



Review

Maternal obesity and childhood wheezing and asthma

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EDUCATIONAL AIMS

The reader will come to appreciate how:

- To review the epidemiologic evidence on the impact of maternal obesity on childhood wheezing and asthma from recent birth cohort studies.
- To discuss potential mechanisms and pathways between maternal obesity and childhood wheezing and asthma.

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SUMMARY

Obesity represents one of the major public health problems worldwide, with an increased prevalence also among women of reproductive age. Maternal pre-pregnancy overweight and obesity are important risk factors for a number of maternal and foetal/neonatal complications. The objective of this review is to provide an overview of the most recent evidence regarding the associations between pre-pregnancy overweight/obesity and wheezing and asthma in childhood. Potential mechanisms, mediators and confounding factors involved in these associations are also discussed. Despite the relatively large body of studies examining these associations and taking into account main confounders and potential mediators, the causal relationship between maternal obesity and wheezing and asthma in childhood is still uncertain. This uncertainty is not trivial, as any prevention strategy aimed at reducing the burden of these conditions would necessarily imply better understanding of the factors that are in the causal chain.

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INTRODUCTION

There is growing evidence on the relationship between early life factors and a wide range of chronic diseases in children and adults [1,2], including obstructive lung disease and asthma [1,3]. The greater impact of maternal compared to paternal asthma and atopy on the development of wheezing and asthma in offspring also suggests a role of the prenatal and in utero environment [2]. Developmental adaptations in foetal life might result in impaired lung growth, and consequently, an increased risk of wheezing and asthma later in life. In addition, pregnancy and perinatal factors affecting the development of the foetal and infant immune system might play a role in the development of respiratory diseases [4,5].

Studies performed in different countries highlighted an increasing trend in the prevalence of several pre-existing and pregnancy related pathologies, including maternal overweight and obesity [6,7]. Obesity represents one of the major public health problems worldwide [8], with an increased prevalence also among women of reproductive age. In western countries, the obesity prevalence in pregnant women has been reported to be up to 30% [9]; while up to 40% of women gain an excessive weight during pregnancy [10].

Maternal pre-pregnancy overweight and obesity and, to a lesser extent, excessive gestational weight gain, are important risk factors for a number of maternal and foetal/neonatal complications [11].

The objective of this review is to provide an overview of the most recent evidence regarding the associations between pre-pregnancy overweight/obesity and wheezing and asthma in childhood. We will further discuss potential mechanisms, mediators and confounding factors involved in these associations. This review is also intended to expand and integrate a previous review

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on maternal obesity and immune dysregulation in mothers and infants [12].

FINDINGS FROM LONGITUDINAL STUDIES

In the past decades many pregnancy and birth cohort studies have been established in Europe [13]. One of the main aims is to gather information on pregnancy and perinatal exposures, and to prospectively collect data on child development, and on the occurrence of a number of diseases. Over time, these cohorts became a precious source of data for conducting studies on potential risk factors for the development of later outcomes in childhood and adulthood. The majority of cohorts collected data on maternal anthropometric measurements, usually maternal weight and height, before pregnancy or in early pregnancy. Maternal overweight and obesity are generally defined based on the body mass index (BMI) and according to the World Health Organization (WHO) definitions: overweight as BMI between 25 and 29.9 kg/m², obesity as BMI \geq 30 kg/m² [14].

Wheezing is one of the most common respiratory symptoms in early childhood with approximately 30% children having at least one wheezing episode in the first 3 years of life [15]. The differential diagnosis of wheezing is extensive and several temporal phenotypes have been described [16,17]. The birth cohort studies assessed child's wheezing and asthma at different ages, from the first months of life until adolescence. Wheezing occurring in the pre-schoolers is regarded as a distinct phenomenon, and at least in part is accompanied by a narrowing (or relative narrowing) of the distal airways. Most of the infants

who wheeze in their first years recover before school age, though sometimes, typically when accompanied with atopy and a more severe clinical course, these children continue to wheeze beyond infancy and can be labelled as asthmatics. Although less commonly, wheezing could also start later and as such is usually linked to an atopic background. In line with these temporal phenotypes we will discuss the existing evidence regarding maternal obesity and preschool and school-aged wheezing separately.

Maternal obesity and preschool wheezing

Studies generally support the positive association between maternal obesity and wheezing in the first years of life in offspring (Table 1) [18–29]. These associations were independent of common confounding factors and potential mediators such as birth weight and child's BMI, atopic background and obesity-related pregnancy complications.

In a large Norwegian study [18], conducted on 32,192 children, maternal obesity, defined as BMI \geq 30, was associated with wheezing in 18-month old children (adjusted RD = 3.3; 95%CI: 1.2–5.3). The authors adjusted for a large number of confounding factors, such as maternal age, education, parity, smoking and history of asthma, and the association was not mediated either by pregnancy complications, caesarean section, premature birth or child's birth weight. However, they did not take into account child's growth in the first 18 months of life that could mediate the associations between maternal BMI and early childhood wheezing. Similar findings, adjusted for child's weight-for length (WFL)

Table 1
Studies reporting associations between maternal overweight/obesity and preschool wheezing.

Author	Subjects	Outcome	Main results
Haberg et al. 2009 [18]	32,281	Wheeze 6–18 months	Positive associations between wheezing and maternal obesity but not overweight. The association was not mediated by pregnancy complications, low birth weight, preterm birth or caesarean section.
Kumar et al. 2010 [19]	1,191	Recurrent wheeze 0–3 years	Positive associations between wheezing and maternal obesity but not overweight. The results were not attenuated after adjustment for child's atopy. Child's BMI slightly attenuated the effects.
Wright et al. 2013 [20]	261	Repeated wheeze 0–2 years	The association between wheezing and maternal BMI \geq 30 was borderline significant.
Guerra et al. 2013 [21]	1,107	Frequent wheeze (\geq 4 episodes) and infrequent wheeze (<4 episodes) up to 14 months	No association between maternal overweight/obesity and infrequent wheeze. For frequent wheeze the positive association was found for maternal obesity but not for overweight. The associations persisted after taking into account child's WFL z-scores.
Leermakers et al. 2013 [22]	4,656	Wheezing at 1, 2, 3 and 4 years	Associations found only for wheezing at the age of 4 years. Obesity was associated with an overall risk of preschool wheezing only among children of mothers with history of asthma/atopy. Infections, child's growth and eczema did not modify the observed associations.
Harpsoe et al. 2013 [23]	38,874	Early transient wheeze at 18 months (assessed until 7 years)	Both overweight and obesity were associated with early transient wheezing.
Caudri et al. 2013 [24]	2,728	Transient early wheeze (wheeze assessed annually until 8 years)	After adjustment the association with maternal BMI remained only for early transient wheeze and borderline for persistent wheeze.
Pike et al. 2013 [25]	934	Transient wheeze in the first 3 years (wheeze assessed until 6 years)	Maternal fat mass (skin fold thickness) and BMI were associated with transient wheeze. Adjustment for infant adiposity gain or BMI at 3 or 6 years did not alter the results.
de Vries et al. 2014 [27]	4,860	Wheezing in the first 5 months of age	Maternal BMI was associated with offspring wheezing. Maternal cortisol levels did not mediate this association.
Zugna et al. 2015 [28]	85,509	Wheezing between birth and 12–24 months	In a pooled analysis of 14 European birth cohorts maternal pre-pregnancy overweight and obesity were both associated with an increased risk of ever and recurrent wheezing in the offspring.
Eising et al. 2015 [26]	2,606	Wheezing in the first year of life and at the age of 5 (consultations and prescriptions)	Maternal BMI was associated with an increased risk of wheezing in the 1 st year of life and more consultations and prescriptions for wheezing until the age of 5 years. In the 1 st year of life the association is largely explained by an impaired lung function, especially in children of non-atopic mothers. At the age of 5 years child's current anthropometrics slightly changed the results.

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