Prenatal and Early-life Fructose, Fructose-containing Beverages, and Mid-Childhood Asthma

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At a Glance Commentary:

Scientific Knowledge on the Subject

Many studies have found links between obesity and asthma. Recent studies suggest that in addition to influencing asthma through increasing the risk of obesity, sugar sweetened beverages and high fructose intake may influence the risk of asthma at least in part through distinct mechanisms.

What This Study Adds to the Field

In a US pre-birth cohort, higher maternal intake of sugar sweetened beverages and child total fructose dietary intake were associated with greater odds of current asthma in mid-childhood.

Different sources of dietary fructose intake at different periods (in utero and early life) may influence childhood asthma development partly through mechanisms independent of maternal or child adiposity.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Background: Cross-sectional studies have linked intake of high fructose corn syrup sweetened beverages with asthma in school children.

Objective: To examine associations of maternal prenatal and early childhood intake of sugar sweetened beverages and fructose with current asthma in mid-childhood (median 7.7years).

Methods: We assessed maternal pregnancy (1st and 2nd trimester average) and child (median 3.3years) intake of sugar sweetened beverages and total fructose using food frequency questionnaires in 1068 mother-child pairs from Project Viva, a prospective pre-birth cohort. In a multivariable analysis, we examined associations of quartiles of maternal and child sugar sweetened beverage, juice, and total fructose intake with child current asthma in mid-childhood, assessed by questionnaire as ever doctor-diagnosed asthma plus taking asthma medications or reporting wheezing in the past 12months.

Results: Higher maternal pregnancy sugar sweetened beverage consumption (mean 0.6 servings/day; range 0-5) was associated with younger maternal age, non-white race/ethnicity, lower education and income, and higher pre-pregnancy BMI. Adjusting for pre-pregnancy BMI and other covariates, comparing quartile 4 v. quartile 1, higher maternal pregnancy intake of sugar sweetened beverages (OR 1.70; 95%CI 1.08, 2.67) and total fructose (OR 1.58; 0.98, 2.53) were associated with greater odds of mid-childhood current asthma (prevalence=19%). Higher early childhood fructose intake (quartile 4 v. quartile 1) was also associated with mid-childhood current asthma in models adjusted for maternal sugar sweetened beverages (OR 1.79; 1.07, 2.97) and after additional adjustment for mid-childhood BMI z-score (OR 1.77; 1.06, 2.95).

Conclusion: Higher sugar sweetened beverage and fructose intake during pregnancy and in early childhood was associated with childhood asthma development independent of adiposity.

Abstract word count: 250

The rise in childhood asthma prevalence in the United States occurring from the early 1980's onward is likely multifactorial, with both poor nutrition and excess adiposity hypothesized to be among the important contributors.[1 2-5] Concurrent with the rise in asthma has been increased caloric intake from added sugars, most notably in sugar sweetened beverages, which has been linked to the obesity epidemic.[6-9] Fructose, often in the form of high fructose corn syrup, is commonly added as a sweetener to sugar sweetened beverages (e.g. fruit drinks and soda).[10-13] Natural sources of dietary fructose include fruits and their juices.[10]

Many studies have found links between obesity or overweight and asthma, though the biologic mechanisms of these associations and their implications for asthma therapy are still imperfectly understood.[14] Recent studies suggest that in addition to influencing asthma through increasing the risk of obesity, high fructose intake may influence the risk of lung diseases at least in part through distinct mechanisms. Independent of elevated body mass index (BMI), high intakes of sugar sweetened beverages and fruit juices were cross-sectionally associated with higher asthma rates in 2 to 9 year-old children as well as with a higher prevalence of chronic obstructive pulmonary disease in adults in the 2003-2006 National Health and Nutrition Examination Survey (NHANES). In addition to their adiposity-related inflammatory potential,[15,16,17-21] beverages containing excess free fructose may have specific effects on the gut that may have downstream influences on the lung. Specifically, it has been hypothesized that excess free fructose increases intestinal formation and absorption of advanced glycation end products, which may interact with the receptor of advanced glycation end products, a potential mediator of [22-26] obstructive lung disease development.

Few groups have studied longitudinal associations of early life exposure to fructose and its beverage sources with asthma risk. Independently of sugar intake in early childhood, higher

maternal intake of free sugar during pregnancy was associated with increased risk of atopy and atopic asthma by age 7-9 years in the Avon Longitudinal Study of Parents and Children.[27] We hypothesized that during critical periods of lung and immune growth and development, higher maternal prenatal and early childhood intake of fructose and its beverage sources would be associated with increased asthma in mid-childhood, and that those associations would, in part, be independent of adiposity in the mother or child.

METHODS

Study design and subjects

Between 1999 and 2002 we recruited women into Project Viva in early pregnancy from eight obstetric offices of Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts.[22] Details of recruitment and retention are published.[22] Of the 2128 women who delivered a live singleton infant, we excluded from this analysis 195 with no maternal pregnancy or early childhood exposure data and 865 with no mid-childhood outcome data. Thus, our sample size for analysis was 1068 mother-child pairs. Compared with the 1068 participants in this analysis, the 1060 non-participants were somewhat less likely to have college-educated mothers (58% v. 71%) and to have annual household income exceeding $70,000 (54% v. 62%), and mean maternal age was slightly lower (31.1 v. 32.5 y). Maternal pre-pregnancy BMI (mean 25.2 v. 24.6 kg/m^2) and intake of pregnancy sugar-sweetened beverages (mean 0.7 v. 0.6 servings/day), however, were similar.

After obtaining written informed consent, we performed in-person study visits with participating mothers at the end of the 1st and 2nd trimesters of pregnancy and with mothers and children

during the first few days after delivery. We conducted in-persons visit with mothers and children in early childhood (median 3.3 y) and mid-childhood (median 7.7 y). The institutional review board of Harvard Pilgrim Health Care approved this study protocol.

Maternal prenatal and child dietary assessment of sugar sweetened beverage and fructose intake

We obtained data on consumption of beverages during pregnancy from semi-quantitative food frequency questionnaires (FFQ) that expectant mothers completed after the first and second research visits, at mean (SD) gestational ages of 11.9 (3.5) and 29.2 (2.6) weeks. Each of the two FFQs was slightly modified for use in pregnancy from a commonly used adult FFQ from which sugar sweetened beverage intake predicted a number of cardiometabolic outcomes.[28-32] Participants endorsed categories of frequency of beverage consumption from "never/less than 1 per month" to a maximum of "2 or more glasses per day" for some fruit juices, "4 or more cans per day" for soda, and "6 or more glasses per day" for water. The time referent for the 1st trimester FFQ was "during this pregnancy," that is, from the woman's last menstrual period until she completed the FFQ. For the 2nd trimester FFQ, the time referent was the previous 3 months. The FFQ included 3 questions on regular (sugary) soda intake, 3 questions on sugar-free soda, 5 questions on fruit juice, and 1 question on fruit drinks. We defined sugar-sweetened beverages as regular soda and fruit drinks.

We also assessed the children's dietary intakes using an 88-item semi-quantitative child FFQ previously validated among preschool-aged children, which was completed by the mothers in early childhood (median 3.3 years).[33] Participants endorsed categories of frequency of beverage consumption from "never" to a maximum of "5 or more times per day." The time referent was

"during the past month." The FFQ included 1 question on regular (sugary) soda intake, 1 questions on sugar-free soda, 2 questions on fruit juice (orange juice and other 100% juice), 1 question on fruit drinks, and 1 question on hot chocolate. We defined sugar-sweetened beverages as regular soda and fruit drinks.

Using the Harvard nutrition composition database (derived from the US Department of Agriculture and supplemented with information from manufacturers), we computed fructose intake by multiplying the frequency response of each item (foods and beverages) on the FFQ by the fructose content based on average serving size.[34]

Mid-childhood outcome – current asthma

On the mid-childhood questionnaire (median 7.7 years), we used asthma questions from the International Study of Asthma and Allergies in Childhood.[27] The main outcome was current asthma in mid-childhood, defined as mother's affirmative response to the child ever having a doctor-diagnosis of asthma, plus either report of wheezing or asthma medication use in the past 12 months, based on the mid-childhood questionnaire. The comparison group had no asthma diagnosis ever, and no wheezing or asthma medication use in the past 12 months.

In a supplementary analysis, we examined mid-childhood blood levels of high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and tumor necrosis factor receptor 2 (TNFR2) among 562 participants. We used an immunoturbidimetric high-sensitivity assay on a Hitachi 911 analyzer to determine hsCRP concentrations (Roche Diagnostics). We measured plasma IL-6 by enzyme-linked immunosorbent assay and we measured TNFR2 by ELISA (R&D).

Covariates

Using data from interviews and mailed questionnaires, we obtained information on maternal and child socio-demographics including maternal age, race/ethnicity, education, pregnancy smoking status, and household income and child sex and race/ethnicity. At the mid-childhood visit, trained research staff measured each child's height to the nearest 0.1 cm with a calibrated stadiometer (Shorr Productions, Olney, MD) and weight to the nearest 0.1 kg with a calibrated scale (Tanita model TBF-300A, Tanita Corporation of America, Inc., Arlington Heights, IL). We calculated age- and sex-specific body mass index (BMI, kg/m^2) z-scores using US national reference data.[35]

Statistical analysis

We used multivariable logistic regression models to examine associations of maternal pregnancy and early childhood sugar sweetened beverage, juice, and total fructose intake (by quartiles) with current asthma in mid-childhood. We also examined exposures as continuous variables. To assess the shape of the exposure-outcome associations, we fit generalized additive models with penalized splines for continuous exposures. Associations were similar for 1^{st} and 2^{nd} trimester maternal diet, so we averaged the two trimesters for analyses of prenatal dietary exposures. We built multivariable logistic regression models in which we adjusted for maternal education, smoking during pregnancy, and pre-pregnancy BMI; household income; and child sex, race/ethnicity, and exact age at the time of the mid-childhood assessment. We further adjusted models with early childhood exposures for mother's pregnancy sugar sweetened beverage intake. Adding other potentially confounding variables, including parental asthma and maternal gestational weight gain, diet quality score, and vitamin D intake, did not materially change the

observed associations, so we did not include them in our final models. In subsequent models, we also adjusted for mid-childhood BMI z-score, a potential mediator. We also implemented mediation analysis via the *mediation macro* developed by VanderWeele[36] to examine the extent to which the exposure – outcome associations were mediated through BMI z-score (indirect effect).

As a supplementary analysis, we used multivariable linear regression models, with the same exposures and covariates, and log transformed hsCRP, IL-6, and TNFR2 as continuous outcomes.

To increase sample size and reduce bias due to missing data, we imputed missing covariates. Using a chained equation multiple imputation method (PROC MI in SAS), we generated 50 imputed data sets including all Project Viva participants with live births (n = 2,128). The imputation model included all exposures, outcomes, and covariates under study, as well as additional potential predictors. In final analytic models, we combined imputed data sets using PROC MIANALYZE in SAS. Participants with missing exposure or outcome data for a given exposure–outcome analysis were excluded from that analysis. We conducted all analyses using SAS version 9.4 (SAS Institute, Cary NC) and R Version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Mean (SD) maternal age at enrollment was 32.5 (5.0) years and pre-pregnancy BMI was 24.6 (5.1) kg/m^2; 10% smoked during pregnancy, 71% were ≥college graduates, and 62% had household incomes >$70,000 per year. 51% of the children were female and 32% were non-

white. At mid-childhood, 19% of children had current asthma, 12% were obese (BMI ≥95th percentile for age and sex), and mean (SD) BMI z-score was 0.37 (0.99). (Table 1)

Correlates of higher pregnancy sugar sweetened beverage intake included younger maternal age, higher pre-pregnancy BMI, and smoking during pregnancy as well as indicators of disadvantage/lower SES including lower education and household income. Higher pregnancy sugar sweetened beverage intake was also correlated with child current asthma (15% in quartile (Q) 1 v. 27% in Q4) and BMI z-score (mean 0.30 units in Q1 v. 0.50 in Q4) in mid-childhood. Associations were similar for pregnancy fructose intake. (Table 1)

Mothers consumed mean (SD) 32.5 (10.2) grams/day of fructose in pregnancy and children consumed 27.8 (11.6) grams/day in early childhood. As illustrated in Supplementary Figure 1, the largest source of fructose-rich beverage intake was citrus juice for moms (0.8 [0.7] serving/day, range 0-4.4) and non-citrus juice for children (1.1 [1.1] servings/day, range 0-5.0). Mothers reported more sugar sweetened beverage intake in the form of soda and punch (0.6 [0.8] serving/day, range 0-5.1) compared to children (0.2 [0.5] serving/day, range 0-5.1).

In logistic regression models adjusted for socio-demographic variables and maternal pre-pregnancy BMI, comparing quartile 4 v. quartile 1, higher pregnancy intake of sugar sweetened beverages (OR 1.70; 95% CI, 1.08, 2.67) and total fructose (OR 1.58; 95% CI, 0.98, 2.53) were associated with greater odds of mid-childhood current asthma (Table 2). Associations of quartile 2 and quartile 3 v. quartile 1 were null with effect estimates close to 1.0. Covariate-adjusted spline models suggested that most of the studied exposure – current asthma associations were fairly linear (Figure 1A and 1B).

In models adjusted for maternal sugar sweetened beverages, comparing quartile 4 v. quartile 1, higher early childhood intake of total fructose (OR 1.79 95% CI, 1.07, 2.97) was associated with greater odds of mid-childhood current asthma. These results were almost the same after additionally adjusting for mid-childhood BMI z-score (OR 1.77; 95% CI, 1.06, 2.95). Results for early childhood sugar sweetened beverages were null before (OR 1.19; 95% CI 0.73, 1.93) and after (OR 1.20, 95% CI 0.74, 1.94) adjusting for mid-childhood BMI z-score. (Table 2) As shown in Table 2, ORs for early childhood fructose and current asthma were 1.51, 1.38, and 1.79 for quartiles 2, 3, and 4 v. quartile 1, respectively. The results from the Vanderweele *mediation macro*[36] confirmed that the exposure – outcome associations were not mediated through mid-childhood BMI z-score (ORs for the indirect effect were close to 1.0 and the CIs crossed 1.0).

In Supplementary Table 1 we show associations of maternal pregnancy and early childhood intake of sugar sweetened beverages, juice, and total fructose with hsCRP, IL-6, and TNFR2 levels (log transformed) in mid-childhood. In multivariable linear regression models, comparing quartile 4 v. quartile 1, higher early childhood intake of sugar sweetened beverages was associated with higher levels of log transformed hsCRP before (β 0.35 95% CI, -0.05, 0.74) and after (β 0.36 95% CI, -0.01, 0.74) adjusting for mid-childhood BMI z-score, although CIs were wide and crossed 0. All other associations were null. (Supplementary Table 1) We also examined associations of maternal prenatal and child fructose intake with mid-childhood plasma leptin and adiponectin, but both were null.

DISCUSSION

Higher intake of fructose containing beverages or total nutrient fructose in the prenatal and early childhood periods was associated with greater odds of later childhood asthma in our

pre-birth cohort. While sugar sweetened beverages as well as juices were significant sources of fructose for the mothers, the primary source of fructose in early childhood was fruit juice. The American Academy of Pediatrics recommends consumption of no more than 4 to 6 ounces (approximately one to two servings) per day of fruit juice for children 1 to 6 years old.[37] In the highest quartile of fruit juice consumption in our cohort, children were drinking a mean of 3.9 servings (range 3 to 10 servings) per day.

In addition to assessing the influence of sugar sweetened beverage intake on asthma, we focused on dietary fructose intake because (1) it is a major contributor to total sugar intake,[10] (2) for many pregnant women and most small children, sugar sweetened beverages may not be the primary contributor to total fructose or sugar intake and, (3) there is biologic evidence that fructose may have specific airway effects (see below).

Higher intake of sugar sweetened beverages and fructose may influence asthma either through increasing adiposity, and adiposity related pulmonary restriction and inflammation, or through adiposity-independent mechanisms.[16] In a mouse model, Singh and colleagues found that high-fat or high-fructose-diet led to reduced nitric oxide related bronchodilation and increased oxo-nitrosative stress without evidence for inflammatory cell infiltrate or goblet cell metaplasia, supporting the hypothesis that high-fructose diet could influence asthma through adiposity-independent mechanisms.[26] Mediation analyses suggested that child BMI did not mediate the associations of prenatal or early childhood consumption of fructose with mid-childhood risk of asthma.

Murine model studies support the hypothesis that there are direct as well as adiposity-mediated inflammatory effects of sugars, including fructose, on the airways as well as other

target organs.[17-21, 38, 39] In a short overnight study of C57BL/6 mice, Kierstein and colleagues[39] suggested a direct effect of high sugar consumption, which increased susceptibility to allergic airway inflammation and activation of the innate immune system in part through impairment of carbohydrate recognition surfactant protein D (SP-D) which is immunoprotective and prevents pulmonary inflammation.[39] Dietary fructose has also been specifically and directly implicated in upregulation of lung inflammation[23] through the influences of excess free fructose on the receptor of advanced glycation end products in the lung.[40] This evidence is stronger, however for inflammation related to COPD than for asthma.

That is not to discount potential obesity-mediated effects. A short-term rodent model study of combined diet and pollution exposure conducted by Sun and colleagues[16] suggested an adiposity-mediated effect of fructose. Rats fed a high fructose diet and exposed to ozone had higher macrophage infiltrates in adipose tissue with upregulation of proinflammatory genes and downregulation of anti-inflammatory genes.

We further pursued evidence for the biologic plausibility that the association we found between intake of sugar sweetened beverages/fructose and asthma could relate to upregulation of adiposity-related innate cytokines and biomarkers of inflammation. We examined, but did not find associations of maternal prenatal or early childhood intake of sugar sweetened beverages, juice, and total fructose with peripheral blood levels of hsCRP, IL-6, and TNFR2 measured in the children at the mid-childhood visit. As the inflammatory influences of fructose may have occur in the lung compartment, but not systemically or may have occurred at an earlier point in time not captured by our measurements, the absence of association prior intake of fructose with these systemic markers years later does not exclude the possibility that fructose had caused innate cytokine/adipokine-mediated inflammation specific to the airways.[39]

A strength of Project Viva is our longitudinal study design, which included collection of detailed dietary data both during pregnancy and early childhood. These are life-stages critical for immune and lung development, and therefore for the early origins of asthma.[41, 42] In contrast with our longitudinal study design, most previous studies of associations of sources of fructose intake with asthma have been cross-sectional, focused on older children and adults, and focused on soda or sugar sweetened beverages without comprehensive dietary data on other sources of fructose, including juice or fruit consumption. In a nationally representative sample of 15,960 US high school students, Park et. al[43] found that participants who consumed more soda (2 or more servings per day) had greater odds of asthma compared to those who reported no soda intake (adjusted OR 1.28; 95% CI, 1.02, 1.62) and this association was independent of obesity.[43] In an Australian study of people 16 years of age and older, Shi et. al [44] reported that higher sugar sweetened beverage consumption (reported intake of ½ liter or more daily) was associated with greater odds of asthma compared to those who did not report sugar sweetened beverage consumption (adjusted OR 1.26; 95% CI, 1.01, 1.58). DeChristopher et. al[23] conducted a more comprehensive cross-sectional evaluation of associations of fructose containing beverages with asthma in children 2-9 years of age evaluated in NHANES during 2003-2006. Higher excess free fructose beverage intake [apple juice and sugar sweetened beverages (non-diet soft drinks and fruit drinks)] was associated with greater odds of asthma. After controlling for other beverage intake, higher apple juice intake by itself (≥5 times per week compared to ≤1 time per month was also associated with higher asthma prevalence.[23]

One of the few longitudinal studies of maternal sugar sweetened beverage ingestion and childhood asthma risk was conducted by Maslova and colleagues[45]. In adjusted analyses, this study of 60,466 Danish mother-child pairs did not find associations of maternal prenatal sugar

sweetened beverage intake with childhood asthma at age 7 years (OR 1.07; 95% CI 0.90, 1.28). The null findings of this study may have been limited by the low consumption of sugar sweetened beverages.[45] Our study include a relatively wide range of sugar sweetened beverage consumption and BMI. In addition, the relatively large sample size allowed us to evaluate independent associations of prenatal and early childhood intake of sugar sweetened beverages, juice, and total fructose intake with mid-childhood asthma.

While there is diversity in income and socioeconomic status in Project Viva, a limitation of our cohort is that it is relatively advantaged. Our results may not be generalizable to more socio-economically disadvantaged populations. Loss to follow-up, although regrettable, is common in cohort studies in early life. We observed some differences in baseline covariates between participants and those lost to follow-up, but we did not observe differences in maternal sugar sweetened beverage intake. Furthermore, sugar sweetened beverage intake was self-reported, and there may have been inaccuracy in assessment because of recall, social desirability, or other biases. Nevertheless, we anticipate that ranking was preserved within the cohort as relative disadvantage (lower income, less education) was associated with higher sugar sweetened beverage intake. Higher parental and child intake of sugar sweetened beverage intake, including intake of sweetened juices,[46] has been described as a contributor to the higher prevalence of obesity in disadvantaged populations.[6] Policy discussions are ongoing at the national as well as local Boston level as to how to reduce total sugary drink intake, in part by increasing access to affordable healthier choices of drinks.[1, 47] These discussions include consideration of the harms and benefits of fruit juice, which contains both sugars that may be obesogenic as well as antioxidants and other healthy components.[48, 49 1, 47]

In conclusion, in our cohort, maternal prenatal sugar sweetened beverage intake and early childhood total fructose intake were associated with asthma in mid-childhood. Our findings contribute to the literature that should be considered when developing recommendations regarding consumption and availability of these drinks during pregnancy and early childhood. Further evaluation of potential mechanisms for influences total fructose with asthma development is warranted, including further assessment of effects of fructose and fructose metabolites on airway inflammation or hyper-reactivity that may be independent of obesity.

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Table 1. Characteristics of mother-child pairs according to quartiles of maternal pregnancy (1st and 2nd trimester average) sugar sweetened beverages and total fructose intake (N=1068)

		Maternal sugar sweetened beverage intake				Maternal total fructose intake			
	Total n=1068	**Q1** n=283	**Q2** n=251	**Q3** n=260	**Q4** n=259	**Q1** n=257	**Q2** n=267	**Q3** n=277	**Q4** n=252
					N (%) or mean (SD)				
Maternal characteristics									
Age (years)	32.5 (5.0)	34.0 (4.4)	33.3 (4.7)	32.2 (4.7)	30.5 (5.4)	33.5 (4.6)	32.7 (4.9)	32.6 (4.9)	31.2 (5.2)
Education, %									
. <College graduate	306 (29)	50 (18)	68 (27)	66 (25)	114 (44)	65 (25)	75 (28)	70 (25)	88 (35)
. ≥College graduate	762 (71)	233 (82)	183 (73)	194 (75)	145 (56)	192 (75)	192 (72)	207 (75)	164 (65)
Household income, %									
. ≤$70,000	402 (38)	82 (29)	91 (36)	96 (37)	125 (48)	83 (32)	96 (36)	105 (38)	110 (44)
. >$70,000	666 (62)	201 (71)	160 (64)	164 (63)	134 (52)	174 (68)	171 (64)	172 (62)	142 (56)
Pregnancy smoking status, %									
. Never	750 (70)	199 (70)	183 (73)	180 (69)	176 (68)	172 (67)	174 (65)	199 (72)	193 (77)
. Former	214 (20)	61 (22)	55 (22)	58 (22)	40 (15)	61 (24)	65 (24)	51 (19)	37 (15)
. During pregnancy	104 (10)	23 (8)	13 (5)	22 (8)	43 (17)	24 (9)	28 (10)	27 (10)	22 (9)
Pre-pregnancy BMI (kg/m^2)	24.6 (5.1)	23.7 (4.4)	24.2 (4.5)	25.0 (5.5)	25.5 (5.6)	24.8 (5.3)	24.2 (4.8)	24.6 (5.3)	24.6 (4.8)
Pregnancy weight gain (kg)	15.6 (5.3)	15.7 (4.8)	16.2 (5.1)	15.2 (5.2)	15.1 (6.1)	15.6 (5.3)	15.5 (5.5)	16.0 (5.0)	15.2 (5.5)
Child characteristics									
Sex, %									
. Male	522 (49)	134 (47)	126 (50)	123 (47)	131 (51)	126 (49)	132 (49)	124 (45)	132 (52)

. Female	546 (51)	149 (53)	125 (50)	137 (53)	128 (49)	131 (51)	135 (51)	153 (55)	120 (48)
Race/ethnicity, %									
. Black	148 (14)	22 (8)	30 (12)	36 (14)	55 (21)	20 (8)	33 (12)	47 (17)	43 (17)
. Hispanic	39 (4)	7 (2)	7 (3)	10 (4)	14 (5)	7 (3)	4 (1)	12 (4)	15 (6)
. White	722 (68)	202 (71)	176 (70)	183 (70)	155 (60)	190 (74)	180 (67)	191 (69)	155 (62)
. Other	159 (15)	52 (18)	38 (15)	31 (12)	35 (14)	40 (16)	50 (19)	27 (10)	39 (15)
Mid-childhood (median 7.7 years)									
BMI z-score	0.37 (0.99)	0.30 (0.98)	0.28 (0.87)	0.40 (1.02)	0.50 (1.06)	0.38 (0.95)	0.35 (0.99)	0.36 (0.98)	0.38 (1.03)
Current asthma, %									
. No	868 (81)	240 (85)	211 (84)	218 (84)	188 (73)	220 (86)	220 (82)	226 (82)	191 (76)
. Yes	200 (19)	43 (15)	40 (16)	42 (16)	71 (27)	37 (14)	47 (18)	51 (18)	61 (24)

Table 2. Associations of maternal pregnancy (1st and 2nd trimester average) and early childhood sugar sweetened beverage, juice, and total fructose intake (continuous and Quartiles 2, 3, and 4 v. Quartile 1) with current asthma in mid-childhood.

Exposures	N	Model 0 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Maternal prenatal				
Sugar sweetened beverages	1053			
Continuous servings/day		1.36 (1.13, 1.63)	1.20 (0.98, 1.47)	1.18 (0.96, 1.45)
Quartiles (v. Quartile 1)				
. Quartile 2		1.06 (0.66, 1.69)	1.01 (0.62, 1.63)	1.02 (0.63, 1.66)
. Quartile 3		1.08 (0.68, 1.71)	0.97 (0.60, 1.56)	0.96 (0.59, 1.56)
. Quartile 4		2.11 (1.38, 3.22)	1.70 (1.08, 2.67)	1.68 (1.07, 2.65)
Juice	1053			
Continuous servings/day		1.22 (1.04, 1.43)	1.11 (0.94, 1.32)	1.12 (0.95, 1.33)
Quartiles (v. Quartile 1)				
. Quartile 2		0.83 (0.52, 1.31)	0.92 (0.57, 1.48)	0.90 (0.56, 1.46)
. Quartile 3		0.95 (0.60, 1.49)	0.87 (0.54, 1.40)	0.89 (0.55, 1.42)
. Quartile 4		1.40 (0.91, 2.14)	1.27 (0.81, 1.99)	1.31 (0.83, 2.05)
Total fructose	1053			
Continuous 15 grams/day		1.35 (1.08, 1.69)	1.19 (0.94, 1.50)	1.18 (0.94, 1.50)
Quartiles (v. Quartile 1)				
. Quartile 2		1.27 (0.79, 2.03)	1.27 (0.78, 2.06)	1.27 (0.78, 2.06)
. Quartile 3		1.34 (0.85, 2.13)	1.19 (0.73, 1.93)	1.20 (0.74, 1.95)
. Quartile 4		1.90 (1.21, 2.98)	1.58 (0.98, 2.53)	1.60 (0.99, 2.57)
Early childhood				
Sugar sweetened beverages	924			
Continuous servings/day		1.43 (1.09, 1.87)	1.09 (0.79, 1.49)	1.07 (0.78, 1.48)
Quartiles (v. Quartile 1)				
. Quartile 2		1.11 (0.68, 1.82)	0.96 (0.58, 1.61)	0.96 (0.58, 1.61)
. Quartile 3		0.99 (0.59, 1.68)	0.71 (0.40, 1.24)	0.73 (0.41, 1.29)
. Quartile 4		1.79 (1.18, 2.70)	1.19 (0.73, 1.93)	1.20 (0.74, 1.94)
Juice	924			
Continuous servings/day		1.12 (1.00, 1.26)	1.10 (0.97, 1.23)	1.10 (0.98, 1.24)
Quartiles (v. Quartile 1)				
. Quartile 2		1.19 (0.77, 1.84)	1.20 (0.76, 1.89)	1.24 (0.79, 1.95)
. Quartile 3		0.81 (0.47, 1.41)	0.70 (0.39, 1.25)	0.69 (0.39, 1.24)
. Quartile 4		1.50 (0.95, 2.36)	1.49 (0.93, 2.40)	1.53 (0.95, 2.47)
Total fructose	924			
Continuous 15 grams/day		1.20 (0.97, 1.48)	1.16 (0.93, 1.45)	1.16 (0.93, 1.45)
Quartiles (v. Quartile 1)				
. Quartile 2		1.62 (0.98, 2.68)	1.51 (0.90, 2.54)	1.48 (0.87, 2.49)
. Quartile 3		1.42 (0.85, 2.37)	1.38 (0.81, 2.36)	1.34 (0.78, 2.30)

. Quartile 4	1.93 (1.18, 3.15)	1.79 (1.07, 2.97)	1.77 (1.06, 2.95)

Model 0. Unadjusted

Model 1. Adjusted for maternal education, smoking during pregnancy, and pre-pregnancy body mass index; household income; and child age, sex, and race/ethnicity.

Early childhood exposures additionally adjusted for mother's sugar sweetened beverage intake (1^{st} and 2^{nd} trimester average).

Model 2. Model 1 additionally adjusted for child body mass index z-score in mid-childhood.

Figure 1. General additive models (splines) illustrating associations of maternal pregnancy and early childhood sugar sweetened beverage, juice, and total fructose intake with current asthma in mid-childhood (log-scale odds ratios and 95% CIs).

Figure 1 footnote. Adjusted for maternal education, smoking during pregnancy, and pre-pregnancy body mass index; household income; and child age, sex, and race/ethnicity. Early childhood exposures additionally adjusted for mother's sugar sweetened beverage intake (1st and 2nd trimester average).