



## Revisión

### Sugar-sweetened beverage consumption and obesity in children's meta-analyses: wrong answers to right questions

*Consumo de bebidas azucaradas y obesidad en metaanálisis de estudios realizados en niños: respuestas equivocadas para preguntas correctas*

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#### Abstract

**Background:** recent studies assert that sugar-containing drinks may play a key role in the etiology of obesity. However, scientific reviews show contradictory results. Whether there is just association or clear causation still is a matter of debate. It is also subject to discussion whether the quality/adequacy of the different studies may influence their outcome.

**Objective:** the aim of this study is to explore the most recent scientific evidence focused on sugar-sweetened beverages (SSB) and child obesity and to further analyze the adequacy of the meta-analyses in terms of their results, with special emphasis in the methodology, clarity and transparency of their procedures.

**Methods:** only meta-analyses of randomized control trial studies were selected. The search was performed on PubMed and Cochrane Website until January, 2016. Adherence to PRISMA statement was assessed.

**Results:** six meta-analyses were included. All of them showed some degree of evidence of heterogeneity in their pool estimates. Two of them showed a positive association between SSB and obesity but the other four found no association. The adherence to the PRISMA criteria was higher in two of the meta-analyses that showed opposite conclusions regarding the association or non-association of SSB and obesity in children. Thus, there is no relation between the adequacy of the meta-analyses to the PRISMA criteria and the results obtained.

**Conclusion:** the use of meta-analysis as a scientific tool still demands more polishing, agreement and spread out use by researchers. SSB are being accused of being the main cause of the existing obesity, and obviously they are part of the problem, but this subject requires a broader approach that includes a thorough analysis of diet and lifestyle and a stronger body of scientific evidence based on data from epidemiological studies conducted in different populations.

#### Key words:

Sugar-sweetened beverage. Obesity. Children. Meta-analyses.

#### Resumen

**Antecedentes:** estudios recientes afirman que las bebidas azucaradas desempeñan un papel clave en la etiología de la obesidad. Sin embargo, las revisiones científicas muestran resultados contradictorios. Si es solo una asociación o es claramente una causa continúa siendo un tema de debate. También se discute si la calidad/adequación de los diferentes estudios puede influir en sus resultados.

**Objetivo:** el objetivo de este estudio fue explorar la evidencia científica más reciente enfocada a las bebidas azucaradas y a la obesidad infantil y analizar la adecuación de los metaanálisis en términos de sus resultados, con especial énfasis en la metodología, claridad y transparencia de sus procedimientos.

**Método:** se seleccionaron metaanálisis realizados con estudios de ensayos aleatorios controlados. La búsqueda se realizó en PubMed y en Cochrane hasta enero de 2016. Se evaluó la adherencia a los criterios PRISMA.

**Resultados:** se incluyeron seis metaanálisis. Todos ellos mostraron cierto grado de heterogeneidad en sus estimaciones ponderadas. Dos de ellos mostraron asociación positiva entre bebidas azucaradas y obesidad, pero los otros cuatro no encontraron asociación. La adhesión a los criterios PRISMA fue mayor en dos metaanálisis que mostraron conclusiones opuestas sobre la asociación o no asociación de las bebidas azucaradas y la obesidad en niños. Por lo tanto, no existe relación entre la adecuación de los metaanálisis a los criterios PRISMA y los resultados obtenidos.

**Conclusión:** el uso del metaanálisis como herramienta científica todavía requiere un mayor refinamiento, consenso y difusión por parte de los investigadores. Las bebidas azucaradas están siendo acusadas de ser la causa principal de la obesidad existente, y es obvio que son parte del problema, pero este tema requiere un enfoque más amplio que incluya un análisis exhaustivo de la dieta y del estilo de vida y una evidencia científica más sólida fundamentada en datos de estudios epidemiológicos realizados en diferentes poblaciones.

#### Palabras clave:

Bebidas azucaradas. Obesidad. Niños. Metaanálisis.

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## INTRODUCTION

Although obesity is the result of an imbalance of energy homeostasis, the true mechanisms underlying this process and effective strategies for prevention and treatment remain unknown. In general, obesity reflects complex interactions of genetic, metabolic, cultural, environmental, socioeconomic, and behavioral factors (1). It has been suggested that the intake of sugar-sweetened beverages (SSB) may promote weight gain and obesity by increasing overall energy intake (2).

There are some studies asserting that sugar-containing drinks may play a key role in the etiology of overweight and obesity in children and adults. In Europe, epidemiological studies focusing on beverage intake and obesity are rather scarce (3). Regarding children and adolescents, there are few studies addressing this subject. However, recent scientific reviews show contradictory findings, highlighting the weaknesses of many studies, which describe the current evidence as "not conclusive" (4), "equivocal" (5), "probable" (6) and "strong" (2,7,8).

Although the relation between SSB and obesity exists, whether this is a mere association or a real causation effect still remains controversial if based on current available scientific evidence. Thinking that the raise in childhood obesity occurs due to a single dietary factor, sugary drinks in this case, is a very simplistic approach that underestimates the real problem. Dietary elements work together with a lot of others factors like computer use less physical activity, higher portions sizes, etc. that lead to obesity. Most studies fail to detect how SSD or other aspects of diet and lifestyle have contributed to excess body weight. Whether the effect of sugar and calories from SSBs is worse than the effect of some other food is unclear (9). As Hu (2013) wrote in his article (10), from a public health point of view, identifying dietary determinants of long-term weight gain is critical for reducing the prevalence of obesity in the population. However, for many other scientists dietary determinants are not enough. It is really important to clarify the overall lifestyle involved. As it is well known, obesity is a multifactorial condition. Then, the magnitude of effects depends on the amount and length of exposure. Furthermore, according to Gibson (8), most of the evidence is dominated by American studies where SSD consumption tends to be higher. That may be less applicable to the European context, where consumption is substantially lower.

On the other hand, it is well known that the use of review articles and meta-analysis has become an important method employed in epidemiological research. However, the analysis of published papers in a meta-analysis has several considerable limitations (11). One of those is that studies may differ considerably in their designs, data collection methods and the definition of the exposure and confounder variables. A special dilemma arises when separate studies adjust for different confounding factors. Sometimes, the pooled estimate from a group of studies is published even if strong statistically significant heterogeneity between studies results was found (12).

It is also subject to debate whether the quality and adequacy of the different studies may influence the outcome. It is logical that

when the study is conducted within a rigorous methodological frame, publishing clear results will positively influence the generation of new knowledge and, in consequence, the reliability of reached conclusions will increase. In this sense, there is a new trend of using different tools to assess the methodological aspects of each study to legitimize the quality of the scientific information. Some of these tools are AMSTAR, A Measurement Tool to Assess Systematic Reviews; GRADE, Grading of Recommendations Assessment, Development and Evaluation; and PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (13). These are scales and verification of data quality lists, which differ among one another in terms of their items, validity and scoring system. Most of them are a valuable resource for readers, reviewers and journal editors, but they are in constant update. Then, we must be especially careful when considering their use and when interpreting the resulted information that arises from them.

For all the above reasons, the aim of this study is to explore the most recent scientific evidence focused on SSB and child obesity and to analyze the adequacy of the meta-analyses in terms of their results, with special emphasis on the applied methodology and the clarity/transparency of their procedures. Furthermore, to analyze the possible causes for which a consensus has not yet been found in the scientific evidence available on this topic and why it still remains a source of intense debate.

## MATERIALS AND METHODS

### SYSTEMATIC SEARCH AND SELECTION CRITERIA

We searched the literature for published meta-analyses of epidemiologic studies, whose primary aim was to describe the relation between SSB intake and obesity in children. Only meta-analyses including Random Control Trials (RCTs) were selected. The search was performed accessing PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) and Cochrane Collaborative Website (<http://www.cochrane.org>) between January, 2001 and January, 2016, using the following search terms: "beverage(s)" or "soft drink(s)" or "soda" AND "obesity" or "weight", including MESH-terms. In addition, reference lists of the retrieved articles were searched to find other additional relevant reviews.

Articles were considered as eligible for inclusion if they were: a) systematic reviews and meta-analyses that include at least two RCTs in their study selection; b) studies with a primary focus oriented towards SSB intake and obesity in children. Exclusion criteria were: a) reviews of dietary behaviors or patterns that identified SSB intake as one of many of the factors, but did not study exclusively their impact on body weight; b) systematic reviews and meta-analyses which did not include any RCT study in their analysis; c) articles published prior to the past decade (not earlier) because the discussion regarding the need for a systematic approach to reviewing the literature has evolved, and also a consensus has emerged by which a systematic approach is to be preferred over other more subjective approaches (14).

## DATA ABSTRACTION

A data extraction form was designed to obtain descriptive information of each meta-analysis evaluated, including information of the study population, the RCTs included in each one, specific details of database searches, inclusion and exclusion criteria, heterogeneity of the pooled analyses and conclusions (the final statement on the association between SSB consumption and obesity/weight gain or not), adherence to PRISMA (13), data regarding the journal in which the reviews were published (the impact factor of each one, the year of publication of the article) and industry funding. Those studies which did not specify industry funding of any sort were considered by default as “not supported by the industry”. Authors that received funding for different activities were not taken into account.

In addition, the data obtained from the primary studies included in each review (RCTs) in terms of relation to the outcomes, population studied, type of intervention, conclusions as well as funding were gathered.

## ADEQUACY ASSESSMENT

Among all the assessment tools that have been elaborated during the last few years to assess the adequacy of systematic reviews and meta-analyses, we employed PRISMA (13) adherence. This tool was not designed to become an instrument for evaluating the quality of the articles. It was conceived for enhancing clarity and transparency of published systematic reviews and meta-analyses. It allow to assess whether a step has been completed or not, but not necessarily whether it has been done in the correct way (<http://www.prisma-statement.org>). It comprises 27 items; each of them has an assigned value of 1 for “yes”, 0 for “no” and 0.5 for cases in which the answer is “partial”.

## RESULTS

In total, six meta-analyses were included in our study. The main characteristics of the reviews are presented in table I. Malik et al., Forshee et al., Vartanian et al. and Mattes et al. (7,15-17) documented their search strategies and the inclusion and exclusion criteria. All meta-analyses performed their searches in more than one database, with at least one of them being in either Medline or PubMed, and a second source was also searched (either a database or hand-searched reference lists). Three meta-analyses (15,17,18) included a flowchart of the “study search and selection process” as recommended by PRISMA. A test of heterogeneity was developed in all the studies. The  $I^2$  index, which measures the extent of the heterogeneity following with a p-value for this statistic, was showed in most of the studies. Substantial heterogeneity was present in most of the cases (it means a high  $I^2$  index and a p-value for this  $I^2$  lower than 0.05). When the  $I^2$  Index was low, the p-value did not show statistical significance. This situation indicated the presence of heterogeneity, which somewhat compromises the validity of the

pooled estimates (19). Only Vartanian study (7) showed heterogeneity as a Q statistics value, and in this case it was low.

Table II depicts adherence to PRISMA (11) percentages. Similarly to the results obtained by Bes Rastrollo et al. study (20), only two systematic reviews (15,18) which specifically used PRISMA guidelines to report their data were identified. Adherence to PRISMA guidelines (13) was 85% and 94%, respectively. In other studies, such as Mattes et al., Kaiser et al., Forshee et al. or Vartanian et al. (7,16,17,21), adherence to PRISMA was 83%, 74%, 72% and 50%, respectively. The last two papers were published before PRISMA (13) was routinely used, but back then, there was a similar available tool called QUORUM.

Two of the articles included found a positive association between SSB and obesity (7,15). On the other hand, four articles found no association between SSB and obesity (16-18,21).

Table III shows the data obtained from the primary studies (RCTs) included in each review. Of all RCTs, only two authors were included in all six meta-analyses (22,23) and one author was included in four meta-analyses (24). Three meta-analyses (7,18,21) included RCTs which were not considered in any other meta-analysis (25-32). In some of these RCTs, authors studied different variables, conducted different interventions in different populations, and also some of them did not include a study-drop-outs analysis, nor did assessed compliance among other sources of heterogeneity. Most of the included studies lacked long term follow-up, keeping usually less than ten weeks long, suggesting the need of longer term data to conduct further analysis.

## QUALITY OF META-ANALYSIS

Some authors recently reviewed the quality of SR on SSB and some health outcomes using the validated instrument AMSTAR, which is a one-page tool with eleven questions. Weed et al. (33) concluded that “the comprehensive reporting of epidemiologic evidence and use of systematic methodologies to interpret evidence was underused in published reviews on SSB and health”. They suggest a dubious quality in the currently available scientific evidence in this area with the exception of a few studies. Massougoudji et al. (34) concluded that “there is no consensus on the strength of the evidence on causality, and that available quality-assessment tools have limitations, and many contextual factors beyond the intrinsic characteristics of the reviews may influence their conclusions”.

According to the analyses of Keller et al., the quality of the original papers or RCTs included in the reviews or meta-analyses could have suffered from some bias that may hence also introduce some errors (35).

## DISCUSSION

Our findings indicated that, opposed to our expectations, there is no clear relation between the adequacy of the meta-analyses (using PRISMA criteria) and the results reached.

Table I. Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Kaiser et al. 2013 (21)	Children/ adolescents and adults	<p>Databases searched: PubMed, PsycINFO, the Cochrane Collaborative Website, SCOPUS, and Dissertation Abstracts (PROQUEST)</p> <p>RCTs included:                      James et al. 2004                      Ebbeling et al. 2006                      Muñoz 2006 (unpublished data)                      Albala et al. 2008                      Sichiari et al. 2009                      Tate et al. 2012                      De Ruyter et al. 2012                      Ebbeling et al. 2012</p> <p>Inclusion and exclusion:                      Included: a) human trials; b) ≥ 3 weeks duration; c) random assignment to conditions differing only in consumption of SSBs; and d) including a body weight/composition indices (BMI) outcome</p>	<p>Heterogeneity:                      Effect size: 0.06; (95% CI: -0.01, 0.13)  <math>I^2 = 59\%</math> (<math>p = 0.02</math>) in all weight categories                      Effect size: 0.25; (95% CI: 0.13, 0.38)  <math>I^2 = 49\%</math> (<math>p = 0.07</math>) only in subjects with overweight / obese at baseline</p> <p>No positive association between consumption of SSB and obesity or overweight indicators</p> <p>Reducing consumption of SSBs in individuals of all weight categories explains 0.09% of the variance in body weight or BMI change. Among individuals who are overweight or obese at baseline, reducing the consumption of SSBs explains 1.54% of the variance in body weight or BMI change</p> <p>The current evidence for the effects of reducing SSB intake on obesity is equivocal. Well-designed studies are required. Even if statistical significance is ignored, the point estimates of effects on BMI reduction are small, accounting for only 1.5% of the variance observed in those who were overweight at baseline</p>	Yes	Obesity reviews  Impact factor 2013: 6.87	No and yes

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**Table 1 (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated**

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Malik et al. 2013 (15)	Children/ adolescents	<p><i>Databases searched:</i> PubMed (since 1966), EMBASE (since 1947), and the Cochrane library since 1951) databases</p> <p><i>RCTs included:</i> James et al. 2004 Ebbeling et al. 2006 Sichieri et al. 2009 De Ruyter et al. 2012 Ebbeling et al. 2012</p> <p><i>Inclusion and exclusion:</i> <i>Included:</i> a) were original research (not review, abstract, editorial, letter, or commentary); b) were prospective cohort studies or clinical trials conducted in children or adults; c) reported multivariable-adjusted coefficients for the association between SSBs and body weight from prospective cohort studies or the difference in changes in body weight between intervention and control groups from clinical trials; d) did not combine SSBs with other beverages, foods, or lifestyle factors as a composite exposure; and e) had a control group and intervened for at least two weeks in clinical trials</p> <p><i>Excluded:</i> did not consider cross-sectional or ecologic studies</p>	<p><i>Heterogeneity:</i> <math>I^2 = 74.6\%</math> (<math>p = 0.003</math>)</p> <p><i>Positive association</i> in children as well as in adults</p> <p>Non-significant difference in change in BMI from reducing SSB consumption (weighted mean difference [WMD]: -0.17; 95% CI: -0.39, 0.05; <math>I^2 = 74.6\%</math>; <math>p = 0.003</math>) in the random-effects model</p> <p>From the fixed-effects model results were significant (WMD: -0.12; 95% CI: -0.22, -0.02). This difference is likely a result of the random-effects model giving greater statistical weight to smaller studies and having wider CI in the presence of heterogeneity compared with the fixed-effects model</p> <p>Meta-regressions and sensitive analyses were performed: when stratified by intervention modality, they observed a significant weight reduction among the three RCTs that provided non-caloric beverages as substitutes for SSBs: -0.34 (95% CI: -0.50, -0.18; <math>I^2 = 0\%</math>). In contrast, they did not find a significant intervention effect in the two RCTs that used focused school-based education to discourage SSB consumption: 0.01 (95% CI: -0.19, 0.20; <math>I^2 = 59.6\%</math>)</p>	Yes	American Journal of Clinical Nutrition  Impact Factor 2013:6.50	No

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**Table 1 (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated**

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Te Morenga et al. 2012 (18)	Children/ adolescents	<p><i>Databases searched:</i> OVID Medline, Embase, PubMed, Cumulative Index to Nursing and Allied Health Literature, Scopus and Web of Science electronic databases</p> <p><i>RCTs included:</i> Davis et al. 2009 Ebbeling et al. 2006 James et al. 2004 Paineau et al. 2008 Sichieri et al. 2009</p> <p><i>Inclusion and exclusion:</i> <i>Included:</i> English language studies were required to report intake of total sugars, component of total sugars (expressed in absolute amounts or as a % of total energy), or intake of sugar containing foods or beverages, assessed by continuous or categorical variables; and at least one measure of body fatness Adults and children free from acute illness (those with diabetes or other non-communicable diseases in which conditions were regarded as stable could be included) RCT required being of at least two weeks duration, and prospective cohort studies were required to be of at least one year duration <i>Excluded:</i> Animal studies, cross sectional studies, and case-control studies</p>	<p>Used a random effects model for the analysis</p> <p><i>Heterogeneity:</i> <math>I^2 = 82\%</math> (<math>p = 0.001</math>) in all studies included</p> <p><i>No positive association</i></p> <p>Trials conducted in children with recommendations to reduce intake of SSB and food showed no overall change in body weight</p> <p>They found no association between the advice to reduce intake of dietary sugars and change in BMI or BMI z-score in children (0.09, 95% CI -0.14 to 0.32). Significant heterogeneity was observed (<math>I^2 = 82\%</math>, <math>p = 0.001</math>). Excluding the study by Davis et al. (34), which showed a high risk of bias for two or more validity criteria, it did not alter the effect estimate</p>	Yes	British Medical Journal Impact factor 2012: 1.58	No

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Table 1 (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some other considerations	Journal published, impact factor	Industry funding and conflict of interest
Mattes et al. 2011 (17)	Adults and children/adolescents	<p>Databases searched: PubMed, hand-searched references plus four other databases</p> <p>RCTs included (this study only included RCT): James et al. 2004 Ebbeling et al. 2006 James et al. 2007 Sichieri et al. 2009 Albala et al. 2008 Muñoz 2006 (unpublished data)</p> <p>Inclusion and exclusion: Included: randomized controlled trial, ≥ 3-wk duration, in humans. An outcome as weight, BMI, obesity, % body fat or some other indicator of adiposity. No language restriction was applied Excluded: subjects were not pregnant, acutely ill or under severely stressed conditions (e.g., soldiers in field exercises, sugar cane harvesters in intense heat, etc.)</p>	<p>Fixed effects meta-analysis</p> <p>Heterogeneity: I<sup>2</sup> = 0% (p = 0.643) all studies except James et al. 2007 I<sup>2</sup> = 22.36% (p = 0.266) all studies I<sup>2</sup> = 31.23% (p = 0.213) all studies except Muñoz et al. 2006 I<sup>2</sup> = 0% (p = 0.522) all studies except Muñoz et al. 2006 and James et al. 2007 I<sup>2</sup> = 0% (p = 0.529) all studies except Albala et al. 2008 and James et al. 2007</p> <p>No positive association. Data are not conclusive. Six of the trials included in their study showed significant dose-dependent increase in weight among studies that added SSB to the diet but also found no effect on BMI in other six studies which intended to reduce SSB</p> <p>“Current evidence does not support conclusively that consumption of nutritive sweetened beverage (NSB) uniquely contributed to obesity or that reducing their consumption decreases BMI levels in general”</p> <p>The overall estimate of standardized mean difference in BMI was extremely close to zero (-0.037; SE = 0.042; p = 0.378). The CI 95% was -0.120 to 0.046, indicating that the overall effect estimate was not significant. Heterogeneity I<sup>2</sup> = 0.00% not significant (p = 0.643). As a sensitivity analysis, they repeated the meta-analysis in four different ways, but the results were not noticeably different from that of the primary analysis.</p>	<p>Partially</p> <p>Limitations: - Data from adults and children were not taken into account as separate groups</p> <p>The author excluded three RCTs that were included in other of the meta-analyses (Vartanian et al. 2007) because “they were not experiments related to the effects of SSBs on weight or obesity”.</p>	Obesity reviews Impact factor 2011: 6.87	Yes and yes

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**Table 1 (Cont.). Sugar-sweetened beverages and obesity in children and adolescents: characteristics of meta-analyses evaluated**

SR and year of publication	Population group	Databases searched, RCTs included, and inclusion and exclusion criteria	Heterogeneity, some details of methodology and conclusions (meta-analysis estimates)	PRISMA adherence and some others considerations	Journal published, impact factor	Industry funding and conflict of interest
Forshee et al. 2009 (16)	Children/ adolescents	<i>Databases searched:</i> Medline hand-searched references, plus six others databases that contain unpublished scientific studies  <i>RCTs included:</i> Ebbeling et al. 2006 James et al. 2004  <i>Inclusion and exclusion:</i> <i>Included:</i> English language with human subjects < 19 y of age, developed between 1966-2006 <i>Excluded:</i> ecologic and cross-sectional designs	Used both fixed-effects and random-effects models and included both longitudinal and RCT studies without performing a sensitivity analysis excluding longitudinal studies  <i>Heterogeneity:</i> $I^2 = 73.9\%$ ( $p = 0.001$ ) in all studies included (highly significant)  <i>No positive association</i> between consumption of SSB and BMI: "The level of association between SSB intake and BMI in other studies, even that showing statistical significance, was rather small"  "The meta-analysis found that the association between SSB intake and BMI was <i>near zero</i> , based on the current body of scientific evidence" (BMI change per one serving of SSB increase: 0.03, 95% CI: -0.01 to 0.07)	Partially  Limitations - No flow chart - Use of different instruments to assess SSB intake and body weight gain, and to estimate effect sizes  Different units of time were used among the studies	American Journal of Clinical Nutrition  Impact factor 2008: 6.74	Yes (American Beverage Assoc.) and no
Vartanian et al. 2007 (7)	Adults and children/ adolescents	<i>Databases searched:</i> MEDLINE, PsycINFO, Web of Science, and hand-searched references  <i>RCTs included:</i> Tordoff et al. 1990 DiMeglio et al. 2000 Grandjean et al. 2000 Raben et al. 2002 James et al. 2004 Van Wymelbeke et al. 2004 Ebbeling et al. 2006  <i>Inclusion and exclusion:</i> Studies and reviews published up to 2007	<i>Heterogeneity:</i> no $I^2$ data. They use the value of $q = 24.57$ , $p = 0.001$  <i>Positive and strong association</i>  "Recommendations to reduce soft drink consumption are strongly supported by the available science" (overall average body weight effect size: 0.24, 95% CI: 0.18-0.29) ( $p < 0.001$ ; $q = 24.57$ , $p = 0.001$ )  "We found clear associations of soft drink intake with increased energy intake and body weight". This association was, surprisingly, more present in studies that were not funded by the industry than in those that were  They postulate that "future research with a more uniform methodology (ideally experimental designs) would help to clarify the impact of soft-drink consumption on nutrition and health outcomes" and that "intake of SSB was associated with poor nutrition, increased body weight and displacement of more healthy beverages"	No  Limitations: - No forest or funnel plot  No sensitivity analysis or meta-regression	American Journal of Public Health  Impact factor 2007: 3.56	No and no mention



Table II. PRISMA checklist in %

PRISMA Checklist	Malik et al. 2013 (15)	Te Morenga et al. 2012 (18)	Mattes et al. 2011 (17)	Kaiser et al. 2013 (Update of Mattes et al. 2011) (21)	Forshee et al. 2009 (16)	Vartanian et al. 2007 (7)
Yes %	25.5 (94%)	23.5 (85%)	23 (83%)	20 (74%)	19.5 (72%)	13.5 (50%)
No %	1.5 (6%)	3.5 (15%)	4 (17%)	7 (26%)	7.5 (28%)	13.5 (50%)
Grading of association between SSB and Ob	+	-	-	-	-	+

We believe that controlled trials and systematic reviews with inadequate methodology are more prone to bias (36). It is clear that, in this particular issue, the analysis of the methodology developed is not enough to shed light on this task. Otherwise it is not understood how the meta-analyses with the highest and the lowest adherence to PRISMA found a positive association between SSB and obesity in both cases. This very same situation was also detected in the Keller et al. (35) analyses using the AMSTAR analysis of quality. This situation leads us to consider several points.

First of all, small sample sizes, short follow-ups and different dietary measurement tools used are linked to problems in exposure measurements that can influence the direction of the association between SSBs and weight and change research results (35).

Despite we consider that systematic reviews and meta-analyses of RCTs are the “gold standard” of evidence, and furthermore that the PRISMA checklist used for this analysis as a good tool of items guidelines, the statistical methods for pooling data from different sources have to be better implemented in order to minimize heterogeneity between studies. Our work is based on a limited group of meta-analyses and each one of them, in turn, presents a certain degree of heterogeneity, which indicates different features in each of the included studies. This heterogeneity cannot be ignored; quite the opposite, it is mandatory to find out with further research why these differences are present since they may compromise somehow the validity of the pooled estimates. Even, there are authors who claim that a pooled estimate should not be published if heterogeneity between studies is high, and that in many publications of meta-analysis the problem of heterogeneity is not sufficiently assessed (12). As far as we understand, heterogeneity is another ingredient to account for, but in no way we consider that a study with high heterogeneity should not be published. A meta-analysis should just extract a common estimate when it may truly assume that a common parameter exists; otherwise, it would be advisable to use it just to show and highlight the differences between the results of the various studies available, in order to clarify that it is not possible to combine what is so different (37). Even studies with negative results should be taken into account with the same academic value as the ones with positive results; it is important not to forget that negative findings also contribute to the improvement of science.

Another relevant aspect to consider in our analysis is the possible existence of economic interests and their consequent bias when reaching conclusions. The debate over the influences

of corporate sponsorship on research findings has been always highly thrashed out. However, the issue of “funding source” has recently taken on a special interest, particularly in the realm of obesity research. Addressing this issue is of paramount importance especially in the nutrition field, because inexact data may have negative repercussions in general public health. Bes Rastrollo et al. (20) published a survey where financial conflicts of interest and reporting bias regarding the association between SSB and weight gain were analyzed in a series of studies. Their results show that those systematic reviews with stated sponsorship or conflicts of interest with food or beverage companies were five times more likely to report conclusions of negative association between SSB intake and weight gain (or obesity) than those which reported no industry sponsorship nor conflict of interest. Nonetheless, this study did not consider the methodological quality of the meta-analyses, but focused mainly on sponsor influence. To add more confusion to the subject, other authors such as Kaiser et al. (38) states that, “in general, the quality of industry-funded studies seems better than non-industry funded research; there is evidence that shows that industry-funding was associated with higher quality reporting”. Scientific research must always pursue the truth, regardless of financial or other interests. The consequences of reaching biased conclusions may affect directly from health care practitioners to the process of decision-making by health policy institutions, posing a threat for public health. Industry and science need to work together in order to achieve worthwhile goals, especially nowadays when research resources are scarce. Kaiser et al. (38) underline that efforts to increase the overall quality of the scientific literature can be achieved through activities that support high quality in reporting and create transparency. Approaching questions from different perspectives with diverse methods but with a strong ethical commitment may be on the one hand appealing to the industry and, on the other hand, able to produce solid outcomes free of sponsor bias (39). Research funding is beneficial and necessary, and scientist should remain aware of potential bias of all types (38,40). In addition, conflicts of interest are not always related to financial relationships, but can also occur because of personal relationships, academic competition, intellectual passion, or political engagement (41). It is very difficult to identify these types of influences, and we cannot exclude their presence in reviews not funded by industry.

**Table III. Characteristics of the RCTs included in the meta-analysis**

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
DiMeglio and Mattes (29)	2000	Body weight change	7 males and 8 females Age: 22.8 ± 2.73 years	Carbohydrate dietary loads of 1,880 kJ/day were consumed as liquid (soda) or solid (jelly beans) during two four-week periods separated by a four-week washout	Clear positive effect of load of calorically sweetened beverages on subsequent changes in body weight - given soft drinks to consume gained weight over the course of the experiment	Supported by USDA HATCH project (U.S. Department of Agriculture)
Raben et al. (31)	2002	Body weight, fat mass, and blood pressure in overweight subjects	41 subjects (35 women and 6 men; n = 21 for sucrose group and n = 20 for sweetener group) Age: 20-50 y, overweight	For ten weeks, one group received supplemental drinks and foods containing sucrose, while the other group received similar drinks and foods containing artificial sweeteners	Clear positive effect of load of calorically sweetened beverages on subsequent changes in body weight Given soft drinks to consume gained weight over the course of the experiment	Supported by the Danish Research and Development Programme for Food Technology 1990-1994 and Danisco Sugar. Coca Cola (Nordic and Eurasia Divisions), which provided soft drinks for the study
Tordoff and Allewa (28)	1990	Body weight	21 males aged 22.9 ± 0.8 y and 9 females aged 28.2 ± 2.7 y Normal weight	For three weeks, one group received 1,150 g soda sweetened with aspartame or high-fructose corn syrup per day	Positive effect of load of calorically sweetened beverages on subsequent changes in body weight	Supported by the US Department of Agriculture's Competitive Research Grants Program grant 87-CRGR 1-2316
Ebbeling et al. (45)	2006	Body weight: change in BMI (in kg/m <sup>2</sup> )	103 adolescents, aged 13-18 y	For 25 weeks, replacing SSBs with non-caloric beverages + instructions and motivation (decreased consumption)	The beneficial effect on body weight of reducing SSB consumption increased with increasing baseline body weight, offering additional support for American Academy of Paediatrics guidelines to limit SSB consumption	Supported by grants from the National Inst. of Diabetes and Digestive Kidney Diseases, the Charles H. Hood Found., and awarded by the National Inst. of Health to support the General Clinical Research Centre at the Children's Hospital Boston No funding from the food industry
James et al. (22)	2004	Body weight: overweight and obesity (BMI)	644 children, aged 7-11 y	One-year educational intervention program focused on decreasing consumption of carbonated drinks and overweight and obesity	School-based education programme produced a modest reduction in the number of carbonated drinks consumed, which was associated with a reduction in the number of overweight and obese children	Funded from unrestricted educational grants from GlaxoSmithKline, Aventis, and Pfizer and from internal resources within Bourmemouth Diabetes and Endocrine Centre. JJ received a research scholarship from the Florence Nightingale Foundation No funding from the food industry

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Table III (Cont.). Characteristics of the RCTs included in the meta-analysis

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
Van Wymelbeke et al. (32)	2004	Energy balance and hunger ratings	12 men and 12 women, aged 20-25 y	4 beverages contained either sucrose (100 g/l, 1,672 kJ) or intense sweeteners (null energy content) and were flavored with either orange (O) or raspberry (R). Food intake (FI) was measured in the lab during 2-consecutive-day periods, carried out on 10 successive weeks	No statistically significant effect of soft drink consumption on weight gain	Sponsored by SEV, Bourg la Reine, France; the French Ministry of Research and Technology (AGROBIO-Aliments Demail Programme) and the Regional Council of Burgundy (Dijon, France)
Grandjean et al. (30)	2000	Hydration status (body weight, urine and blood)	18 healthy adult males, aged 24-39 y	During 1 week treatment, on four separate occasions, subjects consumed water or water plus varying combinations of beverages Clinical guidelines were used to determine the fluid allowance for each subject Beverages were carbonated, caffeinated caloric and non-caloric colas and coffee Body weight, urine and blood assays were measured before and after each treatment	No statistically significant effect of soft drink consumption on weight gain	Supported by a grant from The Coca-Cola Company
Sichieri et al. (24)	2009	Body weight (BMI)	1,140 children, aged 9-12 y	Educational intervention program focused on decreasing consumption of carbonated drink from March to December 2005	BMI increased slightly in both groups, with no significant difference Only in a subgroup analysis, girls who were overweight at baseline showed a statistically significant reduction in BMI	Supported by the Brazilian National Research Council-CNPq
De Ruyter et al. (46)	2012	Body weight	641 children, aged 7-9 y	During 18-month a double-blind design was used Replacing SSBs with non-caloric beverages (reducing consumption) It was the most rigorous to date	Masked replacement of sugar-containing beverages with non-caloric beverages could reduce weight gain and fat accumulation in normal-weight children	Supported by grants from the Netherlands Organization for Health Research and Development, the Netherlands Heart Foundation, and the Royal Netherlands Academy of Arts and Sciences

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**Table III (Cont.). Characteristics of the RCTs included in the meta-analysis**

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
Ebbeling et al. (23)	2012	Body weight	244 adolescents, aged 14-16 y, conducted exclusively in overweight adolescents	Replacing SSBs with non-caloric beverages during 1 year (reducing consumption)	Examined the sustained effects of their interventions on body weight at 1 year post-intervention. The beneficial effects of the interventions dissipated after the interventions had ended	Supported by grants from the National Inst. of Diabetes and Digestive and Kidney Diseases and from the National Center for Research Resources to the Boston Children's Hospital General Clinical Research Center, the Harvard Catalyst Clinical and Translational Science Center, and the New Balance Foundation
Sichieri et al. (47)	2013	BMI, height, weight	1,134 students, aged 10-11 y	Secondary analysis of a randomized trial of fourth graders followed over 1 year	An adverse effect of SSBs on body weight was found. It confirmed that consumption of SSBs is a significant risk factor for BMI gain. It is a duplicate study population	Funded by a grant from the Brazilian National Research Institute (CNPq) and by a scholarship from the Foundation of Research from Rio de Janeiro State (FAPERJ)
James et al. (48)	2007	BMI, height, weight, and waist circumference	434 children, aged 10-14 y	Educational intervention program focused on decrease consumption of SSB and diet carbonated drink. It was a follow-up analysis of a previous school based intervention (James et al. 2004). The sustained effects of their interventions on body weight at 2 y post-intervention were examined	No significant effects were found. It showed that the beneficial effects of the interventions dissipated after the interventions had ended	Funded by internal resources within the Bournemouth Diabetes and Endocrine Centre. JJ received a research scholarship from the Florence Nightingale Foundation (Band Trust Scholarship)
Albala et al. (49)	2008	Body fat and BMI	98 children, aged 8-10 y	During a 16-week intervention, SSBs were replaced with flavored milk beverages providing 80 kcal and 11 g carbohydrate/serving	No beneficial intervention effect on body weight was found	Supported by a grant from the Fogarty International Center, National Institutes of Health
Muñoz (unpublished data) (50)	2006	BMI	303 university undergraduate students	During 1 month, one group received information on the health risks associated with soda consumption, and the other group, on the obesity risks associated with soda consumption	The intervention program did not affect SSB consumption, so no effect on adiposity would be expected	Doctoral dissertation

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Table III (Cont.). Characteristics of the RCTs included in the meta-analysis

RCT author	Year of publication	Outcome analyzed	Population group	Type of intervention	Conclusion	Funding
Davis et al. (26)	2009	Body composition	68 adolescents, aged 14-18 y	Educational intervention program focused on decrease consumption of carbohydrate during 16 weeks	No significant intervention effects on measured risk factors, with the exception of a beneficial effect on glycemic response to oral glucose, were found	Supported by the National Inst. of Cancer (NCI), University of Southern California Center for Transdisciplinary Research on Energetics and Cancer, the National Inst. of Child Health and Human Development, the Dr Robert C. and Veronica Atkins Found., the National Cancer Inst. (Cancer Control and Epidemiology Research Training Grant), and from NCR/NIH
Paineau et al. (27)	2008	Body weight: change in BMI	1,013 children, mean age 7.7 y	Educational intervention program focused on decreasing consumption of sugar intake for 8 months	Family dietary coaching improves nutritional intake in free-living children and parents, with beneficial effects on weight control in parents	Funded by the French Ministry of Research (2002 Reseau Alimentation Reference Europe 31), and by the ELPAS study's private partners (Avenance Enseignement, the Centre d'Etudes et de Documentation du Sucre, and the Louis Bonduelle Foundation)

Another important element to consider, as mentioned above, is that consumption of SSB is usually associated with an unhealthy lifestyle characterized by a higher caloric intake, less practice of exercise, smoking habit and presence of a poorly balanced dietary pattern. According to Khan et al. (42), sugar content should not be the sole determinant of a healthy diet. There are many other factors in the diet. Rather than just focusing on one energy source, the whole diet should be considered for health benefits (42).

Lastly, unintentional or inadvertent omissions or unclear or misleading statements in research reporting are another source of bias in health research. In this sense, there is now a tendency to reject studies that produce non-significant results. Many authors do not publish their data when it shows negative results to avoid rejection by editors of scientific literature, thus creating a vicious circle. Therefore, a great number of trials have not been published yet. Including all data, regardless of their results (either positive or negative), is imperative in order to increase reliability and, in turn, produce a solid foundation which will support conclusions with more scientific strength. Lack of information may lead to questioning the validity and adequacy of an entire analysis. It is imperative to avoid this kind of publication bias.

In this sense, the lack of a statistically significant result ( $p$ -value  $> 0.05$ ) does not mean that there was no underlying effect: it means that no effect was detected. A small study may not have the power to detect a real difference. As opposite, small responses are less likely to be detected. A study with many replicates might result in a statistically significant result but have a small effect size (and so, perhaps, be unimportant). The importance of an effect size is a biological, physical or social question, and not a statistical one (43).

Evidently, available adherence or quality-assessment tools have limitations, and many contextual factors beyond the intrinsic characteristics of the reviews may influence their results (34). The meta-analysis area still requires more refining, consensus and widespread use by the scientific community (12).

From another point of view, it seems that lowering SSB intake as an isolated measure will not produce a decrease in obesity prevalence (44). The suggestion that SSB consumption is the main cause of obesity cannot explain why overweight and diabetes have also increased in regions with limited intakes of SSB such as Asia and Africa. Therefore, current evidence alone is insufficient to demonstrate such a role in the global obesity epidemic. Many other causal factors should be taken into account as well. The confusing message as several nutrition researchers stand in opposite to others about the available evidence of SSB has turned a purely scientific dialogue into an intensely emotional one (42).

Summarizing, scientists need to practice good science, sponsors must commit to transparency and no influence, media needs to practice responsible scientific journalism, and we all need to base our evaluations on scientific data and not on predetermined opinions rooted in our own emotion-laden bias for or against specific funding sources (40).

Why do we remain incapable of reaching a true consensus regarding this issue? Are there so huge interests that can mask the results so treacherously that could lead us to the other side

of the street? The first step is to firmly underline that funding should not lead to conclusions that are either for or against the industry. To finance must imply to generate a better service and to guarantee the continuity of that service, especially in times of economic crisis as the one that science crosses in the last times. The ethics and professionalism of scientists have nothing to do with financial aid. Ethics and professionalism must always exist with or without funding.

In conclusion, to formally accuse SSB of causing the current obesity pandemic is a narrow approach of this subject. At this point, the evidence currently available is not capable of supporting with strength this relationship. The limited data and the heterogeneity of methods employed make it impossible to reach any conclusion. They surely may contribute to a certain degree. However, better-designed, best quality and longer-term studies and a broader approach that includes a thorough analysis of diet and lifestyle with a stronger body of scientific evidence based on data from epidemiological studies conducted in different populations are needed in order to reach real science-based conclusions to establish this relationship properly.

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## DECLARATION OF INTEREST

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