

Excess free fructose, high-fructose corn syrup and adult asthma: the Framingham Offspring Cohort

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(Submitted 18 October 2017 – Final revision received 5 January 2018 – Accepted 22 January 2018 – First published online 28 March 2018)

Abstract

There is growing evidence that intakes of high-fructose corn syrup (HFCS), HFCS-sweetened soda, fruit drinks and apple juice – a high-fructose 100% juice – are associated with asthma, possibly because of the high fructose:glucose ratios and underlying fructose malabsorption, which may contribute to enteral formation of pro-inflammatory advanced glycation end products, which bind receptors that are mediators of asthma. Cox proportional hazards models were used to assess associations between intakes of these beverages and asthma risk, with data from the Framingham Offspring Cohort. Diet soda and orange juice – a 100% juice with a 1:1 fructose:glucose ratio – were included for comparison. Increasing intake of any combination of HFCS-sweetened soda, fruit drinks and apple juice was significantly associated with progressively higher asthma risk, plateauing at 5–7 times/week *v.* never/seldom, independent of potential confounders (hazard ratio 1.91, $P < 0.001$). About once a day consumers of HFCS-sweetened soda had a 49% higher risk ($P < 0.011$), moderate apple juice consumers (2–4 times/week) had a 61% higher risk ($P < 0.007$) and moderate fruit drink consumers had a 58% higher risk ($P < 0.009$), as compared with never/seldom consumers. There were no associations with diet soda/orange juice. These associations are possibly because of the high fructose:glucose ratios, and fructose malabsorption. Recommendations to reduce consumption may be inadequate to address asthma risk, as associations are evident even with moderate intake of these beverages, including apple juice – a 100% juice. The juice reductions in the US Special Supplemental Nutrition Program for Women, Infants, and Children in 2009, and the plateauing/decreasing asthma prevalence (2010–2013), particularly among non-Hispanic black children, may be related. Further research regarding the consequences of fructose malabsorption is needed.

Keywords: Glycation: Excess free fructose: High-fructose corn syrup: Fructositis: Receptor of advanced glycation endproducts: Apple juice: Fruit drinks

There is growing evidence that intakes of high-fructose corn syrup (HFCS)⁽¹⁾, HFCS-sweetened soft drinks^(2–5) and fruit drinks^(3,4) are associated with asthma. Results of a rigorous food elimination diet with HFCS⁽¹⁾ – a scientifically recognised method to assess food sensitivity recommended by a panel of experts, established by the National Institute of Allergy and Infectious Diseases, often referred to as ‘the Guidelines’⁽⁶⁾ – provided evidence that intake of HFCS-sweetened foods and beverages is associated with airway mucus hypersecretion, asthma, chronic bronchitis and idiopathic joint pain⁽¹⁾. Recent epidemiological studies, by the US Centers for Disease Control (CDC), provided evidence that US high-schoolers (n 15 960)⁽²⁾ who regularly consumed HFCS-sweetened soda were 64% more likely to have asthma than never consumers, independent of smoking and BMI. Researchers suggested that the link may

be because of the preservatives, on the basis of their review of prior research⁽²⁾. However, a review of these prior studies showed no strong scientific evidence that preservatives in soda are associated with chronic respiratory conditions⁽⁷⁾. Importantly, the preservatives in HFCS-sweetened soda are also in diet soda, and diet soda *has not* been found to be associated with asthma⁽⁷⁾. Other epidemiological research studies are consistent with the possibility that the associations may be with the HFCS in US soft drinks. For example, in New Zealand, soda is sweetened with sucrose⁽⁸⁾, and in a 2005 study (the International Study of Asthma and Allergies in Childhood) researchers found no association between ‘fizzy’ drinks and asthma⁽⁹⁾. In an Australian study (where soda is sweetened with sucrose), intake (>0.5 litre/d) of soft drinks was associated with asthma, among current smokers. There were no associations

Abbreviations: AGE, advanced glycation end products; CDC, US Centers for Disease Control; EFF, excess free fructose; enFruAGE, extracellular newly identified fructose associated advanced glycation end products; FHS-OS, Framingham Heart Study Original-Cohort Study; HFCS, high-fructose corn syrup; HR, hazard ratio; NHANES, (US) National Health and Nutrition Examination Survey; SSB, sugar-sweetened beverages; T2D, type 2 diabetes.

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among non/ex-smokers, suggesting that the link was due to smoking rather than the soda (smokers may have been more likely to drink soda than non/ex-smokers)⁽¹⁰⁾.

A case study with HFCS food elimination results led to the development of a biochemical hypothesis that may explain the asthma association. According to the 'fructositis' hypothesis, underlying fructose malabsorption results in the intestinal formation of pro-inflammatory advanced glycation end products (enFruAGE) between unabsorbed fructose and partially digested dietary proteins that, once absorbed, promote asthma⁽¹⁾. The intestinal environment after a meal may be highly conducive to enFruAGE formation⁽⁷⁾, as the phosphates from phosphoric acid^(11–13) in soda^(14,15) and the bicarbonate^(12,13) in pancreatic juice are catalysts of the Maillard reaction, which produces pro-inflammatory advanced glycation end products (AGE)^(11–13). Researchers recently tested this hypothesis. They found that fructose, as remains in the digestive tract of fructose malabsorbers, forms AGE – under conditions compatible with the intestines – within a time frame well within the window of digestion, but not with glucose^(16,17). Notably, fructose malabsorption occurs after consumption of foods and beverages with high fructose:glucose ratios,^(18–21) including HFCS^(22–24), agave syrup^(25,26), crystalline fructose and apple juice⁽²⁷⁾, but not after consumption of sucrose or equivalent monomers of fructose and glucose^(18–21). Importantly, researchers from the University of California found that fructose to glucose ratios (1.9:1⁽²⁸⁾ and 1.5:1⁽²⁹⁾) in popular US sodas exceeded levels that are generally recognised as safe (1.2:1)^(22–24), which provided evidence that there has been more excess free fructose (EFF) in the US food supply than previously thought. Notably, HFCS has been ubiquitous in the US food supply since the 1990s^(30–34). Further evidence of a possible role for an enteral FruAGE/receptors of advanced glycation end products (RAGE) pathway in asthma arose when researchers discovered that RAGE, which are highly concentrated in the lungs⁽³⁵⁾, are mediators of asthma⁽³⁶⁾.

We recently epidemiologically tested whether intake of high fructose:glucose ratios was associated with asthma using US nationally representative health survey data (National Health and Nutrition Examination Survey (NHANES))⁽⁴⁾. If a high fructose:glucose ratio (EFF) and fructose malabsorption underlie the HFCS/soda/asthma link, then, in addition to HFCS-sweetened soda and fruit drinks, apple juice – owing to its $\geq 2:1$ fructose to glucose ratio⁽²⁷⁾ – would also be associated with asthma. Our results support this hypothesis. Children (n 1961) who moderately (2–4 times/week) consumed apple juice – a 100% juice – were more than two and a half times as likely to have asthma, and children who regularly consumed any combination of HFCS-sweetened soda, fruit drinks and apple juice were five times more likely to have asthma, as compared with seldom/never consumers, independent of sex, BMI and total energy intake. There was no association with orange juice⁽⁴⁾ – a 100% juice with a 1:1 fructose:glucose ratio⁽²⁷⁾. There were no associations with atopic dermatitis⁽⁴⁾. We also found that adults (n 2801) who regularly consumed HFCS-sweetened soda were nearly twice as likely to have chronic bronchitis, independent of smoking, and exposure to in-home smoke, but not with diet drinks⁽³⁷⁾.

Results from two longitudinal cohorts provided further evidence that asthma may be associated with high fructose juice (e.g. apple juice) intake^(5,38,39). In a US study (n 1111), asthma risk was 34% higher among children who regularly consumed

100% juice (exclusive of orange juice), as compared with seldom/never consumers. There was no association with orange juice⁽⁵⁾. In a Danish study, children (n 2406) who frequently consumed 100% juice (type not distinguished) were twice as likely to have asthma than never/seldom consumers^(38,39).

Methods

Study objectives

Epidemiological studies with longitudinal data are lacking. Therefore, we tested the hypothesis that consumption of HFCS-sweetened soda, fruit drinks and apple juice, but not orange juice or diet soda, increases asthma risk, independently of potential confounders. Fruit drinks were included, as many varieties contain apple juice and are sweetened with HFCS. Survival analysis was conducted with longitudinal data from the Framingham Heart Study-Offspring cohort (FHS-OS)⁽⁴⁰⁾. The FHS-OS was ideally suited to this investigation, as participants were enrolled starting in 1971 – before widespread use of HFCS^(23,24,40,41) – and were followed up for >30 years⁽⁴⁰⁾. US soft drink producers switched from the use of sucrose to HFCS in non-diet soda around 1984^(33,34,41,42).

Participants

The FHS-OS is a prospective study with offspring (5013) of the Original Cohort (Framingham, Massachusetts). Participants were adult, predominantly non-Hispanic White men and women, with a mean age of 47.9 (SD 9.7); 39% were overweight and 17% were obese at baseline. Participants were medically examined and responded to health questions approximately every 4 years, with the exception of an 8-year gap between examinations 1 and 2. Food and beverage intake frequency was obtained via the Willett Food Frequency Questionnaire (FFQ), beginning with examination 3 (1984)⁽⁴⁰⁾. This study focused on data from examinations 3–7 (1984–2001) – a period with approximately 17 follow-up years. Participants were excluded from analyses if they self-reported bronchodilator/aerosol use and/or history of asthma/wheezing during examinations 1 and 2 – that is 'have you had asthma/wheeze (since last exam)'. Onset of risk was defined as 1984, as it coincides with a shift by major US soft drink producers from the use of sucrose to HFCS^(33,34,41,42). The FHS-OS was approved by the US-National Heart, Lung and Blood Institute of the National Institutes of Health. Participants gave written consent.

There were between 2692 and 2696 participants with complete responses to analyses questions, depending upon the beverage. A flow chart showing exclusions is provided as the online Supplementary Material.

Beverage intake

We analysed intake frequency of non-diet soda – the high-EFF beverage most consumed by US adults^(43,44) – fruit drinks, apple juice and any combination of these beverages (referred to as ttleFF), as self-reported at each examination via the Willett FFQ⁽⁴⁰⁾. During the study period, HFCS was the main sweetener in US soda⁽⁴⁵⁾. Intake frequencies were estimated for

examination 4 (average of examinations 3 and 5), as examination 4 lacked an FFQ. For individual analyses, intake frequencies were reduced from seven to four (\leq once/week, 2–4 times/week, 5–7 times/week and $>$ once a day), except for individual analyses with apple juice and fruit drinks, with three levels (\leq once/week, 2–4 times/week, \geq 5 times/week), as fewer people reported consumption $>$ once a day. To analyse intake frequencies for any combination of non-diet soda, fruit drinks and apple juice, the following values were assigned, based on responses for each beverage, and then summed per respondent: 0.016, that is 0.5/30, for never or $<$ 1/month; 0.066, that is 2/30, for 1–3 times/month; 0.143, that is 1/7, for 1 time/week; 0.429, that is 3/7, for 2–4 times/week; 0.857, that is 6/7, for 5–7 times/week; 2.5, for 2–3 times/d; and 4, for \geq 4 times/d. Sums were then divided into quintiles to establish five intake frequencies for any combination of HFCS-sweetened soda, fruit drinks and apple juice. For comparison, we also analysed diet soda and orange juice – a juice with a 1:1 fructose:glucose ratio⁽²⁷⁾. The FFQ directed participants to estimate their usual intake of a standardised portion of a given food item. The suggested serving size for fruit and soft drinks was a can or glass, as compared with a small glass for juice⁽⁴⁰⁾.

Ascertainment of end points

Incident asthma was defined as self-reported asthma (at each examination), including wheezing or asthma (have you had asthma/wheeze since the last examination of short duration, long duration or with respiratory infections). Two analysis models were used. The first model analysed asthma risk on the basis of the first self-reported incidence of asthma – after risk onset. The second model analysed multiple end points, and it reflects risks associated with persistent (recurring) asthma.

Potential confounders

Potential confounders were selected based on existing research^(2–5). Adjustments were made for sex, age, history of smoking, education level (non-high-school graduate; high-school graduate; college; post baccalaureate) and time-varying covariates, including interim smoking (smoked cigarettes/cigars/pipes since the last examination), total energy intake and BMI (continuous variable) – a comorbidity of asthma. We also adjusted for type 2 diabetes (T2D) – as recent research indicates that T2D is a comorbidity of asthma, for reasons that remain unclear⁽⁴⁶⁾. T2D status was based upon fasting glucose concentration \geq 6.99 mmol/l (\geq 126 mg/dl), T2D treatment status or both. If fasting glucose was unavailable, a participant was T2D positive if non-fasting blood glucose was \geq 11.1 mmol/l (\geq 200 mg/dl) or there was a known history of T2D. Diabetes status was updated if diabetes status was missing and it was provided in the previous examination⁽⁴⁰⁾.

Statistical analysis

There were 445 exclusions owing to self-reported bronchodilator/aerosol use or history of asthma/wheezing before examination 3. Participants with implausible energy intakes (n 160), as established by the FHS ($<$ 600 and $>$ 4000), were also excluded from the analyses. Cox proportional hazards models with time-varying

covariates, with time on study as the time scale, were used for analyses. After verifying proportional hazards assumptions by using the Schoenfeld and scaled Schoenfeld residuals for the models – as a whole and individually, including plots for each predictor ($P \geq 0.05$) – we examined incident asthma over approximately 17 years of follow-up, using multivariable-adjusted Cox proportional hazards models to estimate hazard ratios (HR). Risk onset was defined as 11 years (1984) from the mid-point (1973) of enrolment (1971–1975). Person-time was calculated from baseline (1983–1987) to examination 7 (1998–2001), death, loss to follow-up, incident asthma (model 1) or persistent/recurring asthma (model 2).

Covariates were updated at each time point (examinations 3–7). For missing data, the last value was carried forward for BMI, smoking status and T2D status – a protocol used in existing sugar-sweetened beverages (SSB) research⁽⁴⁷⁾. For total energy intake, subsequent values were used if the prior examination value was missing, as examination 5 had 304 missing values and examination 6 had 132 missing values. Total energy intake for examinations 3 and 4 were estimated by averaging values from examinations 5, 6 and 7, as total energy intake was not available in the data set for examinations 3 and 4. Analyses of individual beverages included additional adjustments for the other high-EFF beverages, to enable independent assessment of each high-EFF beverage. For example, the HR for non-diet soda reflects asthma risk, which is independent of fruit drinks and apple juice. Within each model, potential mediators were analysed in two ways: the first included age, sex, education level, total energy intake, BMI, history of smoking and interim smoking as potential confounders, and the second included further adjustment for T2D status, to assess associations independent of blood glucose. Stata version 13.1 was used and a two-tailed P value $<$ 0.05 with 95% CI that did not include 1 was considered statistically significant.

Results

Baseline characteristics

A higher percentage of participants frequently (\geq 5 times/week) consumed orange juice (43.6%) as consumed HFCS-sweetened soda (31%) and diet soda (37.8%). Nearly half of the participants (46.7%) reported intake of tHFF approximately once or more per day at baseline (examination 3). Within this combination, the percentage of respondents who regularly (\geq 5 times/week) consumed non-diet soda (31%, n 2394) was higher than apple juice (5.1%, n 2392) or fruit drinks (8.1%, n 2388) (Table 1). Men consumed non-diet soda or any combination of non-diet soda, fruit drinks and apple juice more frequently than women, and frequent consumption of these beverages was associated with higher prevalence of current/recent smoking, whereas women were more likely to consume diet soda. Frequent (\geq 5 times/week) orange juice consumers were less likely to have smoked since the prior examination than frequent consumers of non-diet soft drinks (Table 2). Increasing consumption of all sugar-containing beverages was associated with higher total energy intakes ranging from approximately 7113 kJ (1700 kcal) for \leq once/week to approximately 8786 kJ (2100 kcal) for more than once/d consumption.

Table 1. Baseline characteristics of adults aged 24–72 years in the Framingham Offspring Cohort – 1984* (Mean values and standard deviations)

<i>n</i>	2396
Age (years)	
Mean	51.5
SD	9.8
Sex (% male)	46.5
BMI (kg/m ²)	
Mean	26.0
SD	4.5
≤Target weight ≤24.9 (%)	38.4
Overweight >24.9–≤29.9 (%)	41.0
Obese >29.9 (%)	20.6
Energy intake (kJ/d)	
Mean	7761
SD	2326
Energy intake (kcal/d)	
Mean	1855
SD	556
Education level (%)	
0–11 years (<high-school graduate)	5.2
12 years (high-school graduate)	33.2
13–15 years (some college)	28.3
16+ years (≥college graduate)	33.3
Diabetes (% yes)	3.7
History of smoking (% yes)	60.1
Smoked cigarettes since the past examination (% yes)	18.8
Smoked cigars/pipes since the past examination (% yes)	<1.0
Intake frequency ttiEFF (%) (<i>n</i> 2396)	
<3 times/months	11.7
About once/week	19.3
2–4 times/week	22.3
About once/d	25.9
>Once/d	20.8
Intake frequency non-diet soda (%) (<i>n</i> 2394)	
≤Once/week	49.5
2–4 times/week	19.5
5–7 times/week	17.2
>Once/d	13.8
Intake frequency diet soda (%) (<i>n</i> 2394)	
≤Once/week	48.1
2–4 times/week	14.1
5–7 times/week	15.3
>Once/d	22.5
Intake frequency orange juice (%) (<i>n</i> 2392)	
≤Once/week	32.1
2–4 times/week	24.3
5–7 times/week	36.9
>Once/d	6.7
Intake frequency apple juice (%) (<i>n</i> 2392)	
≤Once/week	79.5
2–4 times/week	15.4
≥ 5 times/week	5.1
Intake frequency fruit drinks (%) (<i>n</i> 2388)	
≤Once/week	82.0
2–4 times/week	9.9
≥ 5 times/week	8.1

ttiEFF, combination of high-fructose corn syrup-sweetened soft drinks, fruit drinks and apple juice.

* Characteristics are based upon self-reported responses to the medical and FFQ administered at baseline (1984).

Relationship with asthma

Greater intake of any combination of HFCS-sweetened soda, fruit drinks and apple juice was significantly associated with progressively higher asthma risk, rising from 59% higher for moderate (2–4 times/week) consumers to a plateau of 89% higher among 5–7 times/week *v.* never/seldom consumers

Table 2. Baseline characteristics of participants by beverage intake frequency in the Framingham Offspring Cohort

Intake frequencies	ttiEFF (<i>n</i> 2396)				HFCS-sweetened soft drinks (<i>n</i> 2394)				Orange juice (<i>n</i> 2392)				Diet soft drinks (<i>n</i> = 2394)			
	<3/ month	About once/week	About 2–4/ week	About 5–7/ week	<3/ month	About once/week	About 2–4/ week	About 5–7/ week	<3/ month	About once/week	About 2–4/ week	About 5–7/ week	<3/ month	About once/week	About 2–4/ week	About 5–7/ week
%	11.7	19.3	22.3	25.9	20.8	49.5	19.5	17.2	13.8	32.1	24.3	36.9	6.7	48.1	14.1	15.3
Sex (%)																
Male	31	34	45	54	59	36	54	62	55	47	49	44	54	49	45	46
Smoking history																
Yes (%)	60	60	61	59	61	59	59	64	62	64	60	57	58	59	60	63
Smoked since last examination																
Yes (%)	17	18	17	18	23	17	17	22	25	25	19	14	16	23	12	15
BMI (kg/m ² , %)																
≤Target	38	44	42	35	34	48	45	45	36	36	41	39	38	46	37	32
Overweight	40	38	42	44	39	37	39	43	41	42	39	42	38	39	43	42
Obese	22	18	16	21	27	15	16	12	23	12	20	19	24	15	20	26
Total energy intake																
Mean kJ	6745	7097	7637	8013	8792	7264	7942	8194	8776	7214	7934	7980	8587	7783	7578	7691
Mean kcal	1611	1695	1824	1914	2100	1735	1897	1957	2096	1723	1895	1906	2051	1859	1810	1837
T2D																
Yes (%)	7.8	5.0	2.6	1.8	3.8	4.5	2.8	1.9	4.5	3.0	3.1	4.5	5.0	1.7	4.4	3.8

ttiEFF, combination of high-fructose corn syrup-sweetened soft drinks, fruit drinks and apple juice; T2D, type 2 diabetes.

Table 3. Asthma risk according to beverage consumption in adults, the Framingham Offspring Cohort (Hazard ratios (HR) and 95% confidence intervals)

Asthma risks†	Cox proportional hazards model 1			Cox proportional hazards model 2		
	HR	95% CI	P	HR	95% CI	P
	Adjusted for sex, age, ever smoked, education level and time-varying covariates such as BMI, smoking, total energy intake n 2696, no. of obs = 8864			Further adjusted for diabetes, type 2 n 2696, no. of obs 8862		
ttlEFF‡	Ref.			Ref.		
<3 times/month	1.21	0.85, 1.72	0.284	1.22	1.03, 1.85	0.258
About once/week	1.59	1.12, 2.25	0.009*	1.61	1.36, 2.49	0.008*
About 2–4 times/week	1.89	1.36, 2.62	0.000*	1.91	1.37, 2.66	0.000*
About 5–7/week	1.40	0.98, 2.00	0.067°	1.41	0.99, 2.02	0.058°
>Once/d						
Non-diet soft drinks‡	Further adjusted for FD and AJ			Further adjusted for FD and AJ		
≤once/week	Ref.			Ref.		
2–4 times/week	0.99	0.73, 1.34	0.960	1.00	0.73, 1.35	0.980
5–7 times/week	1.48	1.09, 2.01	0.011*	1.49	1.10, 2.02	0.011*
>Once/d	0.94	0.68, 1.31	0.726	0.94	0.71, 1.36	0.736
Fruit drinks‡	Further adjusted for ndSoda and AJ			Further adjusted for ndSoda and AJ		
≤once/week	Ref.			Ref.		
2–4 times/week	1.58	1.12, 2.22	0.009*	1.58	1.12, 2.23	0.009*
≥5 times/week	0.85	0.52, 1.38	0.506	0.85	0.52, 1.38	0.532
Apple juice‡	Further adjusted for ndSoda and FD			Further adjusted for ndSoda and FD		
≤Once/week	Ref.			Ref.		
2–4 times/week	1.61	1.14, 2.28	0.007*	1.61	1.14, 2.28	0.007*
≥5 times/week	1.08	0.65, 2.09	0.792	1.08	0.60, 1.94	0.793
Diet soda						
≤Once/week	Ref.			Ref.		
2–4 times/week	1.00	0.72, 1.40	0.974	1.00	0.72, 1.40	0.985
5–7 times/week	0.83	0.57, 1.21	0.343	0.83	0.57, 1.21	0.334
>Once/d	0.94	0.73, 1.21	0.637	0.93	0.72, 1.20	0.585
Orange juice						
≤once/week	Ref.			Ref.		
2–4 times/week	0.99	0.73, 1.33	0.931	0.99	0.73, 1.33	0.931
5–7 times/week	1.12	0.88, 1.43	0.350	1.12	0.88, 1.43	0.350
>Once a day	0.78	0.44, 1.38	0.391	0.78	0.44, 1.38	0.392

ttlEFF, combination of high-fructose corn syrup-sweetened soft drinks, fruit drinks and apple juice; ndSoda, HFCS-sweetened soft drinks; FD, fruit drinks; AJ, apple juice; Ref., referent values; HFCS, high-fructose corn syrup.

* Significant associations. ° Association that approached significance.

† Asthma refers to the first incidence of asthma/whoze as self-reported during examinations (3–7), after the onset of risk (1984).

‡ Beverages with fructose:glucose ratios that exceed 1:1. During the Framingham Heart Study-Offspring Study period (1984–2008), HFCS was the main sweetener in US soft drinks⁽⁴⁵⁾. The fructose:glucose ratio in AJ is ≥2:1⁽²⁷⁾. In HFCS-sweetened soft drinks the ratio has been measured as 1.5:1 for HFCS with 60% fructose⁽²⁹⁾ and 1.9:1 for HFCS with 65% fructose⁽²⁸⁾ – higher than the 1.2:1 ratio that is generally recognised as safe^(22,23).

($P < 0.001$), independent of potential confounders including age, sex, BMI, smoking, education level and total energy intake. Asthma risk did not change materially after further adjustment for T2D (HR 1.91; 95% CI 1.37, 2.66, $P < 0.001$) (Table 3). Among > once/d *v.* seldom/never consumers, the asthma association (41% higher) approached statistical significance ($P = 0.058$) (Table 3). Among 2696 participants, there were 363 incident cases of asthma over 17 years of follow-up (26 828 person-years – an incidence rate of 13.5% (Table 4). Regular (5–7 times/week) consumers of HFCS-sweetened soda had a 48% higher asthma risk (HR 1.48; 95% CI 1.09, 2.01, $P < 0.011$) compared with never/seldom consumers, independent of potential confounders. Asthma risk did not change materially after further adjustment for T2D (HR 1.49; 95% CI 1.10, 2.02, $P < 0.011$) (Table 3).

Moderate consumers (2–4 times/week) of fruit drinks had 58% higher asthma risk (95% CI 1.12, 2.22; $P < 0.009$) and moderate consumers of apple juice had 61% higher asthma risk, compared with never/seldom consumers (95% CI 1.14, 2.28; $P < 0.007$), independent of sex, age, smoking history,

education level, BMI and total energy intake. There were no significant changes in risk, after further adjustment for T2D. There was no association between diet soda or orange juice intake and asthma (Table 3).

There were 18.4 incident cases of asthma, per 1000 person-years, among frequent consumers (approximately once a day) of any combination of HFCS-sweetened soda, fruit drinks and apple juice – a number that was double that of never/seldom consumers (9.0). Persistent asthma (incident and recurrent cases) was also significantly higher with increasing consumption of high-EFF beverages (Table 4). Crude risks are available as the online Supplementary Table S1.

Discussion

Consumption of HFCS-sweetened soda, fruit drinks and apple juice – beverages with high fructose:glucose ratios – was significantly associated with increased asthma risk. There was no association with diet soda. Orange juice – a 100% juice with a 1:1 fructose:glucose ratio – and a fairly comparable

Table 4. Asthma risk (fully adjusted) by consumption of high-fructose corn syrup (HFCS)-sweetened soft drinks, fruit drinks and apple juice (tttEFF) in adults – The Framingham Offspring Cohort† (Hazard ratios (HR) and 95 % confidence intervals)

Asthma risks		Intake frequencies				
Incident						
tttEFF‡		< 3/month	About once/week	About 2–4 times/week	About once/d	> Once/d
Person-years		7285	5492	4793	4987	4769
Cases of incident asthma		66	62	67	92	76
Cases/1000 person-years		9.0	11.3	14.0	18.4	15.9
HR fully adjusted§		1.00	1.22	1.61*	1.91*	1.41°
95 % CI			1.03, 1.85	1.36, 2.49	1.37, 2.66	0.99, 2.02
P			0.258	0.008	< 0.001	< 0.058
Recurrent						
tttEFF‡		< 3/month	About once/week	About 2–4 times/week	About once/d	> Once/d
Person-years		8129	6077	5377	5618	5477
Cases recurrent asthma		157	131	138	178	168
Cases per 1000 person-years		19.3	21.5	25.7	31.7	30.7
HR fully adjusted§		1.00	1.18	1.52*	1.81*	1.49*
95 % CI			0.93, 1.49	1.20, 1.92	1.45, 2.26	1.18, 1.89
P			0.170	< 0.001	< 0.001	0.001
Incident						
HFCS-sweetened soda‡			≤ Once/week	2–4 times/week	5–7 times/week	> Once/d
Person-years			16388	4712	2987	3196
Cases of incident asthma			193	58	61	51
Cases/1000 person-years			11.8	12.3	20.4	16.0
HR fully adjusted			1.00	1.00	1.49*	0.94
95 % CI				0.73, 1.35	1.10, 2.02	0.68, 1.32
P				0.980	0.011	0.736
Recurrent						
HFCS-sweetened soda‡			≤ Once/week	2–4 times/week	5–7 times/week	> Once/d
Person-years			17973	5247	3323	3680
Cases recurrent asthma			408	136	116	115
Cases/1000 person-years			22.7	25.9	34.9	31.2
HR fully adjusted			1.00	1.24*	1.64*	1.13
95 % CI				1.022, 1.50	1.32, 3.03	0.91, 1.41
P				0.032	0.001	0.264

* Significant associations. ° Association that approached significance.

† Incident and recurrent asthma (cases per 1000 person-years) are shown by beverage intake frequency for tttEFF and HFCS-sweetened soda.

‡ Beverages with fructose:glucose ratios that exceed 1:1⁽²⁶⁾. The fructose:glucose ratio in apple juice is ≥ 2:1⁽²⁶⁾. In HFCS-sweetened soft drinks, the ratio has been measured as 1.5:1 for HFCS with 60 % fructose⁽²⁸⁾, and 1.9:1 for HFCS with 65 % fructose⁽²⁷⁾ – higher than the 1:2:1 that is generally recognised as safe^(22,23).

§ HR are adjusted for age, sex, education level and time-varying covariates such as BMI, history of smoking, interim smoking and type 2 diabetes.

|| Analyses with HFCS-sweetened soda were further adjusted for intake frequency of non-diet fruit drinks, and apple juice, as we were interested in assessing the relative risk of asthma independent of these other high-excess free fructose beverages.

amount of total fructose (11 g) as non-diet soda (14.5 g) and apple juice (15.7 g)⁽²⁷⁾, per 8 ounce cup (237 ml), was also not associated with asthma, despite a higher consumption propensity (≥ 5 times/week, 43.6 %) as HFCS-sweetened soda (≥ 5 times/week, 31 %). The highest risk (91 %) was seen among participants who consumed any tttEFF about once a day (5–7 times/week). However, moderate tttEFF consumers (2–4 times/week) were also at higher risk (61 %), relative to never/seldom consumers, independent of potential confounders, including T2D. Moderate apple juice and fruit drink consumers (2–4 times/week) also had increased asthma risk (61 and 58 % higher), as did regular consumers (5–7 times/week) of HFCS-sweetened soda (49 % higher), relative to seldom/never consumers. It is worth noting that the asthma risk (91 %) among participants who regularly (5–7 times/week) consumed any combination of all three high-EFF beverages, relative to seldom/never consumers, was 42 percentage points higher than the asthma risk (49 %) among participants who regularly consumed HFCS-sweetened soda, exclusive of fruit drinks and apple juice.

Notably, > once/day HFCS-sweetened soda intake was not associated with asthma, nor was ≥ 5 times/week intake of fruit

drink and apple juice. The association between > once a day consumption of any combination of HFCS-sweetened soda, fruit drinks and apple juice and asthma approached statistical significance, albeit at a lower HR (1.41, $P = 0.058$) than among 5–7 times/week consumers (1.91, $P < 0.001$). This paradox may be due to insufficient statistical power. Another possible explanation is that persistent exposure to high immunogen (enFruAGE) concentration, over extended time periods, leads to attenuated effects over time, as chronic stimulations are known to result in a tolerogenic immune response⁽⁴⁸⁾. We observed similar plateaus in our prior childhood asthma study with NHANES⁽⁴⁾. Interestingly, in a CDC (adult) study ($n = 146\,990$), intake of SSB (HFCS-sweetened soda, fruit drinks, sports/energy drinks and sweet tea) was associated with asthma, among non-obese (BMI < 30) participants. There was no association among obese (BMI ≥ 30) participants⁽³⁾. This is consistent with the hypothesis that persistent intakes lead to attenuated effects and immune system tolerance. In the US CDC study of high-schoolers, ≥ 3 times/d non-diet soda intake was associated with asthma⁽²⁾. It is noteworthy that, of these studies, this (FHS-OS) analysis is the only one wherein participants were

followed up over an extended time period (approximately 17 follow-up years) v. analyses of data from a snapshot in time.

Importantly, the lack of association with orange juice and diet soda, combined with the strong associations across all high-EFF beverages – independent of potential confounders, including T2D status – provide further evidence that the increased asthma risk may be due to the high fructose:glucose ratio in HFCS-sweetened soda, fruit drinks and apple juice. A ranking of beverages by increased asthma risk and their fructose to glucose ratios aligns well with our results as follows: (61%) apple juice, $\geq 2:1$; (58%) fruit drinks (the ratio for fruit drinks likely lies somewhere between apple juice and HFCS, as many varieties are sweetened with HFCS and contain apple juice); (49%) HFCS-sweetened soda (the ratio may be between 1.9:1 and 1.5:1, depending upon fructose percentage as found by independent laboratories (65% fructose⁽²⁸⁾ and 60% fructose respectively⁽²⁹⁾); and (None) orange juice, 1:1⁽²⁷⁾. The negative results with orange juice were similarly negative in our prior childhood asthma study⁽⁴⁾ and in the longitudinal birth cohort study – Project Viva⁽⁵⁾. These results support our hypothesis. Consumption of beverages with high fructose:glucose ratios (HFCS-sweetened soda, fruit drinks and apple juice) increases asthma risk, independently of blood glucose, age, sex, BMI, total energy intake, education level and smoking. This may be because of fructose malabsorption, and enteral formation of pro-inflammatory enFruAGE, but more studies of mechanism are needed.

Researchers have sought to understand the causes of fructose malabsorption. However, they remain inconclusive, as no glucose and fructose transporters (GLUT2) or EFF transporters (GLUT5) genetic mutations have been identified, nor is there evidence that depressed levels of these transporters are responsible for the condition^(18–21). Rather, research suggests that our current food supply contains EFF (high fructose:glucose ratios), from HFCS, agave syrup, crystalline fructose, apple juice and other combination juices with apple juice, that we *have not* evolved to consume^(19,20). Notably, the list of foods that naturally contain high fructose:glucose ratios is short. It includes primarily apples, watermelons, pears and mangoes⁽²⁷⁾.

Although HFCS-sweetened soda and fruit drinks are major sources of EFF – the fructose type associated with fructose malabsorption^(18–21,49,50) – the potential for a further asthma effect from intake of HFCS-sweetened foods is possible, as HFCS has been ubiquitous in the US food supply since the 1990s^(30–34), and foods other than beverages have been more significant sources of HFCS for some people. This becomes evident with a comparison of average per capita daily HFCS intake (65 g)^(24,30,31,51,52) relative to average daily HFCS intake derived from 'SSB'^(43,44). For example, a 20 oz (590 ml) bottle of cola, coincidentally, contains 65 g, that is 1004 kJ (240 kcal), from HFCS^(14,15) – the same amount as average per capita daily HFCS intake (65 g), as reported before industry-influenced increases in consumer-level loss allowances^(51–54). Notably, only adolescent boys (1142 kJ/d (273 kcal/d)) and men aged 20–39 years (1054 kJ/d (252 kcal/d)) consumed this amount of HFCS (kJ/d (kcal/d)) from SSB, whereas intakes by other age/sex groups ranged from 176 kJ/d (42 kcal/d) for women aged ≥ 60 years to 590 kJ/d (141 kcal/d) for 6- to 11-year-old

boys^(43,44). Therefore, this study may be underestimating the true asthma risk associated with HFCS intake, as HFCS as a preferred sweetener was not exclusive to beverages. Its use became ubiquitous during the time period of this study^(30,31,33,34). Notably, these HFCS intake levels from SSB were measured during a time (2005–2008) when average HFCS intake was lower than peak (approximately 80 g p/d, 1999)^(24,51–54), as reported before retroactively applied subjective increases in consumer-level loss allowances^(51–54).

Enrolment in the FHS-OS (1971–1975)⁽⁴⁰⁾ preceded widespread use of HFCS. However, by 1984, average per capita intake had increased to approximately 20 g/d, and later to approximately 80 g/d (>1 lb/week)^(24,51–54). In average daily intake of 65 g of HFCS, there are 13–19 g of EFF, depending on the fructose percentage (60%⁽²⁹⁾ or 65%⁽²⁸⁾). From a fructose malabsorption perspective, these levels appear problematic, given that fructose levels as low as 12.5–25 g are associated with adult fructose malabsorption^(18–21,55–59), and given that one cup of apple juice contributes another 8–9 g of EFF to the daily EFF load from HFCS⁽²⁷⁾. Limited fructose malabsorption research with children indicates that they test positive at lower intakes^(49,50).

The fate of unabsorbed EFF in the intestines has recently been tested. Incubation of amino acids⁽¹⁶⁾ and ovalbumin (a model egg protein)⁽¹⁷⁾ with fructose – but not glucose – at concentrations and pH that would be present in the intestines after a meal led to a time- and dose-dependent formation of FruAGE intermediates, as measured by fluorescence, within 30 min⁽¹⁷⁾ and 1 h⁽¹⁶⁾ of incubation – a time frame well compatible with the digestive process. This provides evidence that fructose malabsorption may underlie the intestinal *in situ* formation of pro-inflammatory FruAGE. These end products may initiate a cascade of symptoms, including airway mucous hypersecretion that promotes asthma⁽¹⁾. Although RAGE are located in many tissues, the lungs have the highest concentration⁽³⁵⁾, and evidence suggests that they are mediators of asthma⁽³⁶⁾. There is evidence that glycated peptides, seven amino acids long, with α -carboxy-methyl-lysine (CML) and α -carboxy-ethyl-lysine – well-studied AGE – were capable of triggering pro-inflammatory cytokine gene expression, without requiring a specific amino acid sequence^(60,61). This is important, as conditions in the intestines, with proteins at various digestion levels, may be conducive to the formation and absorption of a potentially large quantity of heterogeneous glycated peptides. Because of their small size, these extracellular newly identified enFruAGE may leave the vascular compartment and trigger pro-inflammatory signalling that increases asthma risk. Since the discovery that receptors of AGE are mediators of asthma, additional studies have confirmed that RAGE are major mediators of pulmonary inflammatory responses across pulmonary conditions⁽⁶²⁾.

Most recently, results of another *in vitro* study, with meal resembling systems, provided further evidence that FruAGE may form in the intestines. Their results showed that only the meal with fructose (as remains in the intestines of fructose malabsorbers) formed CML, and it occurred well within the time window of digestion (1 h). There was no CML formation with glucose⁽⁶³⁾. This research provided further evidence that these

intestinally formed immunogens may accumulate in body tissues and contribute to asthma and its comorbidities^(1,7). Notably, asthma patients have increased risk of CHD^(47,64), rheumatoid arthritis⁽⁶⁵⁾ and T2D⁽⁶⁶⁾, for reasons that remain inconclusive. In prior studies, we found that intakes of non-diet soda, fruit drinks and apple juice, but not diet soda⁽⁶⁷⁾ or 100% orange juice⁽⁶⁸⁾, were associated with idiopathic arthritis⁽⁶⁷⁾ and CHD⁽⁶⁸⁾. Furthermore, the paradox in dietary AGE (dAGE) research provides indirect support for this hypothesis. Serum and urinary AGE were not associated with intake of foods previously thought to be high in dAGE (fast foods, hamburgers and fries), as hypothesised. Rather, the association was with intake of HFCS-sweetened foods, including cold cereals, breads and sweets⁽⁶⁹⁾.

The results of this study, along with others, have important implications for public policy. They support the possibility that the 100% juice reductions in the US Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) in 2009^(70,71), and the plateauing/decreasing asthma prevalence seen in 2010–2013, particularly among non-Hispanic black children⁽⁷²⁾, may be related. WIC is a federally supported nutrition assistance programme that serves > one-quarter of the pregnant women, half the infants and many children <5 years of age in the USA^(70,71). The 2009 revision eliminated 100% juice from the infants food package, and reduced quantities for women and children⁽⁷¹⁾. Furthermore, in a recent report by the US CDC, childhood asthma prevalence doubled from 1980 to 1995 (a period with a rapid rise in average per-capita HFCS consumption) and then increased more slowly from 2001 to 2010. The increase from 2001 to 2009 was followed by a plateau and then a decline in 2013. Researchers noted that current asthma prevalence ceased to increase among children in recent years and that the non-Hispanic black–white disparity stopped increasing, mainly owing to plateauing prevalence among non-Hispanic black children⁽⁷²⁾. Although soft drink consumption has declined over the past decade^(43,44), our prior childhood (ages 2–9 years) asthma study results with nationally representative NHANES data from 2003 to 2006⁽⁴⁾ suggest that the asthma decline, among non-Hispanic black children in 2012, may be more attributed to the decline in apple juice consumption than soft drink consumption, as moderate apple juice consumers were more than two and a half times as likely to have asthma as compared with seldom/never consumers, whereas intake of non-diet soda was associated with asthma prevalence, only when consumed in combination with apple juice and fruit drinks⁽⁴⁾.

Results of another study were recently published wherein early childhood fructose intake was associated with mid-childhood asthma, independent of BMI⁽⁷³⁾. However, this research is a re-analysis of an earlier study (2014), of the same mother–child pairs (Project Viva)⁽⁵⁾. In the first published study, researchers found that intake of juice at 2 years of age, excluding orange juice, was associated with mid-childhood asthma⁽⁵⁾. In the re-analysis, no distinction was made between orange juice and apple juice. Researchers concluded in both analyses that the asthma association is with total fructose^(5,73). However, this interpretation is inconsistent with their earlier results⁽⁵⁾. Importantly, it is inconsistent with this study's results, with findings from our analysis with NHANES^(4,7) and with the

case study that motivated this research⁽¹⁾. Furthermore, across epidemiological studies, associations are independent of BMI, providing evidence that mechanisms are independent of adiposity^(2–5,73). Importantly, CDC researchers recently assessed whether population-level changes in weight status affected asthma prevalence trends over time (1988–2014 NHANES). They found that, although obesity was a risk factor for asthma throughout the period, asthma prevalence increased only among children with normal weight. They concluded that the data do not support a contribution of obesity trends to increasing asthma prevalence trends⁽⁷⁴⁾. The results presented herein support the hypothesis that the asthma association is with fructose to glucose ratios that exceed 1:1 (EFF), with underlying fructose malabsorption, and with formation of asthma-triggering immunogens in the GI lumen between unabsorbed EFF and partially digested dietary peptides.

This study has limitations. First, outcomes were based on self-report, which is subject to reporting bias. However, these results are consistent with existing studies, and with another recently published cross-sectional study of US adults with doctor-diagnosed current asthma. Individuals with doctor-diagnosed active asthma who drank non-diet soda three or more times/week had higher odds (2.8; 95% CI 1.51, 5.10, $P=0.001$) of overnight hospitalisation compared with seldom consumers, independent of age, education, sex, race/ethnicity, weight status, smoking and self-rated health⁽⁷⁵⁾. Second, a myriad of foods contribute to EFF intake (cold cereals, breads, snack bars, desserts, sweets, ketchup, sauces and so on)^(30–34), which were not accounted for in this study. Foods, other than beverages, are major sources of HFCS for many age groups, as adolescent boys and men aged 20–39 years were the only ones consuming SSB at levels consistent with HFCS average per-capita consumption^(43,44). Foods sweetened with agave syrup and crystalline fructose were also not considered. This exposure underestimation may have attenuated our ability to quantify the true risk. Third, this study is not nationally representative. Participants were mainly non-Hispanic white Americans, which does not allow consideration of race/ethnicity on this relationship. In particular, we may be underestimating the true risk among African Americans as they have higher fructose malabsorption prevalence than non-Hispanic whites and Hispanics⁽⁷⁶⁾. However, in existing studies, associations with asthma were independent of race/ethnicity^(2–5,58). Fourth, although we were able to adjust for education level, we were not able to account for income – a possible confounder – as it was not available. However, in our prior studies of childhood asthma⁽⁴⁾, and adult chronic bronchitis⁽³⁷⁾, associations were independent of socioeconomic status. Fifth, we were not able to assess occupational or environmental air quality factors as a potential confounder, as this information was not available in the data. Sixth, this study with adults did not quantify risks in children. More research is needed, particularly with children, as fructose malabsorption research indicates that they test positive at lower intakes^(49,50). Seventh, we were unable to assess associations before 1984, to test the hypothesis that non-diet soda, when sweetened with sucrose, is not associated with asthma, as examinations 1 and 2 lacked an FFQ. More biochemical, clinical and consequences of fructose malabsorption research is needed.

Conclusion

Moderate and frequent consumption of HFCS-sweetened soda, fruit drinks and apple juice, but not diet soda or orange juice, increased asthma risk, independent of age, sex, smoking, BMI, education level, total energy intake and T2D. This may be because of the high fructose:glucose ratio in these beverages, fructose malabsorption and formation of asthma-triggering immunogens (enFruAGE) in the GI lumen. Recommendations to reduce sugar-sweetened beverage consumption may be inadequate to address asthma risk, as associations are evident even with moderate intake of apple juice – a 100% juice. The 100% juice reductions in the WIC in 2009, and the plateauing/decreasing asthma prevalence (2010–2013), particularly among non-Hispanic black children, may be related. Intervention studies and more research of consequences of fructose malabsorption are needed.

Acknowledgements

The FHS is funded by the National Heart, Lung and Blood Institute (HHSN268201500001I; NO1-HC-25195; HL076784; AG028321; HL070100; HL060040; HL080124; HL071039; HL077447; 6R01-NS-17950; and HL107385). This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

L. R. D. C. researched and developed the biochemical hypothesis, designed the epidemiology research, performed all of the analyses and wrote the manuscript. L. R. D. C. holds a Master's of Science in Biochemistry, Molecular Biology, New York Medical College, Valhalla, NY; she has additionally completed advanced coursework in immunology, epidemiology and biostatistics. K. L. T. provided critical review, reviewed all statistical analyses and contributed to editing the manuscript. All authors read and approved the final manuscript.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit <https://doi.org/10.1017/S0007114518000417>

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