

Sugar Sweetened Beverages Intake and Risk of Non-Communicable Chronic Diseases in Longitudinal Studies: A Systematic Review and Meta-Analysis with 1.5 Million Individuals

Leonardo Pozza Santos (✉ leonardo_pozza@yahoo.com.br)

Universidade Federal de Pelotas <https://orcid.org/0000-0002-3993-3786>

Denise Petrucci Gigante

Federal University of Pelotas: Universidade Federal de Pelotas

Felipe Mendes Delpino

Federal University of Pelotas: Universidade Federal de Pelotas

Ana Paula Maciel

Federal University of Pelotas: Universidade Federal de Pelotas

Renata Moraes Bielemann

Federal University of Pelotas: Universidade Federal de Pelotas

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Abstract

This study aimed to examine longitudinal associations between sugar-sweetened beverages (SSB) intake and type 2 diabetes, obesity, coronary heart disease and stroke in adults. We performed a systematic review and meta-analysis searching for articles in the *Pubmed*, *Lilacs*, *Web of Science*, *Cochrane*, *Embase*, and *Scopus* databases. After screening of titles and abstracts, 27 longitudinal studies were included for the narrative synthesis with all of them presenting medium or high methodological quality. None of the selected studies were from low-income countries and only three were conducted in middle-income countries. Type 2 diabetes was the most investigated disease – outcome in 15 out of 27 studies. Around 80% of the studies enrolled more than 10,000 individuals in the sample, and almost half of them followed the subjects for less than 10 years. A total of 1.5 million individuals were included in the pooled analyses, and results indicated that SSB intake increased the risk of type 2 diabetes (RR = 1.20; 95%CI. 1.13 – 1.28), obesity (RR = 1.17; 95%CI. 1.10 – 1.25), coronary heart disease (RR = 1.15; 95%CI. 1.06 – 1.25), and stroke (RR = 1.10; 95%CI. 1.01 – 1.19) in adults after adjustment for all potential confounders. Our systematic review and meta-analysis demonstrated that consumption of SSB intake appears to increase the risk non-communicable chronic disease, being the strongest evidence for type 2 diabetes. Actions are needed to be taken to reduce the SSB intake and its consequences worldwide.

Introduction

Non-communicable chronic diseases (NCD) are the leading cause of deaths worldwide [1]–[3], and behavioral risk factors, like unhealthy eating habits, are the main determinants for the development of NCD [4], [5]. Despite the adherence of healthy dietary patterns have recently improved, mainly in high-income countries [6], the consumption of unhealthy food items is still high [6]–[8]. In this context, sugar-sweetened beverages (SSB) are among the unhealthy food items most associated with adverse outcomes, especially with NCD [9]–[12]. SSB are beverages sweetened with different forms of added sugar, including carbonated and non-carbonated soft drinks, fruits and sports drinks, and they are characterized by low nutritional quality [13].

In 2010, almost 200 thousand deaths around the world were attributable to SSB consumption, being type 2 diabetes the leading cause [14]. Singh *et al.* [14] also estimated that the majority of mortality attributable to SSB intake occurred in low- and middle-income countries (LMIC), while high-income countries accounted for a quarter of the total deaths. Since then, the consumption of SSB is apparently decreasing, although the prevalence remains high, mainly in specific sub-groups such as men and younger individuals [15]–[19].

Association between SSB intake and health-related outcomes is well reported in literature. Several investigations have shown that high SSB intake increases the risk of obesity-related diseases [9], [10], [12], [20]. However, the effects of SSB consumption on NCD, like type 2 diabetes, appear to be only partially explained by obesity status, being part of this effect independent of adiposity [11]. Despite the scientific literature regarding the association between SSB consumption and NCD has increased in the last years, the magnitude of the association is quite heterogeneous among studies.

As SSB intake is an important and suitable target for environmental interventions [20], understanding the strength, consistency and biological gradient of the association between SSB consumption and health-related outcomes is important. Based on these evidence, comprehensive approaches to reduce SSB consumption, such as public health interventions and taxation, may be better planned. Therefore, we performed a systematic review and meta-analysis of longitudinal studies with adults to assess the association between SSB intake and NCD, namely type 2 diabetes, obesity, coronary heart disease (CHD) and stroke.

Methods

Search strategy

This study is a systematic review and meta-analysis performed according to the PRISMA statement [21]. We searched studies that observed the association between SSB intake and type 2 diabetes, obesity, CHD or stroke in adults published until December 2020. We considered SSB as any drink with added sugar, such as soft drinks, artificial fruit juices, and sports drinks.

The articles' search was carried out using the *Pubmed*, *Lilacs*, *Web of Science*, *Cochrane*, *Embase*, and *Scopus* databases. The terms used on the articles' search were based on the MeSH terms along with other non-MeSH terms to complement the searching, as following: "soft drinks", "processed juice", "sugar-sweetened drinks", "sugar-sweetened beverage", "fruit juices", "artificially-sweetened soda", "artificially sweetened beverages", "sugar-sweetened soft drinks", "diet soda", "fruit-flavored drinks", "sports and energy drinks", "bottled fruit juices" with the Boolean operator "OR" between the terms, and "AND" "obesity", "coronary disease", "diabetes", "cerebral vascular

accident”, “cerebrovascular accident”, “stroke” and “cerebrovascular disease”, also utilizing “OR” between the terms. This systematic review was registered and approved on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD420212342060).

Inclusion criteria

We included longitudinal studies (cohort) carried out with adults (≥ 20 years old) not belonging to specific groups (individuals with an initial diagnosis of any morbidity or institutionalized, for example) and investigating the association between the intake of one or more types of SSB with at least one of the four outcomes of interest (type 2 diabetes, obesity, CHD and stroke).

Exclusion criteria

Systematic and non-systematic reviews, cross-sectional and intervention studies, and studies with animals or in vitro were excluded. We also excluded those investigations that reported data from dietary patterns without showing results exclusively for sugar sweetened beverages.

Study selection

Two independent reviewers (APM and FMD) conducted the articles’ selection, and, in case of disagreements, the judgment was left to a third one (DPG). After excluding duplicates, the selection started by reading the titles, followed by abstracts, according to the inclusion and exclusion criteria. Finally, the eligible articles were selected from a full reading of the manuscripts. We also evaluated the reference lists of all included articles to identify relevant studies that might not have been initially located.

Meta-analysis

In the meta-analysis, we included studies that evaluated the association between SSB intake and risk of type 2 diabetes, obesity, CHD and/or stroke, and reported data as Odds Ratio (OR), Hazard Ratio (HR) or Relative Risk (RR). We pooled the RR across studies through the DerSimonian and Laird random-effects model [22]. We considered HR values as RR since their results are very similar [23]. ORs were converted into RRs using the following equation: $RR = OR / [(1 - P_o) + (P_o \times OR)]$, in which P_o represents the incidence of the outcome of interest in the nonexposed group [24]. We used the fixed-effects model to calculate article-specific RR for studies that assessed values stratified by sex or different subgroups. In case of missing information for OR, HR or RR in the manuscripts, we contacted authors in two different occasions, with a delay from 30 days between each contact.

For studies assessing the isolated risk of different types of SSB, we included results for the most consumed beverage in the sample under analysis. For all studies, the cut-off point assumed was one or more servings of SSB per day. We considered low/moderate intake one or less portion of SSB per day and the intake of two or more portions of SSB per day was classified as high intake. The HR, OR and RR with the greatest adjustments for confounding were considered as the final effect.

We used the Higgins I^2 test to estimate statistical heterogeneity among studies [25]. This test varies from 0–100% and the higher the values the higher heterogeneity. We used the cut-off points proposed by Higgins *et al.* [26] to classify heterogeneity, considering moderate heterogeneity those values of I^2 between 50% and 74.9% and high heterogeneity when I^2 values were $\geq 75\%$. Analyses were performed through R language utilizing the *Rstudio* program and *miniMeta* package [27].

Quality of evidence and risk of publication bias

The methodological quality of the studies was assessed by two independent reviewers (APM and FMD), using the Newcastle-Ottawa Scale (NOS), which assesses longitudinal studies quality based on sample selection criteria, comparability between groups, and evaluation of exposure or outcome [28]. This scale includes eight items, and each of them receives a star when the study is classified as high quality, except for the comparability item, which can receive two stars when results were adjusted by sex and other factors. Thus, the total NOS scale score varied from 0 to 9. We classified studies which scored less than five points in the NOS with poor quality, those studies with five or six points as medium quality, while articles which scored seven or more points were classified as high-quality studies. Such classification was based on previous published papers [29], [30].

Risk of publication bias was assessed using the funnel plot, and the funnel plot asymmetry was tested using the Egger’s and Begg’s test [31].

Results

Figure 1 summarizes the studies selection process. A total of 18755 titles and abstracts were screened after duplicates have been removed. The screening of titles and abstracts retrieved 98 articles for further consideration. After exclusion of 69 manuscripts which have not met the inclusion criteria, our systematic review included findings from 27 longitudinal studies evaluating the association between SSB intake and type 2 diabetes, obesity, CHD and stroke (Figure 1).

Notwithstanding the 27 included studies have been conducted in 12 different countries, more than a half of them came from United States. In addition, almost all studies were conducted in high-income countries, with only three of them from middle-income countries (China, Thailand, and Mexico). Almost half of the included studies enrolled between 10,000 and 50,000 individuals in the sample. In terms of follow-up period, almost 20% of the selected papers followed their sample for more than 20 years. Finally, type 2 diabetes was the most frequent outcome in the included studies (n=15). Stroke was the outcome in five, while obesity was the outcome in four studies and CHD in three of them (Table 1).

Table 1

Characteristics of the 27 papers selected by systematic review on the longitudinal association between sugar sweetened beverages intake and non-communicable chronic diseases in adults.

Category	Number of studies	%
Year of publication		
Between 2000 and 2010	7	25.9
Between 2010 and 2020	20	74.1
Region		
North America	15	55.6
Europe and Central Asia	6	22.2
South Asia or East Asia and Pacific	5	18.5
Latin America and Caribbean	1	3.7
Country's income level		
High-income	24	88.9
Middle-income	3	11.1
Gender		
Only male	2	7.4
Only female	7	25.9
Both	18	66.7
Sample size		
<10,000	5	18.5
10,000 – 50,000	13	48.2
>50,000	9	33.3
Follow-up duration		
Up to 10 years	13	48.2
10 to 20 years	9	33.3
More than 20 years	5	18.5
Outcome		
Type 2 diabetes	15	55.6
Obesity	4	14.8
Coronary heart diseases	3	11.1
Stroke	5	18.5
Quality assessment (Newcastle-Ottawa Scale)		
Medium	6	22.2
High	21	77.8
Total	27	100.0

Quality assessment

The scores obtained in the NOS varied from 5 to 9. The majority of articles were classified as high-quality studies (21 studies; 77.8%), while six were classified as medium quality. None of the included articles scored less than five points in the NOS. Five studies classified as medium quality did not clearly state about the representativeness of the exposed cohort, five studies did not report on the assessment of outcome and four medium quality studies did not state well the adequacy of follow-up cohorts (Supplementary table 1).

Association between SSB intake and type 2 diabetes

Fifteen investigations assessed the association between SSB intake and diabetes (Table 2). In 13 studies, diabetes was the only outcome [9], [32]–[43], while one study assessed diabetes and weight gain as the main outcomes [44] and another one assessed diabetes and stroke [45]. Results were considerably consistent in showing that SSB intake has been associated with higher risk of type 2 diabetes, since only one study did not find any statistically significant association [32]. Schultze *et al.* [44], Palmer *et al.* [33], de Koning *et al.* [35] and Hirahatake *et al.* [41] showed that the consumption of more than one portion of SSB per day increased the risk of type 2 diabetes in United States, after controlling for several confounders, including dietary intake and body mass index. In addition, study conducted by the InterAct consortium from eight European countries also revealed positive effects of SSB intake on the risk of type 2 diabetes after adjustment for demographic and lifestyle characteristics [9].

Table 2

Description of studies selected by systematic review about the longitudinal effects of sugar sweetened beverages intake on diabetes in adults.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Schulze et al., 2004 United States	Nurses' Health Study II 91,249 women 24 - 44 years 8 years of follow-up	Sugar-sweetened soft drinks Diet soft drinks Fruit juice	≥ 1 sugar-sweetened soft drink/day	Weight gain and diabetes	Age, alcohol intake, physical activity, smoking, BMI, diet, food items associated with soft drink consumption	Total sugar-sweetened soft drinks: (≥ 1 /day) RR 1.83 (1.42 - 2.36) Sugar-sweetened cola (≥ 1 /day) RR 1.87 (1.43-2.45) Fruit punch (≥ 1 /day) RR 2.00 (1.33-3.03)
Montonen et al., 2007 Finland	The Finnish Mobile Clinic Health Examination Survey 4,304 men and women 40 - 69 years 5 years of follow-up	Sugar-sweetened fruit juice (berry) Soft drinks	Intake of different sugars, including sweetened beverages, were calculated and divided into quartiles.	Diabetes	Age, sex, BMI, energy intake, smoking, geographic area, physical activity, family history of diabetes, prudent dietary pattern score, and conservative pattern score	Sugar-sweetened fruit juice Quartile 4 (51g/day) RR 1.56 (1.08-2.26) Soft drinks Quartile 4 (143g/day) RR 1.60 (0.93 - 2.76)
Palmer et al., 2008 United States	The Black Women's Health Study 43,960 women 21 - 69 years 10 years of follow-up	Regular soft drinks 1 can or 12oz bottle (336g) Sugar-sweetened fruit juice 6 oz (168g)	≥ 1 servings day	Diabetes	Age, family history of diabetes, physical activity, smoking, education, dietary glycemic index, coffee intake, red meat, processed meat and fiber cereals	Sugar-sweetened soft drinks 1/day: RR 1.11 (0.96-1.28) ≥ 2 /day: RR 1.24 (1.06 - 1.45) Sweetened fruit juice 1/day: RR 1.17 (1.02-1.33) ≥ 2 /day: RR 1.31 (1.13-1.52)

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Nettleton et al., 2009 United States	Multi-Ethnic Study of Atherosclerosis (MESA) 5,011 men and women 45 - 84 years 6 years of follow-up	Diet soft drinks (diet soft drinks and unsweetened mineral water) Sugar-sweetened soft drinks (sugar-sweetened soft drinks, non-alcoholic beer and sweetened mineral water)	≥ 1 serving/day	Diabetes	Age, sex, race, examination site, energy intake, education, time spent in active and inactive activities during leisure, smoking, regular use of dietary supplements, intake of various foods and nutrients, baseline waist circumference, baseline BMI and change in waist circumference or body weight	There was no association between sweetened beverages and incidence of diabetes (data not shown)
Odegaard et al., 2010 China	Singapore Chinese Health Study 63,256 individuals aged 45-74 years	With sugar: carbonated soft drinks, carbonated drinks Diet: Low-calorie or no-calorie soft drinks and other non-calorie beverages	≥2 servings / week	Diabetes	Age, sex, height, physical activity, smoking, education, nutritional intake, and adiposity measures	Soft drinks (≥2 per week) RR 1.34 (1.17 - 1.52)
de Koning et al., 2011 United States	Health Professionals Follow-Up Study (HPFS) 40,389 men 40 - 75 years 20 years of follow-up	Caffeinated and caffeine-free soft drinks, other sugar-sweetened carbonated beverages and sugar-sweetened non-carbonated beverages Artificially sweetened, caffeinated/caffeine-free and non-carbonated low-calorie beverages Serving: Quartile 1 (never) Quartile 2 (2/month) Quartile 3 (1-4 times/week) Quartile 4 (4.5 times/week to 7.5 times/day)	1 serving/day	Diabetes	Smoking, physical activity, alcohol intake, family history of type 2 diabetes, high blood pressure, use of diuretics, multivitamin intake, diet quality, weight change and adherence to a low-calorie diet, total energy intake and BMI	Total sugar-sweetened beverages (1/day) HR 1.16 (1.08 - 1.25)

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Eshak et al., 2013 Japan	The Japan Public Health Center-based (JPHC) 27,585 men and women 40 - 59 years 10 years of follow-up	Soft drinks (cola, flavored juices and non-100% fruit) 100% fruit juice 100% vegetable juice 1 glass (250ml)	Drinking almost every day (≥ 1 serving/day)	Diabetes	Age, BMI, family history of diabetes, education, occupation, smoking, alcohol intake, history of hypertension, leisure-time physical activity, coffee consumption and green tea intake, intake of some nutrients and total energy intake	Drinking soda almost every day OR 1.79 (1.11 - 2.89) women OR 0.98 (0.68 - 1.42) men
Fagherazzi et al., 2013 France	Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale - European Prospective Investigation into Cancer and Nutrition cohort (E3N Study) 66,118 women 14 years of follow-up	100% fruit juices Sugary drinks (sugar-sweetened/artificially sweetened soft drinks or water with added fruit syrup)	> 359 mL/week of sugar-sweetened beverages	Diabetes	Education, smoking, physical activity, hypertension, hypercholesterolemia, use of hormone replacement therapy, family history of diabetes, self-reported use of antidiabetic drugs, alcohol intake, intake of omega-3 fatty acids, intake of carbohydrates, coffee, fruits, vegetables and consumption of processed meats, total energy intake and Mediterranean dietary pattern	> 359 mL/week of sugar-sweetened beverages HR 1.30 (1.02 - 1.66)
Romaguera et al., 2013 Europe	European Prospective Investigation on Cancer and Nutrition (EPIC-InterAct) 15,374 men and women 16 years of follow-up	Soft drinks, carbonated drinks, isotonic drinks and diluted syrup Juices and nectars 1 glass 8.8 oz (250g)	≥ 1 glass/day	Diabetes	Sex, smoking, alcohol, consumption, education and physical activity, total juices, nectars and soft drinks were mutually adjusted, total energy intake, BMI, waist circumference, presence of hyperlipidemia and hypercholesterolemia, consumption of various food items and Mediterranean diet index	Total sugar-sweetened soft drinks (≥ 1 glass/day) HR 1.21 (1.05, 1.41)

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
O'Connor et al., 2015 UK	The EPIC-Norfolk study 24,653 men and women 40 - 79 years 10.8 years of follow-up	Sugar-sweetened soft drinks Sweetened tea or coffee Beverages with sweetened milk Artificially sweetened beverages and Serving: soft drinks and artificially sweetened beverages, 336 g/day; tea or coffee and sugar-sweetened milk drinks, 280 g/day; fruit juice, 150 g/day	1 serving/day	Diabetes	Age, sex, occupational social class, education, family history of diabetes, physical activity, smoking, alcohol consumption, intake of other sugary drinks and various food items, total energy intake, BMI and waist circumference	Soft drinks (336g/day) HR 1.14 (1.01 - 1.32) Beverages with sweetened milk (280g/day) HR 1.27 (1.09-1.48) Sweetened tea or coffee (280g/day) HR 1.03 (0.99-1.07)
Micha et al., 2017 United States	National Health and Nutrition Examination Surveys (NHANES) 16,620 men and women ≥ 25 years 13 years of follow-up	Sugar-sweetened beverages 8 oz/day	1 serving/day (8oz)	Diabetes CHD Stroke	Sex, age, race, education, energy intake and BMI	Sugar-sweetened beverages in 50-year-olds (8oz/day) RR 1.27 (1.11 - 1.46) diabetes RR 1.26 (1.15 - 1.37) CHD No information on beverages for stroke
Papier et al., 2017 Thailand	Thai Cohort Study (TCS) 39,175 men and women Average age among men (33 y/o) and women (28 y/o) 8 years of follow-up	Any sweetened carbonated beverage or soft drink	≥1 per day	Diabetes	Age, area of residence, education, income, physical activity, consumption of fruits/vegetables, fried foods and alcohol, smoking, hypertension at onset and baseline BMI	Sugar-sweetened soft drinks (≥1 per day) OR 2.4 (1.5 - 3.9) women OR 1.3 (0.9 - 2.1) men

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Drouin-Chartier et al., 2019 United States	Nurses' Health Study (NHS) 76,531 women 30 - 55 years 26 years of follow-up and NHS II 81,597 women 25 - 42 years 22 years of follow-up and Health Professionals' Follow-up Study (HPFS) 34,224 men 40 - 75 years 26 years of follow-up	Sugar-sweetened carbonated or non-carbonated beverages (soda, punch, lemonade, fruit juice or sugar-sweetened iced tea) 100% fruit juice Artificially sweetened beverages Serving: 240ml/day 8 oz	Change from 1 serving/week to 1 serving/day over 4 years	Diabetes	Race, family history of diabetes, physical examination during a 4-year cycle, early menopausal status and postmenopausal hormone level (NHS and NHSII), oral contraceptive use (NHSII), simultaneous change in smoking status, onset and change in level of physical activity, onset and change in alcohol consumption, onset and change in Alternative Healthy Eating Index (AHEI) score, onset and change in intake of water, coffee, tea, milk, sugar-sweetened and artificial beverages, baseline BMI and baseline calorie intake	Sugar-sweetened beverages (1/day) RR 1.15 (0.98 – 1.35)
Hirahatake et al., 2019 United States	Coronary Artery Risk Development in Young Adults (CARDIA) study 4,719 men and women 18 - 30 years 30 years of follow-up	Sugar-sweetened soft drinks and fruit drinks Artificially sweetened beverages e.g., soda and fruit juices sweetened with non-nutritive sweeteners Serving: 8 oz/day	1 serving/day	Diabetes	Education, smoking, dietary behavior, mean energy intake, cumulative physical activity, mean aMED score, baseline BMI, change in weight from baseline to diabetes diagnosis, and end of follow-up	Sugar-sweetened beverages (1 serving/day) HR 1.06 (1.01 – 1.10) (≥2/servings/day) HR 1.27 (0.93– 1.74)
Stern et al., 2019 Mexico	Mexican Teachers' Cohort (MTC) 76,667 women ≥25 years 7 years of follow-up	Sugar-sweetened soft drink (cola-flavored soda or flavored soda) Serving: 355 ml	1 serving/day	Diabetes	Age, region of residence, inventory of household goods, smoking, family history of diabetes, physical activity, food and beverage groups, and baseline BMI	Sugar-sweetened soft drink (1 serving/day) HR 1.27 (1.16 - 1.38)
RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease.						

Studies which analyzed SSB intake in grams, milliliter or ounce instead portion also found positive associations with type 2 diabetes. Four different studies showed an increased risk of type 2 diabetes as increased the consumption of SSB, independent of sociodemographic and nutritional characteristics, with effect measures varying from 1.18 RR to 1.34 HR [37], [38], [40], [45]. One of these studies also adjusted the analyses for waist circumference [38], suggesting that the effects of SSB intake on risk of type 2 diabetes appear to be independent of central adiposity.

The positive effects of SSB intake on the risk of type 2 diabetes was also observed in studies conducted in middle-income countries. Stern *et al.* [42], analyzing data from almost 80,000 women from the Mexican Teachers' Cohort, found that the consumption of one portion of sweetened soft drinks per day increased the hazard of type 2 diabetes in 1.27 times (HR = 1.27; 95C.I. 1.16 – 1.38), after adjusting for several confounders, including dietary intake and body mass index. In 40,000 Chinese Singaporeans, SSB intake increased the risk of type 2 diabetes, independent of lifestyle and dietary confounders [43]. The authors also found that 5-year weight gain was an effect modifier of the association between SSB intake and type 2 diabetes. Finally, data from a cohort study from Thailand [39], observed that SSB intake increased the risk of type 2 diabetes more than two times, independent of demographic and nutritional characteristics. However, positive results were found for women only.

Association between SSB intake and obesity

The effect of SSB intake on obesity status was investigated by four studies with three of them presenting positive associations [46]–[48] and one with null results [49] (Table 3). In the Framingham Heart Study [46], the consumption of one or more soft drinks per day increased the odds of obesity by 31% (OR = 1.31; 95%C.I. 1.02; 1.68), while the consumption of two or more soft drinks per day increased the odds by 50% (OR = 1.50; 95%C.I. 1.06; 2.11). Data from the Korean National Health and Examination Survey [47] showed that men and women who have consumed one or more portion of SSB per day presented higher odds of obesity when compared to those who consumed less than one portion per day. Both studies adjusted analyses for several confounders, but only the first one adjusted for dietary characteristics.

Table 3

Description of studies selected by systematic review about the longitudinal effects of sugar sweetened beverages intake on obesity, coronary heart disease and stroke in adults.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Dhingra et al., 2007 United States	Framingham Heart Study 6,154 men and women Average age 52.9 years 3 years of follow-up	Regular sodas and diet sodas Serving: 12 oz	≥ 1 soft drink/ day	Obesity	Age, sex, physical activity, smoking, dietary intake of saturated fat, trans fat, fiber, magnesium, total calories and glycemic index	Soft drinks (≥ 1 /day) OR 1.31 (1.02 – 1.68) ≥ 2 /day: OR 1.50 (1.06-2.11)
Boggs et al., 2013 United States	Black Women's Health Study 19,479 women 21 - 39 years 14 years of follow-up	Sugar-sweetened soft drinks	≥ 1 sugar-sweetened soft drink/day	Obesity	Age, baseline BMI, vigorous exercise, walking as an exercise, education, geographic region, smoking, alcohol intake, parity and dietary patterns, intake of restaurant-made hamburgers	1/day: HR 1.08 (0.98-1.20) ≥ 2 /day: HR 1.12 (1.00-1.25)
Shin et al., 2018, Korea	Korean National Health and Nutrition Examination Survey 12,112 men and women 35 - 65 years 4 years of follow-up	Sugar-sweetened beverages (soft drinks, fruit juice and sweetened rice drinks)	≥ 1 sugar-sweetened beverage/day	Obesity	Age, energy consumption, family income, education, alcohol consumption, smoking and physical activity	Sugar-sweetened beverages ≥ 1 day: OR 1.59 (1.22 - 2.08) women ≥ 1 day: OR 1.41 (1.13 - 1.76) men

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease; CVD - Cardiovascular disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Garduno-Alanis et al., 2020	The HAPIEE Study 26,634 men and women 45 - 69 years 3 years of follow-up	Sugar-sweetened beverages (soft drinks) Artificially sweetened soft drinks Fruit juice Serving: 200ml	≥1 sugar-sweetened beverage/day	Obesity	Age, sex, education, marital status, smoking, alcohol consumption, physical activity, energy intake, fruit and vegetable consumption and previous diagnoses of chronic diseases such as diabetes, CVD or cancer	Sugar-sweetened beverages (≥1/day) Total sugar-sweetened beverages (≥1/day) Czech Republic OR 0.28 (0.02-0.54) Russia OR 1.38 (0.62-2.15) Poland OR 0.83 (0.29-1.37)
Fung et al., 2009	Nurses' Health Study (NHS) 88,520 women 34 - 59 years 24 years of follow-up	Beverages sweetened with cola sugar, caffeinated and caffeine-free Other carbonated sugar-sweetened beverages Non-carbonated sweetened beverages Artificially sweetened beverages	≥2 servings/day	Coronary disease	Age, smoking, alcohol intake, parental history of myocardial infarction before 60 years of age, physical activity, aspirin use, menopausal status and postmenopausal hormone use, history of hypertension and high cholesterol and alternative healthy eating index (AHEI)	Total sweetened beverages (1 to < 2/day) RR 1.23 (1.06-1.43) (≥ 2/day) RR 1.35 (1.07 - 1.69) Total sugar-sweetened beverages (2/day) RR 1.28 (1.14-1.44)
de Koning et al., 2012	Health Professionals Follow-Up Study (HPFS) 42,883 men 40 - 75 years	Sugar-sweetened cola drinks (caffeinated and caffeine-free) Other sugar-sweetened carbonated beverages Sugar-sweetened non-carbonated beverages (fruit punch, lemonade or fruit drinks) Artificially sweetened beverages Serving: 355 ml (12 oz)	1 serving/day	Coronary disease	Smoking, physical activity, alcohol intake, multivitamin use, family history of CHD, pre-enrollment weight gain, weight loss, adherence to a low-calorie diet,	Total sugar-sweetened beverages (1/day) RR 1.19 (1.11 - 1.28)

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease; CVD - Cardiovascular disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Keller et al., 2020 United States	Harvard Pooling Project (HPP) 284,345 men and women ≥ 35 years	Sugar-sweetened beverages (carbonated/non-carbonated and caffeinated/caffeine-free soft drinks, sports drinks and fruit drinks with any type of added sugar) All types of coffee All types of tea (unsweetened) Unsweetened, whole or low-fat cow's milk 100% fruit juice Artificially sweetened beverages Serving: 355 ml (12 oz)	1 serving/day	Coronary disease	Nutrient intake, total energy intake, BMI, history of hypertension and high cholesterol, smoking, physical activity, education and alcohol consumption	Sugar-sweetened beverages (1/day) Men HR 1.09 (1.02-1.17) Women HR 1.06 (0.97-1.15) Combination of men and women HR 1.08 (1.02 - 1.14)
Bernstein et al., 2012 United States	Nurses' Health Study (NHS) 84,085 women aged 30 to 55 years old 28 years of follow-up and Health Professionals Follow-Up Study (HPFS) 43,371 men 40 - 75 years 22 years of follow-up	Caffeine-free and low-calorie cola Other low-calorie carbonated beverages Sugar-sweetened, caffeinated and caffeine-free cola Other sugar-sweetened carbonated beverages	≥ 1 serving/day	Stroke	Other types of beverages, age, calendar time, various food items and nutrients, physical activity, smoking, menopausal status in women, parental history of early myocardial infarction, multivitamin use, vitamin E supplement use, and aspirin use at least once a week. BMI, energy intake and weight change	Sugar-sweetened beverages (1/day) Men RR 1.08 (0.89-1.32) Women RR 1.14 (1.02-1.27)
Eshak et al., 2012 Japan	43,149 men and women aged 40 to 59 years old 18 years of follow-up	Soft drinks (cola, flavored juices and non-100% fruit juices) Serving: 250g	Nearly daily intake (≥1 glass/day)	Stroke	Age, history of hypertension, history of diabetes, smoking, alcohol intake, leisure-time physical activity, work status, dietary intake quintiles adjusted for energy from selected foods and nutrients, BMI, and total energy intake	Men Stroke HR 0.76 (0.62, 1.06) Women Stroke HR 1.21 (0.88, 1.68)

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease; CVD - Cardiovascular disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Larsson et al., 2014 Sweden	The Swedish Mammography Cohort 32,575 women 49 - 83 years	Sugary drinks (soft drinks and juice) Coffee, tea, milk Serving: 200ml	≥ 1 serving/day	Stroke	Education, family history of early myocardial infarction, smoking, physical activity, history of hypertension, aspirin use, total energy intake, consumption of alcohol and various beverages and food items, and waist circumference	Sugar-sweetened beverages (1 to < 2/day) Women 1.06 (0.88-1.30) Men 1.17 (0.98-1.39) Combination between men and women RR 1.12 (0.99 - 1.28) (≥ 2 /day) Women 1.14 (0.92-1.41) Men 1.22 (1.02-1.45) Combination between men and women RR 1.19 (1.04 - 1.36)
Pase et al., 2017 United States	Framingham Heart Study Offspring 2,888 men and women ≥ 45 years 10 years of follow-up	Sugary beverages (sugar-sweetened soft drinks, fruit juice and fruit drinks) Sugar-sweetened soft drinks (carbonated, with high sugar content, e.g., cola) Artificially sweetened soft drinks Fruit juice	1- 2 servings/day	Stroke	Age, gender, education, total caloric intake, dietary guideline adherence index (DGA), physical activity, smoking, and cardiometabolic variables	Total sugar-sweetened beverages (1- 2/day) HR 1.22 (0.77-1.94) (> 2/day) HR 0.88 (0.42-1.83)

RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease; CVD - Cardiovascular disease.

Author, year, country	Sample	Drinks included	Cut-off point	Outcome	Confounders used in the analysis	Main results
Pacheco et al., 2020 United States	California Teachers Study 106,178 women Average age 51.2 20 years of follow-up	Regular sodas and fruit-based sodas Serving: 355g (12 oz) Sweetened bottled water or iced tea, other beverages with added vitamin C Serving: 237g (8 oz)	≥ 1 serving/day	Stroke	Age, race, socioeconomic status, smoking, alcohol intake, family history of cardiovascular disease, physical activity, aspirin use, multivitamin use, menopausal status and hormone therapy use, oral contraceptive use, history of hypertension, BMI, total energy intake and fruit and vegetable intake	Sugar-sweetened soft drinks (≥ 1/day) HR 1.21 (1.04-1.41)
RR - Relative risk; HR - Hazard ratio; OR - Odds ratio; BMI - Body Mass Index; CHD - Coronary heart disease; CVD - Cardiovascular disease.						

Garduno-Alanis *et al.* [48], analyzing data from the Health, Alcohol and Psychosocial factors in Eastern Europe, found that SSB intake increased the risk of obesity, independent of several confounders, including dietary characteristics as well as medical history of CVD, cancer and diabetes. Interesting to notice that results were only significant in Poland and Russia, but not in Czech Republic.

Association between SSB intake and coronary heart disease

Three longitudinal studies included in our systematic review hypothesized that SSB intake is a risk factor for CHD (Table 3). One study included only women in the sample [50], one study enrolled only men [51], and the other one included both men and women in the sample [52]. The investigation that analyzed data for men and women from the Harvard Pooling Project observed that the intake of more than one portion of SSB per day increased the hazard of CHD (HR = 1.08; 95% C.I. 1.02; 1.14). Stratification by sex revealed that results were significant for men but not for women [52].

In addition, the consumption of two or more portions of SSB per day increased almost 30% the risk of CHD in 90 thousand women from the Nurses' Health Study [50]. The authors adjusted the analyses for several confounders, including lifestyle and nutritional characteristics, and health status. De Koning *et al.* [51], in turn, found that more than one portion of SSB increased by almost 20% the risk of CHD (RR = 1.19; 95% C.I. 1.11 – 1.28) in more than 40 thousand men from the Health Professionals Follow-up Study. The results were also adjusted for several confounders.

Association between SSB intake and stroke

Five studies investigated the association between SSB intake and stroke [53]–[57] (Table 3). Larsson *et al.* [54], analyzing data from the Cohort of Swedish, showed that the consumption of two or more portions of SSB was associated with higher risk of stroke (RR = 1.19; 95% C.I. 1.04; 1.36). Nevertheless, when they stratified results by sex, association was significant for men only (RR = 1.22; 95% C.I. 1.02; 1.36). The authors adjusted the results for several confounders including dietary characteristics and waist circumference, suggesting that the effect of SSB on stroke may be independent of central adiposity.

Bernstein *et al.* [57] and Pacheco *et al.* [56], on the other hand, found significant results for women only. The first study observed that the consumption of one or more portion of SSB increased the risk of stroke only in women (RR = 1.14; 95% C.I. 1.02; 1.27), after 28 years of follow-up [57]. Similarly, one or more portion of SSB per day (more than 355g) increased the hazard of stroke in more than 100,000 women, after adjustment for several confounders, including dietary characteristics and body mass index [56].

Nevertheless, two longitudinal studies did not observed effects of SSB intake on the risk of stroke after controlling for potential confounders in 40,000 men and women from Japan [53] or in almost 3000 men and women from US [55], after 18 and 10 years of follow-up, respectively.

Meta analysis

From the 27 studies selected in the systematic review, 26 were included in our meta-analysis as one investigation did not present OR, HR or RR in results. Figure 2 shows that the grouped effect of SSB on obesity and type 2 diabetes was positive. When obesity was the main outcome analyzed, we observed a positive pooled effect of SSB intake on the risk of obesity in the four studies included in the meta-analysis, with low heterogeneity among them ($I^2 = 36\%$; $p\text{-value} = 0.20$). Results comparing low/moderate intake vs. no intake, and high

intake vs. no intake (available for only two studies) showed that intake of SSB increased the risk of obesity by, on average, 17% (RR = 1.17; 95%CI. 1.10 – 1.25).

We also observed a positive pooled effect of low/moderate intake of SSB on the risk of type 2 diabetes in adults (RR = 1.20; 95%CI. 1.13 – 1.28). From the 14 studies included, eight presented positive results. The I^2 statistics indicated moderate heterogeneity among studies ($I^2 = 70\%$; p-value <0.01). Results comparing high intake vs. no intake (available for 6 out of 14 studies) showed that the pooled effect was even larger: high intake of SSB increased the risk of diabetes by 32% (RR = 1.32; 95%CI. 1.22; 1.44).

In Figure 3, we have the meta-analysis results for the association between SSB intake and CHD as well as stroke. The pooled effect revealed that SSB intake increased the risk of CHD by 15% (RR = 1.15; 95%CI. 1.06 – 1.25), with moderate heterogeneity among the included studies. When stroke was the outcome, the pooled estimates from the five included studies showed that low/moderate intake of SSB increased the risk of stroke by 10 % (RR = 1.10; 95%CI. 1.01 = 1.19), with low heterogeneity among studies ($I^2 = 43\%$; p-value = 0.14). Results comparing high intake vs. no intake (available for only three out of five studies) were not statistically significant.

Risk of bias across studies

Funnel plot (Supplementary figure 1) along with Beeg's and Egger's test showed no evidence of publication bias for the meta-analysis of the effect of SSB intake on diabetes (p-value for Begg & Mamzudar test = 0.87; p-value for Egger's test = 0.046). For the other outcomes analyzed in this study (obesity, CHD and stroke), we were not able to test the risk of bias due to the small number of publications included in the meta-analysis [58].

Discussion

Our systematic review and meta-analysis, which included longitudinal studies with adults, showed considerably consistent results on the association between SSB intake and NCDs. According to the prospective studies included in our review, artificially sugar-sweetened beverages increased the risk of type 2 diabetes, obesity, CHD and stroke, with increased risks of low/moderate SSB intake ranging from 10% for stroke to 20% for type 2 diabetes.

Type 2 diabetes was the outcome presenting the strongest association with SSB intake according to our systematic review and meta-analysis. In fact, this is not the first systematic review showing prospective association between SSB intake and type 2 diabetes. Imamura *et al.* [11] have found that higher consumption of SSB increased the incidence of type 2 diabetes by 18%, with adiposity attenuating this effect (RR = 1.13; 95% C.I. 1.06 to 1.21). The authors also estimated that, over 10 years, two million people developed type 2 diabetes in US and almost 100 thousand in UK due to consumption of SSB [11]. Greenwood *et al.* [59] have found similar results: SSB intake increased the risk of type 2 diabetes by 20% (RR 1.20; 95%CI. 1.12; 1.29), with the risk being attenuated after adjustment for BMI, indicating that adiposity is involved in the causal pathway. In our review, most studies which included type 2 diabetes as the outcome have adjusted results for BMI or waist circumference, and there were not differences among effect measures of studies adjusting or not adjusting analyses by measures of adiposity.

Results for the other outcomes (obesity, CHD and stroke) were less evident in our review, both due to the smaller number of selected studies as well as due to the smaller magnitude of the associations. In consonance with our findings, previous published reviews have already demonstrated that SSB intake is positively associated with weight gain and cardiovascular diseases [12], [13], [60]. Malik *et al.* [60] have found that effects of SSB intake on weight gain is observed not solely in adults, but even in children. The authors showed that an increase of one-serving in SSB intake per day incremented weight gain in 0.12 Kg in adults and BMI in 0.05 Kg/m² in children [60]. In addition, two systematic reviews and meta-analyses of prospective studies have suggested that SSB consumption increases the risk of stroke by 13% (RR = 1.13; 95%CI. 1.02 to 1.24) [61] and the risk of CHD by 17% (RR = 1.17; 95%CI. 1.07 to 1.28) [62], results quite similar to the ones presented in our study.

SSB intake may increase the risk of NCDs by different causal pathways. The first one is through weight gain and excess adiposity caused by excessive daily energy intake [13]. But weight gain and adiposity are not the only causal pathway involved in this relationship, as most studies included in our review have adjusted the results for anthropometric measures, like BMI and waist circumference, and, even so, results remained significant. SSB intake also increases the risk of NCD via high glycemic load, which, in turn, leads to insulin resistance, inflammation and dyslipidemia [13], [63]–[65]. This pathway may help to better understand why the type 2 diabetes was the outcome presenting the strongest association with SSB intake.

Another interesting result evidenced by our study is the lack of investigations on the longitudinal associations between SSB intake and NCD from LMIC. None of the selected studies were conducted in low-income countries and only three in middle-income countries, which is troublesome since LMIC are the settings with the highest burden of deaths attributable to SSB consumption [14]. Estimates for global consumption of SSB with data from 2010 indicated that Latin America and Caribbean, a region comprised by LMIC, presented the highest rates of SSB intake [8]. Moreover, despite there is current evidence of decreasing in SSB intake, trends information on SSB consumption are mostly available for high-income countries with few published data from LMIC.

There is an increasing concern on the standardization of food classification to assess dietary intake in epidemiological studies [66], [67]. Despite the concerning about that, standardized and harmonized protocols to assess SSB intake have not been developed so far. It becomes more evident when we look on the way SSB intake was assessed and categorized in the included studies. While some investigations evaluated only the frequency of consumption, not considering the portion size, other classified consumption in grams, milliliters or ounce.

But even those studies taking portion size into account, the cut-off to define high consumption also varied. In addition, the reviewed studies included different types of SSB, since solely soft drinks up to beverages with sweetened milk, tea, or coffee. It is important to define a standard approach to assess SSB intake in epidemiological studies to make comparisons easier as well as to objectively define a cut-off of SSB intake that indicates health risks at both individual and populational levels.

Finally, we should also consider that more than a half out of the 27 investigations included in our review followed-up the enrolled individuals for less than 10 years. Despite scarce evidence on how long takes for environmental factors, such as dietary intake, induce NCDs [68], [69], studies following individuals for short periods may not have enough time to address the cumulative exposure of SSB intake associated with the onset or the clinical detection of the diseases analyzed. Considering the long latency period of NCD [70], longitudinal studies should have to consider following the sample for longer periods, which is a challenge in the research practice.

Our study has limitations that are important to be mentioned. The first limitation is the possibility of residual confounding, which is common in observational studies [71]. Even though the included studies have adjusted for several confounders like socioeconomic, dietary and body composition characteristics, errors in measuring these characteristics can exist resulting in residual confounding in our meta-analysis. In addition, gray literature, such as academic thesis and conference papers, is more likely to present null results and have not been included here, which can increase the risk of publication bias [72].

As strengths of our systematic review, we can indicate the inclusion of only longitudinal studies, which decreases the risk of reverse causality in the associations investigated. In addition, our systematic review focused in more than one NCD and find similar results for type 2 diabetes, obesity, CHD and stroke, despite differences in the number of included studies for each outcome. This aspect of our study helps to increase the consistency in the association between SSB intake and NCDs.

In conclusion, longitudinal studies with adults demonstrated that consumption of SSB intake appears to increase the risk of type 2 diabetes, obesity, CHD and stroke. The evidence was stronger for type 2 diabetes, and more studies including obesity, CHD and stroke as the main outcome are needed. In addition, longitudinal studies about the association between SSB intake and NCD in LMIC are crucial to better understand this association in these settings. Political programs and actions are important to be developed to reduce the SSB intake and, by consequence, decrease the worldwide incidence of NCD.

Declarations

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Conflict of interest

The authors declare they do not have any conflict of interest.

Availability of data and material

Not applicable.

Author's contribution

LPS: Data analysis, drafting, critical revision and editing of the manuscript. RMB: Proposed the idea, supervision of the project and critical revision of the manuscript. FMD and APM: literature search, data analysis and critical revision of the manuscript. DPG: supervision of the project, literature search and critical revision of the manuscript.

Consent for publication

All authors have read and approved the final version of the manuscript.

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Figures

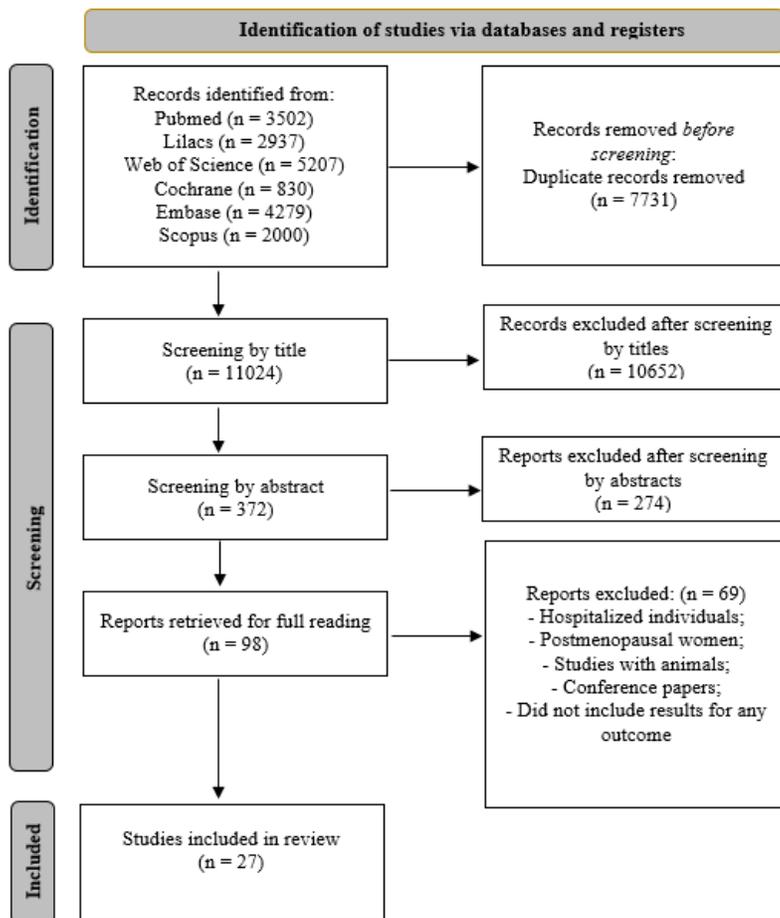


Figure 1

Flow diagram of articles selection stages.

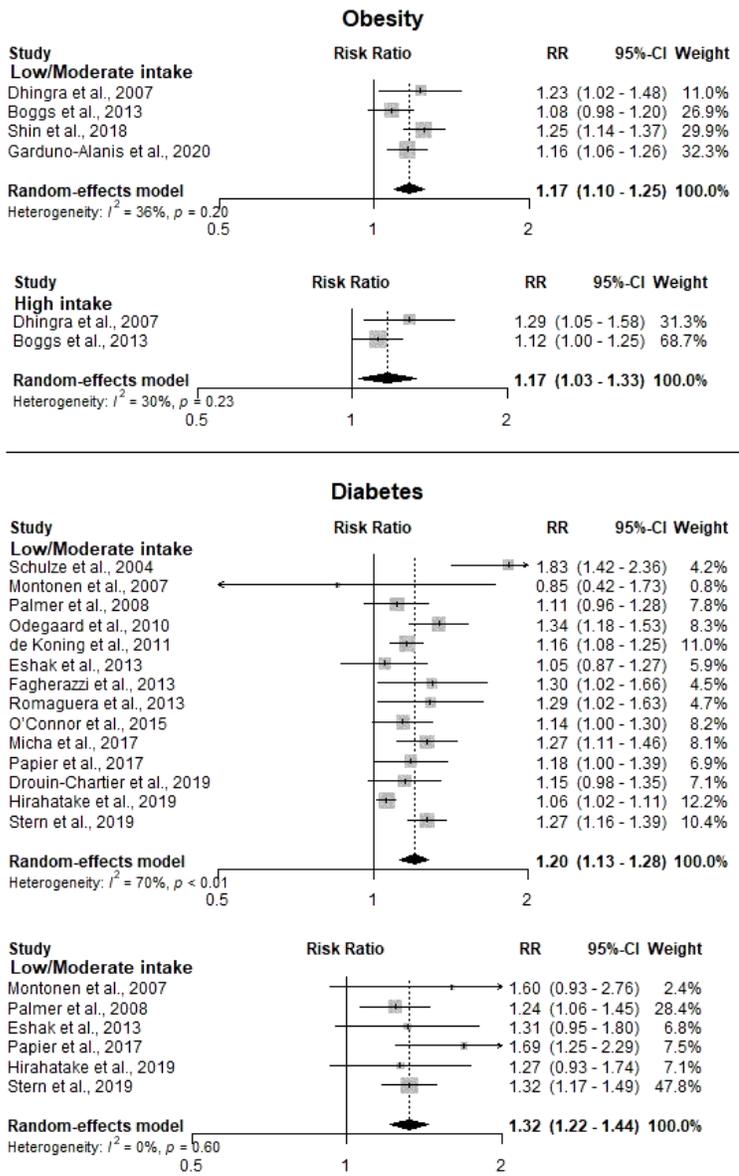


Figure 2

Pooled effect for the association between sugar sweetened beverages intake and obesity and type 2 diabetes among adults.

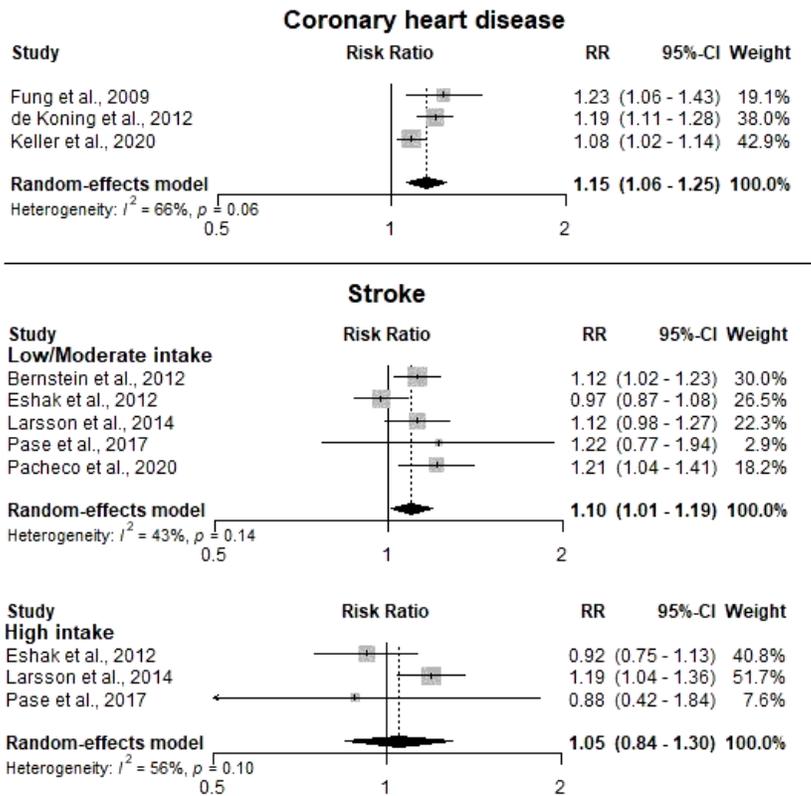


Figure 3

Pooled effect for the association between sugar sweetened beverages intake and coronary heart disease and stroke among adults.

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