Maternal complications in pregnancy and wheezing in early childhood: A pooled analysis of 14 birth cohorts

Maternal Complications in Pregnancy and Wheezing in Early Childhood.

A pooled analysis of Fourteen Birth Cohorts.

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Abstract

Background: Evidence on the effect of maternal complications in pregnancy on wheezing in offspring is still insufficient.

Methods: A pooled analysis was performed on individual participant data from fourteen European birth cohorts to assess the relationship between several maternal pregnancy complications and wheezing symptoms in the offspring.

Exposures of interest included hypertension and preeclampsia, diabetes, as well as pre-pregnancy overweight (body mass index between 25 and 29.9) and obesity (body mass index ≥30) compared with normal weight (body mass index between 18.5 and 24.9). Outcomes included both ever and recurrent wheezing from birth up to 12-24 months of age.

Cohort-specific crude and adjusted risk ratios (RR) were calculated using log-binomial regression models and then pooled using a random effects model.

Results: The study included 85 509 subjects. Cohort-specific prevalence of ever wheezing varied from 20.0% to 47.3%, and of recurrent wheezing from 3.0% to 14.3%. Adjusted pooled RR for ever and recurrent wheezing were: 1.02 (95% CI: 0.98-1.06) and 1.20 (95% CI: 0.98-1.47) for hypertensive disorders; 1.09 (95% CI: 1.01-1.18) and 1.23 (95% CI: 1.07-1.43) for preeclampsia; 1.04 (95% CI: 0.97-1.13) and 1.24 (95% CI: 0.86-1.79) for diabetes; 1.08 (95% CI: 1.05-1.11) and 1.19 (95% CI: 1.12-1.26) for overweight; 1.12 (95% CI: 1.08-1.17) and 1.16 (95% CI: 0.97-1.39) for obesity. No heterogeneity was found in RR estimates among the cohorts, except for diabetes and recurrent wheezing (P=0.027).

Conclusions: Preeclampsia, maternal pre-pregnancy overweight and obesity are associated with an increase risk of wheezing in the offspring.

Key words (MESH terms)

Hypertension, Pregnancy-Induced

Pre-eclampsia

Diabetes, Gestational

Overweight

Obesity

Key messages

Maternal hypertensive disorders of pregnancy and in particular preeclampsia, pre-pregnancy overweight, and obesity are associated with an increased risk of developing wheezing disorders, mainly of recurrent wheezing, in early childhood.

These results add evidence on the relationship between early life factors and wheezing disorders in childhood.

Introduction

There is growing evidence of a relationship between early life factors and a wide range of chronic diseases in children and adults, including obstructive lung diseases and asthma. [1,2] With regard to wheezing and asthma, the greater influence of maternal vs paternal asthma and atopy on the development of disease in offspring suggests a role of the pre- and peri-natal environment.[3] Developmental adaptations in foetal life might result in impaired lung growth, and subsequently to an increased risk of wheezing and asthma throughout postnatal life. [4]

Studies performed in different settings highlighted an increasing trend in the prevalence of pre-existing and pregnancy related pathology, including chronic hypertension, preeclampsia, diabetes and maternal overweight and obesity.[5,6] Relatively few studies have investigated whether maternal complications and conditions in pregnancy are associated with widely recognized problems such as wheezing and asthma in early childhood, and results are somewhat inconsistent. In a large cross-sectional study Rusconi et al [7] found a relationship between both hypertensive disorders of pregnancy and diabetes in pregnancy and different wheezing phenotypes in young children. An association between maternal hypertension, preeclampsia, and diabetes and wheezing/asthma in the first years of life has been also suggested in one recent birth cohort study[8], whereas earlier studies on maternal hypertensive disorders revealed mixed findings.[9-12]

A larger number of studies conducted in prospective birth cohorts recently found a positive association between maternal pre-pregnancy obesity and an increase of risk of wheezing or asthma in infants and young children[12-18] and of asthma symptoms in adolescents.[19] In

addition, excessive weight gain during pregnancy has been also associated with wheezing in preschoolers and asthma diagnosis at school age.[7,16]

The aim of the present study was to assess the relationship of maternal hypertensive disorders of pregnancy, maternal diabetes and pre-pregnancy overweight and obesity with wheezing symptoms developing from birth up to 12-24 months of age in offspring. We conducted an analysis of maternal complications and conditions pooling data from several European birth cohorts participating in the CHICOS (Developing a Child Cohort Research Strategy for Europe) project (http://www.chicosproject.eu*)* to provide robust results across heterogeneous settings and to have sufficient statistical power even for rare complications.

Methods

Potential cohorts to be included were identified through the Environmental Health Risks in European Birth Cohorts (ENRIECO) inventory *(http://www.birthcohort.net*) and through direct contact with researchers participating in the CHICOS project.

Birth cohorts were eligible if they had started the enrollment after 1990, and if they had suitable information on maternal complications and conditions in pregnancy and on wheezing from birth up to 12-24 months of age.

All original cohort studies were approved by their local Ethical Committee and provided written informed consent to use their data.

Exposures and outcomes

Exposures of interest were maternal hypertensive disorders of pregnancy, diabetes and pre-pregnancy maternal overweight and obesity. Women were considered as affected by hypertensive disorders of pregnancy if they suffered from at least one of the following: chronic hypertension before pregnancy, hypertension in pregnancy, preeclampsia or eclampsia. As eclampsia is the end stage of preeclampsia characterized by generalized seizures and it is rare, we will use the term preeclampsia hereinafter. Preeclampsia was additionally studied as an independent exposure of interest. Maternal diabetes was defined as either chronic diabetes before pregnancy or overt diabetes or glucose intolerance in pregnancy. Overweight and obesity were defined on the basis of pre-pregnancy body mass index (BMI), obtained by the ratio of weight (kg) to height $(m)^2$. Women were defined overweight if their BMI was between 25 and 29.9 and obese if their BMI was equal or higher than 30.[20] The reference category were women with BMI between 18.5 and 24.9. Information on exposures of interest was obtained during pregnancy or at birth by different sources (Table S1, Online Supplementary Data).

We focused on two outcomes of interest: ever wheezing and recurrent wheezing from birth up to 12-24 months of age, depending on the time of data collection of each cohort. “Ever wheezing” was defined as at least one episode of wheezing, while “recurrent wheezing” was defined as at least 4 episodes of wheezing. If the information on number of episodes ≥4 was not available, recurrent wheezing was defined as at least two episodes of wheezing occurring at different times-span (for example in the first 6 months and between 6 and 15 months). Information on wheezing symptoms were obtained from parental questionnaire (Table S2, Online Supplementary Data).

Statistical analysis

A pooled analysis of fourteen birth cohorts was performed using a two-stage approach: cohort-specific risk ratios (RR) with 95% confidence intervals (95% CI) were calculated using log-binomial regression models and then pooled using a random effects model[21,22]. In each pooled analysis, only the cohorts in which there were at least two expected events of interest among the exposed, under the null hypothesis of no effect, were considered.

The following potential confounders were considered: maternal country of birth, maternal educational level at child birth, maternal asthma, maternal smoking in pregnancy, maternal parity at the index pregnancy, and maternal age at delivery.

RR were first adjusted for the selected confounders (aRR), then the maternal complications and conditions were further included in the regression models (mutually aRR). The mutually aRR for preeclampsia was not adjusted for maternal hypertensive disorders of pregnancy. Since women may have had more than one pregnancy over the observational period, robust variance was estimated to allow for intra-group correlation. All the regression models were performed on the set of children with no missing data for any of the outcomes, exposures and confounders.

Several sensitivity analyses were conducted. We performed each pooled analysis by excluding and including the DNBC cohort because of its large size. Also, potential effect modification by maternal asthma was evaluated by introducing an interaction term in the

193 logistic regression model. Finally, we excluded cohorts for which information on number of
194 episodes of wheezing (≥4) was not available to evaluate the robustness of results.
195
196 Statistics were performed using statistical software STATA 11.1.[23]

197 **Results**

198 Fourteen cohorts were eligible for the present study and agreed to participate (Table 1).

199 The study included 85 509 singleton subjects with available information on both ever and
200 recurrent wheezing. We excluded twins from the analysis, as maternal complications and
201 conditions in pregnancy and outcomes may be different in twins. Descriptive characteristics
202 of the cohorts are reported in Table 1 and in Table S3 in the Online Supplementary Data.

203 Prevalence of outcome, exposure variables, and potential confounders differed between
204 cohorts (all tests of heterogeneity (χ^2): P<0.001). Ever wheezing ranged from 20.0% in
205 NINFEA cohort to 47.3% in INMA Sabadell cohort, while recurrent wheezing ranged from
206 3.0% in NINFEA cohort to 14.3% in INMA Valencia cohort. Maternal hypertensive disorders of
207 pregnancy ranged from 1.7% in INMA Gipuzkoa cohort to 9.4% in DNBC cohort, and
208 preeclampsia ranged from 0.9% in INMA Menorca cohort to 2.9% in Southampton Women's
209 Survey cohort. Occurrence of maternal diabetes or glucose intolerance in pregnancy ranged
210 from 0.80% in KOALA cohort to 19.2% in INMA Sabadell cohort. Prevalence of pre-pregnancy
211 overweight and obesity ranged from 11.3% and 2.9% in the CoNER cohort to 37.9% and
212 16.4% in the EDEN cohort, respectively.

213 Overall crude RR, aRR and mutually aRR for ever and recurrent wheezing are reported in
214 Table 2, while cohort-specific RR are reported in Table S4 and Table S5 in the Online
215 Supplementary Data. Overall, adjusted estimates were close to crude estimates, showing a
216 weak confounding effect.

217 Preeclampsia (mutually aRR, 1.09, 95% CI: 1.01-1.18), maternal pre-pregnancy overweight
218 (mutually aRR, 1.08, 95% CI: 1.05-1.11) and obesity (mutually aRR, 1.12, 95% CI: 1.08-1.17)
219 were associated with an increased risk of ever wheezing (Table S2 and Figure S1, Online

Supplementary Data). The estimated associations between maternal hypertensive disorders of pregnancy (mutually aRR, 1.02, 95% CI:0.98-1.06) or maternal diabetes (mutually aRR, 1.04, 95% CI:0.97-1.13) and ever wheezing (Figure S1, Online Supplementary Data) were weaker but consistent with the other maternal complications and conditions. All estimated values increased when analyses were conducted on recurrent wheezing, although confidence intervals were larger. Mutually aRR for maternal hypertensive disorders of pregnancy was 1.20 (95% CI: 0.98-1.47, Figure 1A), for preeclampsia was 1.23 (95% CI: 1.07-1.43, Figure 1B), for maternal diabetes was 1.24 (95% CI: 0.86-1.79, Figure 1C), for maternal pre-pregnancy overweight was 1.19 (95% CI: 1.12-1.26, Figure 1D) and for obesity was 1.16 (95% CI: 0.97-1.39, Figure 1E).

When excluding DNBC cohort, the main differences in the estimated RR were observed for the associations between obesity and ever wheezing (mutually aRR, 1.03, 95% CI: 0.94-1.14), between maternal hypertensive disorders of pregnancy and recurrent wheezing (mutually aRR, 1.36, 95% CI: 1.10-1.68,) and between preeclampsia and recurrent wheezing (mutually aRR, 1.56, 95% CI: 1.06-2.29). None of the estimated associations, however, changed direction when the DNBC cohort was excluded from the analyses.

No evidence of heterogeneity in the mutually aRR estimates was observed, with the exception of the association between diabetes and recurrent wheezing (P=0.027). Maternal asthma was not an effect modifier of the associations found.

When we excluded those cohorts for which information on number of episodes (>=4) was not available (CoNER, GASPii, INMA Menorca, INMA Valencia and NINFEA), results for recurrent wheezing were similar to those obtained in the complete dataset (Table 2):

mutually aRR for maternal hypertensive disorders of pregnancy: 1.17, 95% CI: 0.97-1.40; mutually aRR for preeclampsia: 1.31, 95% CI: 1.04-1.65; mutually aRR for maternal diabetes: 1.04, 95% CI: 0.88-1.24; mutually aRR for overweight, 1.19, 95% CI: 1.12-1.26; mutually aRR for obesity, 1.16, 95% CI: 0.95-1.41.

Discussion

We investigated the association between selected complications and conditions in pregnancy and wheezing in the first two years of life, by combining data of more than 80 000 subjects from 14 birth cohorts in Europe: we found that hypertensive disorders of pregnancy and in particular preeclampsia, and pre-pregnancy overweight and obesity are associated with an increased risk of developing wheezing disorders, mainly of recurrent wheezing.

Few and conflicting data on the effect of hypertensive disorders of pregnancy on wheezing or asthma in offspring[7-12] were previously observed. Data were particularly scarce on preeclampsia if analysed separately from hypertension, probably because of the relatively low prevalence of the condition (1,4 to 8%, worldwide, with the highest prevalence in developing countries and in the USA).[24] Two previous studies in Norway and in USA did not find an association between preeclampsia and asthma in offspring.[11],[12]

Interestingly Stick et al[25] demonstrated that newborn infants born at term from mothers with hypertension before or during pregnancy had a reduction of lung function, similarly to those exposed to maternal smoking in pregnancy, which is a well known risk factor for altered prenatal lung development.In preeclampsia, a disturbed regulation of vascular growth in the feto-maternal unit leads to an overproduction of antiangiogenic factors, which are markedly increased also in amniotic fluid.[24,26] This has been shown to cause sustained abnormalities of

the lung in rat offspring.[26]

It is therefore possible that preeclampsia may alter fetal lung vessel development, predisposing offspring to asthma later in life.

Several studies reported positive association between maternal pre-pregnancy obesity and an increased risk of asthma or wheezing in infants and young children.[12-16,27] Recently, Pike et al[17] found that both pre-pregnancy maternal BMI and body fat mass were associated with transient early wheezing but not with persistent wheezing or asthma in the first 6 years of offspring life. Leermakers et al[18] found an association between maternal obesity and wheezing at the ages of 1 to 4 years only in offspring with a maternal history of asthma or atopy. Potential biological mechanisms underlying this association are still unclear. Furthermore, because maternal and offspring weight are correlated[28] and previous studies have shown that obesity in young children[29] and weight gain acceleration in early infancy[30] are associated with increased risks of asthma symptoms and impaired lung development in infancy[31], it is possible that child weight/weight gain may account at least for a part of the association found.

We did not find an association between maternal diabetes and ever wheezing up to 12-24 months of life, although for recurrent wheezing we obtained an aRR of 1.25 (95% CI: 0.86-1.79). Prevalence of maternal diabetes was quite different among the cohorts, reflecting both the well-known higher prevalence in Northern compared to Southern Europe and the heterogeneities in screening practice and policy.[32] In a cross sectional study on a large number of children maternal diabetes (before or during pregnancy) was associated with

persistent wheezing at 6 years of life (OR: 1.84; 99% CI: 1.06-3.20).[7] More recently Risnes et al[8] in a birth cohort study found that maternal diabetes was associated with increased asthma risk in 6 year old children (OR= 3.63, 95% CI: 1.46-9.04). Further evaluation is needed to confirm these associations and to explain the underlying biological mechanisms.

Adjusting for birth weight or gestational duration, or other perinatal or postnatal factors, in regression models is a common approach to estimate the associations between complications or conditions in pregnancy and a health outcome in the offspring. However, in many scenarios, rather than being true confounders, these variables act as potential mediators. Accordingly, in our study we assumed that birth weight, gestational duration, mode of delivery, and also breastfeeding were potential mediators in the pathway between hypertensive disorders of pregnancy, diabetes, overweight/obesity and wheezing. Since we were primarily interested in the total effect of maternal complications and not in studying to what extent these effects are explained by potential mediators, we did not adjust for these mediators. In addition, as repeatedly discussed and empirically verified [33-35], adjustment for these variables would have also introduced a spurious association between the exposure and the outcome (so called collider bias) in the presence of unmeasured variables that confound the mediator-outcome relationship. Had our approach of treating birth weight, gestational duration, mode of delivery, and breastfeeding as potential mediators been incorrect, our results would have been affected potentially by confounding bias from these variables. To test the potential impact of this bias we carried out models adjusting for these variables and found that the relative risk estimates for all exposures of interest were only moderately changed after adjustment (data not shown). The largest change in estimate was found for

diabetes, with a relative risk for recurrent wheezing of 1.17 (95% CI: 0.95,1.45) when adjusting for birth weight, gestational duration, mode of delivery and breastfeeding *versus* a relative risk of 1.24 (95% CI:0.86,1.79) without adjustment (Table 2).

Pooling data from several cohorts and hence providing strong statistical power and robust results is the greatest strength of our study. This also enables us to compare results among different European birth cohorts; absence of heterogeneity in the associations suggests that residual confounding is an unlikely explanation for our findings.

As expected, there was variability in the distribution of maternal complications, confounders and outcomes among the cohorts. Besides a true differential distribution, the observed variability may also be due to differences in the study design, selection of the population, as well as to wording and timing of the questions. Furthermore, collection of the exposures of interest, although conducted at latest at birth, relied on different sources, and above all, ascertainment of complications (e.g. diabetes in pregnancy) might be different in different countries and, as already discussed, might have inherent problems.[32] Some cohorts lack data on hypertension and diabetes before pregnancy; however this would probably change the prevalence of these disorders in pregnancy very little, as women chronically affected by these diseases have a high probability to be diagnosed in pregnancy. Prevalence of ever and especially recurrent wheezing were not directly comparable among cohorts: this again could be in part a true difference but could also be due to different time-points at which the information was collected and to the lack of information on exact number of wheezing episodes in some cohorts. In spite of all these sources of variability, we found fairly

337 homogeneous effects across the different cohorts, indicating that our results are robust.
338 The collected information is mainly questionnaire-based and self-reported, therefore
339 misclassification is possible, although in larger cohorts information on maternal
340 complications were obtained by obstetric records or link with routine data-bases
341 (Supplementary data). However, measurements of exposure prior to outcome suggests that the
342 within study bias in exposure assessments is non-differential with respect to outcome, and it is
343 expected to make our estimates conservative. Furthermore, some of the exposures
344 investigated in our study, and especially preeclampsia, are well-defined conditions, for which
345 we expect a minimal role for misclassification. Maternal reports of wheezing, although
346 widely accepted in epidemiological studies, might overestimate the presence of the
347 condition, in particular for ever wheezing, as parents might label as wheezing an isolated
348 episode of noisy breathing.[36] Recurrent wheezing is less affected by this source of bias and is
349 more likely to configure a pathological condition; consistently, associations were larger when
350 we studied recurrent instead of ever wheezing.
351

352 We only studied children under two years, and follow up studies at older ages are needed in
353 order to clarify the contribution of these maternal factors to wheezing persisting into school
354 age, and to a diagnosis of asthma. It is well known that in most cases wheeze is a transient
355 condition and the majority resolves during the first few years of childhood. However, young
356 children with wheezing, especially if recurrent, consume a disproportionately high amount
357 of health care resources [36]. Furthermore, longitudinal studies have shown that about 25% of
358 children with persistent asthma start to wheeze in the first 6 months of age, and up to 75%
359 by the age of three years.[36] Wheezing of early onset has been also associated with a

360 congenital impairment of lung function that may track into adult life in susceptible

361 individuals and that might predispose them to chronic respiratory diseases.[1]

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Figures legend

Figure 1. Associations between several maternal complications in pregnancy and recurrent wheezing in childhood.

A. Hypertensive disorders of pregnancy

B. Maternal preeclampsia

C. Maternal diabetes

D. Maternal pre-pregnancy overweight

E. Maternal pre-pregnancy obesity

ES: Cohort specific and combined mutually adjusted risk ratios; 95% CI: 95% confidence interval; D+L: DerSimonian and Laird random-effects method; I-V: inverse-variance fixed-effects method; I-squared: percentage of between-studies heterogeneity; % weight (D+L): set of weights attributed to each cohort by the random effects analysis.

* SWS: Southampton Women's Survey

460 **Table 1.** Descriptive characteristics of the fourteen cohorts

Cohort	Country	Enrolment		No of subjects*
		Years	Developmental period	
CoNER	Italy	2004-2005	Birth	413
DNBC	Denmark	1996-2002	Pregnancy	65 492
EDEN	France	2003-2006	Pregnancy	1770
FAROE V	Faroes	2007-2009	Birth	418
GASPii	Italy	2003-2004	Birth	665
Generation R	Netherlands	2001-2006	Pregnancy/birth	5692
Generation XXI	Portugal	2005-2006	Pregnancy/birth	992
INMA Gipuzkoa	Spain	2006-2008	Pregnancy	547
INMA Menorca	Spain	1997-1998	Pregnancy	468
INMA Sabadell	Spain	2004-2007	Pregnancy/birth	609
INMA Valencia	Spain	2004-2005	Pregnancy	706
KOALA	Netherlands	2000-2003	Pregnancy	2654
NINFEA	Italy	2005-2011	Pregnancy	1919
Southampton Women's Survey	UK	1998-2002	Pre-pregnancy	2944

461 *Number of children with information on both ever and recurrent wheezing

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Table 2. Overall associations of maternal complications and conditions in pregnancy and wheezing in childhood

Maternal complications/conditions	Ever wheezing	Recurrent wheezing
Hypertensive disorders		
No		
Yes		
%		
	28.2	
27.9%		
8.6		
9.0		
RR (95% CI)	1.05 (0.94-1.17)	1.18 (0.97-1.44)
aRR (95% CI)	1.05 (0.97-1.14)	1.21 (0.99-1.47)
Mutually aRR (95% CI)	1.02 (0.98-1.06)	1.20 (0.98-1.47)
Preeclampsia		
No		
Yes		
%		
	27.9	
30.5%		
8.6		
10.7		
RR (95% CI)	1.14 (1.03-1.27)	1.38 (1.07-1.78)
aRR (95% CI)	1.12 (1.04-1.20)	1.31 (1.14-1.51)
Mutually aRR (95% CI)	1.09 (1.01-1.18)	1.23 (1.07-1.43)
Diabetes		
No		
Yes		
%		
	28.1	
32.5%		
8.6		
10.4		
RR (95% CI)	1.09 (0.97-1.23)	1.21 (0.90-1.62)
aRR (95% CI)	1.08 (1.00-1.17)	1.19 (0.87-1.64)
Mutually aRR (95% CI)	1.04 (0.97-1.13)	1.24 (0.86-1.79)

Overweight			
No			
Yes			
	%		
		27.3	
	30.0%		
	8.0		
	9.8		
RR (95% CI)		1.11 (1.05-1.17)	1.24 (1.17-1.31)
aRR (95% CI)		1.08 (1.05-1.11)	1.18 (1.12-1.25)
Mutually aRR (95% CI)		1.08 (1.05-1.11)	1.19 (1.12-1.26)
Obesity			
No			
Yes			
	%		
		27.3	
	31.6%		
	8.0		
	11.5		
RR (95% CI)		1.11 (1.02-1.21)	1.29 (1.09-1.54)
aRR (95% CI)		1.08 (0.99-1.17)	1.22 (1.05-1.43)
Mutually aRR (95% CI)		1.12 (1.08-1.17)	1.16 (0.97-1.39)

RR=relative risk;
aRR=adjusted relative risk; 95% CI: 95% confidence interval