

Fructose consumption from different food sources and cardiometabolic biomarkers: cross-sectional associations in US men and women

Xinyi Li, Hee-Kyung Joh, Jinhee Hur, Mingyang Song, Xuehong Zhang, Yin Cao, Kana Wu, Edward L. Giovannucci

Supplementary Figure 1. Flowchart describing how study population was generated

Supplementary Figure 2. Percentage differences (95% confidence intervals) in biomarker concentrations associated with 20 g/d fructose intake stratified by (A) physical activity quartiles and (B) BMI categories

Supplementary Figure 3. Percentage differences (95% confidence intervals) in biomarker concentrations associated with 20 g/d fructose intake stratified by (A) age (B) smoking status and (C) alcohol consumption

Supplementary Table 1. Top 10 food contributors of fructose in each cohort

Supplementary Table 2. Characteristics of participants at blood draw according to quartiles of SSB fructose, juice fructose and fruit fructose in the combined cohort

Supplementary Table 3. Biomarker concentrations according to total fructose quartiles in HPFS, NHS and NHSII

Supplementary Table 4. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d total fructose in sensitivity analyses

Supplementary Table 5. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in the combined cohort with additional adjustment for fiber intake

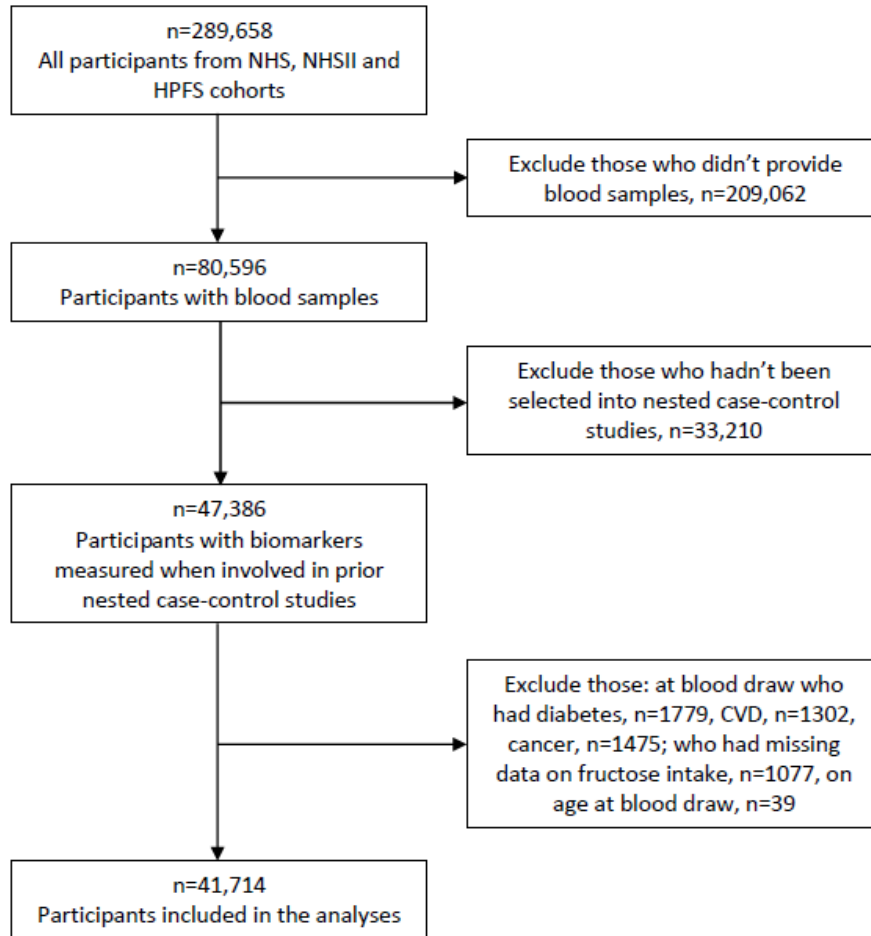
Supplementary Table 6. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in the combined cohort not adjusted for BMI

Supplementary Table 7. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in HPFS

Supplementary Table 8. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in NHS

Supplementary Table 9. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in NHSII

Supplementary Figure 1. Flowchart describing how study population was generated. CVD, cardiovascular diseases.



Supplementary Table 1. Top 10 food contributors of fructose in each cohort ¹

HPFS		NHS		NHSII	
Apple	10.7%	Apple	11.0%	Apple	9.2%
Orange juice	9.2%	Orange juice	10.3%	Hawaiian Punch, lemonade, and other non-carbonated fruit drinks	8.5%
Banana	5.5%	Banana	5.1%	Orange juice	7.9%
Coke, Pepsi, and other cola with sugar	5.0%	Hawaiian Punch, lemonade, and other non-carbonated fruit drinks	4.3%	Coke, Pepsi, and other cola with sugar	5.8%
Hawaiian Punch, lemonade, and other non-carbonated fruit drinks	3.2%	Coke, Pepsi, and other cola with sugar	4.1%	Banana	4.5%
Grape and raisin	3.2%	Orange	3.2%	Grape and raisin	3.9%
Orange	3.1%	Grape and raisin	3.1%	Other fruit juices	2.3%
Other carbonated beverage with sugar	2.5%	Apple sauce	2.4%	Orange	2.1%
Apple juice	1.9%	Cantaloupe	1.8%	Other carbonated beverage with sugar	2.0%
Apple sauce	1.7%	Apple juice	1.8%	Apple juice	1.7%

¹ The contribution was calculated as weight percentage of total fructose and ranked in decreasing order.

Supplementary Table 2. Characteristics of participants at blood draw according to quartiles of SSB fructose, juice fructose and fruit fructose in the combined cohort ¹

	SSB fructose		Juice fructose		Fruit fructose	
	Quartile 1 n=10,428	Quartile 4 n=10,428	Quartile 1 n=10,428	Quartile 4 n=10,428	Quartile 1 n=10,428	Quartile 4 n=10,428
Age at blood draw, y	52.7 ± 9.9	51.0 ± 9.5	51.7 ± 9.7	52.5 ± 9.9	50.6 ± 9.1	53.3 ± 10.3
Fructose intake, g/d	36.5 ± 11.3	53.8 ± 15.3	37.4 ± 13.9	49.7 ± 13.6	38.1 ± 16.2	48.4 ± 12.1
SSB fructose intake, g/d	0.1 ± 0.1	21.0 ± 17.6	6.2 ± 13.1	7.7 ± 12.6	10.2 ± 16.9	4.1 ± 8.0
Juice fructose intake, g/d	5.2 ± 6.2	6.5 ± 6.9	0.6 ± 0.5	14.4 ± 7.3	5.3 ± 6.5	6.3 ± 6.8
Fruit fructose intake, g/d	13.6 ± 9.0	10.0 ± 7.0	11.8 ± 9.1	12.7 ± 7.9	4.2 ± 1.9	22.2 ± 7.6
Percentage fructose from SSB, %	0.3	37.1	12.8	13.2	20.1	7.3
Percentage fructose from juice, %	13.3	12.0	1.8	29.8	13.8	12.3
Percentage fructose from fruit, %	36.0	19.4	31.9	25.7	12.6	47.2
Percentage energy from fructose, %	8.3	12.2	8.5	11.1	8.7	11.0
Percentage energy from total carbohydrates, %	49.4	53.1	48.5	53.4	46.5	55.1
Percentage energy from fat, %	30.7	30.2	32.4	28.7	33.6	27.7
Total energy intake, kcal/d	1778 ± 462	1792 ± 493	1830 ± 528	1660 ± 431	1841 ± 531	1783 ± 487
AHEI score ²	48.0 ± 8.9	42.9 ± 8.0	44.7 ± 9.3	46.8 ± 8.3	41.5 ± 8.2	49.5 ± 8.3
Physical activity, MET-h/week	20.6 ± 20.4	16.0 ± 18.0	18.1 ± 19.1	18.8 ± 19.1	14.9 ± 17.3	22.6 ± 21.0
BMI, kg/m ²	25.8 ± 4.9	25.7 ± 5.1	26.1 ± 5.2	25.0 ± 4.5	26.0 ± 5.3	25.2 ± 4.5
Current smokers, %	8.6	12.2	12.0	7.5	17.0	5.0
Pack-years of smoking among ever-smokers	9.2 ± 15.4	8.4 ± 15.2	11.1 ± 17.4	7.0 ± 13.4	12.5 ± 18.8	6.4 ± 12.2
Alcohol intake, g/d	7.3 ± 11.1	4.3 ± 7.9	6.4 ± 11.2	5.2 ± 8.4	8.7 ± 13.5	4.1 ± 6.8
Hypertension, %	19.1	19.7	17.9	18.9	19.4	17.4
Hypercholesterolemia, %	30.1	32.3	30.8	30.8	31.0	30.5
Cholesterol-lowering drug use, %	3.9	4.2	3.8	4.2	3.8	4.0
Regular aspirin or NSAID use, ³ %	52.0	51.6	53.8	48.2	53.9	49.0

¹ Values are means ± SDs for continuous variables and percentages for categorical variables unless otherwise specified. All variables were standardized by age at blood draw. MET, metabolic equivalent of task; AHEI, Alternative Healthy Eating Index; SSB, sugar-sweetened beverages; NSAID, nonsteroidal anti-inflammatory drug.

² Excluded SSB, fruit juice and fruit in the score calculation.

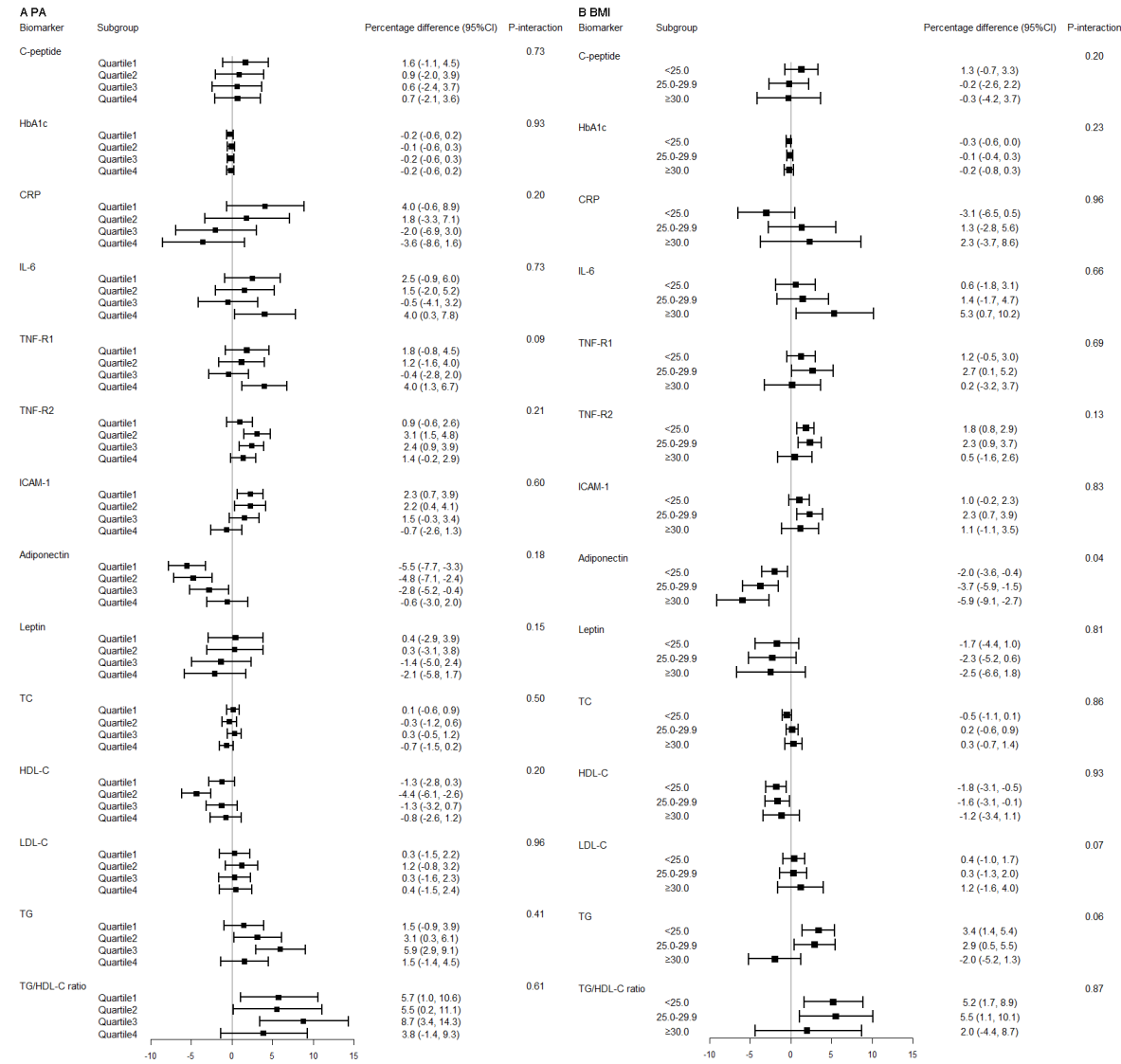
³ Regular users were defined as ≥2 tablets of aspirin (325 mg/tablet) or NSAIDs per week.

Supplementary Table 3. Biomarker concentrations according to total fructose quartiles in HPFS, NHS and NHSII ¹

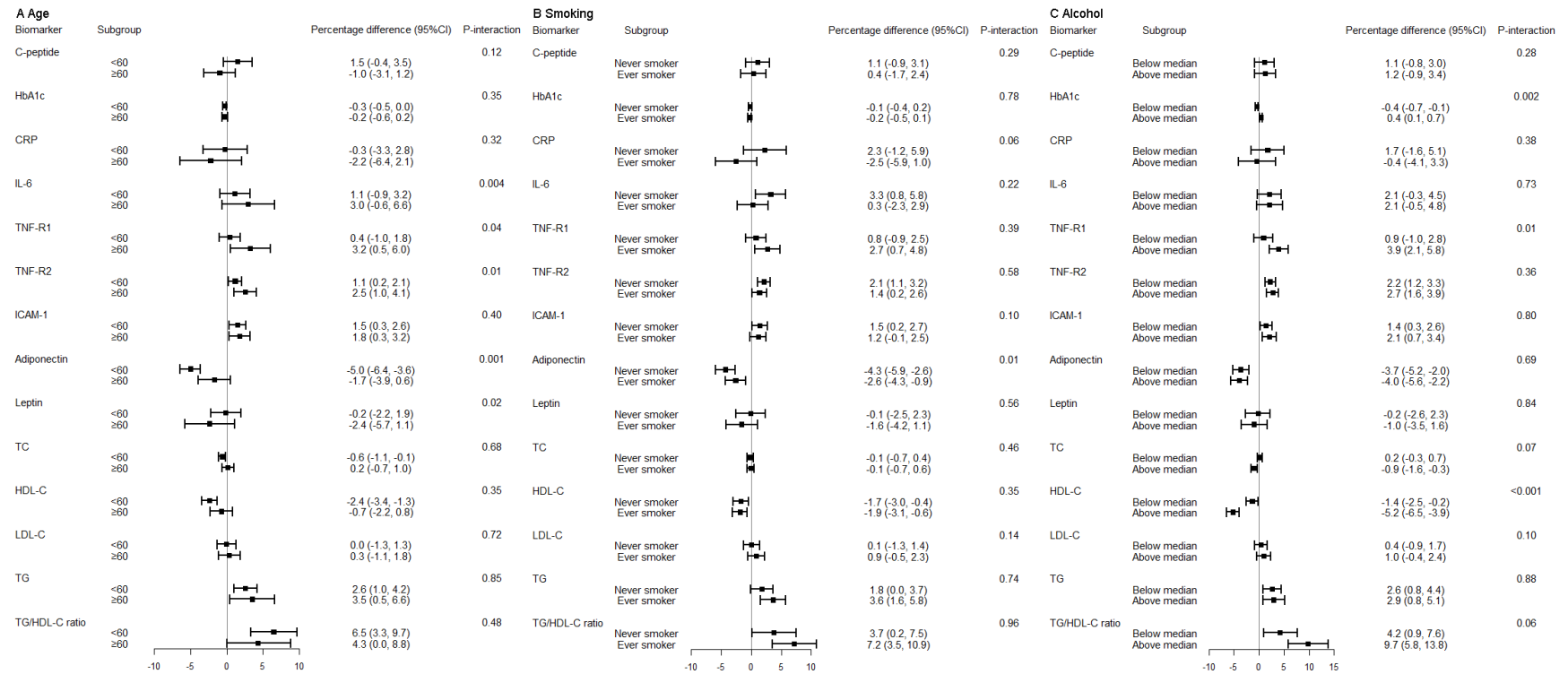
	HPFS (n=6858)		NHS (n=15,400)		NHSII (n=19,456)	
	Quartile 1 n=1714	Quartile 4 n=1714	Quartile 1 n=3849	Quartile 4 n=3849	Quartile 1 n=4864	Quartile 4 n=4863
Insulinemic/glycemic markers						
C-peptide, ng/mL	2.0 (1.4--2.9)	1.9 (1.3--2.8)	1.7 (1.2--2.4)	1.6 (1.2--2.3)	1.4 (1.0--1.9)	1.4 (1.0--2.0)
HbA1c, %	5.7 (5.4--5.9)	5.6 (5.4--5.8)	5.4 (5.2--5.6)	5.4 (5.2--5.6)	5.2 (5.1--5.4)	5.3 (5.1--5.5)
Inflammatory markers						
CRP, mg/L	1.1 (0.6--2.2)	0.9 (0.5--2.0)	1.7 (0.8--3.8)	1.6 (0.7--3.6)	0.9 (0.4--2.3)	0.8 (0.3--1.9)
IL-6, pg/mL	1.0 (0.7--1.6)	1.0 (0.7--1.4)	1.1 (0.7--1.7)	1.1 (0.8--1.8)	0.9 (0.7--1.4)	0.9 (0.7--1.4)
TNF-R1, pg/mL	1225 (1075--1495)	1378 (1138--1638)	1259 (1074--1486)	1323 (1120--1585)	1109 (956--1292)	1074 (960--1252)
TNF-R2, pg/mL	2349 (2023--2734)	2604 (2182--3032)	2471 (2074--2895)	2575 (2193--3052)	2159 (1876--2521)	2236 (1951--2539)
ICAM-1, ng/mL	246 (217--285)	255 (222--294)	241 (214--281)	248 (215--285)	230 (204--257)	236 (206--271)
Adiponectin, ng/mL	6788 (4875--9732)	6443 (4507--8789)	10475 (7753--13241)	10572 (7724--13345)	8493 (6393--11383)	7861 (5754--10552)
Leptin, ng/mL	7.6 (4.7--11.5)	6.3 (3.9--10.0)	24.2 (14.1--39.4)	22.0 (11.9--36.1)	19.4 (12.6--30.4)	17.7 (11.4--28.5)
Lipid markers						
TC, mg/dL	202 (180--227)	199 (172--223)	220 (194--246)	223 (196--249)	195 (173--219)	192 (172--218)
HDL-C, mg/dL	44 (37--55)	41 (35--49)	61 (51--73)	58 (48--69)	62 (52--75)	58 (50--67)
LDL-C, mg/dL	127 (106--148)	126 (104--148)	136 (112--162)	140 (118--163)	109 (90--128)	109 (94--132)
TG, mg/dL	121 (80--175)	123 (89--171)	106 (78--149)	113 (81--158)	90 (64--133)	91 (65--135)
TG/HDL-C ratio	2.8 (1.6--4.5)	3.0 (1.9--4.7)	1.8 (1.2--2.7)	2.0 (1.3--3.0)	1.3 (0.9--2.1)	1.5 (1.0--2.2)

¹CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride. The log-transformed biomarker concentrations were back transformed and are presented as median values (IQRs).

Supplementary Figure 2. Percentage differences (95% confidence intervals) in biomarker concentrations associated with 20 g/d fructose intake stratified by (A) physical activity quartiles (medians for quartile 1 to 4: 7.9, 19.5, 33.0 and 57.8 MET-hours/week in HPFS, 2.2, 6.7, 14.2 and 30.2 MET-hours/week in NHS, and 2.1, 7.7, 16.0 and 36.2 MET-hours/week in NHSII) and (B) BMI categories in the combined cohort (n=41,714). Models were adjusted for the same set of covariates as in Table 2.



Supplementary Figure 3. Percentage differences (95% confidence intervals) in biomarker concentrations associated with 20 g/d fructose intake stratified by (A) age (B) smoking status and (C) alcohol consumption in the combined cohort (n=41,714). Models were adjusted for the same set of covariates as in Table 2.



Supplementary Table 4. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d total fructose in sensitivity analyses ¹

	Among controls	Among participants with fasting samples	Among participants without a history of hypertension or hypercholesterolemia	Among participants whose FFQ preceded blood draw by at least 1 year
Insulinemic/glycemic markers				
C-peptide				
n	6578	8960	6676	10,214
Model 1	-1.7 (-3.6, 0.2)	-2.5 (-4.0, -0.9) **	-1.9 (-3.8, 0.0)	-2.3 (-3.9, -0.7) *
Model 2	0.8 (-1.2, 2.8)	0.9 (-0.6, 2.5)	1.7 (-0.3, 3.8)	1.2 (-0.5, 2.9)
HbA1c				
n	5556	7131	4944	7782
Model 1	-0.1 (-0.3, 0.1)	0.0 (-0.2, 0.3)	0.0 (-0.3, 0.2)	-0.1 (-0.4, 0.1)
Model 2	-0.2 (-0.4, 0.0)	-0.1 (-0.3, 0.2)	-0.1 (-0.3, 0.2)	-0.2 (-0.5, 0.0)
Inflammatory markers				
CRP				
n	9351	11,614	9178	13,095
Model 1	-6.9 (-10.1, -3.7) ***	-5.9 (-8.8, -2.9) ***	-6.2 (-9.4, -2.9) ***	-6.6 (-9.3, -3.7) ***
Model 2	-0.1 (-3.4, 3.3)	0.5 (-2.5, 3.5)	-0.3 (-3.6, 3.1)	-0.1 (-3.0, 2.8)
IL-6				
n	6169	7814	6260	8051
Model 1	-1.0 (-3.3, 1.3)	-0.8 (-2.8, 1.3)	-0.1 (-2.4, 2.2)	-2.5 (-4.6, -0.3) *
Model 2	1.9 (-0.5, 4.3)	1.8 (-0.2, 4.0)	1.3 (-1.0, 3.7)	0.7 (-1.6, 3.0)
TNF-R1				
n	1987	2442	1928	1982
Model 1	1.5 (-0.1, 3.1)	2.1 (0.6, 3.7) *	1.5 (-0.1, 3.1)	3.1 (1.1, 5.1) **
Model 2	1.5 (-0.1, 3.1)	1.7 (0.2, 3.2) *	1.3 (-0.3, 2.9)	2.8 (0.7, 4.8) *
TNF-R2				
n	6166	7286	6055	7904
Model 1	2.4 (1.4, 3.5) ***	2.3 (1.4, 3.2) ***	3.3 (2.3, 4.3) ***	2.8 (1.9, 3.8) ***
Model 2	2.1 (1.0, 3.2) ***	1.9 (0.9, 2.8) ***	2.4 (1.4, 3.4) ***	2.3 (1.3, 3.3) ***
ICAM-1				
n	3382	4188	3106	5264
Model 1	0.7 (-0.5, 1.9)	0.2 (-0.9, 1.3)	0.7 (-0.5, 1.9)	0.2 (-0.8, 1.2)
Model 2	2.0 (0.7, 3.2) **	1.3 (0.2, 2.5) *	1.3 (0.0, 2.5) *	1.3 (0.3, 2.3) *
Adiponectin				
n	7714	9568	7683	10,583
Model 1	-2.5 (-4.0, -1.0) **	-3.0 (-4.4, -1.5) ***	-3.2 (-4.8, -1.7) ***	-2.8 (-4.2, -1.4) ***
Model 2	-3.0 (-4.5, -1.4) ***	-3.2 (-4.6, -1.7) ***	-3.3 (-4.9, -1.8) ***	-3.3 (-4.7, -1.9) ***
Leptin				

n	5114	6782	5775	6544
Model 1	-6.6 (-9.4, -3.7) ***	-7.3 (-9.7, -4.9) ***	-6.2 (-8.8, -3.5) ***	-8.2 (-10.7, -5.6) ***
Model 2	-0.6 (-3.0, 1.9)	-1.8 (-3.8, 0.4)	-1.4 (-3.7, 1.0)	-2.0 (-4.3, 0.3)
Lipid markers				
TC				
n	7572	10,683	8515	10,196
Model 1	-0.5 (-1.1, 0.1)	-0.4 (-0.9, 0.1)	-1.1 (-1.6, -0.6) ***	-0.5 (-1.1, 0.0) *
Model 2	-0.2 (-0.8, 0.3)	-0.2 (-0.6, 0.3)	-0.4 (-1.0, 0.2)	-0.1 (-0.6, 0.4)
HDL-C				
n	4398	5902	4443	7070
Model 1	-3.4 (-4.6, -2.1) ***	-4.0 (-5.0, -2.9) ***	-3.5 (-4.7, -2.3) ***	-3.3 (-4.4, -2.3) ***
Model 2	-2.3 (-3.6, -1.0) ***	-2.1 (-3.1, -1.0) ***	-1.5 (-2.7, -0.3) *	-1.8 (-2.8, -0.8) ***
LDL-C				
n	3714	4947	3708	5798
Model 1	-0.1 (-1.5, 1.3)	0.7 (-0.4, 1.9)	-0.4 (-1.7, 0.9)	0.1 (-1.0, 1.2)
Model 2	0.0 (-1.4, 1.4)	0.2 (-0.9, 1.4)	-0.1 (-1.5, 1.3)	0.3 (-0.8, 1.4)
TG				
n	5164	7430	5769	6680
Model 1	1.4 (-0.6, 3.4)	1.9 (0.2, 3.6) *	0.8 (-1.0, 2.7)	1.4 (-0.4, 3.3)
Model 2	2.8 (0.9, 4.8) **	2.7 (1.1, 4.3) **	2.5 (0.7, 4.4) *	2.9 (1.1, 4.7) **
TG/HDL-C ratio				
n	2881	4200	3152	4782
Model 1	5.5 (1.7, 9.5) **	6.2 (3.1, 9.5) ***	4.8 (1.4, 8.4) *	4.5 (1.5, 7.6) **
Model 2	8.3 (4.4, 12.2) ***	6.2 (3.2, 9.3) ***	4.7 (1.3, 8.2) *	5.8 (2.8, 8.8) ***

¹ Models were adjusted for the same set of covariates as in Table 2. CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; ref, reference. * 0.005≤P<0.05, ** 0.001≤P<0.005, *** P<0.001.

Supplementary Table 5. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in the combined cohort with additional adjustment for fiber intake ¹

	Total fructose	SSB fructose	Juice fructose	Fruit fructose
Insulinemic/glycemic markers				
C-peptide (n=12,433)				
Model 1	-2.1 (-3.5, -0.7) **	6.1 (4.2, 8.1) ***	0.0 (-3.0, 3.0)	-11.2 (-13.1, -9.3) ***
Model 2	1.5 (0.1, 3.0) *	3.2 (1.4, 5.0) ***	4.0 (1.1, 6.9) *	-5.6 (-8.0, -3.1) ***
HbA1c (n=9912)				
Model 1	-0.1 (-0.3, 0.1)	0.1 (-0.2, 0.3)	0.3 (-0.1, 0.7)	-0.4 (-0.7, -0.1) *
Model 2	-0.1 (-0.4, 0.1)	-0.3 (-0.6, -0.1) *	0.5 (0.1, 0.9) *	0.2 (-0.2, 0.6)
Inflammatory markers				
CRP (n=16,810)				
Model 1	-5.9 (-8.3, -3.4) ***	12.7 (9.3, 16.2) ***	-8.2 (-13.1, -3.1) **	-18.9 (-22.1, -15.6) ***
Model 2	1.0 (-1.5, 3.6)	6.2 (3.2, 9.2) ***	2.9 (-2.0, 8.1)	-5.2 (-9.6, -0.5) *
IL-6 (n=11,011)				
Model 1	-0.7 (-2.5, 1.0)	5.6 (3.5, 7.8) ***	-2.9 (-6.4, 0.7)	-9.9 (-12.4, -7.4) ***
Model 2	2.1 (0.3, 3.9) *	2.2 (0.2, 4.2) *	1.8 (-1.6, 5.4)	-3.8 (-7.1, -0.4) *
TNF-R1 (n=3314)				
Model 1	1.9 (0.6, 3.2) *	2.1 (0.5, 3.7) *	0.1 (-2.6, 2.8)	-0.8 (-2.9, 1.3)
Model 2	1.7 (0.3, 3.0) *	0.5 (-1.0, 2.1)	1.2 (-1.4, 3.8)	0.7 (-1.9, 3.4)
TNF-R2 (n=10,708)				
Model 1	2.4 (1.6, 3.1) ***	3.1 (2.2, 4.0) ***	-1.4 (-2.9, 0.2)	0.0 (-1.2, 1.2)
Model 2	1.9 (1.1, 2.7) ***	1.8 (0.9, 2.7) ***	-0.6 (-2.1, 0.9)	1.0 (-0.5, 2.5)
ICAM-1 (n=6248)				
Model 1	0.5 (-0.4, 1.4)	3.0 (1.9, 4.2) ***	-1.2 (-3.0, 0.6)	-4.8 (-6.1, -3.5) ***
Model 2	1.6 (0.7, 2.6) ***	1.5 (0.4, 2.5) *	0.8 (-0.9, 2.6)	-0.9 (-2.6, 0.8)
Adiponectin (n=13,893)				
Model 1	-3.1 (-4.3, -1.9) ***	-6.2 (-7.6, -4.8) ***	-3.9 (-6.2, -1.5) **	3.0 (1.1, 4.9) **
Model 2	-3.7 (-4.9, -2.5) ***	-4.1 (-5.5, -2.7) ***	-6.6 (-8.8, -4.4) ***	0.1 (-2.2, 2.5)
Leptin (n=9831)				
Model 1	-6.4 (-8.4, -4.4) ***	5.3 (2.7, 8.0) ***	-9.7 (-13.8, -5.3) ***	-17.3 (-20.2, -14.4) ***
Model 2	-0.6 (-2.3, 1.2)	1.5 (-0.6, 3.6)	0.9 (-2.8, 4.7)	-6.9 (-10.2, -3.5) ***
Lipid markers				
TC (n=14,979)				
Model 1	-0.4 (-0.9, 0.0) *	0.8 (0.4, 1.3) ***	-0.1 (-1.0, 0.8)	-2.2 (-2.9, -1.5) ***
Model 2	0.0 (-0.4, 0.4)	0.3 (-0.2, 0.8)	0.2 (-0.7, 1.0)	-0.6 (-1.4, 0.2)
HDL-C (n=8623)				
Model 1	-3.6 (-4.5, -2.7) ***	-4.3 (-5.4, -3.2) ***	0.5 (-1.4, 2.4)	0.3 (-1.0, 1.7)
Model 2	-1.9 (-2.8, -1.0) ***	-2.2 (-3.3, -1.2) ***	0.1 (-1.6, 1.8)	1.2 (-0.4, 2.9)
LDL-C (n=7169)				

Model 1	0.5 (-0.5, 1.5)	2.4 (1.1, 3.6) ***	0.6 (-1.4, 2.7)	-2.1 (-3.5, -0.6) **
Model 2	0.7 (-0.2, 1.7)	1.5 (0.3, 2.6) *	0.6 (-1.3, 2.5)	-0.6 (-2.4, 1.1)
TG (n=10,234)				
Model 1	1.6 (0.2, 3.1) *	6.1 (4.4, 7.8) ***	1.0 (-1.9, 4.1)	-6.0 (-8.2, -3.7) ***
Model 2	2.8 (1.4, 4.2) ***	3.1 (1.5, 4.7) ***	4.9 (2.2, 7.8) ***	-1.0 (-3.7, 1.8)
TG/HDL-C ratio (n=6092)				
Model 1	5.4 (2.7, 8.1) ***	10.6 (7.3, 14.1) ***	1.7 (-3.4, 7.2)	-4.3 (-8.0, -0.5) *
Model 2	5.9 (3.3, 8.5) ***	6.7 (3.7, 9.8) ***	4.7 (-0.1, 9.7)	-0.6 (-5.1, 4.1)

¹ Models were adjusted for the same set of covariates as in Table 2 except fiber intake was additionally adjusted in Model 2, and each fructose source was mutually adjusted for other sources. CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; ref, reference. * 0.005≤P<0.05, ** 0.001≤P<0.005, *** P<0.001.

Supplementary Table 6. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in the combined cohort not adjusted for BMI¹

	Total fructose	SSB fructose	Juice fructose	Fruit fructose
Insulinemic/glycemic markers				
C-peptide (n=12,433)				
Model 1	-2.1 (-3.5, -0.7) **	6.1 (4.2, 8.1) ***	0.0 (-3.0, 3.0)	-11.2 (-13.1, -9.3) ***
Model 2	-1.9 (-3.3, -0.4) *	2.6 (0.8, 4.5) *	0.4 (-2.5, 3.3)	-7.8 (-9.9, -5.6) ***
HbA1c (n=9912)				
Model 1	-0.1 (-0.3, 0.1)	0.1 (-0.2, 0.3)	0.3 (-0.1, 0.7)	-0.4 (-0.7, -0.1) *
Model 2	-0.3 (-0.6, -0.1) **	-0.3 (-0.6, -0.1) *	0.3 (-0.1, 0.7)	-0.3 (-0.6, 0.0)
Inflammatory markers				
CRP (n=16,810)				
Model 1	-5.9 (-8.3, -3.4) ***	12.7 (9.3, 16.2) ***	-8.2 (-13.1, -3.1) **	-18.9 (-22.1, -15.6) ***
Model 2	-6.1 (-8.6, -3.6) ***	5.1 (2.0, 8.4) **	-4.7 (-9.6, 0.5)	-10.9 (-14.7, -7.0) ***
IL-6 (n=11,011)				
Model 1	-0.7 (-2.5, 1.0)	5.6 (3.5, 7.8) ***	-2.9 (-6.4, 0.7)	-9.9 (-12.4, -7.4) ***
Model 2	-0.8 (-2.6, 1.1)	1.7 (-0.3, 3.8)	-1.7 (-5.2, 1.9)	-5.0 (-7.8, -2.1) ***
TNF-R1 (n=3314)				
Model 1	1.9 (0.6, 3.2) *	2.1 (0.5, 3.7) *	0.1 (-2.6, 2.8)	-0.8 (-2.9, 1.3)
Model 2	0.7 (-0.7, 2.0)	0.5 (-1.1, 2.1)	-0.4 (-3.0, 2.3)	0.0 (-2.2, 2.3)
TNF-R2 (n=10,708)				
Model 1	2.4 (1.6, 3.1) ***	3.1 (2.2, 4.0) ***	-1.4 (-2.9, 0.2)	0.0 (-1.2, 1.2)
Model 2	1.2 (0.5, 2.0) **	1.7 (0.8, 2.6) ***	-1.5 (-3.0, 0.0)	1.0 (-0.3, 2.3)
ICAM-1 (n=6248)				
Model 1	0.5 (-0.4, 1.4)	3.0 (1.9, 4.2) ***	-1.2 (-3.0, 0.6)	-4.8 (-6.1, -3.5) ***
Model 2	1.1 (0.2, 2.0) *	1.3 (0.3, 2.4) *	0.4 (-1.3, 2.2)	-1.4 (-2.8, 0.0) *
Adiponectin (n=13,893)				
Model 1	-3.1 (-4.3, -1.9) ***	-6.2 (-7.6, -4.8) ***	-3.9 (-6.2, -1.5) **	3.0 (1.1, 4.9) **
Model 2	-1.6 (-2.8, -0.3) *	-3.7 (-5.1, -2.3) ***	-4.1 (-6.4, -1.7) **	1.7 (-0.3, 3.7)
Leptin (n=9831)				
Model 1	-6.4 (-8.4, -4.4) ***	5.3 (2.7, 8.0) ***	-9.7 (-13.8, -5.3) ***	-17.3 (-20.2, -14.4) ***
Model 2	-7.5 (-9.5, -5.4) ***	-0.3 (-2.8, 2.2)	-8.8 (-12.9, -4.6) ***	-12.5 (-15.7, -9.2) ***
Lipid markers				
TC (n=14,979)				
Model 1	-0.4 (-0.9, 0.0) *	0.8 (0.4, 1.3) ***	-0.1 (-1.0, 0.8)	-2.2 (-2.9, -1.5) ***
Model 2	-0.3 (-0.7, 0.2)	0.4 (-0.1, 0.8)	0.0 (-0.8, 0.8)	-1.4 (-2.1, -0.7) ***
HDL-C (n=8623)				
Model 1	-3.6 (-4.5, -2.7) ***	-4.3 (-5.4, -3.2) ***	0.5 (-1.4, 2.4)	0.3 (-1.0, 1.7)
Model 2	-0.7 (-1.7, 0.2)	-1.7 (-2.8, -0.6) **	1.3 (-0.5, 3.1)	0.6 (-0.9, 2.0)
LDL-C (n=7169)				

Model 1	0.5 (-0.5, 1.5)	2.4 (1.1, 3.6) ***	0.6 (-1.4, 2.7)	-2.1 (-3.5, -0.6) **
Model 2	0.2 (-0.7, 1.2)	1.4 (0.2, 2.6) *	0.5 (-1.4, 2.4)	-1.3 (-2.8, 0.2)
TG (n=10,234)				
Model 1	1.6 (0.2, 3.1) *	6.1 (4.4, 7.8) ***	1.0 (-1.9, 4.1)	-6.0 (-8.2, -3.7) ***
Model 2	0.4 (-1.0, 1.8)	2.3 (0.7, 4.0) *	1.8 (-1.0, 4.7)	-1.4 (-3.8, 1.2)
TG/HDL-C ratio (n=6092)				
Model 1	5.4 (2.7, 8.1) ***	10.6 (7.3, 14.1) ***	1.7 (-3.4, 7.2)	-4.3 (-8.0, -0.5) *
Model 2	2.6 (0.0, 5.3)	5.1 (2.0, 8.4) **	1.7 (-3.3, 6.9)	-0.5 (-4.6, 3.7)

¹ Models were adjusted for the same set of covariates as in Table 2 except BMI was not adjusted in Model 2, and each fructose source was mutually adjusted for other sources. CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; ref, reference. * 0.005≤P<0.05, ** 0.001≤P<0.005, *** P<0.001.

Supplementary Table 7. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in HPFS ¹

	SSB fructose	Juice fructose	Fruit fructose
Insulinemic/glycemic markers			
C-peptide (n=3946)			
Model 1	5.7 (2.7, 8.7) ***	0.6 (-4.7, 6.2)	-12.4 (-15.5, -9.2) ***
Model 2	5.2 (2.3, 8.1) ***	4.1 (-1.2, 9.7)	-7.8 (-11.3, -4.2) ***
HbA1c (n=1919)			
Model 1	-0.2 (-0.8, 0.4)	0.8 (-0.3, 2.0)	0.1 (-0.7, 0.8)
Model 2	-0.4 (-1.0, 0.2)	1.4 (0.3, 2.6) *	0.5 (-0.4, 1.3)
Inflammatory markers			
CRP (n=4109)			
Model 1	7.6 (2.3, 13.2) **	-5.5 (-14.3, 4.3)	-16.9 (-21.9, -11.6) ***
Model 2	3.7 (-1.3, 8.9)	3.8 (-5.5, 13.9)	-5.7 (-11.7, 0.8)
IL-6 (n=2037)			
Model 1	0.9 (-2.9, 4.9)	3.5 (-4.1, 11.8)	-8.8 (-13.2, -4.2) ***
Model 2	-1.3 (-5.1, 2.6)	6.7 (-1.1, 15.1)	-3.2 (-8.3, 2.2)
TNF-R1 (n=250)			
Model 1	0.9 (-3.7, 5.8)	5.8 (-5.0, 17.8)	1.3 (-4.8, 7.7)
Model 2	0.8 (-4.1, 6.0)	3.6 (-7.2, 15.6)	1.1 (-5.9, 8.6)
TNF-R2 (n=2126)			
Model 1	4.0 (2.4, 5.6) ***	0.0 (-3.3, 3.4)	0.0 (-2.1, 2.1)
Model 2	3.1 (1.5, 4.8) ***	-0.3 (-3.5, 3.1)	0.7 (-1.6, 3.1)
ICAM-1 (n=2148)			
Model 1	3.6 (1.8, 5.5) ***	0.7 (-2.5, 3.9)	-4.7 (-6.6, -2.7) ***
Model 2	1.8 (-0.1, 3.6)	2.6 (-0.5, 5.8)	-2.9 (-5.1, -0.7) *
Adiponectin (n=2455)			
Model 1	-4.5 (-7.7, -1.1) *	-9.9 (-15.2, -4.4) ***	0.5 (-3.5, 4.6)
Model 2	-3.4 (-6.7, 0.1)	-11.2 (-16.2, -5.9) ***	0.4 (-4.0, 5.0)
Leptin (n=2762)			
Model 1	2.4 (-2.4, 7.3)	-5.8 (-14.1, 3.4)	-21.7 (-26.2, -17.0) ***
Model 2	3.0 (-0.9, 7.1)	-0.8 (-8.0, 7.0)	-11.0 (-15.6, -6.1) ***
Lipid markers			
TC (n=2612)			
Model 1	1.1 (-0.1, 2.3)	1.3 (-1.0, 3.7)	-2.4 (-3.8, -0.9) **
Model 2	1.3 (0.1, 2.4) *	2.1 (-0.1, 4.4)	-1.0 (-2.5, 0.5)
HDL-C (n=1738)			
Model 1	-2.6 (-4.7, -0.5) *	-1.2 (-5.4, 3.1)	-1.3 (-3.8, 1.4)
Model 2	-0.8 (-2.8, 1.3)	-0.8 (-4.7, 3.4)	-0.4 (-3.1, 2.3)
LDL-C (n=2094)			
Model 1	1.6 (-0.5, 3.7)	3.3 (-0.7, 7.4)	-1.1 (-3.5, 1.3)

Model 2	1.7 (-0.3, 3.8)	3.7 (-0.1, 7.7)	0.9 (-1.6, 3.5)
TG (n=1598)			
Model 1	5.8 (1.6, 10.1) *	2.4 (-5.1, 10.6)	-3.4 (-8.0, 1.4)
Model 2	4.4 (0.5, 8.5) *	4.2 (-3.2, 12.1)	0.6 (-4.4, 5.8)
TG/HDL-C ratio (n=1516)			
Model 1	9.2 (3.2, 15.6) **	2.4 (-8.3, 14.4)	-1.8 (-8.4, 5.3)
Model 2	6.1 (0.5, 12.0) *	4.7 (-5.6, 16.2)	1.4 (-5.6, 8.9)

¹ Models were adjusted for the same set of covariates as in Table 2, and each fructose source was mutually adjusted for other sources. CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; ref, reference. * 0.005≤P<0.05, ** 0.001≤P<0.005, *** P<0.001.

Supplementary Table 8. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in NHS ¹

	SSB fructose	Juice fructose	Fruit fructose
Insulinemic/glycemic markers			
C-peptide (n=6550)			
Model 1	6.4 (3.1, 9.9) ***	0.8 (-3.3, 5.1)	-10.7 (-13.4, -7.9) ***
Model 2	2.3 (-0.7, 5.3)	4.4 (0.5, 8.4) *	-7.5 (-10.2, -4.6) ***
HbA1c (n=5711)			
Model 1	-0.2 (-0.6, 0.2)	0.4 (-0.1, 1.0)	-0.4 (-0.8, 0.1)
Model 2	-0.6 (-0.9, -0.2) **	0.5 (-0.1, 1.0)	-0.4 (-0.8, 0.1)
Inflammatory markers			
CRP (n=9054)			
Model 1	11.9 (6.2, 18.0) ***	-5.8 (-12.7, 1.7)	-15.1 (-19.8, -10.1) ***
Model 2	6.7 (1.8, 11.9) *	6.2 (-0.8, 13.7)	-7.4 (-12.4, -2.0) *
IL-6 (n=5926)			
Model 1	7.4 (3.5, 11.4) ***	-2.0 (-7.1, 3.4)	-9.5 (-13.1, -5.7) ***
Model 2	3.3 (-0.4, 7.0)	2.6 (-2.5, 8.0)	-3.9 (-7.9, 0.3)
TNF-R1 (n=1729)			
Model 1	2.8 (-0.4, 6.1)	1.8 (-2.4, 6.1)	-0.5 (-3.4, 2.6)
Model 2	0.3 (-2.7, 3.4)	3.0 (-0.9, 7.2)	0.8 (-2.4, 4.0)
TNF-R2 (n=5847)			
Model 1	3.4 (1.7, 5.1) ***	-1.7 (-3.9, 0.6)	-0.2 (-2.0, 1.6)
Model 2	1.7 (0.1, 3.3) *	-0.7 (-2.9, 1.6)	0.8 (-1.1, 2.7)
ICAM-1 (n=3130)			
Model 1	1.1 (-0.8, 3.0)	-1.7 (-4.2, 1.0)	-4.7 (-6.6, -2.6) ***
Model 2	0.2 (-1.5, 1.9)	0.3 (-2.2, 2.8)	-0.2 (-2.3, 2.0)
Adiponectin (n=8100)			
Model 1	-7.5 (-9.5, -5.5) ***	-2.0 (-5.1, 1.1)	3.1 (0.7, 5.4) *
Model 2	-5.4 (-7.4, -3.4) ***	-4.3 (-7.1, -1.4) **	1.2 (-1.2, 3.7)
Leptin (n=3372)			
Model 1	4.0 (-1.2, 9.6)	-9.0 (-16.0, -1.4) *	-7.5 (-12.9, -1.7) *
Model 2	-1.0 (-4.9, 3.0)	1.3 (-4.6, 7.6)	-4.6 (-9.2, 0.2)
Lipid markers			
TC (n=6741)			
Model 1	0.8 (-0.1, 1.8)	0.3 (-1.0, 1.7)	-1.5 (-2.5, -0.5) **
Model 2	0.4 (-0.5, 1.2)	0.3 (-1.0, 1.5)	-1.0 (-2.0, 0.0)
HDL-C (n=5565)			
Model 1	-4.2 (-5.8, -2.6) ***	0.9 (-1.4, 3.3)	0.7 (-1.1, 2.5)
Model 2	-2.0 (-3.5, -0.4) *	0.6 (-1.5, 2.8)	0.5 (-1.3, 2.3)
LDL-C (n=3757)			
Model 1	2.1 (0.1, 4.1) *	-0.4 (-3.1, 2.4)	-2.6 (-4.6, -0.6) *

Model 2	1.2 (-0.6, 3.1)	-0.7 (-3.3, 1.8)	-2.8 (-4.8, -0.7) *
TG (n=4428)			
Model 1	5.0 (1.8, 8.2) **	4.6 (-0.1, 9.4)	-4.0 (-7.3, -0.6) *
Model 2	3.5 (0.6, 6.5) *	6.8 (2.4, 11.3) **	0.1 (-3.5, 3.7)
TG/HDL-C ratio (n=3293)			
Model 1	6.0 (1.0, 11.2) *	2.2 (-4.6, 9.5)	-3.1 (-8.2, 2.3)
Model 2	3.5 (-1.0, 8.2)	5.0 (-1.5, 11.8)	1.9 (-3.5, 7.7)

¹ Models were adjusted for the same set of covariates as in Table 2, and each fructose source was mutually adjusted for other sources. CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; ref, reference. * 0.005≤P<0.05, ** 0.001≤P<0.005, *** P<0.001.

Supplementary Table 9. Percentage of differences (95% CIs) in biomarker concentrations associated with 20 g/d of fructose from SSB, juice and fruit in NHSII ¹

	SSB fructose	Juice fructose	Fruit fructose
Insulinemic/glycemic markers			
C-peptide (n=1937)			
Model 1	6.4 (2.8, 10.1) ***	-4.6 (-10.7, 1.9)	-10.6 (-15.4, -5.5) ***
Model 2	2.5 (-0.7, 5.9)	3.2 (-3.1, 9.9)	-3.1 (-8.3, 2.4)
HbA1c (n=2282)			
Model 1	0.4 (0.1, 0.7) *	-0.4 (-1.1, 0.4)	-1.0 (-1.7, -0.4) **
Model 2	0.1 (-0.2, 0.4)	0.2 (-0.5, 0.8)	-0.2 (-0.9, 0.4)
Inflammatory markers			
CRP (n=3647)			
Model 1	17.1 (10.9, 23.6) ***	-17.6 (-26.9, -7.0) **	-32.0 (-38.7, -24.4) ***
Model 2	9.0 (3.8, 14.5) ***	-1.7 (-11.4, 9.0)	-14.0 (-22.1, -5.1) **
IL-6 (n=3048)			
Model 1	6.7 (3.7, 9.8) ***	-7.6 (-13.2, -1.7) *	-11.9 (-16.6, -6.8) ***
Model 2	3.3 (0.5, 6.1) *	-0.9 (-6.4, 4.9)	-3.6 (-8.8, 1.9)
TNF-R1 (n=1335)			
Model 1	1.3 (-0.5, 3.1)	-2.3 (-5.7, 1.2)	-2.6 (-5.7, 0.6)
Model 2	-0.1 (-1.8, 1.7)	-0.7 (-4.0, 2.7)	-1.3 (-4.6, 2.1)
TNF-R2 (n=2735)			
Model 1	2.2 (1.0, 3.4) ***	-1.7 (-4.0, 0.8)	0.0 (-2.2, 2.2)
Model 2	0.8 (-0.4, 2.1)	0.0 (-2.3, 2.3)	2.8 (0.5, 5.3) *
ICAM-1 (n=970)			
Model 1	5.0 (3.1, 7.0) ***	-3.6 (-7.4, 0.4)	-5.6 (-8.9, -2.2) **
Model 2	2.5 (0.6, 4.5) *	-1.3 (-5.0, 2.4)	-0.5 (-4.0, 3.2)
Adiponectin (n=3338)			
Model 1	-5.7 (-8.1, -3.2) ***	-3.2 (-8.1, 2.0)	5.2 (0.6, 10.0) *
Model 2	-3.2 (-5.6, -0.7) *	-8.0 (-12.6, -3.2) **	-1.4 (-5.8, 3.2)
Leptin (n=3697)			
Model 1	7.6 (3.8, 11.4) ***	-13.1 (-19.4, -6.4) ***	-22.2 (-26.9, -17.2) ***
Model 2	2.7 (-0.3, 5.8)	1.4 (-4.5, 7.6)	-10.0 (-14.7, -5.0) ***
Lipid markers			
TC (n=5626)			
Model 1	0.6 (0.0, 1.2)	-1.3 (-2.7, 0.1)	-2.9 (-4.2, -1.7) ***
Model 2	0.0 (-0.6, 0.6)	-0.3 (-1.6, 0.9)	-1.6 (-2.9, -0.4) *
HDL-C (n=1320)			
Model 1	-6.0 (-8.0, -4.0) ***	1.0 (-3.1, 5.2)	2.2 (-1.4, 6.0)
Model 2	-3.6 (-5.5, -1.7) ***	0.8 (-2.8, 4.5)	0.0 (-3.4, 3.6)
LDL-C (n=1318)			
Model 1	3.1 (0.9, 5.5) *	-1.5 (-5.8, 2.9)	-2.2 (-5.9, 1.6)

Model 2	2.0 (-0.2, 4.2)	-0.4 (-4.3, 3.7)	1.1 (-2.7, 5.0)
TG (n=4208)			
Model 1	6.0 (3.7, 8.3) ***	-3.1 (-7.3, 1.3)	-9.3 (-13.2, -5.3) ***
Model 2	1.8 (-0.3, 3.9)	3.3 (-0.7, 7.5)	-0.7 (-4.7, 3.5)
TG/HDL-C ratio (n=1283)			
Model 1	16.7 (10.4, 23.3) ***	-3.4 (-13.2, 7.6)	-11.3 (-19.3, -2.5) *
Model 2	8.8 (3.4, 14.5) **	0.8 (-8.0, 10.5)	-2.9 (-11.1, 6.1)

¹ Models were adjusted for the same set of covariates as in Table 2, and each fructose source was mutually adjusted for other sources. CRP, C-reactive protein; IL-6, interleukin 6; TNF-R1, tumor necrosis factor receptor 1; TNF-R2, tumor necrosis factor receptor 2; ICAM-1, intracellular adhesion molecule 1; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; ref, reference. * 0.005≤P<0.05, ** 0.001≤P<0.005, *** P<0.001.