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**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.

**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.

**Keywords:** Maternal obesity, wheezing, asthma, foetal programming, cohort studies

## 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 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 on maternal obesity and immune dysregulation in mother and infant [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's 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/m<sup>2</sup>, obesity as BMI  $\geq$  30 kg/m<sup>2</sup> [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 neither 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) z-scores were reported also by Guerra et al. [21], but only for frequent episodes of wheeze ( $\geq 4$  episodes) in the first 14 months of life.

Although asthma diagnosis in preschool age is rather uncertain, Reichman et al. [29] reported a 1.5-fold increased risk of parent-reported asthma diagnosis in 3-year-old children born to obese mothers. In a recent study conducted on 2606 children [26] a higher maternal BMI was associated with an increased risk of childhood wheezing in the first year of life; the association was largely explained by impaired lung function, especially in children of non-atopic mothers. However, lung function was of minor influence compared to child's anthropometrics for the associations between maternal obesity and consultations and prescriptions for wheezing illnesses in 5-year-olds.

In a pooled analysis of 85,509 children from 14 European birth cohorts [13], maternal pre-pregnancy overweight and obesity were both positively associated with any wheezing (overweight OR=1.08; 95% CI: 1.05-1.11, obesity OR=1.12; 95% CI: 1.08-1.17) and recurrent wheezing in the first two years of life (overweight OR=1.19; 95% CI: 1.12-1.26, obesity OR=1.16; 95% CI: 0.97-1.39). These associations were independent of several pregnancy complications and the results changed only moderately after taking into account potential mediators, such as child's birth weight, gestational age, delivery mode and breastfeeding.

Although studies that assessed maternal BMI as a continuous variable suggest that the risk of early wheeze rise progressively with an increase in maternal BMI [29-32] other studies found the effect for maternal obesity (BMI  $>30$  kg/m<sup>2</sup>) and not for overweight (BMI 25-29.9 kg/m<sup>2</sup>) [23,24,26,27]. However, two large studies [13,28] confirmed that also children of mothers who are overweight suffer more from wheezing compared to children born to mothers of normal weight. Moreover, most of the studies found that maternal obesity is a risk factor for both transient and recurrent wheezing in the first years of life.

Maternal history of asthma and atopy were usually considered as potential confounders but the adjustment rarely attenuated the associations found between pre-pregnancy obesity and early wheezing. However, Leermakers et al. [27] stratified the analyses by maternal history of asthma and atopy and found that maternal pre-pregnancy BMI was associated with an overall increased risk of preschool wheezing only in children with familial asthma or atopy predisposition. Other potential mediating factors, such as pregnancy and delivery complications, child's birth weight and current BMI had a minor influence on the observed associations.

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

Author	Subjects	Outcome	Main results
<b>Haberg et al. 2009</b> <sup>23</sup>	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.
<b>Kumar et al. 2010</b> <sup>24</sup>	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.
<b>Wright et al. 2013</b> <sup>25</sup>	261	Repeated wheeze 0-2 years	The association between wheezing and maternal BMI $\geq$ 30 was borderline significant.
<b>Guerra et al. 2013</b> <sup>26</sup>	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.
<b>Leermakers et al. 2013</b> <sup>27</sup>	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.
<b>Harpsoe et al. 2013</b> <sup>28</sup>	38,874	Early transient wheeze at 18 months (assessed until 7 years)	Both overweight and obesity were associated with early transient wheezing.
<b>Caudri et al. 2013</b> <sup>29</sup>	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.
<b>Pike et al. 2013</b> <sup>30</sup>	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.
<b>de Vries et al. 2014</b> <sup>32</sup>	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.
<b>Zugna et al. 2015</b> <sup>13</sup>	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.
<b>Eising et al. 2015</b> <sup>31</sup>	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 <sup>st</sup> year of life and more consultations and prescriptions for wheezing until the age of 5 years. In the 1 <sup>st</sup> 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.

### Maternal obesity and wheezing at school age

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The evidence supporting an association between maternal obesity and persistence of wheezing symptoms in older children is less conclusive (Table 2). Pike et al. found no association between maternal adiposity and persistent wheezing or doctor-diagnosed asthma at the age of six years [30]. No association was found for late-onset wheezing and only borderline effect for wheezing persisting until the age of eight years was found in children from the PIAMA cohort study [29]. In the study of Sholtens et al. [34] maternal pre-pregnancy BMI (as a continuous measurement) and overweight defined as BMI $\geq$ 25 kg/m<sup>2</sup> were positively associated with childhood wheeze and asthma at 8 years of age, but the effect was evident only in children who were at high risk due to a positive family history of asthma.

On the contrary, a study of 38,874 children from Denmark [28] showed that both increased pre-pregnancy maternal weight and gestational weight gain when mutually adjusted were independently associated with persistent and late-onset wheeze, as well as with childhood asthma assessed at the age of 7 years. In a large cohort study from the Netherlands, maternal obesity, but not overweight was associated with current wheezing and ever asthma diagnosed by a doctor in 7-8 years old children [35]. The effect of maternal obesity on childhood current wheezing was both direct and mediated through child's BMI, while the effect on ever asthma was not mediated through child's BMI. They found no interaction/effect modification by parental history of asthma.

A recent meta-analysis [36] that included 108,321 mother-child pairs from fourteen observational studies confirmed the effect of maternal obesity on childhood ever wheeze/asthma (OR=1.49; 95%CI: 1.22-1.83) and current wheeze/asthma (OR=1.35; 95%CI: 1.08-1.68). The effects of maternal overweight were borderline significant for both ever and current wheeze/asthma. It should be noted that there was a significant heterogeneity among the studies included in the meta-analysis with the outcomes measured from birth until 18 years of age.

In brief, the association between maternal obesity and persistence of wheezing at school age is still controversial. It appears that the effect of maternal overweight/obesity on wheezing in offspring is more pronounced in the first years of life and that the effects seen in older children are less evident for overweight than for obesity. Moreover, it seems that the effects on wheezing at school age are more likely mediated through child's overweight and obesity.

Table 2. Studies reporting associations between maternal overweight/obesity and wheezing in school-aged children

Author	Subjects	Outcome	Main results
Scholtens et al. 2010 <sup>34</sup>	3963	Wheeze and asthma at 8 years	Wheeze and asthma were associated with maternal BMI $\geq$ 25 only in children with positive family history of asthma. Birth weight and child's BMI slightly attenuated the observed associations. They found no associations

			with sensitization to inhalant allergens and bronchial hyper-responsiveness.
<b>Harpsoe et al. 2013</b> <sup>28</sup>	38874	Persistent and late-onset wheeze (assessed at 18 months and 7 years)	Both overweight and obesity were associated with persistent wheeze and late-onset wheeze. They also found an association with doctor-diagnosed ever and current asthma and no association with atopic eczema or hay fever.
<b>Pike et al. 2013</b> <sup>30</sup>	934	Persistent wheeze (<3 years and at 6 years)	The positive associations found between maternal BMI and transient and ever wheeze only. No associations with ever or current asthma, current or persistent wheeze, child's atopy, exhaled nitric oxide or spirometry. Adjustment for infant adiposity gain or BMI did not alter the results.
<b>Caudri et al. 2013</b> <sup>29</sup>	2728	Persistent wheeze and late onset at 8 years (assessed annually)	They found a positive association between maternal BMI and persistent wheeze, but not late-onset wheeze. After adjustment the associations remained only borderline significant for persistent wheeze.
<b>Harskamp-van Ginkel et al. 2015</b> <sup>35</sup>	3185	Wheeze and asthma in the first 7-8 years	Maternal pre-pregnancy obesity was associated with higher risks of both asthma and wheezing. Offspring BMI was a mediator in the association between maternal BMI and offspring wheezing, but not for asthma. There was no interaction by parental asthma.

### *Maternal obesity and asthma in childhood and adolescence*

Some of the studies discussed in the previous section found an effect of maternal overweight and obesity also on asthma diagnosis in school-aged children [28,34,35].

Several other studies evaluated the associations between maternal obesity and asthma in older children [37-41]. In a registry-based study of 189,783 children born in Stockholm, Sweden Lowe et al. found that higher maternal BMI was consistently associated with an increased risk of asthma in the child [37]. They assessed asthma in terms of asthma medication use and hospitalization at different ages during the first ten years of life. At age 6 to 8 years, the effect of maternal BMI was somewhat stronger in girls than in boys.

Maternal BMI was associated with current wheezing and asthma also in adolescents but only among those without parental history of atopy [38]. These results were contrary to those reported by Scholtens et al. [34] that found an association between maternal overweight (BMI $\geq$ 25 kg/m<sup>2</sup> vs. normal weight) with wheeze and asthma only in children born to parents with asthma or allergy. The discrepancy between these two findings might be due to different age groups of children (adolescents vs. school-aged children), different phenotypic characteristics or potential residual confounding.

A recent study from the United States [41] found that both maternal overweight and obesity increased the overall risk of asthma in children up to 18 years of age, but in asthma subtype analysis the associations were seen only for asthma onset before 12 years of age. Moreover, after stratification by allergic background the associations were stronger for asthma without allergic background compared to the allergic one. Additionally, they reported sex-specific patterns for the associations with allergic

and non-allergic asthma: the association was observed with non-allergic asthma only in boys and with allergic asthma only in girls.

A positive association between maternal BMI and asthma in 16-year-olds was also confirmed by Ekström et al. [40]; in this study adolescent's overweight mediated to some extent the observed association.

## **POTENTIAL MECHANISMS AND PATHWAYS BETWEEN MATERNAL OBESITY AND CHILDHOOD WHEEZING AND ASTHMA**

Despite the large number of studies reporting associations between maternal obesity and wheezing and asthma in offspring and a number of biologically plausible mechanisms that might explain these findings, the causal relationship is still uncertain. This uncertainty is not trivial as preventing outcomes implies acting on the risk factors that are in the causal chain.

In this section, we summarize some of the main proposed mechanisms and potential pathways by which maternal obesity may increase the risk of wheezing and asthma in offspring.

### *Maternal obesity as an inflammatory state*

Inflammatory and immunological factors are the most commonly suggested biological mechanism that could explain the link between maternal obesity and childhood wheezing. Obesity is known to be a state of chronic, low-grade systemic inflammation accompanied with increased levels of several pro-inflammatory factors [38]. Plasma levels of inflammatory markers, including tumour necrosis factor alpha (TNF- $\alpha$ ), interleukin 6, and C-reactive protein (CRP) are higher in obese pregnant women compared with pregnant women of normal weight [39].

A parallel increase in inflammatory responses has been observed also in the placenta; this might lead both to a foetal exposure to an inflammatory environment and also to structural changes which might impair placental oxygen diffusing capacity [40,41]. Furthermore, leptin, a pro-inflammatory cytokine, is elevated both in circulation of obese pregnant women and in the cord blood of their children [42,43]. Conversely, adiponectine that has been shown to attenuate airways inflammation in animal models [44] has been also reported to have low concentrations both in obese women and in their newborns [42,45]. The associations between elevated C-reactive protein in maternal circulation of obese women [46] and early life production of lipopolysaccharide-stimulated TNF- $\alpha$  [35] and wheezing in offspring have been also reported. In addition, excess maternal weight gain in pregnancy is associated with increased early life TNF- $\alpha$  and asthma in childhood [35].

Finally, pregnancy itself represents a condition that modulates the maternal immune system [47], which together with a pro-inflammatory state caused by obesity might affect foetal and infant immune system development and predispose the offspring to later wheezing and asthma.

### *Dietary patterns in pregnant obese women*

Intake of specific nutrients or different dietary patterns may be linked to maternal obesity that during pregnancy may alter the developing foetus susceptibility to wheezing and asthma in childhood [48,49]. However, most of the studies showed weak evidence of the association between maternal dietary patterns and child wheezing [50].

Obese women are also more likely to have low serum vitamin D levels [51] and this has been associated with elevated risk of childhood infections and wheezing [52]. Finally, although still speculative the lack of some “anti-inflammatory nutrients”, such as probiotics, antioxidants and omega-3 long-chain fatty acids might modulate developmental programming of the infant immune system and increase the risk of asthma and allergy [53].

#### *Obesity and microbiome*

Altered infant gut composition, acting on the immune system development, has been suggested to be a risk factor for later asthma and allergy [54,55]. Obesity is related to altered microbial colonization (reduced proportion of Bacteroides) [56], which might alter infant gut colonization and influence the subsequent risk of wheezing and asthma. This is a complex mechanism where several other factors, that are closely related to maternal obesity, such as dietary patterns, some obesity-related pregnancy complications like infections and the associated antibiotic therapy, as well as the mode of delivery influence the diversity and the composition of infant gut and therefore might play a role in this pathway as well.

#### *Obesity-related complications in pregnancy*

Maternal overweight and obesity are the most common high-risk obstetric conditions linked to a number of other both short-and long-term adverse reproductive outcomes. Pre-pregnancy BMI and gestational weight gain are both associated with an increased risk of hypertensive disorders of pregnancy [11]; preeclampsia – a pregnancy induced severe form of hypertension with proteinuria has been associated with wheezing phenotypes [28,57]. Preeclampsia might affect placental development and compromise the developing foetus [58]. In addition, it often results in spontaneous or medically induced preterm delivery and caesarean section, which, in turn, have been associated with an excess of wheezing disorders in offspring [59,60].

#### *Maternal and childhood obesity*

Maternal obesity is associated with rapid foetal growth, large-for-gestational-age infants, and increases the child’s own risk of being overweight and obese [11], which in turn has been associated to childhood wheezing and asthma [61]. The relationship between maternal and child’s overweight and obesity could be explained by genetic or/and epigenetic imprinting [62,63] shared environmental factors, such as diet and physical activity habits, or foetal programming.

## **CONCLUSION**

A large number of possible mechanisms, both direct and indirect, have been proposed in order to explain the relationship between maternal obesity and childhood wheezing (Figure 1).

Some of them might be causal while others may act as confounding or mediating factors. Many recent studies, in particular prospective longitudinal birth cohort studies, took into account many of these factors trying to reduce potential confounding. However, it is usually difficult to gather information on all of these potential confounders and, in addition, adjustment for an intermediate factor might bias causal inference. Mediation analysis [31] showed that the relationship between maternal BMI and wheezing is partially mediated by child’s overweight/obesity. Moreover, the association between

maternal obesity and increased risk of wheezing in the child may be due to confounding by unmeasured common environmental (e.g. life-style, diet or exercise) or genetic factors as was suggested in a sibling-pair study from Lowe et al. [64].

Finally, the notion that common exposures such as obesity and increased weight gain in pregnancy may have an impact on childhood subsequent common diseases such as wheezing and asthma is in line with the recent attention to epigenetic modifications seen early in life [65].

## **FUTURE DIRECTIONS**

Given the conflicting data on wheezing and asthma assessed at the school age, future studies should carefully define and analyse the most important confounding factors and potential intermediates. Analyses should also include differential effects by sex and familial history of asthma/atopy.

Further research is needed into the physiological basis and mechanisms for increased risk of wheezing and asthma among children of obese women along with effective interventions to advance the care and prevent the adverse outcomes of obese reproductive age women and their children.

## **CONFLICT OF INTEREST STATEMENT**

The authors have no conflicts of interest.

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Figure 1. Possible biological mechanisms, confounders and mediators of the relationship between maternal obesity and wheezing and asthma in childhood

