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The ecologic validity of fructose feeding trials: supraphysiological feeding of fructose in human trials requires careful consideration when drawing conclusions on cardiometabolic risk

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Background: Select trials of fructose overfeeding have been used to implicate fructose as a driver of cardiometabolic risk.

Objective: We examined temporal trends of fructose dose in human controlled feeding trials of fructose and cardiometabolic risk.

Methods: We combined studies from eight meta-analyses on fructose and cardiometabolic risk to assess the average fructose dose used in these trials. Two types of trials were identified: (1) substitution trials, in which energy from fructose was exchanged with equal energy from other carbohydrates and (2) addition trials, in which energy from fructose supplemented a diet compared to the diet alone.

Results: We included 64 substitution trials and 16 addition trials. The weighted average fructose dose in substitution trials was 101.7 g/day (95% CI: 98.4–105.1 g/day), and the weighted average fructose dose in addition trials was 187.3 g/day (95% CI: 181.4–192.9 g/day).

Conclusion: Average fructose dose in substitution and addition trials greatly exceed national levels of reported fructose intake (49 ± 1.0 g/day) (NHANES 1977–2004). Future trials using fructose doses at real world levels are needed.

Keywords: fructose, HFCS, dose, cardiometabolic risk, meta-analysis

Introduction

With the increase in high-fructose corn syrup (HFCS) consumption since 1970s, there has been rising interest in the role of sugars toward the development of cardiometabolic diseases (1). Particular attention has focused on the "fructose hypothesis," which suggests that the metabolic and endocrine responses unique to fructose are the main drivers in the etiology of obesity, diabetes, and cardiometabolic risk (2, 3). While this perspective is well supported by lower

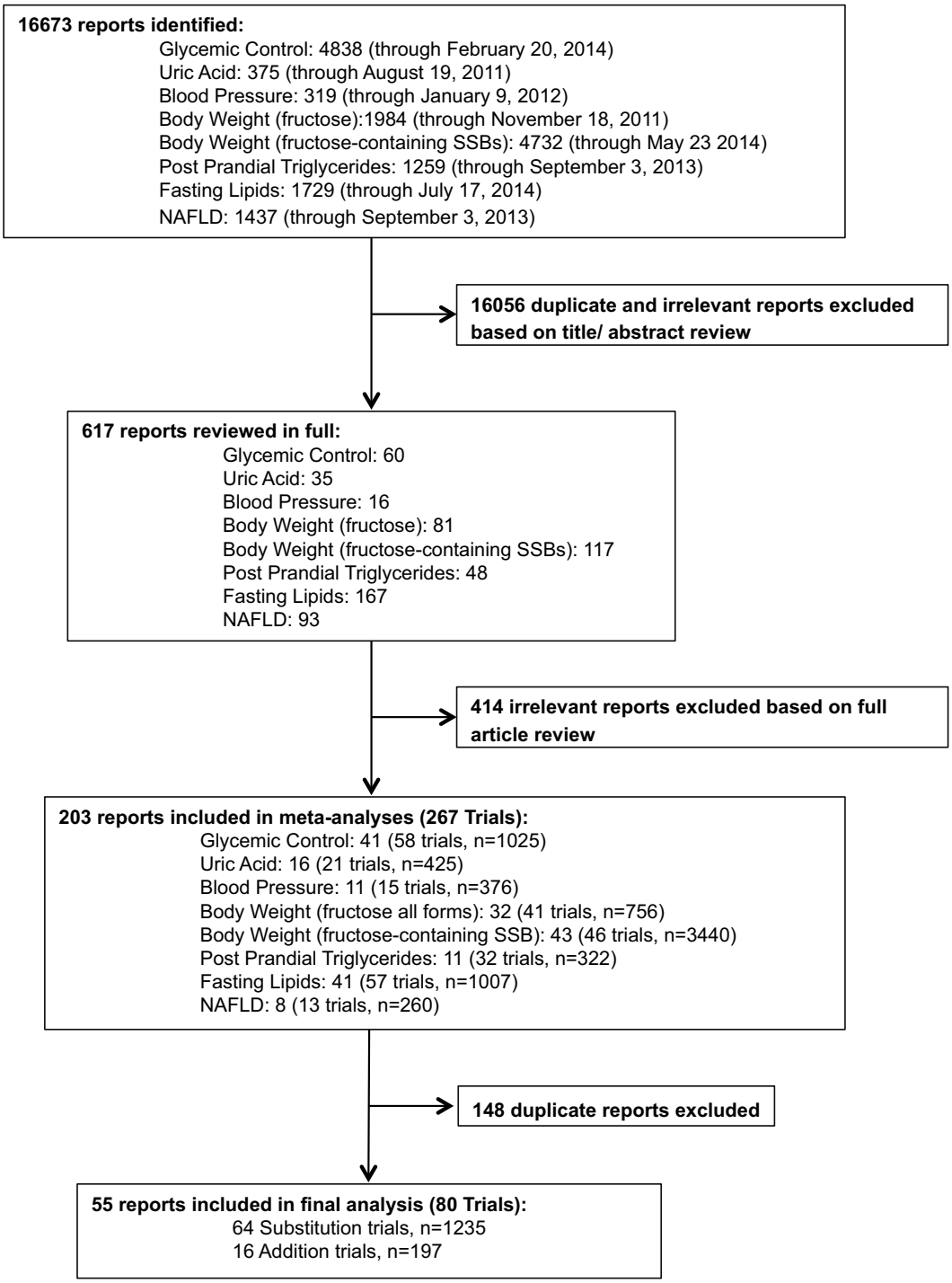

FIGURE 1 | Systematic search and selection strategy. Flow of literature for eight separate searches of the effect of fructose on: glycemic control (fasting blood glucose, fasting blood insulin, HbA1c), uric acid, blood pressure, body weight (fructose), body weight (fructose-containing sugars-sweetened beverages, post prandial triglycerides, fasting lipids, and NAFLD.

quality evidence from ecological studies (4) and animal models (5–7), it is not well supported by the highest level of evidence from controlled trials in humans (8–13).

A main limitation of these trials has been the use of extreme levels of fructose feeding not representative of real world conditions. The present analysis aims to quantify the dose of fructose used in trials assessing the effects of fructose and cardiometabolic risk, and compare it to national levels of fructose consumption in the United States at the average and 95th percentile levels of intake based on the

TABLE 1 | Characteristics of trials investigating the effect of fructose on cardiometabolic risk.

Reference	Subjects[a]	Age (years)	Setting	Design	Feeding control[b]	Randomization	Fructose dose[c]	Fructose form[d]	Comparator	Diet[e]	Follow-up	MQS[f]	Energy Balance	Funding sources[g]
SUBSTITUTION TRIALS														
(15)	5 HTG (3M:2F) 4 N (3M:1F)	42.8 ± 14.2	IP/OP, Israel	C	Met	No	300 g/d (55% E)	Mixed	Starch	77:05:18	∼24 d	7	Neutral	Agency
(16) (Study 1)	3 HTG	19 ± 0	IP, Australia	C	Met	No	∼255 g/d (50–52% E)	Mixed	Glucose	77:09:14	1 wk	6	Neutral	Agency
(16) (Study 2)	2 HTG	19 ± 0	IP, Australia	C	Met	No	∼255 g/d (52–55% E)	Mixed	Glucose	77:09:14	1 wk	6	Neutral	Agency
(17)	16 DM1	10 (2–16)	OP, Finland	C	Supp	No	∼40 g/d (20% E)	Mixed	Starch	45:35:20	1 wk	4	Neutral	Industry
(18)	10 type 4 HTG (5 DM2)	53.5 (26-67)	IP, Finland	C	Met	Yes	∼77.5 g/d (∼17% E)	Liquid	Starch, sucrose	45:35:20	10–20 d	6	Neutral	Agency
(19)	10 DM1 (5M:5F)	25.5 (19–70)	IP, Finland	C	Met	No	75 g/d (15% E)	Mixed	Starch	40:40:20	10 d	7	Neutral	Agency
(20)	12 N (8M:4F)	(20–26)	IP, Germany	C	Met	No	162 g/d (∼33% E)	Liquid	Glucose, sucrose	90:00:10	10 d	7	Neutral	–
(21)	68 N	(13–55)	OP, Finland	P	Dietary Advice	No	70 g/d (∼14% E)	Mixed	Sucrose	-	72 wks	5	Neutral	–
(22) (LC)	4 HTG (4M:0F)	48 ± 8.8	IP, USA	C	Met	No	∼39.5 g/d (9% E)	Liquid	D-Maltose	45:40:15	2 wks	7	Neutral	Agency and industry
(22) (HC)	4 HTG (4M:0F)	48 ± 8.8	IP, USA	C	Met	No	∼122 g/d (17%E)	Liquid	D-Maltose	85:00:15	2 wks	4	Neutral	Agency and industry
(22)	2 DM2 (2M:0F)	41 ± 1.4	IP, USA	C	Met	No	∼40 g/d (9% E)	Liquid	D-Maltose	45:40:15	2 wks	7	Neutral	Agency and industry
(23)	15 N	(21–35)	OP, Denmark	P	Supp	Yes	+250 g/d (+50% E)	Liquid	Glucose	44:38:18	1 wk	6	Positive	Agency and industry
(24)	16 type 4 HTG	57 (38–80)	OP, Poland	C	Supp	No	80 g/d	Liquid	Starch	45:50:15	28 d	7	Neutral	–
(25) – N (HF)	12 N (12M:0F)	39.8 ± 8.3	IP/OP, USA	C	Met	No	101.3 g/d (15% E)	Solid	Starch	43:42:15	5 wks	8	Neutral	–
(25) – N (LF)	12 N (12M:0F)	39.8 ± 8.3	IP/OP, USA	C	Met	No	50.6 g/d (7.5% E)	Solid	Starch	43:42:15	5 wks	8	Neutral	–
(25) – HI (HF)	12 HI (12M:0F)	39.5 ± 7.3	IP/OP, USA	C	Met	No	101.3 g/d (15% E)	Solid	Starch	43:42:15	5 wks	8	Neutral	–
(25) – HI (LF)	12 HI (12M:0F)	39.5 ± 7.3	IP/OP, USA	C	Met	No	50.6 g/d (7.5% E)	Solid	Starch	43:42:15	5 wks	8	Neutral	–
(26)	8 N (4M:4F)	26.7 (20–32)	IP/OP, USA	C	Met	Yes	∼79 g/d (14% E)	Liquid	Sucrose	∼43:40:17	2 wks	8	Neutral	Agency
(27)	11 N (4M:7F)	39.5 ± 11.4	IP/OP, USA	C	Met	No	∼81 g/d (13.2% E)	Mixed	Sucrose	55:30:15	2 wks	7	Neutral	Agency and industry
(28)	12 DM1 (6M:6F) 12 DM2 (5M:7F)	23 (15–32) 62 (36–80)	OP, USA	C	Met	Yes	∼137 g/d (21% E)	Mixed	Starch	55:30:15	8 d	8	Neutral	Industry

(Continued)

TABLE 1 | Continued

Reference	Subjects[a]	Age (years)	Setting	Design	Feeding control[b]	Randomization	Fructose dose[c]	Fructose form[d]	Comparator	Diet[e]	Follow-up	MQS[f]	Energy Balance	Funding sources[g]
(29)	7 DM2 (3M:4F)	50.9 ± 8.4	IP/OP, USA	C	Met	No	∼98 g/d (13.2% E)	Mixed	Sucrose	55:30:15	2 wks	7	Neutral	Agency and industry
(30) EXP 1	23 OW/OB	22.2	OP, France	P	Met	Yes	36 g/d (25%E)	Liquid	Glucose, galactose	25:50:25	2 wks	8	Negative	Industry
(30) EXP 2	18 OW/OB	22.2	OP, France	P	Met	Yes	36 g/d (25%E)	Liquid	Glucose, galactose	25:50:25	2 wks	8	Negative	Industry
(31)	10 DM2	64.4 (54–71)	OP, Ireland	C	Supp	No	55 g/d (11.6% E)	Liquid	Starch	42:38:20	4 wks	7	Neutral	Industry
(32)	18 DM2 (3M:15F)	57 ± 3.0	OP, USA	P	Supp	Yes	60 g/d (10% E)	Mixed	Starch	50:35:15	12 wks	8	Neutral	Agency and industry
(33)	8 DM2 (5M:3F)	40 ± 6.9	OP, France	C	Supp	Yes	30 g/d (8% E)	Mixed	Starch	50:30:20	8 wks	8	Neutral	Agency and industry
(34) – NGT	9 N (3M:6F)	48	OP, USA	C	Supp	No	∼79 g/d (15% E)	Mixed	Glucose	∼53:32:16	4 wks	8	Neutral	–
(34) – IGT	9 IGT (3M:6F)	53	OP, USA	C	Supp	No	∼64 g/d (15% E)	Mixed	Glucose	∼53:32:16	4 wks	8	Neutral	–
(35)	14 DM2 (14M:0F)	60 ± 4 (54–71)	IP/OP, USA	C	Met/Supp	No	∼55 g/d (12% E)	Mixed	Starch	53:27:20	23 wks	8	Neutral	Agency and industry
(36)	13 DM2 (5M:8F)	54 ± 11	OP, USA	C	Supp	Yes	60 g/d (7.5% E)	Mixed	Starch	50:35:15	26 wks	8	Neutral	Agency and industry
(37)	10 IR (10M: 0F)	47	IP, USA	C	Met	No	167 g/d (20% E)	Solid	Starch	51:36:13	5 wks	4	Neutral	–
(38)	8 DM2 (4M:4F)	55 ± 11.2	IP, USA	P	Met	No	∼100 g/d (13% E)	Mixed	Sucrose	55:30:15	12 wks	6	Neutral	Agency and industry
(67)	14 DM1, 6 DM2	46.9 ± 13.1	OP, France	P	Supp	Yes	∼25 g/d (5% E)	Mixed	Starch, sucrose	55:30:15	52 wks	7	Neutral	Agency and industry
(68)	6 DM2 (4M:2F)	53.7 ± 10.2	IP, USA	C	Met	No	∼100 g/d (13% E)	Mixed	Sucrose	55:30:15	100 d	4	Neutral	Agency and industry
(39)	6 DM1 (3M:3F) 12 DM2 (4M:8F)	23 (18–34) 62 (40–72)	OP, USA	C	Met	Yes	∼120 g/d (20% E)	Mixed	Starch	55:30:15	4 wks	8	Neutral	Agency
(40)	14 N (7M:7F)	34 (19–60)	IP/OP, USA	C	Met	Yes	∼120 g/d (20% E)	Mixed	Starch	55:30:15	4 wks	8	Neutral	Agency
(41)	10 DM2 (4M:6F)	61 ± 9.5	IP, Finland	C	Met	Yes	∼55 g/d (10% E)	Liquid	Starch	50:30:20	4 wks	9	Neutral	Agency
(42)	16 DM2 (7M:9F)	54.2 ± 9.2	OP, Brazil	C	Supp	No	63.2 g/d (20% E)	Liquid	Starch, sucrose	55:30:15	4 wks	7	Neutral	Industry
(43)	24 N (12M:12F)	41.3 ± 20.0	OP, USA	C	Met	Yes	85 g/d (17% E)	Mixed	Glucose	55:30:15	6 wks	9	Neutral	Agency
(44) – P1	24 N (12M:12F)	14.6 ± 1.2	OP, USA	P	Met	Yes	64.19 g/d (12% E)	Mixed	Starch	30:55:15	1 wk	9	Neutral	Agency and industry
(44) – P2	12 N (6M:6F)	14.8 ± 1.32	OP, USA	C	Met	Yes	∼151.32 g/d (24% E)	Mixed	Starch	60:25:15	1 wk	9	Neutral	Agency and industry

(Continued)

TABLE 1 | Continued

Reference	Subjects[a]	Age (years)	Setting	Design	Feeding control[b]	Randomization	Fructose dose[c]	Fructose form[d]	Comparator	Diet[e]	Follow-up	MQS[f]	Energy Balance	Funding sources[g]
(45)	12 N (6M:6F)	15.3 ± 0.8	OP, USA	C	Met	Yes	128.5g/d (40% E)	Mixed	Starch	60:25:15	8 d	9	Neutral	Agency and industry
(46)	25 DM2	62.3 ± 10.1	OP, Israel	P	Supp	Yes	22.5 g/d (4.5% E)	Liquid	Starch	–	12 wks	5	Neutral	–
(47)	6 OB (3M:3F)	15.2 ± 1.22	OP, USA	C	Met	Yes	∼149.1 g/d (24% E)	Mixed	Starch	60:25:15	1 wk	9	Neutral	Agency and industry
(48)	7 OW/OB (0M:7F)	(50–72)	IP, USA	C	Met	No	∼125 g/d (25% E)	Liquid	Starch	55:30:15	10 wks	7	Neutral	Agency
(49)	32 OW/OB (16M:16F)	53	IP/OP, USA	P	Met/Supp	No	∼182 g/d (+ 25% E)	Liquid	Glucose	55:30:15	10 wks	6	Positive	Agency
(50)	11 N (11M:0F)	24.6 ± 2.0	OP, Switzer-land	C	Met	Yes	∼+213 g/d (+ 35% E)	Liquid	Glucose	55:30:15	1 wk	8	Positive	Agency
(51) (LF)	29 N (29M:0F)	26.3 ± 6.6	OP, Switzer-land	C	Supp	Yes	∼40 g/d (7% E)	Liquid	Glucose, starch	51:14:35	3 wks	9	Positive	Agency
(51) (HF)	29 N (29M:0F)	26.3 ± 6.6	OP, Switzer-land	C	Supp	Yes	∼80 g/d (13% E)	Liquid	Glucose, sucrose	55:13:32	3 wks	9	Positive	Agency
(52)	131 OW/OB (29M:102F)	38.8 ± 8.8	OP, Mexico	P	Dietary advice	Yes	∼60 g/d (13% E)	Solid	Starch	55:30:15	6 wks	9	Negative	Agency
(53)	20 N (12M:8F)	30.5 ± 8.93	OP, Germany	P	Supp	Yes	∼+150 g/d (+ 22% E)	Liquid	Glucose	50:35:15	4 wks	7	Positive	Agency
(54)	32 OW/OB (16M:16F)	54 ± 8	IP/OP, USA	P	Met/Supp	No	∼+182 g/d (+ 25% E)	Liquid	Glucose	55:30:15	10 wks	6	Positive	Agency
(54)	48 N (27M:21F)	27.6 ± 7.1	IP/OP, USA	P	Met/Supp	No	∼+168 g/d (+ 25% E)	Liquid	Glucose HFCS	55:30:15	2 wks	6	Positive	Agency
(55)	28 CKD (17M:11F)	59 ± 15	OP, Poland	C	Dietary advice	No	∼56 g/d (10% E)	Mixed	Starch	55:30:15	6 wks	8	Neutral	Agency
(56)	31 OW/OB (16M:15F)	53.7 ± 8.1	IP/OP, USA	P	Met/Supp	No	∼+182 g/d (+25% E)	Liquid	Glucose	55:30:15	10 wks	6	Positive	Agency
(57)	9 N (9M:0F)	22.7 ± 1.8	OP, Switzer-land	C	Supp	Yes	∼80 g/d (+13% E)	Liquid	Glucose sucrose	55:31:14	3 wks	9	Positive	Agency
(58) – (NEB)	32 OW/OB (32M:0F)	33.9 ± 10.0	OP, UK	P	Met/Supp	Yes	∼204 g/d (25% E)	Liquid	Glucose	55:30:15	8 wks	10	Neutral	Agency
(58) – (PEB)	32 OW/OB (32M:0F)	33.9 ± 10.0	OP, UK	P	Met/Supp	Yes	∼+204 g/d (+25% E)	Liquid	Glucose	55:30:15	8 wks	10	Positive	Agency
(59)	28 N (28M:0F)	22.5 ± 1.6	OP, Switzer-land	P	Supp	Yes	∼212 g/d (+24% E)	Liquid	Glucose	–	7 d	9	Positive	Agency
(60)	9 N (4M:5F)	20.9 ± 2	OP, USA	C	Met	Yes	∼129 g/d (25% E)	Liquid	Glucose	50:34:16	8 d	8		–

(Continued)

TABLE 1 | Continued

Reference	Subjects[a]	Age (years)	Setting	Design	Feeding control[b]	Randomization	Fructose dose[c]	Fructose form[d]	Comparator	Diet[e]	Follow-up	MQS[f]	Energy Balance	Funding sources[g]
(61)	40 N (40M:20F)	17.9 ± 1.9	OP, USA	C	Supp	Yes	∼50 g/d (+10% E)	Liquid	Glucose	–	2 wks	7	Positive	Agency
(62)	21 OW (11M:10F)	13.5 ± 2.5	OP, USA	P	Supp	Yes	∼+99 g/d (+19.8% E)	Liquid	Glucose	–	4 wks	5	Neutral	Agency
(63)	73 OW (0M:73F)	39.7 ± 8.6	OP, Denmark	P	Supp	Yes	∼+60 g/d (+13.6% E)	Liquid	Glucose	45:34:21	4 wks	9	Positive	Agency
(61)	7 OW (3M:4F)	18 ± 0.4	OP, USA	C	Supp	Yes	∼+50 g/d (+6.7% E)	Liquid	Glucose	–	2 wks	8	Positive	Agency
ADDITION TRIALS														
(23)	8 N	21–35	OP, Denmark	C	Supp	No	∼250 g/d (∼+50% E)	Liquid	Diet alone	44:38:18	1 wk	5	Positive	Agency and industry
(30) EXP 2	14 OW/OB	22.2	OP, France	P	Met	Yes	∼+100 g/d (+97% E)	Liquid	Diet alone	0:35:65	2 wks	8	Negative	Industry
(64)	7 N (7M:0F)	24.70 ± 3.44	OP, Switzerland	C	Supp	No	∼+104 g/d (+18% E)	Liquid	Diet alone	55:30:15	4 wks	7	Positive	Agency
(65) (N)	8 N (8M:0F)	24.5 ± 4.5	OP, Switzerland	C	Supp	Yes	∼213 g/d (+35% E)	Liquid	Diet alone	55:30:15	7 d	9	Positive	Agency and industry
(65)	16 OFFDM2 (16M:0F)	24.7 ± 5.2	OP, Switzerland	C	Supp	Yes	∼220 g/d (+35% E)	Liquid	Diet alone	55:30:15	1 wk	8	Positive	Agency and industry
(49)	17 OW/OB (9M:8F)	52.5 ± 9.2	IP/OP, USA	C	Met/Supp	No	∼182 g/d (25% E)	Liquid	Diet alone	55:30:15	10 wks	6	Positive	Agency
(50)	11 N (11M:0F)	24.6	OP, Switzerland	C	Met/Supp	Yes	∼213 g/d (+35%E)	Liquid	Diet alone	55:30:15	7 d	8	Positive	Agency
(66)	8 N (8M:0F)	24.8 ± 3.2	OP, Switzerland	C	Supp	No	∼+212 g/d (+35% E)	Liquid	Diet alone	55:30:15	1 wk	6	Positive	Agency
(53)	10 N (7M:3F)	32.8 ± 9.3	OP, Germany	C	Supp	No	∼+150 g/d (+22% E)	Liquid	Diet alone	50:35:15	4 wks	6	Positive	Agency
(54)	17 OW/OB (9M:8F)	52.5 ± 9.3	IP/OP, USA	C	Met/Supp	No	∼+182 g/d (+25% E)	Liquid	Diet alone	55:30:15	10 wks	5	Positive	Agency
(54)	16 N (9M:7F)	28.0 ± 6.8	IP/OP, USA	C	Met/Supp	No	∼+168 g/d (+25% E)	Liquid	Diet alone	55:30:15	2 wks	6	Positive	Agency
(56)	16 OW/OB (9M:7F)	52.5 ± 9.3	IP/OP, USA	C	Met/Supp	No	∼+182 g/d (+25% E)	Liquid	Diet alone	55:30:15	10 wks	5	Positive	Agency
(58)	15 OW/OB (15M:0F)	35.0 ± 11.0	OP, UK	C	Supp	No	∼+203 g/d (+25% E)	Liquid	Diet alone	55:30:15	2 wks	8	Positive	Agency
(59) (F1.5)	7 N (7M:0F)	22.5 ± 1.6	OP, Switzerland	C	Supp	Yes	∼+104 g/d (∼+14% E)	Liquid	Diet alone	–	7 d	9	Positive	Agency

(Continued)

TABLE 1 | Continued

Reference	Subjects[a]	Age (years)	Setting	Design	Feeding control[b]	Randomization	Fructose dose[c]	Fructose form[d]	Comparator	Diet[e]	Follow-up	MQS[f]	Energy Balance	Funding sources[g]
(59) (F3.0)	17 N (17M:0F)	22.5 ± 1.6	OP, Switzerland	C	Supp	Yes	~212 g/d (+~24%E)	Liquid	Diet alone	–	7 d	10	Positive	Agency
(59) (F4.0)	10 N (10M:0F)	22.5 ± 1.6	OP, Switzerland	C	Supp	Yes	~293 g/d (~30% E)	Liquid	Diet alone	–	7 d	11	Positive	Agency

C, crossover; CKD, chronic kidney disease; d, days; DM1, person with diabetes mellitus type-1; DM2, person with diabetes mellitus type-2; E, energy; F, female EXP, experiment; F1.5/3.0/4/0, fructose at 1.5, 3.0, or 4.0 kg/day; HC, high carbohydrate; HF, high fructose; HI, hyperinsulinemic; HTG, hypertriglyceridemic; IGT, impaired glucose tolerance; IP, inpatient; IR, insulin resistant; LC, low carbohydrate; LF, low fructose; M, male; N, normal; NEB, neutral energy balance; OFFDM2, offspring of persons with type-2 diabetes mellitus; OP, outpatient; OW/OB, overweight/obese; P, parallel; PEB, positive energy balance; P1/2, protocol 1/2; Supp, supplement; UK, United Kingdom; USA, United States of America; wks, weeks.

[a]We applied an intention-to-treat analysis to Thorburn et al. carrying forward the baseline data of a participant that dropped out of the study halfway.

[b]Metabolic (Met) feeding control represents the provision of all meals, snacks, and study supplements (test sugars and foods) consumed during the study under controlled conditions. Supplement (Supp) feeding control represents the provision of study supplements. Certain studies provided partial-metabolic (Met/Supp) feeding, containing a metabolic and a supplemental period. Dietary advice represents the provision of counseling on the appropriate test and control diets.

[c]Doses were administered on a g/day, % energy, or g/kg body weight basis. Doses preceded by "~" represent an average dose calculated based on the average reported energy intake or weight of participants. If these data were not available, then the average dose was based on a 2000-kcal intake or 70-kg weight. Plus signs indicated excess energy provided by fructose.

[d]Fructose was provided in one of three forms: (1) liquid, where all or most of the fructose was provided as beverages or crystalline fructose to be added to beverages; (2) solid form, where fructose was provided as solid foods; or (3) mixed, where all or most of the fructose was provided as a combination of beverages, solid foods, and/or crystalline fructose.

[e]Values for energy are in the form of carbohydrate: fat: protein. "_" indicates that the information was not available.

[f]Trials with a score ≥8 were considered to be of higher quality, according to the Heyland Methodological Quality Score.

[g]Agency funding includes those from government, university, or non-profit health agency sources.

National Health and Nutrition Examination Survey (NHANES 1977–2004) (14).

Materials and Methods

We collated studies previously identified in a series of meta-analyses and systematic reviews of the effects of fructose on various cardiometabbolic endpoints (8–13). We included controlled dietary trials across all populations investigating the effect of fructose on fasting blood lipids (Chiavaroli et al., unpublished study), postprandial triglycerides (13), blood pressure (9), glycemic control (Cozma et al., unpublished study), uric acid (11), non-alcoholic fatty liver disease (NAFLD) (12), body weight using mixed forms of fructose (solid, liquid, mixed) (10), and body weight from fructose-containing sugars-sweetened beverages only (Choo et al., unpublished study). Trials lasting <7 days, using intravenous administration or possessing unsuitable endpoints or comparators were excluded. Two types of trials were identified for the purposes of this analysis-substitution trials, in which fructose was exchanged for equal amounts of energy from other carbohydrates, or addition trials, in which a control diet was supplemented with additional energy from fructose compared to the control diet alone without the excess energy. Duplicate studies between meta-analyses were removed, and fructose dose data were extracted from each study when available and reported in grams per day. A weighted average fructose dose used across all studies was calculated according to the sample size of each trial, and reported as a mean and 95% confidence interval.

Results

The search and selection process can be found in **Figure 1**. A total of 16,673 reports were identified between all meta-analyses, and 203 reports (267 trials) were included after excluding reports based on title and abstract. After combining eligible trials and removal of duplicates from the meta-analyses, 64 substitution trials (1235 participants) and 16 addition trials (197 participants) were included in this analysis.

Trial Characteristics

Table 1 provides a detailed summary of trial characteristics. There were 64 substitution trials involving 1235 participants (15–63) and 16 addition trials involving 197 participants (23, 30, 49, 50, 53, 54, 56, 58, 59, 64–66). Sample sizes of substitution and addition trials tended to be small [median number of participants, 12.5 (IQR: 9–24) and 12.5 (IQR: 8–16) for substitution and addition trials, respectively]. A majority of trials used a crossover design (69 and 94% of substitution and addition trials, respectively). Participants in substitution trials tended to be middle aged males and females [55% males; median age, 39.5 years (IQR: 23.4–53 years)], whereas participants in addition trials tended to be younger males [81% males; median age, 24.7 years (IQR: 23.5–33.9 years)]. Study duration was relatively short in both types of trials [median, 4 weeks (IQR: 2–6 weeks) and median 1.5 weeks, (IQR: 1–4 weeks) in substitution and addition trials, respectively] and predominantly took place in the United States for substitution trials and Europe for addition trials under an outpatient setting. Comparators in substitution trials included starch (30%), glucose (26%), sucrose (8%),

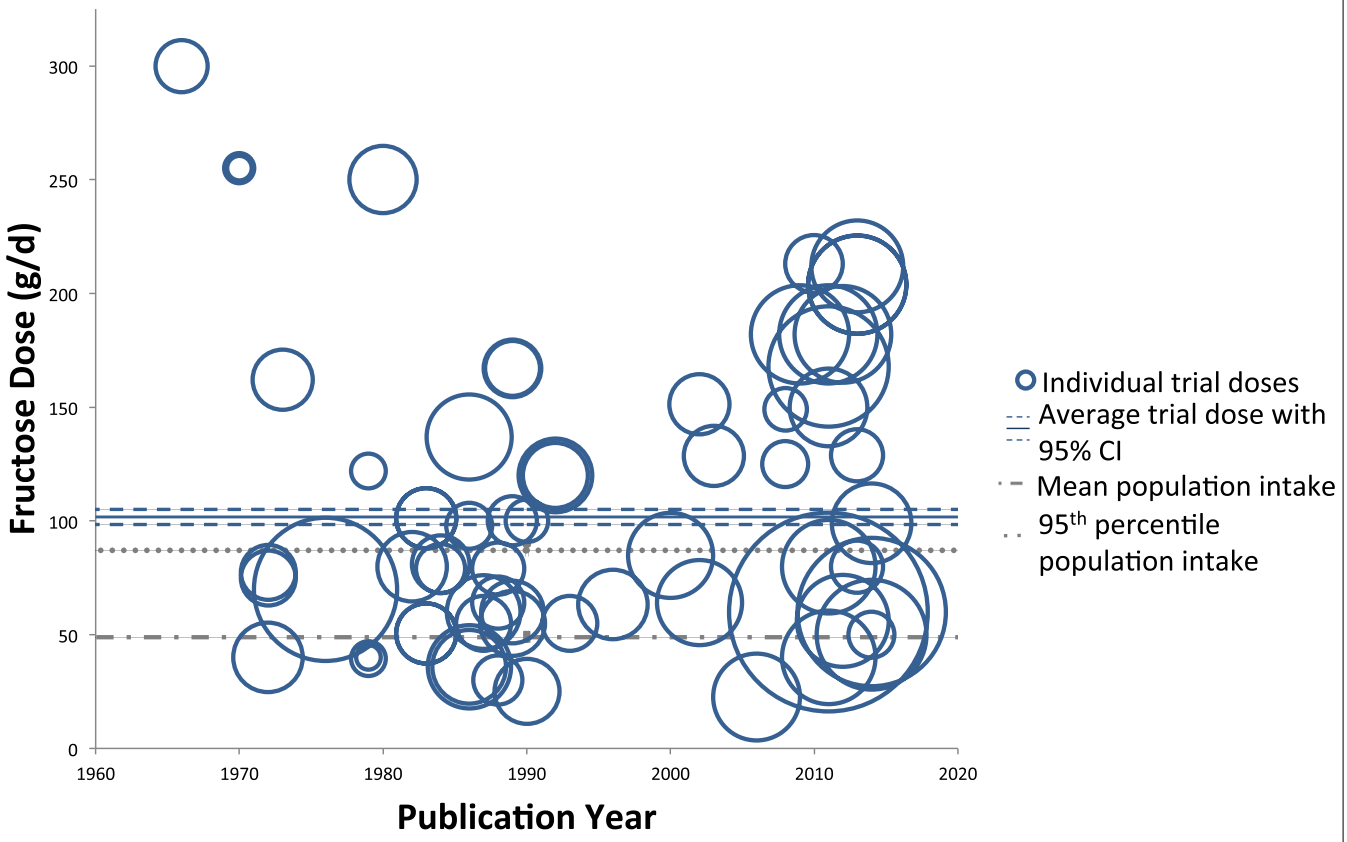

FIGURE 2 | Trends of fructose dose in substitution trials. Individual trials are plotted based on date of publication and fructose dose used. Sample size of each trial is represented by the size of its respective circle. The weighted average fructose dose across all substitution trials was 101.7 g/day (95% CI: 98.4–105.1 g/day), indicated by the solid and dashed blue lines.

D-maltose (3%), galactose (2%), and HFCS (1%) and comparators in all addition trials were diet alone.

Fructose Dose

Figures 2 and **3** show trends of fructose dose in substitution and addition trials plotted against the average and 95th percentile intakes of fructose in the United States (49 ± 1.0 and 87 ± 4.0 g/day, respectively). Substitution trials were conducted from 1966 to 2014 with most conducted during 1980s and a recent resurgence in 2010s, while the addition trials were conducted from 1980 to 2013 with most conducted after the mid 2000s. The weighted average fructose dose in substitution trials was two times higher than reported average population intake levels [101.7 g/day (95% CI: 98.4–105.1 g/day)], whereas the weighted average fructose dose in the addition trials was much greater, at ~3.7 times the amount of the reported average population intake levels [187.3 g/day (95% CI: 181.4–192.9 g/day)].

Discussion

This analysis, which combined the trials identified from eight meta-analyses, aimed to examine the trends of fructose dose in controlled dietary trials assessing the effects of fructose on various cardiometabolic outcomes. We identified 64 substitution trials, in which fructose was provided in isocaloric substitution for other carbohydrate sources (usually starch), and 16 addition trials, in which fructose supplemented diets with excess energy compared to the same diets without the excess energy. The average weighted fructose dose was 101.7 g/day (95% CI: 98.4–105.1 g/day) in substitution trials from 1966 to 2014, whereas the average weighted fructose dose was nearly twice as high at 187.3 g/day (95% CI: 181.4–192.9 g/day) in the 16 addition trials from 1980 to 2013.

There were differences observed in the temporal trends between substitution and addition trials. Most substitution trials were conducted in 1980s with a resurgence that followed in 2010s. The reason for this pattern is unclear. A growing interest in fructose trials early on may have reflected the initial interest in fructose as a potentially beneficial alternative sweetener (69–71). By controlling for energy, substitution trials provided a rigorous study design, which allowed for the assessment of whether fructose had a unique set of metabolic or endocrine responses beyond its energy across a wide dose range. The emergence of the addition trials in 2000s may have grown out of the consistent lack of effect or even the benefit (glycemic control) seen in the substitution trials (8) and the concern stimulated by the ecological analysis of Bray et al. (4) linking fructose from HFCS with the epidemic of overweight and obesity. The recent resurgence of substitution trials in 2010s appears to have been to reconcile the role of energy from that

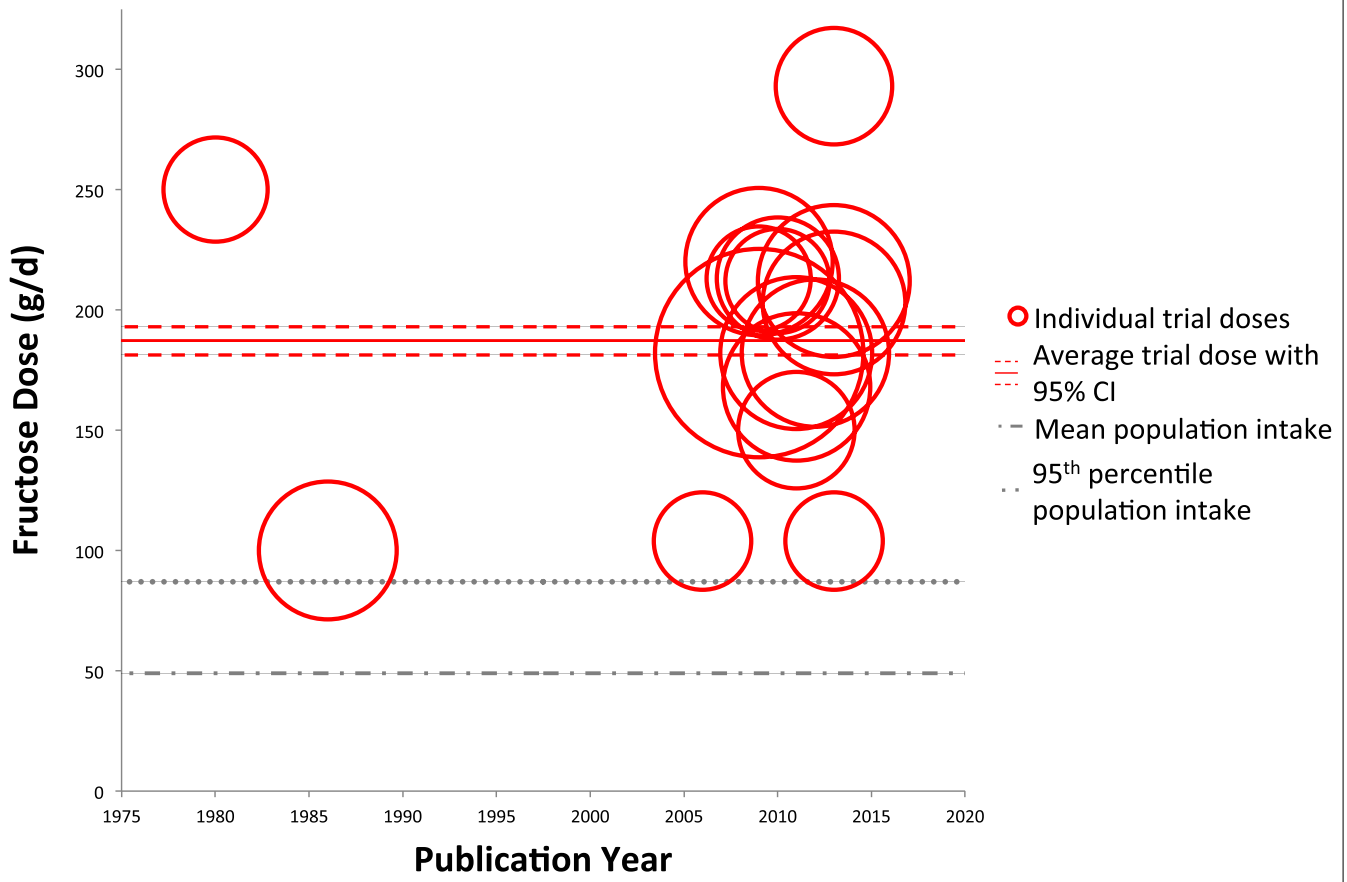

FIGURE 3 | Trends of fructose dose in addition trials. Individual trials are plotted based on date of publication and fructose dose used. Sample size of each trial is represented by the size of its respective circle. The weighted average fructose dose across all addition trials was 187.3 g/day (95% CI: 181.4–192.9 g/day), indicated by the solid and dashed red lines.

of fructose in the addition trials. To test whether overfeeding of fructose differs from overfeeding of any other macronutrient (usually glucose or starch), these trials have compared fructose with other sources of carbohydrate under conditions of matched overfeeding.

Irrespective of any control for energy, the levels of intake observed in the available trials has been well beyond population levels of consumption. Compared to levels of reported fructose intake assessed by the National Health and Examination Survey in the United States (NHANES 1977–2004), the doses used in both the substitution and the addition trials exceeded the average and 95th percentile levels of fructose consumption (49 ± 1.0 and 87 ± 4.0 g/day, respectively). Furthermore, all addition trials used doses of fructose above the 95th percentile of reported intake, with the weighted average dose more than double that amount. While the present analysis suggests that these trials using supraphysiological doses of fructose feeding are not representative of levels normally consumed in the diet, the important caveat remains that underreporting from national population intake surveys, such as NHANES, may underestimate the actual amount of fructose consumed (72). However, taking into consideration the potential for underreporting when interpreting calculated trial means compared to reported population means, if an estimated level of 50% underreporting were present (average and 95th percentile fructose intake of 100 and 172 g/day, respectively), the fructose dose in substitution trials would reach levels representative of true dietary intake [101.7 g/day (95% CI: 98.4–105.1 g/day)], while supraphysiological doses of fructose in addition trials would still persist [187.3 g/day (95% CI: 181.4–192.9 g/day)]. Another important consideration is that fructose consumption has been changing with time in NHANES. HFCS (a main proxy for fructose consumption) availability has been declining since it peaked in 1999 (73). Variability of fructose consumption over time should be taken into consideration when predicting the true population average intake.

The implications of our findings suggest a potential lack of ecological validity when drawing conclusions from addition trials using unrealistically high doses of fructose. As with the excess consumption of any macronutrient, an adverse effect on cardiometabolic risk factors may be irrelevant under levels of normal dietary consumption and lead to unnecessary concern and confusion regarding the safety of fructose. Two trial designs have helped to clarify whether adverse effects relate to excess energy (either from fructose or any macronutrient in general) or specific metabolic and

endocrine properties inherent to fructose itself. In a series of systematic reviews and meta-analyses of controlled trials to determine the effect of fructose on various cardiometabolic outcomes, a consistent signal for harm has only been shown in the addition trials (8–10, 12, 13). Substitution trials have failed to show differences in body weight (10), fasting triglycerides (74), postprandial triglycerides (13), uric acid (9), glucose, insulin (8), or markers of NAFLD (12) with improvements seen in blood pressure (9) and glycemic control (8, 75). These findings hold even under conditions of overfeeding as long as the excess energy is matched. The one exception may be for an effect on fasting triglycerides at a high dose threshold as seen in some subgroup analyses (76, 77). Taken together, these findings suggest that fructose appears to be a determinant of cardiometabolic risk only in as much as it contributes to excess energy in the diet.

Conclusion

Most trials on fructose and cardiometabolic risk have used doses of fructose well beyond reported population levels of intake. While such high doses may be useful for determining a cause-effect relationship, replication of these studies using fructose doses closer to dietary levels are warranted and could help to establish a threshold beyond which excess energy from fructose demonstrate a signal for harm under real world conditions.

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