth	1.30 (0.90, 1.89)	1.17 (0.79, 1.73)

[a] Adjusted for maternal age, parity, education, asthma and child gender.

a)


Children in Norway born between January 1999 and July 2006 (n= 443,300)
Live born and residing in Norway at age 8 years (n= 425,318)
Singletons (n=409,962)
Information on gestational age and birth weight (n=407,028)
Gestational age of 22 weeks or longer and birth weight at least 500 grams (n= 406,972)
Valid maternal ID for identification of siblings (n=406,907)

b)


Children in the MoBa cohort
(n=114,761)
Children linked to MBRN
(n=114,262)
Children still alive and residing in Norway
(n= 112,225)
Singletons
(n= 108,389)
Information on gestational weight and birth weight
(n= 107,899)
Gestational age of 22 weeks or longer and birth weight at least 500 grams
(n= 107,892)
Information from questionnaire at 18 and 30 gestational weeks, in addition to when the child is 6 months
(n=81,207)
Children reached 7 years by April 1st 2013
(n=45,028)

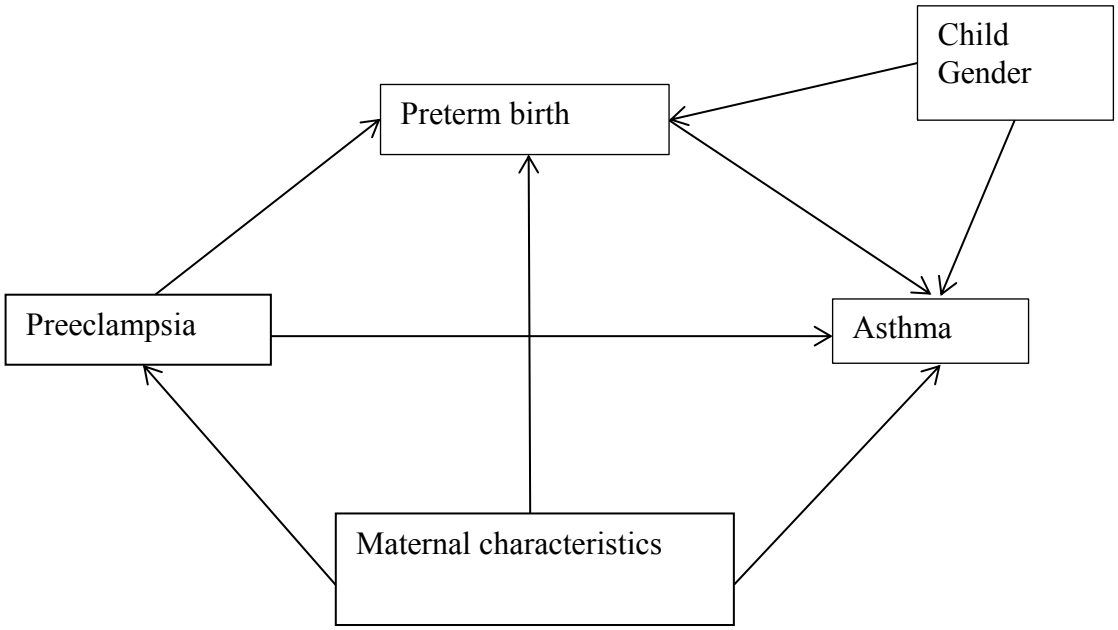

Child
Gender
Preterm birth
Preeclampsia
Asthma
Maternal characteristics

Table E1 Relative risks of asthma at 7 years in children born to mothers with pre-eclampsia when excluding women with chronic hypertension before pregnancy

Registry linkage (n= 404,626)				
Pre-eclampsia	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]
No	388,769	3.5	1	1
Yes	15,857	4.9	1.37 (1.27, 1.47)	1.31 (1.22, 1.40)
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]
Neither	371,352	3.4	1	1
Preterm birth only	17,417	6.0	1.73 (1.63, 1.85)	1.65 (1.55, 1.76)
Pre-eclampsia only	12,180	4.4	1.27 (1.16, 1.38)	1.20 (1.10, 1.31)
Preeclampsia and preterm birth	3,677	6.5	1.89 (1.67, 2.15)	1.86 (1.64, 2.10)
Relative excess risk due to interaction			-0.11 (-0.38, 0.17)	0.00 (-0.27, 0.27)
MoBa (n= 44,780)				
Pre-eclampsia	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [b]
No	43,083	4.8	1	1
Yes	1,697	6.4	1.35 (1.12, 1.63)	1.20 (1.00, 1.46)
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [b]
Neither	41,466	4.7	1	1
Preterm birth only	1,617	7.1	1.52 (1.27, 1.83)	1.40 (1.16, 1.68)
Pre-eclampsia only	1,322	5.3	1.14 (0.90, 1.43)	1.02 (0.81, 1.29)
Preeclampsia and preterm birth	375	10.4	2.23 (1.65, 3.01)	1.91 (1.41, 2.57)
Relative excess risk due to interaction			0.57 (-0.19, 1.33)	0.49 (-0.18, 1.16)

[a] Adjusted for maternal age, parity, education, asthma and child gender.

[b] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table E2 Relative risks of asthma at 7 years in children born to mothers with pre-eclampsia when excluding women results from multiple imputation analysis

Registry linkage (n=406,907)					
Pre-eclampsia	n	% asthma	Unadjusted RR(95% CI)	Adjusted RR (95 % CI) [a]	Adjusted RR (95 % CI)[a,b]
No	390,578	3.6	1	1	1
Yes	16,329	4.9	1.37 (1.28, 1.47)	1.31 (1.22, 1.40)	1.31 (1.22, 1.40)
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]	Adjusted RR (95 % CI)[a,b]
Neither	372,992	3.4	1	1	1
Preterm birth only	17,586	6.0	1.74 (1.64, 1.85)	1.67 (1.57, 1.77)	1.67 (1.57, 1.77)
Pre-eclampsia only	12,466	4.4	1.28 (1.17, 1.39)	1.22 (1.12, 1.32)	1.21 (1.12, 1.32)
Preeclampsia and preterm birth	3,863	6.4	1.87 (1.65, 2.11)	1.80 (1.59, 2.03)	1.80 (1.59, 2.03)
Relative excess risk due to interaction			-0.15 (-0.42, 0.12)		
MoBa (n=45,028)					
Pre-eclampsia	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [c]	
No	43,281	4.8	1	1	
Yes	1,747	6.4	1.33 (1.11, 1.60)	1.20 (1.00, 1.45)	
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [c]	
Neither	41,645	4.7	1	1	
Preterm birth only	1,636	7.1	1.51 (1.26, 1.82)	1.41 (1.18, 1.69)	
Pre-eclampsia only	1,352	5.3	1.12 (0.89, 1.41)	1.02 (0.81, 1.29)	
Preeclampsia and preterm birth	395	10.1	2.16 (1.61, 2.91)	1.89 (1.41, 2.52)	
Relative excess risk due to interaction					

[a] Adjusted for maternal age, parity, education, asthma and child gender.
[b] Additional adjustment for maternal smoking during pregnancy available for 84% of the study population.
[c] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table E3 Relative risks of asthma at 7 years in children born to mothers with pre-eclampsia when stratified by parity

Registry linkage (n=406,907)					
Nulliparous (n= 164,683)	Pre-eclampsia	N	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]
	No	154,958	3.7	1	1
	Yes	9,725	4.9	1.35 (1.23, 1.48)	1.31 (1.19, 1.43)
Parous (n= 242,224)	Pre-eclampsia	N	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]
	No	235,620	3.5	1	1
	Yes	6,604	4.8	1.37 (1.23, 1.53)	1.33 (1.19, 1.48)
MoBa (n=45,028)					
Nulliparous (n= 19,511)	Pre-eclampsia	N	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [b]
	No	18,413	4.9	1	1
	Yes	1,098	6.5	1.33 (1.05, 1.68)	1.20 (0.94, 1.52)
Parous (n= 25,517)	Pre-eclampsia	N	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [b]
	No	24,868	4.7	1	1
	Yes	649	6.2	1.31 (0.96, 1.77)	1.21 (0.89, 1.64)

[a] Adjusted for maternal age, education, asthma and child gender.

[b] Adjusted for maternal age, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table E4 Relative risks of maternal report of current doctor diagnosed asthma at 7 years in children born to mothers with pre-eclampsia

Pre-eclampsia	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]
No	25,508	5.7	1	1
Yes	988	8.6	1.52 (1.23, 1.88)	1.37 (1.10, 1.71)
Pre-eclampsia in combination with preterm birth	N	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]
Neither	24,525	5.5	1	1
Preterm birth only	983	9.4	1.69 (1.38, 2.08)	1.60 (1.26, 2.02)
Pre-eclampsia only	760	6.9	1.26 (0.95, 1.65)	1.11 (0.82, 1.51)
Preeclampsia and preterm birth	228	14.1	2.56 (1.85, 3.54)	2.62 (1.77, 3.89)
Relative excess risk due to interaction			0.61 (-0.34, 1.55)	0.91 (-0.22, 2.05)

[a] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table E5 Logistic regression model of the direct and indirect effects through preterm birth, low birth weight and delivery by caesarean section of pre-eclampsia on asthma at 7 years

Registry linkage (n=406,907)		
Component	Adjusted Odds Ratio[a]	(95% CI)
Direct Effect	1.11	(1.04, 1.18)
Indirect Effect	1.21	(1.18, 1.24)
Total Effect	1.34	(1.26, 1.43)
MoBa (n=45,028)		
Component	Adjusted Odds Ratio[b]	(95% CI)
Direct Effect	1.03	(0.83, 1.27)
Indirect Effect	1.19	(1.11, 1.27)
Total Effect	1.22	(0.98, 1.52)

[a] Adjusted for maternal age, parity, education, asthma and child gender.
[b] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Pre-eclampsia and childhood asthma

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Abstract

Studies of pre-eclampsia and childhood asthma are conflicting, and none did a formal mediation analysis of preterm birth.

We examined the association between pre-eclampsia and asthma at 7 years using national registries, including all births in Norway from 1996 to 2006 (n=406,907), and a subsample of children in the Norwegian Mother and Child Cohort Study (MoBa) (n=45,028) using log-linear regression~~. We calculated relative risks (RR) and 95% confidence intervals (CI). Additionally, W~~we performed a mediation analysis of preterm birth, and a sibling comparison to evaluate unobserved confounding.

There was a positive association between pre-eclampsia and asthma in the registry study, with an adjusted RR of 1.31 (95% CI: 1.22, 1.41), but not MoBa, adjusted RR of 1.19 (95% CI: 0.99, 1.44). The odds ratio for the direct effect not mediated through preterm birth and the indirect effect in the registry linkage were 1.19 (95 % CI: 1.10, 1.29) and 1.12 (95% CI: 1.11, 1.14) respectively. The sibling comparison indicated no association between pre-eclampsia and asthma, adjusted ~~odds ratio~~OR 1.07 (95% CI: 0.87, 1.33).

In this large study, which used different datasets and analytic approaches, there was little evidence for an association between pre-eclampsia and childhood asthma. The association was weak and largely explained by pre-term birth and confounders shared by siblings. ~~In conclusion, pre-eclampsia was positively associated with childhood asthma. This might be largely explained by mediation through preterm birth, but we also cannot exclude a potential influence of unobserved confounding.~~

Keywords: Asthma and pre-eclampsia

Introduction

Asthma is the most common chronic disease in children, and is characterized by reversible airway obstruction and inflammation [1]. There is a genetic predisposition in development of asthma [2]. However, despite decades of research, there are few established environmental causes, but pregnancy and early childhood are recognized as crucial time periods for the developing airways and immune system [3].

Pre-eclampsia is a characterized by pregnancy-induced hypertension, in combination with proteinuria, occurring in between 2% and 8% of pregnancies [4]. Early-onset pre-eclampsia may affect placental development, with a subsequent reduced blood flow to the fetus [5]. Furthermore, pre-eclampsia often results in an earlier delivery, as delivery is the only intervention that will reverse the condition completely. Both preterm birth and low birth weight are associated with childhood asthma [6-8].

A few studies have examined the association between pre-eclampsia and childhood asthma in school age or later [9-12], one of which reported a positive association [10]. Other studies have evaluated the association between pre-eclampsia and childhood wheezing phenotypes, both of which indicated a positive association [13, 14]. As far as we know, none of the previous studies conducted a formal mediation analysis to quantify the magnitude of the association between pre-eclampsia and childhood asthma mediated through preterm birth. Only one study performed a sibling comparison analysis [10] , in order to evaluate the potential role of unobserved confounding at sibling level [15]. Most previous studies had a relatively modest sample size, and therefore limited power to evaluate pre-eclampsia as a risk factor for asthma.

The heterogeneity and inconsistent results of previous studies indicate that we need to address this research question using different methodological approaches and carefully assess potential influence from confounding and mediating factors.

The objectives of the current study were 1) to examine the association between pre-eclampsia and childhood asthma, and 2) to evaluate whether preterm birth might mediate the association between pre-eclampsia and childhood asthma. We evaluated these objectives in both a national registry-based study and in a large prospective pregnancy cohort including detailed questionnaire information for additional potential confounding factors. The registry-based study included all births in Norway between January 1999 and July 2006, and the large number of children was the basis for using a sibling design.

Methods

Study subjects

The registry-based study included information from the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD) and the Norwegian Education Database. This linkage encompassed all children born in Norway and registered in the MBRN between January 1999 and July 2006 (n= 443,300). Only live-born singletons with a valid national identification number, a birth weight of 500 grams or more, a gestational age of 22 weeks or longer, and who were alive and living in Norway at their eight birthday were eligible for the current study (Figure 1). This left 406,907 children in the analysis.

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective pregnancy cohort administered by the Norwegian Institute of Public Health [16, 17]. MoBa recruited pregnant women between 1999 and 2008, at approximately 18 weeks gestation. The participation rate was 41%. Mothers could participate in the cohort with more than one pregnancy, resulting in a cohort of 95,000 mothers and 114,500 children. All participants gave a written informed consent. In this study, we included children with information from questionnaires administered at 18-and 30 gestational weeks, in addition to questionnaires administered when the child was 6 months, with a birth weight 500 grams or more, a gestational age of 22 weeks or longer, and had reached 7 years by April 1st 2013 (Figure 1). This left 45,028 children born between January 2000 and March 2006 in the analysis. Data from MoBa was linked to the MBRN and the NorPD.

The Norwegian Data Inspectorate and the Regional Committees for Medical and Health Research Ethics of South/East and West Norway approved this study.

Pre-eclampsia

In Norway, pregnant women carry a standardized chart to all antenatal examinations during pregnancy. At the time of delivery, the midwife transfers information from this chart to the MBRN notification form which is mandatory for all births. The MBRN has 5 checkoff boxes relevant to pre-eclampsia: (1) HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count); (2) eclampsia; (3) early pre-eclampsia (diagnosed before 34 weeks); (4) mild pre-eclampsia; and (5) severe pre-eclampsia. We defined pre-eclampsia (yes/no) as a registration of any of these conditions in the MBRN. We combined information on gestational age at birth with information on pre-eclampsia into four mutually exclusive categories (neither, pre-eclampsia only, preterm birth only and pre-eclampsia with preterm birth). Preterm birth was defined as a gestational age of less than 37 weeks.

Childhood asthma

The child's asthma status was defined by evaluating dispensed asthma medications as registered in the NorPD. The NorPD contains information on all dispensed prescriptions from all Norwegian pharmacies since January 2004. Asthma medications included inhaled short- and long-acting beta(2)-agonists (R03AC), inhaled corticosteroids (R03BA), fixed-dose combinations of inhaled beta(2)-agonists and corticosteroids (R03AK), and leukotriene antagonists (R03DC). A child was defined as having asthma at 7 years if there was at least one dispensed prescription for asthma medications in the past 12 months in addition to at least one second dispensed prescription within 12 months after the first. In a secondary analysis within the MoBa cohort, we defined children as having asthma if the mother in the questionnaire at age 7 had reported that the child was doctor diagnosed with asthma and also had either current symptoms or had used asthma medications in the past 12 months.

Covariates

We used information on characteristics that could potentially influence the association of interest. Child characteristics included sex (male/female). Maternal characteristics included age at delivery (entered as a continuous variable), parity (categorized into primiparous, 1, 2 and 3 or more), education (categorized into less than high school, high school, up to 4 years of college and 4 or more years of college), maternal asthma (categorized as yes/no) and smoking during pregnancy (categorized as yes/no). Additional information from questionnaires in MoBa included maternal pre-pregnancy body-mass index (BMI; entered as a continuous variable).

Statistical analysis

We did descriptive analyses showing the distribution of pre-eclampsia by the covariates. The further analysis was done in several steps. First, we used national registry data and evaluated the association between pre-eclampsia and the child's risk of asthma using log-binomial regression models, reporting relative risks (RR) and 95 % confidence intervals (CI), accounting for the dependency between siblings by using robust cluster variance estimation. The multivariable analyses adjusted for the maternal age, parity, education, maternal asthma and the child's gender. Additional adjustment for maternal smoking during pregnancy was explored among the 75% of children for whom this information was available in the registry. Secondly, we repeated the analysis in the subsample of children participating in the MoBa cohort. In the multivariable analyses using MoBa data we further adjusted for pre-pregnancy BMI in addition to the characteristics mentioned above. Thirdly, we conducted a secondary analysis in MoBa using a questionnaire based asthma definition as the outcome.

Fourth, we evaluated the independent and combined effect of preterm birth and pre-eclampsia on asthma development, and subsequently calculated the relative excess risk due to

interaction, before moving on to a formal mediation analysis. Figure 2 shows the theoretical framework underlying our mediation analysis. The mediation analysis was performed by a logistic decomposition of the total effects into indirect and direct effects using the ldecomp command in the Stata software [18]. We also explored conventional multivariable adjustment for preterm birth as an alternative approach to obtain an estimate of the direct effects of pre-eclampsia. Last, we used the national registry data and conducted an analysis of sibling pairs discordant for asthma using conditional logistic regression analysis, reporting odds ratios (OR) and 95% CI. This approach compares the distribution of pre-eclampsia between sibling pairs discordant for asthma.

The amount of missing covariate information was generally low (<2%). Nevertheless, we explored robustness of the results using multiple imputation by chained equations imputing a total of 20 datasets. The statistical significance level was 5%. The analysis was conducted using Stata version 14 (Statacorp, Texas).

Results

Distribution of pre-eclampsia by maternal and child characteristics

The prevalence of pre-eclampsia was 4%, while 5% of children had asthma at 7 years. The prevalence of pre-eclampsia decreased with maternal age, parity, educational level and smoking, while it increased with maternal pre-pregnancy BMI (table 1). Furthermore, there was a higher prevalence of pre-eclampsia among mothers with asthma and among mothers delivering preterm (table 1).

Pre-eclampsia and asthma at 7 years

There was a positive association between pre-eclampsia and asthma at 7 years in the registry study, with an adjusted RR of 1.31 (95 % CI: 1.22, 1.41), but not in MoBa, with an adjusted RR of 1.19 (95% CI: 0.99, 1.44) (table 2). The difference in the strength of the association in the registry study and the MoBa cohort was mostly explained by additional adjustment for maternal pre-pregnancy BMI in MoBa. The adjusted RR was 1.27 (95% CI: 1.06, 1.53) without adjustment for pre-pregnancy BMI. There was no change in the observed associations after exclusion of mothers with pre-existing hypertension before pregnancy (online supplementary table E1). The multiple imputation analysis also gave similar results (online supplementary table E2). Furthermore, there was no difference in the observed associations among primiparous and multiparous mothers (online supplementary table E3). In MoBa, the magnitude of the association between pre-eclampsia and asthma at 7 years was larger and only statistically significant when using maternal report of doctor diagnosed asthma at 7 years as an outcome (online supplementary table E4).

Combined effects of pre-eclampsia and preterm birth on asthma at 7 years

Around 4% of children were born preterm by mothers who did not have pre-eclampsia, 3% of children were born at term to mothers who had pre-eclampsia, while 1% of children were born preterm to mothers who had pre-eclampsia. There was a positive association between being born at term to mothers with pre-eclampsia and asthma at 7 years in the registry-based study, adjusted RR 1.21 (95% CI: 1.11, 1.32), but not in MoBa, adjusted RR 1.01 (95% CI: 0.80, 1.28) (table 2). There was some indication in MoBa that the association between pre-eclampsia and preterm birth in combination with asthma was greater than the independent associations seen for these two exposures (table 2 and table E4). However there was no statistically significant excess relative risk due to interaction.

The mediating effect of preterm birth on the association between pre-eclampsia and asthma at 7 years

Pre-eclampsia was around 6 times more prevalent among those born preterm (Table 1), and preterm birth was also a risk factor for asthma (table 2). We therefore evaluated the potential indirect effect of pre-eclampsia on asthma mediated through preterm birth. The results from the mediation analysis indicated a significant direct effect of pre-eclampsia on childhood asthma in the registry-based study, adjusted OR 1.19 (95% CI: 1.10, 1.29), while the indirect effect was 1.12 (95% CI: 1.11, 1.14) (table 3).There was no direct effect in MoBa, adjusted OR 1.11 (95 % CI: 0.89, 1.37) (table 3). When adjusting for preterm birth a covariate, the results yielded an adjusted RR of 1.17 (95% CI: 1.10, 1.27) in the registry linkage and 1.10 (95% CI: 0.91, 1.33) in MoBa. Secondary analyses evaluated the combined indirect effect of preterm birth, low birth weight and delivery by caesarean section (Table E5). The results of the direct effect not mediated through these three pregnancy outcomes was OR 1.11 (95% CI:1.04, 1.18) in the registry linkage and 1.03 (95 % CI: 0.83, 1.27) in MoBa.

Sibling pair analysis of pre-eclampsia and asthma at 7 years

There were a total of 5,923 sibling groups (of two or more children) with at least two siblings discordant for asthma. The sibling pair analysis indicated no significant association between pre-eclampsia and childhood asthma, adjusted OR 1.07 (95% CI: 0.87, 1.33) (table 4).

Discussion

In this large-scale prospective study, we observed a positive association between pre-eclampsia and school-age asthma. Our findings indicate that that this association could be largely explained by a mediating effect of preterm birth. Furthermore, we cannot exclude the possibility of unobserved confounding due to characteristics that are shared by siblings.

Strengths and limitations of the study

The different methodological approaches in this study have their strengths and limitations and when interpreting the results these should be taken into consideration. The overall analysis in the registry linkage had the best power, but is likely to be hampered by some unobserved confounding. We therefore explored the association in the sub-set of individuals participating in MoBa with more detailed information on potential confounding factors, and added a registry based sibling comparison analysis. Results from the MoBa analyses might be influenced by selection bias due to the participation rate [17], and the sibling comparison conducted within the registry linkage had limited power due to the modest number of discordant sibling pairs available for analysis. However, there was sufficient power to detect a significant association between preterm birth and asthma in the sibling pair analysis. Our study also has additional limitations. Using the MBRN to classify pre-eclampsia might have resulted in misclassification, as indicated by a validation study [19]. The prevalence of asthma at 7 years was similar when the asthma definition was based on the prescription registry (4.8%) or maternal report through questionnaires (5.8%), which strengthens the reliability of an asthma prevalence of around 5% at age 7. However, this is a lower prevalence than in some other European countries, but not all. For example, the estimated prevalence of asthma at approximately 7 years is 11% in the Avon Longitudinal Study of Parents and Children (ALSPAC) [20], while current asthma at 6 years was only

reported for 3% in Generation R [21]. It was also not possible to distinguish between full versus half siblings. The results of the sibling pair analysis might therefore not account for shared genetic predisposition to a full extent as would be expected based on a comparison of known full siblings. Although we did not know the ethnicity of the study participants, excellent Norwegian language skills were a requirement for participation in MoBa and the overwhelming majority of MoBa participants are assumed to be of European descent.

The mediation analysis conducted in this study assumes no residual or unobserved confounding for the association between pre-eclampsia and asthma, pre-eclampsia and preterm birth, in addition to the association between preterm birth and asthma. A mediation analysis may also cause a spurious association due to collider stratification bias [22]. We adjusted for a wide range of maternal characteristics, but we cannot exclude the possibility that our observed associations still may be influenced by residual confounding. The results should therefore be interpreted with caution. Furthermore, the direct effect is to be interpreted as the residual association not mediated through preterm birth.

Comparison with previous studies

Four previous studies have examined the association between pre-eclampsia and childhood asthma [9-12]. A large Danish registry based study observed an incidence rate ratio of 1.19 (95% CI: 1.15, 1.24) between pre-eclampsia and asthma [10]. In contrast, a Norwegian historical cohort study (n=617) indicated no association between pre-eclampsia and asthma at 10 years of age, odds ratio 0.72 (95% CI: 0.19, 2.77) for severe pre-eclampsia [9]. Similarly, findings from ALSPAC indicated no association between pre-eclampsia and asthma at 7 years, adjusted odds ratio 1.23 (95% CI: 0.80–1.88) [12]. A large Norwegian registry study of all live births 1967-1993 (n = 1,548,429), which linked the MBRN to the National Insurance Administration Register, indicated that pregnancy complications

(including pre-eclampsia) may represent risk factors for childhood asthma [11]. The current study further contributes information to these previous studies by conducting a formal mediation analysis of the indirect due to preterm birth.

Interpretation of findings

Our finding of a stronger association between pre-eclampsia leading to preterm birth is likely to reflect an underlying severity of pre-eclampsia. Of the three studies of pre-eclampsia and school-age asthma that adjusted for gestational age, one found no association even before adjustment [12], one indicated that the association was attenuated and became non-significant after multivariable adjustment for gestational age [10], while the third found no association after adjustment for a number of factors without specifically examining the influence of adjustment for gestational age [9]. Our study is therefore the first to attempt to quantify the indirect effects of pre-eclampsia on childhood asthma explained by preterm birth, and indicated evidence of a direct effect of pre-eclampsia on childhood asthma in the registry linkage [23]. As expected, the estimate of the combined indirect effect of preterm birth, low birth and delivery by caesarean section was larger than observed for preterm birth alone. However, a significant direct effect of preelampsia not mediated through these three pregnancy outcomes was still found in the registry analyses.

A potential explanation for a direct effect between pre-eclampsia and asthma not mediated through poor placental function leading to poor intra uterine growth and preterm birth, is an influence of immunological mechanisms. Maternal immune tolerance is important to ensure a healthy pregnancy outcome, and pre-eclampsia is hypothesized to be partly due to a maladaptation of this necessary immune tolerance during pregnancy [24-26]. Studies are beginning to unravel the potential interactions between the innate and the adaptive immune system that are required to maintain a healthy pregnancy [24]. One might speculate that the

failure of the necessary immunological adaptions during pregnancy also could have consequences for the offspring's development of immune-related diseases such as asthma.

The fact that we observed a direct effect of pre-eclampsia on asthma development not mediated through preterm birth in the registry linkage and not in MoBa could be explained by the additional adjustment for pre-pregnancy BMI in MoBa. Overweight and obesity is a well-known risk factor for pre-eclampsia [27, 28]. This might be explained by the systemic inflammation and subsequent immunological changes observed among those who are obese or overweight [29]. We have previously found maternal obesity during pregnancy to increase the risk of wheezing in infancy [30], and thus maternal BMI might confound the association between pre-eclampsia and childhood asthma.

A sibling comparison allows an evaluation of the likelihood that unobserved background characteristics shared by siblings are influencing the observed associations [15]. Only one previous study performed a sibling comparison when evaluating the association between pre-eclampsia and childhood asthma [10]. In line with our findings, this previous study indicated no association between pre-eclampsia and asthma, supporting the notion that the weak direct effect observed in the overall analysis in the registry-based study might be influenced by confounding due to unobserved background characteristics shared by siblings. However, it is important to acknowledge that any sibling comparison is more susceptible to confounding by unobserved background characteristics not shared by siblings [15].

Conclusion

In this large study, which used different datasets and analytic approaches, there was little evidence for an association between pre-eclampsia and childhood asthma. The association was weak and largely explained by pre-term birth and confounders shared by siblings. ~~Pre-eclampsia was positively associated with childhood asthma. This might be~~

~~largely explained by mediation through preterm birth, but we also cannot exclude a potential influence of unobserved confounding.~~

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Proposed twitter feed: Pre-eclampsia shows no strong evidence for an association with childhood asthma at 7 years.

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Figure legends

Figure 1 Illustration of sample selection

(a) Registry-based study

(b) The Norwegian Mother and Child Cohort Study

Figure 2 Theoretical framework

Maternal background characteristics include maternal age, parity, education, body-mass index, asthma and smoking during pregnancy.

Table 1 Distribution of pre-eclampsia by maternal and child characteristics

	Registry linkage (n=406,907)		**MoBa (n=45,028)**	
Characteristics	n	% pre-eclampsia	n	% pre-eclampsia
Pre-eclampsia				
No	390,578		43,281	
Yes	16,329	4.0	1,747	3.9
Maternal age at delivery, years				
<25	70,123	4.9	4,996	5.5
25-29	137,239	4.1	15,457	4.3
30-34	135,788	3.5	17,300	3.2
35+	63,757	3.9	7,275	3.4
Maternal parity				
Nulliparous	164,683	5.9	19,511	5.6
1	146,081	2.8	16,045	2.6
2	68,174	2.6	7,407	2.4
3+	27,969	2.7	2,065	3.0
Maternal education				
Less than high school	77,340	4.2	3,789	4.5
High school	148,773	4.4	14,479	4.4
Up to 4 years of college	137,854	3.9	18,387	3.6
More than 4 years of college	29,950	3.1	8,206	3.3
Missing	12,990	2.7	167	5.4
Maternal asthma				
No	389,995	4.0	43,199	3.8
Yes	16,912	5.3	1,829	5.2
Maternal smoking at start of pregnancy				
No	268,177	4.1	39,868	4.0
Yes	72,409	3.4	4,968	2.8
Missing	66,321	4.2	192	2.1
Maternal pre-pregnancy BMI				
Underweight (<18.5)	NA		1,253	2.4
Normal weight (18.5-24.9)	NA		28,421	2.7
Overweight (25-29.9)	NA		9,865	5.2
Obese (>=30)	NA		4,238	8.7
Missing	NA		1,251	4.6
Year of birth				
1999	55,155	4.3		
2000	54,974	4.2	1,102	4.5
2001	52,630	4.1	3,265	4.2
2002	51,643	4.3	6,878	4.3
2003	52,861	3.7	10,060	3.6
2004	53,459	3.7	10,632	3.9
2005	53,347	3.8	11,828	3.7

2006	32,838	3.9	1,263	3.6
Child gender				
Male	208,643	4.1	22,975	3.9
Female	198,264	4.0	22,053	3.8
Preterm birth				
No	385,458	3.2	42,997	3.1
Yes	21,449	18.0	2,031	19.5

There were significant differences in the distribution of pre-eclampsia by all maternal and child characteristics ($p<0.003$) except for child gender (p-value 0.109 in the registry linkage and in 0.639 MoBa).

Table 2 Relative risks of asthma at 7 years in children born to mothers with pre-eclampsia

Registry linkage (n=406,907)					
Pre-eclampsia	n	% asthma	Unadjusted RR(95% CI)	Adjusted RR (95 % CI) [a]	Adjusted RR (95 % CI)[a,b]
No	390,578	3.6	1	1	1
Yes	16,329	4.9	1.37 (1.28, 1.47)	1.31 (1.22, 1.41)	1.29 (1.19, 1.39)
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [a]	Adjusted RR (95 % CI)[a,b]
Neither	372,992	3.4	1	1	1
Preterm birth only	17,586	6.0	1.74 (1.64, 1.85)	1.66 (1.56, 1.76)	1.67 (1.56, 1.78)
Pre-eclampsia only	12,466	4.4	1.28 (1.17, 1.39)	1.21 (1.11, 1.32)	1.21 (1.10, 1.32)
Preeclampsia and preterm birth	3,863	6.4	1.87 (1.65, 2.11)	1.83 (1.62, 2.07)	1.75 (1.52, 2.01)
Relative excess risk due to interaction			-0.15 (-0.42, 0.12)	-0.04 (-0.30, 0.22)	-0.13 (-0.41, 0.16)
MoBa (n=45,028)					
Pre-eclampsia	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [c]	
No	43,281	4.8	1	1	
Yes	1,747	6.4	1.33 (1.11, 1.60)	1.19 (0.99, 1.44)	
Pre-eclampsia in combination with preterm birth	n	% asthma	Unadjusted RR (95% CI)	Adjusted RR (95 % CI) [c]	
Neither	41,645	4.7	1	1	
Preterm birth only	1,636	7.1	1.51 (1.26, 1.82)	1.39 (1.15, 1.67)	
Pre-eclampsia only	1,352	5.3	1.12 (0.89, 1.41)	1.01 (0.80, 1.28)	
Preeclampsia and preterm birth	395	10.1	2.16 (1.61, 2.91)	1.86 (1.38, 2.50)	
Relative excess risk due to interaction			0.53 (-0.21, 1.26)	0.46 (-0.19, 1.11)	

[a] Adjusted for maternal age, parity, education, asthma and child gender.
[b] Additional adjustment for maternal smoking during pregnancy available for 84% of the study population.
[c] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table 3 Logistic regression model of the direct and indirect effects through preterm birth of pre-eclampsia on asthma at 7 years

Registry linkage (n=406,907)		
Component	Adjusted Odds Ratio[a]	(95% CI)
Direct Effect	1.19	(1.10, 1.29)
Indirect Effect	1.12	(1.11, 1.14)
Total Effect	1.34	(1.25, 1.44)
MoBa (n=45,028)		
Component	Adjusted Odds Ratio[b]	(95% CI)
Direct Effect	1.11	(0.89, 1.37)
Indirect Effect	1.09	(1.05, 1.14)
Total Effect	1.21	(0.98, 1.49)

[a] Adjusted for maternal age, parity, education, asthma and child gender.
[b] Adjusted for maternal age, parity, education, asthma and child gender, maternal smoking during pregnancy and pre-pregnancy body-mass index.

Table 4 Sibling pair analysis of associations between pre-eclampsia in combination with preterm birth with asthma at 7 years

(n= 5,923 discordant sibling groups)

Pre-eclampsia	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]
No	1	1
Yes	1.16 (0.94, 1.42)	1.07 (0.87, 1.33)
Pre-eclampsia in combination with preterm birth	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]
Neither	1	1
Preterm birth only	1.57 (1.32, 1.88)	1.55 (1.28, 1.87)
Pre-eclampsia only	1.17 (0.94, 1.46)	1.09 (0.86, 1.38)
Preeclampsia and preterm birth	1.30 (0.90, 1.89)	1.17 (0.79, 1.73)

[a] Adjusted for maternal age, parity, education, asthma and child gender.