

## Systematic Review with Meta-Analysis

# Sugar-sweetened beverages and risk of hypertension and CVD: a dose–response meta-analysis

Bo Xi<sup>1</sup>, Yubei Huang<sup>2</sup>, Kathleen Heather Reilly<sup>3</sup>, Shuangshuang Li<sup>1</sup>, Ruolong Zheng<sup>4</sup>, Maria T. Barrio-Lopez<sup>5,6</sup>, Miguel A. Martinez-Gonzalez<sup>5,7</sup> and Donghao Zhou<sup>8\*</sup>

<sup>1</sup>Department of Epidemiology and Health Statistics, School of Public Health, Shandong University, Jinan, People's Republic of China

<sup>2</sup>Department of Epidemiology and Biostatistics, Tianjin Medical University Cancer Institute and Hospital, Tianjin, People's Republic of China

<sup>3</sup>Independent Consultant, New York, USA

<sup>4</sup>Department of Cardiology, Jiangyin People's Hospital, Jiangyin, People's Republic of China

<sup>5</sup>Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain

<sup>6</sup>Department of Cardiology and Cardiac Surgery, University Clinic of Navarra, Pamplona, Spain

<sup>7</sup>CIBERobn, Instituto de Salud Carlos III, Pamplona, Spain

<sup>8</sup>Department of Endocrinology, Linyi People's Hospital, 27 East part of Jiefang Road, 276003 Linyi, People's Republic of China

(Submitted 11 June 2014 – Final revision received 3 December 2014 – Accepted 4 December 2014 – First published online 4 March 2015)

### Abstract

A number of prospective cohort studies have investigated the associations between consumption of sugar-sweetened beverages (SSB) and the risk of hypertension, CHD and stroke, but revealed mixed results. In the present study, we aimed to perform a dose–response meta-analysis of these prospective studies to clarify these associations. A systematic literature search was conducted using the PubMed and Embase databases up to 5 May 2014. Random- or fixed-effects models were used to calculate the pooled relative risks (RR) with 95% CI for the highest compared with the lowest category of SSB consumption, and to conduct a dose–response analysis. A total of six prospective studies (240 726 participants and 80 411 incident cases of hypertension) from four publications on hypertension were identified. A total of four prospective studies (194 664 participants and 7396 incident cases of CHD) from four publications on CHD were identified. A total of four prospective studies (259 176 participants and 10 011 incident cases of stroke) from four publications on stroke were identified. The summary RR for incident hypertension was 1.08 (95% CI 1.04, 1.12) for every additional one serving/d increase in SSB consumption. The summary RR for incident CHD was 1.17 (95% CI 1.10, 1.24) for every serving/d increase in SSB consumption. There was no significant association between SSB consumption and total stroke (summary RR 1.06, 95% CI 0.97, 1.15) for every serving/d increase in SSB consumption. The present meta-analysis suggested that a higher consumption of SSB was associated with a higher risk of hypertension and CHD, but not with a higher risk of stroke.

**Key words:** Sugar-sweetened beverages: Hypertension: CHD: Stroke: Meta-analysis

Consumption of sugar-sweetened beverages (SSB), including soft drinks, fruit drinks, iced tea, and energy and vitamin water drinks, has increased in the USA and Europe over the past three decades<sup>(1)</sup>. A higher consumption of SSB has been associated with weight gain, obesity<sup>(2)</sup>, the metabolic

syndrome and diabetes<sup>(3)</sup>, which may be attributed to their high energy and sugar content and lack of nutrients.

To date, a few studies have investigated the associations between SSB consumption and the risk of hypertension, CHD and stroke<sup>(4–13)</sup>. However, the results have been inconsistent,

**Abbreviations:** ASB, artificially sweetened beverage; BP, blood pressure; RR, relative risk; SSB, sugar-sweetened beverage.

\* **Corresponding author:** D. Zhou, fax +86 539 8216079, email donghaozhou@163.com

with some reporting a positive association and others finding no relationship. Although two recent systematic reviews<sup>(14,15)</sup> have commented on the associations of SSB consumption with the risk of CVD and hypertension, they did not quantify the associations using a meta-analysis. Thus, it is still unclear whether SSB consumption is associated with cardiovascular risk.

In the present study, we performed a systematic review and meta-analysis of prospective cohort studies to clarify the dose–response associations between SSB consumption and the risk of hypertension, CHD and stroke.

## Materials and methods

### Literature and search strategy

The Meta-analysis of Observational Studies in Epidemiology guidelines were followed for the present study<sup>(16)</sup>. A literature search was performed using databases including PubMed and Embase. The search terms included ‘sugar-sweetened beverages’ (or ‘soft drink’ or ‘soft drinks’ or ‘beverage’ or ‘beverages’ or ‘carbonated soft drinks’ or ‘fruitades’ or ‘fruit drinks’ or ‘sports drinks’ or ‘energy and vitamin water drinks’ or ‘sweetened iced tea’ or ‘punch’ or ‘fruit punch’ or ‘cordials’ or ‘squashes’ or ‘lemonade’ or ‘soda’ or ‘soda-pop’); ‘hypertension’ (or ‘HBP’ or ‘high blood pressure’ or ‘blood pressure’); ‘coronary heart disease’ (or ‘CHD’ or ‘angina’ or ‘ischemic heart disease’ or ‘IHD’ or ‘myocardial ischemia’ or ‘myocardial infarction’ or ‘MI’ or ‘coronary artery disease’ or ‘atherosclerosis’ or ‘cardiovascular disease’ or ‘CVD’ or ‘vascular disease’ or ‘vascular event’); ‘stroke’ (or ‘ischemic stroke’ or ‘cerebral infarction’ or ‘cerebrovascular disease’); and ‘prospective’ (or ‘cohort’ or ‘follow up’ or ‘following’ or ‘longitudinal’ or ‘incidence’). The search strategy is given in detail in the online Supplementary material. The search was limited to studies carried out in human subjects only. The reference lists of retrieved articles were also screened. The literature search was limited to the English language. If more than one article was published on the same cohort, only the study with the largest sample size was included. The literature search was updated on 5 May 2014.

### Inclusion criteria and data extraction

Studies included in the meta-analysis met all the following inclusion criteria: (1) evaluated any association between SSB consumption and the risk of hypertension, CHD or stroke; (2) used a prospective cohort design; (3) provided the amount of SSB consumption, distributions of cases and person-years, and relative risks (RR) or hazard ratios (HR) with 95% CI for at least three exposure categories. The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of study; (4) sex of participants; (5) age distribution of the study population at baseline; (6) average duration of follow-up; (7) number of cases and study population; (8) outcome; (9) RR or HR with 95% CI for all categories of SSB consumption; (10) covariates used in adjustment. To assess the compliance with the inclusion/exclusion criteria, two authors (B. X. and

D. Z.) independently searched and assessed the abstracts and full-text articles. If there was a discrepancy in the screening decision, a third investigator was asked to discuss and resolve it.

The quality of each study was assessed by the Newcastle–Ottawa quality scale (see online Supplementary Table S1)<sup>(17)</sup>, which is a validated scale for non-randomised studies in meta-analyses. This scale assigned a maximum of nine points for each study. The following three broad perspectives are considered: selection of cohorts (four points); comparability of cohorts (two points); ascertainment of the exposure and outcome of interest (three points).

### Statistical analyses

Fixed-effects<sup>(18)</sup> or random-effects<sup>(19)</sup> models, selected on the basis of whether there was a between-study heterogeneity, were used to calculate the pooled RR with 95% CI for the highest compared with the lowest category of SSB consumption. Dose–response analyses were also conducted. The *Q* test and the *I*<sup>2</sup> statistic<sup>(20)</sup> were used to examine between-study heterogeneity. *P* < 0.10 for the *Q* test or *I*<sup>2</sup> > 50% represented significant heterogeneity, and random-effects models were used when significant heterogeneity was present; otherwise, fixed-effects models were used.

The generalised least-squares trend estimation, reported by Greenland & Longnecker<sup>(21)</sup> and Orsini *et al.*<sup>(22)</sup>, was used to calculate study-specific slopes (linear trends) for the dose–response analyses based on the results across the categories of SSB consumption. We extracted data on the amount of SSB consumption, the distribution of cases and person-years, and RR with 95% CI for at least three categories of exposure to SSB. The definition of the median or mean level of SSB consumption in each category of the included studies has been described elsewhere<sup>(23)</sup>. The dose–response results in the forest plots are presented for every one serving/d increment in SSB consumption. Doses reported as servings/week (or month) were converted to servings/d. For example, one serving/week is equal to 1/7, which is approximately 0.143 servings/d. Doses reported as cups/d (or week or month) were treated as servings/d (or week or month), although this may introduce some small degree of inaccuracy. A four-knot restricted cubic spline model was applied to obtain three spline transformations of aggregated SSB intakes. Then, the restricted cubic spline model was nested within the generalised least-squares trend model to obtain the *P* value for non-linearity. We tested the joint null hypothesis that the regression coefficients of the last two spline transformations were all equal to zero<sup>(22,24)</sup>. If the test for the non-linear association was not significant, the simple generalised least-squares trend model without the restricted cubic spline model was used to test the linear hypothesis.

To examine the stability of the present results, we performed influence analysis by exclusion of one study at a time. Meta-regression analyses were used to examine the potential sources of heterogeneity between studies. Begg’s test<sup>(25)</sup> and Egger’s test<sup>(26)</sup> were used to examine publication bias. *P* < 0.05

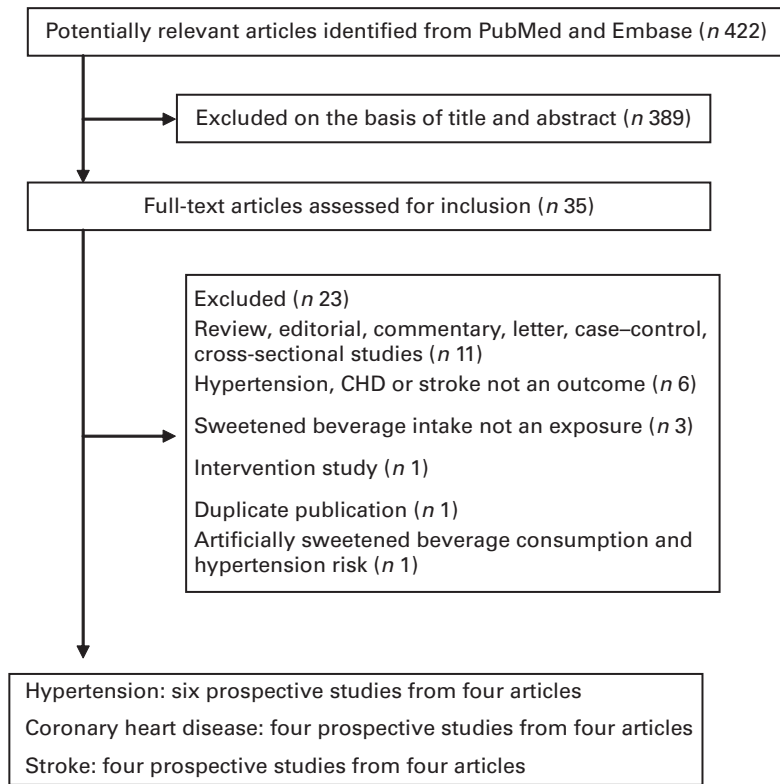


Fig. 1. Flow diagram of the literature search and study selection.

represented statistical significance. All statistical analyses were performed using STATA version 12 (StataCorp LP).

## Results

### Characteristics of the included prospective studies

The results of the literature search are shown in Fig. 1. If the original publications provided several independent studies, they were considered as separate studies in the following data analysis. The duration of follow-up ranged from 6 to 38 years for hypertension, 10 to 24 years for CHD, and 10 to 28 years for stroke. The characteristics of the included prospective studies are listed in Table 1 and online Supplementary Table S1.

### Sugar-sweetened beverage consumption and risk of hypertension

#### Highest v. lowest intake

A total of six prospective studies from four publications, including 240 726 participants and 80 411 incident cases of hypertension, were included in the meta-analysis. The highest intake of SSB was positively associated with the risk of hypertension (random-effects model: RR 1.10, 95% CI 1.06, 1.15,  $P < 0.001$ ; Fig. 2(a)) compared with the lowest level, with significant evidence of heterogeneity ( $I^2 = 46.7\%$ ,  $P = 0.095$ ). In the sensitivity analyses, RR were stable, ranging from 1.11

(95% CI 1.06, 1.16) to 1.16 (95% CI 1.08, 1.24). There was no evidence of publication bias as revealed by Begg's test ( $P = 0.71$ ) and Egger's test ( $P = 0.25$ ).

#### Dose-response analysis

The test for the non-linear association between SSB consumption and the risk of hypertension was not significant ( $P$  for non-linearity = 0.22; Fig. 3(a)). Under the linear hypothesis, a higher consumption of SSB was significantly associated with an increased risk of hypertension (summary RR 1.08, 95% CI 1.04, 1.12). An increase in one serving/d was associated with a higher risk of developing hypertension ( $P$  for trend  $< 0.05$ ).

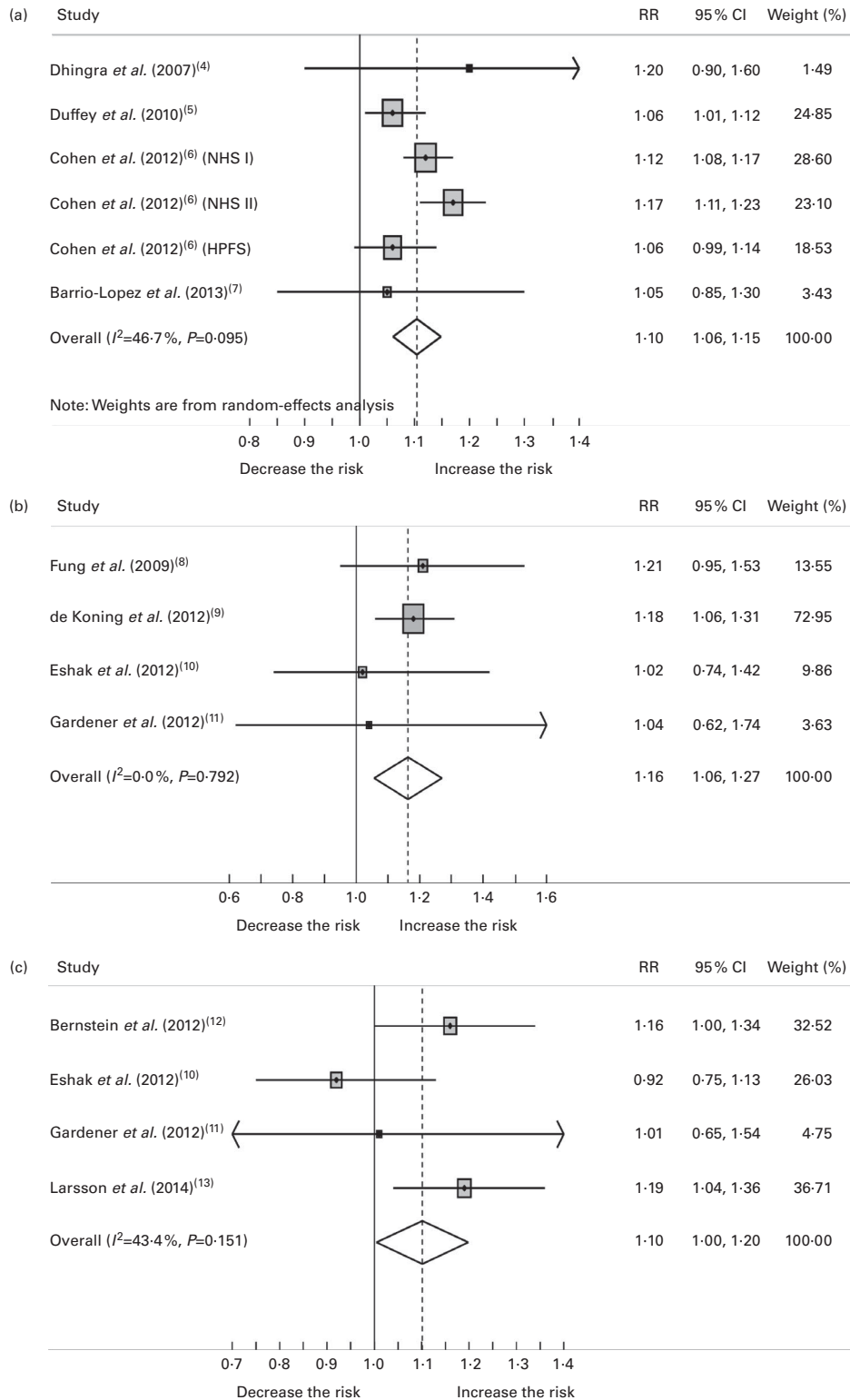
### Sugar-sweetened beverage consumption and risk of CHD

A total of four prospective studies from four publications, including 194 664 participants and 7396 incident cases of CHD, were included in the meta-analysis. An apparent significant association between SSB intake and the risk of CHD was found (RR 1.16, 95% CI 1.06, 1.27) for the highest compared with the lowest consumption of SSB in the fixed-effects model ( $P < 0.001$ ; Fig. 2(b)), with no evidence of heterogeneity ( $I^2 = 0\%$ ,  $P = 0.792$ ). These results were stable after excluding each study at one time, with RR ranging from 1.13 (95% CI 0.94, 1.35) to 1.18 (95% CI 1.07, 1.30). There was no evidence of publication bias as revealed by Begg's test ( $P = 0.31$ ) and Egger's test ( $P = 0.30$ ).

**Table 1.** Characteristics of the included prospective studies examining the association between sugar-sweetened beverage consumption and the risk of hypertension, CHD and stroke

Study	Country	Sex	Baseline age (years)	Participants (n)	Cases (n)	Follow-up period (years)	Case ascertainment	Study quality
<b>Hypertension</b>								
Dhingra <i>et al.</i> (2007) <sup>(4)</sup>	USA	Men and women	Mean 52.9	6039	1004	8	SBP/DBP ≥ 130/85 mmHg or taking anti-hypertensive drugs	7
Duffey <i>et al.</i> (2010) <sup>(5)</sup>	USA	Men and women	Range 18–30	2639	609	20	SBP/DBP ≥ 130/85 mmHg or taking anti-hypertensive drugs	7
Cohen <i>et al.</i> (2012) <sup>(6)</sup> (NHS I)	USA	Women	Range 30–55	88 540	42 022	38	Self-reported but also validated in a subsample	8
Cohen <i>et al.</i> (2012) <sup>(6)</sup> (NHS II)	USA	Women	Range 25–42	97 991	21 873	16	Self-reported but also validated in a subsample	8
Cohen <i>et al.</i> (2012) <sup>(6)</sup> (HPFS)	USA	Men	Range 40–75	37 360	13 439	22	Self-reported but also validated in a subsample	8
Barrio-Lopez <i>et al.</i> (2013) <sup>(7)</sup>	Spain	Men and women	Mean 36	8157	1464	6	SBP/DBP ≥ 130/85 mmHg or taking anti-hypertensive drugs	7
<b>CHD</b>								
Fung <i>et al.</i> (2009) <sup>(8)</sup>	USA	Women	Range 34–59	88 520	3105	24	Medical records	8
de Koning <i>et al.</i> (2012) <sup>(9)</sup>	USA	Men	Range 40–75	42 883	3683	22	Self-reported and validated via medical records	8
Eshak <i>et al.</i> (2012) (men) <sup>(10)</sup>	Japan	Men	Range 40–59	39 786	360	18	Registry and medical records	8
Eshak <i>et al.</i> (2012) <sup>(10)</sup> (women)	Japan	Women	Range 40–59	20 911	93	18	Registry and medical records	8
Gardener <i>et al.</i> (2012) <sup>(11)</sup>	USA	Men	Mean 69 (SD 10)	2564	155	10	Annual check-up	7
<b>Stroke</b>								
Bernstein <i>et al.</i> (2012) <sup>(12)</sup> (HPFS)	USA	Men	Range 40–75	43 371	1416	22	Self-reported and validated via medical records	8
Bernstein <i>et al.</i> (2012) <sup>(12)</sup> (NHS)	USA	Women	Range 30–55	84 085	2938	28	Self-reported and validated via medical records	8
Eshak <i>et al.</i> (2012) <sup>(10)</sup> (men)	Japan	Men	Range 40–59	39 786	1133	18	Registry and medical records	8
Eshak <i>et al.</i> (2012) <sup>(10)</sup> (women)	Japan	Women	Range 40–59	20 911	789	18	Registry and medical records	8
Gardener <i>et al.</i> (2012) <sup>(11)</sup>	USA	Men	Mean 69 (SD 10)	2564	225	10	Annual check-up	7
Larsson <i>et al.</i> (2014) <sup>(13)</sup>	Sweden	Men and women	Range 49–83 (women) and 45–79 (men)	68 459	3510	10.3	Registry	9

SBP, systolic blood pressure; DBP, diastolic blood pressure; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study.



**Fig. 2.** Meta-analysis of the association between sugar-sweetened beverage consumption (highest v. lowest) and the risk of incident (a) hypertension, (b) CHD and (c) stroke.

The subgroup analysis by race suggested that there was a significant association between SSB intake and the risk of hypertension in Caucasians (RR 1.18, 95% CI 1.07, 1.30), but not in East Asians (RR 1.02, 95% CI 0.74, 1.42).

*Dose-response analysis*

The test for the non-linear association between SSB consumption and the risk of hypertension was not significant ( $P$  for non-linearity=0.82; Fig. 3(b)). A higher consumption of SSB

was significantly associated with an increased risk of CHD. For example, one serving/d increase in SSB consumption relatively increased the risk of developing CHD by 17% (RR 1.17, 95% CI 1.10, 1.24,  $P$  for trend <0.001).

### Sugar-sweetened beverage consumption and risk of stroke

A total of four prospective studies from four publications, including 259 176 participants and 10 011 incident cases of stroke, were included in the meta-analysis. The highest intake of SSB was marginally associated with the risk of total stroke (fixed-effects model: RR 1.10, 95% CI 1.00, 1.20,  $P$ <0.05; Fig. 2(c)) compared with the lowest level, with little evidence of heterogeneity ( $I^2 = 43.4\%$ ,  $P=0.151$ ). However, these results were not stable after exclusion of each study at one time, with RR ranging from 1.07 (95% CI 0.95, 1.20) to 1.17 (95% CI 1.06, 1.28). There was no evidence of publication bias as revealed by Begg's test ( $P=0.31$ ) and Egger's test ( $P=0.38$ ).

The subgroup analysis by types of stroke suggested that there were no significant associations between SSB intake and the risk of either ischaemic stroke (RR 1.16, 95% CI 0.93, 1.46) or haemorrhagic stroke (RR 0.86, 95% CI 0.71, 1.04). However, SSB intake was associated with a higher risk of stroke in Caucasians (RR 1.17, 95% CI 1.06, 1.28), but not in East Asians (RR 0.92, 95% CI 0.75, 1.13).

### Dose-response analysis

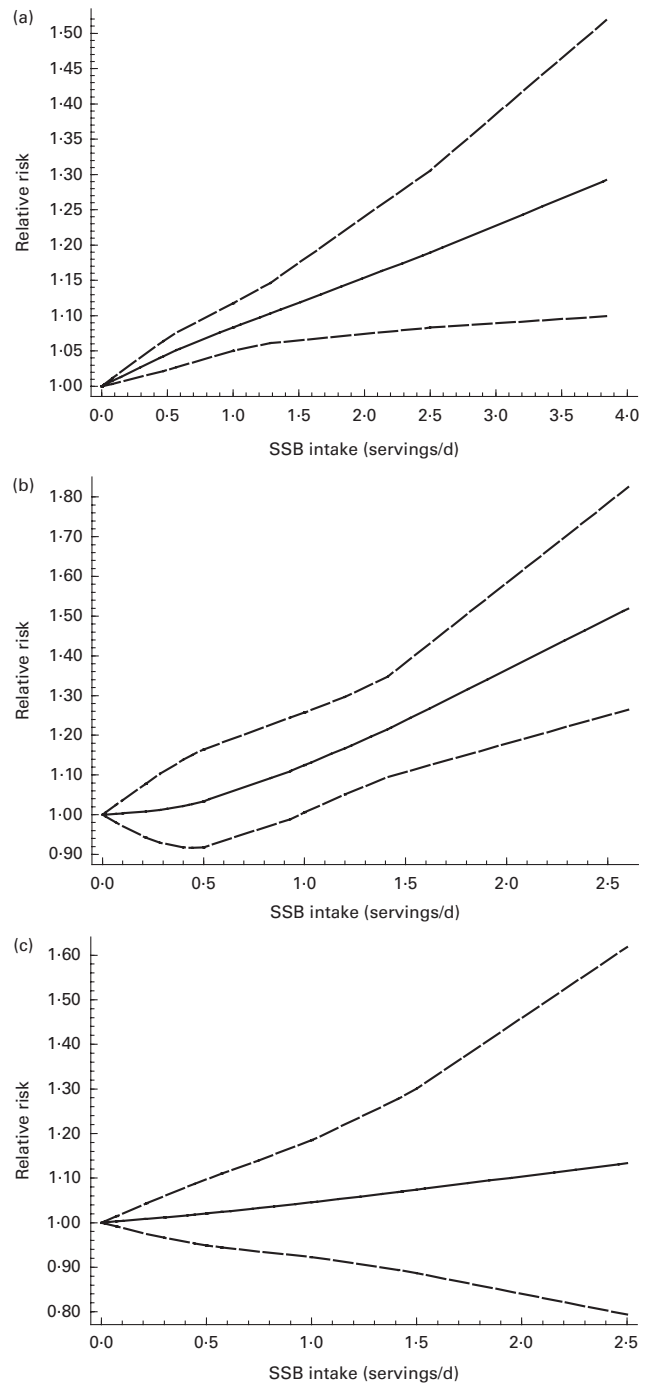
The test for the non-linear association was not significant ( $P$  for non-linearity=0.82; Fig. 3(c)). There was no significant association between SSB consumption and the risk of stroke (summary RR 1.06, 95% CI 0.97, 1.15,  $P$  for trend >0.05).

### Between-study heterogeneity

To examine the potential sources of heterogeneity between the included studies for hypertension outcome, meta-regression analyses were performed with the following independent variables: sex; age; origin of country; sample size of the studies; mean BMI; mean age of the populations; whether adjustment for confounders was made or not; sex proportion of the participants; length of follow-up; study quality. However, none of these variables was identified as a relevant source of heterogeneity, suggesting that other unknown or unmeasured factors might be responsible for the observed heterogeneity in the association between SSB intake and the risk of hypertension.

### Discussion

To our knowledge, this is the first quantitative meta-analysis investigating the association between SSB consumption and the risk of hypertension, CHD and stroke. In the present meta-analysis, a higher consumption of SSB was associated with an increased risk of hypertension and CHD, but not with the risk of stroke. These observed associations were independent of dietary and lifestyle factors, such as BMI or energy intake.



**Fig. 3.** Dose-response association between sugar-sweetened beverage (SSB) consumption and the risk of incident (a) hypertension, (b) CHD and (c) stroke (for every serving/d increase). —, Best-fitting restricted cubic spline; ---, 95% CI.

### Comparison with other studies

Several meta-analyses have addressed the association between SSB consumption and the risk of obesity<sup>(2,27)</sup>, the metabolic syndrome, type 2 diabetes<sup>(3)</sup>, pancreatic cancer<sup>(28)</sup> and colon cancer<sup>(29)</sup>. Because SSB include high energy and sugar content, it is not surprising that SSB consumption may be



significantly associated with an increased risk of obesity and weight gain, as shown in prospective studies and randomised controlled trials, respectively<sup>(2)</sup>. In another meta-analysis, a higher consumption of SSB was associated with an increased risk of type 2 diabetes<sup>(3)</sup>. However, available evidence in two meta-analyses suggests that a higher consumption of SSB is not associated with either pancreatic<sup>(28)</sup> or colon cancer<sup>(29)</sup>.

Less attention has been paid to the association between SSB consumption and cardiovascular risk, such as CHD or stroke. A recent meta-analysis of the association between SSB intake and the risk of CHD conducted by Huang *et al.*<sup>(30)</sup> included the same studies, and demonstrated the same strength of the association. However, that meta-analysis did not address whether SSB consumption is associated with the risk of hypertension and stroke. For hypertension, Dhingra *et al.*<sup>(4)</sup> reported that consumption of  $\geq 1$  serving of soft drink per d was not significantly associated with an increased risk of higher blood pressure (BP; RR 1.18, 95% CI 0.96, 1.44). However, in a subsequent study, Cohen *et al.*<sup>(6)</sup> found that participants who consumed  $\geq 1$  serving/d had an adjusted HR for incident hypertension of 1.13 (95% CI 1.09, 1.17) compared with those who did not consume SSB. Furthermore, the PREMIER Study (an 18-month behavioural intervention trial) conducted by Chen *et al.*<sup>(31)</sup> has suggested that after controlling for potential confounders, each 1 serving/d reduction in SSB consumption was associated with a 1.8 mmHg (95% CI 1.2, 2.4) reduction in systolic BP and 1.1 mmHg (95% CI 0.7, 1.4) reduction in diastolic BP. This association did not substantially change after further adjustment for weight change over the same period. The different findings on the association between SSB intake and the risk of hypertension, CHD and stroke might be due to biological mechanisms or to other reasons (study population, design, sample size or other factors). Based on the present meta-analysis of prospective studies, each additional 1 serving/d increase in SSB consumption was associated with a 8 and 17% relative increase in the risk of incident hypertension and CHD, respectively. In the present meta-analysis, we did not find any significant association between SSB consumption and the risk of incident stroke, although a significant association was found in studies conducted in Caucasians. Currently, convincing reasons for the absence of any significant association in the total population but finding an association only in some ethnic subgroups are unknown. It is possible that genetic factors may play some role in the association of SSB intake with the risk of stroke.

The association between artificially sweetened beverage (ASB) intake and the risk of CVD has already been reviewed by Pereira<sup>(32)</sup> who reported that ASB intake may increase the risk of CVD; however, there could be a reverse causality bias because obese individuals may tend to preferentially consume ASB in order to reduce their weight gain and are also more likely to develop CVD. Furthermore, evidence from experimental studies supports that replacing SSB with ASB may be beneficial to decrease the risk of obesity.

## Mechanisms

The effect of BMI and total energy intake could not fully explain the positive association between SSB consumption and the risk of incident hypertension or CHD, since both potential mediators have been controlled for in the majority of the included studies. Fructose, one of the major sweeteners in SSB, has been suggested to result in acute and chronic elevations of serum uric acid concentration, thereby leading to the activation of the renin–angiotensin system and, consequently, acute endothelial dysfunction, renal microvascular alteration and chronic Na retention<sup>(33)</sup>. This mechanism may explain why SSB consumption could increase the risk of incident hypertension. With respect to the observed association between SSB consumption and the risk of CHD, fructose has been found to increase the levels of several circulating inflammatory factors, such as C-reactive protein, IL-6, TNF receptor 1 and TNF receptor superfamily, which are known to influence atherosclerosis, plaque stability and thrombosis, and are key factors in the pathogenesis of CVD<sup>(34)</sup>. Fructose has also been associated with increased insulin resistance, reduced HDL-cholesterol, higher visceral fat stores and higher TAG concentrations, as well as with reduced endothelial NO production. All these changes have been associated with a higher risk of CHD<sup>(5,8)</sup>.

## Strengths and limitations

The strengths of the present study included the prospective study design, the large sample size, the long duration of follow-up and adjustment for many dietary and lifestyle factors in the included studies. However, several limitations should be considered. First, because of the observational nature of these studies, the possibility of residual and unmeasured confounding may have influenced the results. Second, errors may exist in measuring SSB consumption using FFQ since accuracy is dependent on an individual's memory and reporting. However, misclassification is usually non-differential and, thus, more likely to lead to an underestimation of the association. Third, all the studies used SSB consumption at baseline as exposure, and it is possible that participants may have changed their beverage habits during the follow-up period. Fourth, the majority of the included participants were white Americans. This limits the generalisability of our findings to other ethnic populations. Fifth, only several prospective studies were included for each outcome; however, the sample sizes of total incident cases were large enough ( $n > 6000$ ) and sufficient statistical power was available. Sixth, different criteria were used to define the outcomes. For hypertension, some studies used self-reported hypertension<sup>(6)</sup>, whereas others used systolic BP/diastolic BP  $\geq 130/85$  mmHg<sup>(4,5,7)</sup>. However, the significant association remained in each subgroup (RR 1.09, 95% CI 1.06, 1.13 for studies using self-reported hypertension; RR 1.04, 95% CI 1.01, 1.08 for studies using systolic BP/diastolic BP  $\geq 130/85$  mmHg). With respect to the endpoints of CHD and stroke, the definitions were similar for each outcome (mostly via medical records). Seventh, dietary assessment errors (e.g. FFQ) affect the accuracy of

the estimated 'doses'. Additionally, different confounders were adjusted for in each study, and this may have affected the accuracy of our estimates in the dose–response meta-analysis. Eighth, the present results might have been potentially underestimated, as the included studies had adjusted for variables such as BMI, history of diabetes and hypertension in the models. Those variables could be in the causal pathway for the association between SSB intake and the risk of CHD/stroke. Ninth, although meta-regression was used to explore the potential sources of heterogeneity for the outcome of hypertension, none of the known variables was identified as a specific source of heterogeneity. Thus, caution should be exercised while interpreting pooled estimates showing large heterogeneity. Tenth, it is unclear whether the association that we have found is due to the sugar content of SSB or to related lifestyle factors associated with the consumption of SSB, such as other dietary practices, sedentary behaviours or lack of physical activity. However, the vast majority of the included studies have controlled for these dietary and lifestyle factors in the models. Nevertheless, further randomised controlled trials are warranted to confirm the observed association.

In conclusion, a higher consumption of SSB was associated with a higher risk of hypertension and CHD, but not with the risk of stroke. Notably, recent evidence suggests that increasing water intake in place of SSB was associated with a lower risk of weight gain<sup>(35)</sup> and type 2 diabetes<sup>(36)</sup>. The present results support recommendations to reduce the consumption of SSB in order to prevent and control CVD, although further large prospective studies or randomised controlled trials are warranted to confirm the observed association.

### Supplementary material

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/S0007114514004383>

### Acknowledgements

The present study was supported by the Natural Science Foundation of Shandong Province (grant no. ZR2012HL26). The funder had no role in the design and analysis of the data or in the writing of this article.

The authors' contributions are as follows: B. X. designed the research; B. X. and D. Z. searched the databases and checked them according to the eligible criteria and exclusion criteria; M. T. B.-L., M. A. M.-G. and R. Z. acquired the data; B. X. and Y. H. analysed the data; B. X. wrote the draft of the paper; B. X., Y. H., K. H. R., S. L., R. Z., M. T. B.-L., M. A. M.-G. and D. Z. revised the paper; D. Z. was responsible for the final content. All the authors read and approved the final manuscript.

None of the authors has any conflict of interest to declare.

### References

- Nielsen SJ & Popkin BM (2004) Changes in beverage intake between 1977 and 2001. *Am J Prev Med* **27**, 205–210.
- Te Morenga L, Mallard S & Mann J (2012) Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* **346**, e7492.
- Greenwood DC, Threapleton DE, Evans CE, *et al.* (2014) Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose–response meta-analysis of prospective studies. *Br J Nutr* **112**, 725–734.
- Dhingra R, Sullivan L, Jacques PF, *et al.* (2007) Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* **116**, 480–488.
- Duffey KJ, Gordon-Larsen P, Steffen LM, *et al.* (2010) Drinking caloric beverages increases the risk of adverse cardiometabolic outcomes in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr* **92**, 954–959.
- Cohen L, Curhan G & Forman J (2012) Association of sweetened beverage intake with incident hypertension. *J Gen Intern Med* **27**, 1127–1134.
- Barrio-Lopez MT, Martinez-Gonzalez MA, Fernandez-Montero A, *et al.* (2013) Prospective study of changes in sugar-sweetened beverage consumption and the incidence of the metabolic syndrome and its components: the SUN cohort. *Br J Nutr* **110**, 1722–1731.
- Fung TT, Malik V, Rexrode KM, *et al.* (2009) Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr* **89**, 1037–1042.
- de Koning L, Malik VS, Kellogg MD, *et al.* (2012) Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. *Circulation* **125**, 1735–1741.
- Eshak ES, Iso H, Kokubo Y, *et al.* (2012) Soft drink intake in relation to incident ischemic heart disease, stroke, and stroke subtypes in Japanese men and women: the Japan Public Health Centre-based study cohort I. *Am J Clin Nutr* **96**, 1390–1397.
- Gardener H, Rundek T, Markert M, *et al.* (2012) Diet soft drink consumption is associated with an increased risk of vascular events in the Northern Manhattan Study. *J Gen Intern Med* **27**, 1120–1126.
- Bernstein AM, de Koning L, Flint AJ, *et al.* (2012) Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr* **95**, 1190–1199.
- Larsson SC, Akesson A & Wolk A (2014) Sweetened beverage consumption is associated with increased risk of stroke in women and men. *J Nutr* **144**, 856–860.
- Malik VS, Popkin BM, Bray GA, *et al.* (2010) Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* **121**, 1356–1364.
- Malik AH, Akram Y, Shetty S, *et al.* (2014) Impact of sugar-sweetened beverages on blood pressure. *Am J Cardiol* **113**, 1574–1580.
- Stroup DF, Berlin JA, Morton SC, *et al.* (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**, 2008–2012.
- Wells GA, Shea B & O'Connell D, *et al.* (2014) The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) (accessed May 2014).
- DerSimonian R & Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177–188.





19. Mantel N & Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* **22**, 719–748.
20. Higgins JP, Thompson SG, Deeks JJ, *et al.* (2003) Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560.
21. Greenland S & Longnecker MP (1992) Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. *Am J Epidemiol* **135**, 1301–1309.
22. Orsini N, Bellocco R & Greenland S (2006) Generalized least squares for trend estimation of summarized dose–response data. *Stata J* **6**, 40–57.
23. Rong Y, Chen L, Zhu T, *et al.* (2013) Egg consumption and risk of coronary heart disease and stroke: dose–response meta-analysis of prospective cohort studies. *BMJ* **346**, e8539.
24. Orsini N, Li R, Wolk A, *et al.* (2012) Meta-analysis for linear and nonlinear dose–response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* **175**, 66–73.
25. Begg CB & Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**, 1088–1101.
26. Egger M, Davey Smith G, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
27. Forshee RA, Anderson PA & Storey ML (2008) Sugar-sweetened beverages and body mass index in children and adolescents: a meta-analysis. *Am J Clin Nutr* **87**, 1662–1671.
28. Gallus S, Turati F, Tavani A, *et al.* (2011) Soft drinks, sweetened beverages and risk of pancreatic cancer. *Cancer Causes Control* **22**, 33–39.
29. Zhang X, Albanes D, Beeson WL, *et al.* (2010) Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Natl Cancer Inst* **102**, 771–783.
30. Huang C, Huang J, Tian Y, *et al.* (2014) Sugar sweetened beverages consumption and risk of coronary heart disease: a meta-analysis of prospective studies. *Atherosclerosis* **234**, 11–16.
31. Chen L, Caballero B, Mitchell DC, *et al.* (2010) Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. *Circulation* **121**, 2398–2406.
32. Pereira MA (2013) Diet beverages and the risk of obesity, diabetes, and cardiovascular disease: a review of the evidence. *Nutr Rev* **71**, 433–440.
33. Feig DI, Kang DH & Johnson RJ (2008) Uric acid and cardiovascular risk. *N Engl J Med* **359**, 1811–1821.
34. Hotamisligil GS (2006) Inflammation and metabolic disorders. *Nature* **444**, 860–867.
35. Pan A, Malik VS, Hao T, *et al.* (2013) Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. *Int J Obes (Lond)* **37**, 1378–1385.
36. Pan A, Malik VS, Schulze MB, *et al.* (2012) Plain-water intake and risk of type 2 diabetes in young and middle-aged women. *Am J Clin Nutr* **95**, 1454–1460.