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a systematic literature review
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Review Article

Sugar-sweetened beverages, vascular risk factors and events: a systematic literature review

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Abstract

Objective: A high intake of sugar-sweetened beverages (SSB) has been linked to weight gain, obesity and type 2 diabetes; however, the influence on CVD risk remains unclear. Therefore, our objective was to summarize current evidence for an association between SSB consumption and cardiovascular risk factors and events.

Design: The article search was performed in August 2013. Two independent researchers performed the article search and selection, data extraction and quality assessment. Eligible studies reported the intake of SSB and one of the following outcomes: change in blood pressure, blood lipid or blood sugar, or CVD events such as stroke or myocardial infarction. Only intervention and longitudinal studies were included.

Subjects: Only studies in adults (aged 18+ years old) were considered.

Results: Two of four prospective studies found clear direct associations between SSB consumption and CHD, while two of three studies, including both men and women, found direct associations between SSB consumption and stroke; however, the association was significant among women only. All included studies examining vascular risk factors found direct associations between SSB consumption and change in blood pressure, blood lipid or blood sugar.

Conclusions: The reviewed studies generally showed that SSB intake was related to vascular risk factors, whereas associations with vascular events were less consistent. Due to a limited number of published papers, especially regarding vascular events, the strength of the evidence is still limited and hence more studies are needed before firm conclusions can be made.

Keywords
Sugar-sweetened beverages
Vascular disease
Review

Dietary carbohydrates are essential for body functions as they are the main source of energy. To ensure a balanced diet, the Institute of Medicine, Food and Nutrition Board recommends that 45–55% of the total energy intake is provided by carbohydrates(1). Added sugar (table sugar) is added to foods and beverages during industrial processing, and hence refers to sugars that are not naturally occurring(2).

Studies show that added sugar (over-) consumption, specifically in the form of sugar-sweetened beverages (SSB), seems to be linked to different harmful health outcomes such as obesity and diabetes(3–5). SSB may also potentially increase the risk of CVD through their high amount of rapidly absorbable carbohydrates that may, via an elevated hepatic de novo lipogenesis, result in hypertension, accumulation of visceral and ectopic fat, and increased TAG and LDL cholesterol (LDL-C) and decreased HDL cholesterol (HDL-C) levels(6,7). The increased glycaemic load caused by a high SSB intake may lead to inflammation, β-cell dysfunction and insulin resistance, as suggested by Malik et al. (2010) who, in their pooled meta-analysis from three prospective cohorts, reported that participants in the highest category of SSB intake had a 20% greater risk of developing metabolic syndrome than those in the lowest category of intake(8). Most previous literature reviews on potential health consequences of a high intake of SSB have focused on obesity, metabolic syndrome or diabetes as their outcome of interest(9–11). Furthermore, of those previous reviews that assessed associations between SSB consumption and CVD risk and events, most were not systematic(3,12,13) or did not

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include a quality assessment of the included studies. For instance, the systematic review by Sonestedt et al. (2012) examined the association between sugar intake (SSB, sucrose and fructose) and type 2 diabetes, CVD and related metabolic risk factors, but included five primary studies (four prospective cohort studies and one randomised controlled trial (RCT)) regarding SSB consumption and CVD, only\(^5\). Furthermore, Althuis and Weed (2013) in their more recent review, which included just four prospective cohort studies on SSB consumption and CHD/stroke, stressed the need for more updated reviews specifically based on results from studies on SSB intake and CHD and stroke\(^14\). Finally, in a recent review of reviews that assessed the quality of published reviews regarding SSB and health, it was concluded that systematic literature reviews assessing the quality of included studies are generally lacking\(^11\).

The primary aim of the present systematic review was therefore to review the results from published studies examining the association between SSB consumption and related vascular events and risk factors until 2013. The secondary aim was to assess the quality of the original papers included in the review using a validated quality assessment tool from the Academy of Nutrition and Dietetics. Finally, we wanted to examine if there was evidence that the association between SSB consumption and CVD was mediated by diabetes, hypertension, BMI or energy intake.

**Method**

**Search methods and terms used**
The literature search was performed through the platforms PubMed/MEDLINE and Web of Knowledge by two independent researchers in August 2013. The terms used for the article search combined key terms for SSB and CVD: Metabolic Syndrome X, Glucose, Insulin, Subcutaneous Fat, Abdominal, Intra-Abdominal Fat, Cardiovascular Diseases, Blood Pressure, Hypertension, Inflammation, Protein, Cholesterol, Triglycerides, Lipoproteins, HOMA, Waist Circumference, Carbonated Beverages, Soda, Dietary Sucrose, Sucrose, Fructose, Sweetening Agents, Glucose, Energy Drinks, Beverages, Adult.

**Selection of articles**
The selection of articles was performed in three steps. First, papers in the database search were selected based on their title. Second and third, all abstracts and full texts of papers identified in the first step were screened by the two researchers. (For further details, see online supplementary material: Expanded Method.)

**Data extraction and quality assessment**
The quality of each study included in the review was independently assessed by the same two researchers who selected the papers using the Academy of Nutrition and Dietetics’ (formerly the American Dietetic Association (ADA)) Quality Criteria Checklist: Primary Search from the *ADA Evidence Analysis Manual* \(^15\). (For further details, see online supplementary material: Expanded Method.)

**Selection criteria**
The following criteria were used to include or exclude articles for this systematic literature review.

**Exposure.** There is no official definition for SSB; however, as a convention, SSB are defined as beverages containing added sugar\(^14,16\). In the present review, SSB include carbonated or non-carbonated sodas, fruit drinks and sport drinks (Fig. 1). The definition of SSB used in each study is given in the online supplementary material, Supplemental Table 1.

**Study design.** Longitudinal and intervention studies were included. Cohort studies had to have a minimum length of follow-up of 1 year and intervention studies had to have a follow-up of at least 4 weeks.

**Outcome.** We included studies looking at SSB consumption in relation to CVD and CVD risk factors such as change in blood pressure (hypertension), HDL-C, LDL-C, TAG, blood glucose and insulin resistance, and in relation to CVD events such as stroke and CHD as they were the only end points that could be reviewed. (For further details, see online supplementary material: Expanded Method.)

**Subjects.** Only studies in adults (aged 18+ years old) were considered.

**Language.** English.

**Article types.** Original articles published up to 31 August 2013.

**Time period.** The article search was performed in August 2013.
Results

The initial literature search resulted in 657 papers. After the titles and abstracts were screened, the full-text papers of forty-two articles were screened for the final inclusion. The evaluation of full-text articles resulted in the inclusion of ten prospective studies and one RCT in the review (Fig. 2). Nine studies included both men and women(17–25), one study included men only(26) and another one women only(27). Most studies were from the USA, one was from Japan(18), one from Spain(25) and another from Denmark(24). The number of participants ranged from 810 to 97 991 among prospective studies, with including more than 30 000 participants(18,19,21,26,27) and five less than 10 000 participants(17,20,22,23,25). The RCT included forty-seven participants(24).

Regarding dietary intake, nine of the eleven included studies assessed it using an FFQ, one used a 24 h recall(23) and the RCT used a 7 d record(24). Among prospective studies, three studies examined change in SSB(23,25,27) and the others used either a single dietary assessment at baseline or a cumulative average of SSB intake collected by multiple FFQ.

In total, five studies examined associations between intake of SSB and vascular events; three of these studies further examined mediating influences of various vascular risk factors. In addition, six studies examined associations between intake of SSB and vascular risk factors.

The list of excluded articles after full-text screening and reasons for exclusion are given in the online supplementary material, Supplemental Table 2. The characteristics of each of the included studies are presented in Tables 1 and 2.

Studies on vascular events

Four papers reported results for CHD, which was defined as fatal and non-fatal myocardial infarction (MI) in three of the papers(17,26,27), and as IHD in one paper(18). One paper reported results for combined vascular events which included stroke, MI and vascular death(17).

Three studies examined baseline (or cumulative average) SSB intake and CHD(17,18,26) and one study examined both baseline SSB intake and change in SSB intake and CHD(27).

Among studies examining baseline (or cumulative average) SSB intake and CHD, de Koning et al. (2012) reported that for each additional serving of SSB, the relative risk (RR) of CHD was 1-19 (95% CI 1-11, 1-26) and Fung et al. (2009) found that women who consumed more than two SSB daily had a 39% greater risk of developing CHD over the following 24 years (RR = 1-39; 95% CI 1-11, 1-75; P < 0·001) compared with women who drank SSB less than once monthly(27). In contrast, the studies by Eshak et al. (2012) and Gardener et al. (2012) did not find any association between baseline SSB intake and CHD(17,18). In their analysis of change of SSB intake and CHD, Fung et al. (2009) found that a 2 servings/d increase in SSB increased the risk of developing CHD by 28% (RR = 1-28; 95% CI 1-14, 1-44; P < 0·001) among women.

Three of five papers reported results for stroke, which were classified either as ischaemic or haemorrhagic or of unknown type, fatal or non-fatal(17–19). All studies examined baseline (or cumulative average) SSB intake and stroke.

Bernstein et al. (2012) reported that women consuming one or more serving of SSB daily were 19% more likely to develop stroke (RR = 1-19; 95% CI 1-00, 1-42) while no significant association was found for men (RR = 1-08; 95% CI 0-82, 1-41)(19). Similarly, a high intake of SSB was also directly associated with an increased risk of stroke for women (hazard ratio (HR) = 1-39; 95% CI 1-01, 1-91; P < 0·01), but an inverse association was found for men (HR = 0·74; 95% CI 0-59, 0-96; P = 0·01), in the study by Eshak et al. (2012)(18). Finally, Gardener et al. (2012) did not find an association between SSB intake and risk of stroke; however, the authors reported a direct association, e.g. that a high SSB consumption was associated with an increased risk of combined vascular events (stroke, MI and vascular death) among healthier subjects (e.g. those without obesity, or a history of diabetes or metabolic syndrome) at baseline. In this subgroup, daily high SSB intake was associated with an increased risk of vascular events of 57% (HR = 1-57; 95% CI 1-05, 2-35)(17).

In summary, of the five identified prospective studies using vascular events as outcomes(17–19,26,27), two found direct associations between SSB consumption and CHD(26,27), two between SSB consumption and stroke(18,19), and another one between SSB consumption and combined vascular events(17).

Studies on mediation of vascular events risk related to sugar-sweetened beverages consumption by vascular risk factors

Three of five studies included potential mediators of the relationships between SSB consumption and vascular events in their statistical analysis (Table 1)(18,19,20).

Diabetes and hypertension

Two studies(19,20) adjusted for diabetes in one of their models and a third study mentioned diabetes as a potential intermediate risk factor in the pathway between SSB
Table 1 Description of studies on SSB intake, mediators and risk of vascular events

<table>
<thead>
<tr>
<th>Reference (authors and date)</th>
<th>Study design</th>
<th>Data set used and country</th>
<th>Gender</th>
<th>No. of participants analysed</th>
<th>Exposure†</th>
<th>Dietary data collection method(s)</th>
<th>Mediators</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Results: association‡ and RR/HR/OR (95% CI)</th>
<th>Mediation analysis</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Koning et al. (2012)</td>
<td>Prospective</td>
<td>HPFS, USA</td>
<td>M</td>
<td>n 42 883</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>DB, HT, TAG, chol</td>
<td>Incident CHD (total and non-fatal)</td>
<td>22 years</td>
<td>+ (RR 1·19 (1·11, 1·26))** (for each additional serving/d)</td>
<td>No effect (DB &amp; HT)</td>
<td>A</td>
</tr>
<tr>
<td>Eshak et al. (2012)(18)</td>
<td>Prospective</td>
<td>Japan Public Health Centre-based cohort I, Japan</td>
<td>M+F</td>
<td>n 39 786</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>EI, BMI</td>
<td>IHD</td>
<td>18 years</td>
<td>(M: HR 1·10 (0·77, 1·57; P = 0·54)) F: HR 0·89 (0·32, 2·45; P = 0·98) (daily intake v. never) + (RR 1·28 (1·14, 1·44) (2 servings/d increase) + (RR 1·39 (1·11, 1·75))** (≥2 SSB/d v. &lt; 1 SSB/month)</td>
<td>No effect (BMI &amp; TEI)</td>
<td>A</td>
</tr>
<tr>
<td>Fung et al. (2009)(27)</td>
<td>Prospective</td>
<td>NHS, USA</td>
<td>F</td>
<td>n 88 520</td>
<td>Change in SSB Baseline SSB</td>
<td>FFQ</td>
<td>DB</td>
<td>CHD</td>
<td>24 years</td>
<td>+ (RR 1·28 (1·14, 1·44)) (daily intake v. never)</td>
<td>No effect (BMI &amp; TEI)</td>
<td>A</td>
</tr>
<tr>
<td>Gardener et al. (2012)(17)</td>
<td>Prospective</td>
<td>Northern Manhattan Study, USA</td>
<td>M+F</td>
<td>n 2564</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>Confounders</td>
<td>MI Combined events (stroke, MI, vascular death)</td>
<td>10 years</td>
<td>+ (women: RR 1·19 (1·00, 1·42))** (men: RR 1·08 (0·82, 1·41)) (daily intake v. never)</td>
<td>Attenuation from RR 1·19 to 1·14 (P &lt; 0·05) (DB &amp; HT) No effect (BMI &amp; TEI)</td>
<td>A</td>
</tr>
<tr>
<td>Bernstein et al. (2012)(16)</td>
<td>Prospective</td>
<td>NHS and HPFS, USA</td>
<td>M+F</td>
<td>n 84 085 (HPFS: n 43 371)</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>DB, HT, EI, BMI</td>
<td>Total stroke</td>
<td>NHS: 28 years HPFS: 22 years</td>
<td>+ (women: RR 1·39 (1·01, 1·91))** (men: HR 0·74 (0·59, 0·96; P = 0·001) (daily intake v. never) x (HR 1·00 (0·65, 1·54) (daily intake v. never)</td>
<td>No effect (BMI &amp; TEI)</td>
<td>A</td>
</tr>
<tr>
<td>Eshak et al. (2012)(14)</td>
<td>Prospective</td>
<td>Public Health Centre-based cohort I, Japan</td>
<td>M+F</td>
<td>n 39 786</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>EI, BMI</td>
<td>Total stroke (ischaemic and haemorrhagic)</td>
<td>18 years</td>
<td>+ (women: RR 1·39 (1·01, 1·91))** (men: HR 0·74 (0·59, 0·96; P = 0·001) (daily intake v. never) x (HR 1·00 (0·65, 1·54) (daily intake v. never)</td>
<td>No effect (BMI &amp; TEI)</td>
<td>A</td>
</tr>
<tr>
<td>Gardener et al. (2012)(17)</td>
<td>Prospective</td>
<td>Northern Manhattan Study, USA</td>
<td>M+F</td>
<td>n 2564</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>Confounders</td>
<td>Total stroke</td>
<td>10 years</td>
<td>+ (women: RR 1·19 (1·00, 1·42))** (men: RR 1·08 (0·82, 1·41)) (daily intake v. never)</td>
<td>Attenuation from RR 1·19 to 1·14 (P &lt; 0·05) (DB &amp; HT) No effect (BMI &amp; TEI)</td>
<td>A</td>
</tr>
</tbody>
</table>

SSB, sugar-sweetened beverages; RR, relative risk; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; NHS, Nurses’ Health Study; M, male; F, female; DB, diabetes; HT, hypertension; chol, cholesterol; EI, energy intake; MI, myocardial infarction; TEI, total energy intake; -, no mediation analysis.

*P < 0·05, **P < 0·01.
†SSB included drinks sweetened with sugar; artificially sweetened beverages and 100% fruit juice were not included.
‡†, direct association; ×, no association; –, inverse association.
Table 2: Description of studies on SSB intake and associations with vascular risk factors

<table>
<thead>
<tr>
<th>Reference (authors and date)</th>
<th>Study design</th>
<th>Data set used and country</th>
<th>Gender</th>
<th>No. of participants analysed</th>
<th>Exposure†</th>
<th>Dietary data collection method(s)</th>
<th>Outcome(s)</th>
<th>Follow-up</th>
<th>Results: association‡ and RR/HR/OR (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension/ high BP</td>
<td>Duffey et al. (2010)[20]</td>
<td>Prospective</td>
<td>CARDIA, USA</td>
<td>M + F</td>
<td>n 2774 Baseline SSB</td>
<td>FFQ + DH</td>
<td>BP</td>
<td>20 years</td>
<td>+ * (RR 1.06 (1.01, 1.12); from one quartile to the next)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Cohen et al. (2012)[21]</td>
<td>Prospective</td>
<td>NHS I and II and HPFS, USA</td>
<td>M + F</td>
<td>n 88,540 Baseline SSB</td>
<td>FFQ</td>
<td>High BP</td>
<td>NHS I: 38 years NHS II: 16 years HPFS: 22 years</td>
<td>+ (HR 1.13 (0.99, 1.27); daily intake v. never)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Dhingra et al. (2007)[22]</td>
<td>Prospective</td>
<td>Framingham Offspring Study, USA</td>
<td>M + F</td>
<td>n 6039 Baseline SSB</td>
<td>FFQ</td>
<td>BP</td>
<td>(OR 1.19 (0.96, 1.44); daily intake v. never)</td>
<td>+ * (decrease of 0.7 (0.12, 1.25) mmHg in SBP and 0.4 (0.02, 0.75) mmHg in DBP)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Chen et al. (2010)[23]</td>
<td>Prospective</td>
<td>PREMIER (intervention study), USA</td>
<td>M + F</td>
<td>n 810 Change in SSB</td>
<td>24 h recall</td>
<td>BP</td>
<td>18 months</td>
<td>+ * (one quartile to the next)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Barrio-Lopez et al. (2013)[24]</td>
<td>Prospective</td>
<td>SUN cohort, Spain</td>
<td>M + F</td>
<td>n 8157 Change in SSB</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>6–8 years</td>
<td>+ ** (OR 1.6 (1.3, 2.1); highest v. lowest quintile)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Mærsk et al. (2012)[20]</td>
<td>RCT</td>
<td>N/A, Denmark</td>
<td>M + F</td>
<td>n 47 Change in SSB</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>6 months</td>
<td>+ * (P &lt; 0.05)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Barrio-Lopez et al. (2013)[25]</td>
<td>RCT</td>
<td>SUN cohort, Spain</td>
<td>M + F</td>
<td>n 8157 Change in SSB</td>
<td>Baseline SSB</td>
<td>7 d dietary record</td>
<td>6 months</td>
<td>+ * (P &lt; 0.05) ( % change from baseline to 6 months SSB v. milk, diet cola, water (data not shown))</td>
<td>A</td>
</tr>
<tr>
<td>TAG</td>
<td>Duffey et al. (2010)[20]</td>
<td>Prospective</td>
<td>CARDIA, USA</td>
<td>M + F</td>
<td>n 2774 Baseline SSB</td>
<td>FFQ + DH</td>
<td>TAG</td>
<td>20 years</td>
<td>+ * (RR 1.06 (1.01, 1.13; P &lt; 0.05) (one quartile to the next)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Dhingra et al. (2007)[22]</td>
<td>Prospective</td>
<td>Framingham Offspring Study, USA</td>
<td>M + F</td>
<td>n 6039 Baseline SSB</td>
<td>FFQ</td>
<td>Hypertriacylglycerolaemia</td>
<td>4 years</td>
<td>+ (OR 1.25 (1.04, 1.51); ≥ 1 SSB/d)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Barrio-Lopez et al. (2013)[25]</td>
<td>RCT</td>
<td>SUN cohort, Spain</td>
<td>M + F</td>
<td>n 8157 Change in SSB</td>
<td>FFQ</td>
<td>Hypertriacylglycerolaemia</td>
<td>6–8 years</td>
<td>+ * (OR 1.7 (1.1, 2.6); highest v. lowest quintile)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Mærsk et al. (2012)[20]</td>
<td>RCT</td>
<td>N/A, Denmark</td>
<td>M + F</td>
<td>n 47 Change in SSB</td>
<td>Baseline SSB</td>
<td>7 d dietary record</td>
<td>6 months</td>
<td>+ * (P &lt; 0.05)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Barrio-Lopez et al. (2013)[25]</td>
<td>RCT</td>
<td>SUN cohort, Spain</td>
<td>M + F</td>
<td>n 8157 Change in SSB</td>
<td>Baseline SSB</td>
<td>7 d dietary record</td>
<td>6 months</td>
<td>+ * ( % change (‰) from baseline to 6 months: SSB 32.7 (8.6) v. milk – 0.301 (8.1), diet cola – 14.1 (8.1), water – 14.2 (7.7); P = 0.001)</td>
<td>A</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Duffey et al. (2010)[20]</td>
<td>Prospective</td>
<td>CARDIA, USA</td>
<td>M + F</td>
<td>n 2774 Baseline SSB</td>
<td>FFQ + DH</td>
<td>HDL-C, LDL-C</td>
<td>20 years</td>
<td>+ * (high LDL-C (RR 1.18 (1.02, 1.36; P &lt; 0.05), low HDL-C (RR 1.06 (1.02, 1.10; P &lt; 0.05) (one quartile to the next)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Dhingra et al. (2007)[22]</td>
<td>Prospective</td>
<td>Framingham Offspring Study, USA</td>
<td>M + F</td>
<td>n 6039 Baseline SSB</td>
<td>FFQ</td>
<td>LDL-C</td>
<td>4 years</td>
<td>+ (OR 1.32 (1.06, 1.64); ≥ 1 SSB/d)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Barrio-Lopez et al. (2013)[25]</td>
<td>RCT</td>
<td>SUN cohort, Spain</td>
<td>M + F</td>
<td>n 8157 Change in SSB</td>
<td>FFQ</td>
<td>HDL-C</td>
<td>6–8 years</td>
<td>+ * (OR 1.0 (0.7, 1.6); highest v. lowest quintile)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Mærsk et al. (2012)[20]</td>
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<td>N/A, Denmark</td>
<td>M + F</td>
<td>n 47 Change in SSB</td>
<td>Baseline SSB</td>
<td>7 d dietary record</td>
<td>6 months</td>
<td>+ * (P &lt; 0.05)</td>
<td>A</td>
</tr>
</tbody>
</table>
Table 2 Continued

<table>
<thead>
<tr>
<th>Reference (authors and date)</th>
<th>Study design</th>
<th>Data set used and country</th>
<th>Gender</th>
<th>No. of participants analysed</th>
<th>Exposure</th>
<th>Dietary data collection method(s)</th>
<th>Outcome(s)</th>
<th>Follow-up</th>
<th>Results: association and RR/HR/OR (95 % CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mærsk et al. (2012)(24)</td>
<td>RCT</td>
<td>N/A, Denmark</td>
<td>M + F</td>
<td>n 47</td>
<td>Intervention</td>
<td>Consumption of 1 litre SSB/d</td>
<td>Cholesterol</td>
<td>6 months</td>
<td>+ (total cholesterol) * (% change (i) from baseline to 6 months: SSB 11.4 (3.2) v. milk 0.634 (3.0), diet cola −5.893 (3.0), water −0.159 (2.8); P = 0.004)</td>
<td>A</td>
</tr>
<tr>
<td>Dhingra et al. (2007)</td>
<td>Prospective</td>
<td>Framingham Offspring Study, USA</td>
<td>M + F</td>
<td>n 6039</td>
<td>Baseline SSB</td>
<td>FFQ</td>
<td>FBG</td>
<td>4 years</td>
<td>+ (OR 1.25 (1.05, 1.48))</td>
<td>B</td>
</tr>
<tr>
<td>Duffy et al. (2010)(26)</td>
<td>Prospective</td>
<td>CARDIA, USA</td>
<td>M + F</td>
<td>n 2774</td>
<td>Baseline SSB</td>
<td>FFQ + DH</td>
<td>FBG</td>
<td>20 years</td>
<td>x (RR 1.00 (0.95, 1.12))</td>
<td>A</td>
</tr>
<tr>
<td>Barrio-Lopez et al. (2013)(28)</td>
<td>Prospective</td>
<td>SUN cohort, Spain</td>
<td>M + F</td>
<td>n 8157</td>
<td>Change in SSB</td>
<td>FFQ</td>
<td>FBG</td>
<td>6–8 years</td>
<td>+ (OR 1.6 (1.1, 2.2)) (highest v. lowest quintile) x (P = 0.05)</td>
<td>A</td>
</tr>
</tbody>
</table>

SSB, sugar-sweetened beverages; RR, relative risk; HR, hazard ratio; BP, blood pressure; RCT, randomised controlled trial; CARDIA, Coronary Artery Risk Development in Young Adults; NHS, Nurses’ Health Study; HPFS, Health Professionals Follow-up Study; SUN, Seguimiento Universidad de Navarra (University of Navarra Follow-up); N/A, not applicable; M, male; F, female; ASB, artificially sweetened beverages; DH, diet history; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; FBG, fasting blood glucose; SDP, systolic blood pressure; DBP, diastolic blood pressure.

*P < 0.05, **P < 0.01.
†SSB included drinks sweetened with sugar; artificially sweetened beverages and 100 % fruit juice were not included.
‡‡, direct association; x, no association.

The six studies that explored associations between SSB and vascular risk factors

Energy intake and BMI

The authors concluded that BMI and total energy intake were not directly associated with the association between SSB intake and vascular risk factors considered hypertension, HDL-C, TAG, glucose and insulin resistance (HOMA-IR) in addition to some obesity outcomes such as visceral adipose tissue (VAT) and subcutaneous abdominal adipose tissue (SAAT) assessment of insulin resistance (HOMA-IR) in addition to some obesity outcomes such as visceral adipose tissue (VAT) and subcutaneous abdominal adipose tissue (SAAT).

The authors further examined change in SSB intake and vascular risk factors over a period of 18 months (VAT and subcutaneous abdominal adipose tissue (SAAT) assessment of insulin resistance (HOMA-IR) in addition to some obesity outcomes such as visceral adipose tissue (VAT) and subcutaneous abdominal adipose tissue (SAAT).

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or high blood pressure. In the study by Duffey et al. (2010), higher SSB intake (from one quartile to the next) was associated with a significant increase in the risk of hypertension (RR=1.06; 95% CI 1.01, 1.12) (20). Dhingra et al. (2007) found that the daily consumption of one or more servings of SSB was associated with increased odds of having developed high blood pressure (OR=1.18; 95% CI 0.96, 1.44) at 4-year follow-up. However, this trend was not statistically significant, and the analysis combined SSB and artificially sweetened beverage consumption (22). In contrast, no concurrent changes in blood pressure were found in the intervention study by Mærsk et al. (2012) which compared the effect of the intake of one litre of SSB with those of milk and artificially sweetened beverages on changes in total fat mass and ectopic fat deposition (24). Similarly, Barrio-Lopez et al. (2013) did not find any significant association between baseline quintile of SSB and any vascular risk factor (25) and only a small significant increase was reported for SBP but not SBP in the study by Chen et al. (2010) (23).

The consumption of one or more servings of SSB daily was found to be associated with increased odds of hypertriglycerolaemia (OR=1.25; 95% CI 1.04, 1.51) and high LDL-C (OR=1.32; 95% CI 1.06, 1.64) over the subsequent four years in the study by Dhingra et al. (2007) (22). In the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study, associations between SSB and 20-year development in HDL-C, LDL-C and TAG concentrations were examined by Duffey et al. (2010). In this latter study the authors reported that, compared with milk or fruit juice consumption, moving from one quartile of SSB intake to the next was associated with attainment of high TAG (RR=1.06; 95% CI 1.01, 1.13; P<0.05), high LDL-C (RR=1.18; 95% CI 1.02, 1.36; P<0.05) and low HDL-C (RR=1.06; 95% CI 1.02, 1.10; P<0.05) levels (20). In a third prospective study looking at change in SSB intake among Spanish men and women, participants who increased their SSB consumption (upper quintile) had significantly higher risk of developing hypertriglycerolaemia (OR=1.7, 95% CI 1.1, 2.6) (25). Finally, Mærsk et al. (2012) found that mean relative change from baseline to 6-month follow-up in TAG (32.7 (SD 8.6) %; P=0.001), total cholesterol (11.4 (SD 3.2) %; P=0.004) and VAT/SAAT (18.1 (SD 6.0) %; P=0.004) was higher in the intervention group who consumed one litre of SSB daily compared with that in the water (TAG: −14.2 (SD 7.7) %; total cholesterol: −0.159 (SD 2.8) %; VAT/SAAT: −3.90 (SD 5.7) %), milk (TG: −0.301 (SD 8.1) %; total cholesterol: −6.634 (SD 3.0) %; VAT/SAAT: −12.5 (SD 6.1) %) and artificially sweetened beverages groups (TAG: −14.1 (SD 8.1) %; total cholesterol: −5.89 (SD 3.0) %; VAT/SAAT: 4.59 (SD 5.5) %) (24).

Impaired fasting blood glucose was directly associated with SSB intake in the study by Dhingra et al. (2007) (OR=1.25; 95% CI 1.05, 1.48) (22) and in the study by Barrio-Lopez et al. (2013) (OR=1.6; 95% CI 1.1, 2.2) (25), but not in the prospective study by Duffey et al. (2010) (20). Finally, no changes in plasma glucose or HOMA-IR were reported by Mærsk et al. (2012) (24).

In summary, six studies using vascular risk factors as outcomes found direct associations between baseline or change in SSB consumption and changes in blood pressure or lipid metabolism (Table 2) (20–25). Whereas when examining baseline SSB intake, one study only found a small direct association with DBP but not SBP (25) and another did not find any significant associations (25).

**Quality of studies**

Among the eleven identified studies, nine were of good quality (quality score: A) and two were of medium quality (quality score: B); see online supplementary material, Supplemental Table 3. None of the studies was classified with a negative quality score. Quality scores were not related to the conclusions of the papers about SSB and CVD. The two studies with a quality score of B were prospective (17,22). They both had non-detailed descriptions of exposure and outcome factors or procedures (17,22), and one study (19) presented some ambiguity regarding outcome definition and measurements. The strength of the evidence was graded as ‘fair’ for the association between SSB and vascular risk factors, and as ‘limited to fair’ for the association between SSB and vascular events as well as for diabetes, hypertension, BMI and energy intake as mediators (see online supplementary material, Supplemental Tables 4 and 5).

**Discussion**

The present review of the literature linking intake of SSB to cardiovascular risk factors and events found weak evidence for a direct association between SSB and vascular events (CHD or stroke). The restricted number of studies as well as the discrepant results for different subgroups in relation to stroke limited the strength of this evidence. However, a high intake of SSB was generally associated with vascular risk factors, e.g. increased blood pressure and hyperlipidaemia. Our findings are in accordance with the results from Malik et al. (2010) who, based on a review of ten studies on cardiovascular risk, concluded that accumulating data suggest a direct association between SSB intake and the development of hypertension, adverse lipid parameters, inflammation and clinical CHD, although the evidence is limited (3). More recently, a systematic review on the impact of SSB on blood pressure from Malik et al. (2014) showed that SSB intake was directly associated with high blood pressure and consequent hypertension (28).

In the present review, most studies related to vascular risk factors found direct associations. The finding of a direct association between SSB and subsequent change in CVD risk factors is further sustained by findings from a recent meta-analysis and two smaller short-term RCT that were not included in the present review as the duration of
the intervention was <4 weeks. The meta-analysis by Huang et al. (2014) of four longitudinal studies on SSB consumption and CHD risk showed that an increase of one serving of SSB daily was associated with a 16% increased risk of CHD and individuals with the highest SSB intake had 17% greater risk of CHD than individuals with the lowest SSB intake (29). The first RCT randomly assigned twenty-nine subjects to six 3-week interventions assessing the effects of SSB consumed in small to moderate quantities on lipid and glucose metabolism, and showed a direct relationship between low to moderate SSB quantities on lipid and glucose metabolism, and showed a consistent relationship between fructose and glucose effects could not be made and more studies examining relationships between fructose or glucose and risk of developing vascular events are needed to determine whether limiting the proportion of fructose in SSB would be an adequate strategy for the prevention of vascular events and other chronic diseases.

In general, the evidence for an association between SSB and stroke seemed stronger for women than for men, with two studies finding a direct association among women and no association among men (18,19). These results are in agreement with the findings from the review by Fried and Rao (2003), who reported that associations between high-glycaemic-index foods, including beverages such as SSB, and higher serum TAG concentrations and risk of CHD were stronger for women (37). The somewhat stronger associations generally seen for women may relate to gender differences in lipid and glucose metabolism as well as hypertension between men and women. Increased CVD risks have been described primarily in postmenopausal women, indeed, premenopausal women have a higher serum TAG concentrations and risk of CHD (37). For stroke, results are two to three times higher among postmenopausal women than for women of the same age who have not yet reached menopause and furthermore seem to exceed the death rates for same-age men (38). (For further details, see online supplementary material: Expanded Discussion.)

The majority of the included studies had a quality score of A, indicating a low bias level. The two studies (17,22) which were graded level B had methodological gaps that may have affected their conclusion. Despite the majority of studies being attributed an A score, the total strength of the evidence was graded 'limited to fair' because of the low number of studies and inconsistent results from different studies. Regarding vascular events in particular, only two studies found a direct association between SSB intake and CHD (26,27) and one study found a direct association for combined vascular events (17). For stroke, results for women were more consistent, although no association was found among the three reviewed studies in general (17,19). Therefore, to strengthen the evidence, more well-designed studies are needed. When only quality A studies are considered, the strength of the evidence increases from 'limited to fair' to 'fair to good' regarding the association between SSB and stroke and decreases from 'limited to fair' to 'limited' regarding the association between SSB and blood glucose. The present review is the first to systematically review published studies on SSB and CVD with a focus on mediation of associations by
differences in risk factors such as blood pressure, blood lipids and blood sugar. Furthermore, the review used a validated quality assessment tool and the grading of the strength of the evidence, which provide a more critical evaluation.

One limitation to our review is the inclusion of only published articles. Publication bias, favouring studies that show an association between SSB and CVD, cannot be excluded and it is possible that the inclusion of unpublished articles and reports would have limited the positive findings further. In addition, most included studies, eight of eleven, were from the USA, and therefore generalisation to other populations of different racial and ethnic backgrounds may not be possible.

The majority of included studies (n 10) assessed dietary intake using an FFQ. Any diet assessment method, including FFQ, is prone to measurement errors or recall bias that might lead to over- or underestimation of dietary intake. Obese people tend to under-report their sugar and fat intakes more than normal-weight individuals and consequently this may have inflated results in some cases. Therefore, studies included in the review might have suffered from such bias.

As with any assessment tool, the quality criteria and the grading of the strength of the evidence checklists of the Academy of Nutrition and Dietetics (former ADA) present some limitations, and our quality assessment approach may hence also introduce some errors. In addition, assessing the degree of the evidence may be subject to interpretation and may consequently introduce some bias. In this regard, the assessment of the quality and strength of the evidence by two independent researchers rather than one limits the opportunity for bias.

Conclusion

The strength of the evidence relating SSB and CVD is still limited. The reviewed papers generally showed discrepant results for the association between SSB intake and vascular events, while the evidence for an association between SSB and vascular risk factors was stronger. However, due to the limited number of studies investigating these associations and the discrepant results, further studies are needed.

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Supplementary material

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References


