

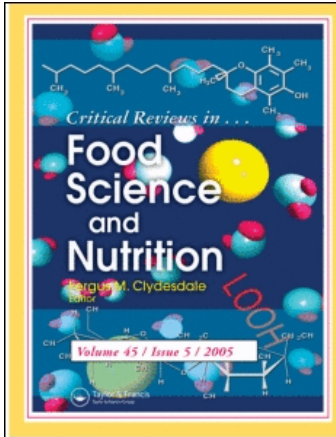
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Evidence-Based Review on the Effect of Normal Dietary Consumption of Fructose on Development of Hyperlipidemia and Obesity in Healthy, Normal Weight Individuals

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In recent years, there has been episodic speculation that an increase in consumption of fructose from foods and beverages is an underlying factor responsible for the relatively recent increase in obesity and obesity-related diseases such as diabetes. Reports in support of this hypothesis have been published, showing that concentrations of triglycerides (TG) are higher and concentrations of insulin and hormones associated with satiety are lower in animals following the ingestion of fairly large quantities of fructose, compared to other carbohydrates. However, results from human studies are inconsistent. A possible reason for the inconsistent results is that they are dependent on the particular study population, the design of the studies, and/or the amount of fructose administered. A systematic assessment of the strength and quality of the studies and their relevance for healthy, normal weight humans ingesting fructose in a normal dietary manner has not been performed. The purpose of this review was to critically evaluate the existing database for a causal relationship between the ingestion of fructose in a normal, dietary manner and the development of hyperlipidemia or increased body weight in healthy, normal weight humans, using an evidence-based approach. The results of the analysis indicate that fructose does not cause biologically relevant changes in TG or body weight when consumed at levels approaching 95th percentile estimates of intake.

Keywords triglycerides, fructose, body weight, healthy, human, normal diet

INTRODUCTION

Carbohydrates (sugars and starches) are needed in the diet to provide energy to cells in the body, particularly the brain. Sugar is a generic term for any caloric sweetener, and the most common sugars in the human diet include the monosaccharides glucose and fructose and the disaccharide, sucrose (“table sugar” in layman’s terminology). Fructose is naturally present in many fruits and is used as an added sugar (either as such or as a component of high fructose corn syrup or sucrose) in products such as soft drinks. High fructose corn syrup contains

approximately 52% (dry weight) glucose, 43% fructose, and 5% other saccharides (Silliman and Coulston, 1991). High fructose corn syrup and sucrose have a similar composition of glucose and fructose. Fructose and glucose have the same chemical formula (C₆H₁₂O₆), but differ in the orientation of the hydrogen and oxygen atoms around the carbons. The structural differences account for the differences in properties and metabolism in the body. Fructose is sweeter than glucose; therefore use of fructose in food products allows a reduction in the quantity of sweetener and the total calories of the product. High fructose corn syrup has become very popular with food manufacturers, particularly manufacturers of beverages because of its ease of use in manufacturing and decreased cost to sweeten a food compared to sucrose (Silliman and Coulston, 1991). The average daily intake of fructose has increased from 16 g/day in 1986 to 49 g/day in 2004 (Glinsmann et al., 1986), although the consumption of

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fructose from naturally occurring sources has remained fairly steady (Marriott et al., 2009).

Concurrent with the increased use of fructose along with total sugars in the diet, there has been an increase in obesity and associated diseases such as diabetes or heart disease. Therefore, numerous studies in experimental animals and humans have been initiated to examine the relationship between the consumption of fructose and alterations in biochemical processes associated with increased body weight and/or development of diabetes and/or heart disease such as increases in triglycerides (or triacylglycerol (TG)), and/or alterations in glucose regulation. Whereas the results of some of these studies support the hypotheses that fructose ingestion is associated with lipogenesis and insulin resistance, other studies indicate that the effect of fructose on lipid or carbohydrate metabolism is no different from that of other carbohydrates such as glucose, sucrose, or starch. Although several reviews describing the results of the studies have been published, a systematic, unbiased evaluation of the strength and the quality of the studies and their relevance for healthy, normal weight humans ingesting fructose in a normal dietary manner has not been performed.

The purpose of this review is to use an evidenced-based system to determine if a causal relationship exists between the consumption of fructose in a normal, dietary manner and the development of alterations in lipid or carbohydrate metabolism and obesity in normal weight, healthy individuals. This evidence-based review is based on guidance developed by FDA for an evidence-based review of health claims for dietary supplements. Although this guidance was developed to help identify purported benefits of dietary ingredients, it can also be used to determine whether a food ingredient such as fructose produces biologically significant effects in humans.

EVIDENCE-BASED REVIEW

FDA Guidance for Evidence-Based Review

The US Food and Drug Administration (FDA) published new guidance for health claim petitioners in January 2009 (FDA-CFSAN, 2009). This guidance was created to notify producers of dietary ingredients that FDA will conduct an evidence-based review to determine if claims are substantiated by the totality of all available, credible evidence.

Based on the new guidance provided by FDA (2009), only those studies for which conclusions about a substance/disease relationship can be drawn (studies should identify a substance and disease or health condition that is measurable) should be considered. Studies should then be evaluated by the following criteria:

- Type (human intervention and observational studies will take precedence over other types)
- Methodological quality
- Totality of evidence for and against the claim

In an intervention study, a designated quantity of the substance of interest is provided to subjects either in the form of a conventional food or dietary supplement. According to FDA, human intervention studies are the most reliable category of studies for determining a cause-and-effect relationship because the substance is provided under a controlled environment. However, information from a poorly designed intervention study from which no scientific conclusions about the substance/disease relationship can be drawn will not be considered. Intervention studies should be scrutinized for the following critical elements before determining that they are worthy of additional review:

- if the mechanism of action of the substance in a diseased population is the same as that of a non-diseased population; and the disease that is the subject of the claim is the primary endpoint;
- the study included an appropriate control group similar in all aspects to the experimental group (with the exception of the substance);
- the study was designed to measure the independent role of the substance in reducing the disease;
- relevant baseline data were not significantly different between groups;
- appropriate statistical analyses were performed;
- valid biomarkers of disease risk were measured; the length of the study was sufficient; the study included a follow-up assessment of change in intake (if the intervention involved dietary advice) and;
- the study population was relevant for the general U.S. population or the population subgroup identified in the proposed claim.

Each study passing the initial evaluation should then be evaluated for methodological quality (i.e. how well the study was designed and outcomes were determined). A number of factors should be considered during this phase of the evaluation procedure including:

- whether the studies were randomized, blinded, and/or placebo controlled;
- if the inclusion/exclusion criteria and key information on the characteristics of the study population were provided (in order for potential mitigating factors to be identified);
- whether subject attrition was assessed, explained, and reasonable;
- if the study included a mechanism for compliance verification; if statistical analyses were performed on all subjects (including dropouts);
- whether the study measured the actual onset of a disease or a risk factor in its development or whether the onset of the disease was confirmed through medical records or pathology reports (preferred) or less specific methods such as death certificates.

Depending on the degree to which each of these methodological factors is addressed, the study should be given a high, moderate, or low quality rating. Studies that are so deficient in methodological quality that conclusions cannot be drawn about the substance/disease relationship should be eliminated from further review.

In contrast to intervention studies, observational studies measure associations between the substance and disease, rather than the cause and effect between an intervention and an outcome. In the new guidance document, FDA states that “because of the limited ability of observational studies to control for variables, they are often susceptible to confounders.” Therefore, observational studies are not considered to be as reliable as intervention studies. However, according to FDA, “observational studies from which scientific conclusions can be drawn, in some situations, can be support for a substance/disease relationship for a significant scientific agreement (SSA) or qualified health claim” (FDA-CFSAN, 2009).

As part of the new evidence-based review system, observational studies should be evaluated for the substance/disease relationship by demonstrating: evidence of intake (i.e. do biological samples demonstrate a strong correlation between intake of the material and the concentration of the substance or metabolite in the sample?); use of scientifically acceptable and validated dietary assessment methods and; use of a quantifiable amount of the actual material of interest (preferred) versus a whole food containing ingredients other than the material of interest.

Observational studies that pass this evaluation should also be graded for methodological quality (low, moderate, or high) by assessing whether potential confounders of the disease of interest were adjusted for and food frequency questionnaires were utilized to estimate dietary intake (preferred) rather than single, 24-hour diet recall or diet records.

In the new guidance document, FDA (2009) stipulates that reports which discuss a number of different studies in limited detail should only be used to “identify reports of additional studies that may be useful to the health claim review and as background about the substance/disease relationship,” but should not be used as a source of information for studies performed on the material of interest because “the critical elements of a study must be reviewed to determine whether any scientific conclusions can be drawn from it.” Animal and in vitro studies can be used as background information for potential mechanistic information, but cannot be used to draw any conclusions about the relationship between the substance and disease in humans.

After reviewing each study for quality, the totality of the database should be examined to determine if it is credible enough to support a cause and effect relationship. Within each study type (e.g. intervention, prospective cohort, case-control, or cross-sectional), the studies should be reviewed for the number of studies and subjects per group, methodological quality (high, moderate, or low), outcome (e.g. statistically significant beneficial effect, no effect, or adverse effect), consistency, and relevance to the general U. S. population.

In general, observational studies should not be used to rule out the findings from intervention studies because observational studies are only able to identify possible associations and do not demonstrate a cause and effect. However, findings from one intervention study should not rule out consistent findings from several observational studies.

Principles mentioned in this guidance (FDA-CFSAN, 2009) were used to critically examine the existing database on the relationship of normal, dietary fructose intake to alterations in lipid and/or glucose metabolism and body weight gain in healthy, normal weight human subjects.

LITERATURE SEARCH AND STUDY SELECTION

Search Terms for Scientific Literature

The first step of the evidence-based review was to develop a means of obtaining all relevant, published literature on the relationship between fructose intake and changes in lipid or carbohydrate metabolism that could potentially lead to hyperlipidemia and/or body weight gain. Literature searches were limited to studies conducted in humans because the guidance on which this review is based indicates that in vitro and experimental animal studies should not be used to draw any definitive conclusions about the relationship between the substance and disease in humans. The searches were also limited to normal humans ingesting fructose in order to determine whether a cause and effect relationship existed between fructose intake and changes in lipid or glucose metabolism and/or body weight. In accordance with FDA guidance, “normal” subjects are “free from health problems that would complicate the interpretation of the study or increase the sensitivity of the subject to the toxic potential of the food or food additive.” Studies in which fructose was administered parenterally were also excluded from the search.

A comprehensive search of the published literature was performed in SCOPUS, a registered trademark of Elsevier B.V., and the largest abstract and citation database of research literature and quality web sources, available by subscription only. The following search string was utilized: ((TITLE-ABS-KEY(fructose AND (glyceraldehyde OR triglyceride OR triacylglycerol OR lipid OR cholesterol) AND (healthy OR normal) AND human AND (oral OR fed OR intake OR meal OR diet*) AND clinical) OR (TITLE-ABS-KEY(fructose AND (“body weight” OR diabetes OR “blood glucose” OR obesity OR insulin) AND (healthy OR normal) AND human AND (oral OR diet* OR fed OR intake OR meal) AND clinical))). An additional literature search was performed in Pub Med (US National Library of Medicine, Bethesda, MD; available online at <http://www.ncbi.nlm.nih.gov/sites/entrez>), using the terms fructose AND (healthy OR normal) AND human AND diet AND clinical to obtain additional studies. All searches were conducted March 20–25, 2009.

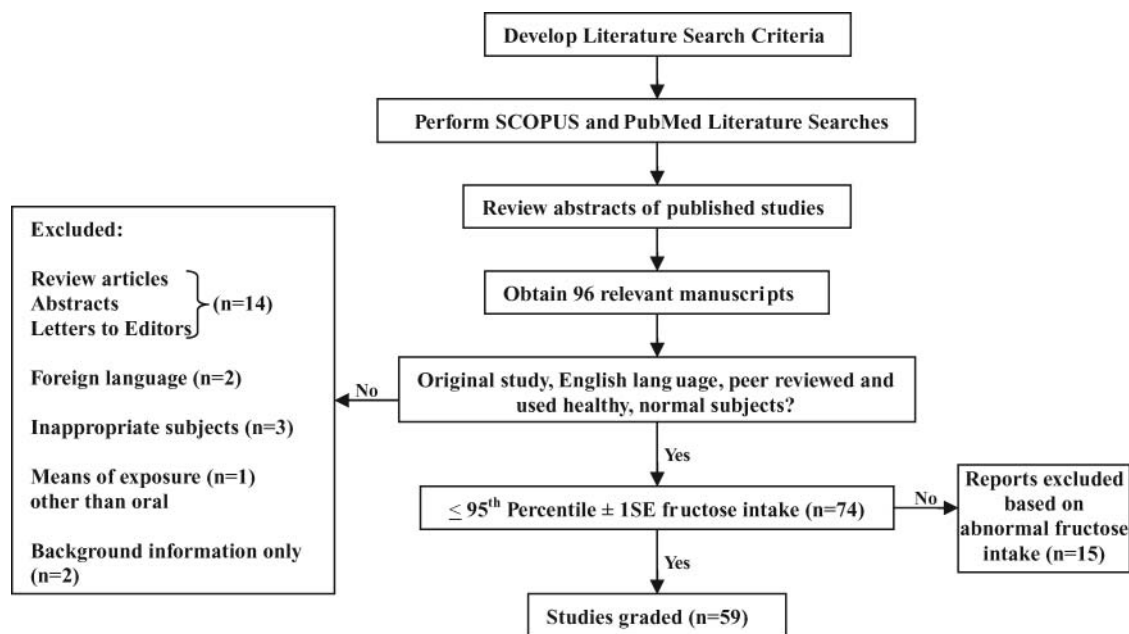


Figure 1 Summary of the decision process for retrieval and inclusion of literature (n = number of articles).

Study Selection Criteria

A review of abstracts of the studies obtained in the searches identified a total of 96 published manuscripts mentioning the clinical effect of fructose consumption on blood lipids or glucose, insulin, body weight, or obesity in healthy or normal human subjects (Fig. 1).

The 96 studies identified by the search were obtained, reviewed, and evaluated. The 14 review articles, abstracts, or letters to editors (as shown in Table 1) were used for background information, but were not used as a source of information for studies performed on the material of interest, because accord-

ing to the FDA review system, the critical elements of a study must be presented in order for one to determine whether any scientific conclusions can be drawn from it. These elements are not present in reviews; therefore the review articles were not evaluated for the effect of fructose on biomarkers of obesity or disease. No additional studies were identified in these reviews that were relevant to the evaluation. Two foreign language studies (Mehnert, 1976; Macor et al., 1990) also were not reviewed. An additional four studies were excluded from the analysis because they examined the effect of fructose on diseased, gastrectomized, or obese subjects (Shima et al., 1972; Rutkowski et al., 1999; Sunehag et al., 2008); or utilized inter-duodenal infusion as a means of exposure (Rayner et al., 2000). Two additional studies by Sievenpiper et al. (1998a, 1998b) were used to develop scoring criteria but were not used in the analysis because the studies examined factors pertinent to the proper design of studies with fructose (such as relationship of glucose and insulin responses to different volumes of fructose solutions) rather than the relationship of fructose ingestion to the development of disease.

The remaining 74 references were reviewed and the levels of fructose ingested in each study were calculated based on: quantity (g/day), percentage of energy, and percentage of carbohydrate intake. Of these, 15 studies involving concentrations of fructose higher than a predetermined cutoff value for normal consumption were rejected from the analysis (Supplemental Table 1). Data from a recent study published by Marriott et al. (2009) were used to establish the cutoff value, prior to review of any of the other literature. In Marriott et al. (2009), mean daily intakes of fructose were determined using NHANES 1999–2004 dietary intake data for 25,165 individuals, aged 1 year

Table 1 Review articles, abstracts or letters to the editor identified by the literature search*

Reference
Gaby (2005)
Havel (2005)
Lane and Cha (2009)
Nakagawa et al. (2005)
Neilson (2007)
Levine (1986)
Macdonald (1976)
Macdonald (1999)
McGuinness and Cherrington (2003)
Pedersen et al. (1978)
Rumessen (1992)
Tappy and Jequier (1993)
Truswell (1994)
Wolever et al. (1995)

*Used only for background information.

and older. Groups were classified according to gender and age (9–13, 14–18, 19–30, 31–50, 51–70, and 71 + years). Mean fructose intakes from the highest groups of the 95th percentile consumers (plus one standard error) were used as cutoff values. Consumption at percentiles higher than the 95th was not reported in this study. Based on the absolute amount, the percentage of energy intake and the percentage of carbohydrate intake, 95th percentile consumption values are 136.1 g/day (in 19–30 year old males), 18.8% (in 19–30 year old females), and 29.2%, (in 19–30 year old females), respectively. The 95th percentile fructose consumption (plus one standard error) of males aged 19–22 (as an absolute amount) also is reported (134 ± 12.2 g/day) in the Marriott et al. (2009) study. Because this intake is higher than that of 19–30 year old males, an absolute value of 146 g/day was used as the cutoff value (if the study included 19–22 year old males rather than 19–30 year old males). Using the 95th percentile values (plus one standard deviation) as intake limits for normal consumption is a reasonable assumption, based on the fact that FDA recognizes the 90th percentile intake estimates as upper limits of intake of dietary ingredients when evaluating dietary ingredient notifications. Ninetieth percentile intake estimates are commonly compared to concentrations of dietary ingredients used in safety studies to determine if adverse effects could occur in humans under normal conditions of use. We acknowledge that by limiting our analysis to the 95th percentile consumers (plus one standard error) we are omitting data that are pertinent for consumers of fructose at the 96th–100th percentile levels; however, intakes of any food ingredient higher than the 95th percentile would not be considered normal by authoritative bodies.

According to Marriott et al. (2009), subjects ingesting fructose at approximately 140 g/day ingest approximately 20 g fructose from naturally occurring sources such as grain products, fruit and fruit products, vegetables, and alcoholic and nonalcoholic beverages, and 120 g/day from added sources such as milk and milk products, grain products, sugars and sweets, and nonalcoholic beverages. According to USDA data, foods with the highest fructose content are generally in the beverages, fruits and fruit juices, and sugars and sweets categories (USDA, 1987). Examples of foods with fructose content > 3 g/serving are shown in Table 2.

Study Grading Criteria

A total of 59 studies were graded according to the following set of criteria, which were developed by the authors based on the criteria developed by the FDA for an evidence-based review of data for health claims, FDA guidelines for the conduct of human studies to demonstrate safety of food ingredients (FDA-CFSAN, 1993), and an understanding of factors that could affect the outcome of studies examining the effect of fructose on human health. As mentioned previously, the evaluation system designed by the FDA is designed to assess the beneficial effects of a dietary ingredient on health, rather than harmful effects. The

FDA evaluation system does not provide guidance on the scale that should be used to evaluate studies, point values that should be assigned to certain variables, or the scores associated with low, moderate, or high quality studies. The FDA evaluation system was used only to provide a framework for an evidence-based grading process for studies investigating the adverse effects of fructose, which we developed. Because intervention studies are considered to be more reliable than observational studies (FDA-CFSAN, 2009), studies of these two types were evaluated for quality on a different scale.

Intervention Study

The ability of each study to meet the individual factors identified below as being important criteria was graded on a 2-point scale developed by the authors (minimum = 0; maximum = 2). The factors are based on the new FDA criteria for an evidence-based review of human study data, as well as an understanding of the factors which may confound the results of studies examining the effect of fructose ingestion on the parameters measured in the study. The maximum number of points that could be obtained from an intervention study was 40. Based on the total point score, each intervention study was given a low (<20), moderate (20–29) or high quality grade (≥ 30). In addition to evaluating the strength of each study, we have included a short description of each study meeting the criteria and its interpretation.

1. Subjects

- A. Sufficient number? Studies that used at least ten subjects/group or a number of subjects calculated to be sufficient for uncovering a statistically significant effect were scored higher than others.
- B. Clinically shown to be disease free? Studies that used subjects clinically shown to be free of diseases that could influence outcome such as heart, liver, or kidney disease, hypertriglycerolemia or diabetes were scored higher than those that did not exclude such subjects.
- C. Normal weight or Body Mass Index (BMI)? Normal weight is defined as BMI of 18.50–24.99. BMI of ≥ 25.00 is considered being overweight and ≥ 30.00 is obese (WHO, 2006). Studies using subjects with BMI ≥ 30.00 were eliminated prior to review. Studies that used subjects of normal weight were scored higher than those using normal plus overweight subjects in order to uncover a possible cause and effect relationship between fructose intake and body weight (BW).
- D. Gender? Studies that used both genders with data analyzed together and separately were scored higher than others.
- E. Age (wide or narrow)? Studies that used subjects with a wide range, analyzed separately and together, were scored higher than others because the subjects should be selected to reflect the general population.

Table 2 Foods with fructose content >3 g/serving

Food Category/Food	Portion Size	Fructose content (g)
Baked Products		
Fruitcake, 7 inch diameter	1/12 cake	12.8
Fried cherry pie	1 pie	4.6
Baked, fruit pie	1/6 pie	4.2
Beverages		
Alcoholic beverages		
Beer cooler	12 fl oz (1 can)	14.3
Wine cooler	8 fl oz	12.8
Brandy, cherry	1.5 fl oz	6.8
Carbonated Beverages		
Lemon-lime	12 fl oz (1 can)	22.4
Cola	12 fl oz (1 can)	16.3
Pepper-type	12 fl oz (1 can)	16.2
Ginger ale	12 fl oz (1 can)	13.5
Root beer	12 fl oz (1 can)	11.8
Fruit Drinks		
Punch, prepared from dry mix	2 tbsp and 8 fl. oz. water	11.0
Cherry, canned	8 fl oz	10.3
Punch, canned	8 fl oz	9.2
Prepared lemonade (from frozen concentrate)	8 fl. oz	8.7
Prepared punch (from frozen concentrate)	8 fl. oz	5.4
Canned thirst-quencher drink	8 fl oz	5.1
Dairy Products		
Strawberry, lowfat yogurt	8 oz.	5.9
Fast food shake (chocolate, strawberry, or vanilla)	10 fl oz	4.7-5.1
Fruits and Fruit Juices		
Fruit Juice		
Prune juice, bottled	8 fl oz	20.2
Apple juice, canned, sweetened	1 cup (2 serving sizes) ^a	19.1
Pear juice, raw	8 fl. oz	17.8
Apple juice, canned unsweetened	8 fl. oz	13.9
Grape juice (from frozen concentrate)	8 fl. oz	11.0
Orange juice ^b	8 fl. oz	7.4-11.5
Grapefruit juice raw	8 fl. oz	4.4
Raw fruit		
Watermelon	1/16 melon	15.9
Pears	1 pear (2.5 inch diameter)	10.6
Papaya	1 papaya	8.2
Pomegranates	1 pomegranate	7.2
Mangos	1 mango	6.0
Cherries	10 cherries	4.2
Carambola	1 carambola	4.1
Grapes, European	10 grapes	3.8
Kiwifruit, without skin	1 kiwifruit	3.3
Orange	1 orange (2 ⁵ / ₈ inch diameter)	3.3
Canned fruits		
Applesauce, sweetened	1 cup (2 standard serving sizes)	19.1
Fruit cocktail	1 cup (2 standard serving sizes)	17.0
Pineapple	1 cup (2 standard serving sizes)	16.2-18.4
Peaches	1 cup (2 standard serving sizes)	14.6

Table 2 Foods with fructose content >3 g/serving (*Continued*)

Food Category/Food	Portion Size	Fructose content (g)
Pears	1 cup halves (2 standard serving sizes)	9.5–15.0
Dried Fruits		
Raisins	1 cup (4 standard serving sizes)	49.0
Figs	10 figs (3.3 standard serving sizes) ^c	48.6
Peaches	1 cup (4 standard serving sizes)	25.0
Apricots	1 cup (4 standard serving sizes)	15.9
Prunes	5 prunes	7.3
Grains and Cereals		
Ready-to Eat Bran flakes with raisins	3/4 cup (standard serving size)	3.2
Sugars and Sweets (1)		
High fructose corn syrup	2 tbsp	15.7
Honey	1 tbsp	8.9
Frosting, canned, chocolate	1 cup	6.5
Sundae, fast food (strawberry)	1 sundae	5.6
Molasses, Regular	2 tbsp	5.2
Vegetables		
Tomato Puree	1 cup	8.5

Values for fructose content were obtained from an extensive review of scientific literature and from research funded by the Human Nutrition Information Service, USDA as described in USDA (1987). Values were "based primarily on food samples analyzed by high-pressure liquid chromatography or gas chromatography." Only data for beverages produced in the US are included. Only commercial samples are used for baked products because home recipes for these products vary considerably. Categories with all foods containing <3 g fructose/serving (fast food entrees, legumes, meat and poultry products, nuts and seeds, and miscellaneous) are not included; ^aServing sizes per USDA data based on a 2000 kcal diet (USDA, 2004; 2005); ^bincludes raw, canned, unsweetened, or frozen concentrate, reconstituted; ^c(USDA, 2004).

F. Inclusion/Exclusion criteria (are potential confounders adjusted for)? Studies that excluded subjects whose use of drugs could alter responses (including alcohol), as well as a history of eating disorders or dieting were scored higher than others. Those studies that also conducted physical examinations and laboratory tests to screen individuals with medically significant abnormalities from the clinical study were scored highest. Laboratory tests should include the following—electrocardiograph, urinalysis, and various tests on blood (for example complete blood counts, blood urea nitrogen, serum creatinine, tests of liver function, fasting blood sugar, electrolytes, protein, and albumin) and other tests that may be indicated by the nature of the test material (e.g. blood lipid profiles).

II. Conduct

- Randomized? Randomized studies were scored higher than others. Methods of randomization should be described and analyses should be presented that demonstrate effectiveness of the methods (FDA-CFSAN, 1993).
- Blinded? Scoring was as follows—double >single >non-blinded. Studies should be performed blind to avoid selection bias in patient and physician responses.

C. Crossover and/or Proper Control? Crossover studies which included a proper control group such as sucrose or glucose were scored highest, followed by crossover studies without a control.

D. Appropriate baseline parameters measured? Studies measuring glucose, insulin, blood lipids, and BW parameters at time zero were scored higher than those that did not measure all parameters.

E. Proper risk factor measured? Studies measuring body weight or several biochemical parameters associated with development of obesity or effect on body weight, food intake, or satiety were scored higher than those only examining one biochemical parameter.

F. Proper statistical analysis? Studies utilizing analysis of variance or a computer-based statistical program to analyze results were scored higher than those using multiple tests on repeated measured data.

III. Dosing

- Dose appropriate (also volume appropriate if a liquid)? Studies employing a dose over the 95th percentile limit were rejected; also, studies employing the use of large volumes of fructose in solution were graded lower than others, based on the findings of Sievenpiper et al. (1998a,

- 1998b) that the glycemic response to fructose in solution is highly dependent on volume.
- B. Given in bolus or throughout the day? Studies administering divided doses were scored higher than bolus dose studies conducted first thing in the morning.
 - C. Dosing for more than one day? Studies that were performed over multiple days were scored higher than those performed over a single day.
 - D. Different doses tested? Studies with more than one dose were scored higher than studies with a single dose.
 - E. Dose administered as liquid only, liquid with meal, or in solid food? Studies which used fructose incorporated into normal (solid food) diet were scored the highest. Studies giving fructose in liquid form with a meal were scored higher than those administering fructose in liquid only.
 - F. Diet and beverage (other than water) intake controlled (all diets prepared)? Studies with prepared diets were scored higher than those with ad lib diets.
 - G. Diets in studies provide similar amounts of energy? Studies with caloric intake adjusted for energy requirement of individuals (isoenergetic) were scored highest. Studies with equal energy intake in fructose and control diets (isocaloric) were scored higher than those with unequal energy intake.
 - H. Verification of compliance (intake) conducted in-house and if not, was compliance measured? Studies in which compliance was verified or intake was in-house were scored higher than outpatient studies with no evidence of compliance.
 - I. Reason for attrition explained? Studies were scored on attrition following: no attrition > explained attrition > unexplained attrition.
- B. Clinically shown to be disease free? Studies that used subjects clinically shown to be free of diseases that could influence outcome such as heart, liver, or kidney disease, hypertriglyceridemia, or diabetes were scored higher than those that did not exclude such subjects.
 - C. Normal weight or BMI? Studies that used subjects of normal weight were scored higher than those using overweight subjects in order to uncover a possible cause and effect relationship between fructose intake and BW.
 - D. Inclusion/Exclusion criteria (are potential confounders adjusted for)? Studies that excluded subjects with potential confounders such as a history of use of drugs that could alter responses (including alcohol), as well as eating disorders, or smoking, were scored higher than others.

II. Conduct

- A. Study Type (case report, cross sectional or cohort)? Scoring: cohort > cross sectional > case report.
- B. Proper risk factor measured? Studies that measured food intake or satiety were scored higher than studies that only measured a biochemical parameter strongly associated with the development of obesity or BW.
- C. Proper statistical analysis? Studies that used multifactorial analysis and analyzed data according to quintiles of fructose intake were scored higher than those which just used regression.

III. Intake

- A. Evidence of (intake) (e.g. fructose, glucose concentration in serum or urine)? Studies with biological evidence of intake were scored higher than those with none.
- B. Was the content of the material in the food supply accurately determined? Studies using up-to-date, published nutrient database data scored higher than those that used older or internally developed databases that were not based on published data.
- C. Use of proper dietary assessment methods (24 hour dietary recall or food frequency questionnaire)? Studies utilizing assessment methods were scored higher than those without.

Observational Study

The maximum number of points that could be obtained from an observational study was 20. The ability of each study to meet the individual factors identified below as being important criteria was graded on a 2 – point scale (minimum = 0; maximum = 2). The factors are based on the new FDA criteria for an evidence-based review of human study data, as well as an understanding of the factors which may confound the results of studies examining the effect of fructose ingestion on the parameters measured in the study. Based on the total point score, each observational study was given a low (<10) or moderate (10–20) quality grade.

I. Subjects

- A. Sufficient number? Studies in which the number of subjects used was calculated to be sufficient for uncovering a statistically significant effect were scored higher than others.

STUDY RESULTS AND DATA REVIEW

Intervention Studies

The design and results of intervention studies that were graded are shown in Supplemental Tables 2–5. The studies were organized according to study duration, the amount of fructose administered in each meal, and the primary endpoints that were measured (e.g. TG, glucose regulation, body weight, or food intake) in order to determine if there was a causal relationship between fructose ingestion and biologically relevant changes in the primary endpoints.

Longer Term Intervention Studies: Effect of Fructose on Triglycerides and Body Weight

The design and results of longer term studies are shown in Supplemental Table 2. In general, longer term (>1 day) studies in which fructose was ingested with a meal were judged to be of higher quality than those in which fructose was ingested as a bolus, liquid dose. The majority of the long-term studies received moderate quality scores (20–29 points), with four receiving high quality scores (≥ 30 points) and only one receiving a low score (<20 points). The longer-term studies tended to be better controlled, screened, and reported and utilized more appropriate statistical methods and consumption patterns than shorter-term studies. Concentrations of fructose ingested in the long term studies ranged from 136 g/day for seven days to 50 g/day for 13 weeks.

In a high quality seven day, randomized, crossover study (score = 33) conducted by Snehag et al. (2002), twelve healthy, nonobese adolescents (six males, six females) were maintained at home on prepared, isocaloric diets containing 60% carbohydrate, 25% fat, and 15% protein, with 10% or 40% of the carbohydrate (6 or 24% of dietary energy) content provided by fructose (low fructose or high fructose diet, respectively). The amount of food provided to each participant was based on the energy intake of each participant the week prior to the test. The total amounts of fructose ingested in the low and high fructose diets were estimated to be 36 and 133 g/day in females and 40 and 136 g/day in males. A different group of twelve subjects also was exposed to a high carbohydrate/low fat diet or a low carbohydrate, high fat diet, with 20% of carbohydrate as fructose (approximately 55 g/day fructose). Therefore, the ability of fructose to affect biochemical parameters (e.g. TG, glucose, insulin, the insulin by product C-peptide, or free fatty acid) in a dose-dependent manner could be assessed. In this study, the increase in dietary fructose had no effect on any of the parameters that were measured, indicating that fructose has no effect on lipid or carbohydrate metabolism when the caloric intake of individuals is not increased.

In a moderate quality, randomized, crossover study (score = 26), the effect of ingestion of an energy balanced (control) diet or a diet with a 50% excess energy (approximately 914 kcal/day) provided as fat (approximately 57.1 g/day), or glucose, fructose, or sucrose (approximately 123 g/day) for four days on energy balance was assessed in eight normal weight and five obese women (McDevitt et al., 2000). The study was conducted in-house, in a whole body calorimeter. There were no significant differences between normal weight and obese women in macronutrient oxidation or balances, so data were pooled. Overconsumption of glucose, fructose, or sucrose induced glycogen storage on Day 1 (approximately 100 g), but thereafter stimulated carbohydrate oxidation so that balance was achieved on Days 3 and 4. Fat oxidation was proportionally suppressed by sugar ingestion. There were also no significant differences between the various sugars in carbohydrate oxidation, carbohydrate balance, energy balance, fat oxidation, or fat balance. On

average, 12% of the excess energy was stored as glycogen and 88% as fat for all dietary conditions (including overconsumption of fat). This study shows that ingestion of a high fructose diet did not disproportionately stimulate fat storage compared to glucose or sucrose and that the net effect of overconsumption of sugar on fat balance (regardless of type) is similar to an excess of dietary fat.

In a five day, crossover study that was considered to be low quality for purposes of the assessment (score = 14), 17 young adults (ten males and seven females) were administered a liquid formula diet (45% carbohydrate, 45% fat, and 10% protein). The intake of the formula diet was adjusted according to the normal intake of energy prior to the experiment (2100–3350 kcal), in order to keep body weight constant (Macdonald, 1972). The fats used were sunflower seed oil or cream, and the carbohydrates were either: glucose plus fructose, glucose plus starch, or fructose plus starch. The fructose content provided 18% of the energy requirement for each individual, and varied from 95–151 g/day per person. In this study, in either sex, TG decreased with ingestion of sunflower oil and tended to increase with ingestion of cream (regardless of the type of carbohydrate co-administered). In males consuming sunflower seed oil, the TG concentration on Day 4 was reduced (by approximately 10% or 24%) when fructose plus starch or glucose plus starch were in the diet (respectively). In males consuming cream, the TG concentration on Day 4 was increased by 13% when the subjects ingested starch plus fructose and 22% when the subjects ingested glucose plus starch. In females, the response of TG to either fat was not altered by addition of fructose or glucose. The results showed that the effect of fructose or glucose on TG is dependent on type of fat administered and gender.

The effect of two dietary protocols with different amounts of carbohydrate and fat on energy balance was assessed in a high quality study (score = 31) involving twelve normal adolescents (six males and six females) (Treuth et al., 2003). In the first protocol, a low fat (25% energy)/high carbohydrate (60%) diet or a high fat (55% energy)/low carbohydrate (30% energy) was ingested in a crossover fashion. Fructose was present at 21% of the carbohydrate in the low fat diet and 20% of the carbohydrate in the high fat diet. The average amount of fructose ingested in the first study was 88 g (low fat/high carbohydrate diet) or 43 g (high fat/low carbohydrate diet) in males and 69 g (low fat/high carbohydrate diet) or 36 g (high fat/low carbohydrate diet) in females. In the second protocol, a different group of subjects received a low fat/high carbohydrate diet containing 11% or 40% of the carbohydrate from fructose in a crossover manner. The amount of fructose ingested in the 40% diet was higher than the cutoff limit; therefore the 40% results were not included in this review. An analysis of data from the two protocols showed that increasing fructose consumption from approximately 40 g/day to 80 g/day had no effect on TG or insulin in males or females.

The effect of ingestion of 1.5 g fructose/kg body weight (approximately 103.5 g/day fructose) for four weeks on blood lipids was assessed in seven healthy males, with an average age

of 24.7 years (Lê et al., 2006). In this moderate quality study (score = 25), fructose was consumed as a 20% solution with the three main meals, which provided 18% excess energy intake over that of the baseline, low sucrose, low fructose (<20 g/day) diet consumed for two weeks prior to the study (55% carbohydrate, 30% fat, and 15% protein). With respect to the baseline diet, ingestion of fructose caused significant increases in fasting TG, very low density lipoprotein triglyceride (VLDL-TG), lactate, glucose, and leptin (a hormone involved in satiety) without causing any changes in body weight, body fat, insulin sensitivity, energy expenditure, or liver or muscle lipid content. In this study, fructose consumption did not cause deposition of lipid in muscle or liver. However, in muscle biopsies taken from five of the participants, there were changes in expression of three enzymes involved in insulin resistance (steroyl-CoA desaturase-1, glucose transporter-4, and acetyl-CoA carboxylase-2) (Lê et al., 2008). Because there was no equicaloric carbohydrate control in either of these studies, it is unknown if the changes attributed to ingestion of fructose were due to increased intake of calories or fructose. However, it should be noted that although an increase in TG was noted after consumption of fructose and consumption of fructose provided an approximately 400 additional calories per day, there was no effect on body weight or body fat.

Hallfrisch et al. conducted a crossover study in groups of twelve men with abnormally high insulin responses to a sucrose load (hyperinsulinemics) and twelve normal men. The results of lipid and glucose analyses are reported in two separate publications (Hallfrisch et al., 1983a, 1983b), which received scores of high (score = 30) and moderate quality (score = 29), respectively. Each group of subjects was fed diets (15% protein, 42% fat, 43% carbohydrate) containing 0%, 7.5%, or 15% of daily energy intake (38 kcal/kg bw) as fructose for five weeks each. Based on a 2700 calorie diet, the amount of fructose consumed was 0 g, 50 g or 100 g/day. Weekly fasting plasma, TG, high density lipoprotein cholesterol (HDL-C), free fatty acid, insulin, glucose, or glucagon in normal individuals were not altered by consumption of fructose. However, after consumption of 50 g or 100 g fructose, fasting blood glucose and gastric inhibitory peptide (GIP), a hormone which stimulates the release of insulin in response to glucose, were higher in the combined population (including hyperinsulinemics), although TG was higher only in hyperinsulinemics. Consumption of 100 g fructose also caused a higher insulin response to sucrose challenge in both normal individuals and hyperinsulinemics and a higher glucose response to sucrose challenge in the combined population. In this study, GIP and glucose response data in normal individuals ingesting fructose were not analyzed separately from hyperinsulinemic subjects. Therefore, one cannot conclude that fructose alters any parameter that was measured in this study in normal individuals except for short-term insulin response to a sucrose challenge.

The effect of ingestion of a prepared diet (15% protein, 55% carbohydrate, and 30% fat) containing 20% or <3% of dietary energy as crystalline fructose for 28 days on fasting serum lipids, glucose or lactate (measured on Days 1, 7, 14, 21, and 28) of

fourteen healthy, adult subjects (seven per sex) was assessed by Swanson et al. (1992) in a moderate quality, crossover study (score = 28). The average amounts (and ranges) of fructose ingested in the respective diets were 88 g/day (67–134 g/day) and 5 g/day (3.8–7.6 g/day). The carbohydrate in the low fructose diet was predominantly starch. Over the course of the study, fasting cholesterol, low density lipoprotein cholesterol (LDL-C), and HDL-C decreased in the low fructose group and remained similar to baseline in the high fructose group. There was no effect of either diet on the ratio of serum HDL-C to LDL-C. On the first day of the study, peak plasma TG were greater in subjects ingesting the high fructose diet (152 ± 18 mg/dL) than the low fructose diet (117 ± 12 mg/dL) and plasma glucose was lower in the high fructose diet (110 ± 7 mg/dL) than the low fructose diet (119 ± 7 mg/dL). However, there was no difference in either TG or glucose between groups for the remainder of the study. Serum lactate was also elevated on Day 1 in the high fructose group. Although lactate decreased in the high fructose group over the remainder of the study, it remained elevated (with respect to the low fructose group) at the end of the study. The results of this study indicate that alterations in lipid and glucose metabolism caused by ingestion of fructose are transient and suggest that short-term studies which show an effect of fructose on lipid metabolism are not predictive of responses that occur after longer term ingestion of fructose.

Bantle et al. (2000) conducted a similar, high quality crossover study (score = 32) in 24 healthy subjects (12 per sex) ingesting prepared, *isoenergetic* diets (55% carbohydrate, 15% protein and 30% fat) over a course of 42 days. Diets were nearly identical in nutrient composition, with the exception that 17% energy (341 kcal) came from crystalline fructose in one diet and 14% crystalline glucose (280 kcal) plus 3% crystalline fructose (60 kcal) in another diet. The amount of fructose in 2000 kcal diets was approximately 80 g (high fructose diet) and 10 g (low fructose diet). The quantity of each diet that was provided to each subject was not mentioned; therefore the range of fructose intakes could not be calculated. On the last day of the study, plasma glucose and insulin were lower in subjects consuming the high fructose than the low fructose diet in the morning, but not in the afternoon or evening. Throughout the study, fasting or postprandial plasma TG of women was not affected by consumption of either diet. Men ingesting the high fructose diet had significantly greater fasting and postprandial TG concentrations than men ingesting the low fructose diet throughout the study. However, over the course of the study, fasting plasma TG decreased in both groups (with respect to baseline). The fructose diet had no significant effect on fasting plasma cholesterol, HDL-C or LDL-C in either men or women (values for these parameters decreased over the course of the study regardless of diet). At the end of the study, the body weights of the subjects ingesting the high fructose or low fructose diets were not significantly different from each other. Over the course of the study, both groups lost approximately 1.3 kg, indicating that if caloric intake is controlled, the consumption of a high fructose diet can actually result in weight loss. Furthermore, the authors suggest

that the consumption of a high fructose diet does not increase triglyceride levels with respect to baseline, if caloric intake is controlled. In a 24-hour metabolic profile on the last day, with either diet, insulin peaked in the morning, TG in the afternoon (at around 2 pm), and glucose at night, suggesting that short-term studies that are generally conducted in the morning hours are not of adequate duration to assess the effect that consumption of fructose throughout the day has on TG, insulin and glucose cycles which occur throughout the day, regardless of diet.

The effect of ingestion of a high fructose diet for four weeks on several different indices of metabolism in nine normal (3 male and 6 female) subjects was compared to responses in nine glucose-intolerant individuals (Koh et al., 1988). In this moderate quality study (score = 25), either fructose or glucose was incorporated (at 15% of energy) into an isocaloric, prepared diet (15–20% protein, 30–35% fat, 50–55% carbohydrate) based on each subject's typical consumption of 1200–2200 kcal/day (with the exception of one subject ingesting 3000 kcal/day). The amount of each sugar ingested varied from 45–122 g/day in either diet, which was administered in a crossover fashion. In this study, fasting insulin concentration was higher in subjects ingesting the high glucose than the high fructose diet. There was no difference in fasting TG, total cholesterol, VLDL-C, LDL-C and HDL-C, glucose, lactate, pyruvate, or urate in subjects receiving either diet. There was no effect of diet on body weight, arm circumference, and triceps and subscapular skinfold difference (compared to baseline). The results suggested that lower insulin concentrations in subjects ingesting high fructose diets do not lead to increases in serum TG or body weight when usual caloric intake is not increased.

Bossetti et al. (1984) investigated the effect of ingestion of a high fructose or sucrose diet for 7 or 14 days on lipoprotein, glucose and insulin levels in eight normal (4 female, 4 male) subjects. In this moderate quality study (score = 27), meals were prepared and each sugar was incorporated into the drinks consumed with prepared meals (12–20% protein, 35–35% fat and 35–49% carbohydrate). Diets were isocaloric and based on each subject's typical energy consumption (1500–2900 kcal/day). The amounts of fructose and sucrose in each diet (average and range) were 78.5 g/day and 50–107 g/day, respectively. After 7 or 14 days of consuming either of the two sugars in a crossover manner, there was no effect on fasting TG, total cholesterol, LDL-C, HDL-C, the LDL-C/HDL-C ratio, mean glucose, mean insulin, or the insulin/glucose ratio.

In a two year, moderate quality study (score = 24) designed to assess the effect of fructose, sucrose, or xylitol ingestion on tooth caries, 116 subjects were maintained on a diet containing fructose (2.1 kg/month, $n = 35$), sucrose (2.2 kg/month, $n = 33$), or xylitol (1.5 kg/month; $n = 48$) as the only sweetening agent (Huttunen, 1976; Huttunen et al., 1976). The subjects were allowed to consume the diet without restrictions, but were instructed to avoid consumption of sweet fruits and other sweets. Because compliance was not strictly monitored, the amount of each sugar actually ingested could have varied substantially. However, on a daily basis, it is estimated that the participants

ingested 70 g/day fructose or sucrose or 50 g/day xylitol. In this study, TG, glucose, urate, lactate, or pyruvate concentrations and BW did not differ between groups. This study is limited by the fact that the first lipid measurements were obtained five months after the start of the study (an acute effect could have been missed) and there was no isocaloric group ingesting no sweeteners (or a non caloric sweetener). Also, it is assumed that the only sugar-containing foods that were ingested were the ones that were supplied. Additional fructose, sucrose, and or xylitol in products which are readily available such as ready-made products could have been consumed. Therefore, this study is not considered to be as reliable as some of the other, better controlled studies that were performed with fructose.

Crapo and Kolterman (1984) performed a moderate quality crossover study (score = 22) in eleven subjects (seven women, four men) in which crystalline fructose was substituted for dietary sucrose (baseline) for a period of 14 days. Meals were prepared by the investigators and provided to subjects based on their typical consumption of energy (1830–3000 kcal/day). The diets contained approximately 55% carbohydrate (of which sucrose or fructose was 24%), 30% fat, and 15% protein. The approximate amount of sucrose or fructose administered was 63–99 g/day. Fasting TG, lactate, pyruvate, and uric acid were not affected by changing the sugar from sucrose to fructose. Furthermore, no change in fasting TG concentration occurred after ingestion of fructose in two subjects that had somewhat elevated plasma TG concentrations at baseline (193 mg/dl and 207 mg/dl, respectively). Fasting total cholesterol and HDL cholesterol were lower than baseline (sucrose diet) after ingestion of fructose. Furthermore, in response to a 50 g glucose challenge, the glucose and insulin responses from 30–60 minutes were lower after the consumption of fructose than sucrose. These data indicate the short-term changes in glucose or insulin concentration caused by substitution of fructose for sucrose do not have any bearing on fasting TG concentrations.

In a 13-week, single-blind, randomized study designed to assess the clinical safety of sucralose (a chlorinated sucrose derivative with no caloric value) in humans (which was considered to be of moderate quality (score = 28) for an assessment of the effect of fructose on health), 31 (17 male, 14 female) control subjects received 50 g/day fructose (25 g/day at 10 am and 4 pm in liquid) in addition to their normal diet. Compliance was assessed by an independent witness. Subjects included in the study had no history of drug or alcohol use, no sensitivity to sugar and normal physical exams, electrocardiograms (ECGs), and serum biochemistries and urinalyses (McLean Baird et al., 2000). According to the published manuscript, there were no changes in biochemical analyses (including TG, urea and uric acid), BW, physical exams or urinalysis after 13 weeks of consumption of fructose (compared to baseline values). However, data supporting these conclusions were not available in the published manuscript. Data for TG and BW were obtained from the sponsor of the study. As shown, in Table 3 and Fig. 2, there was no effect of ingestion of fructose on TG (compared to the baseline diet). Furthermore, although caloric intake increased

by 200 kcal/day with ingestion of fructose, body weights of either males (73.1 ± 2.3 kg at baseline and 74.4 ± 2.3 kg at end of study) or females (64.4 ± 1.9 kg at baseline and 65.6 ± 1.7 kg at end of study) ingesting fructose did not increase significantly ($p < 0.05$).

The results of the long-term studies in which concentrations of TG were measured are summarized in Table 3 and Fig. 2. As shown, the only long-term study that suggests ingestion of fructose is associated with metabolic abnormalities leading to increased concentrations of plasma TG was a study by Lê et al. (2006), in which approximately 105 g/day fructose was ingested by men in addition to an isoenergetic diet. As noted in Table 3 and Fig. 2, the initial TG concentration of the men who participated in the study was considerably lower than the participants of other studies. Therefore, the low sucrose, low fructose baseline diet that the participants consumed for two weeks prior to the study was not considered to be normal. The other long-term studies show that when fructose is substituted isocalorically with sucrose or glucose in a normal diet, there is no effect on fasting plasma TG levels. Furthermore, none of the studies in which body weight was measured showed an adverse effect of fructose consumption on body weight.

Also noted in Table 3 and Fig. 2, the initial TG values of the subjects used in long-term studies varied widely (from approximately 57 mg/dl to 149.5 mg/dl). Although subjects with higher baseline values tended to have higher fasting concentrations of TG after administration of fructose than those with lower values, there was no evidence to suggest that the long-term response of TG to fructose ingestion was augmented in subjects with high baseline TG values.

Fasting TG values for all studies in which a time course was available (except the Huttunen et al. (1976) study) are shown in Fig. 2. The corresponding studies for each of the doses administered in the figure are as follows: 50 g/day: McLean Baird et al. (2000); 85 g/day: Bantle et al. (2000); 88 g/day: Swanson et al. (1992); 103.5 g/day: Lê et al. (2006). Values for the Huttunen et al. (1976) study are not included in the figure because the first values were measured after five months.

Shorter Term Studies: Effect of Fructose on Triglycerides

Twelve short-term studies which met the inclusion criteria investigated the role of fructose administration on TG. The design and results of these studies are summarized in Supplemental Table 3. Five were performed with fructose administered as a bolus dose in water (Macdonald et al., 1978; Bohannon et al., 1980; Moore et al., 2000; Nuttal et al., 2000; Parks et al., 2008) and seven were performed with fructose administered in a matrix including fat (Cohen and Schall, 1988; Otto et al., 1993; Jeppesen et al., 1995a; Jeppesen et al., 1995b; Abrahama et al., 1998; Singleton et al., 1999; Chong et al., 2007). Six of the studies received low quality scores (<20 points) and six received moderate quality scores (20–29 points). None received a high quality score (≥ 30 points). Moderate quality studies were

generally better screened and controlled, used more subjects (of both sexes), and measured more parameters than low quality studies. The amounts of fructose administered in these studies varied from 100 g/day to 3.5 g/day.

Fructose Administered as a Bolus Dose in Water

In a low quality crossover study (score = 18) conducted on five men and four women, which included some subjects that were obese or had a family history of diabetes, subjects were administered 100 g fructose, glucose, or sucrose in 250 ml water after an overnight fast (Bohannon et al., 1980). Plasma and/or serum concentrations of TG, glucose, insulin, glucagon, and growth hormone were measured up to 300 minutes after dosing. Until approximately 240 minutes after dosing, the plasma concentration of glucose and serum concentration of insulin were lower and the plasma glucagon concentration was higher after fructose compared to glucose. From approximately 180 minutes after fructose consumption until the end of the study, plasma growth hormone concentrations were decreased (compared to glucose and baseline). Over the course of the study, TG increased slightly in all groups. By the end of the study, TG increased (with respect to baseline) by 5 g/dl, 14 g/dl, and 24 g/dl in the glucose, sucrose, and fructose groups (respectively). It is not known if the TG responses are significantly different from each other because statistical analyses to uncover such differences were not performed.

In a moderate quality crossover study (score = 27) involving four males and two females, the effect of consumption of a bolus dose of sugar solutions containing different ratios of glucose and fructose (100:0, 50:50, or 25:75) on several different biomarkers was assessed four hours prior to and after consumption of a standardized lunch (providing 37% of the subject's daily energy needs) (Parks et al., 2008). The sugar solutions contained approximately 85 g glucose plus 0 g fructose (100:0), 43 g glucose plus 43 g fructose (50:50), or 21 g glucose plus 64 g fructose (25:75). Compared to the solution containing 100:0 glucose:fructose, there was no effect of mixtures containing either 25:75 or 50:50 glucose:fructose on leptin, adiponectin, GIP, or non-esterified fatty acids (NEFA) (although fasted serum concentrations of insulin and glucose were lower after consumption of mixtures containing glucose and fructose compared to 100% glucose). During the four hour period after consumption of the sugar solutions, there was a slight decrease in TG (compared to baseline) in subjects consuming solutions containing 100:0 (-0.42 ± 0.27 nmol/l.hr) or 25:75 glucose:fructose (-0.15 ± 0.36 nmol/l.hr), and a slight increase in TG in subjects ingesting the solution containing 50:50 glucose:fructose (0.19 ± 0.23 nmol/l.hr; $p < 0.05$ compared to 100:0 glucose:fructose). Over the six hour period following lunch and the entire course of the experiment, serum TG rose for all groups (including those that ingested 100:0 glucose:fructose prior to lunch). Postprandial serum TG concentrations in subjects ingesting 50:50 glucose (3.68 ± 1.08 nmol/l.hr) or 25:75 glucose:fructose (4.11 ± 1.21 nmol/l.hr) were significantly higher ($p < 0.05$) than

Table 3 Triglyceride levels in long term studies (fasting unless otherwise noted)

Evaluation System Score (Quality)	Subjects/Duration	Fast (Y/N)?	Intake	Triglyceride (TG) Levels (mg/dl)					Reference
				BL	Peak	EOS	EOS-BL	% Change	
25 (Moderate)	7 M/4 weeks	Y	103.5 g/day fru	57	83.7	83.7	26.7	47	Lê et al. (2006)
22 (Moderate)	4 M, 7 F/2 weeks	Y	63–99 g/day fru	94	ND	84	–10	–10.6	Crapo and Kolterman (1984)
24 (Moderate)	M, F/2 yrs	Y	70 g/day fru	130	127	111.2	–18.8	–14.5	Huttunen et al. (1976)
		Y	70 g/day suc	133	132	111.2	–21.8	–16	
		Y	50 g/day xylitol	135	132	111.6	–18.4	–14	
25 (Moderate)	3 M, 6 F/4 weeks	Y	45–122 g/day fru	ND	ND	74	ND	ND	Koh et al. (1988)
		Y	45–122 g/day glu	ND	ND	72	ND	ND	
27 (Moderate)	4 M, 4 F/2 weeks	Y	78.5 g/day fru (avg)	71	ND	50	–21	–30	Bosetti et al. (1984)
		Y	78.5 g/day glu (avg)	53	ND	56	3	–6	
33 (High)	6 M, 6 F/1 week	Y	36–40 g/day fru	ND	ND	87	ND	ND	Sunehag et al. (2002)
		Y	55 g/day fru	ND	ND	91	ND	ND	
		Y	133–136 g/day fru	ND	ND	102	ND	ND	
32 (High)	12 M, 12 F/6 weeks	Y	85 g/day fru (M)	117.9	119.3	111.2	–6.7	–5.6	Bantle et al. (2000)
		Y	15 g/day fru + 70 g/day glu (M)	117.9	117.9	84.6	–33.3	–28.2	
		Y	85 g/day fru (F)	103.7	103.7	82.8	–20.9	–20.1	
		Y	15 g/day fru + 70 g/day glu (F)	103.7	103.7	86.3	–17.4	–16.8	
		N ^a	85 g/day fru (M)	111.2	240	111.3	0.1	0.1	
		N ^a	15 g/day fru + 70 g/day glu (M)	80.1	160	80.1	0	0	
		N ^a	85 g/day fru (F)	80	146.8	82.3	2.3	3	
		N ^a	15 g/day fru + 70 g/day glu (F)	89	115.7	86.3	–2.7	–3	
31 (High)	6 M, 6 F/2 days	Y	44 g/day fru (M, low fat)	ND	ND	80.1	ND	ND	Trueth et al. (2003)
		Y	88 g/day fru (M, low fat)	ND	ND	100	ND	ND	
		Y	43 g/day fru (M, high fat)	ND	ND	77	ND	ND	
		Y	40 g/day fru (F, low fat)	ND	ND	94.3	ND	ND	
		Y	66 g/day fru (F, low fat)	ND	ND	82	ND	ND	
		Y	36 g/day fru (F, high fat)	ND	ND	75	ND	ND	
30 (High)	12 M/5 weeks	Y	100 g/day fru	93	ND	92.1	–0.9	–1	Hallfrisch et al. (1983a)
		Y	50 g/day fru + 50 g/day starch	93	ND	94.7	1.7	2	
		Y	100 g/day starch	93	ND	85.7	–7.3	–8	
28 (Moderate)	17 M, 14 F/13 weeks	Y	50 g/day fru	135.6	135.6	106.4	–29.2	–22	McLean Baird et al. (2000) ^c
28 (Moderate)	7 M, 7 F/4 weeks	Y	5 g/day fru (avg)	90.8	90.8	81	–9.8	–11	Swanson et al. (1992)
		Y	88 g/day fru (avg)	103.2	103.2	85.4	–17.8	–17	
		N ^b	5 g/day fru (avg)	116.6	116.6	113.9	–2.7	–2	
		N ^b	88 g/day fru (avg)	149.5	149.5	116.6	–32.9	–22	
14 (Low)	10 M, 7 F/5 days	Y	40% fru + 60% CS + oil (M)	ND	ND	ND	ND	–10	Macdonald (1972)
		Y	40% fru + 60% glu + oil (M)	ND	ND	ND	ND	–23	
		Y	40% glu + 60% CS + oil (M)	ND	ND	ND	ND	–24	
		Y	40% fru + 60% CS + double cream (M)	ND	ND	ND	ND	13	
		Y	40% fru + 60% glu + double cream (M)	ND	ND	ND	ND	–5	
		Y	40% glu + 60% CS + double cream (M)	ND	ND	ND	ND	22	
		Y	40% fru + 60% CS + oil (F)	ND	ND	ND	ND	–32	
		Y	40% fru + 60% glu + oil (F)	ND	ND	ND	ND	–18	
		Y	40% glu + 60% CS + oil (F)	ND	ND	ND	ND	–31	
		Y	40% fru + 60% CS + double cream (F)	ND	ND	ND	ND	10	
		Y	40% fru + 60% glu + double cream (F)	ND	ND	ND	ND	1	
		Y	40% glu + 60% CS + double cream (F)	ND	ND	ND	ND	–4	

Avg = average; BL = blood lipids; CS = corn starch; EOS = end of study; F = females; fru = fructose; glu = glucose; M = males; ND = not determined; suc = sucrose; yrs = years. TG reported in mmol/L were multiplied by 89 to achieve TG in mg/dl. TG values are fasting unless indicated otherwise (^avalues over a 24-hour period, which included consumption of meals; ^bvalues after consumption of breakfast); ^cData for TG were not available in the published manuscript and were obtained from the sponsor of the study.

Evaluation system score (quality) for intervention studies as described in section entitled “Study Grading Criteria”: low (<20), moderate (20–29) or high (≥30)

those ingesting 100:0 glucose:fructose (1.23 ± 1.03 nmol/l.hr). The data suggest that ingestion of a bolus, liquid mixture containing 43 g glucose plus 43 g fructose (50:50) or 21 g glucose plus 64 g fructose (25:75) the morning after an evening fast leads

to augmentation of the TG response to a lunch meal (compared to glucose).

In a study that was considered to be of low quality (score = 13), six healthy males were maintained on a fixed carbohydrate

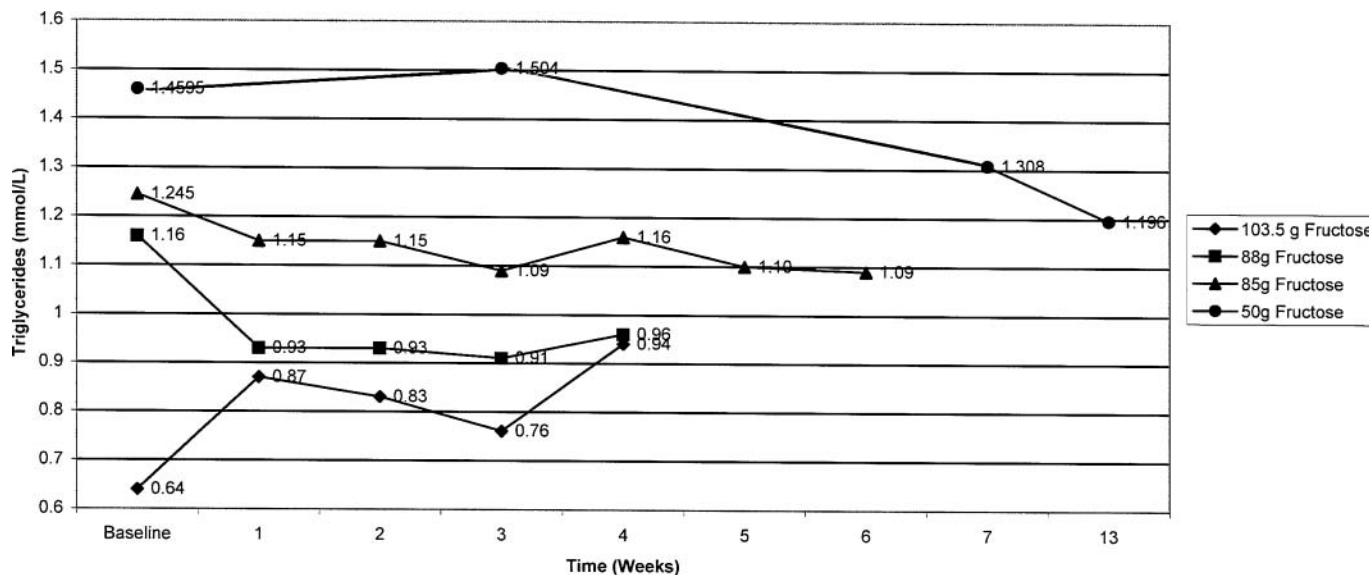


Figure 2 Fasting triglyceride levels in studies that provided time course data.

(200 g) diet for three days prior to the study, and then were administered 50 g fructose in 500 ml water or water alone after an overnight fast (Nuttal et al., 2000). Plasma values of a number of different biochemical parameters associated with lipid or carbohydrate metabolism were assessed over a period of eight hours. Ingestion of fructose caused increases in insulin, C-peptide, glucagon, lactate, and alanine and a decrease in NEFA (compared to the water control) up to approximately four hours after ingestion. There was no significant effect ($p < 0.05$) of fructose ingestion on TG, amino nitrogen, or urea nitrogen. Conclusions that can be drawn from this study are limited because the study design did not include a sugar other than fructose.

The effect of ingestion of a solution containing 75 g glucose with or without 7.5 g fructose on concentrations of blood lipids measured up to two hours later was assessed in a moderate quality study (score = 24) involving eleven subjects (five men, six women) (Moore et al., 2000). There was no effect of fructose on peak plasma glucose or insulin between groups; however, the increase in serum glucose from baseline was less when glucose was ingested with fructose than when glucose was ingested alone. There was no effect of the inclusion of fructose on TG, NEFA or glucagon (compared to ingestion of glucose alone). However, plasma concentrations of TG decreased slightly with respect to baseline when glucose was ingested alone and remained steady with fructose. Blood lactate increased when fructose was added to glucose. The authors concluded that small amounts of fructose improve the glycemic response to an oral glucose load without altering the insulin or TG response.

Nine healthy, nonobese male dental or medical students (age was not provided) were administered 0.25, 0.5, 0.75, or 1.0 g glucose, sucrose, fructose, or sorbitol per kg bw (upper dose was estimated to be 80 g) in water in a study that was ranked low quality (score = 15) (Macdonald et al., 1978). Insulin secretion was lower after fructose consumption than glucose or

sucrose consumption (regardless of dose). Over the course of the 90 minute study, plasma TG decreased (with respect to baseline) after fructose, glucose, or sucrose consumption (regardless of dose). The investigators noted that ingestion of 0.5 or 1.0 g/kg fructose was associated with increased pyruvate, lactate, and uric acid and decreased glycerol. However, the responses were variable and generally not dose dependent to fructose (with the exception of pyruvate). Furthermore, because the responses were only observed for 90 minutes, it is likely that the study was not of sufficient duration to uncover any longer-term effect of fructose on any biochemical parameter that was measured.

Fructose Administered as a Bolus Dose with other Nutrients

In a moderate quality, randomized, crossover, single blind study (score = 22) in eight healthy men and six healthy women that included some subjects that were obese (BMI ranged from 22–31 kg/m²), administration of 0.75 g fructose/kg bw (bw not listed) plus 0.5 g oil/kg bw (approximately 60 grams) was associated with increases in blood TG, VLDL-TG, lactate, CO₂ production, and carbohydrate oxidation, and decreases in insulin, fat oxidation rate, and synthesis of NEFA over a six hour period (compared to responses elicited by 0.75 g glucose/kg bw plus 0.5 g oil/kg bw) (Chong et al., 2007). At 240 min, TG increased by approximately 80.2 g/dl and 57.9 g/dl (compared to baseline) in subjects ingesting fructose plus oil or glucose plus oil, respectively. At 240 min, newly synthesized fatty acids from fructose made up approximately 0.4% of circulating VLDL-TG, whereas newly synthesized TG-glycerol made up 38%. The data suggested to the authors that fructose impaired TG clearance or absorption rather than increasing synthesis. Similar to other studies that were conducted with fructose administered in a liquid that did not contain fat, increases in TG after consumption

of fructose did not occur until approximately three hours after ingestion.

A similar, low quality crossover study (score = 14) was conducted by Abraha et al. (1998), in three male and six female subjects with body mass indices within the normal range. The subjects were administered a scrambled egg breakfast cooked in double cream and butter along with 0.75 g/kg fructose in a drink (approximately 54 g) or 0.75 g/kg starch (approximately 52 g) in toasted bread. Postprandial plasma insulin and glucose concentrations were significantly lower and slightly lower (not significant) with fructose than starch, until approximately three hours after the ingestion of fructose. After approximately 180 minutes of ingesting the meal containing either fructose or starch, similar decreases in plasma NEFA and increases in plasma TG were observed (compared to baseline values). From 240 to 360 min (the end of the study), plasma NEFA were lower and TG were higher in subjects ingesting fructose. The results of this study are consistent with results of some other short-term studies, which show slightly greater increases in TG three to four hours after ingestion of fructose, compared to other carbohydrates.

In a series of two moderate quality studies (scores = 20, 21) in eleven subjects that were slightly overweight (some of which had abnormally high baseline TG values), the TG response to ingestion of various sugars in the presence of fat was assessed (Jeppesen et al., 1995a, 1995b). In the first study, the addition of 50 g fructose to a fat load of 40 g resulted in higher postprandial concentrations of TG in plasma after approximately three hours (which continued to study termination ten hours after dosing). The authors also noted that the higher the fasting TG concentration, the greater the magnitude of the effect of fructose on TG. In the second study, 5 g of fat was administered with or without 50 g of fructose, and the TG response was compared to that of a 40 g or 80 g fat load (without fructose). The TG response with 5 g fat plus 50 g fructose was higher than that of 5 g fat approximately four hours after dosing, and was similar to that of a 40 g bolus dose of fat. Conclusions that can be drawn from these studies are limited because there is no control sugar or carbohydrate, caloric intake differed between groups and some of the subjects were not of normal weight and had hypertriglycerolemia. However, in a similar, moderate quality study (score = 24) conducted in nonobese, normolipidemic medical students (nine males, twelve females) ingesting a 40 g fat bolus with or without 50 g fructose, glucose or sucrose, or 100 g sucrose, consumption of fat with 50 g fructose resulted in significantly greater TG response than fat alone, fat plus 50 g glucose, or fat plus sucrose, and a similar TG response as fat plus 100 g sucrose seven hours after dosing (Cohen and Schall, 1988). A low quality study (score = 16) conducted by Singleton et al. (1999) showed that ingestion of a milkshake containing 108 g cream + 30 g fructose produced a similar increase in TG as a milkshake containing 108 g cream + 17.5 g glucose (until six hours after ingestion of the milkshake). Both of these milkshakes induced a higher TG response than a milkshake containing cream without sugar, and TG values (regardless of whether glucose, fructose or aspartame were added)

correlated with initial TG values. Additional experiments performed by Singleton et al. (1999) showed that sweetness and palatability did not account for the effect of glucose or fructose on TG.

In a low quality crossover study (score = 18) designed to assess the effect of various enteral formulas on postprandial metabolism, eight nonobese males were administered five different formulas (Biosorb Sonde, Biosorb Sonde plus, Fresubin diabetes, Enrich Abbott, or Salvimulsin Diabetes) containing 23–25 g carbohydrates, twice over a four-hour period (Otto et al., 1993). Saccharides contained in the formulas were maltodextrin (Biosorb Sonde, Biosorb Sonde plus and Enrich Abbott), fructose (Fresubin diabetes), and xylitol (Salvimulsin Diabetes). The total amount of fructose, xylitol, and maltodextrin administered in the different formulas was 7 g, 23–25 g, and 5 g (respectively) in two divided doses. All formulas except Biosorb Sonde contained 1.0–1.5 g fiber. There were no significant differences in postprandial blood glucose concentrations between formulas; however, the insulin response was greater after ingestion of the maltodextrin containing formulas than the fructose and xylitol containing formulas. There was no effect of fructose on postprandial TG, total cholesterol, HDL-C or LDL-C, compared to the other formulas, suggesting that ingestion of formulas containing small amounts of fructose (3.5 g) along with other nutrients has no effect on TG compared to other types of sweeteners.

In conclusion, the results of the low and moderate quality short-term studies that have investigated the effect of fructose on lipid and carbohydrate metabolism consistently show that serum lactate is increased approximately three hours after ingestion of approximately 30–100 g/day fructose. They also generally show that postprandial TG are increased by the consumption of approximately 30–100 g/day fructose, glucose, sucrose, or starch, with the TG response to fructose slightly higher than that of other types of carbohydrate three to four hours after meal consumption. Smaller amounts of fructose (approximately 7.5 g) ingested in solutions containing glucose, fat and/or fiber do not affect the TG response. Although the majority of the studies indicate that ingestion of 30–100 g/d fructose in a bolus dose (with or without other nutrients) causes a transient decrease in serum insulin (compared to other carbohydrates), studies performed with lower concentrations show no effect of fructose on insulin. An additional study which investigated the effect of fructose on insulin, GIP, and leptin showed that although serum insulin was decreased after fructose ingestion, there was no effect of fructose on leptin or GIP.

Shorter Term Studies: Effect of Fructose on Food Intake

The design and results of the six short-term studies which investigated the effect of fructose on food intake or satiety are shown in Supplemental Table 4. All of these studies received scores within the moderate quality range (score = 21–26).

In a moderate quality study (score = 22) in eight healthy, normal weight men administered 75 g glucose, 75 g fructose,

or 75 g glucose plus 75 g fructose one hour later (all as a bolus in liquid), plasma glucose, insulin, and glucagon-like peptide (GLP-1) concentrations were greater with glucose or glucose plus fructose than fructose over a two hour period. However, there was no difference in satiety, hunger, or food intake of an ad libitum meal offered two hours after administration of glucose, fructose, or glucose plus fructose. From this study, the authors concluded that the administration of fructose had no effect on food intake and there was a disconnect between the levels of GLP-1 and insulin and satiety (Kong et al., 1999).

The results of a moderate quality (score = 26) study conducted by Rodin (1990) show that ingestion of 50 g fructose in a 500 ml drink 38 minutes prior to a buffet lunch resulted in lower food intake in eight, normal weight subjects (four per sex) than either 50 g glucose or 0.25 g aspartame, although plasma glucose and insulin were lower after consumption of fructose than glucose. The subjects given the fructose preload also consumed less fat, compared to all other groups. In aspartame and water groups there was a negative correlation between intake and plasma glucose and insulin, but there was no such relationship when fructose or glucose were ingested, suggesting that insulin concentration after ingestion of carbohydrates does not regulate food intake. In a similar moderate quality study (score = 21) in groups of five subjects who ingested 50 g glucose, 50 g fructose, or water 2.25 hours prior to being offered an ad libitum meal, male and female subjects who drank the fructose containing solution consumed approximately 400 or 600 fewer calories than males or females (respectively) who drank the glucose containing solution, and approximately 200 fewer calories than subjects who drank water prior to the meal (Spitzer and Rodin, 1987). There was no preference for the type of food eaten (carbohydrate, fat, or protein) between groups (although females appeared to prefer more fat and less carbohydrate after fructose). There were no differences in numbers of subjects feeling sick after ingestion of the different sugar solutions, suggesting that the different results were not due to gastric upset.

In moderate quality study (score = 21) in eight women subjects given a standardized breakfast followed by a 500 ml liquid bolus containing either 50 g fructose or glucose 30 min or 135 min prior to the next meal, there was no difference in food consumption between groups, suggesting that ingestion of fructose after a meal (i.e. in a nonfasted state) also has no effect on food consumption, relative to glucose (Guss et al., 1994).

When 40 g fructose or glucose were incorporated into the breakfast meals of groups of ten subjects, there was no difference in plasma glucose, insulin or intake of food, fat, protein, or carbohydrate ingestion at a lunch offered 2.25 hours later. When 50 g fructose or glucose were given as a 500 ml liquid preload (instead of in breakfast food), serum glucose and insulin were initially lower in the fructose group; however, there was no difference in food intake at lunch between groups. The results of this moderate quality study (score = 24) showed that there is a disconnection between the relationships of insulin to food intake when a large amount of fructose is ingested in a liquid bolus vs. when it is presented in food (Rodin et al., 1988).

Stewart et al. (1997) performed a moderate quality (score = 24) randomized study in which 13 male subjects were administered water or a cereal containing either 30 g fructose or glucose as sweetener, followed by a pizza meal 30 min or 120 min later. At 30 min, blood glucose was highest after consumption of glucose and lowest after consumption of water (control). At 120 min, plasma glucose concentrations were comparable between water and fructose and higher with glucose. Total caloric intake (which included the cereal) after glucose was higher than the control at 120 min, but not 30 min. Compared to the control, there was no effect of fructose on total food intake. The authors concluded that there was no relationship between the glycemic response to glucose or fructose and satiety.

In a moderate quality study (score = 26) in 19 male, non-fasted subjects consuming bolus doses of fructose and glucose (for a total carbohydrate load of 75 g) at various ratios (from 80:20 to 20:80), intake of pizza offered 80 minutes later (as well as intake of total calories) was higher in subjects ingesting more fructose and less glucose (Akhavan and Anderson, 2007). This study was the only one in which food and energy intake were increased after fructose consumption. However, it should be noted that food was offered 80 minutes after sugar administration, when differences in serum insulin and glucose levels between dietary glucose and fructose are apparent. Ghrelin (a peptide hormone produced by the stomach and upper small intestine that stimulates growth hormone secretion and food intake (Havel, 2005)) secretion was measured in both groups. The differences in food consumption were not due to differences in ghrelin secretion between groups, as there was no effect of ingestion of liquids containing different ratios of fructose and glucose on ghrelin.

In conclusion, the majority of the short-term (<1 day) studies that have been performed with a bolus dose of 30–75 g fructose or glucose prior to food consumption indicate that fructose had no effect on food consumption or satiety compared to glucose, although the plasma insulin and glucose responses with fructose consumption are suppressed with respect to glucose.

Shorter Term Studies: Miscellaneous Studies that Examined the Effect of Fructose on Carbohydrate Metabolism without Determining the Effect on TG or Food Intake

The effect of short-term fructose ingestion on carbohydrate metabolism has been measured in numerous studies that do not provide any information about TG, satiety, or food intake. The design and results of these studies are summarized in Supplemental Table 5. The grades of these studies are equally distributed between those associated with low (<20 points) or moderate quality (20–29 points).

Numerous additional short-term studies (from 90 minutes to 8 hours) have shown that plasma glucose and insulin concentrations are lower and lactate are generally higher in subjects ingesting 35–124 g fructose after an overnight fast (compared to sucrose or glucose), regardless of whether the sugars were

administered in liquid (with or without fat) or in solid food (Swan et al., 1966; Kelsay et al., 1974; Manso and Jover, 1979; Akgun and Ertel, 1980; Crapo et al., 1980; Crapo et al., 1982; Tappy et al., 1986; Reiser et al., 1987; Kim et al., 1988; Schwarz et al., 1989; Anderson et al., 1990; Tappy and Jequier, 1993; Fukagawa et al., 1995; Blaak and Saris, 1996; Lee and Wolever, 1998). These studies received scores of 12, 14, 9, 18, 16, 24, 22, 19, 19, 23, 13, 22, 23, and 23, respectively.

In contrast to the aforementioned studies, the moderate quality study (score = 25) by Bantle and Laine (1983) indicates that peak serum concentrations of insulin do not vary in healthy subjects ingesting 42 g fructose, glucose, sucrose, potato starch, or wheat starch, when consumed as part of a normal breakfast. In a moderate quality study (score = 21) comparing the effect of ingestion of 30 g sucrose or fructose in a bolus oral dose or with food, Vessby et al. (1990) noted that although the insulin and glucose responses to 30 g fructose were less than 30 g sucrose when the sugars were administered as a bolus liquid, they were not significantly different from each other when they were administered in a breakfast meal. A plausible explanation for the different responses of insulin to fructose when it ingested as part of a meal is that the response of insulin to fructose is augmented when fructose is consumed with glucose (Anderson et al., 1990) (score = 13). Other low (score = 7) or moderate quality studies (score = 19) conducted by Stansbie and Sheriff (1978) or Reiser et al. (1987), respectively, support this hypothesis.

Several short-term studies in which 75 g fructose or glucose was administered as a bolus dose indicate that energy expenditure and carbohydrate oxidation are increased and lipid oxidation is decreased in response to fructose ingestion (compared to glucose) (Tappy et al., 1986; Schwarz et al., 1989; Kruszynska et al., 1993; Blaak and Saris, 1996). The results of these studies (which received scores of 22, 23, 15, and 23, respectively) suggest that when administered in an isocaloric manner, more carbohydrate and less fat is burned after consumption of fructose than glucose.

In the moderate quality study (score = 23) by Schwarz (1989), fructose concentrations were measured in plasma after administration of a 75 g bolus dose of fructose (or glucose) in liquid to 20 subjects. These investigators noted that plasma glucose increased by 2.5 mmol/l by 120 min after glucose and plasma fructose increased by 0.4 mmol/l after fructose. These data show that under the conditions of bolus dosing after a fast, glucose is absorbed 6-fold better than fructose. Kelsay et al. (1974) also measured fructose concentrations in plasma of five subjects ingesting 75 g fructose with and without a meal, and found the fructose concentration in serum was greater when it is administered alone than when it is administered with breakfast. Under conditions in this low quality study (score = 14), the plasma concentration of glucose after administration of 75 g glucose (with or without a meal) was approximately 10-fold higher than the fructose concentration after administration of 75 g fructose (with or without a meal), suggesting that fructose was not as well absorbed as glucose in this study. The fact that the blunted glucose and insulin responses to fructose could

be due to poor absorption of fructose under the conditions of bolus dosing is not considered as a plausible explanation for the blunted response in any of the studies that were conducted, perhaps due to the fact that fructose concentrations and adverse events were not recorded in the majority of them.

In the moderate quality study (score = 21) performed by Vessby et al. (1990), diarrhea was noted in 1/8 of the subjects ingesting 30 g fructose in a liquid, indicating that a dose of 30 g fructose, when administered in a liquid, has the potential to be malabsorbed.

Reiser et al. (1987) noted that nine subjects ingesting 105 g fructose in drinks complained of gastric discomfort. These investigators hypothesized that the insulin responses could therefore be affected by hormones released in response to stress (such as corticoids or insulin). However, because these hormones were not measured in this lower quality study (score = 19), it is unknown if they were released in response to the fructose load.

In conclusion, the results of the majority of low to moderate quality, short-term studies that have investigated the effect of fructose on glucose, insulin, lactate, energy expenditure, and carbohydrate oxidation have fueled the hypothesis that ingestion of high amounts of dietary fructose induce abnormalities in carbohydrate metabolism that promote lipogenesis. However, the results of these studies may be confounded by fructose malabsorption (particularly studies that have been conducted with bolus, liquid doses). Because metabolic responses to fructose could be affected by hormones (such as corticoids or catecholamines) released in response to stress induced by fructose, the results of the short-term studies that have been conducted with large, bolus doses of fructose may not accurately predict responses that may occur with ingestion of the same amount of fructose distributed over the day (either with or without meals). Therefore, the results of these studies are generally considered to be of little value for an assessment of biologically relevant effects of dietary fructose in normal individuals.

OBSERVATIONAL STUDIES

Four observational studies were located in the search (Wu et al., 2004; Slyper et al., 2005; Aeberli et al., 2007; Bingham et al., 2007) (Supplemental Table 6). As noted previously, these studies are not considered to be as reliable as the intervention studies. Based on a total possible point score of 20, each observational study was given a low (<10) or moderate (10–20) quality grade. Three of the studies were considered to be of moderate quality and one was low.

Two of the observation studies utilized subjects that were of normal weight or overweight/obese (Aeberli et al., 2007; Bingham et al., 2007). In these moderate quality studies (scores = 18 and 16, respectively), no associations between total dietary fructose intake and obesity or body weight were uncovered. However, in a study utilizing 74 Swiss children, Aeberli et al. (2007) showed that overweight children ($n = 43$) had

a higher percentage of fructose intake from sweets and drinks (combined) compared to normal weight children ($40.0 \pm 31.7\%$ vs $23.4 \pm 26.0\%$) and lower percentage from fruit and vegetables ($41.9 \pm 31.4\%$ vs $58.1 \pm 31.4\%$). Intake from sweets or drinks as separate entities was not determined. Multivariate regressions showed that total fructose intake was a significant predictor of LDL particle size, but not other lipid parameters such as HDL-C, LDL-C, total cholesterol or TG. It should be noted that the intake of fructose reported in this was relatively low (approximate average and range of 2 g/day and 0–12 g/day, respectively), compared to the average fructose intake of approximately 50 g/day by similar-aged children reported by Marriott et al. (2009). Although it is possible that fructose intake is lower in Swiss than American children, it is likely that fructose intake was underreported in this study. Furthermore, the effect of decreased fiber and increased protein intake in obese children was not factored into the statistical analyses performed with fructose. Therefore, this study is not considered to be particularly reliable.

The moderate quality study (score = 16) by Bingham et al. (2007) was a fairly large-scale study performed in male and females with a fairly wide age range. In this study, urinary concentrations of various sugars were measured (to confirm reported intakes) and data were analyzed according to quintiles of intake of various sugars. The average fructose intake was 25 g/day in normal weight individuals (BMI $<25 \text{ kg/m}^2$) and 26 g/day in obese individuals (BMI $>30 \text{ kg/m}^2$). Urinary fructose actually was higher in normal weight than obese people, and people with the lowest intake of fructose had the highest odds ratio for being obese. In this study, the odds ratio for obesity was significant for urinary sucrose and urinary sucrose/fructose ratio and urinary glucose was significantly higher in obese compared to normal weight individuals, suggesting that the intake of glucose may be related to the development of obesity.

Wu et al. (2004) performed a moderate quality (score = 15), large scale, cohort study of 1999 healthy women (aged 25–69) from two nurse's health studies (one conducted 1976–1990 and another 1989–1999) in which the relationship of several characteristics to fructose intake was assessed. Women in the highest quintile of energy from fructose (free or including fructose from sucrose) had higher energy and carbohydrate intakes, physical activity, and glycemic load, and lower BMI, cholesterol, fat and protein intakes, alcohol intake, and smoking incidence than those in the lowest quintile of fructose intake. Because this study was confounded by many factors that can affect BMI, one cannot conclude that there was a causal relationship between ingestion of fructose and lower body weight. However, it can be concluded that, in general, women with higher fructose intakes exhibited behaviors that were associated with a healthier lifestyle than those with lower fructose intakes. Wu et al. (2004) noted that C-peptide was positively correlated with fructose intake; however, it negatively correlated with carbohydrate and did not correlate with sucrose. C-peptide positively correlated with punch (which contained fructose) and caffeine-containing beverages (which may contain other sugars), did not correlate

with ingestion of orange or apple juice (which contained fructose) and negatively correlated with raisins (which contained fructose), suggesting that factors other than fructose are associated with elevations in C-peptide.

The study by Slyper et al. (2005) examined the effect of glycemic load on blood lipids of 32 adolescents and young adults of various body weights. Some of the individuals were hyperlipidemic or had a family history of coronary disease. This study achieved a lower grade (score = 9) than the other observational studies due to low sample size and other methodological deficiencies. There was no correlation between dietary intake of fructose or any other dietary constituent measured and TG. There was a significant negative correlation with HDL and glycemic load, index, and total sugar, carbohydrate, or fructose intake (in decreasing order). Glycemic load was the only independent predictor of HDL cholesterol, accounting for 21.1% of its variation. Total sugar, total calories, starch, and sucrose correlated better with glycemic load than fructose. Fat and protein intake also correlated with glycemic load, indicating that subjects who ate more sugar also ate more protein and fat. Because the only statistical analyses that were performed were correlations, the extent to which the interactions of all of the dietary factors influenced the responses of each factor could not be determined. Therefore, this study is considered to be of limited value in assessing the effect of dietary fructose on blood lipids.

In conclusion, the results of one moderate quality (score = 16) observational study indicate that the ingestion of approximately 25 g fructose per day has no effect on body weight of male or female adults. Other, low (score = 9) to moderate quality (score = 15 or 18) observational studies that have investigated the relationship of body weight to fructose intake have not demonstrated that there is a causal relationship (due to possible confounding by other variables not being taken into account by the types of analyses that were performed). Additional observational studies that have shown an association with fructose ingestion with higher C-peptide or lower HDL concentrations are not considered to be of sufficient quality for one to conclude that fructose ingestion was responsible for the effects that were noted. Furthermore, although the two studies in which the relationship of fructose intake to TG concentration was assessed suggest that fructose ingestion has no effect on TG, they were performed with low concentrations of fructose relative to average consumption.

CONCLUSIONS FROM THE OVERALL BODY OF EVIDENCE

The purpose of this study was to use a systematic, evidence-based approach to determine if a causal relationship existed between the ingestion of fructose in a normal, dietary manner and the development of alterations in lipid and/or carbohydrate metabolism and increases in body weight in normal weight,

healthy humans. The existing database was searched for studies investigating the effect of fructose on blood lipids, glucose, insulin, obesity, or body weight of humans. Studies that used diseased or overweight humans or levels of fructose consumption greater than estimated 95th percentile (\pm SE) intake levels in the highest groups of consumers were not included. The remaining studies were graded according to a scale developed by the authors, based on guidance provided by FDA for evaluation of health claims. Although few studies received high quality scores, the database is considered to be sufficient for the assessment.

The results of the majority of the short-term studies (that were generally low or moderate in quality) indicate that ingestion of fructose with or without food is associated with a decrease in serum glucose or insulin compared to other carbohydrates and increased fasting lactate over the course of a few hours. The majority of the short-term studies also show that after approximately three hours of ingestion of 30–100 g/day fructose, sucrose, glucose, or starch (either in a liquid bolus or in a meal), increases in plasma TG are slightly higher with fructose than other types of carbohydrate. However, there is no evidence which suggests that plasma TG are increased after long-term ingestion of up to 133 g/day fructose in women and 136 g/day fructose in men (the highest levels of intake in the graded studies), when it is not consumed in caloric excess. The results of the long-term studies also indicate that the TG response to the ingestion of fructose is not dependent on the initial, fasting TG level. There is also no convincing evidence which indicates that ingestion of up to approximately 100 g/day fructose (the highest level of intake used in studies designed to assess the effect of fructose on blood lipids) instead of glucose or sucrose is associated with an increase in food intake or body weight. Although intakes of fructose in these studies are slightly lower than the 95th percentile intake calculated for the highest groups of consumers (136 g/day in 19–30 year old females and 146 g/day in 19–22 year old males), they support the conclusion that fructose does not cause biologically relevant changes in TG or body weight when consumed at levels approaching 95th percentile estimates of intake.

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Supplemental Table 1 Intervention studies not meeting inclusion criteria^a

Grams Fructose/day	% Total Energy Intake	% CHO Intake	Comments	Reference
300	49.8% (calc avg)	46% (calc avg)	Subjects with CHTG or normal subjects ingested 300 g fru or 300–350 g starch throughout day for 10–38 days. Abdominal pain and diarrhea observed with fru. TG fru > TG starch in 3/5 subjects with CHTG. TG fru = starch in normal subjects. Subjects on fru lost or maintained weight.	Kaufmann et al. (1966)
300	Cannot determine	50% (calc)	Same results and subjects as reported as in Kaufmann et al. (1966)	Kaufmann et al. (1967)
250 (added)	49% (avg) (calc)	50% (calc)	Fru or glu diet (for one week) provided an additional 1000 kcal/day in EI. Decreased cellular insulin binding (reduced affinity) and insulin sensitivity with fru compared to glu. TG not measured.	Beck-Nielsen et al. (1980)
234 (added)	24.7% (calc) ^b	25% (calc)	Fru diet provided an additional 3640 kJ/d (870 kcal/day) in EI compared to control diet. Fru administered in a drink with meals for 7 days. Increased TG with fru compared to lower calorie control diet.	Abdel-Sayed et al. (2008)
216.3 (avg)	25%	40% (calc)	Fru administered at 3 g/kg bw/day (+ 800–1000 kcal/day EI compared to control) in a drink with meals for 6 days. Increased TG with fru compared to lower calorie control diet. No effect of fru on BW.	Faeh et al. (2005)
214 (calc)	26% (calc)	39% (calc)	Fru administered at 3.5 g/kg fat free mass (+35% EI compared to control) in a drink with meals for 7 days to 6 normal males and 16 males with family history of Type II diabetes. Increased TG with fru compared to lower calorie control diet. Responses greater in offspring of diabetics.	Lê et al. (2009)
M: approx. 200; F: 146 (estimated) ^c	25%	40% (calc)	Fru administered in diet at 3.5 g/kg fat-free mass/day (+30% EI compared to control) for 6 days. Increased TG and BW with fru compared to lower calorie control diet. Responses in M > F.	Couchevin et al. (2008)
180 (calc) ^d	36.5% (calc)	40%	Diet consisted of CHO intake of 7.5 kg bw/day (40% fru) + 50 g calcium caseinate + vitamins for 5 days. Increased TG in postmenopausal women and men (but not premenopausal women) compared to baseline diet. No effect of fru on BW.	Macdonald (1966)
168	20%	40% (calc)	Normal diet plus fru or starch consumed for 5 weeks. EI 3260 kcal/day for fru diet and 3220 kcal/day for starch diet Beneficial effect of fru on glucose tolerance (compared to starch). TG and BW not measured.	Reiser et al. (1989b)
167	20%	40% (calc)	Fru or starch added to normal diet of normal or hyperinsulinemic men. EI for both diets was 3240 kcal/day. TG fru > TG starch (especially in hyperinsulinemic men).	Reiser et al. (1989a)
M: 163–176 (169 avg); F: 132–142 (137 avg); M and F calc avg 153 ^e	25%	45% (calc)	Diet containing fru or glu administered over 10 weeks. All subjects were overweight or obese. Fasting TG increased with glu but not fru (compared to baseline) and postprandial TG increased with fru but not glu (compared to baseline). Similar increase in BW between groups.	Stanhope et al. (2009)
Cannot determine	50–55%	64–69%	Three subjects ingested diets containing fru or glu for 7 days. EI not mentioned; however, diets were described to be “hypercaloric”. TG fru = TG glu.	Nestel et al. (1970)
151	27.6%	43.5% (calc)	All subjects had coronary artery disease. Diet containing fru administered for 4 days. EI increased from 1696 to 2186 g/day. TG increased with fru diet compared to baseline diet.	Palumbo et al. (1977)
141 based on basal caloric intake of 1743 kcal/day ^f	25%	45%	Seven slightly overweight M (BMI = 26.1 ± 1.0 kg/m ²) with normal fasting TG ingested beverages containing fru or glu (at 25% EI) with 3 meals over 24 hours. TG fru = TG glu.	Stanhope et al. (2008)
96–150; 135 (calc avg) Avg fru < 136.1 ^g	30%	55%	Female subjects administered glu or fru at 30% EI in beverage with 3 daily meals providing a mean EI of 1804 ± 129 kcal/day. TG fru > TG glu throughout day. No effect of fru (compared to glu) on hunger during the study or ad libitum food intake the day after the study.	Teff et al. (2004)

avg = average; BMI = body mass index; BW = body weight; calc = calculated; CDC = Centers for Disease Control; CHO = carbohydrate; CHTG = carbohydrate induced hyperglyceridemia; EI = energy intake; F = female; fru = fructose; glu = glucose; M = male; SE = standard error.

Calculations were made using the following conversions; 1 g fru = 4 kcal energy, 1 kcal = 4.184 KJ energy; 1 g fru = 16.736 KJ energy.

^aInclusion criteria were fru intake < 136.1 g/day, < 18.8% of energy and < 29.2% of CHO intake (for overall population) and < 146 g/day if study used 19–22 year old males; ^bCalculation based on basal caloric intake of 2653 kcal/d (determined by Mifflin equation and activity factor of 1.5). Mifflin equation: REE = 10 × weight (kg) + 6.25 × height (cm) – 5 age (years) + 5, 176.7 cm height; ^cCalculation based on BW calculated using BMIs (provided) and estimated avg height from CDC Advance Data (Ogden et al., 2004); ^dCalculation based on 60 kg avg male/female BW (BW of subjects was not provided). ^eSome F met one inclusion criterion for fru (<136 g/day); ^fDetermined by Mifflin equation and avg height of 176.5 cm (CDC Advance Data) × activity factor of 1.3 = 2265 kcal; ^gRejected because subjects were calorie restricted and given a larger amount of fru than 95th percentile intake for females. Caloric intake was approximately 200 kcal lower than that calculated for avg caloric intake of 19–30 year old females (2033 g/day) and fru intake > 95th percentile ± SE intake for highest group of F (108.2 g/day) as determined by Marriott et al. (2009).

Supplemental Table 2 Intervention studies with fructose ingestion with a meal with duration > 1 day

Evaluation System Score (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
33 (High)	12/group, (6M, 6F) Age: 13–16 yrs Randomized	F: 36, 55 or 133 g/day fru M: 40, 55 or 136 g/day fru	Prepared, isocaloric diets Protocol 1: 30% CHO, 55% fat and 15% protein or 60% CHO, 25% fat and 15% protein (fru = 20% of CHO in both diets) Protocol 2: 60% CHO, 25% fat and 15% protein, with 10% or 40% of the CHO intake (6 or 24% of dietary energy) content from fru	7 day/diet	Increase in fru intake had no effect on GLU, INS, C-peptide, TG, or free fatty acid	Sunehag et al. (2002)
26 (Moderate)	13/group (all F) 8 normal bw: 5 obese Age: 53.1 yrs (avg) ^a Age: 52.4 yrs (avg) ^b Randomized, in house	123.4 g/day fru 123.4 g/day glu 123.4 g/day suc 57.1 g/day fat Administered in 5 meals/day	Fed control diet or diets with 50% excess energy (approximately 914 kcal/day) as CHO or fat	4 day/diet	Fat or CHO oxidation or balance: fru = glu = suc; Fat balance: no significant difference between treatments (12% and 88% excess energy stored as glycogen and fat, respectively)	McDevitt et al. (2000)
14 (Low)	17/group (10M, 7F) Age: 18–21 yrs BW: 68–93 kg	Fru: 129 g/day (avg); 95–151 g/day (18% energy requirement), CHO equal in all: 40% fru + 60% CS or 40% fru + 60% glu or 40% glu + 60% CS Approx. 103.5 g/day fru (1.5 g fru/kg bw/day)	Liquid formula, isoenergetic 45% CHO, 45% fat, 10% protein; Fat: sunflower seed oil or double cream Fru consumed as a 20% solution with the 3 main meals (18% excess energy)	5 day/diet	TG: the effect of fru is dependent on type of fat administered and sex. In M only, after ingestion of sunflower oil, the TG concentration is higher with fru than glu Significant increases in fasting TG, VLDL-TG, lactate, glu and leptin without any changes in BW, body fat, ins sensitivity, energy expenditure, or liver or muscle lipid; fru did not cause deposition of lipid in muscle or liver	Macdonald (1972)
25 (Moderate)	7 (all M) Age: 24.7 yrs (avg) No crossover	Approx. 103.5 g/day fru (1.5 g fru/kg bw/day)	Fru consumed as a 20% solution with the 3 main meals (18% excess energy)	4 wk	Changes in expression of 3/16 genes associated with ins resistance in skeletal muscle; results of some (but not most) enzymes involved in lipid and CHO metabolism changed in muscle	Lê et al. (2006)
24 (Moderate)	5/7 subjects from previous study No crossover	Approx. 103.5 g/day fru (1.5 g fru/kg bw/day)	Fru consumed as a 20% solution with the 3 main meals (18% excess energy)	4 wk	Changes in expression of 3/16 genes associated with ins resistance in skeletal muscle; results of some (but not most) enzymes involved in lipid and CHO metabolism changed in muscle	Lê et al. (2008)

30 (High)	24/group (all M)- 12 "CHO sensitive men" and 12 men with normal ins responses Age: 39 yrs (avg)	15% ST (0 g/day fru) 7.5% fru/7.5% ST (approx 50 g/day fru) 15% fru (approx 100 g/day fru)	Prepared diet, 38 kcal/kg bw 2/3 meals/day at facility	5 wk/diet	TG: fru = fru/ST = ST (normals) TG: fru = fru/ST > ST (hyperinsulinemics) Total cholesterol and LDL-C: fru = fru/ST > ST (combined) HDL-C or FFA: fru = fru/ST = ST (either group or combined) INS: fru = fru/ST = ST (either group or combined) GLU and GIP: fru > fru/ST > ST (combined) Glucagon: fru = fru/ST = ST (either group or combined)	Hallfrisch, et al. (1983a)
29 (Moderate)	24/group (all M)- 12 "CHO sensitive men" and 12 men with normal ins responses Age: 39 yrs (avg)	15% ST (0 g fru) 7.5% fru/7.5% ST (approx 50 g/day fru) 15% fru (approx 100 g/day fru)	Prepared diet, 38 kcal/kg bw 2/3 meals/day at facility	5 wk/diet	INS: fru = fru/ST = ST (either group or combined) GLU and GIP: fru > fru/ST > ST (combined) Glucagon: fru = fru/ST = ST (either group or combined)	Hallfrisch et al. (1983b)
31 (High)	12/group 6M, 6F Age: 13-16 yrs Randomized	Study 1: M- 88 g/day fru (low fat/high CHO); 43 g/day fru (high fat/low CHO); 36 g/day fru (low fat/high CHO); Study 2: M-44 g/day fru (low fat/high CHO/low fru); F- 40 g/day fru (low fat/high CHO/low fru) ^c	Prepared, isocaloric diet 3 meals and 2 snacks at home	2 day/diet	TG: no effect from fru INS: no effect from fru INS: concentrations were lower with the high fat/low CHO diet than the low fat/high CHO diet (both sexes)	Treuth et al. (2003)
28 (Moderate)	14/group 7M, 7F Age: 19-60 yrs	High fru: 88 g/day fru avg (range 67-134 g/day) Low fru: 5 g/day fru avg (3.8-7.6 g/day)	Prepared, isoenergetic diets of common foods with crystalline fru added to 20% of energy of different calorie diets (1600, 2100, 2600 or 3200 kcal)	To 28 days	GLU: High fru = low fru (other than Day 1) TG: High fru = low fru (other than Day 1) Peak Lactate: High fru > low fru (until day 28) Cholesterol: High fru > low fru No effect on ratio HDL-C/LDL-C	Swanson et al. (1992)
32 (High)	24/group 12M, 12F Randomized	Fru diet: 85 g/day fru, 17 g/day glu, 3 g/day suc, 20 g/day lac Glu diet: 81 g/day glu, 15 g/day fru, 3 g/day suc, 10 g/day lac	Prepared, isoenergetic diets provided by center; crystalline fru added	42 day /diet Dinner at facility	GLU, INS (postprandial): glu > fru at 2 hrs only BW: fru = glu TG: fru > glu (M); both decreased over course of study	Bantle et al. (2000)
25 (Moderate)	9/group 3M, 6F, 9 subjects with impaired glu tolerance (IGTS) Age: 54 +/- 6 yrs	45-122 g/day fru 45-122 g/day glu sugar = 15% of calories adjusted for energy requirements	Prepared meals, sugar incorporated into isocaloric diet based on subject's typical consumption	4 wk/sugar	Cholesterol, LDL-C, HDL-C: fru = glu GLU(fasting): fru = glu in normals, glu > fru in IGTS INS (fasting): glu > fru (both groups) TG, total cholesterol, VLDL-C, LDL-C and HDL-C, lactate, pyruvate, urate: fru = glu in normals	Koh et al. (1988)

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Supplemental Table 2 Intervention studies with fructose ingestion with a meal with duration > 1 day (Continued)

Evaluation System Score (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
27 (Moderate)	8/ group 4M, 4F Age: 20–32 yrs 116 subjects Age: 35 (11M, 24F) fru; 21 (12M, 19F) suc; 49 (14M, 35F) xyl Age: 13–55 yrs BW: 44–105 kg (some ow) No crossover	78.5 g/day (avg) fru (50–107 g/day range) 78.5 g/day (avg) suc (50–107 g/day range)	Prepared meals, sugar incorporated into drink of isocaloric diet	7 or 14 days	Total cholesterol (fasting), total TG, LDL-C, HDL-C, LDL-C/HDL-C, mean GLU, mean INS or INS/GLU: fru = suc BW, TG, glu, urate, lactate or pyruvate: fru = suc = xyl	Bossetti, et al. (1984) Huttunen et al. (1976) Huttunen (1976); Maikinen and Scheinin (1976) ^d
24 (Moderate)	116 subjects Age: 35 (11M, 24F) fru; 21 (12M, 19F) suc; 49 (14M, 35F) xyl Age: 13–55 yrs BW: 44–105 kg (some ow) No crossover	Approx. 70 g/day fru (2.1 kg/month) Approx. 70 g/day suc (2.2 kg/month) Approx. 50 g/day xyl (1.5 kg/month) Sugar intake varied with individual	Ad lib consumption of test sugar. Instructed to avoid consumption of sweet fruits and other sweets	2 yrs		Huttunen et al. (1976) Huttunen (1976); Maikinen and Scheinin (1976) ^d
22 (Moderate)	11/group 4M, 7F	63–99 g/day fru or suc (diet)	Prepared meals, isocaloric based on subject's typical consumption (1830–3000 kcal/day). Fru at 24% of total CHO	14 days	Lactate (fasting), pyruvate, TG, uric acid: fru = suc Total cholesterol (fasting) and HDL-C: suc > fru Lactate and pyruvate: response to fru challenge > glu challenge No changes in biochemical analyses (including TG, urea and uric acid), BW, physical exams or urinalysis in fru group (compared to baseline) according to published manuscript. Only data available were serum TG, urea and uric acid for fru group ^e	Crapo and Kolterman (1984)
28 (Moderate)	Fru group: 31 (17M, 14F) Sucralose group: 77 (47M, 30F) Age: 19–57 yrs Single blind, randomized No crossover	50 g/day fru 125–500 mg/day sucralose	Liquid bolus twice daily, along with normal diet	13 weeks		McLean Baird et al. (2000)

avg = average; bw = body weight; CHO = carbohydrate; CS = comstarch; F = female; FFA = free fatty acid; fru = fructose; glu = glucose; HDL-C = high density lipoprotein cholesterol; ins = insulin; INS = plasma insulin; LDL-C = low density lipoprotein cholesterol; M = male; OW = over weight; ST = starch; suc = sucrose; lac = lactose; TG = triglycerides; VLDL-TG (or VLDL-C) = very low density lipoprotein TG or (cholesterol); yrs = years; xyl = xy/itol.

All subjects fasted overnight and met criteria of normal weight (BMI 18.5 to 24.9 kg/m²) unless indicated otherwise. Studies were conducted in a crossover manner unless stated otherwise. Conversions: Fru: 1 g = 4 kcal; 1 kcal = 4184 KJ; 1 g fru = 16.736 KJ; fat: 1 g = 9 kcal.

^aAverage age of normal bw subjects; ^bAverage age of obese subjects; ^cAdditional groups with high fru intake in protocol 2 were not included because fru intake was greater than cutoff value; ^done study with additional references for methodology. ^eData were not available in the published manuscript and were obtained from the sponsor of the study.

Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥30).

Supplemental Table 3 Short term studies (<24 hours) investigating the effect of a bolus dose of fructose on triglycerides

Evaluation System Score (Quality)	Subjects/Study Design	Dose/Matrix	Time Course	Result	Reference
Studies with bolus dose administered in water					
18 (Low)	9/group; 5 M/4 F Included 2 obese and 3 with distant family history of diabetes	100 g fru; 100 g glu; 100 g suc Administered in 250 ml bolus dose	To 300 min	INS: glu > fru > suc TG: fru > suc > glu EOS TG: fru > BL at 300 min Glucagon: fru > suc > glu GH: glu > suc > fru	Bohannon et al. (1980)
15 (Low)	9/group, All M "Not Obese" Age: "Young"	Administered 0.25, 0.5, 0.75 or 1.0 g glu, suc, fru or sor per kg bw (approximately 20, 40, 60, or 80 g of each sugar) 4 ml/kg bw, liquid bolus (approximately 320 ml)	To 90 min	INS: glu > suc > fru > sor; TG: suc > glu > sor > fru at 1 g/kg BW Significant decrease in TG (compared to BL with all sugars), no dose-response to fru intake	Macdonald et al. (1978)
27 (Moderate)	6/group 4M, 2F Age: 18–45 yrs	85.3 +/- 22.3 g glu (100:0); 42.7 +/- 11.1 g of glu + 42.7 +/- 11.1 g fru (50:50); 21.3 +/- 5.6 glu + 64.1 +/- 16.7 g fru (25:75) Bolus providing 14% of subjects energy needs followed 4 hrs later by a std lunch. Isoenergetic	To 10 hrs (pre and post std lunch)	GLU: 100:0 > 50:50 > 25:75 (fasted, but not fed state) INS: 100:0 > 50:50 > 25:75 (fasted) INS: 100:0 > 50:50 = 25:75 (fed) NEFA: 100:0 = 50:50 = 25:75 (fasted or fed) TG: 50:50 > 100:0; 25:75 = 100:0 glu (fasted) TG: 50:50 = 25:75 > 100:0 (fed) TG: 50:50 = 25:75 > 100:0 (overall)	Parks et al. (2008)
13 (Low)	6/group, All M Age: 19–39 yrs BW: 56–95 kg (78.5 kg avg) Fixed CHO (200 g) diet for 3 days prior to study	50 g fru; 0 g fru (control), no control CHO 500 ml liquid bolus	To 8 hours	INS, C-peptide, glucagon, lactate, alanine: fru > control NEFA: control > fru TG, amino nitrogen, urea nitrogen: control = fru	Nuttal et al. (2000)
24 (Moderate)	11/group 5M, 6F Age: 29 +/- 2 yrs Single blind	75 g glu +/- 7.5 g fru liquid bolus (vol unknown), no control with 7.5 g addition of another CHO	To 120 min	INS, glucagon, NEFA, TG: glu = glu + fru Lactate: glu + fru > fru from 45–90 min. No difference at 120 min NEFA decreased from BL in both groups TG decreased from BL in glu but not glu + fru group	Moore et al. (2000)
Studies with bolus dose administered with other nutrients					
22 (Moderate)	14/group 8M, 6F Age: 21–64 yrs BMI: 22–31 (avg 25.3) kg/m ² (avg is ow) Randomized, single blind	Approx 60 g fru Approx 60 g glu Based on 80 kg BW (BW not listed). Drink (vol unknown) containing 0.75 g sugar/BW and 0.5 g oil/kg BW, plus a small amount of tracer sugars and palmitate to determine fate	To 360 min	GLU, VLDL-TG, lactate CO ₂ production, CHO oxidation: fru > glu INS, fat oxidation rate and synthesis of NEFA: glu > fru	Chong et al. (2007)

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Supplemental Table 3 Short term studies (<24 hours) investigating the effect of a bolus dose of fructose on triglycerides (*Continued*)

Evaluation System Score (Quality)	Subjects/Study Design	Dose/Matrix	Time Course	Result	Reference
14 (Low)	6/group 3M, 3F Age: 30–61 yrs	0.75 g/kg (approx. 54 g) fru in liquid 0.75 g/kg ST (approx. 52 g) in toasted bread Fat and protein (32 g) containing breakfast with fru in drink or ST in bread	To 6 hrs	INS: ST > fru TG : fru > ST NEFA: ST > fru	Abraha et al. (1998)
20 (Moderate)	11/group 7M, 4F Age: 51 +/- 4 yrs BMI (avg): 25.1 kg/ m ² (ow) Fasting TG = 0.46 –2.81 mmol/L (> 2.3 mmol/L considered high)	50 g fru + 40 g fat; 0 g fru + 40 g fat with 40 mg vitamin A 300 ml liquid bolus with 108 g cream +/- fru; no control with 50 additional g of another CHO	10 hrs	TG: fat + fru > fat – fru; Increase in TG with fru dependent on BL TG level	Jeppesen et al. (1995a)
21 (Moderate)	11/group 8M, 3F Age: 51 +/- 3 yrs BMI (avg): 26.6 kg/ m ² (ow) Fasting TG = 0.48 –3.69 mmol/L (>2.3 mmol/L considered high)	5 g fat (12 g cream) ± 50 g fru 40 g fat (108 g cream) + 0 g fru 80 g fat (216 g cream) + 0 g fru with 40 mg vitamin A 300 ml liquid bolus CHO and/or fat intake different in each group	10 hrs	TG: fat + fru > fat – fru; Response of TG to fat + fru similar to 40 g fat	Jeppesen et al. (1995b)
24 (Moderate)	8/group 9M, 12F Age: 18–23 yrs Randomized	50 g fru; 50 g glu; 50 g suc; 100 g suc; 0 g sugar 300 ml liquid bolus containing 40 g fat, 3 g chocolate flavoring	To 7 hrs	Increase in total postprandial lipemia and postprandial TG after 50 g fru and 100 g suc (similar)	Cohen and Achall (1988)
16 (Low)	22/group 12M, 10F Age: 27.3 +/- 6.3 yrs BMI (avg): 25.3 +/- 4.5 kg/ m ² (some were ow)	Milkshake (vol unknown) 108 g cream (plain); 108 g cream + 30 g fru; 108 g cream+ 17.5 g glu; 108 g cream + 1 g asp CHO variable, fat equal	To 8 hrs	TG: glu = fru > plain (although concentration of fru > glu); Peak TG correlated with baseline TG and INS	Singleton et al. (1999)
18 (Low)	8/group, All M Age: 24–35 yrs	Fresubin diabetes (3.5 g fru) or other formulas containing 2.5 g xyl or 11.8–13.8 g mal Formulae contained fat, protein and fiber Total amount of fru, xyl or mal administered = 7 g, 5 g or 23–25 g (respectively)	To 4 hrs (at 2 hr and at 4 hr)	INS: mal > fru = xyl Total cholesterol, HDL-C or LDL-C: similar TG: no effect of fru	Otto et al. (1993)

asp = aspartame; avg = average (mean); BL = baseline; BMI = body mass index; BW = body weight; EOS = end of study; F = female; fru = fructose; GH = growth hormone; glu = glucose; GLU = plasma glucose; HDL-C = high density lipoprotein cholesterol; INS = plasma insulin; LDL-C = low density lipoprotein cholesterol; M = male; mal = maltodextrin; NEFA = non-esterified fatty acid; ow = over weight; sor = sorbitol; suc = sucrose; ST = starch; std = standard; TG = triglycerides; VLDL-TG = very low density lipoprotein TG; vol = volume; xyl = xylitol; yrs = years.

All subjects fasted overnight and met criteria of normal weight (BMI 18.5 to 24.9 kg/ m²) unless indicated otherwise. Studies were conducted in a crossover manner unless stated otherwise. Conversions: Fructose: 1 g = 4 kcal; fat: 1 g = 9 kcal; 1 kcal = 4.184 KJ; 1 g fru = 16.736 KJ.

Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥30).

Supplemental Table 4 Effect of short term (<1 day) consumption of fructose on food intake

Evaluation System Score (Quality)	Subjects/Study Design	Dose/Matrix	Time Course	Result	Reference
Studies with bolus dose administered in water					
22 (Moderate)	8 M/group Age: 27 +/- 6.8 yrs Randomized	75 g fru, 75 g glu, 75 g F + 75 g glu (1 hour later) 300 ml liquid bolus containing sugar. Ad lib meal provided 120 min after treatment	To 180 min	GLU: glu+ fru > fru to 90 min; glu > glu+ fru > fru to 150 min INS: glu = glu+ fru > fru to 90 min; glu+ fru > glu > fru to 120 min; glu = glu + fru = fru to 180 min GLP-1: glu > fru + glu > fru to 60 min; glu = glu + fru = fru after 60 min Food intake, fullness, satiety, hunger: fru = fru+ glu = glu Disconnect between effect on GLP-1 and INS and satiation	Kong et al. (1999)
26 (Moderate)	4/sex/group Age: 22-50 yrs Randomized	50 g fru 50 g glu 0.25 g asp unflavored, unsweetened water 500 ml bolus, followed 38 min later with identical, preweighed lunch	To 48 min	GLU: glu > fru = asp = water INS: glu >> fru > asp = water Caloric or fat intake: water = asp > glu > fru (especially in M)	Rodin (1990)
21 (Moderate)	5/sex/group; Undergraduate students (no age listed); slightly ow (9.8 +/- 10% ow) double blind No crossover	50 g fru; 50 g glu, 50 g glu + asp (to increase sweetness to fru value), water (control) 500 ml liquid bolus. Ad lib meal offered 2.25 hours after ingestion of sugar	To 2.25 hrs	Food intake: glu > water > fru	Spitzer and Rodin (1987)
Studies with bolus dose administered with other nutrients					
26 (Moderate)	19 M/group Age: 18-35 yrs Randomized Nonfasted	60 g fru/15 g glu (80:20); 48.75 g fru/26.25 g glu (65:35); 37.5 g fru/37.5 g glu (50:50); 15 g fru/60 g glu (20:80); 75 g suc; 0 g sugar Std breakfast consumed 4 hr prior to sugar ingestion	BCI: 75 min post dose Food intake: 80 min post dose	GLU: 20:80 > suc = 50:50 > 65:35 > 80:20 > water INS: 20:80 > suc = 50:50 > 65:35 > 80:20 > water Appetite: water > 50:50 > 80:20 = 65:35 = suc > 20:80 Food intake (test meal): water > 80:20 = 65:35 > 50:50 > suc = 20:80 Total EI: 80:20 = 65:35 > 50:50 = water > suc = 20:80 Ghrelin: no difference between sugar groups	Akhavan and Anderson (2007)
21 (Moderate)	8 F (two groups) Age: 20.8 +/- 1 yrs Nonfasted	5 g fru+ asp 50 g fru 5 g glu + asp 50 glu Std breakfast followed by 500 ml liquid bolus 30 min or 135 min prior to meal	To 135 min	Food ingestion: fru = glu (at either time)	Guss et al. (1994)
24 (Moderate)	10/group, roughly equal numbers of M:F Age: 20-43 yrs No crossover	Study 1: 50 g fru, 50 g glu 500 ml liquid bolus containing sugar Study 2: 40 g fru (with food), 40 g glu (with food) Breakfast with 15 g sugar followed by snack with 25 g sugar (preload). Identical, pre-weighed lunch offered 2.25 hours after preload	To 155 min	Study 1: GLU, INS: glu > fru; Food intake at lunch: glu = fru Study 2: GLU, INS, food intake at lunch, or ingestion of protein, fat or CHO: fru = glu; Response is different from response with sugars in liquid. Much higher peak GLU and INS when fru is in food rather than in a liquid bolus; disconnect between relationship of INS to food intake when large amount of fru is in a liquid bolus vs. when it is presented in food	Rodin et al. (1988)
24 (Moderate)	13 M Age: 18-35 yrs Randomized	30 g fru; 30 g glu; 0 g sugar Cereal with or without sugar followed by pizza meal 30 or 120 min later	To 30 or 120 min	GLU: glu > fru > water Meal intake: water > fru = glu (30 or 120 min) TCI: glu = fru = water (after 30 min) TCI: glu > fru = water (after 120 min)	Stewart et al. (1997)

asp = aspartame; BCI = biochemical indices; CHO = carbohydrate; EI = energy intake; F = female; fru = fructose; GLU = plasma glucose; glu = glucose; GLP-1 = glucagon-like peptide; INS = plasma insulin; M = male; ow = overweight; std = standard; suc = sucrose; TCI = total caloric intake; yrs = years; >> denotes much greater than.

All subjects fasted overnight and met criteria of normal weight (BMI 18.5 to 24.9 kg/m²) unless indicated otherwise. Studies were conducted in a crossover manner unless stated otherwise. Conversions: fru: 1 g = 4 kcal; fat: 1 g = 9 kcal; 1 kcal = 4.184 KJ; 1 g fru = 16.736 KJ.

Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20-29) or high (≥30).

Supplemental Table 5 Miscellaneous short term (<1 day) studies that examined the effect of fructose on carbohydrate metabolism without determining the effect on TG or food intake

Evaluation System Score (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
Liquid bolus dose (not with meal)						
13 (Low)	20/group 11M, 9F	91 g glu 124 g fru, 71 g glu + 124 g fru 64 g ST + 124 g fru 64 g ST CHO variable	Liquid bolus (0.33 kg/L) Unknown volume	To 90 min	INS: glu + fru > glu > ST + fru > ST > fru	Anderson et al. (1990)
19 (Low)	24/group 15M, 9F Age: 30–64 yrs Majority normal weight Excluded: medications or overt disease.	60 g glu (1 g/kg bw) 54 g CS (0.9 g/kg bw) 60 g glu + 105 g fru (1.75 g/kg bw) 54 g CS + 105 g fru 1.75 g fru + water CHO variable	Added to drinks at 0.33 g/ml	90 min	INS: glu + fru (highest CHO) > glu > CS + fru > CS = fru	Reiser et al. (1987)
12 (Low)	4/group, all M Age: 21–27 yrs BW not given	100 g fru 100 g glu CHO equal	Liquid bolus volume unknown	To 8 hr	INS: glu > fru (before 3 hr); glu = fru = BL (at 4 hr) NEFA: glu > fru (to 8 hr)	Swan et al. (1966)
23 (Mod- erate)	10/group Age: 27.8 ± 2.5 yrs	75 g fru 75 g glu 75 g suc 75 g CS ¹³ C labeled	400 ml liquid bolus	To 360 min	GLU: CS > glu > suc > fru INS: CS = glu > suc >> fru NEFA: fru = suc = CS = glu EE: suc = fru > CS = glu CHO oxidation: fru = suc > glu = CS Decrease in lipid oxidation: fru > suc > CS = glu	Blaak and Saris (1996)
22	16/group 6M, 2F Age: 18–29 yrs 4M, 4F Age: 66–80 yrs	75 g fru 75 g glu Administered with caffeine or vitamin C	500 ml liquid bolus	To 180 min	INS and GLU: glu > fru Older group had higher INS and GLU than young group Uric acid : fru > glu EE: fru = glu (even when adjusting for bw or fat-free mass) Cholesterol: glu = fru Alanine: fru > glu Branched-chain and aromatic amino acids: glu = fru	Fukagawa et al. (1995)
22 (Mod- erate)	17 subjects 6M, 11F (used in 2 separate experiments) Exp. 1: 10 subjects Exp. 2: 6 subjects Age: 19–50 yrs	75 g fru 75 g glu In a second experiment 6 subjects received propranolol before 75 g fru	300 ml liquid bolus	To 240 min	INS: glu > fru EE: fru > glu CHO oxidation: fru > glu to 180 min Decrease in lipid oxidation: fru > glu FFA: fru = glu	Tappy et al. (1986)
19 (Low)	6–12/group, M/F Age: 21–27 yrs BW: within 80%–123.1% of ideal No crossover	75 g fru 75 g glu 75 g suc CHO equal	300 ml liquid bolus	3 hrs	INS: glu > fru = suc No increase over BL with fru	Kim et al. (1988)
15 (Low)	6 subjects 3M, 3F Age: 49±13 yrs No crossover	75 g fru No control CHO	390 ml liquid bolus	To 240 min	INS, GLU: small increase over BL with fru Lower serum NEFA, glycerol, lipid oxidation; increased lactate, EE (by 12%), CHO oxidation after fru compared to BL	Kruszynska et al. (1993)
7 (Low)	6/group, all M Age: 29.3 yrs (avg) BW: no information No crossover	1 g/kg bw fru (est. 70 g) 1 g/kg bw glu + 1 g/kg fru, 60 min later CHO variable	Unknown volume of liquid bolus	To 45 min	INS: fru + glu > fru Lactate: fru > fru + glu Pyruvate: fru > fru + glu	Stansbie et al. (1978)

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Supplemental Table 5 Miscellaneous short term (<1 day) studies that examined the effect of fructose on carbohydrate metabolism without determining the effect on TG or food intake (*Continued*)

Evaluation System Score (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
9 (Low)	Group size-unknown, M/F Age: 16–25 yrs	52.5 g fru 52.5 g glu 52.5 g gla (based on 75 g/kg bw)	Unknown volume of liquid bolus	To 3 hr	GLU: glu > fru > gla INS: glu > gla > fru NEFA: gla > glu = fru	Manso et al. (1979)
23 (Moderate)	8/group 4M, 4F Age: 21–33 yrs	5 or 50 g fru 25 or 50 g glu 25 or 50 g suc 50 g glu + 50 g fru 25 or 50 g CHO in bread	500 ml liquid bolus	To 120 min	INS, GLU: glu > bread > suc > fru to 120 min Insulin AUC increased linearly as dose of CHO increased, but the glucose AUC did not	Lee and Wolever (1998)
22 (Moderate)	8 normal weight subjects 4M, 4F Age: 23.1 ± 0.8 yrs No crossover	50.4 g fru (divided) 16.8 g fru (300 mg/kg fru/FFM) once per hr for 3 hrs; Responses compared to BL or 7 obese subjects.	Radiolabelled glucose (30 µg/kg/min) or glucagon (3 ng/kg/min) infused, ^a followed by ingestion of radiolabeled fru once per hour for 3 hours.	To 180 min	Decrease in NEFA compared to BL Gluconogenesis increased but no increase in endogenous glucose production Simulation of net CHO oxidation and inhibition of net lipid oxidation by fru	Paquot et al. (1996)
With a meal						
14 (Low)	5/group, all M Age: 29–37 yrs No data on BW, disease status or possible confounders	72 g fru +/- meal 72 g glu +/- meal 36 g fru/36 g glu + meal 72 g suc + meal Meal w/o sugar CHO equal	Sugar w/wo 800 kcal Breakfast: (34% fat, 19% protein, 48% carb)	To 3 hrs	Lactate and pyruvate: fru = suc = fru/glu > glu at 1 hr; approx same at 3 hr	Kelsay et al. (1974)
23 (Moderate)	20/group 10M, 10F Age: M: 18–29 yrs F: 19–25 yrs	75 g fru 75 g glu	200–300 ml liquid meal containing 35 g protein, 23 g lipid plus 75 g sugar	To 6 hr	GLU, INS: glu > fru to 180 min Lactate, energy expenditure, CHO oxidation, respiratory quotient: fru > glu to 120–180 min Lipid oxidation: glu > fru to 180 min FFA: fru = glu	Schwarz et al. (1989)
24 (Moderate)	10/group, 4M, 6F Age: 34.3 ± 4 yrs Blinded	63 g fru (cake) 63 g suc (cake) 52 g fru (ice cream) 52 g suc (ice cream)	Sugar (in cake or ice cream)	To 180 min	GLU, INS: glu > fru (cake or ice cream) to 60 min Lower glucose responses for both suc and fru in ice cream than cake	Crapo et al. (1982)
16 (Low)	9/group, 2M, 7F Age: 56 ± 2 yrs Excluded: use of drugs affecting GLU or INS	50 g glu 50 g suc 50 g fru CHO equal	500 ml liquid w/wo corn oil, egg albumin	To 180 min	INS: glu = suc > fru to 120 min GLU: glu = suc > fru to 120 min (w/wout meal)	Crapo et al. (1980)
25 (Moderate)	10/group, 7M, 3F Age: 22–29 yrs Randomized	42 g fru 42 g glu 42 g suc 42 g potato starch 43 g wheat starch	Normal breakfast food with 24–25% of calories as test CHO	To 240 min	GLU: glu > wheat > suc = potato > fru INS (peak): glu = potato = wheat = suc = fru INS (180 min): wheat ≫ glu > potato > fru = suc	Bantle et al. (1983)
18 (Low)	5–10/group, all M Age: 19–62 yrs	35 g fru 35 g suc 35 g sor CHO equal	Breakfast food; Sugar supplies (140/400 cal) 35% of energy	To 180 min	INS: suc > fru > sor	Akgun and Ertel (1980)

(Continued on next page)

Supplemental Table 5 Miscellaneous short term (<1 day) studies that examined the effect of fructose on carbohydrate metabolism without determining the effect on TG or food intake (*Continued*)

Evaluation System Score (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
21 (Moderate)	Oral study: 8/group, 2M, 6F Dietary study ^b (4/sex) Age: 46–71 yrs BMI: slightly higher than avg	30 g suc 30 g fru 30 g sor 30 g mal	300 ml liquid or with a meal	To 120 min	GLU, INS: suc > fru = mal > suc after the liquid load GLU: suc = fru = mal = sor after the meal INS: suc = fru = mal > sor after the meal No difference in fasting C-peptide between groups in either the oral fluid load or dietary experiment	Vessby et al. (1990)
25 (Moderate)	32/group 13M, 19F Age: 20–41 yrs BW: 45.2–96.2 kg BMI: 18.3–29.7 Double blinded Randomized	10 g fru 0 g fru	60 ml bolus liquid prior to 50 g CHO meal (mashed potatoes)	To 120 min	GLU: water > fru when fru ingested 30 or 60 min prior to, but not at the same time as food.	Heacock et al. (2002)

avg = average (mean); BL = baseline; BW = body weight; CHO = carbohydrate; CS = cornstarch; EE = energy expenditure; F = female; FFA = free fatty acids; FFM = fat free mass; fru = fructose; gla = galactose; GLU = plasma glucose; glu = glucose; INS = plasma insulin; M = male; mal = maltose; NEFA = non-esterified fatty acid; sor = sorbitol; ST = starch; suc = sucrose; >> indicates much greater than.

^aGlu was administered *i.v.* prior to and during fru ingestion; ^b4 subjects (gender not specified) also participated in the oral study.

All subjects fasted overnight and met criteria of normal weight (BMI 18.5 to 24.9 kg/m²) unless indicated otherwise. Studies were conducted in a crossover manner unless stated otherwise. Conversions: fru: 1 g = 4 kcal; fat: 1 g = 9 kcal; 1 kcal = 4.184 KJ; 1 g fru = 16.736 KJ.

Evaluation system score (quality) for intervention studies as described in section entitled “Study Grading Criteria”: low (<20), moderate (20–29) or high (≥30).

Supplemental Table 6 Observational studies on fructose intake

Evaluation System Score (Quality)	Subjects	Assessment Method	Result	Reference
16 (Moderate)	471 nw (203 M, 298 F); 404 obese (191 M, 255 F) ^a Age: 45–75 yrs	Food frequency questionnaire and confirmation of intake with urinalysis	Nw: Dietary fru intake = 95% CI or 25 g/day (range 24–26) Obese: Mean dietary fru intake = 95% CI or 26 g/day (range 25–27). No associations between dietary fru intake or urinary fru and obesity	Bingham et al. (2007)
15 (Moderate)	1999 ow F Age: 25–69 yrs	Two food frequency questionnaires over a 4 year period	Group 1: 8.5% of energy from free fruc (38.8 g/day); BMI = 25.4 ± 0.2 kg/m ² Group 2: 4.9% of energy from free fruc (22.1 g/day); BMI = 25.2 ± 0.2 kg/m ² Group 3: 2.7% of energy from free fruc (11.8 g/day); BMI = 26.2 ± 0.2 kg/m ² . BMI inversely associated with fructose intake (p < 0.02)	Wu et al. (2004)
9 (Low)	32 healthy M and F Age: 11–25 years with wide range of Z-scores (1.18–2.64)	Three day food diary	Mean dietary fru intake = 26 g/day (0–73) No correlation between dietary intake of fru and TG	Slyper et al. (2005)
18 (Moderate)	74 subjects nw and ow Swiss children (not presented by gender) Age: 6–14 yrs	Two 24-hr dietary recalls, and one-day dietary record	Nw: Fru intake of 1.99 g/day (range 0.12–12.3) Ow: Fru intake of 1.62 g/day (range 0.15–11.38 g/day) No associations between dietary fru intake and obesity	Aeberli et al. (2007)

BMI = body mass index; CI = carbohydrate intake; F = females; fru = fructose; M = males; nw = normal weight; ow = overweight; TG = triacylglycerin; yrs = years; Z-scores = The deviation of an individual's value from the median value of a reference population, divided by the standard deviation of the reference population. Z-scores are used for population based assessments of child growth (WHO, 1997).

^aNumbers reported for M, F include excluded subjects.

Evaluation system score (quality) for observational studies as described in section entitled “Study Grading Criteria”: low (<10) or moderate (10–20).