

EDITORIAL

Clinical & Experimental Allergy

Gestational weight gain and offspring asthma: A novel opportunity for primary prevention research

This editorial discusses the findings of the paper in this issue by Ekström et al. [7], pp. 283–291.

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The success of secondary prevention efforts in asthma – such as the benefits of inhaled corticosteroids on asthma control [1] – has encouraged the asthma community to focus more on ways to prevent asthma from developing in the first place. Indeed, the primary prevention of chronic lung diseases was the focus of a recent workshop by the U.S. National Heart, Lung, and Blood Institute [2]. Although this growing interest in primary prevention is welcome, there are serious challenges ahead. For starters, the heterogeneity of asthma [3] suggests a low likelihood that any single intervention will prevent all subtypes – let alone the diverse collection of asthma-related atopic diseases (e.g. atopic dermatitis, food allergy, and allergic rhinitis).

Among the modifiable risk factors for incident asthma, elevated body mass index (BMI) is one of the more attractive options. Cross-sectional studies linked obesity and asthma long ago, but the temporal sequence was unclear: Did obesity cause asthma, or, as many assumed, did asthma cause obesity? In the late 1990s, in a prospective cohort of ~85 000 nurses, we established that obesity preceded the development of doctor-diagnosed asthma [4]. Although scepticism was common for years, the consistency of the obesity–asthma association, in diverse populations worldwide [5], eventually has led to a general acceptance of the association [1]. That said, it remains unclear whether preventing obesity (or losing weight when already obese) will truly lower one's risk of developing asthma. While this uncertainty applies to most of the putative

risk factors for asthma, obesity-related interventions do have a particular attraction: even if the interventions have little impact on risk of asthma, the interventions still are likely to have important public health benefits [6]. Accordingly, obesity-related interventions are likely to be an early target for future primary prevention trials or community campaigns to prevent asthma.

In the current issue, Ekstrom and colleagues report on a less studied aspect of the obesity–asthma story: the relationship between maternal BMI during pregnancy and risk of asthma in offspring [7]. Although other researchers have linked higher maternal BMI to offspring asthma, there are limited data on the association between maternal BMI and risk of other atopic diseases. Likewise, it is unclear whether associations are limited to early childhood or whether they persist into adolescence. Moreover, a study with longer offspring follow-up could perform novel analyses on whether the child's *own* overweight mediates the association between maternal BMI during pregnancy and offspring asthma. The new study addresses all of these issues.

Briefly, the investigators analyzed data from 3294 children in a Swedish birth cohort [7]. Maternal BMI was assessed around week 10 of pregnancy, while offspring health outcomes were assessed multiple times up to age 16 years. The authors found that maternal BMI was positively associated with risk of asthma in both early childhood and adolescence. By contrast, maternal BMI was not associated with IgE sensitization, eczema, or rhinitis. A causal inference test indicated that the child's own overweight partly mediated the association between maternal obesity and offspring asthma at age 16 years. The authors concluded that obesity prevention strategies during maternal pre-pregnancy and early childhood might help to prevent childhood asthma.

A notable limitation of the new study is the availability of only one assessment of maternal BMI. Pregnancy is a time of major weight gain for many women – beyond the additional weight of the growing

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fetus and placenta – and the Swedish results invite questions about the impact of gestational weight gain (not just maternal BMI at week 10) on risk of offspring asthma. Along these lines, Danish investigators recently reported that both maternal BMI at week 16 and gestational weight gain were independent risk factors for offspring asthma [8]. Similar findings were reported by Dutch investigators for early childhood wheezing [9]. In turn, larger gestational weight gain is associated with increased BMI among offspring [10]. Taken together, these studies suggest the preventive value of moderating weight gain during pregnancy itself.

While it would be easy to recommend that pregnant women avoid 'high' BMI during pregnancy, obstetricians and mid-wives have provided inconsistent advice on this topic for decades; the optimal weight gain (or BMI at any given week) is not known. Anecdotally, for women who start pregnancy at normal weight, Boston obstetricians tend to recommend a 1–2 kg weight gain during the first trimester and then 0.5 kg per week during the rest of the pregnancy; this typically sums to a total weight gain of 12 to 15 kg at term. However, several medical textbooks and online parenting sources encourage gains of 10 to 20 kg; this 10-kg window translates into a substantial BMI difference, with likely implications for risk of offspring asthma. Although slightly different advice is given for women who start pregnancy underweight versus overweight, and for women with single versus twin gestations, the evidence base for all of these recommendations is sparse. What exactly are the short- and long-term health consequences of different maternal BMIs during pregnancy, for both the mother's health and for that of her offspring?

Although this uncertainty is disheartening, it does suggest 'equanimity' regarding the optimal weight gain during pregnancy and suggests an opportunity to perform a novel interventional study – namely, a trial that would randomly assign women in early pregnancy to different levels of weight gain for the purpose of studying the impact of gestational weight gain (and week-specific BMIs) on mother–child outcomes. Before committing to this ambitious trial, it would be very helpful to analyze existing databases to better under-

stand the weight gain advice given (if any) and the characteristics of women who gain small vs. large amounts during their pregnancy; analyses also should, of course, try to replicate and extend the previously cited findings on the link between large gestational weight gain and offspring asthma [8, 9]. If the observational data continue to support a hypothesis that specific levels of gestational weight gain are associated with lower or higher risk of offspring asthma, and that the most 'asthma protective' weight gain is not associated with unfavourable outcomes, these observational findings would support the further design and implementation of the proposed primary prevention trial.

Because the trial would involve two 'vulnerable' populations (pregnant women and young children), it would seem to require particularly stringent safety monitoring. Such concerns are mitigated, however, if the target weight gains lay within the very wide bounds of current recommendations and clinical practice. Another challenge would be the investigator's inability to double-blind the assigned group. Moreover, investigators would need to address the dietary and exercise changes that helped subjects to achieve their randomly assigned target weight gain as these weight-related factors could have their own independent effects on asthma risk [11]. Despite these challenges, the scientific advantages are compelling; pregnancy provides a unique situation where a broad range of weight gains is currently viewed as both healthy and desirable. Epidemiologic studies like the one by Ekstrom and colleagues [7] invite the scientific community to determine the gestational weight gain (and maternal BMI) that optimizes maternal and child health. The answer to this fundamental question will come from increased collaboration between observational and interventional researchers who work together to design randomized trials with multiple health outcomes, including asthma. These multidisciplinary, multi-purpose trials provide greater efficiency than the traditional, single-disease studies, and they are likely to be critical for our ongoing efforts to prevent childhood asthma.

Conflict of interest: The author declares no conflict of interest.

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