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Prenatal Exposures and the Development of Childhood Wheezing Illnesses

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Abstract

Purpose of review—To critically evaluate and summarize studies published between July 2015 and June 2016 linking prenatal exposures and the onset of childhood wheezing illnesses, and to discuss future research directions in this field.

Recent findings—The aggregated evidence indicates a consistent detrimental effect of prenatal exposure to parental smoking, outdoor air pollution, and maternal stress on childhood wheezing illnesses. Less consistent evidence suggests an adverse impact of maternal obesity during pregnancy and prenatal exposure to antibiotics on these outcomes. There is insufficient evidence to support an association between *in utero* exposure to acetaminophen or prenatal levels of specific nutrients (such as vitamin D, folic acid, or polyunsaturated fatty acids) and childhood wheezing illnesses.

Summary—Several common potentially modifiable prenatal exposures appear to be consistently associated with childhood wheezing illnesses (e.g., parental smoking, outdoor air pollution, and maternal stress). However, the effect of many other prenatal exposures on the onset of childhood wheezing illnesses remains unclear. The existing scientific evidence from the past year does not allow us to make any new recommendations on primary prevention measures. Intervention studies will best demonstrate whether changing the prenatal environment can prevent childhood wheezing illnesses and asthma.

Keywords

Asthma; children; maternal; pregnancy; prenatal; risk factor; wheezing

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Conflict of Interest

The authors declare that they have no relevant conflicts of interest to disclose.

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Introduction

Pregnancy is a critical period of human development and alterations that occur *in utero* can lead to long-term programming of the airway, lung, and immune functions [1]. Based on this, there has been great interest in identifying prenatal exposures that modify the risk of developing childhood wheezing illnesses, such as asthma, as this could lead to primary prevention interventions [2]. The purpose of this review is to critically evaluate and summarize the most recent evidence linking prenatal exposures and the onset of childhood wheezing illnesses, and to discuss future research directions in this field. To this end, we searched the MEDLINE database for original research articles (including systematic reviews with meta-analysis) published in English between July 1, 2015 and June 30, 2016 using the following terms: ('prenatal' or 'pregnancy' or 'maternal' or 'mother') and ('wheezing' or 'asthma' or 'allergic diseases' or 'atopy'). Only studies which measured prenatal exposures and in which outcomes were assessed in children (0–21 years of age) were included in this review. The mechanisms through which different prenatal exposures may lead to childhood wheezing illnesses have been described elsewhere and are not discussed here [1, 3–6].

Maternal Diet

It has been suggested that the prenatal consumption of a Western diet can explain the increased prevalence of childhood wheezing illnesses in developed countries [3, 7, 8]. Indeed, numerous studies have shown a relationship between *in utero* exposure to certain maternal nutrients, food groups, or dietary patterns with a decreased or increased risk of these diseases. In a retrospective cohort study in the United States, von Ehrenstein *et al* found a dose-dependent association of fast food consumption during pregnancy and asthma risk at age 3.5 years [7]. Because this study assessed fast food consumption during pregnancy between 3–6 months after delivery, recall bias is a possibility. Furthermore, the specific components of fast food that could be detrimental for the child's respiratory health were not studied, and it is possible that fast food *per se* is not responsible for the increased risk of asthma, but actually related to another risk factor that could explain this association (e.g., low prenatal fruit and vegetable consumption, maternal obesity, or socioeconomic factors). To summarize the evidence of maternal diet on childhood wheezing illnesses, Beckhaus *et al* conducted a meta-analysis of 32 observational (mostly prospective) studies published between January 2002 and November 2014 [8]. The authors found an inverse association between the prenatal intake of vitamin D, vitamin E, or zinc and the risk of childhood wheeze up to age 8 years, but not with asthma *per se*. In addition, they found no association between the prenatal intake of vitamin A, vitamin C, folic acid, calcium, copper, magnesium, selenium, vegetables, fruits, fish, meat, dairy, fats, sweetened beverages, or a Mediterranean diet and childhood wheezing or asthma.

Three prospective studies published after the meta-analysis by Beckhaus *et al* found no association of prenatal vitamin D with several childhood wheezing phenotypes or asthma between ages 1–6 years [9–11]. These 3 prospective studies measured vitamin D levels in maternal and/or umbilical cord blood (in contrast to the meta-analysis by Beckhaus *et al*, which only included studies that used food frequency questionnaires). More recently, 2 double blind, multicenter, placebo-controlled randomized controlled trials (RCTs) have

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attempted to end the debate of a potentially beneficial effect of prenatal vitamin D on childhood wheezing illnesses. Chawes *et al* randomized 623 Danish pregnant women to receive either a) 400 international units (IU)/day of vitamin D plus an additional 2,400 IU/day of vitamin D or b) 400 IU/day of vitamin D plus placebo [12]. The number of respiratory-related episodes was significantly lower in the treatment group when compared to the placebo group, but there was no association between the type of intervention and persistent wheeze or asthma at age 3 years. In another study, Litonjua *et al* randomized 876 pregnant women in the United States to receive either a) 400 IU/day of vitamin D plus an additional 4,000 IU/day of vitamin D or b) 400 IU/day of vitamin D plus placebo [13]. Children in the treatment group had a marginally significant ~20% decreased risk of recurrent wheeze or asthma at age 3 years when compared to the placebo group (p=0.051). Children in the treatment group also had a decreased number of positive allergen-specific immunoglobulin E tests, but there was no association between the type of intervention with the number of lower respiratory tract infections, serum total immunoglobulin E level, or eczema. Thus, these prenatal intervention trials do not support a beneficial effect of prenatal vitamin D on childhood wheezing illnesses. However, both studies may have been underpowered to detect any significant associations due to suboptimal enrollment or assumptions in their power calculations that were not reflected in their study population. Furthermore, in both of these RCTs, interventions were started on average after the second trimester, while airway and lung development starts early in the first trimester.

The results of a recent retrospective cohort study of the association of prenatal folic acid and childhood wheezing illnesses done in the United States contradict the negative findings of the meta-analysis by Beckhaus *et al* described above. Veraanki *et al* found that children born to women with a history of exposure to folic acid during either the first trimester of pregnancy or the first trimester and beyond (assessed by prescription filling of folic acid-containing supplements or medications) had ~20% increased odds of asthma between ages 4.5 to 6 years [14]. In contrast, no association was noted for children born to women exposed after the first trimester, which suggests that the timing of folic acid exposure during pregnancy may be critical in its effects on childhood respiratory health. Because the United States mandates folic acid food fortification and women could have obtained folic acid from over-the-counter medications, misclassification of the predictor was one of the study limitations. Furthermore, there were some differences in several sociodemographic and/or pregnancy-related characteristics across the different folic acid groups, which raises the possibility of residual or unmeasured confounding.

A new meta-analysis examined the association of prenatal intake of omega-3 polyunsaturated fatty acids (PUFA) and childhood wheezing illnesses [15]. In this study, the authors included 8 RCTs published up to August 2014 that allocated pregnant woman to either an omega-3 PUFA-related intervention vs. placebo or regular diet. There was no association between the type of intervention and childhood wheeze or asthma up to age 16 years. Overall, the RCTs were considered of high quality. One birth cohort in the Netherlands also found no evidence to suggest a protective effect of prenatal omega-3 PUFA levels on childhood asthma at age 6 years; however, there was an inverse association with prenatal omega-6 PUFA levels [16].

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Prenatal Exposure to Environmental Pollutants

Three recent longitudinal studies have supported the hypothesis that maternal, paternal, and/or parental (i.e., both maternal and paternal) smoking during pregnancy has a negative influence on respiratory health in the offspring [17–19]. In a birth cohort from the Netherlands, the authors found ~50% increased odds of persistent wheeze and ~65% increased odds of asthma at age 6 years in children whose mothers smoked at least 5 cigarettes per day through the pregnancy, but not in children whose mothers smoked only during the third trimester or whose fathers but not mothers smoked [17]. One retrospective cohort study in Finland found similar odds for asthma up to age 10 years in children exclusively exposed to maternal prenatal smoking, but found even higher odds for those exclusively exposed to paternal smoking [18]. To further evaluate the independent effects of prenatal maternal and paternal smoking, as well as the potentially confounding effect of postnatal exposure to tobacco smoke, Vardavas *et al* combined data from 15 European birth cohort studies, showing that prenatal-only maternal passive smoking without active smoking, prenatal-only maternal active without passive smoking, and prenatal-only maternal active plus passive smoking increased the odds of 2-year wheeze by ~10%, ~30%, and ~50%, respectively [19].

In regards to other types of environmental pollutants, a nested-case control study in Canada found that prenatal exposure to higher levels of nitrogen monoxide, nitrogen dioxide, carbon monoxide, sulfur dioxide, and particular matter of ≤10 μm (PM_{10}) increased the risk of asthma in preschoolers, particularly in low birth weight infants, but there was no association between any of these exposures and asthma in school-aged children [20]. In addition, there was no association with prenatal exposure to particulate matter of ≤2.5 μm ($PM_{2.5}$) with asthma in preschool- or school-aged children. This study used administrative data and, therefore, lacked individual-level data for both the exposures and certain important confounders, such as markers of socioeconomic status. In a cross-sectional study in China, stronger associations of prenatal exposure to nitrogen dioxide and sulfur dioxide with asthma in preschool-aged children were found, but not for PM_{10} [21]. In a birth cohort in the United States examining the association of prenatal exposure to $PM_{2.5}$ and asthma up to age 6 years, Hsu *et al* examined if a potential gender-by-environment interaction and/or the timing of the exposure during pregnancy could explain some of the inconsistent results [22]. Using state-of-the-art hybrid spatiotemporal and satellite-derived data, as well as advanced statistical modeling, the authors found that higher prenatal $PM_{2.5}$ exposure did increase the risk of asthma up to age 6 years, but only in boys and when the mother was exposed in mid-gestation.

Maternal Stress

Four new studies have reinforced prior findings of a detrimental effect of prenatal maternal stress on childhood wheeze or asthma [23–26]. In one of these, van de Loo *et al* conducted a meta-analysis of 10 observational studies published up to November 2013, showing that maternal stress during pregnancy increases the risk of asthma-related outcomes (i.e., wheeze, asthma, or asthma-related symptoms) up to age 14 years by ~60% [26]. The majority of studies in this meta-analysis had a longitudinal design and all were rated as

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moderate-to-high quality. There was high heterogeneity in the definitions of the exposure and the outcome; however, the authors obtained comparable results in subgroup analyses restricting to similar studies. In the other 3 studies published in this field, prenatal maternal stress was also found to increase the risk of wheeze or asthma in preschool- or school-aged children, although the associations were not as strong [23–25].

Maternal Obesity

Two recently published studies have continued to explore the relationship of maternal weight with childhood wheezing outcomes [27, 28]. In a birth cohort in the Netherlands, Eising *et al* found that each unit increase in maternal prenatal body mass index was associated with ~2% more wheezing days in the first year of life and ~3% more consultations for wheezing illnesses by age 5 years in the offspring [27]. In this study, the association for infant wheezing days was mainly noted for children born to non-atopic mothers, whereas that for 5-year wheezing consults was mainly noted for children born to atopic mothers. Furthermore, their findings suggested that neonatal lung function could be mediating some of these associations, particularly in infants. In another prospective study in the same country, prenatal maternal obesity increased the odds of wheezing and asthma up to age 8 years by ~2-fold, but the association with wheezing appeared to be partially mediated by the infant's body mass index [28].

Prenatal Exposure to Medications

In spite of numerous recent studies examining the relationship between prenatal exposure to antibiotics or acetaminophen and childhood wheezing illnesses, there is still an ongoing debate regarding possibility of confounding leading to biased results. First, both medications are frequently taken together, so examining their independent effects is challenging. Second, there is a possibility of confounding by indication or shared genetic or environmental factors. For instance, both antibiotics and acetaminophen are taken in the setting of maternal prenatal infections, which could be the actual factor responsible for an increased risk of childhood wheezing illnesses, rather than the medications. Third, women with a history of asthma, tobacco smoke, or other sociodemographic factors (e.g., maternal nutritional status, poverty, or outdoor pollutants) may be at a higher risk of acute respiratory infections, for which they may use medications during pregnancy, and these maternal or environmental characteristics are what actually lead to an increased risk of childhood wheezing illnesses in the offspring.

Four new studies examined the association of prenatal exposure to antibiotics and childhood wheezing illnesses while taking into account the possibility of confounding, with somewhat contradictory results [29–32]. In a meta-analysis of 10 observational studies published up to September 2014, Zhao *et al* found that maternal exposure to antibiotics during pregnancy increased the odds of childhood wheeze or asthma up to age 14 years by ~20% [29]. The authors noted a high heterogeneity between studies; however, the association persisted in subgroup analyses according to the study design, how the use of antibiotics was assessed, and the age of childhood wheeze or asthma onset. Likewise, there was still an association when including only longitudinal studies that adjusted for parental history of allergic

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diseases. In a retrospective cohort in the United States, prenatal use of antibiotics was associated with increased odds of asthma between ages 4.5–6 years in a dose-dependent manner, even after adjusting for maternal history of asthma [31]. In a prospective study in the same country, positive associations with asthma up to age 7 years were noted for prenatal use of penicillin and chloramphenicol when used in the first trimester of pregnancy, but not when used later or for other classes of antibiotics [30]. In a prospective study in Italy, the authors also found a positive association with recurrent wheeze up to 18 months of age, although only when antibiotics were used in the third trimester of pregnancy [32]. Thus, the time in pregnancy during which the fetus may be more susceptible to an effect of exposure to antibiotics remains unclear.

In the case of prenatal exposure to acetaminophen, 3 recent published studies have attempted to address confounding, with mixed results [33–35]. Two retrospective cohorts found an increased risk of asthma at age 3 years or later in children whose mothers had used acetaminophen during pregnancy, even after adjusting for numerous potential confounders [33, 34]. In one of these, there was a slightly higher risk in mothers using acetaminophen during the first trimester or in more than one trimester [34]. In the second study, the association of maternal use of acetaminophen and asthma persisted in separate models by different indications, such as pain, fever, and respiratory tract infections, which suggests that the association could not be fully explained by confounding by indication [33]. Furthermore, there was no association of maternal use of acetaminophen outside pregnancy or paternal use of this medication and childhood asthma, which also minimizes the risk of confounding by shared environmental factors. In contrast to these 2 studies, in a birth cohort in Italy, the association of prenatal use of acetaminophen during the first or third trimester of pregnancy and ever wheeze at age 18 months was only significant in unadjusted analyses, but disappeared after adjusting for potential confounders [35]. A similar pattern was noted for the outcome of recurrent wheeze or asthma at age 18 months. Further subgroup analyses on the prenatal use of acetaminophen for 3 non-infectious diseases (sciatica, migraine, and headache) also revealed no increased risk of childhood wheezing illnesses, suggesting that this association is mostly explained by confounding.

Conclusions, Limitations, and Future Directions

The aggregated evidence of recently published studies focused on prenatal exposures and the risk of childhood wheezing illness indicates a detrimental effect of *in utero* exposure to parental smoking, outdoor air pollution, and maternal stress. Several studies also found a detrimental effect of maternal obesity during pregnancy and prenatal exposure to antibiotics. For health reasons both related and unrelated to childhood wheezing illnesses, it is easy to recommend avoiding or minimizing these exposures. The majority of studies were observational, did not establish dose-response relationships, and by design were subject to numerous bias and confounding effects. There were also major differences in the definitions and time of assessment of the particular exposures and outcomes of interest, the study designs, age groups, and populations of interest between individual studies, which could explain some of the contradictory results. Thus, establishing causation continues to be difficult. In addition, few studies have been conducted to identify critical windows in fetal development (e.g., first, second, or third trimester of pregnancy) or to understand the

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potential mechanisms by which these prenatal exposures could have an effect of childhood wheezing outcomes. It is also unclear how these prenatal exposures may affect the different asthma phenotypes, as childhood wheezing illnesses are a heterogeneous group of diseases [36]. Further research is needed, which should include identifying vulnerable populations, critical susceptibility windows, and well-designed clinical prevention trials. Because most studies have shown relatively weak associations, and none of these factors act in isolation, it is likely that a multi-level intervention will be required to have a substantial impact in the primary prevention of childhood wheezing illnesses. Lastly, a better understanding of asthma phenotypes and endotypes will help to target susceptible populations are for certain exposures.

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Abbreviations

IU	International unit
$PM_{2.5}$	Particular matter of ≤2.5 μm
PM_{10}	Particular matter of ≤10 μm
PUFA	Polyunsaturated fatty acids
RCT	Randomized controlled trial

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Key points

- Recently published studies continue to confirm an increased risk of childhood wheezing illness in children prenatally exposed to parental smoking, outdoor air pollution, and maternal stress on the risk of childhood wheezing illness, with several new studies also finding a detrimental effect of maternal obesity during pregnancy and prenatal exposure to antibiotics.
- There is insufficient evidence to support an association between *in utero* exposure to acetaminophen or prenatal levels of specific nutrients (such as vitamin D, folic acid, or polyunsaturated fatty acids) and childhood wheezing illnesses.
- For reasons both related and unrelated to childhood wheezing illnesses, public health interventions to minimize *in utero* exposure to parental smoking, outdoor air pollution, maternal stress, maternal antibiotics, and maternal obesity should be supported; however, the existing scientific evidence from the past year does not allow us to make any new recommendations on primary prevention measures for childhood wheezing illnesses, including asthma.