

Dietary Influences on Asthma: The Generational Impact of a Sweet Tooth?

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Asthma remains a complex disorder with a heterogeneous phenotype in childhood. Wheeze, one of the central features of asthma, may be transient, late onset, or persistent (1). The incidence of asthma and wheezing in childhood is high and is associated with substantial burden of illness. The etiology is almost certainly multifactorial, with varying degrees of evidence for allergen, hygiene, and diet hypotheses. Historically, the diet hypothesis has been supported by cross-sectional observational studies that have reported dietary salt intake, antioxidant vitamins, trace elements, and fish oil as potential influential risk factors for the asthma phenotype. In a seminal study, Bisgaard and colleagues (2) reported that supplementing mothers in the third trimester of pregnancy with n-3 long-chain polyunsaturated fatty acids reduced the risk of asthma or persistent wheeze in mid-childhood by 7%.

In this issue of the *AnnalsATS*, Wright and colleagues (pp. 217–224) weigh into further aspects of the diet hypotheses (3). They used data from Project Viva, a prospective birth cohort study, to test whether sugar-sweetened beverage and fructose intake among mothers during the first and second trimesters of their pregnancy, as well as the intake of these ingredients in early childhood (median age, 3.3 yr), were associated with an increased incidence of asthma and wheezing in mid-childhood (median age, 7.7 yr) (4). Asthma was defined as the child ever being diagnosed by a doctor combined with either use of asthma medications or reported wheezing in the previous 12 months.

Validated food frequency questionnaires were used to quantify the intake of sugar-sweetened beverages and fructose.

Adjusting for several important covariates, such as maternal smoking, parental asthma, obesity and sociodemographic variables, Wright and colleagues found that those consuming the highest quartile of sugar-sweetened beverages and total fructose intake in pregnancy had a greater risk of mid-childhood current asthma than those in the lowest quartile of intake (odds ratio, 1.95; 95% confidence interval, 1.21–3.15; and odds ratio, 1.57; 95% confidence interval, 0.95–2.58, for sweetened beverage and fructose intake, respectively) (3). Similarly, the highest quartile of early childhood sugar-sweetened beverage and total fructose intake was also associated with mid-childhood current asthma (odds ratio, 1.95; 95% confidence interval, 1.21–3.15; and odds ratio, 1.57; 95% confidence interval, 0.95–2.58, respectively).

Importantly, in adjusted models using splines for continuous variables, the relationship between sugar-sweetened beverage intake and mid-childhood asthma was somewhat linear, suggesting a dose–response relationship. The strengths of this study were the use of prospectively collected data in a large birth cohort and the use of rigorous methodology to quantify intake of sugar-sweetened beverages and total fructose intake.

Similar results were reported by Bédard and colleagues (5) in their Avon Longitudinal Study of Parents and Children. In this study, the association between maternal sugar-sweetened beverages and mid-childhood atopy and

asthma was evaluated. Compared with the lowest quintile of sugar-sweetened beverage consumption, mothers in the highest quintile had greater odds of having children with atopy (odds ratio, 1.38; 95% confidence interval, 1.06–1.78) and asthma (odds ratio, 2.01; 95% confidence interval, 1.23–3.29). In contrast to these studies, Maslova and colleagues (6), who also used a longitudinal cohort study design, failed to demonstrate any significant relationship between maternal consumption of sugar-sweetened beverage and childhood asthma. It may be argued that, compared with the Wright and colleagues (3) and Bédard and colleagues (5) studies, the consumption of sugar-sweetened beverages in the Maslova and colleagues (6) study was restrained in the entire cohort.

Dietary intake of monosaccharides such as fructose might contribute to asthma pathogenesis through one or more possible pathways. One hypothesis is the inflammatory model that proposes that a high-fructose diet increases oxidative-nitrosative stress, promoting an inflammatory cascade that is independent of adiposity. This hypothesis is supported by Singh and colleagues' (7) mouse model and Kierstein and colleagues' study in C57BL/6 mice (8). This hypothesis is supported by a randomized controlled study in healthy young men that demonstrated elevated levels of C-reactive protein in those allocated to a moderate to high intake of sugar-sweetened beverages (9).

Wright and colleagues reported that one of the inflammatory markers,

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high-sensitivity C-reactive protein, when adjusted for mid-childhood body mass index, was significantly elevated in children consuming high quantities of sugar-sweetened beverages and fructose in early childhood but failed to detect any such relationship with inflammatory markers when high consumption occurred during pregnancy (3). Another proposed mechanism is a fructose-induced elevation of uric acid levels with a positive feedback loop that promotes T-helper cell-mediated inflammation.

Whether this mechanism is relevant in the first two trimesters of pregnancy is yet to be determined. The timing is plausible, as the first two trimesters of pregnancy encompass the pseudoglandular period, where neuroepithelial cells expressing neuropeptides and transmitters such as serotonin and calcitonin-related peptides are increasingly noted. Importantly in this phase, smooth muscles adjacent to conducting airways develop. Although the role of airway smooth muscle is well defined in asthma and wheeze, it is not clear how maternal consumption of sugar-sweetened beverages can influence the pseudoglandular phase of development. The unremarkable inflammatory profile in those consuming high quantities of sugar-sweetened beverages adds to the

question of mechanism and warrants further investigation.

Finally, excess free fructose has been demonstrated to negatively influence circulating levels of soluble receptor for advanced glycation end products in adults with pulmonary emphysema. There is, however, currently no known mechanism by which this relationship might influence lung development *in utero*. Furthermore, although there is an association with atopy in early childhood, there is no evidence that offspring of mothers with gestational diabetes have an increased incidence of asthma.

This study by Wright and colleagues is highly instructive (3). There is a growing body of evidence in support of the diet hypothesis demonstrating intergenerational associations between high maternal consumption of sugar-sweetened beverages and total fructose and progeny with asthma and wheeze in middle childhood. These associations appear to be independent of smoking, obesity, and other recognized risk factors. The pathophysiology and mechanisms of these associations are yet to be elucidated, opening an exciting avenue for future investigation. Nevertheless, observational studies examining dietary intake must be interpreted cautiously, and these

findings should not prompt pregnant women or children to alter their fructose intake, nor should guidelines be developed on the basis of this and similar studies. Clearly the ethics and logistics of conducting an interventional, prospective randomized trial of reducing fructose intake to prevent asthma in children may be insurmountable challenges. Studying specific cohorts in whom sugar-sweetened beverages and total fructose intake are limited by necessity (for example, diabetes and hereditary fructose intolerance) may add useful information to this field of research. One could argue that to truly evaluate the diet hypothesis incorporating the best available evidence, such as the combined effect of n-3 long-chain polyunsaturated fatty acids, sugar-sweetened beverages, total fructose, and the like, within the context of daily living, a modified adaptive trial design or a “platform trial” (10) may yield much-needed information. The study by Wright and colleagues will, it is hoped, trigger much-needed pathophysiology research in the field of the diet hypothesis and childhood asthma (3). ■

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

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