See corresponding editorial on page 1189.

Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies[1–3]

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ABSTRACT

Background: The glycemic response to dietary fructose is low, which may improve concentrations of glycated hemoglobin (HbA_{1c}, a marker of dysglycemia). Meanwhile, adverse effects on plasma triacylglycerol (a marker of dyslipidemia) and body weight have been questioned. Such effects are reported inconsistently.

Objective: We aimed to evaluate the effect of fructose on these health markers, particularly examining treatment dose and duration, and level of glycemic control.

Design: A literature search was conducted for relevant randomized and controlled intervention studies of crystalline or pure fructose (excluding high-fructose corn syrup), data extraction, meta-analyses, and modeling using meta-regression.

Results: Fructose intake $<$ 90 g/d significantly improved HbA_{1c} concentrations dependent on the dose, the duration of study, and the continuous severity of dysglycemia throughout the range of dysglycemia. There was no significant change in body weight at intakes $<$100 g fructose/d. Fructose intakes of $<$50 g/d had no postprandially significant effect on triacylglycerol and those of $\leq$100g/d had no significant effect when subjects were fasting. At $\geq$100 g fructose/d, the effect on fasting triacylglycerol depended on whether sucrose or starch was being exchanged with fructose, and the effect was dose-dependent but was less with increasing duration of treatment. Different health types and sources of bias were examined; they showed no significant departure from a general trend.

Conclusions: The meta-analysis shows that fructose intakes from 0 to $\geq$90 g/d have a beneficial effect on HbA_{1c}. Significant effects on postprandial triacylglycerols are not evident unless $>$50 g fructose/d is consumed, and no significant effects are seen for fasting triacylglycerol or body weight with intakes of $\leq$100 g fructose/d in adults. *Am J Clin Nutr* 2008;88:1419–37.

INTRODUCTION

Fructose is often used in regular foods for healthy people (1, 2) and in clinical feeds intended for persons with diabetes (3). Consumption of 50 g fructose/d for $\leq$2 y had no significant effect on fasting plasma triacylglycerol (FPTG) in healthy persons (4), and that dose ($\approx$10% of metabolizable energy intake) was previously considered acceptable in persons with diabetes (5, 6). Most recently, however, fructose has been discouraged for use in diabetes patients on the basis of its supposed effects on plasma triacylglycerol (7), and there is concern about a relation between fasting and nonfasting triacylglycerols and cardiovascular disease (8–10).

There is, however, currently no published attempt to combine relevant observations from intervention studies, ie, a meta-analysis (11), or to consider whether the potentially adverse effects on triacylglycerol may be counterbalanced by a potentially beneficial effect on glycated hemoglobin (HbA_{1c}). Elevated HbA_{1c} is a marker of dysglycemia, which may be present in 50% of the US population (12) and which is linked to cardiovascular disease (13–15). It is unclear, therefore, whether 50 g fructose/d can be said to pose a significant risk of an elevation in plasma triacylglycerol in any group of persons. Intervention studies also have not clarified the lowest dose of fructose that has a significant effect on fasting and postprandial triacylglycerols, below which the hypothesized risk would have little relevance. In addition, the potentially stronger risk factor for cardiovascular disease, HbA_{1c} (13–15), could decline in response to fructose because of fructose's low glycemic index (LGI) (5, 16); such a connection was found for LGI (mainly starch) foods in diabetes patients and a small number of healthy persons (17, 18). Such an effect is by no means certain, because excessive or very high doses of fructose impair insulin sensitivity (19–21), which is expected to drive HbA_{1c} concentrations up. Meanwhile, LGI carbohydrate foods in general (18) and, possibly, modest doses of fructose (22) may improve insulin sensitivity. Thus, the question of whether fructose can consistently lower HbA_{1c} in any persons and the dose at which that lowering may occur are both unclear and worthy of meta-analysis. Clarification is important because dysglycemia (as judged by HbA_{1c} and other measures) is a continuous risk factor for cardiovascular disease independent of diabetes (12, 15, 23, 24). In addition to the above, the role of dietary fructose ($>$50 g/d) in healthy and obese persons is debated because of its possible effects on body weight (25–30). However, there is also no meta-analysis of available intervention studies.

The focus in the present report in on intervention studies using crystalline or pure fructose. We addressed questions about the effects of dose, the duration of treatment, the nature of the carbohydrate exchange with fructose, and the health history, age,

[1] From Independent Nutrition Logic, Wymondham, United Kingdom.
[2] Supported by Danisco Sweeteners, produce of fructose.
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sex, and body mass index of persons consuming the fructose. Studies replacing sucrose, glucose, or starch with fructose were examined. Thus, we were concerned with the ability of fructose to modify the meta-analyzed factors and the doses at which such modification occurs.

MATERIALS AND METHODS

Literature search

An electronic search was conducted with the use of MEDLINE (PubMed, National Library of Medicine, Bethesda, MD; Internet: www.ncbi.nml.nih.gov.80/sites/entrez) and the Cochrane Collaboration (CENTRAL; Internet: www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html). Search terms used were "fructose" and either "meta-analysis" or "triacylglycerol (or 'triglyceride')" or "HbA_{1c} (or 'glycated protein' or 'glycated albumin' or 'fructosamine')" or "diabetes" or "coronary" or "heart disease" or "stroke." The records retrieved were from 1966 to June 6, 2006. A flow chart (**Figure 1**) illustrates the principal stages and processes of the review undertaken.

Inclusion criteria

Data from both randomized and nonrandomized studies were included (analyzed separately and in combination) if they met the following inclusion criteria: *1*) studies in humans who were healthy or who had impaired fasting glucose, impaired glucose tolerance, type 2 diabetes, elevated risk of coronary heart disease, hypertriacylglycerolemia, or other forms of hyperlipidemia; *2*) studies using diets including fructose in either foods or drinks, matched by a comparable control diet with or without another available carbohydrate in place of fructose; *3*) studies specifying the treatment dose (g/d or equivalent) and duration (in wk or equivalent); *4*) studies with assignable designs (crossover, sandwich, parallel, or sequential designs—for totality of evidence); *5*) studies in which the method of food intake control was assignable to 1 of 3 types: *A*) foods provided, usually with nothing else to be eaten and with wastage deducted, *B*) food choice advised with intakes assessed via diary or similar recordings, and *C*) food provided for eating ad libitum with intakes assessed by diary or similar recordings; *6*) studies with a treatment effect provided or calculable as either difference in changescores (eg, follow-up

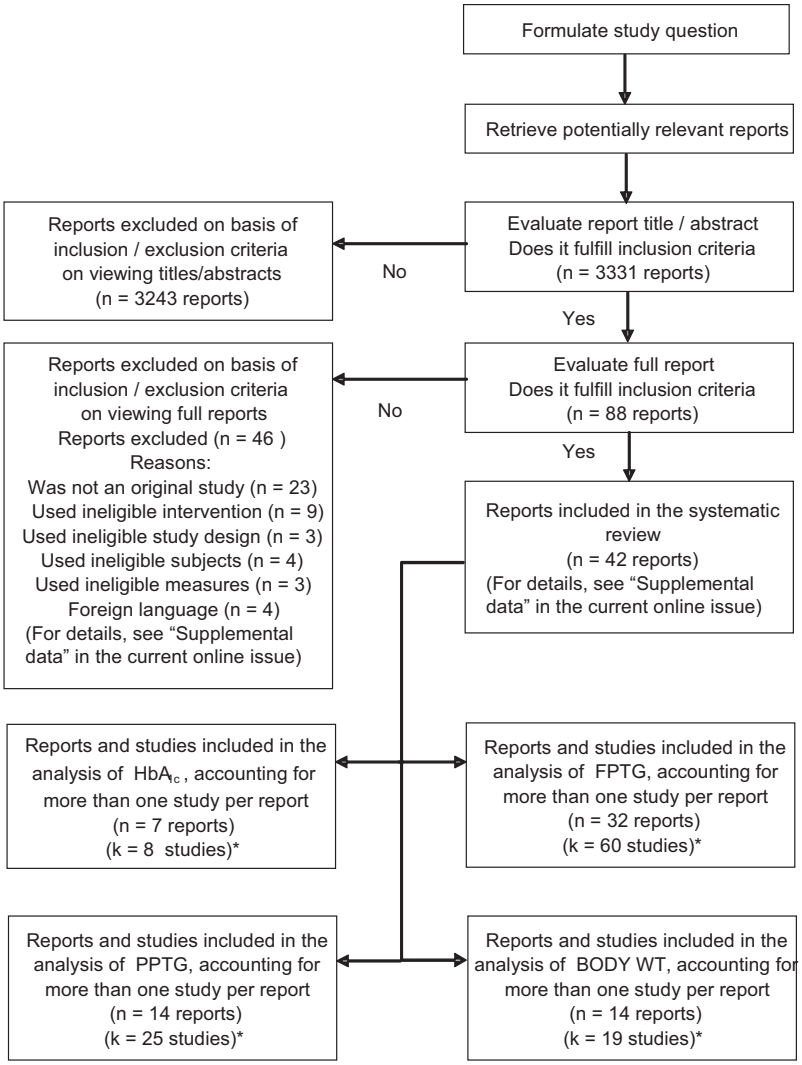

FIGURE 1. Summary of the study methodology, processes of review, and outcomes of inclusion and exclusion criteria. *n*, number of reports; *k*, number of studies. *A further breakdown of studies is given in Table 1; for details of individual studies, see Tables S1–S4 under "Supplemental data" in the current online issue.

minus initial scores in parallel and crossover studies) or difference in end scores (eg, crossover studies without initial scores); *7*) studies with an SE of treatment effect provided or calculable or imputable, as described below; and *8*) studies with relevant scores (measures) (Figure 1).

Exclusion criteria

Reasons for exclusion were as follows: *1*) studies that administered fructose parenterally or as specialized enteral feeds; *2*) studies that used high-fructose corn syrup as a source of fructose; *3*) animal, cellular, epidemiologic, or clinical studies or studies of drugs involving fructose; and *4*) studies in which the participants' disease was other than specified among the inclusion criteria, to avoid persons with either fructose intolerance or overt gastrointestinal, hepatic, or muscular disease. Reports in non-English-language journals were excluded for convenience.

Data extraction

Data were initially extracted, converted to SI units (eg, triacylglycerol, 88.5 mg/dL converted to 1 mmol/L), and compiled into a preliminary database by one of us (GL), an empty copy of which was repopulated independently by the other of us (RT). Disagreements were identified computationally; each was checked independently, and any remaining disagreement was resolved jointly.

Study quality assessment

The numeric 3-item quality score of Jadad (31) was used to assess the quality of each individual intervention study, generalized as follows (minimum grade, 0; maximum grade, 3): low potential of inequality of participants in treatment groups (randomization + 1 or crossover + 1, maximum of + 1), low potential of investigator bias (double blinding + 1 or independent source of funding + 1, maximum + 1), and low potential of bias from attrition (explicit mention of a zero dropout rate for study participants or a higher rate with explicit description of acceptable reasons for dropping out, +1). Individual study factors potentially affecting study quality, and the results were examined by meta-analysis of residuals. For the quality of combined evidence, we adopted the terminology "high, moderate, low, or very low quality of evidence" from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (32, 33).

Calculations

When not published with the intervention studies, SDs of scores for the sampled local population and for the treatment effect were derived by using exact *t*, *P* values, and 95% CIs (34). When this was not possible, the SDs of scores were imputed from CVs dependent on the treatment means, as established elsewhere (18, 35), and additional information from the present studies was used. When the SE of the treatment effect was dependent on the duration of treatment, this information was used to improve the estimates by modeling the ratio of paired to unpaired error on the duration between paired observations.

In studies with repeated measures, it is common to use data from only the last time-point to maintain the independent status of the data analyzed, rather than to use all time-points equally, which would overrepresent studies with a greater number of repeats. This approach was used with body weight and postprandial triacylglycerol (PPTG) because there were few studies with repeated measures. With FPTG, >20% of studies used repeated measures; for these, we combined the repeats by averaging the mean effects and variances across the repeats and located them at the average duration of study, which in this case was $\log_{10}$ transformed to better fit the data. This approach had several theoretical advantages: it discarded no data, so that all observations were represented; it maintained the independent status of data inputted to the analysis; it retained the precision available from the study and minimized undue spurious weighting of those studies with repeated measures; and it kept the inputted data in the middle of the data range, where confidence is maximal. The approach was selected a priori, but the sensitivity of the meta-analysis results to 3 different approaches of handing the repeated measures was assessed subsequently. With HbA_{1c}, 50% of studies had repeated measures, a non-steady state with time was expected because of a 12-wk half-life for this analyte, but there were few studies, and therefore all intermediate data were retained to facilitate fitting of models that included duration of treatment as a determinant. Retaining all intermediate data may cause some bias toward studies with repeated measures because of inclusion of dependent data, but it was used a priori to help avoid bias by having more data fitted across the duration of treatment. The sensitivity of different approaches to handling the repeats was assessed subsequently.

In the analysis of PPTG, the mode of expression of the fructose dose was similar to that of other outcome measures (FPTG, HbA_{1c}, and body weight). The similar mode was achieved by dividing the intake over ≥1 meals containing the fructose by the number of meals over which fructose was ingested and multiplying by 3 typical meals/d.

Statistical analysis

A Stata database was used for data preservation and as a source for calculations and meta-analysis (version 9SE; StataCorp, College Station, TX) with the use of options under the *metan*, *metatrim*, *metareg*, and *nlcom* commands (36). Combined means and trends for studies were weighted by inverse variance for both random- and fixed-effect analyses; we chose random-effects analysis when the extent of inconsistency (I^2) was >0 (ie, when a between-studies variance contributed to total variance) (37, 38). The significance of heterogeneity in meta-analyses was assessed by using the *Q* test [$P > Q$ (37)]. Between-study variance and SE were estimated according to Der Simonian and Laird, and combined mean effects were assessed for significance by using the asymptotic *z* test [$P > |z|$ (39)]. Meta-regressions were fitted by restricted maximum likelihood (REML). The statistical significance of a combined study trend ($P > |\text{kh-}t|$) was assessed by using a *t* test with the STATA option for Knapp and Hartung's modified SE. When applicable, this assessment was checked by using a distribution-free permutations test ($P > |\text{permute}|$) to avoid spurious findings (40). The statistical significance of the REML estimate of between-studies variance (τ^2) was assessed by using a likelihood-ratio test ($P > \chi$), and the corresponding SE between studies was $\sqrt{\tau^2}$. Correlation (*r*) between various dietary inputs was assessed by equal effects, the significance of which was tested by using the *F* ratio ($P > F$). (To review the funnel plots, see Figures S1–S8 under "Supplemental data" in the current online issue.) Pseudo-95% CIs in funnel plots were estimated as *z* score · SE for fixed effects together with *z*

TABLE 1
Number of studies contributing to each analysis by health type, BMI range, and study design[1]

Measure	HbA_{1c}	Fasting plasma triacylglycerol	Postprandial plasma triacylglycerol			Body weight
			<5 h postprandial	>5 h postprandial without adaptation	>5 h postprandial with adaptation	
	k	*k*	*k*	*k*	*k*	*k*
Condition						
Normal	2	27	11	9	2	4
Hyperinsulinemia		3				
Impaired glucose tolerance	1	1				
Type 2 diabetes	5	13	1	1		9
Type 1 diabetes		3				1
Types 1 and 2 diabetes		1				2
Coronary heart disease		2	1			1
Hyperlipidemia		10				2
Total	8	60	13[2]	10	2	19
BMI range						
Not reported (or identifiable)		12	3	2		
Normal-weight[3]		22	1	6		5
Mixed normal-weight and overweight[3]	1	3	8		2	2
Overweight[3]	5	16	1	2		3
Obese[3]	2	7				9
Study design						
Parallel (between participant)	2	3		2		3
Crossover (within participant)	6	33	11	4	2	12
Sandwich (within participant)		4	1			2
Sequence (within participant)		20	1	4		2
Randomization						
Reported	5	20	10	4	2	11
Not reported	3	40	3	6		8
Study quality scores (lowest quality = 0, highest quality = 3)						
0		12		2		2
1	5	23	9	4		7
2	3	25	3	4	2	10
3			1			

[1] All values are *k*(number of studies). HbA_{1c}, glycated hemoglobin.
[2] One influential study ($\Delta\beta_{ij}$ influence statistic 2.26 > 1) comparing fructose and glucose for ≤5 h was outlying (>20 τ) and was discarded before the meta-analysis reported here (43).
[3] Weight categories were as identified by the authors of the reported studies or from BMI (in kg/m^2) as overweight (≥25) or obese (≥30).

score · $(SE^2 + \tau^2)^{0.5}$ when random effects were evident. Regression models based on dose, duration of treatment, and severity of abnormality in a physiologic measure etc (as described in Results) were examined both by retaining constants and by forcing a zero constant to match the theoretical zero effect at zero dose and zero duration and to account for an assumed zero effect at some threshold value below which a determinant would be without effect.

Interpretation

Meta-analyses

The interpretation and use of information on random effects in decision analysis have been described (41, 42). We provide 95% CIs for both the underlying effect and the wider distribution of effect sizes among studies when random effects are indicated. The former indicates whether the treatment has an effect, and the latter forecasts whether the effect would occur consistently among the different groups studied. The distribution of effect sizes is wider because of the random effects, which represents an effect size that varies for undocumented real-world circumstances not included in the meta-analytic model. The implication of random effects is that the effect size is not fixed and the underlying trend summarizes only the average effect. Assuming accurate data inputs, when an underlying effect is significant, an unambiguous or real effect is evident; when the random effect also is significant, the underlying effect is not the same size in all circumstances (ie, the effect size is not fixed). An unambigous effect in 95% of circumstances arises only when the 95% CI for the distribution of effects does not include zero.

RESULTS

Results of the literature search

A total of 3331 reports were identified by the search strategy, of which 42 met the inclusion criteria and were included in the review (Figure 1). Some reports included more than one study; for example, some investigations studied males and females separately (*see* the legend for Figure 1). Four outcome measures

TABLE 2
Background diets, study variables, and correlations with free fructose intake[1]

Investigations	*k*	*k*(NR)	Value	Minimum	Maximum	*r*	*P* > *F*
HbA_{1c}							
Participant age (y)	8	0	52 ± 10[2]	34	62	−0.36	0.377
Male (%)	7	1	39 ± 14	4	6	−0.33	0.462
Study arm size (*n*)	8	0	10.5 ± 2.2	8	14	0.24	0.549
Study duration (wk)	8	0	9.5 ± 7.7	4	26	−0.30	0.467
Fructose-free, treatment diet (g/d)	8	0	57 ± 55	22	88	1.00	<0.001
Proportion that is basal, control diet (%)	7	1	0.8 ± 2.7	0	5.7	0.62	0.139
Fructose-bound (g/d)	6	2[3,4]	1 ± 2	0	4	0.78	0.067
ME (MJ/d)[5]	7	1[6]	8.9 ± 1.3	7.1	10.7	0.22	0.599
Carbohydrate (% of ME)	7	1[6]	51 ± 2	50	55	0.80	0.032
Fat (% of ME)	7	1[6]	32 ± 2	30	55	−0.75	0.030
Protein (% of ME)	7	1[6]	17 ± 2	15	20	−0.61	0.144
Fiber (g/d)	5	3[7]	24 ± 3	20	28	0.53	0.354
P/S (g/g)	5	3[7]	1.0 ± 0.1	0.9	1.2	0.54	0.355
Fasting plasma triacylglycerol							
Participant age (y)	59	0	42 ± 15	10	65	−0.17	0.198
Male (%)	55	4	57 ± 38	0	1	0.10	0.389
Study arm size (*n*)	59	0	8 ± 4	1	16	−0.66	<0.001
Study duration (wk)	59	0	3.9 ± 4.8	0.14	26	−0.26	0.037
Fructose free, treatment diet (g/d)	59	0	135 ± 84	30	350	1.00	<0.001
Percentage that is basal, and thus also present in the basal diet (%)	55	4	2.4 ± 5	0	24	0.10	0.375
Fructose bound							
Lower (g/d)	55	1	1 ± 2	0	6.8	0.20	0.144
Higher (g/d)	5	0	59 ± 20	29	80	0.47	0.431
ME (MJ/d)[5]	59	0	9.7 ± 2.3	5.3	14.6	0.24	0.058
Carbohydrate (% of ME)	58	1	59 ± 16	40	91	0.66	<0.001
Fat (% of ME)	58	1	25 ± 15	0	45	−0.67	<0.001
Protein (% of ME)	58	1	15 ± 3	8	20	−0.14	0.342
Fiber (g/d)	24	35	21 ± 8	0	33	0.00	0.882
P/S (g/g)	32	27	0.9 ± 0.8	0.05	3.8	0.14	0.507
Postprandial plasma triacylglycerol							
≤5 h monitoring after ingestion							
Participant age (y)	13	0	30 ± 15	20	64	—	—
Male (%)	13	0	92 ± 19	0.5	1	—	—
Study arm size (*n*)	13	0	8.9 ± 1.9	5	14	—	—
Adaptation (wk)	13	0	0.3[8]	0	4	—	—
Postprandial period (h)	13	0	2.8 ± 1	1.5	5	—	—
Fructose free in the meal (g/d)	13	0	53 ± 29	17.7	100	—	—
>5 h monitoring after ingestion, no adaptation							
Participant age (y)	8	2	30 ± 11	19	48	—	—
Male (%)	8	2	57 ± 33	0	1	—	—
Study arm size (*n*)	10	0	11.3 ± 7.2	4	22	—	—
Adaptation (wk)	10	0	0.0	—	—	—	—
Postprandial period (h)	10	0	8.5 ± 5	6	23	—	—
Fructose free in the meal (g/d)	10	0	46 ± 19	20	79	—	—
>5 h monitoring after ingestion, with adaptation							
Participant age (y)	2	0	41	40	43	—	—
Male (%)	2	0	50	0	100	—	—
Study arm size (*n*)	2	0	12	12	12	—	—
Adaptation (wk)	2	0	6	6	6	—	—
Postprandial period (h)	2	0	24	24	24	—	—
Fructose free in the meal (g/d)	2	0	85	85	85	—	—
Body weight							
Studies using ≤100 g fructose/d							
Participant age (y)	15	0	50 ± 11	25	65	0.14	0.193
Male (%)	13	0	54 ± 23	17	100	0.08	0.335
Study arm size (*n*)	15	0	12 ± 5	6	24	0.15	0.159
Study duration (wk)	15	0	8.8 ± 7.7	1.4	26	0.015	0.670

(*Continued*)

TABLE 2 (*Continued*)

Investigations	*k*	k(NR)	Value	Minimum	Maximum	*r*	*P* > *F*
Fructose unbound, treatment diet (g/d)	15	0	62 ± 23	22	100	1.000	<0.001
Percentage that is basal, and thus also present in the basal diet (%)	14	1	5.1 ± 7.4	0	24	0.009	0.744
Fructose bound							
Lower (g/d)	15	0	1 ± 2	0	6	−0.12	0.666
Higher (g/d)	2	0	48	30	66	—	—
ME (MJ/d)[5]	15	0	8.6 ± 2.3	5.2	13.7	0.23	0.067
Carbohydrate (% of ME)	13	2	52 ± 5	40	55	0.15	0.184
Fat (% of ME)	13	2	32 ± 4	25	40	0.035	0.539
Protein (% of ME)	13	2	17 ± 3	15	20	0.19	0.138
Fiber (g/d)	10	5	23 ± 9	0	32	0.12	0.327
P/S (g/g)	9	6	1.0 ± 0.3	0.3	1.5	0.034	0.631
Studies using >100 g fructose/d							
Participant age (y)	4	4	38 ± 14	26	54	0.77	0.12
Male (%)	3	1	100 ± 0	100	100	—	—
Study arm size (n)	4	0	84	5	15	0.016	0.876
Study duration (wk)	4	0	1.1 ± 0.6	0.6	2	0.37	0.394
Fructose-unbound, treatment diet (g/d)	4	0	176 ± 48	122	218	1.000	>0.001
Percentage that is basal, and thus also present in the basal diet (%)	4	0	<2 ± <2	<2	<2	—	—
Fructose bound							
Lower (g/d)	3	0	0	0	0	—	—
Higher (g/d)	1	0	66	66	66	—	—
ME (MJ/d)[5]	4	0	12.7 ± 2.3	9.8	14.6	0.62	0.21
Carbohydrate (% of ME)	4	0	69 ± 11	63	85	0.60	0.226
Fat (% of ME)	4	0	18 ± 12	0	26	0.77	0.122
Protein (% of ME)	4	0	13 ± 3	11	16	0.85	0.077
Fiber (g/d)	1	0	0 ± 0	0	0	—	—
P/S (g/g)	0	—	—	—	—	—	—

[1] *k*, the number of studies reporting; k(NR), the number of studies not reporting a variable (eg, see footnotes 3, 4, 6, and 7); HbA_{1c}, glycated hemoglobin; P/S, ratio of polyunsaturated to saturated fatty acids; ME, metabolizable energy.
[2] $\bar{x}$ ± SD (all such values).
[3] Vaisman et al (45) used a regular diet for diabetes patients as the basal diet, which was low in bound fructose, but they did not report a value.
[4] Grigoresco et al (46) used a basal diet that included 12% sugars as milk and fruit, but did not report the contribution from bound fructose.
[5] ME is as reported wherein energy from fiber is disregarded. A mean estimate at present of the contribution from fiber is ≈2.5% of ME.
[6] Vaisman et al (45) used a regular diabetic diet (see also footnote 3).
[7] Grigoresco et al (46), Koivisto and Yki-Jarvinen (22), and Vaisman et al (45).
[8] $\bar{x}$ (all such values).

were examined: HbA_{1c} (8 studies), FPTG (60 studies), PPTG (25 studies), and body weight (19 studies). The studies varied in several aspects—health type, body mass index (BMI; in kg/m^2) range, study design, and various study quality items (**Table 1**). For initial convenience, therefore, the effect of treatment with fructose was assumed to be independent of these categorical variables, all of which are artificial constructs. This assumption was subsequently justified by an analysis of residuals.

A few studies had between-participant comparisons (parallel designs) that reported randomization (Table 1). Most studies had within-participant comparisons, and a high proportion of these studies did not report randomization. Only 1 single-blinded study (44) and 2 double-blinded studies (22, 45) were blinded. Attrition was <20% in all studies. On the 3-item quality score, most studies were grade 1 or 2 (lowest possible quality score, 0; highest, 3).

Observations on background diets

Diets with added fructose (pure or crystalline) were matched with control diets of similar macronutrient composition (**Table 2**). The free fructose (treatment) was exchanged for glucose,

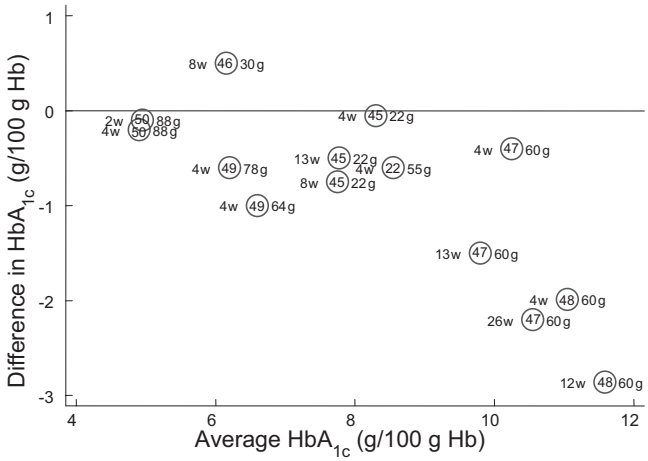

FIGURE 2. Difference in glycated hemoglobin (HbA_{1c}) concentrations due to fructose ingestion. Hb, hemoglobin. The groups of 3 data points indicate the following—left, study duration (w, wk); right, fructose dose (g/d); encircled, references as follows: Koh et al (49), normal at 78 g/d and impaired glucose tolerance at 64 g/d; Swanson et al (50), normal; Grigoresco et al (46), type 2 diabetes; Koivisto and Yki-Jarvinen (22), type 2 diabetes; Osei and Bossetti (47), type 2 diabetes; Osei et al (48), type 2 diabetes; and Vaisman et al (45), type 2 diabetes.

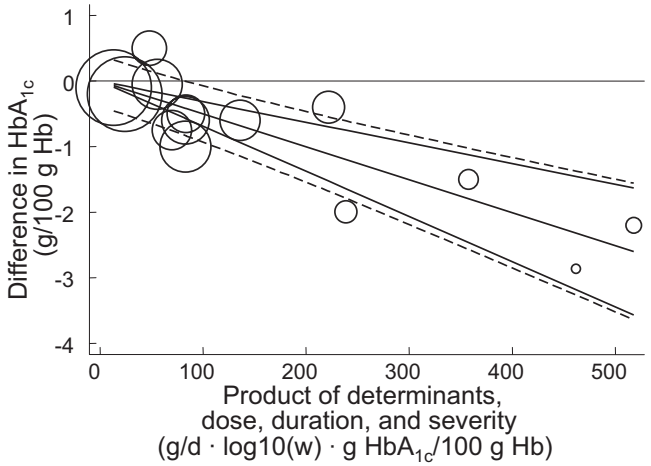

FIGURE 3. Lowering of the glycated hemoglobin (HbA_{1c}) concentration depends on the fructose dose, the duration of treatment, and the severity of abnormality in HbA_{1c}. Hb, hemoglobin; w, wk. Dose = fructose dose (g/d); duration = the length of treatment ($\log_{10}$w); severity = the treatment average HbA_{1c} less a threshold concentration ($\bar{x} \pm$ SE: 4.5 ± 0.9 g HbA_{1c}/100g Hb; $P > |\text{kh-}t| < 0.003$). Such averaging is consistent with the statistical tool called the methods difference plot. The slope of the central trend was $(-5.0 \pm 0.8) \times 10^{-3}$ ($P > |\text{kh-}t| < 0.001$). Also shown are the central trend (and 95% CI) for trend (—) and 95% CI for forecast (- - -). Heterogeneity (I^2) evidenced was 0.44 (between-studies SE = 0.18 g HbA_{1c}/100 g Hb) and was appreciable but not significant ($P > \chi = 0.38$; df = 12). The within-study SE increased with severity, which explained the decreasing precision of studies (as evidenced by changes in bubble sizes) from left to right.

sucrose, or starch-maltodextrin (controls) in all studies but 2, which exchanged fructose for starch-based diets (47, 48). The quantity of bound fructose (sucrose) present was similar in the control and treatment diets. In 55 of the 60 studies monitoring FPTG, the amount of sucrose present was small (<10 g/d). In the remaining 5 studies, it was higher, ranging from 29 to 80 g/d.

Correlation between free fructose and metabolizable energy intakes was low and nonsignificant, except in studies of body weight with >100 g fructose/d, when the correlation was moderate (0.6) and nonsignificant (Table 2). However, because of the dietary manipulations, more fructose generally meant significantly more carbohydrate and less fat in both the control and the treatment arms (Table 2). No study was designed to monitor the effects on the amount and composition of foods eaten.

Glycated protein

A lower HbA_{1c} concentration was found because of the use of fructose (**Figure 2**). A greater absolute effect occurred when glycemic control was poor (treatment average HbA_{1c} was high). No study had fructose intakes of >88 g/d or a treatment duration of >26 wk (Figure 2; also see Table S1 under "Supplemental data" in the current online issue).

Determinants of the effect size were the fructose dose (g/d), the duration of treatment [$\log_{10}$ (wk)], and the severity of dysglycemia (as marked by g HbA_{1c} /100 g Hb above a threshold). All 3 factors interacted to explain the size of the treatment effect (**Figure 3**). Sensitivity of the slope to including repeated measures was assessed by representing different studies with dummy variables, which reduced the slope from 0.50×10^{-3} without dummy variables to 0.48×10^{-3} with them. In addition, no such significant bias was evident because residuals for all time-points within a study, when combined, did not differ significantly from the general trend.

After normalization for the log duration of treatment and the severity of dysglycemia, fructose had a significant dose-dependent effect (from 22 to 88 g/d). The effect in 3 studies of nondiabetic subjects was consistent with that in studies of persons with type 2 diabetes (**Figure 4**).

Most studies had replaced fructose with either starch, maltodextrin, or glucose. No study replaced sucrose with fructose, which therefore remains to be examined. Although carbohydrate intake and fructose dose were correlated (Table 2), fructose dose was the superior determinant of $HbA_{1c,}$ both sensibly (by study design) and statistically explaining much more of the variance among studies ($\tau^2 = 0.03$ and $P > \chi = 0.002$ for fructose compared with $\tau^2 = 0.36$ and $P > \chi = 0.12$ for carbohydrate).

No group of studies departed significantly from the trend shown in Figure 4. Thus, the combined mean residual deviation (RD) for 3 observations of healthy groups was negligible (RD −0.1 g HbA_{1c}/100 g Hb; $P > |z| = 0.12$), as were 10 observations in diabetes patients (0.1; $P > |z| = 0.36$), 4 observations in obese subjects (−0.2; $P > |z| = 0.31$), and 8 observations in overweight persons (0.2; $P > |z| = 0.38$). A single study of impaired glucose tolerance yielded a greater-than-expected effect [Figure 4, point 4 wk(49)64 g] (49).

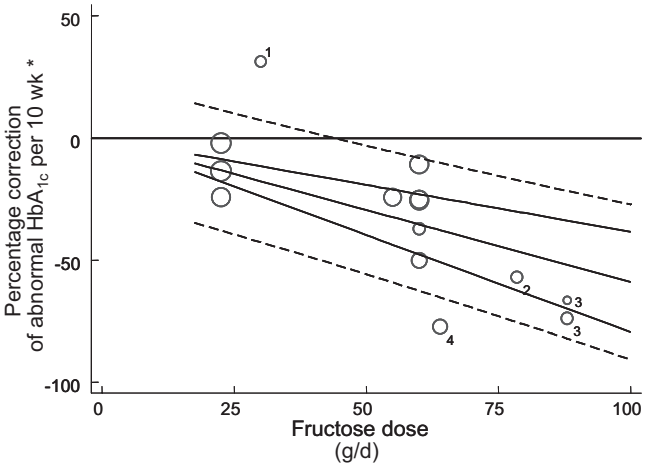

FIGURE 4. Difference in glycated hemoglobin (HbA_{1c}) by fructose dose compared with control. Hb, hemoglobin; w, wk. Curves are trends (and 95% CI) for trend (—) and 95% CI for forecast (- - -). The decrease in HbA_{1c} is normalized for the duration of treatment [$\log_{10}$(w)] and the severity of abnormality in HbA_{1c} (treatment average − 4.45; units: HbA_{1c}/100 g Hb) with which the fructose dose interacts (*see* Figures 2 and 3). Bubbles show study means (smaller bubbles represent a less precise mean). The slope was ($\bar{x} \pm$ SE: $-5.7 \pm 1.0) \times 10^{-3}$ ($P > |\text{kh-}t| < 0.001$), and it equates to a 5.7% correction in the abnormality of HbA_{1c} by 10 g fructose in 10 wk. Heterogeneity had marginal significance [$P > \chi = 0.09$; df = 11, heterogeneity (I^2) = 0.44; between-studies SE = 13% correction]. [1]Indicates the study of Grigoresco et al (46), which was outlying but not removed because it was not considered influential [ΔB_{ij} statistic = 0.25 < 1(critical value)]. [2, 3]Groups of healthy participants in the studies of Koh et al (49) and Swanson et al (50). [4]Group with impaired glucose tolerance in the study of Koh et al (49). All other studies involved groups of type 2 diabetes patients. *The *y*-axis is equal to 100 times the difference in HbA_{1c} (g/100 g Hb) per unit log duration [$\log_{10}$(w)] and per incremental unit of severity [g HbA_{1c}/100 g Hb > 4.45].

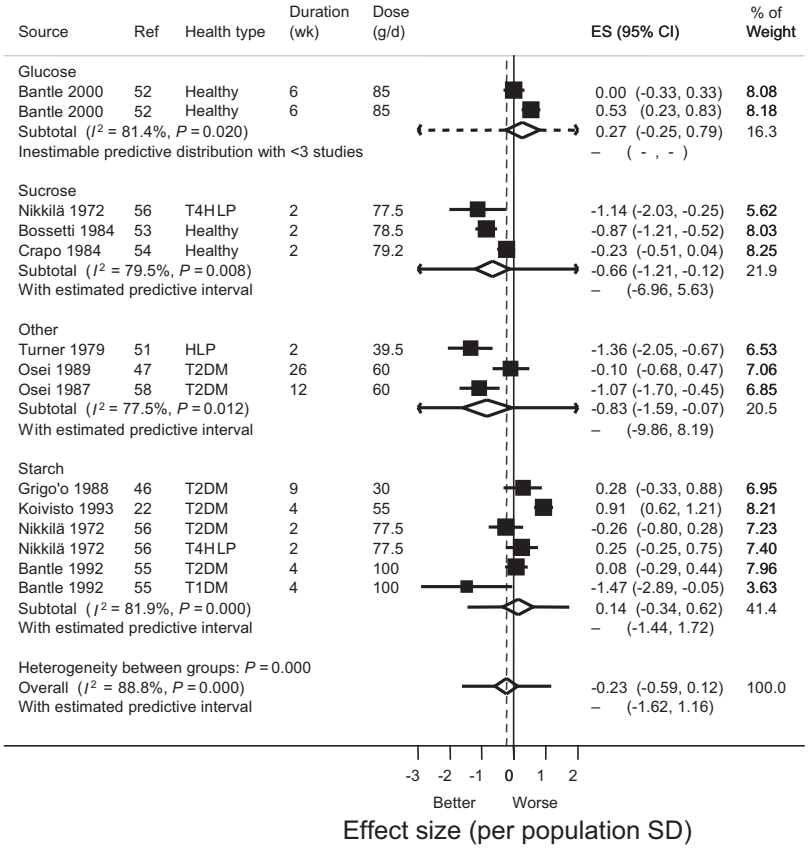

FIGURE 5. Forest plot of randomized controlled trials (RCTs) in humans investigating whether increments in dietary fructose ≤ 100 g/d favor a higher or lower fasting plasma triacylglycerol (FPTG) concentration. ES, effect size; HLP, hyperlipidemic; T1DM, type1 diabetes mellitus; T4HLP, type 4 hyperlipidemic; T2DM, type 2 diabetes mellitus. Weights are from random-effects analysis. Observations are grouped by the type of substrate that was exchanged with fructose (eg, glucose, sucrose, starch, and other). Squares show study means and relative precision (smaller squares indicate less influence). Horizontal bars show 95% CIs for the associated study mean. The diamond at the center indicates the random-effects estimate of the combined mean (−0.23 local population SDs; $P > |z| = 0.20$); the width of the diamond shows 95% CIs for the associated combined mean, and the bar on the diamond is the forecast 95% CI for a similar new study (distribution of effect sizes). The CIs tabulated for the effect (diamond width) when zero is not included are significant ($P > |z| < 0.05$).

No studies examined participants in the normal range of BMI (ie, <25). In addition, groups specified in prior reports as hyperlipidemic, hyperinsulinemic, or at risk of coronary heart disease were not encountered, although such persons may be presumed to be among the overweight or obese and the diabetes groups. Studies in children also were absent (participant age range: 34–62 y; Table 2).

The lack of significant RD for any group by health type or by study design and quality (see "Quality assessment" under "Supplemental data" in the current online issue) suggests that the overall trends shown (Figures 2–4) are reasonable summaries of a general response. Two studies had for-profit funding, but there was no evidence of bias (see "Quality assessment" under "Supplemental data" in the current online issue). Furthermore, both a funnel plot of the residuals for Figure 3 and the corresponding trim-and-fill analysis indicated insignificant error with an asymmetric bias of 0.028 g HbA_{1c}/100 g Hb (95% CI: −0.078, 0.059 g HbA_{1c}/100 g Hb; $P > |z| = 0.72$) or only 1–2% of the range of effects seen in Figure 3. The trim-and-fill analysis provided an estimate of the number of studies that may have been conducted but never published or found (or, more precisely, the number of studies required to balance the symmetry of the funnel plot). Only one such study was estimated, and it favored a greater rather than a lesser effect on HbA_{1c} (see Figure S1 under "Supplemental data" in the current online issue).

Fasting plasma triacylglycerol

Fructose intakes up to 100 g/d

A combination of all health types in the 14 randomized controlled trials (RCTs) by using ≤100 g fructose/d found no significant effect on FPTG (**Figure 5**). This lack of effect was evident whether fructose replaced starch, sucrose, or glucose. Random effects were significant, but systematic deletion of each health type and study design in turn failed to achieve a fixed-effect result. A similar outcome arose when combining all studies, RCTs and non-RCTs [number of studies, $k = 30$; combined mean effect: −0.033 population SD (popSD); 95% CI: −0.224, 0.158 popSD; $P > |z| = 0.736$].

Fructose intakes up to 350 g/d

FPTG increased at the upper end of the range of fructose intakes studied; this in both RCTs ($P > |\text{kh-}t| = 0.05$) and non-RCTs ($P > |\text{kh-}t| = 0.001$) (**Figure 6**; **Table 3**, model 1). Observations for RCTs and non-RCTs overlapped and had similar heterogeneity ($I^2 = 0.93$ and 0.91, respectively) and small, nonsignificant residuals from a combined trend [RD −0.09 (95% CI: −0.39, 0.21) in RCTs; 0.06 (−0.14, 0.28) in

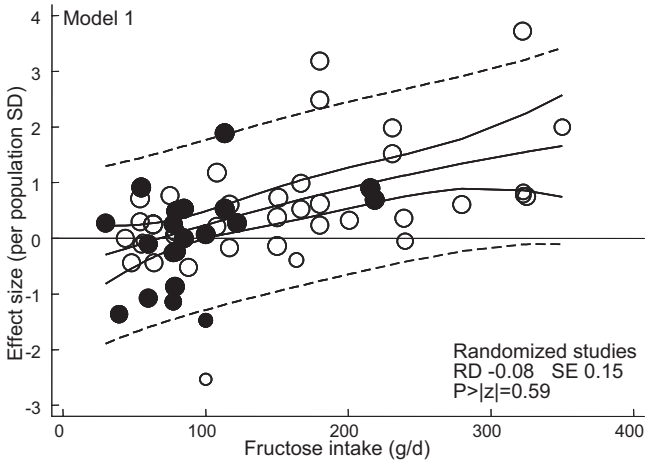

FIGURE 6. Random-effects regression of difference in fasting plasma triacylglycerol (FPTG) concentrations due to dietary fructose compared with control. Data are from 60 studies, combining healthy subjects, type 1 and type 2 diabetes patients, hyperlipidemia patients, persons at risk of coronary heart disease, persons with impaired glucose tolerance, and those with hyperinsulinemia. ●, Randomized controlled trials (RCTs); ○, nonRCTs; relative precision is indicated by bubble size (smaller bubbles indicate less influence). Curves are trends (and 95% CIs) for trend (—) ± 95% CI for forecast (- - -). Effect size dependence on fructose dose (Fr; g/d) = $-0.54 \pm 0.22^{*} + (8.34\times10^{-3}\ \mathrm{Fr} - 6.16\times10^{-6}\ \mathrm{Fr}^2)(1 \pm 0.29)^{**}$, for which $^{*}P > |\text{kh-}t| = 0.019$; $^{**}P > |\text{kh-}t| < 0.001$. Heterogeneity ($I^2$) was significant: $P > \chi < 0.001$; $I^2 = 0.92$; df = 57; between-studies SE = 0.74 population SD.

non-RCTs]. Studies were therefore combined in further analyses. In Figure 6, the 95% CIs for the trend provide information about the underlying mean treatment effect at each fructose dose. Meanwhile, the 95% CI for the distribution of treatment effects is wider (called heterogeneity) and bounds the range of different effect sizes that fructose has due to other circumstances (other determinants), some of which are elucidated below.

Fructose dose, control substrate, duration of treatment, and age of participants

The choice of control substrate (ie, sucrose, glucose, or starch) and the duration of treatment both contributed to heterogeneity and were accounted for in model 2 (Table 3, **Figure 7**). The effect of fructose increased with fructose dose, but the effect size appeared to decrease with the log-duration of treatment (Figure 7). The manner of this decrease was that of an interaction between duration of treatment and the dose of fructose above a threshold dose (Table 3). Thus, larger doses of fructose had a larger effect that declined more rapidly, whereas the lower doses had a smaller effect that declined more slowly. Model 2 proved not to be ideal, in that RDs varied with the age of participants; this variation was found also to be explained by the interaction of the age of the participants, the duration of treatment, and the dose of fructose (model 3 in Table 3 and **Figure 8**). Thus, the apparently more rapid decline after higher doses of fructose appeared more rapid among older participants.

Not all individual studies reported that fructose elevated FPTG, and this finding was more common in the lower range of fructose intakes (Figures 6, 7, and 8). The summary of fructose effects (models 2 and 3) suggests this effect was significant for the underlying trend (Table 3), which is plausible, given the current knowledge of a moderate effect of LGI carbohydrate of FPTG (18).

Choice of control substrate

Individual study data are shown (Figure 8) by type of control substrate—sucrose, glucose, or starch—together with trendlines for model 3 (Table 3). For the sucrose control, the highest doses of fructose elevated FPTG, which decayed with duration of study without a significant departure from the general trend. The same was found for glucose and starch controls (Figure 8). Thus, no substrate control category had combined RDs that deviated significantly ($P > |z| < 0.05$) from the general trend. Nevertheless, results differed significantly between substrates. Fructose replacing starch had a greater effect than did fructose replacing sucrose ($\bar{x} \pm$ SE combined difference: 0.82 ± 0.23 popSD; $P > |\text{kh-}t| = 0.001$). Fructose replacing starch differed insignificantly from fructose replacing glucose (0.32; SE: 0.21; $P > |\text{kh-}t| = 0.13$). Fructose replacing glucose had a marginal, nonsignificantly greater effect than did fructose replacing sucrose (0.50; SE: 0.27; $P > |\text{kh-}t| = 0.07$); the greater effect was in the expected direction.

Background diet

Neither metabolizable energy (ME; in kJ) nor protein (% of ME), carbohydrate (% of ME), dietary fiber (% of ME), fat (% of ME), or the ratio of polyunsaturated to saturated fat (P/S) in background diets explained heterogeneity in results. Of these, carbohydrate and fructose intake were significantly correlated (Table 2); however, substituting carbohydrate for fructose in model 3 was inferior, both by study design and by leaving a greater SE among studies ($\tau = 0.76$ popSD; $P > \chi < 0.001$ for carbohydrate versus $\tau = 0.52$; $P > \chi < 0.001$ for fructose). A possibility that high energy intake was permissive of the effect of fructose on FPTG was investigated as a possible interaction between ME intake and fructose intake. However, that possibility explained none of the heterogeneity, and the effect of such an interaction on FPTG was not statistically significant ($P > |\text{kh-}t| = 0.21$).

Bound fructose in the background diet

There were negligible amounts of bound fructose (sucrose) in the background diets (Table 2) but not in 5 studies from 3 publications (57–59). The combined RDs for these 5 studies did not differ significantly from trend (RD: 0.013 popSD; $P > |z| = 0.94$).

Health and disease states

The rise in FPTG with fructose dose (**Figure 9**) and the decay with time (**Figure 10**) were each apparent in healthy people, people with hyperlipidemia, and possibly in people with coronary heart disease (only 2 studies). None of the health types mentioned had RDs that differed significantly from the 2 trends. However, the data on high intakes of fructose in persons with either type 1 or type 2 diabetes or with other conditions (eg, hyperglycemia or hyperinsulinemia) were missing or were too few to allow an assessment of whether responses at those intakes, too, followed the general trends.

Normal-weight, overweight, and obesity

As for the health types, no weight class range showed a significant departure from the 2 trends, although there is an absence

TABLE 3
Study determinants and the effect of fructose on fasting plasma triacylglycerol in 60 studies[1]

Determinant	REML regression coefficient	CV (%)	$P > \|\text{kh-}t\|$	$P > \|\text{permute}\|$[2]
Model 1 (Excluding distinction between available carbohydrates and ignoring interaction)[3]				
Fructose (g/d)	83×10^{-4}	29	<0.001	<0.0001
Fructose (g^2/d^2)	-61×10^{-7}			
Constant	-540×10^{-3}	22	0.019	NA
Random effects (SE between studies)	± 0.74			
Model 2 (As model 1 but including starch, sucrose, and glucose and duration × dose interaction)[4]				
Fructose (g/d)	36×10^{-4}	16	<0.001	<0.0001
Fructose (g^2/d^2)	16×10^{-6}			
Sucrose	134×10^{-3}	273[5]	0.72	0.69
Glucose	380×10^{-3}	115[5]	0.25	0.23
Starch	853×10^{-3}	36	0.009	0.005
Duration × dose interaction ($\log_{10}$w × g/d)	-95×10^{-4}	31	0.002	0.004
Constant	-1001×10^{-3}	32	0.003	NA
Random effects, SE between studies (popSD)	± 0.64			
Model 3 (as model 2 but including the age × duration × dose interaction)[6]				
Fructose (g/d)	57×10^{-4}	13	<0.001	<0.0001
Fructose (g^2/d^2)	16×10^{-6}			
Sucrose	72×10^{-3}	188[5]	0.59	0.80
Glucose	576×10^{-3}	48	0.046	0.03
Starch	898×10^{-3}	29	0.001	0.002
Duration × dose interaction ($\log_{10}$w × g/d)	-93×10^{-4}	27	0.001	<0.0001
Age × duration × dose interaction ($y \times \log_{10}$w × g/d)	-8×10^{-4}	22	0.001	0.0006
Constant	-1226×10^{-3}	30	0.002	NA
Random effects, SE between studies (popSD)	± 0.52			

[1] REML, restricted maximum likelihood; w, wk. The units are as shown; otherwise, a dummy variable (1 rather than 0) was used. The duration × dose interaction is the study-specific fructose intake (g/d) above a threshold (g/d) multiplied by the $\log_{10}$ of the duration of treatment (w). The value was expressed as a covariate with zero mean for the 60 studies.
[2] The Monte Carlo permutation test used 5000 replications.
[3] For model 1, heterogeneity (I^2) = 0.92 ($P > \chi < 0.001$; df = 57).
[4] For model 2, $I^2 = 0.91$ ($P > \chi < 0.002$; df = 53).
[5] Nonsignificant factors were retained because the differences between substrates were significant.
[6] For model 3, $I^2 = 0.88$ ($P > \chi < 0.001$; df = 52).

of information for high or very high fructose doses in the obese (see Figure S9 under "Supplemental data" in the current online issue). Two-thirds of studies reported on body weights ($k = 40$; $\bar{x}$ ± SD: 75 ± 11; minimum, 59 kg; maximum, 118 kg) in addition to body-weight class, but no association was found between variance of residuals of model 3 and variance in body weight ($P > |\text{kh-}t| = 0.88$).

Age

Model 3 includes an interactive term with age that had a small but significant effect on the decay in FPTG with time (Table 3). The model was fitted with negligible combined residuals for persons <30, 30–50, and >50 y old. Thus, each age group had nonsignificant combined residuals of <0.1 popSD ($P > |\text{kh-}t| > 0.5$). Each of the 3 age groups spanned much of the range of fructose intakes, but studies of longer duration are not available for the youngest and oldest of these age groups (see Figure S10 under "Supplemental data" in the current online issue).

Sex

A rise and a subsequent decay in FPTG were evident in studies in males; however, there were only 2 long-term studies to confirm the effect decays with duration of treatment in females. Neither sex had residuals differing significantly from the trends in model 3 (see Figure S11 under "Supplemental data" in the current online issue).

Effect of solid meals

Both the rise and the decay in FPTG were evident when fructose was consumed with solid meals, with or without fructose in drinks. However, too few long-term studies exist in which fructose was consumed only in liquid form (drinks or liquid meals) to allow confirmation of a trend for the treatment-duration decay. Neither mode of incorporating fructose into the meal had residuals differing significantly from trend (see Figure S11 under "Supplemental data" in the current online issue).

Study quality and potential biases

Study quality items and scores (*see* Methods) did not differ significantly from model 3 trends; combined RDs for each item and score were <10%, and generally <2% of the largest effect of fructose of ≈3 popSD for the highest dose shown in Figures 7–9. The difference in results of the 60 studies according to funding sources (for-profit or not-for-profit) was a combined mean of 0.01 popSD or <1% of the largest fructose effect of 3 popSD. The trim-and-fill analysis and funnel plots indicated errors of ≤0.05 popSD or <2% of the largest (3

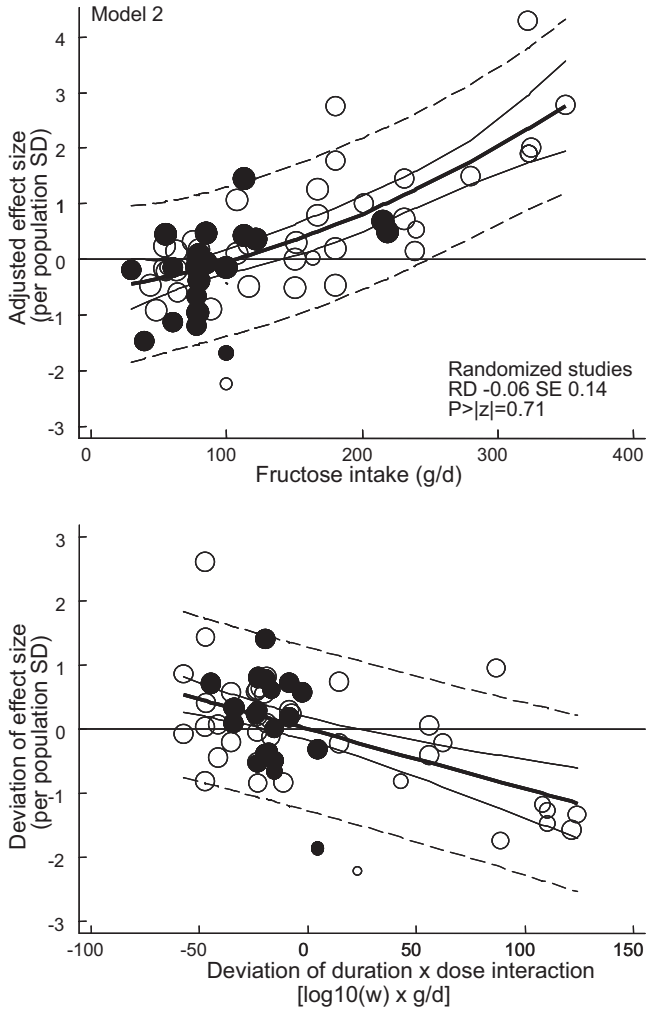

FIGURE 7. Random-effects regression of all controlled trials in humans investigating the difference in fasting plasma triacylglycerol (FPTG) concentrations due to dietary fructose after adjustments. RD, residual deviation; w, wk. Top: model 2 adjusted for the interaction between dose and duration of treatment. Bottom: model 2 adjusted for fructose dose. Curves are trends (and 95% CI) for trend (—) ± 95% CI for forecast (- - -); for simplicity, a single trend is shown for the different control substrates combined (*see* trends for each in Figure 8). Studies had heterogeneity (I^2) [$I^2 = 0.91$ for all studies, 0.90 for randomized controlled trials (RCTs), and 0.91 for non-RCTs].

popSD) effect of fructose; there was no indication of asymmetry or that more studies were needed to replace missing studies.

Handling of repeated measures

We examined 3 approaches to the handing of repeated measures (*see* Methods). Variance in meta-regression coefficients (CV%) for fructose varied across the 3 methods used as follows: 8% for the constant, 7% for the duration × dose interaction, 2% for the age × duration × dose interaction, 8% for sucrose (adjusted to zero constant), 4% for glucose (adjusted to zero constant), and 10% for starch (adjusted to zero constant); the range (due to nonlinearity) was 3–10%. The method we adopted (averaging of repeats and variances within studies) gave coefficients approximately midway between those of the other 2 methods (see Table S5 under "Supplemental data" in the current online issue), although our method was selected a priori for theoretical reasons (*see* Methods). The theory proved valid in practice, returning a smaller variance between studies of 0.28 popSD than the 0.42 popSD seen when the commonly used approach of discarding intermediate repeats was used (2). The substantial reduction in this value is consistent with an absence of repeated measures in most of the remaining studies, which gave rise to more varied observations between studies.

Comparisons with population estimates of total fructose intake

Fructose intakes affecting FTPG may be compared approximately with estimates of fructose intake by adults in the United States (**Figure 11**). The dose of fructose causing a significant effect when combining all studies was above the 99th percentile estimate of fructose intake in female adults (grouped by 19–50 y old and >50 y old), >95th percentile estimate for men aged >50 y, >90th percentile estimate for males aged 19–50 y, and >97th percentile estimate for all adults together. Year-to-year differences in population consumption of fructose suggests these comparsons should be considered approximate (see legend to Figure 11).

When the mode of expression of fructose intake is changed to a percentage of metabolizable energy, the fructose appears to have no significant effect in >97% of all adults, taken together. This lack of effect was apparent both when all intervention studies (irrespective of the control substrate) were combined or when only the studies using a starch control were selected (**Figure 12**). These comparisons, too, should be considered approximate.

Postprandial triacylglycerol

Studies ≤5 h long

Thirteen studies monitored PPTG for ≤5 h. These 13 groups of adults studied were 11 healthy groups, 1 type 2 diabetes group, and 1 postmyocardial infarction group (for details, see Table S3 under "Supplemental data" in the current online issue). Over all studies combined, PPTG showed a small but significant drop (0.02; 95% CI: −0.03, −0.01 mmol/L; $P > |z| = 0.02$), with little but significant heterogeneity ($\tau = 0.02$ mmol/L; $P > \chi = 0.001$).

Studies >5 h long

Twelve studies monitored PPTG for ≥6 h and ≤24 h (for details, see Table S3 under "Supplemental data" in the current online issue). Neither of 2 studies using <50 g eq fructose/d reported a rise in PPTG (**Figure 13**). Above that dose, a plausible but nonsignificant ($P > |\text{kh-}t| = 0.13$) dose-dependency occurred—≈1/6th of that seen for the largest rise in FPTG (Figure 8). Asymmetry in the funnel plot for distribution of data about the trend line in Figure 13 was insignificant [RD −0.026 (95% CI: −0.089, 0.037) mmol/L], and the trim-and-fill analysis estimated that no studies were missing (for the funnel plot, see Figure S6 under "Supplemental data" in the current online issue).

Health type

Information on PPTG in diabetes patients monitored for >5 h after fructose consumption was surprisingly scant—just one study (62) (Figure 13)—compared with 11 studies in healthy persons. The RD for that single study did not differ significantly from trend (0.03 mmol/L; $P > |z| = 0.37$).

Adaptation

Information on PPTG in subjects monitored for >5 h after adaptation was also scant. One study in healthy men and

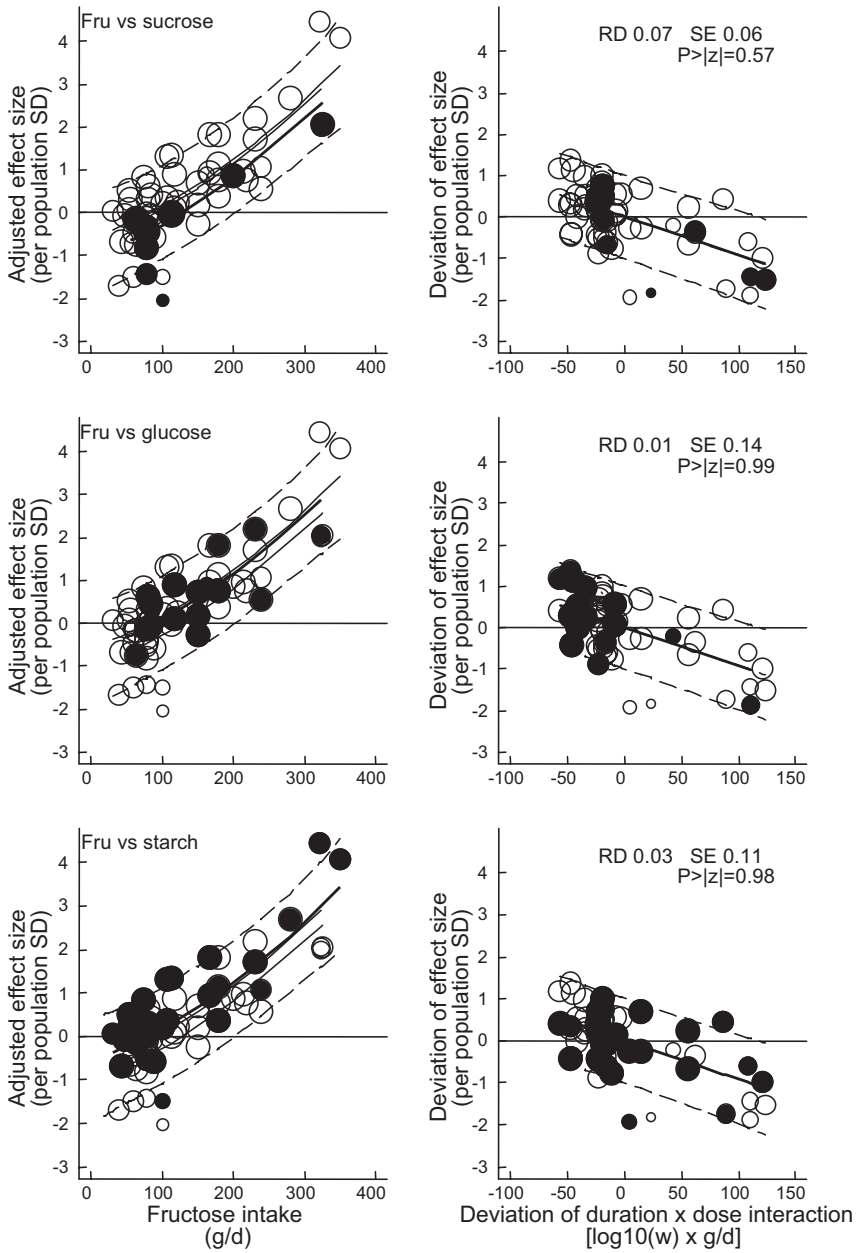

FIGURE 8. Fit of observations on fasting plasma triacylglycerol (FPTG) concentrations to trends for the fructose dose and duration × dose interaction, by reference substrates sucrose, glucose, and starch. RD, residual deviation; Fru, fructose. Data are for model 3 (model 2 also adjusted for age × dose × duration interaction; Table 3); ● and the thicker curves: fructose was matched against a specified control substrate; ○ and the thinner curves: other control substrates were used; - - -, the 95% CI forecast (distribution of effect sizes at any one dose). For clarity of viewing the data, the 95% CIs for the underlying trends were omitted. RD values are the combined mean RD (observed minus predicted for model 3), and SE is the SE of the RD (each with units the same as those on the *y*-axis).

another in healthy women (both: 52) used 85 g fructose/d for 6 wk. The results did not differ significantly from the trend in studies of unadapted persons (RD −0.10 mmol/L; $P > |z| = 0.07$).

Sex

When subjects were monitored for >5 h ($k = 12$), PPTG differed nonsignificantly between the sexes (males > females: 0.06; SE: 0.09 mmol/L; $P > \chi = 0.49$).

Mode of fructose ingestion

When subjects were monitored for >5 h (12 studies), the mode of fructose ingestion made little difference. RDs differed nonsignificantly whether fructose was consumed in both solid foods and drinks together (2 studies: RD −0.1 mmol/L; $P > |z| = 0.0.07$), in liquid meals only (4 studies: RD −0.00; $P > |z| = 0.96$), or in drinks only (with or without other foods low in fructose) (6 studies: RD 0.00; $P > |z| = 0.42$). No study made a direct comparison between fructose in solids and fructose drinks.

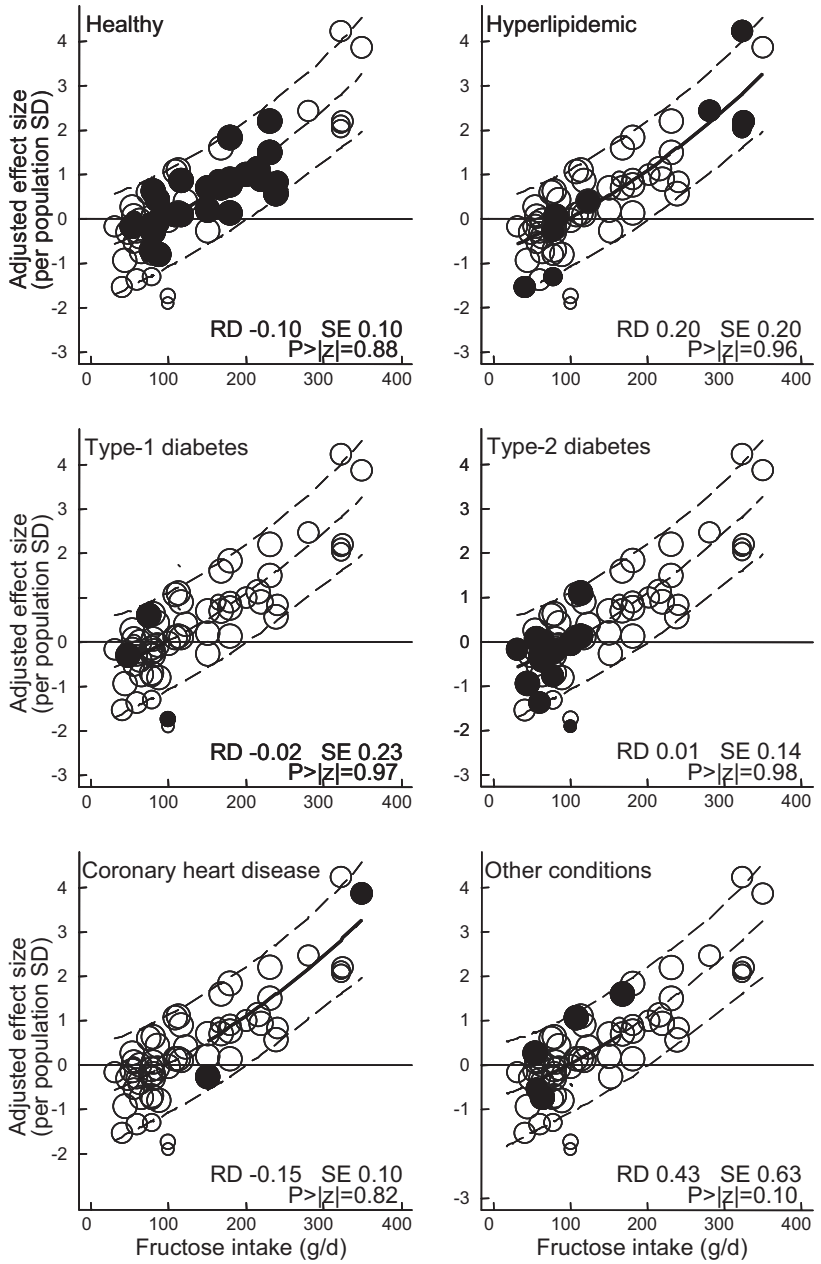

FIGURE 9. Fit of observations on fasting plasma triacylglycerol (FPTG) concentrations to the trend for the fructose dose, by health type. RD, residual deviation. Data are as in Figure 8 compared with dose by health status; ●, specified state; ○, other states. The curves are the central trend (all control substrates combined) and 95% CI for the forecast (ie, for distribution of different effect sizes at any one dose). For clarity in viewing the data, the 95% CIs for the underlying trend (or the mean influence of fructose) are not shown. RD values are the combined mean RD (observed minus predicted for model 3), and SE is the SE of the RD (each with units the same as those on the *y*-axis).

Control substrates

When subjects were monitored for >5 h, studies mainly used glucose as the control ($k = 8$ from 12 studies), and these studies had RDs that did not differ significantly from trend (RD −0.020 mmol/L; $P > |z| = 0.58$). Likewise, 2 studies used starch controls (RD 0.12; $P > |z| = 0.31$), 1 study used sucrose as control (RD −0.12), and another used glucose as control but in only one-half the weight of fructose present in the treatment (RD −0.56).

Body weight

Fructose intake ≤100 g/d

With an oral fructose intake of ≤100 g/d, no significant influence on body weight was evident whether fructose replaced starch, glucose, or sucrose (**Figure 14**) (for further details, see Table S4 under "Supplemental data" in the current online issue). Studies of low precision are fewer in number below the mean than above it, which is consistent with a hesitancy to publish studies showing body weight reduction (publication bias). Also

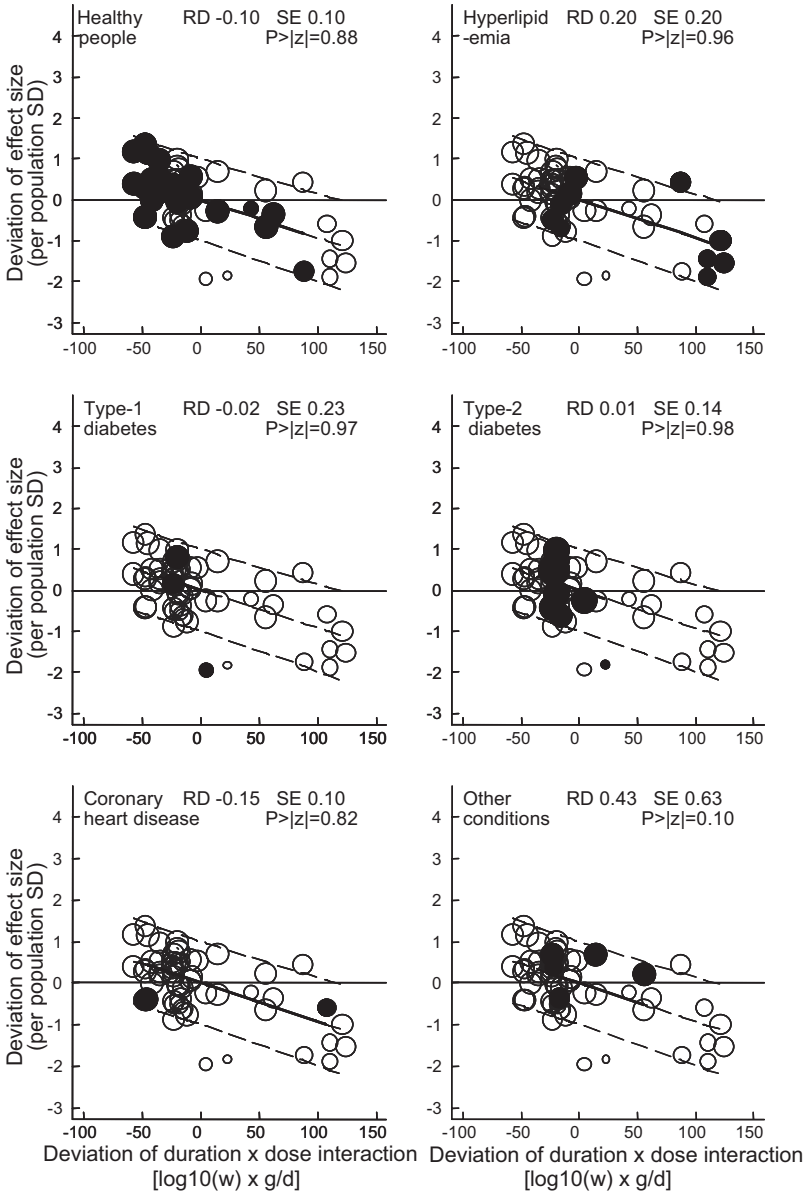

FIGURE 10. Fit of observations on fasting plasma triacylglycerol (FPTG) concentrations to the trend for the duration × dose interaction, by health status. Data are as in Figure 8 for health status: ● and thicker curves, specified state; ○ and thinner curves, other states. The curves are the central trend (all control substrates combined) and 95% CIs for the forecast (ie, for distribution of different effect sizes at any one dose). For clarity of viewing the data, the 95% CIs for the underlying trend (or the mean influence of fructose) are not shown. RD values are the combined mean RD (observed minus predicted for model 3), and SE is the SE of the RD (each with units the same as those on the *y*-axis).

consistent with this hesitancy, the trim-and-fill analysis gave a theoretical estimate of 3 studies that may have been performed but not published (or more precisely, the number of studies needed to balance asymmetry in the funnel plot). Nevertheless, the trim-and-fill analysis also indicated insignificant error in the estimated mean effect, with an asymmetric bias of −0.016 (0.95% CI: −0.078, 0.046; $P > |z| = 0.72$) kg/wk (for further details, see Figure S7 under "Supplemental data" in the current online issue). This combination of the theoretical absence of some studies and no significant bias suggests that the missing studies would have had little weight statistically.

Fructose intake >100 g/d

Four studies (3 reports) provided information on body weight with ingestion of >100 g fructose/d in healthy persons (67), persons at risk of coronary heart disease (59), and hypertriacylglycerolemic patients (51). These studies yielded heterogeneous results ($I^2 = 63\%$, $P > Q = 0.044$; df = 3). A random-effects meta-analysis indicated an overall significant ($P > |z| = 0.018$) rise in body weight of 0.44 (SE: 0.19) kg/wk, which may be overestimated by 0.10 kg/wk (0.95% CI: −0.45, 0.24; $P > |z| = 0.55$) because of asymmetry due to a single possibly missing study (see Figure S8 under "Supplemental data" in the current online issue). At these doses, the number of studies was small ($k = 4$), the combined weighted mean fructose intake was very high (ie, 213 g/d; ≈40% of ME), and the duration of the studies was ≤2 wk. The sparse data on intakes of >100 g/d precluded the examination of a cause for this difference, including possible effects of energy intake.

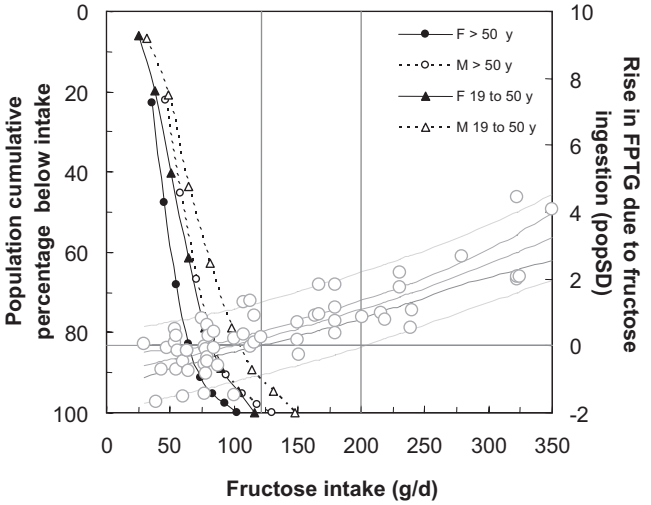

FIGURE 11. Effect on fasting plasma triacylglycerol (FPTG) concentrations of fructose by dose compared with estimates of fructose ingestion by weight in 4 adult subgroups in the US population. Incremental FPTG values (righthand *y*-axis) are from Figure 8 (○), showing in gray—from inside to outside—the central trend (as in Figure 7), the 95% CIs for the underlying trend, and the 95% CI for the distribution of effects at each dose (- - -). Fructose intakes in the population subgroups (lefthand *y*-axis subgroups are indicated in the panel) are estimates from data on the intake of sweeteners (60) assuming a ratio of fructose to glucose of 0.43, which has hardly changed during the past 2 decades (61), and an average intake of 2% of energy from fructose naturally occurring in foods, which tends to overestimate intakes for those consuming large amounts of added sugars. Intake estimates for added sugars were from the Continuing Survey of Food Intake by Individuals 1994–1996, after which average intakes for the whole population appear to have peaked in 1999 and fallen back to 1994–1996 levels by 2005 (61). Conversion from reported intakes as metabolizable energy to weight (in g) used group-specific maintenance expenditures assessed by the D_2O method (60). The vertical lines transect the *x*-axis and the cumulative intakes at a point below which fructose had no significant effect on FPTG elevation, both for the underlying trend (left vertical transection) and for the distribution of effects (right vertical transection).

DISCUSSION

Although the ratio of fructose to glucose from added sugars has been nearly constant over the past 3 decades, a trend toward bulk sweeteners with a lower glycemic response is now possible because of the development of pure fructose and 90% fructose syrup (68), the supply of which is limited only by market demand. It is appropriate, therefore, to be aware of possible adverse or beneficial effects of fructose ingestion—whether to better inform nutritional guidance, to help avoid inappropriate marketing of carbohydrates, or to develop best practice in clinical nutrition (3). Such guidance is beyond the scope of the present discussion, and it may need to take into account the other components of foods that accompany the fructose. In addition, the implications of any balance of effects of fructose on different aspects of metabolism in terms of possible risk to health would have to be ascertained either by using the methods of "complex synthesis" as described in a review of recent developments in meta-analysis (11) or, more directly, with the use of long-term trials. Furthermore, in discussing these issues, it is important to be aware that the effect of dysglycemia on health, the role in health of LGI carbohydrates, and the significance for health of both fasting and postprandial triacylglycerols after fructose ingestion remain controversial.

Of interest here are fructose intakes that are largely in exchange with glucose-loaded carbohydrates. Prior meta-analyses indicate that an excessively high intake of high-glycemic-index carbohydrate has an adverse effect on FPTG and glycated proteins (16, 57) and poses some risk to persons who entered epidemiologic studies with the status of healthy persons (69). In contrast, numerous narrative reviews consider fructose (26, 27, 70–77) mostly by focusing on the adverse effects on FPTG and PPTG, among other possible health markers. On such adverse effects feed many hypotheses of clinical harm (28, 29, 70, 73, 78–83). Often, however, inadequate consideration is given to the dose at which these effects occur and to the question of whether adverse effects in one aspect of metabolism (eg, lipidemia) are countered to any extent by potentially beneficial effects in another (eg, glycemia).

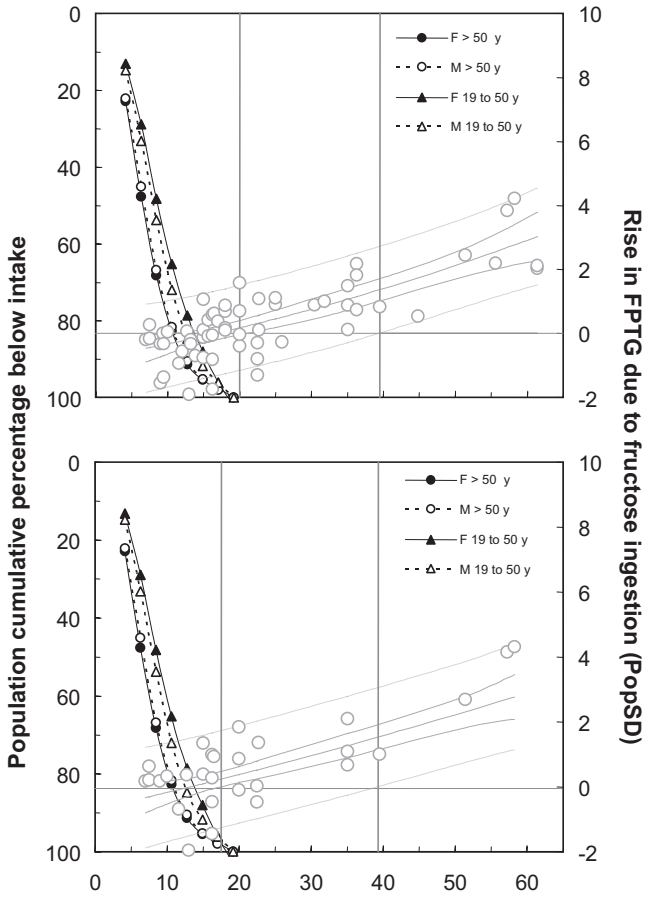

FIGURE 12. Effect on fasting plasma triacylglycerol (FPTG) concentrations of fructose by dose compared with estimates of fructose ingestion relative to energy intake in 4 adult subgroups in the US population. Top: comparison with all intervention studies combined. Bottom: comparison with intervention studies examining fructose versus starch. Data are from Figure 11 and are re-expressed as a percentage of metabolizable energy intake for the intervention studies and as a percentage of metabolizable energy intakes reported for the populations without the conversion to weight (in g) of fructose intake that was used in Figure 11. The vertical lines transect the *x*-axis and the cumulative intakes at a point below which fructose had no significant effect on FPTG elevation, both for the underlying trend (left vertical transection) and for the distribution of effects (right vertical transection).

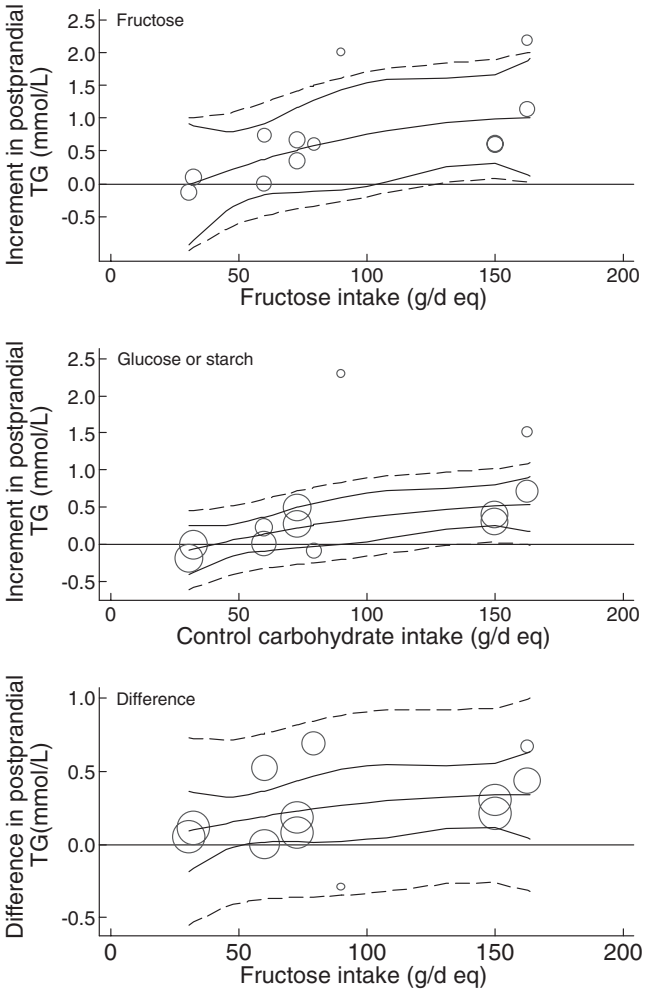

FIGURE 13. Incremental postprandial triacylglycerol (PPTG) concentrations due to ingested fructose compared with that due to ingested glucose or starch. Curves are trends (and 95% CI for trends) (—) ± 95% CI for forecast (- - -) for 12 studies monitoring subjects >5 h after ingestion. Bubbles are study means; the smaller bubbles are less precise. The incremental PPTG (mmol/L) was the average area increment/h of monitoring. The increment due to fructose (top) was $-0.50 \pm 0.37 + (0.018 \text{ dose} - 0.0.00053 \text{ dose}^2) \times (1 \pm 0.32)$ with $P > |\text{kh-}t| = 0.21$ for the constant, 0.014 for the slope, and $P > \chi < 0.001$ (df = 10) for heterogeneity ($I^2 = 0.89$; between-studies SE = 0.34 mmol/L). The increment due to carbohydrates control (middle) was $-0.36 \pm 0.17 + (0.010 \text{ dose} - 0.00027 \text{ dose}^2) \times (1 \pm 0.29)$ with $P > |\text{kh-}t| = 0.09$ for the constant, 0.009 for the slope, and $P > \chi < 0.001$ (df = 10) for heterogeneity ($I^2 = 0.83$; between-studies SE = 0.18 mmol/L). The treatment difference (bottom) was $-0.04 \pm 0.16 + (0.0448 \text{ dose} - 0.00027 \text{ dose}^2) \times (1 \pm 0.60)$ with $P > |\text{kh-}t| = 0.79$ for the constant, 0.13 for the slope (ie, marginal but plausible), and $P > \chi < 0.006$ (df = 10) for heterogeneity ($I^2 = 0.70$; between-studies SE = 0.16 mmol/L).

The present meta-analysis confirms that, within the limits of the studies undertaken, the presence of fructose can improve HbA_{1c} concentrations. In addition, we showed that the size of effect differs between persons according to the severity of their dysglycemia (as marked by HbA_{1c}) and that correction to HbA_{1c} is dependent on the dose of fructose. Similar results also arose for glycated proteins and fasting blood glucose after intervention with LGI (mostly starch) foods (18). A possible limitation in both the present (Figure 4) and the previous (18) meta-analysis with starch foods is the number of studies in persons without diabetes, which is small. On the other hand, in both studies, there is evidence of modifiability of glycated proteins with a mean threshold of effect below the average healthy concentration of blood glucose or glycated protein. Such continuity of effect is in keeping with the concept that dysglycemia is continuous from healthy concentrations of glycemia or HbA_{1c} to well above normal in the diabetic range (*see* Introduction). Moreover, it indicates that dysglycemia is continuously modifiable by fructose (as previously shown to be modifiable with LGI starch foods) throughout the range.

Furthermore, on the basis of the study designs, this meta-analysis supports a view that an LGI carbohydrate, namely, fructose, can be effective without overt modification to dietary energy density or dietary fiber intake. An effect of LGI carbohydrate or of glycemic load independent of fiber was evident elsewhere, also, for mainly starchy foods (18). For both types of carbohydrate, however, the evidence so far is mostly limited to that in adults in studies of <3 mo duration.

Any aim to modify food composition must consider both the beneficial and adverse effects before ascertaining their net balance (33). The potential benefit of lower HbA_{1c} was unaccompanied by effects of fructose (≤100 g fructose/d) on body weight (Figure 13). Thus, a reduction in the HbA_{1c} concentration cannot be explained by a lowering of body weight. Whether very high or excessively high intakes of fructose can influence body weight is of current interest, and the present meta-analysis of studies with a weighted mean intake of fructose at 213 g/d shows a short-term (<2 wk) elevation. However, such a fructose intake is not relevant to the general population, because >99% of people in the United States consume <150 g fructose/d (Figure 11).

It is interesting that the meta-analysis here confirms the fact that fructose at a sufficiently high dose can elevate FPTG, which would counter (to a greater or lesser extent) the potential benefit of further lowering a low HbA_{1c} concentration (or maintaining a low concentration). However, such an adverse effect on FPTG would not be expected to arise with statistical significance among a large majority of people (Figures 11 and 12), and any occurrence may well decay with adaptation. The net balance of dyslipidemia and dysglycemia on these accounts at very high doses of fructose is difficult to appraise for the present because of an absence of information on HbA_{1c} at doses of >88 g/d. It cannot be assumed that the net balance would be adverse.

HbA_{1c} is less sensitive to change than is postprandial blood glucose. Likewise, FPTG appears less sensitive to change than is PPTG. The present meta-analysis suggests that a significant rise in PPTG is not evident unless an equivalent of ≥50 g fructose/d is consumed. More than 50% of the adult population of the United States consumes this amount of fructose (free or bound) (Figure 11). However, the extent to which any rise in PPTG in response to fructose is adverse is difficult to assess. Whether PPTG is a marker of risk after fructose consumption, as it is after consumption of fats or saturated fats (84–87), is not clear. Moreover, the generation of small triacylglycerol-rich lipoprotein particles, such as those generated by fructose, does not itself seem to be a sufficient condition for atherogenesis (9). Until more evidence is available on these aspects, it does not seem possible to assess the net balance of the possible risk factors for fructose consumption at doses of >50 g/d.

Fructose intake among US adults ranges up to 150 g/d (Figure 11), which conveniently divides into 3 bands: 0–50, >50–100, and >100–150 g/d. Our view is that 50 g/d (or less) would be a

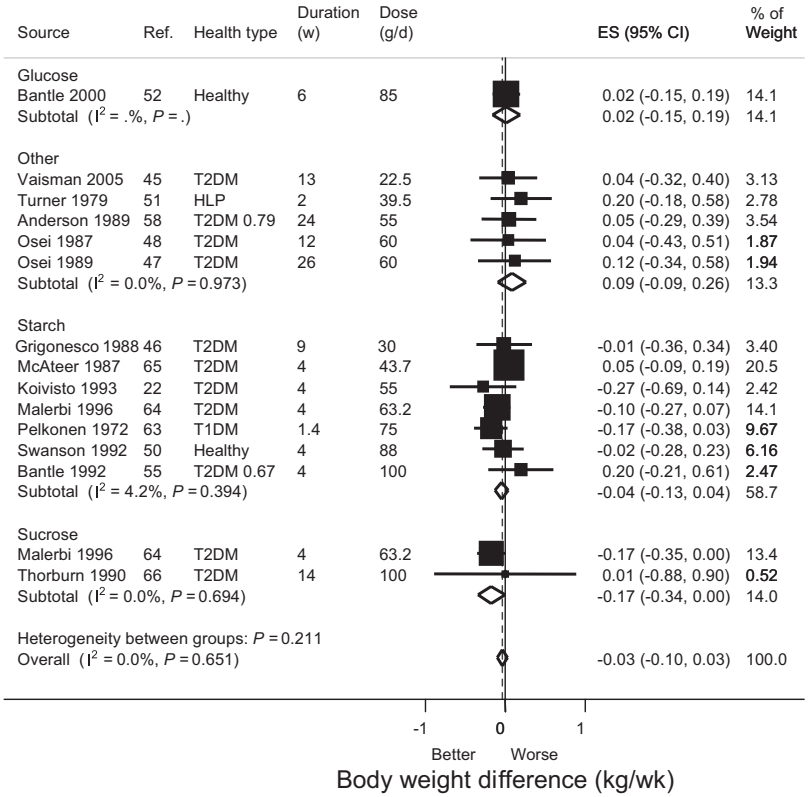

FIGURE 14. Forest plot of the effect of ≤100 g fructose/d on body weight. ES, effect size; HLP, hyperlipidemic; normal, healthy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; T2DM 0.79 and T2DM 0.67, mixed type 1 and 2 diabetes mellitus in which 79% and 67% of patients have T2DM. Observations are grouped by the type of substrate that was exchanged for fructose (ie, glucose, starch, sucrose, and other). Squares show study means and relative precision (smaller squares indicate less influence). Horizontal bars show 95% CIs for the associated study mean. The diamond at the center shows the random-effects estimate of the combined mean (kg/wk). No group had a significant effect ($P > |z| = 0.89$ for glucose, 0.33 for starch, 0.06 for sucrose, 0.33 for other substrates combined, and 0.30 for substrates overall); the width of the diamond shows the 95% CI for the associated combined mean. Distribution of effects was zero (fixed effect). The CIs tabulated for the effect by study (diamond width) not including zero are significant, $P > |z| < 0.05$ (for further information, see Table S6 under "Supplemental data" in the current online issue).

moderate intake. With respect to dysglycemia (marked by HbA_{1c}) and dyslipidemia (marked by either PPTG or FPTG), such moderate intakes of fructose would appear to be acceptable and may favor some improvement of dysglycemia. Our view is that >50–100 g/d is a high fructose intake. At such high fructose intakes, the available data are equivocal (undetermined balance) on the question of whether fructose or starch would pose the greater or lesser net benefit or risk with respect to dysglycemia or dyslipidemia. Fructose intakes of >100 g/d are very high—even excessive, by comparison with observations in adult populations of health professionals, for example (88). Whether a lowering or maintaining of low concentrations of HbA_{1c} by fructose would persist at very high or excessive fructose intakes has not yet been researched.

In conclusion, efforts to reduce fructose consumption could exchange a risk in one group (dyslipidemia in high or very high consumers) for a risk in another group (dysglycemia among moderate or higher consumers). Moderate fructose consumption (<50 g/d, or <10% ME) appears acceptable and potentially beneficial. Whereas a long-term (2-y) study has been conducted on 50 g fructose/d (4), the effect of higher doses on longer-term quality of life in those with elevated dysglycemia or elevated dyslipidemia remains to be studied. Finally, the present observations on HbA_{1c} and FPTG are also relevant for health professionals who are using these markers as potential indicators of disease progression and drug efficacy.

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The authors' responsibilities were as follows—GL: the literature search; extraction, analysis, and interpretation of data; and the writing of the manuscript; and RT: independent search and extraction of data from the literature. Fructose is produced commercially by the organization that commissioned this study, Dansico Sweeteners (United Kingdom). GL holds shares in Independent Nutrition Logic Ltd, and, at the time of this study, RT was employed by Indepdent Nutrition Logic Ltd. Independent Nutrition Logic Ltd is an independent consultancy that takes commissions from many organizations, a full list of which may be found at www.inlogic.co.uk.

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