Artículo Original

# Controversia por limitar el consumo de alimentos y bebidas con fructosa. Una revisión sistemática cualitativa

# Controversy for limiting the consumption of foods and beverages with fructose. A qualitative systematic review

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**RESUMEN**

**Introducción.** La industria del azúcar se ha opuesto a aceptar que sus productos pueden ser la causa raíz principal de la pandemia de enfermedades no transmisibles. **Objetivo.** Analizar las bases que sustentan las posiciones acerca de limitar el consumo de fructosa que se agrega a bebidas y alimentos industrializados mediante la identificación de conceptos principales en artículos de revisión. **Método**. Se hizo una búsqueda en PUBMED con los términos ("fructose"[MeSH Terms] OR "fructose"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]). **Resultados.** La búsqueda obtuvo 246 revisiones donde se localizaron 43 que se referían de manera específica a los efectos metabólicos de la fructosa en la historia natural de la diabetes mellitus de tipo 2. En ellos se analizaron los efectos de la fructosa en obesidad, resistencia a la insulina, hígado graso, síndrome metabólico, envejecimiento prematuro, hiperuricemia, hipertensión, diabetes, daño renal, enfermedad cardiovascular. Sin aportar datos a favor de la inocuidad de la fructosa agregada a bebidas y alimentos, los autores con conflicto de interés desacreditan esos resultados. **Conclusiones.** Los manuscritos de autores con conflicto de interés sirven para sustentar posiciones escépticas hacia la evidencia científica.

**Palabras clave:** Conflicto de interés; Industria de alimentos y bebidas; Fructosa; Enfermedades no transmisibles.

**SUMMARY**

**Introduction.** The sugar industry has opposed accepting that its products may be the main root cause of the pandemic of noncommunicable diseases. **Objective.** Analyze the bases that support the positions about limiting the consumption of fructose that is added to industrialized beverages and foods through the identification of main concepts in review articles. **Method.** A search was made in PUBMED with the terms ("fructose"[MeSH Terms] OR "fructose"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]). **Results.** The search obtained 246 reviews where 43 were located that specifically referred to the metabolic effects of fructose in the natural history of type 2 diabetes mellitus. The effects of fructose on obesity, insulin resistance, fatty liver, metabolic syndrome, premature aging, hyperuricemia, hypertension, diabetes, kidney damage, cardiovascular disease were analyzed. Without providing data in favor of the safety of fructose added to beverages and foods, authors with a conflict of interest discredit these results. **Conclusions.** The papers of authors with conflicts of interest serve to support skeptical positions towards scientific evidence.

**Key words:** Conflict of interest; Food and beverage industry; Fructose; Non-communicable diseases.

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**Introduction**

Type 2 diabetes mellitus (T2DM) is a disease characterized by hyperglycemia that has had dramatic increases in recent decades. DMT2 and other non-communicable diseases (NCDs) account for four out of every five deaths in the Americas (1). The understanding that T2DM is a long-standing subclinical disease gave greater relevance to the identification of prediabetes (preT2DM) and to the search for previous metabolic abnormalities such as insulin resistance or low-grade inflammation (2). Therefore preT2DM were increased, in 2017 it was estimated at 86 million people with prediabetes only in the United States. That means than one in every three inhabitants over 20 years old in that country had this disease (3).

Without taking away the importance of sedentary lifestyle or genetic predisposition, T2DM is produced mainly by modifications in the exposome by the adoption of modern industrialized diets (4). Modern industrialized foods, especially because of their fructose content, produce stress on the genes, either by base sequence or by epigenetic modifications (5). Fructose added to foods and beverages can produce deleterious effects at various levels, because that it is the main root cause for obesity, T2DM, and many other NTD.

Added fructose can directly produce fatty liver that progresses to cirrhosis (5-8). ATP depletion and elevation of uric acid (5-9), which causes inhibition of vascular nitric oxide expressed as hypertension and cerebral infarction (10-11), causes too modification in the expression of RNA genes that produces disturbances in the expression of DNA genes. That results in a decrease in insulin sensitivity and increased maturation of preadipocytes to adipocytes (12-14), fetal oxidative stress and changes in food perception, as sweet addiction from the intrauterine stage (15-16).

This may be the reason why the expectations of the late twentieth century for T2DM were greatly exceeded (17). New projections consider that in the scenario where T2DM has low mortality and the slope of increase is maintained, by 2050 the prevalence will be 33% (18), with an increase in cases in young patients, so the diagnosis should be considered from adolescence (19-20). In this context, fructose is added to beverages and foods, without being the only but the main root of the metabolic modifications that cause NCD, in a context related to pro-inflammatory diets (21-25). However, in opposition the recommendations based on evidence about limiting the consumption of these products, the sugar industry promotes that scientific data are controversial and not conclusive. In this situation, the objective of this research is to identify the main arguments of the controversy about the consumption of fructose in the context of T2DM (figure 1).

**Methods**

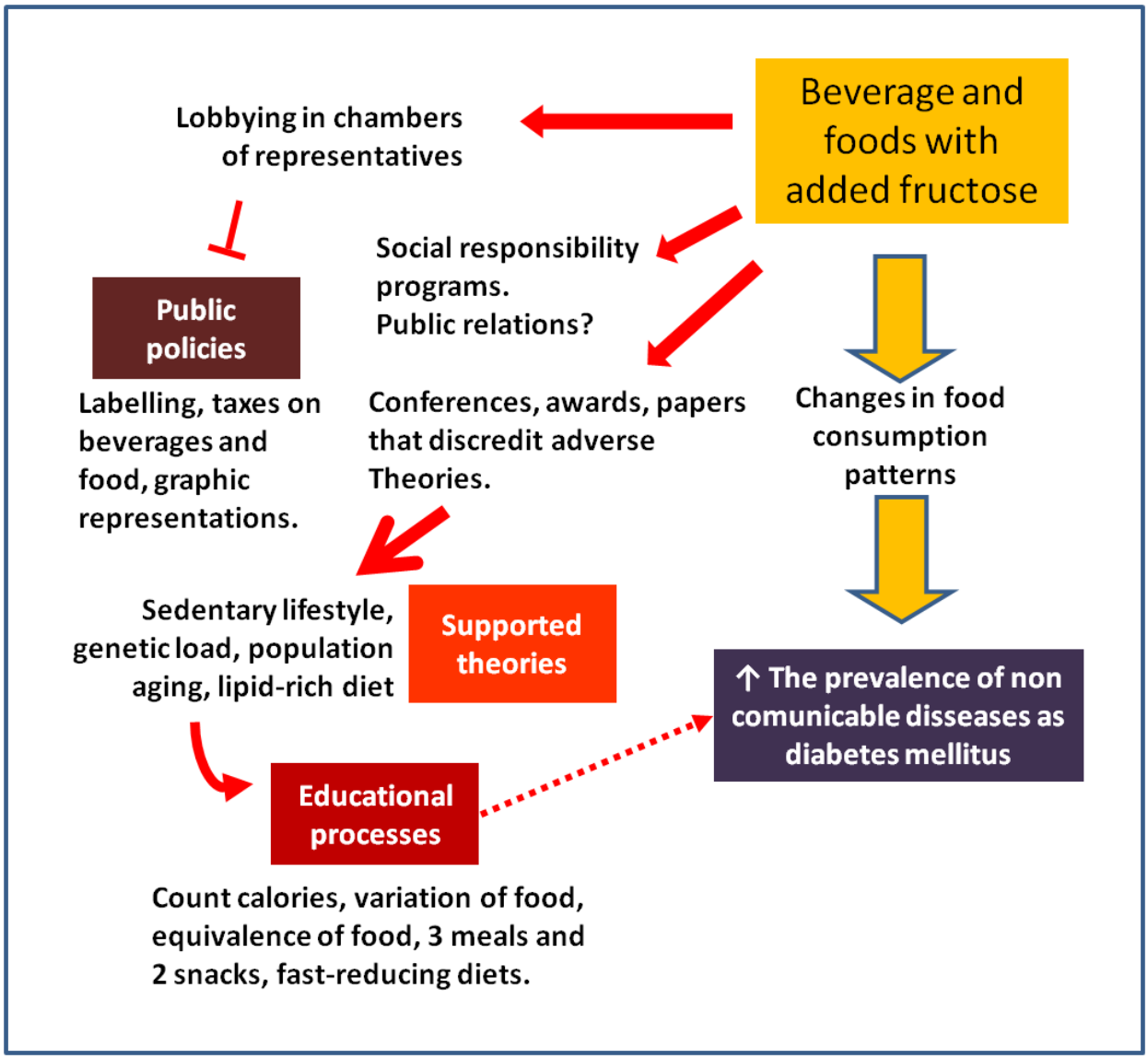
A qualitative systematic review was made. All data used in this study were obtained from PubMed databases, searched in April 2018. To be included, all the publications had to fulfill the following criteria: (i) to be published in peer reviewed journals, (ii) to contain independent data, (iii) to be experimental and association studies, and (vi) to be written in English. The exclusion criteria were as follows: duplicated publications, studies of cases only or case reports, and papers that did not have enough data available.

The role of fructose in the etiopathogenesis of T2DM was selected for which a search was made in PUBMED with the concepts ("fructose" [MeSH Terms] OR "fructose" [All Fields]) AND ("diabetes mellitus" [MeSH Terms] OR ("diabetes" [All Fields] AND "mellitus" [All Fields]) OR "diabetes mellitus" [All Fields]).

Since 2002 articles were found, it was decided to analyze the reviews about the role of fructose in diabetes. A redefined search was made in PUBMED with the terms ("fructose" [MeSH Terms] OR "fructose" [All Fields]) AND ("diabetes mellitus" [MeSH Terms] OR ("diabetes" [All Fields] AND "mellitus" [ All Fields]) OR "diabetes mellitus" [All Fields]) AND ("review" [Publication Type] OR "review literature as topic" [MeSH Terms] OR "review" [All Fields]).

The search obtained 246 items. 37 specifically referred to the metabolic effects of fructose in

**Figure 1**. Processes by which the industry of drinks and foods with fructose modulates policies about the use of its products.




the natural history of T2DM. In eight of them, the authors had a conflict of interest (26). Conflicts of interest refer to receiving funding from the industry, doctoral grants, consultant fees, and nutrition or diabetes foundations (27). These papers were contrasted with the information of those made by authors without this type of financing.

**Results**

Studies on fructose in late nineteenth and early twentieth centuries considered that it could be tolerated better than other monosaccharides in patients with diabetes mellitus prior to the use of insulin and oral hypoglycaemic agents. Studies from the middle of the last century described the metabolic differences between fructose and other monosaccharides in tissues, animals and humans with and without diabetes (27-28). Mainly because insulin did not appear to be required for the metabolism of fructose (29), it was led the promotion of fructose in patients with T2DM (29). The ingestion of fructose produces lower elevations of the postprandial glycemia and lower insulin release than other carbohydrates (30-32). The use of fructose due to its lower glycemic effect appears again in recent reviews (33-35), in spite of it is known that

fructose produces hypertriglyceridemia and decreased insulin sensitivity (36-38). Fructose can cause de novo lipogenesis because enhance the basal level of apoB48 (39).

It is well supported that fructose ingestion is associated with obesity, accelerated aging, insulin resistance, T2DM, nonalcoholic fatty liver disease (NAFL), hypertriglyceridemia, hyperuricemia, chronic diarrhea, irritable bowel syndrome, urticaria (38,40-48), cardiovascular disease (49), breast cancer (42), cognitive impairment and dementia (47).

The associations between hyperuricemia, gout, and T2DM are from the middle of the last century (50). Although it was not known that fructose produced ATP deprivation since phosphofructokinase does not have a repression system [51], which increases the level of this metabolite (41,50). Subsequent studies showed that fructose produces reduced hepatic post-insulin receptor signaling and reduced insulin suppression of glucose production (52). The two-hits model for nonalcoholic fatty liver disease was also described in detail, which explains the pathogenesis of the metabolic syndrome (51,53-54).

Focusing on the diets, restriction of fats in the diet was shown accompanied by a lower probability of obesity if the high consumption of sugar is maintained (9). The vegetables that contains fructose, as fruits, have a protective effect against diabetes and cardiovascular disease because they are eaten whole (unlike what happens when the juice is extracted). The opposite occurs with foods with added sugar (55).

On the reviews of researchers with conflicts of interest it was questioned the scientific evidence in previous papers. They suggest that to cope with T2DM, "avoiding intake of excess calories (from sugar) until solid evidence to support action against fructose until solid evidence is available" (56-57). No conclusive evidence was found to determine that the consumption of fructose or sucrose is a cause of disease in humans, despite the large amount of evidence in animals because studies showing this effect have methodological limitations (58). “While high amounts can be problematic, low consumption of sugar has benefits” (59-60). Cohort studies, as prospective or controlled studies, “do not show that high fructose syrup produces prediabetes or diabetes” (61-62).

**Discussion**

Some of the allegations from several industry-funded studies focus on the fallacy of the false dilemma: a) sugar, especially in the form of high-fructose syrup, added to beverages and foods is a cause of obesity and diabetes, versus b) sugar does not cause obesity and diabetes. According to them, since it has not been possible to demonstrate a homogeneous dose-response effect in all the experimental groups, premise b) is correct. Therefore, in industry-funded studies, it is argued that there is no creation of univocal risk of obesity or disease under conditions of isocaloric exchange of fructose for any carbohydrate (63), even when observed in non-human animals (60): However, epidemiological studies have found an association between the consumption of simple sugars, mainly in the form of beverages rather than in food, and more with fructose than with glucose (9,12,44).

Other arguments to support the interests of the industry-funded studies are: noncommunicable diseases are multifactorial, therefore the pandemic of these diseases can´t be attributed to any food (56,61-62). The upper limit for the ingestion of fructose or sugar added to beverages and foods has not been determined, thus no recommendations can be made to limit sugar consumption to a quantity (59,61). Studies showing the possible effects of sucrose or fructose on the generation of noncommunicable diseases are inconclusive (61). In the industry-funded studies, the data showing an association between noncommunicable diseases and the consumption of sugar added to beverages and foods are misinterpreted in order to discredit the results as a whole (straw man fallacy).

The studies with industry funding are structured primarily in a systematic review format with meta-analysis in accordance with the recommendations of the Cochrane Library Manual (64). In the text, it is made explicit that

the more accurate the research question (objective of the review) the greater the strength of the results of the analysis. In the studies with industry funding, the question is not elaborated with a definite aim. This interferes with the delineation of the criteria that would be considered in a specific review.

Those reviews were structured based on questions such as “evaluate the need for additional clinical evidence regarding the effects of fructose consumption on uric acid in humans” (58); “is there something special about fructose metabolism that increases the risk of obesity and chronic disease, or is the harm is related just to the excess calories it provides” (60); “some of the abnormalities associated with fructose metabolism, such as hypertriglyceridemia and hepatic insulin resistance, may be merely a reflection of the specific pathways of fructose metabolism rather than markers of disease” (61). This last statement shows the intention of a position of skepticism in the face of the evidence that both hypertriglyceridemia and hepatic resistance to insulin are metabolic problems that may reflect progression towards non-alcoholic fatty liver disease (NAFLD), whose prevalence in children is high (65). In turn, NAFLD may have progression to prediabetes and diabetes mellitus type 2, presenting at pediatric ages (66), where the intake of sugar added to beverages and food is a significant contributor since it is added to beverages and baby foods .

A review question should be structured in a defined manner, preferably in a single sentence, based on four key components: the types of population or participants, the types of interventions, the types of comparisons between study groups, and the types of outcome (PICO, by its acronym) (64). This definition supports the type of study design that is the basis for the pre-established eligibility criteria for the review. Studies should have groups to compare the effects, eg dexamethasone against prednisone in mild to moderate asthma, oral vs. intramuscular, single dose versus three days of treatment (67). On the contrary, industry studies, while presenting tables for different groups, do not make strict distinctions between study design or food intake from other sources in the reviews and included high proportions of studies of poor quality (58). While noting these methodological differences as failures attributable to studies (61), including them distorts the results of systematic reviews.

The wide questions are valid at the beginning of a review, but these approaches fall into the possibility of adding different types of situations (such as "apples with oranges"). In the case that a question of this type does not fragment into minor problems, interpretation can be difficult due to heterogeneity. Ambiguous conclusions emanating from extensive analysis of heterogeneous sources would consequently cause the degradation of the evidence as a whole, which could be the intention of the authors (26).

Finally, in order to evaluate the long-term effects of fructose in the system, such as the possibility of developing T2DM diabetes or hypertension, both chronic diseases, it is not appropriate to consider studies of very short duration, except to make explicit the fact that They can answer the question of interest. Considering studies with a duration of 1, 2, 12 weeks confer an important bias, more when uric acid values were not considered as a central point of the studies analyzed in the systematic review and meta-analysis about this metabolite (58).

**Conclusions**

The studies with industry financing focus mainly on the lack of sustenance to establish a limit for sugar added to beverages and food from the point of view that it is not the only responsible factor in the pandemic of non-communicable diseases. While in the context of obesity and non-communicable diseases the addition of fructose to beverages and foods is not the only factor, it is a part of the greatest relevance in the problem. But recognizing that it is not the only one does not mean that it can be considered as incorrect to establish lower limits to the amount of sugar and fructose that is ingested. Therefore, the definition of inflammatory diets where added sugar is an important component will allow to better raise the recommendations about the

maximum limit for the ingestion of this nutrient as an addition to beverages and foods.

**References**


1. Pan American Health Organization. Health in the Americas, 2017 Edition. Summary: Regional Outlook and Country Profiles. Washington, D.C: PAHO.
2. Spranger J, Kroke A, Möhlig M, Hoffmann K, Bergmann MM, Ristow M, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes, 2003;52(3), 812-817.
3. American Diabetes Association. So... Do I have prediabetes? https://doihaveprediabetes.org/?loc=dorg_201707_en_feat_adcouncil
4. Prescott SL, Logan AC. Each meal matters in the exposome: Biological and community considerations in fast-food-socioeconomic associations. Econ Hum Biol. 2017;27(Pt B):328-335. doi: 10.1016/j.ehb.2017.09.004.
5. Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, Shafiu M, Segal M, Glassock RJ, Shimada M, Roncal C, Nakagawa T. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev. 2009;30(1):96-116. doi: 10.1210/er.2008-0033
6. Basaranoglu M, Basaranoglu G, Sabuncu T, Sentürk H. Fructose as a key player in the development of fatty liver disease. World J Gastroenterol. 2013;19(8):1166-72. doi: 10.3748/wjg.v19.i8.1166
7. Nomura K, Yamanouchi T. The role of fructose-enriched diets in mechanisms of nonalcoholic fatty liver disease. J Nutr Biochem. 2012;23(3):203-8. doi: 10.1016/j.jnutbio.2011.09.006
8. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. Nat Rev Gastroenterol Hepatol. 2010;7(5):251-264.
9. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, Shafiu M, Sundaram S, Le M, Lanaspa MA. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes, 2013;62(10):3307-3315.
10. Lehto S, Niskanen L, Rönnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non–insulin-dependent diabetes mellitus. Stroke. 1998;29(3):635-9.
11. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol. 2003;18(6):523-30.
12. Baena M, Sangüesa G, Dávalos A, Latasa MJ, Sala-Vila A, Sánchez RM, Alegret M. Fructose, but not glucose, impairs insulin signaling in the three major insulin-sensitive tissues. Scientific Reports, 2016;6:26149.
13. Su Q, Sud N, Pan K. MicroRNAs in the pathogenesis of lipogenic diet induced hyperlipidemia and insulin resistance. FASE J, 2017;31(1_s), 299-8.
14. Sud N, Zhang H, Pan K, Cheng X, Cui J, Su Q. Aberrant expression of microRNA induced by high-fructose diet: implications in the pathogenesis of hyperlipidemia and hepatic insulin resistance. J Nutr Biochem. 2017;43:125-131
15. Goran MI, Dumke K, Bouret SG, Kayser B, Walker RW, Blumberg B. The obesogenic effect of high fructose exposure during early development. Nat Rev Endocrinol. 2013;9(8):494-500.
16. Rodrigo S, Rodríguez L, Otero P, Panadero MI, García A, Barbas C, Roglans N, Ramos S, Goya L, Laguna JC, Álvarez-Millán JJ, Bocos C. Fructose during pregnancy provokes fetal oxidative stress: The key role of the placental heme oxygenase-1. Mol Nutr Food Res. 2016;60(12):2700-2711
17. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care, 1998;21(9): 1414-1431.

18. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Population Health Metrics, 2010;8(1):29.
19. Fagot-Campagna A. Emergence of type 2 diabetes mellitus in children: epidemiological evidence. J Pedr Endocrinol Metabolism, 2000;13(Suppl): 1395-1402.
20. Ludwig DS, Ebbeling CB. Type 2 diabetes mellitus in children: primary care and public health considerations. JAMA, 2001;286(12):1427-1430.
21. Vissers LET, Waller M, van der Schouw YT, Hébert JR, Shivappa N, Schoenaker DAJ, Mishra GD. A pro-inflammatory diet is associated with increased risk of developing hypertension among middle-aged women. Nutr Metab Cardiovasc Dis, 2017;27(6):564-570.
22. Shivappa N, Bonaccio M, Hébert JR, Di Castelnuovo A, Costanzo S, Ruggiero E, Moli-sani study Investigators. Association of pro-inflammatory diet with low-grade inflammation: results from the moli-sani study. Nutrition. 2018;54:182-188
23. Zhong, X., Guo, L., Zhang, L., Li, Y., He, R., & Cheng, G. (2017). Inflammatory potential of diet and risk of cardiovascular disease or mortality: A meta-analysis. Scientific reports, 7(1), 6367.
24. Tabung 2017. An Empirical Dietary Inflammatory Pattern Score Enhances Prediction of Circulating Inflammatory Biomarkers in Adults
25. Tabung 2018. Association of Dietary Inflammatory Potential With Colorectal Cancer Risk in Men and Women
26. Mozaffarian D. Conflict of interest and the role of the food industry in nutrition research. JAMA. 2017;317(17):1755-1756.
27. Rey-López JP, Gonzalez CA. Research partnerships between Coca-Cola and health organizations in Spain. Eur J Public Health. 2018. doi: 10.1093/eurpub/cky175 [Epub ahead of print]
28. Bhattacharya G. Protection against alloxan diabetes by mannose and fructose. Science. 1953;117(3035):230-1.
29. Renold AE, Hastings AB, Nesbett FB. Studies on carbohydrate metabolism in rat liver slices. III. Utilization of glucose and fructose by liver from normal and diabetic animals. J Biol Chem. 1954;209(2):687-96.
30. Miller M, Craig JW, Drucker WR, Woodward H Jr. The metabolism of fructose in man. Yale J Biol Med. 1956;29(3):335-60.
31. Bantle JP. Clinical aspects of sucrose and fructose metabolism. Diabetes Care. 1989;12(1):56-61
32. Gerrits PM, Tsalikian E. Diabetes and fructose metabolism. Am J Clin Nutr. 1993;58(5 Suppl):796S-799S.
33. Uusitupa MI. Fructose in the diabetic diet. Am J Clin Nutr. 1994;59(3 Suppl):753S-757S.
34. Cozma AI, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V, Wang DD, Mirrahimi A, Yu ME, Carleton AJ, Di Buono M, Jenkins AL, Leiter LA, Wolever TM, Beyene J, Kendall CW, Jenkins DJ. Effect of fructose on glycemic control in diabetes: a systematic review and meta-analysis of controlled feeding trials. Diabetes Care. 2012;35(7):1611-20.
35. Evans RA, Frese M, Romero J, Cunningham JH, Mills KE. Chronic fructose substitution for glucose or sucrose in food or beverages has little effect on fasting blood glucose, insulin, or triglycerides: a systematic review and meta-analysis. Am J Clin Nutr. 2017;106(2):519-529
36. Evans RA, Frese M, Romero J, Cunningham JH, Mills KE. Fructose replacement of glucose or sucrose in food or beverages lowers postprandial glucose and insulin without raising triglycerides: a systematic review and meta-analysis. Am J Clin Nutr. 2017; ajcn145151
37. Daly ME, Vale C, Walker M, Alberti KG, Mathers JC. Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications. Am J Clin Nutr. 1997;66(5):1072-1085.

38. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr. 2002;76(5):911-22
39. Gaby AR. Adverse effects of dietary fructose. Altern Med Rev. 2005;10(4):294-306.
40. Kohen-Avramoglu R, Theriault A, Adeli K. Emergence of the metabolic syndrome in childhood: an epidemiological overview and mechanistic link to dyslipidemia. Clin Biochem. 2003;36(6):413-20.
41. Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. Nutr Rev. 2005;63(5):133-57.
42. Segal MS, Gollub E, Johnson RJ. Is the fructose index more relevant with regards to cardiovascular disease than the glycemic index? Eur J Nutr. 2007;46(7):406-417.
43. Douard V, Ferraris RP. Regulation of the fructose transporter GLUT5 in health and disease. Am J Physiol Endocrinol Metab. 2008;295(2):E227-37.
44. Laville M, Nazare JA. Diabetes, insulin resistance and sugars. Obes Rev. 2009;10 Suppl 1:24-33.
45. Bray GA. Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Adv Nutr. 2013;4(2):220-225
46. Stanhope KL, Schwarz JM, Havel PJ. Adverse metabolic effects of dietary fructose: Results from recent epidemiological, clinical, and mechanistic studies. Curr Opin Lipidol. 2013;24(3):198-206
47. Richelsen B. Sugar-sweetened beverages and cardio-metabolic disease risks. Curr Opin Clin Nutr Metab Care. 2013;16(4):478-84.
48. Moreira PI. High-sugar diets, type 2 diabetes and Alzheimer's disease. Curr Opin Clin Nutr Metab Care. 2013;16(4):440-5
49. Bray GA, Popkin BM. Dietary sugar and body weight: Have we reached a crisis in the epidemic of obesity and diabetes? Diabetes Care. 2014;37(4): 950-956.
50. Macdonald IA. A review of recent evidence relating to sugars, insulin resistance and diabetes. Eur J Nutr. 2016;55(Suppl 2):17-23.
51. Andreu Urra J, Ríos Mozo M. Metabolismo del ácido úrico y diabetes mellitus. Rev Clin Esp 1953;49(3):160-7
52. Johnson RJ, Segal MS, Sautin Y, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr. 2007;86(4):899-906.
53. Wei Y, Wang D, Topczewski F, Pagliassotti MJ. Fructose-mediated stress signaling in the liver: implications for hepatic insulin resistance. J Nutr Biochem. 2007;18(1):1-9.
54. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. Nat Rev Gastroenterol Hepatol. 2010;7(5):251-264.
55. Samuel VT. Fructose induced lipogenesis: from sugar to fat to insulin resistance. Trends Endocrinol Metab. 2011;22(2):60-65.
56. DiNicolantonio JJ, O'Keefe JH, Lucan SC. Added fructose: a principal driver of type 2 diabetes mellitus and its consequences. Mayo Clin Proc. 2015;90(3):372-81.
57. Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev. 2010;90(1):23-46.
58. Tappy L, Mittendorfer B. Fructose toxicity: is the science ready for public health actions? Curr Opin Clin Nutr Metab Care. 2012;15(4):357-361.
59. Wang D, Sievenpiper JL, de Souza RJ, et al. the effects of fructose intake on serum uric acid vary among controlled dietary trials. J. Nutr. 2012;142(5)916-923.
60. Rippe JM, Angelopoulos TJ. Added sugars and risk factors for obesity, diabetes and heart disease. Int J Obes (Lond). 2016;40 Suppl 1:S22-7.
61. Khan TA, Sievenpiper JL. Controversies about sugars: results from systematic reviews and meta-analyses on obesity,

cardiometabolic disease and diabetes. Eur J Nutr. 2016;55(Suppl 2):25-43.
62. Rippe JM, Sievenpiper JL, Lê KA, White JS, Clemens R, Angelopoulos TJ. What is the appropriate upper limit for added sugars consumption? Nutr Rev. 2017;75(1):18-36
63. Tsilas CS, de Souza RJ, Mejia SB, et al. Relation of total sugars, fructose and sucrose with incident type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. CMAJ. 2017;189(20):E711-E720.
64. Rippe JM, Kris Etherton PM. Fructose, sucrose, and high fructose corn syrup: modern scientific findings and health implications. Adv Nutr. 2012;3(5):739-40
65. Higgins JPT, Green S (Eds.). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1. Updated June 2018. Oxford, U.K., Cochrane Collaboration, 2008
66. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. PloS One, 2015;10(10):e0140908.
67. Newton KP, Hou J, Crimmins NA, Lavine JE, Barlow SE, Xanthakos SA, Schwimmer JB. Prevalence of prediabetes and type 2 diabetes in children with nonalcoholic fatty liver disease. JAMA Pediatrics, 2016;170(10), e161971-e161971.
68. Cross KP, Paul RI, Goldman RD. Single-dose dexamethasone for mild-to-moderate asthma exacerbations: Effective, easy, and acceptable. Canadian Family Physician. 2011;57(10):1134-1136.