

Pregnancy Complications and Wheezing and Asthma in Childhood

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Pregnancy is a very particular moment in a woman's life, characterized not only by metabolic and other physiological changes but also by pathological conditions that may have consequences for the fetus (1). The relatively new intuition and evidence that the early stages of life are important for the health of children throughout their life span as well as for future generations (2, 3) have led to the view that the pregnancy period is an important "window" with an impact on health.

This Perspective provides an overview of maternal complications of pregnancy for which the literature suggests a relationship with wheezing and asthma in childhood. More specifically, our research investigated whether maternal preeclampsia, obesity, diabetes, psychological stress during pregnancy, and cesarean delivery (exposures) increase the risk of childhood wheezing, asthma, or altered lung function (outcomes) at any point in childhood (0–17 yr). We searched Medline for articles in English, published from January 2000 until August 2017. In the case of previous meta-analyses, the results of which have been reported, we considered studies published since the meta-analysis was run. Relevant articles were also searched manually from references in the selected articles. The Medline search strategy used is reported in the online supplement.

We specifically focused both on birth cohort studies that prospectively collect data on pregnancy and perinatal exposure, and registry-based cohort studies. Long-term birth cohort studies are essential for envisaging the life-course trajectory of early

potential risk factors for the development of respiratory disorders from childhood to adulthood (4, 5).

In this Perspective we do not address the effect of the maternal environment (e.g., nutrition, pollution, etc.) including smoking, a well-known preventable "environmental" cause of abnormal *in utero* lung development, offspring respiratory symptoms, and diminished lung function persisting into adolescence and adulthood (6). The "smoke history" should represent a stimulus to further study on whether and how exposures to perinatal pathological conditions can affect fetal lung development and immune responses, contributing to alter lung and airway developmental patterns throughout life (4, 7).

For the conditions covered in our overview, we discuss potential mechanisms, as well as mediators and confounding factors involved in associations. This is of paramount importance, as any prevention strategy aimed at reducing the burden of childhood respiratory diseases must act on risk factors that are in the causal chain.

Preeclampsia

Preeclampsia, a relatively rare condition (2–4%) in the general population in industrialized countries but more frequent in low-resource settings (8), has received attention in relation to the development of wheezing and asthma in offspring. An association was first suggested years ago in

a large cross-sectional study (9), and several of the more recent birth cohort studies have provided new insights into this topic (Table 1 [10–16]). These studies generally describe an increased risk of respiratory problems, from early wheezing to asthma, and to a lesser extent altered lung function in offspring of preeclamptic mothers. The results are less clear in smaller cohorts, owing possibly to the relative rarity of preeclampsia.

A pooled analysis of 14 European birth cohorts found an association between preeclampsia and recurrent wheezing in infants up to 24 months of life (12). This finding has been confirmed in another cohort from the United Kingdom (13) in which preeclampsia also showed a weak association with diminished lung function up to school age.

A reduction in airway caliber/compliance shortly after birth was described in children who subsequently wheezed or had asthma later in life (17, 18). Preeclampsia is characterized by abnormal placentation, endothelial activation, and overall antiangiogenic status, with disrupted lung growth and reduced alveolarization (8, 19). Moreover, preeclampsia could cause reduced fetal airway growth because of its association with other factors, namely premature birth, intrauterine (fetal) growth restriction, and low birth weight, which are associated with an increased frequency of wheezing (20, 21). Small body size at birth, which in itself could be associated with small airway size, has been found to be associated with poorer lung function in childhood even in infants born at term (22).

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Table 1. Results of Studies Investigating the Association between Preeclampsia and Wheezing–Asthma

Author	Subjects	Outcome	Type of Study	Results
Nafstad <i>et al.</i> , 2003 (10)	507,605	Severe asthma at 3–11 yr, registered in the National Insurance Administration Register	Cohort based on Norwegian national health registers (children born 1985–1993)	No association
Byberg <i>et al.</i> , 2014 (11)	506	Asthma at 11–13 yr	Matched historical cohort study, Stavanger Study, Norway	No association
Zugna <i>et al.</i> , 2015 (12)	85,509	Wheezing at 12–24 mo	Pooled analysis on individual data from 14 European birth cohorts	Positive associations with wheezing and recurrent wheezing
Shaheen <i>et al.</i> , 2016 (13)	9,076	Wheezing at 18 mo; wheezing and asthma at 7 yr; lung function at 8–9 yr	Avon Longitudinal Study of Parents and Children (ALSPAC), birth cohort, UK	Weak evidence for a positive association with wheezing at 18 mo; no association with wheezing and asthma at 7 yr; weak evidence for a negative association with FEV ₁ and FEF _{25–75%}
Liu <i>et al.</i> , 2015 (14)	115,522 case subjects and 1,155,210 control subjects	Asthma at 3–17 yr	Case-control study, nested in a cohort based on Danish national registers	Positive association with asthma, larger for early-onset (<34 wk gestation) preeclampsia
Magnus <i>et al.</i> , 2016 (15)	65,041 case subjects and 82,271 control subjects	Asthma at 3–17 yr	Case-sibling study; cohort based on Danish national registers	Weak association, significant only for early-onset preeclampsia
	406,907	Asthma at 7 yr	Cohort based on Norwegian national health registers	Positive association with asthma; part of the effect mediated by preterm birth
Stokholm <i>et al.</i> , 2017 (16)	45,028	Asthma at 7 yr	Norwegian Mother and Child Cohort Study (MOBA)	Weak evidence for a positive association with asthma
	5,923 discordant siblings	Asthma at 7 yr	Case-sibling study; cohort based on Norwegian national health registers	Nonsignificant association
	1,698,638	Asthma at 7 yr	Cohort based on Danish national health registers	Positive association with asthma, larger when duration of preeclampsia is ≥14 d
	411	Asthma at 7 yr; lung function: forced flows and bronchial responsiveness to methacholine	Copenhagen Prospective Study on Asthma in Childhood ₂₀₀₀ (COPSAC ₂₀₀₀) birth cohort	Nonsignificant association with asthma; positive association with bronchial responsiveness

Definition of abbreviation: FEF_{25–75%} = forced expiratory flow from 25 to 75% of vital capacity.

In epidemiological studies, controlling for gestational age and birth weight attenuated the associations between preeclampsia and wheezing, asthma, and lung function (12–15). This should indicate that the effect of preeclampsia is partly due to being born preterm and/or of low birth weight. However, adjusting for intermediates such as gestational age or birth weight, as if they were confounders, results in overadjustment and biased estimations of the preeclampsia effect toward the null (23). Even formal mediation analyses, with decompositions of the total effects into direct and indirect effects, require absence of unmeasured confounding, an unrealistic assumption in a complex web of putative causal effects (24). With this caveat, a formal decomposition of effects through mediation analysis was attempted—on the assumption of no residual confounding—in one study only (15) and confirmed a direct effect of preeclampsia on asthma in offspring. On the other hand, the observation of a larger association between preeclampsia and asthma in offspring when the disease manifests itself earlier in pregnancy also underscores the importance of gestational age in explaining part of the relationship (14, 15).

Granted that available descriptive evidence shows an association between preeclampsia and wheezing and asthma, an intriguing problem entails disentangling to what extent the effects on the offspring reflect lung damage from being exposed *in utero* to an unfavorable environment, the ill effects of genetic or epigenetic constitutional maternal features (preeclampsia has a genetic basis involving genes affecting thrombophilia, inflammation, oxidative stress, the renin–angiotensin system, and immune regulation) (8), or other uncontrolled confounders.

To answer this question, sibling studies are instrumental: comparisons within sib-pairs who share the same family environment and maternal genetic and epigenetic background, and who are discordant for the disease, allow for adjusting for shared confounders. Attenuation or disappearance of the association between preeclampsia and asthma in offspring has been reported in case–sibling studies nested in large registries (14, 15). Sibling studies can, however, underestimate the effect of

preeclampsia on asthma. In addition to their reduced sample size, hence reduced power to detect differences in risk, they are also prone to confounding by unobserved (background) characteristics not shared by siblings and when exposure is misclassified (25).

In conclusion, the weight of available epidemiological evidence suggests that preeclampsia increases the risk of wheezing/asthma in offspring, especially when born small or preterm.

Obesity

Obesity, defined as a body mass index (BMI) equal to or exceeding 30 kg/m^2 , is a major public health problem complicating up to 30% of pregnancies in Western countries (1, 26). Several birth cohort studies found an association between maternal obesity and being overweight (BMI between 25 and 29.9 kg/m^2) before pregnancy, and wheezing or asthma from early childhood to adolescence. The results of these studies were summarized in a meta-analysis (27) that included studies published up to October 2013 and in a review article (26). In the meta-analysis (27), the pooled odds ratio of a BMI equal to or exceeding

30 kg/m^2 for asthma/wheezing ever in life in seven studies was 1.49 (95% confidence interval, 1.22–1.83), and for current asthma/wheezing in four studies it was 1.35 (1.08–1.68). Since 2014 six additional cohort studies have confirmed the meta-analysis results (12, 28–32), mainly concentrating on the association between maternal obesity and preschool wheezing. In particular, in a large study with a pooled analysis of individual data of 85,509 young children from 14 European birth cohorts (12), maternal prepregnancy overweight and obesity were both positively associated with any wheezing and recurrent wheezing in the first 2 years of life, the increase in risk being between 8 and 19%.

The relationship between maternal obesity in pregnancy and childhood wheezing or asthma may be due to biological mechanisms, but also to confounders and intermediate factors (Figure 1). Maternal obesity is associated with changes in cytokines, acute-phase proteins, and hormones (33). Placentas of obese mothers also have increased expression of inflammatory cytokines and a marked accumulation of macrophages (34): how this might have an impact on placental function has not been established;

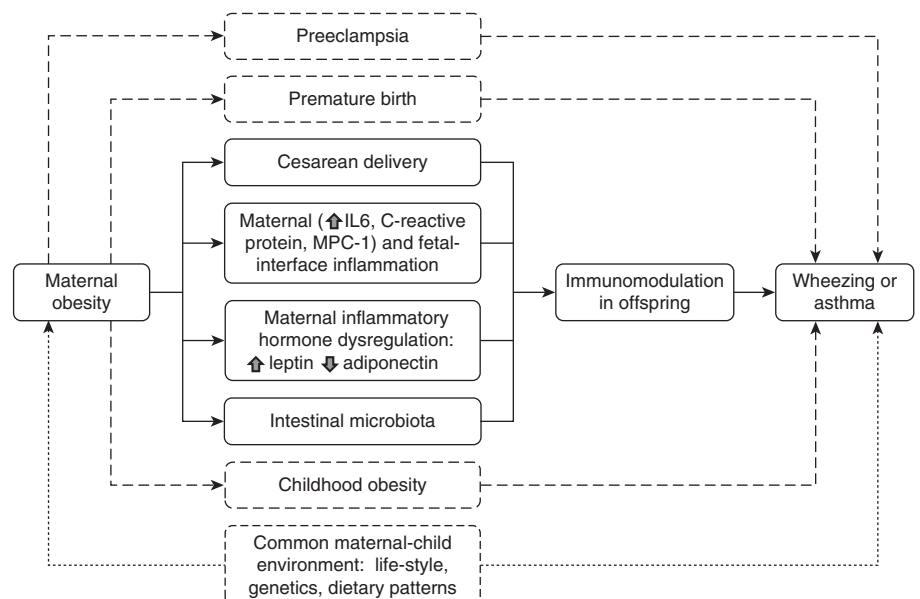


Figure 1. Potential mechanisms of the association between maternal obesity and wheezing and asthma in offspring. Solid lines: pathways that directly act on the immune profile of the fetus. Dashed lines: pathways acting through other mechanisms. Dotted lines: confounding factors that increase the risk of both maternal obesity and offspring asthma and wheezing. MPC-1 = monocyte chemotactic protein-1.

nevertheless, the fetus develops in an inflammatory milieu.

Maternal obesity is associated, partly also via the proinflammatory state of the condition, with pregnancy complications that are risk factors for wheezing and asthma in offspring, in particular preeclampsia, cesarean delivery, premature birth, and delivery of a large-for-gestational-age infant (35). Moreover, irrespective of birth weight, maternal obesity might lead to developmental programming of adiposity in offspring (35), another known risk factor for wheezing and asthma (36) that has been shown to mediate the association between maternal obesity and offspring wheezing (29). Obesity is also related to altered gut microbial colonization, with reduced diversity of microbiota (37). When the diversity is high and diet is rich in fibers and complex carbohydrates there is increased production of short-chain fatty acids that have an effect on T lymphocytes promoting a tolerogenic immune profile (37). Mice fed a high-fiber diet or supplemented with acetate or propionate had increased circulating levels of short-chain fatty acids and were protected against allergic inflammation in the lungs (38, 39). In pregnant mice this diet also led to the suppression of allergic inflammation in offspring (39). This has been confirmed in a study in humans: high fiber intake during pregnancy was associated with high serum acetate levels, giving protection against cough and wheezing in infants (39). Taken together, these studies suggest a link between maternal diet/obesity, gut microbiota, and airway inflammation in offspring.

Finally, as suggested by sib-pair analyses, a common maternal-child “environment” (dietary or other lifestyle habits such as exercise, in addition to genetics) might affect both maternal and childhood obesity (40), hence wheezing and asthma later in life.

To conclude, despite the large number of studies reporting associations between maternal obesity and wheezing and asthma in offspring, and the biologically plausible mechanisms that might explain these findings, the relative contribution of these pathways is unclear, and the possibility exists that the relationship might be confounded by factors for which it is difficult to adjust even in large epidemiological studies.

Diabetes

Gestational diabetes, defined as hyperglycemia identified during pregnancy, increases the risk of a range of adverse maternal and perinatal outcomes that are critical in the relationship with wheezing and asthma, including preeclampsia, obesity, and cesarean delivery (1). Furthermore, experimental studies demonstrate delayed pneumocyte differentiation and lung maturation with reduced surfactant synthesis in diabetic animals (41). This is consistent with human studies showing an increased risk of respiratory distress syndrome in infants born to diabetic mothers. Few prospective cohort studies have specifically investigated the relationship between gestational diabetes and subsequent wheezing or asthma in offspring. In a pooled analysis of 14 European birth cohorts after adjusting for several complications of pregnancy, we did not find an increased risk of wheezing up to 24 months of life, although we were not able to differentiate between gestational and pregestational diabetes (12). Two large registry-based cohorts in Sweden and Finland found a slight association between pregestational and gestational diabetes and asthma hospitalization at school age (42, 43).

Maternal Depression, Anxiety, and Psychological Stress

Depressive and anxiety disorders, which are among the most common morbidities of pregnancy and the perinatal period, have been reported in up to 13% of women (44). Substantial evidence exists that perinatal mental disorders are associated with risks for negative outcomes in childhood, and in particular with developmental and psychological disorders (44). The first article on the relationship between maternal anxiety symptoms and asthma in offspring, however, is relatively recent, as it was published in 2009 (45). Since then a number of studies, mainly birth cohort studies, have been published, and assess multiple types of stressors, all during pregnancy: doctor diagnosis of depression/anxiety, negative life events, and anxiety/depression or psychological distress measured by questionnaires (most of the studies) (46). One meta-analysis found an

association between psychological stress during pregnancy and the development of wheezing disorders or asthma in children of various ages, but especially in preschoolers, with a pooled odds ratio of 1.59 (95% confidence interval, 1.25–2.01) (46).

Subsequent studies, reported in Table 2 (47–56), have confirmed these results.

A point that still needs clarification is the relative contribution of antenatal and postnatal exposure, as anxiety, depression, and stress during pregnancy often continue after birth. Birth cohort studies in which stress was measured both during and after pregnancy are inconclusive (51, 52, 56–58); in addition, in two cohorts, a sex-specific effect was found (51, 52). Boys were more sensitive to prenatal stress, whereas girls showed a stronger relationship between postnatal stress and asthma risk. Sex differences in lung maturation and hence windows of greater vulnerability have been proposed to explain these findings. Finally, in two studies, maternal exposure to stressful life events in pregnancy also enhanced the effects of ambient nitrate—a component of airborne particulate pollution—and of fine particulate exposure on asthma risk in boys (53, 54).

Part of these relationships might be artifactual: mothers who continue to be stressed postnatally may perceive their children's respiratory symptoms differently, and this could result in overreporting of wheezing and possibly also in more frequent diagnosis of asthma. In addition, although all the studies were adjusted for several confounders, psychological stress might alter the mothers' health behavior such as smoking, diet, the propensity to cesarean delivery and breastfeeding, or contribute to poor fetal growth, prematurity, and more rapid postnatal growth. All these factors could influence the relationship between stress in pregnancy and respiratory health in offspring, acting as mediators.

Mechanisms linking prenatal stress to childhood wheezing and asthma are only partly elucidated, and still largely based on experimental studies on acute stress (59). An in-depth discussion of mechanisms is beyond the scope of this Perspective, and will be only briefly addressed. Maternal mental disorders or stressful events in pregnancy may disrupt regulation of the hypothalamic–pituitary axis in both the mother and child, which might intervene in the developing fetal immune system and

Table 2. Results of Studies Investigating the Association between Maternal Depression, Anxiety, and Psychological Stress and Wheezing–Asthma

Author	Subjects	Exposure/Outcome	Type of Study	Results
Hartwig <i>et al.</i> , 2014 (47)	994	Negative life events assessed twice in pregnancy (second and third trimesters) Asthma at 6 and 14 yr	Western Australian Pregnancy Cohort (Raine) study	Positive association with asthma. In stratified analysis, the association was present only in nonasthmatic mothers
Cheng <i>et al.</i> , 2015 (48)	1,152	Depression and anxiety assessed at 26 wk of gestation Wheezing up to 12 mo	Growing up in Singapore toward Healthy Outcome (GUSTO), birth cohort	Positive association between depression and wheezing; no association for anxiety
Liu <i>et al.</i> , 2015 (49, 50)	750,058	Prenatal maternal bereavement (death of a close relative) during pregnancy or up to 1 yr before Depression with or without antidepressant use during pregnancy or up to 1 yr before Asthma up to 15 yr	Cohort based on Danish national health registers	Association between bereavement and asthma in children aged 0–3 yr; no association with asthma at 4–15 yr Association between depression with or without antidepressant use and asthma at 4–15 yr
Rosa <i>et al.</i> , 2016 (51)	417	Prenatal (second-third trimester) and postnatal (48 mo) maternal negative life events Wheezing lifetime and in the past 12 mo up to 4 yr	Pregnancy Cohort in Mexico City, Mexico	Dose-response association between both pre- and postnatal stress and wheeze in both sexes. For current wheeze: interaction between increased postnatal stress and child sex: association greater in girls
Lee <i>et al.</i> , 2016 (52)	765	Pre- and postnatal (12–18 mo) maternal negative life events Asthma up to 6 yr	The Asthma Coalition on Community, Environment, and Social Stress project, pregnancy cohort, USA	In boys, dose-response association between both pre- and postnatal stress and asthma; in girls association only for postnatal exposure When mutually adjusted: association only for postnatal stress and in girls
Bose <i>et al.</i> , 2017 (53)	752	Prenatal nitrate exposure, prenatal negative life events	The Asthma Coalition on Community, Environment, and Social Stress project, pregnancy cohort, USA	Synergistic association between nitrate ambient exposure in pregnancy, maternal stress and sex (boys) and asthma
Lee <i>et al.</i> , 2017 (54)	752	Prenatal fine particulate exposure, prenatal negative life events Asthma up to 6 yr	The Asthma Coalition on Community, Environment, and Social Stress project, pregnancy cohort, USA	Same results for fine particulate exposure
Lee <i>et al.</i> , 2017 (55)	199	Pre- and postnatal (12–18 mo) maternal negative life events Lung function at 6 yr	The Asthma Coalition on Community, Environment, and Social Stress project, pregnancy cohort, USA	Highest level of pre- and postnatal stress inversely associated with FEV ₁ , FVC, and FEF _{25–75%}
Ramratnam <i>et al.</i> , 2017 (56)	467	Pre- and postnatal (up to 3 yr) maternal stress and depression Recurrent wheezing up to 3 years	Urban Environment and Childhood Asthma (URECA), birth cohort, USA	Positive association between postnatal but not prenatal maternal stress and depression and recurrent wheezing

Definition of abbreviation: FEF_{25–75%} = forced expiratory flow from 25 to 75% of vital capacity.

contribute to placental oxidative stress and programming of autonomic imbalance in offspring. The effect of prenatal stress on regulatory mechanisms and immune development has already been described in studies in humans, although the picture is still unclear. Higher evening maternal cortisol and a flattened diurnal rhythm in pregnancy have been associated with infant respiratory illness and recurrent wheezing (60). In a birth cohort at high risk of asthma and allergy, young infants born to mothers with high prenatal stress had altered innate and adaptive immune responses in cord blood (61), possibly indicating an enhanced susceptibility to atopic disorders. However, in the same cohort, exposure to postnatal, not prenatal, stress was associated with recurrent wheezing at the age of 3, whereas neither increased allergic sensitization or type 2 cytokine responses (56). Prenatal stress may also operate through regulation of the fetal epigenome. Maternal chronic stress is associated with offspring DNA methylation at the glucocorticoid receptor gene (62) which is essential in the modulation and functioning of the hypothalamic–pituitary axis. In a prospective mother–child birth cohort, comparisons via whole-genome analysis among mother–child pairs with low and high stress levels revealed a substantial perturbation in DNA methylation in both mothers and children exposed to stress (63). In children but not mothers, calcium and Wnt signaling required for lung maturation in the prenatal period were epigenetically deregulated.

Cesarean Delivery

A meta-analysis published in 2008 found a 20% increase in the risk of asthma among children born by cesarean delivery (64). In this Perspective we focus on studies capable of distinguishing between emergency and planned cesarean delivery, or cesarean delivery before or after rupture of membranes. These studies, reported in Table 3, confirm an increase in the risk of asthma in children born after cesarean delivery but without consensus having been reached on the association with various types of cesarean section (65–75). Inconsistencies might arise from difficulties in controlling for multiple key confounders: complications in pregnancy leading to

cesarean delivery hence confounding by indication, perinatal factors, and factors influencing the choice of delivery method, including preferences of the pregnant woman and clinical practice. Moreover, definitions of cesarean type (elective, planned, scheduled vs. emergency, unscheduled, acute) only partly overlap, adding a further source of variability. Furthermore, there is a great difference in the frequency of cesarean deliveries overall and in the various types of cesarean section. All these considerations point toward inhomogeneity of the exposures and hence possibly also of the effects.

Two studies (68, 69) assessed whether the increase in the risk of childhood asthma remains in a sibling-pair analysis, which should allow for controlling confounding related to shared unmeasured familial factors. The associations generally weakened, remaining in one study (68) for emergency, and in the other (69) for elective cesarean delivery. As already underscored, however, conclusions from sibling-pair analyses require caution because they could be biased by nonshared confounders (25). Three registry-based studies and one large cohort study found an association or a more pronounced association for elective cesarean delivery compared with vaginal delivery in infants born at term (≥ 37 wk of gestational age) (71, 73–75), thus confirming that the association is not due to prematurity or the majority of complications of pregnancy. On the other hand, elective cesarean often results in early term birth (37 up to 38 wk), which has been associated with slightly poorer lung function and asthma up to 40 weeks' gestation (21). Therefore it is still possible that the effect of elective cesarean at term is partly mediated by gestational age.

Distinguishing between planned or elective and emergency cesarean delivery could be important because in planned cesarean delivery fetuses are not exposed to stress-response activation of the hypothalamic–pituitary axis, which normally occurs in labor and which may modify immune function (76). Furthermore, in cesarean delivery performed before rupture of membranes the child is not exposed to maternal bowel flora and shows disturbed gut colonization patterns, which again might affect immunomodulation (77). A further cause

of disturbed gut colonization is the administration of prophylactic antibiotics to all women undergoing cesarean delivery. Finally, infants delivered by elective cesarean have differential DNA methylation of gene regions relevant for later immune-mediated diseases compared with infants delivered vaginally (78). Interestingly, babies born by planned or elective cesarean are also at a small but significantly increased risk of other immune diseases such as type 1 diabetes and juvenile arthritis compared with those born by emergency cesarean delivery (71, 74).

Whether a causal association between cesarean delivery and asthma exists cannot be inferred by epidemiological studies. However, as mentioned above, putative mechanisms are biologically plausible. Because the rate of cesarean delivery is increasing in many countries (in high-income countries this is mainly due to a rise in elective cesarean deliveries), health care professionals and women considering planned cesarean delivery should be made aware of this (71).

Conclusions

This narrative review has dealt with a series of exposures during pregnancy that have been studied, and for which there is now a sufficient body of literature to support or suspect a causal effect on the respiratory health of neonates, infants, and children.

We have focused on epidemiological evidence, gathered through birth cohort studies as the highest level of evidence possible when studying potentially detrimental factors for which randomized studies are not an option, and when the mechanisms via which these exposures carry out their detrimental effects are often still unclear, due to the limitations of animal models.

Besides reporting the current state of knowledge for each maternal condition, we have also highlighted possible problems to help interpretation and future research. Epidemiological observational studies are prone to a variety of possible biases, especially noncomparability of exposed and unexposed subjects, and this problem is clearly present for all the topics and relationships analyzed in this review.

Table 3. Results of Studies Investigating the Association between Types of Cesarean Delivery and Wheezing–Asthma

Author	Subjects	Outcome	Type of Study	Results
Metsälä <i>et al.</i> , 2008 (65)	27,358	Asthma medication up to 3 yr in children with asthma diagnosis	Case-control study, nested in a cohort based on Finnish Medical Birth Register	Positive association for both emergency and planned cesarean delivery
Tollånes <i>et al.</i> , 2008 (66)	619,365	Asthma diagnosis up to 14 yr	Cohort based on Medical Birth Registry of Norway	Positive association for both emergency and planned cesarean delivery
Magnus <i>et al.</i> , 2011 (67)	37,161	Wheezing at 18 mo; current asthma at 36 mo	Norwegian Mother and Child Cohort Study (MOBA)	Positive association for both acute and elective cesarean delivery and asthma at 36 mo; stronger among children of nonatopic mothers
Almqvist <i>et al.</i> , 2012 (68)	175,110; 40,986 discordant sibling pairs	Asthma diagnosis and medication at 9–12 yr	Cohort based on Swedish national health registers + sibling pair analysis	Cohort analysis: positive association for both emergency and elective cesarean delivery and asthma diagnosis; positive association for emergency cesarean with asthma medication. Sibling pair analysis: association for emergency cesarean delivery and asthma medication
Bråbäck <i>et al.</i> , 2013 (69)	199,837	Asthma medication at 2–5 and 6–9 yr	Cohort based on Swedish national health registers + sibling pair analysis	Cohort analysis: positive association for elective cesarean delivery in both age groups. Sibling pair analysis: association for elective cesarean in 2- to 5-yr age group
Van Berkel <i>et al.</i> , 2015 (70)	5,885	Wheezing patterns, asthma, F _{ENO} , and Rint at 6 yr	Generation R study, birth cohort, the Netherlands	Positive association for both elective and emergency cesarean delivery, and early and persistent wheezing. Positive association for elective cesarean and F _{ENO}
Black <i>et al.</i> , 2015 (71) Black <i>et al.</i> , 2016 (72)	321,287 first born at term 40,145 repeat cesarean at term	Asthma requiring hospital admission, asthma medication at 5 yr	Scottish Morbidity Record database linked with other databases, registry study	Increase in risk of asthma for planned cesarean delivery when compared with vaginal delivery but not when compared with unscheduled cesarean
Sevelsted <i>et al.</i> , 2016 (73)	864,049	Asthma medication at 0–15 yr	Cohort based on Danish national registries	Positive association, more pronounced for cesarean delivery before rupture of membranes but present also for cesarean after rupture of membranes
Kristensen and Henriksen, 2016 (74)	790,569 born at term	Asthma diagnosis at 0–14 yr	Cohort based on Danish national registries	Positive association for elective and acute cesarean delivery, more pronounced for elective cesarean
Rusconi <i>et al.</i> , 2017 (75)	67,613	Current asthma at 5–9 yr	Pooled analysis on individual data from nine European birth cohorts	Positive association for elective cesarean delivery. In children born at term the association for elective cesarean was stronger

Definition of abbreviations: F_{ENO} = fractional exhaled nitric oxide; Rint = airway interrupter resistance.

The “smoke history,” however, reminds us that the principle of precaution must guide our decisions, and the fact that study designs are imperfect is not an excuse for dismissing the results altogether. The weight of evidence clearly demonstrates that the fetal period is extraordinarily

important for respiratory diseases: infant wheezing and asthma have been increasingly related to fetal and perinatal factors, also in animal studies. This opens new windows of opportunity for prevention. Even though the increased risk arising from maternal complications is not

great, due to their prevalence in the population the burden of disease is high, and consequently, also the potential for prevention. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Pregnancy complications and wheezing and asthma in childhood.

Franca Rusconi and Luigi Gagliardi

Online Data Supplement

Medline search strategies for exposures and outcomes

Medline search strategies for exposures and outcomes

Preeclampsia:

("pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[All Fields] OR "preeclampsia"[All Fields] OR "hypertension, pregnancy-induced"[MeSH Terms] OR "pregnancy induced hypertension"[All Fields] OR "pregnancy-induced hypertension"[All Fields] OR "pregnancy hypertension"[All Fields] OR ("pregnancy"[All Fields] AND "hypertension"[All Fields]) OR (pre-pregnancy[All Fields] AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields])) OR (("mothers"[MeSH Terms] OR "mothers"[All Fields]) OR ("maternal"[All Fields]) AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields])) OR ("hypertension"[All Fields] AND "pregnancy-induced"[All Fields]) OR ("pregnancy"[All Fields] AND "induced"[All Fields] AND "hypertension"[All Fields])

AND

("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields] OR "respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields])

AND

("child"[MeSH Terms] OR "child"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields] OR "children"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "childhood"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "paediatrics"[All Fields] OR "paediatric"[All Fields])

Limits: English

Obesity:

("obesity"[MeSH Terms] OR "obesity"[All Fields]) **AND** ("Pregnancy"[Mesh] OR "pregnancy"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "mother"[All Fields] OR "maternal"[All Fields] OR "prenatal"[All Fields] OR "pre-pregnancy"[All Fields])

AND

("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields] OR "respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields])

AND

("child"[MeSH Terms] OR "child"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields] OR "children"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "childhood"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "paediatrics"[All Fields] OR "paediatric"[All Fields])

Limits: English

Diabetes

"diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields]) OR ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] AND ("Pregnancy"[Mesh] OR "pregnancy"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "mother"[All Fields] OR "maternal"[All Fields] OR "prenatal"[All Fields] OR "pre-pregnancy"[All Fields]))

AND

("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields] OR "respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields])

AND

("child"[MeSH Terms] OR "child"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields] OR "children"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "childhood"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "paediatrics"[All Fields] OR "paediatric"[All Fields])

Limits: English

Depression, Anxiety, Psychological Stress:

("Depression"[Mesh] OR "depressive disorder"[MeSH Terms] OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "Stress, Psychological"[Mesh] OR "stress"[All Fields] OR "Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh] OR "anxiety"[All Fields]) **AND**

("Pregnancy"[Mesh] OR "pregnancy"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "mother"[All Fields] OR "maternal"[All Fields] OR "prenatal"[All Fields] OR "pre-pregnancy"[All Fields])

AND

("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields] OR "respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields])

AND

("child"[MeSH Terms] OR "child"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields] OR "children"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "childhood"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "paediatrics"[All Fields] OR "paediatric"[All Fields])

Limits: English

Cesarean Delivery:

(cesarean[All Fields] OR caesarean[All fields] OR "cesarean section"[All Fields] OR "caesarean section"[All Fields] OR "cesarean section"[MeSH Terms] OR ("cesarean"[All Fields] AND "section"[All Fields]) OR "cesarean delivery"[all fields] OR "caesarean delivery"[All Fields])

AND

("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields] OR "respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields])

AND

("child"[MeSH Terms] OR "child"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields] OR "children"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "childhood"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields] OR "paediatrics"[All Fields] OR "paediatric"[All Fields])

Limits: English