

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

1 **Abstract**

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

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

6 Methods: We assessed maternal pregnancy (1st and 2nd trimester average) and child (median
7 3.3years) intake of sugar sweetened beverages and total fructose using food frequency
8 questionnaires in 1068 mother-child pairs from Project Viva, a prospective pre-birth cohort. In a
9 multivariable analysis, we examined associations of quartiles of maternal and child sugar
10 sweetened beverage, juice, and total fructose intake with child current asthma in mid-childhood,
11 assessed by questionnaire as ever doctor-diagnosed asthma plus taking asthma medications or
12 reporting wheezing in the past 12months.

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

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

24

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

34 Many studies have found links between obesity or overweight and asthma, though the biologic
35 mechanisms of these associations and their implications for asthma therapy are still imperfectly
36 understood.¹⁴ Recent studies suggest that in addition to influencing asthma through increasing
37 the risk of obesity, high fructose intake may influence the risk of lung diseases at least in part
38 through distinct mechanisms. Independent of elevated body mass index (BMI), high intakes of
39 sugar sweetened beverages and fruit juices were cross-sectionally associated with higher asthma
40 rates in 2 to 9 year-old children as well as with a higher prevalence of chronic obstructive
41 pulmonary disease in adults in the 2003-2006 National Health and Nutrition Examination Survey
42 (NHANES). In addition to their adiposity-related inflammatory potential,^{15,16,17-21} beverages
43 containing excess free fructose may have specific effects on the gut that may have downstream
44 influences on the lung. Specifically, it has been hypothesized that excess free fructose increases
45 intestinal formation and absorption of advanced glycation end products, which may interact with
46 the receptor of advanced glycation end products, a potential mediator of²²⁻²⁶ obstructive lung
47 disease development.

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

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

56 **METHODS**

57 **Study design and subjects**

58 Between 1999 and 2002 we recruited women into Project Viva in early pregnancy from eight
59 obstetric offices of Atrius Harvard Vanguard Medical Associates, a multi-specialty group
60 practice in eastern Massachusetts.²² Details of recruitment and retention are published.²² Of the
61 2128 women who delivered a live singleton infant, we excluded from this analysis 195 with no
62 maternal pregnancy or early childhood exposure data and 865 with no mid-childhood outcome
63 data. Thus, our sample size for analysis was 1068 mother-child pairs. Compared with the 1068
64 participants in this analysis, the 1060 non-participants were somewhat less likely to have college-
65 educated mothers (58% v. 71%) and to have annual household income exceeding \$70,000 (54%
66 v. 62%), and mean maternal age was slightly lower (31.1 v. 32.5 y). Maternal pre-pregnancy
67 BMI (mean 25.2 v. 24.6 kg/m²) and intake of pregnancy sugar-sweetened beverages (mean 0.7 v.
68 0.6 servings/day), however, were similar.

69
70 After obtaining written informed consent, we performed in-person study visits with participating
71 mothers at the end of the 1st and 2nd trimesters of pregnancy and with mothers and children

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

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

77 We obtained data on consumption of beverages during pregnancy from semi-quantitative food
78 frequency questionnaires (FFQ) that expectant mothers completed after the first and second
79 research visits, at mean (SD) gestational ages of 11.9 (3.5) and 29.2 (2.6) weeks. Each of the two
80 FFQs was slightly modified for use in pregnancy from a commonly used adult FFQ from which
81 sugar sweetened beverage intake predicted a number of cardiometabolic outcomes²⁸⁻³²
82 Participants endorsed categories of frequency of beverage consumption from “never/less than 1
83 per month” to a maximum of “2 or more glasses per day” for some fruit juices, “4 or more cans
84 per day” for soda, and “6 or more glasses per day” for water. The time referent for the 1st
85 trimester FFQ was “during this pregnancy,” that is, from the woman’s last menstrual period until
86 she completed the FFQ. For the 2nd trimester FFQ, the time referent was the previous 3 months.
87 The FFQ included 3 questions on regular (sugary) soda intake, 3 questions on sugar-free soda, 5
88 questions on fruit juice, and 1 question on fruit drinks. We defined sugar-sweetened beverages as
89 regular soda and fruit drinks.

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

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

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

102 **Mid-childhood outcome – current asthma**

103 On the mid-childhood questionnaire (median 7.7 years), we used asthma questions from the
104 International Study of Asthma and Allergies in Childhood.²⁷ The main outcome was current
105 asthma in mid-childhood, defined as mother’s affirmative response to the child ever having a
106 doctor-diagnosis of asthma, plus either report of wheezing or asthma medication use in the past
107 12 months, based on the mid-childhood questionnaire. The comparison group had no asthma
108 diagnosis ever, and no wheezing or asthma medication use in the past 12 months.

109
110 In a supplementary analysis, we examined mid-childhood blood levels of high sensitivity C-
111 reactive protein (hsCRP), interleukin 6 (IL-6), and tumor necrosis factor receptor 2 (TNFR2)
112 among 562 participants. We used an immunoturbidimetric high-sensitivity assay on a Hitachi
113 911 analyzer to determine hsCRP concentrations (Roche Diagnostics). We measured plasma IL-
114 6 by enzyme-linked immunosorbent assay and we measured TNFR2 by ELISA (R&D).

115

116 **Covariates**

117 Using data from interviews and mailed questionnaires, we obtained information on maternal and
118 child socio-demographics including maternal age, race/ethnicity, education, pregnancy smoking
119 status, and household income and child sex and race/ethnicity. At the mid-childhood visit,
120 trained research staff measured each child's height to the nearest 0.1 cm with a calibrated
121 stadiometer (Shorr Productions, Olney, MD) and weight to the nearest 0.1 kg with a calibrated
122 scale (Tanita model TBF-300A, Tanita Corporation of America, Inc., Arlington Heights, IL). We
123 calculated age- and sex-specific body mass index (BMI, kg/m²) z-scores using US national
124 reference data.³⁵

125 **Statistical analysis**

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

138 observed associations, so we did not include them in our final models. In subsequent models, we
139 also adjusted for mid-childhood BMI z-score, a potential mediator. We also implemented
140 mediation analysis via the *mediation macro* developed by VanderWeele³⁶ to examine the extent
141 to which the exposure – outcome associations were mediated through BMI z-score (indirect
142 effect).

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

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

155 **RESULTS**

156 Mean (SD) maternal age at enrollment was 32.5 (5.0) years and pre-pregnancy BMI was 24.6
157 (5.1) kg/m²; 10% smoked during pregnancy, 71% were \geq college graduates, and 62% had
158 household incomes $>$ \$70,000 per year. 51% of the children were female and 32% were non-

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

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

167 Mothers consumed mean (SD) 32.5 (10.2) grams/day of fructose in pregnancy and children
168 consumed 27.8 (11.6) grams/day in early childhood. As illustrated in Supplementary Figure 1,
169 the largest source of fructose-rich beverage intake was citrus juice for moms (0.8 [0.7]
170 serving/day, range 0-4.4) and non-citrus juice for children (1.1 [1.1] servings/day, range 0-5.0).
171 Mothers reported more sugar sweetened beverage intake in the form of soda and punch (0.6 [0.8]
172 serving/day, range 0-5.1) compared to children (0.2 [0.5] serving/day, range 0-5.1).
173

174 In logistic regression models adjusted for socio-demographic variables and maternal pre-
175 pregnancy BMI, comparing quartile 4 v. quartile 1, higher pregnancy intake of sugar sweetened
176 beverages (OR 1.70; 95% CI, 1.08, 2.67) and total fructose (OR 1.58; 95% CI, 0.98, 2.53) were
177 associated with greater odds of mid-childhood current asthma (Table 2). Associations of quartile
178 2 and quartile 3 v. quartile 1 were null with effect estimates close to 1.0. Covariate-adjusted
179 spline models suggested that most of the studied exposure – current asthma associations were
180 fairly linear (Figure 1A and 1B).

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

191
192 In Supplementary Table 1 we show associations of maternal pregnancy and early childhood
193 intake of sugar sweetened beverages, juice, and total fructose with hsCRP, IL-6, and TNFR2
194 levels (log transformed) in mid-childhood. In multivariable linear regression models, comparing
195 quartile 4 v. quartile 1, higher early childhood intake of sugar sweetened beverages was
196 associated with higher levels of log transformed hsCRP before (β 0.35 95% CI, -0.05, 0.74) and
197 after (β 0.36 95% CI, -0.01, 0.74) adjusting for mid-childhood BMI z-score, although CIs were
198 wide and crossed 0. All other associations were null. (Supplementary Table 1) We also examined
199 associations of maternal prenatal and child fructose intake with mid-childhood plasma leptin and
200 adiponectin, but both were null.

201 **DISCUSSION**

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

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

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

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

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

226 target organs.^{17-21, 38, 39} In a short overnight study of C57BL/6 mice, Kierstein and colleagues³⁹
227 suggested a direct effect of high sugar consumption, which increased susceptibility to allergic
228 airway inflammation and activation of the innate immune system in part through impairment of
229 carbohydrate recognition surfactant protein D (SP-D) which is immunoprotective and prevents
230 pulmonary inflammation.³⁹ Dietary fructose has also been specifically and directly implicated in
231 upregulation of lung inflammation²³ through the influences of excess free fructose on the
232 receptor of advanced glycation end products in the lung.⁴⁰ This evidence is stronger, however for
233 inflammation related to COPD than for asthma.

234 That is not to discount potential obesity-mediated effects. A short-term rodent model
235 study of combined diet and pollution exposure conducted by Sun and colleagues¹⁶ suggested an
236 adiposity-mediated effect of fructose. Rats fed a high fructose diet and exposed to ozone had
237 higher macrophage infiltrates in adipose tissue with upregulation of proinflammatory genes and
238 downregulation of anti-inflammatory genes.

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

249 A strength of Project Viva is our longitudinal study design, which included collection of
250 detailed dietary data both during pregnancy and early childhood. These are life-stages critical for
251 immune and lung development, and therefore for the early origins of asthma.^{41, 42} In contrast with
252 our longitudinal study design, most previous studies of associations of sources of fructose intake
253 with asthma have been cross-sectional, focused on older children and adults, and focused on soda
254 or sugar sweetened beverages without comprehensive dietary data on other sources of fructose,
255 including juice or fruit consumption. In a nationally representative sample of 15,960 US high
256 school students, Park et. al⁴³ found that participants who consumed more soda (2 or more
257 servings per day) had greater odds of asthma compared to those who reported no soda intake
258 (adjusted OR 1.28; 95% CI, 1.02, 1.62) and this association was independent of obesity.⁴³ In an
259 Australian study of people 16 years of age and older, Shi et. al⁴⁴ reported that higher sugar
260 sweetened beverage consumption (reported intake of ½ liter or more daily) was associated with
261 greater odds of asthma compared to those who did not report sugar sweetened beverage
262 consumption (adjusted OR 1.26; 95% CI, 1.01, 1.58). DeChristopher et. al²³ conducted a more
263 comprehensive cross-sectional evaluation of associations of fructose containing beverages with
264 asthma in children 2-9 years of age evaluated in NHANES during 2003-2006. Higher excess
265 free fructose beverage intake [apple juice and sugar sweetened beverages (non-diet soft drinks
266 and fruit drinks)] was associated with greater odds of asthma. After controlling for other
267 beverage intake, higher apple juice intake by itself (≥ 5 times per week compared to ≤ 1 time per
268 month was also associated with higher asthma prevalence.²³

269 One of the few longitudinal studies of maternal sugar sweetened beverage ingestion and
270 childhood asthma risk was conducted by Maslova and colleagues⁴⁵. In adjusted analyses, this
271 study of 60,466 Danish mother-child pairs did not find associations of maternal prenatal sugar

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

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

294 In conclusion, in our cohort, maternal prenatal sugar sweetened beverage intake and early
295 childhood total fructose intake were associated with asthma in mid-childhood. Our findings
296 contribute to the literature that should be considered when developing recommendations
297 regarding consumption and availability of these drinks during pregnancy and early childhood.
298 Further evaluation of potential mechanisms for influences total fructose with asthma
299 development is warranted, including further assessment of effects of fructose and fructose
300 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)
<i>Race/ethnicity, %</i>									
. 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)
<i>Mid-childhood (median 7.7 years)</i>									
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)
<i>Current asthma, %</i>									
. 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)

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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)
<i>Maternal prenatal</i>				
Sugar sweetened beverages	1053			
Continuous servings/day Quartiles (v. Quartile 1)		1.36 (1.13, 1.63)	1.20 (0.98, 1.47)	1.18 (0.96, 1.45)
. 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 Quartiles (v. Quartile 1)		1.22 (1.04, 1.43)	1.11 (0.94, 1.32)	1.12 (0.95, 1.33)
. 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 Quartiles (v. Quartile 1)		1.35 (1.08, 1.69)	1.19 (0.94, 1.50)	1.18 (0.94, 1.50)
. 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)
<i>Early childhood</i>				
Sugar sweetened beverages	924			
Continuous servings/day Quartiles (v. Quartile 1)		1.43 (1.09, 1.87)	1.09 (0.79, 1.49)	1.07 (0.78, 1.48)
. 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 Quartiles (v. Quartile 1)		1.12 (1.00, 1.26)	1.10 (0.97, 1.23)	1.10 (0.98, 1.24)
. 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 Quartiles (v. Quartile 1)		1.20 (0.97, 1.48)	1.16 (0.93, 1.45)	1.16 (0.93, 1.45)
. 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 (1st and 2nd trimester average).

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

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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).

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