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Review article

Sugar-sweetened beverages consumption and the risk of depression: A meta-analysis of observational studies☆

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ABSTRACT

Background: It remains inconsistent whether sugar-sweetened beverages (SSBs) consumption increases the risk of depression. Thus, we carried out a meta-analysis to evaluate the association between SSBs consumption and the risk of depression.

Methods: PubMed and Web of Science were searched for relevant articles published up to June 2018. Pooled relative risks (*RRs*) and 95% confidence intervals (*CIs*) were calculated by the fixed-effects model or random effect model based on heterogeneity test.

Results: 10 observational studies involving 37,131 depression cases among 365,289 participants were included. The combined risk of depression for the highest versus lowest consumption of SSBs was 1.31 (95% *CI* 1.24–1.39). The findings were consistent in the cross-sectional studies (*RR* = 1.38; 95% *CI* 1.26–1.52) as well as in the cohort studies (*RR* = 1.30; 95% *CI* 1.19–1.41) A nonlinear dose-response relationship was found ($P_{nonlinearity}$ = 0.0103) for depression risk and SSBs consumption. Compared with SSBs nondrinkers, those who drank the equivalent of 2 cups/day of cola might increase the risk of depression by 5% (*RR* = 1.05; 95% *CI* 1.01–1.09). And the equivalent of 3cans/day of cola might have approximately 25% higher risk of depression.

Limitations: 10 studies were included in this meta-analysis, of which only 4 were cohort studies, and more cohort studies need to be performed in the future.

Conclusions: This meta-analysis indicates that SSBs consumption might be associated with a modestly higher risk of depression. The results need to be further confirmed in the future.

1. Introduction

Depression is one of the most common mental disorders, characterized by sadness, lack of interest and guilt or low self-worth. It can heavily weaken people's ability to complete work or cope with daily life. Even more serious is, depression can lead to suicide (WHO, 2017). At present, depression is recognized as one of the leading global causes of increased disability-adjusted life years (DALYs and Collaborators, 2016) and a major contributor to the overall global burden of disease (WHO, 2018). Hence, depression has become a major public health problem and brings a high economic burden to the society.

Depression is a complicated disease caused by interaction of genetic and environmental factors. However, the mechanism of its pathogenesis is still vague. As modifiable factors, environmental factors, such as diet, physical activity, etc. have been extensively studied (Mammen and Faulkner, 2013; Pagliai et al., 2018; Psaltopoulou et al., 2013; Pudrovska and Karraker, 2014; Quirk et al., 2013; Saghafian et al., 2018; Sanhueza et al., 2013; Simon et al., 2015). In terms of diet, characteristics of the Mediterranean diet may be protective (Pagliai et al., 2018; Psaltopoulou et al., 2013). Whereas, Western diet that is rich in fat and sugar may increase the likelihood of depression (Quirk et al., 2013). Sugar-sweetened beverages (SSBs), which are a class of very popular non-alcoholic beverages throughout the world, are characterized by high added sugar content, especially fructose-containing sugar. And overconsumption of added sugar has been hypothesized to increase the risk of depression via several plausible biological pathways, for instance, a higher hypothalamic-pituitary-adrenal (HPA) axis reactivity leading to dysregulation of the stress response, and obesity induced heightened low-grade inflammation and HPA axis non-habituation, etc. (Harrell et al., 2015; McInnis et al., 2014). Recently, a meta-analysis of non-alcoholic beverages suggests that high soft drink intake was associated with increased risk of depression (Kang et al., 2018). However, only 5 studies published from 2010 to

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2015 were included in that meta-analysis. Since 4 of the 5 included studies were cross-sectional designs and there was no evidence for dose-response effects, the conclusion requires further elucidation. As of now, 2 more cohort studies and 1 more cross-sectional study were published (Barros et al., 2017; Knüppel et al., 2017; Sanchez-Villegas et al., 2018). In addition, we identified 1 case-control study (Xia et al., 2017) in relation to this topic. In these studies, however, the magnitude of the association varies. The relationship of SSBs consumption with depression risk and their dose-response relationships are still uncertain (Kang et al., 2018).

Thus, we carried out this meta-analysis (1) to evaluate the association between SSBs consumption and the risk of depression; (2) to evaluate the dose-response relationships to support the causality. Actually, SSBs are modifiable risk factors for depression. Considering its high popular consumption, the prevention efforts will be worthwhile even small effects exist.

2. Methods

This meta-analysis was reported following the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000).

3. Search strategy

We searched all relevant English studies in the databases of PubMed and Web of Science up to June 2018. Search terms were “sugar-sweetened beverage ” (or “sweet drink” or “sweet beverage” or “sweetened beverage” or “sugar-sweetened drink” or “sweetened drink” or “carbonated beverage” or “carbonated drink” or “soft drink” or “soda” or “sodas” or “soda pop” or “cola beverage” or “cola drink” or “cordial” or “cordials” or “cordial beverage” or “cordial drink” or “flavoured water” or “artificial juices” or “fruit-flavoured drink” or “fruit-flavoured beverages”) and “depression” (or “depressive disorder” or “depressive symptoms”)(Avery et al., 2017). In addition, we reviewed the reference lists from all retrieved literature to search for further relevant studies. The detailed search strategy in PubMed is shown in the supplemental Table S1.

4. Inclusion criteria

Studies were included if they met the following criteria: (1) cohort studies, case-control studies and cross-sectional studies; (2) the exposure of interest was SSBs consumption; (3) the outcome of interest was depression, and its definition was based on physicians’ diagnose or professional questionnaires; (4) odds ratio (*OR*), relative risk (*RR*), prevalence ratios (*PR*) or hazard ratio (*HR*) with 95% confidence intervals (*CIs*) were provided or could be calculated. In one article, if it included cross-sectional results in addition to prospective results, then, we see them as two studies. And in one article, if the results were reported respectively by soft drinks and other type of sweetened beverages, we also see them as two studies.

5. Exclusion criteria

(1) search results were presented only with abstracts, whereas the full texts were written in languages other than English and Chinese; (2) unpublished studies; (3) not evaluate the association between SSBs and depression risk; (4) duplicated data; (5) methods of exposure measurement did not adequately reflect the true level of exposure; (6) not adjusted the confounders.

Two investigators performed the literature search independently, if data were duplicated in more than one study, we included the study with the most comprehensive data. If the two investigators held different opinions about the eligibility of an article, it was resolved by reaching consensus.

6. Data extraction

Two investigators extracted the following data from each study independently: the first author's name, publication year, country where the study was performed, age, sex, study design, sample size, measurement of depression, number of cases, the most adjusted *RRs* and 95% *CIs* for the highest versus lowest SSBs consumption (we presented all results with *RR* for simplicity).

For dose-response analysis, we extracted the cases and participants (person-years) and *RR* (95% *CI*) of each category of SSBs consumption or sugar intake from SSBs. The median or mean SSBs consumption or sugar intake from SSBs in each group was required to estimate the dose-response corresponding *RR*. For un-bounded upper or lower categories, we assumed that the amplitude of the boundary is the same as the adjacent category (Bekkering et al., 2008). Because consumption of SSBs and sugar intake from SSBs were used to assess the exposure levels in different studies, and the unit (liter/day, cans/day, or cups/week) of measurement varied considerably among studies being used to assess the consumption of SSBs. First, we used ml per day (ml/day) as the standard unit to measure the intake of SSBs with equivalencies as follows: 1can = 330 ml, 1cup = 200 ml. And then we calculate the sugar content of the SSBs that were consumed, based on the sugar content (11 g/100 ml for soft drinks and 9 g/100 ml for fruit-flavoured drinks) of Pepsi-Cola and Coca Cola series (the most popular brands in the market).

The quality of the included literature was assessed by the Agency for Healthcare Research and Quality (AHRQ) methodology checklist for cross-sectional studies and the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, respectively.

7. Statistical analysis

RRs were used as the common measure of association between the highest versus the lowest consumption of SSBs or sugar intake and the risk of depression. *HR* from cohort studies and *ORs* and *PR* from case-control and cross-sectional studies were considered equivalent to *RRs* for convenience. We weighted the study-specific log *RRs* by the inverse of their variance, to calculate pooled *RRs* with corresponding 95% *CIs* of the association between SSB consumption and the risk of depression. I^2 was used to assess heterogeneity, and I^2 values of 0%, 25%, 50% and 75% represent no, low, moderate and high heterogeneity, respectively (Higgins and Thompson, 2002). The random-effects model (REM) was adopted as the pooling method, if moderate or higher heterogeneity ($I^2 \geq 50\%$) was found; otherwise ($I^2 < 50\%$), the fixed-effects model (FEM) was used (Higgins et al., 2003). For dose-response analysis, we performed a two-stage random-effects dose-response meta-analysis to evaluate the trend from the correlated log *RR* estimates across levels of sugar intake, respectively (Orsini et al., 2012). In the first stage, we adopted generalized least-square regression to estimate a restricted cubic spline model with four knots at the 5th, 35th, 65th and 95th percentiles of the levels of sugar intake (Harrell Jr FE., 2001). Then, we used the restricted maximum likelihood method in a multivariate random-effects meta-analysis to combine the study- specific estimates (Jackson et al., 2010). A *P* value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline and the third spline was equal to 0. Meta-regression with restricted maximum likelihood estimation was adopted to explore the potential covariates, including exposure, study design, year, outcome measures, whether adjusted smoking, whether adjusted BMI and participants, that may have a great impact on between-study heterogeneity (Higgins and Thompson, 2004). Subgroup analysis was conducted by exposure, study design, participants, outcome measures, whether adjusted smoking, whether adjusted BMI and methods of exposure measures. The influence analysis was conducted with one study removed at a time to assess whether the results could have been affected significantly by a single study (Tobias, 1999). A sensitivity analysis was performed after

Table 1
Characteristics of included studies on SSBs intake and depression risk.

Author,year,	Country	Age range or mean age (years)	Study design	Sex	Sample size (cases)	Exposure measurement	Outcome assessment	Exposure	RR (95%CI) for highest vs. lowest category	Adjustments
Shi et al. (2010)	Australia	≥16	C-S-S	Both	4741 (326)	SAMSS Questionnaire	Physician diagnosed	Soft drink	≥0.5 litre/day vs. 0 litre/day 1.63 (1.03–2.58)	Age, gender, education, income, area of residence, smoking (non-smoker, ex-smoker, smoker), drinking (servings/d), physical activity,(none, physical activity, < 150 or ≥ 150 min/d), overweight, diabetes, asthma, CVD, arthritis, osteoporosis, chronic obstructive pulmonary disease, intake of fruit and vegetables (servings/d).
Guo et al. (2014)	America	50–71	C-S	Both	259,555 (11,092)	FFQ	Physician diagnosed	Soft drink	>4 cans/cups per day vs. none 1.30 (1.17–1.44)	Age at baseline, sex, race, education, marital status, smoking, alcoholic beverage intake, physical activity, body mass index, and energy intake.
Guo et al. (2014)	America	50–71	C-S	Both	259,490 (11,120)	FFQ	Physician diagnosed	Fruit drink	>4 cans/cups per day vs. none 1.38 (1.15–1.65)	Age at baseline, sex, race, education, marital status, smoking, alcoholic beverage intake, physical activity, body mass index, and energy intake.
Yu et al. (2015)	China	42.5	C-S-S	Both	3667 (2565)	FFQ	SDS ≥ 50	Soft drink	>4 cups/wk vs. < 1 cup/wk 2.00 (1.15–3.37)	Age, sex and body mass index, smoking status, drinking status, physical activity, marital status, total energy intake, household incomes, employment status, educational levels, visiting friends, living alone and metabolic syndrome, green tea, oolong tea, black tea, coffee and juices.
Barros et al. (2017)	Brasil	37	C-S-S	Both	49,025 (5144)	PNS Questionnaire	PHQ-9 ≥ 20	Soft drinks or artificial juices	≥5 times /week vs . < 5 times/week 1.42 (1.20–1.69)	Age, sex, and education level.
Zahedi et al. (2014)	Iran	12.47	C-S-S	Both	13,486 (2794)	GSHS Questionnaire	GSHS	Sweetened beverages	Daily vs. Seldom 1.41 (1.23–1.61)	Age, sex, family history of chronic disease, mother's education, screen time, socioeconomic status, physical activity and BMI.
Xia et al. (2017)	China	46.22	C−C-S	Both	2702 (1351)	FFQ	SDS ≥ 45	Sugared beverages and snacks	the highest quartile vs. lowest quartile (g/day) 1.09 (0.87–1.35)	Animal foods, fruits, vegetables and salted foods intake. Covariates as follows were matched through propensity score matching: age, sex, BMI, smoking status, drinking status, number of physical illness (classified as "0," "1," and " ≥ 2″), physical activity, energy intake, education level, household income, living alone status, employment status, visiting friend status, and marital status.
Sanchez-Villegas et al. (2018)	Spain	33.4	C-S	Both	15,546 (769)	SQFFQ	Physician-provided diagnosis	Sweetened drinks	the highest quartile vs. lowest quartile (g/day) 1.12 (0.90–1.41)	Sex, smoking, BMI, physical activity, energy intake, prevalence of CVD, hypertension or dyslipidaemia and recruitment period, diabetes prevalence during the follow-up.
Knüppel A. (2017)	UK	35–55	C-S	Both	2304 (741)	SQFFQ	CES-D ≥ 16	Sweet food/ beverages	the highest tertile vs. lowest tertile (g/day) 1.47 (0.98–2.22)	Age, sex, ethnicity, marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration, energy intake from other foods, modified DASH diet score, fish, coffee and tea intake.
Knüppel A. (2017)	UK	35–55	C-S-S	Both	9895 (1229)	SQFFQ	CES-D ≥ 16	Sweet food/ beverages	the highest tertile vs. lowest tertile (g/day) 1.08 (0.84–1.39)	Age, sex, ethnicity, marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration, energy intake from other foods, modified DASH diet score, fish, coffee and tea intake.

C-S-S, cross-sectional study; SAMSS, the South Australian Monitoring and Surveillance System; C-S, cohort syudy; FFQ, Food Frequency Questionnaire; SDS, Self-Rating Depression Scale; PNS, The National Survey on Health; PHQ-9, Patient Health Questionnaire-9; GSHS, Global School Health Survey; C−C-S, case-control study; SQFFQ, Semi-Quantitative Food Frequency Questionnaire; CES-D, Center of Epidemiologic Studies Depression Scale.

Table 2
Summary risk estimates of depression for SSBs consumption by study characteristics.

	Number of studies	*RR* (95% *CI*)	I^2 (%)	$P_{heterogeneity}$
All studies	10	1.31 (1.24–1.39)	29.2	0.176
Study design				
Cohort	4	1.30 (1.19–1.41)	0.0	0.483
Case-control	1	1.09 (0.88–1.36)		
Cross-sectional	5	1.38 (1.26–1.52)	35.2	0.186
Exposure				
SSBs	7	1.35 (1.26–1.44)	9.9	0.353
SSBs and sweet food	3	1.13 (0.97–1.32)	0.0	0.403
Participants				
Children and adolescents	1	1.41 (1.23–1.61)		
Adults	9	1.29 (1.21–1.38)	29.8	0.180
Adjusted smoking				
Yes	8	1.27 (1.18–1.37)	30.2	0.187
No	2	1.41 (1.27–1.57)	0.0	0.949
Adjusted BMI				
Yes	6	1.31 (1.22–1.40)	40.7	0.134
No	4	1.34 (1.18–1.53)	27.8	0.245
Exposure measures				
FFQ and SQFFQ	7	1.26 (1.17–1.36)	32.4	0.181
Other questionnaires	3	1.42 (1.28–1.58)	0.0	0.922
Outcome measures				
Physician diagnosed	4	1.30 (1.20–1.41)	1.5	0.385
Self-reported questionnaires	6	1.33 (1.22–1.45)	47.4	0.091

SSBs, sugar-sweetened beverages; *RR*, relative risk; *CI*, confidence interval; BMI, Body Mass Index; FFQ, Food Frequency Questionnaire; SQFFQ, Semi-Quantitative Food Frequency Questionnaire.

excluding the cross-sectional result from Knüppel et al. (Knüppel et al., 2017) and including a combined result from Guo et al. (Guo et al., 2014) on soft drink and fruit drink. Egger regression asymmetry test and the funnel plot were used to evaluate publication bias (M et al., 1997). All statistical analyses were carried out using STATA Version 12 (StataCorp, College Station, Texas, USA). A two-sided $P \leq 0.05$ was considered statistically significant.

8. Result

8.1. Search results and study characteristics

The search strategy identified 347 articles from PubMed, 437 articles from Web of Science. 695 articles were remained after excluding duplicates, 633 articles were excluded after reviewing the title or abstract. 52 articles were excluded after reviewing the full text. The detailed steps of the literature search are shown in Fig. S1. The detailed steps for articles that are excluded by full text reading were listed in Table S2.

As a result, 8 articles including 10 studies (Barros et al., 2017; Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018; Shi et al., 2010; Xia et al., 2017; Yu et al., 2015; Zahedi et al., 2014) met the inclusion criteria and were included in the meta-analysis. One article (Knüppel et al., 2017) included two studies for reporting prospective results and cross-sectional results independently. Besides, one article (Guo et al., 2014) also included two studies for the results were apart into soft drink and fruit drink.

Of all 10 studies, 4 were cohort studies (Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018), 5 were cross-sectional studies (Barros et al., 2017; Knüppel et al., 2017; Shi et al., 2010; Yu et al., 2015; Zahedi et al., 2014) and 1 was case-control study (Xia et al., 2017). Depression was assessed by physician in 4 studies (Guo et al., 2014; Sanchez-Villegas et al., 2018; Shi et al., 2010). And self-reported questionnaires, including Patient Health Questionnaire–9 (PHQ-9 scores ≥ 20), Global School Health Survey (GSHS), Self-Rating Depression Scale (SDS scores ≥ 45) and Center of Epidemiologic Studies Depression Scale (CES-D scores ≥ 16) were used to create a binary variable of depression based on a specific cutoff of a scale in 6 studies (Barros et al., 2017; Knüppel et al., 2017; Xia et al., 2017; Yu et al., 2015; Zahedi et al., 2014).

SSBs consumption was used to measure the level of exposure in 6 studies (Barros et al., 2017; Guo et al., 2014; Shi et al., 2010; Yu et al., 2015; Zahedi et al., 2014). Sugar intake (g/day) from SSBs was used to measure the level of exposure in 1 study (Sanchez-Villegas et al., 2018). SSBs and sweet food/snacks consumption were mixed as the exposure in 3 studies conducted by Knüppel A (Knüppel et al., 2017) and Xia Y (Xia et al., 2017), respectively. Because SSBs contain a large amount of added sugar, and high added sugar in SSBs has been hypothesized the key contributor to depression, thus the association of depression with SSBs consumption is major related to the sugar content. Although the mixed exposure of SSBs and sweet food/snacks consumption was presented in 3 studies, it was measured by sugar intake, and we chose *RR*s for the highest versus the lowest category of SSBs consumption or sugar intake in all studies, so this mixed exposure could not have a significant effect on the combined results. Thus, in the following, we uniformly use SSBs consumption as the exposure for convenience. In dose-response analysis, for the sake of comparison, we converted the SSBs consumption into the sugar intake (g/day), based on the amount of sugar (g/100 ml) in SSBs that are common in the market. SSBs were identified as soft drinks, sugared or sweetened beverages, or artificial juice. The detail types of SSBs in the original studies were presented in Table S3.

SSBs intake was measured by food frequency questionnaire (FFQ) in most included studies (Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018; Xia et al., 2017; Yu et al., 2015). Questionnaires that obtained from the South Australian Monitoring and Surveillance System (SAMSS), Population-based National Survey on Health (PNS) and Global School Health Survey (GSHS) were used in other studies (Barros et al., 2017; Shi et al., 2010; Zahedi et al., 2014).

The baseline characteristics of the studies were shown in Table 1.

The quality assessment showed that the Newcastle-Ottawa score of the cohort studies ranged from 8 to 9. For the case-control study, the Newcastle-Ottawa score was 8. The quality score of the Agency for Healthcare Research and Quality (AHRQ) methodology checklist ranged from 7 to 8 for cross-sectional studies (Zeng et al., 2015). The detailed quality assessment was shown in Table S4, Table S5 and Table S6.

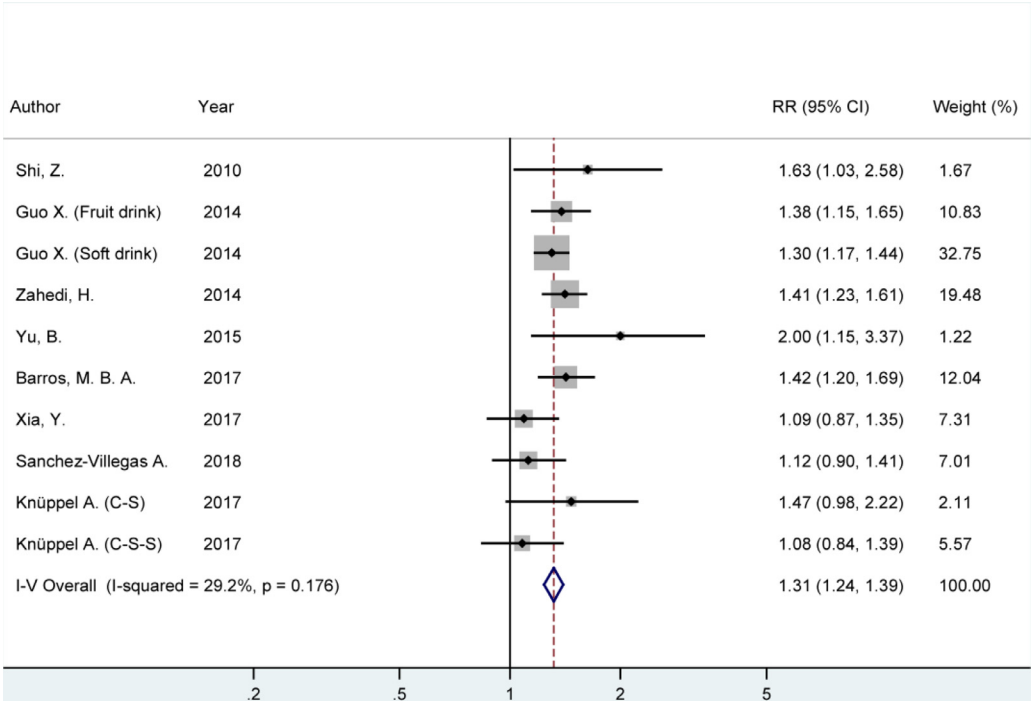

Fig. 1. Forest plot of the relative risks (*RRs*) with corresponding 95% confidence intervals (*CIs*) of studies on sugar-sweetened beverages consumption and risk of depression. The size of grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% *CIs*.

9. Quantitative synthesis

The main results of the studies are shown in Table 2.

Ten studies (Barros et al., 2017; Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018; Shi et al., 2010; Xia et al., 2017; Yu et al., 2015; Zahedi et al., 2014) involving 37,131 depression cases among 365,289 participants were used to explore the relationship between SSBs consumption and the risk of depression. The pooled *RRs* of depression for the highest versus the lowest consumption of SSBs was 1.31 (95% *CI* 1.24–1.39; I^2 = 29.2%; $P_{heterogeneity}$ = 0.176; FEM; Fig. 1).

In the subgroup analysis of exposure, SSBs consumption (Barros et al., 2017; Guo et al., 2014; Sanchez-Villegas et al., 2018; Shi et al., 2010; Yu et al., 2015; Zahedi et al., 2014) indicated an adverse effect on the risk of depression (*RR* = 1.35; 95% *CI* 1.26–1.44; I^2 = 9.9%; $P_{heterogeneity}$ = 0.353; FEM). The result from SSBs and sweet food consumption (Knüppel et al., 2017; Xia et al., 2017) also showed increased risk of depression, but the result was not statistically significant (*RR* = 1.13; 95% *CI* 0.97–1.32; I^2 = 0.0%; $P_{heterogeneity}$ = 0.403; FEM).

SSBs consumption was associated with an increased risk of depression both in children and adolescents (*RR* = 1.41, 95%*CI* 1.23–1.61) and adults (*RR* = 1.29, 95%*CI* 1.21–1.38; I^2 = 29.8%; $P_{heterogeneity}$ = 0.180; FEM).

For dose-response analysis, we adopted data from seven studies involving 25,386 depression cases (Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018; Shi et al., 2010; Yu et al., 2015). A nonlinear association was found ($P_{nonlinearity}$ = 0.0103) between SSBs consumption and risk of depression. The comparison group was dosed 0 g/day of sugar intake from SSBs and the *RRs* with 95% *CIs* of depression risk were 1.01 (95% *CI* 0.97–1.04), 1.05 (95% *CI* 1.01–1.09), 1.16 (95% *CI* 1.09–1.23), 1.25 (95% *CI* 1.17–1.33) and 1.25 (95% *CI* 1.14–1.36) for sugar intake from SSBs at 14.2, 24.3, 48.5, 94.4 and 163.4 g/day, respectively (Fig. 2). The threshold of sugar intake was in the region of 24 g/day (2 cups/day of cola) (*RR* = 1.05; 95% *CI* 1.01–1.09). Compared to non-consumption of SSBs, ingesting sugar 24.3 g/day (2 cups/day of cola) from SSBs might increase the risk of depression by 5%. And the depression risk might increase by 25%, when sugar intake was at 90.8 g/day (3cans/day of cola). The detailed characteristics of the studies and participants included in the dose-response analysis are shown in Table S7.

10. Meta-regression, influence analysis and sensitivity analysis

As shown in Fig. 2, low heterogeneity (I^2 = 29.2%) was found in the analysis of SSBs intake and depression. Hence, meta-regression was performed with the covariates of exposure (*P* = 0.081), study design (*P* = 0.696), year (*P* = 0.113), outcome measures (*P* = 0.870), whether adjusted smoking (*P* = 0.183), whether adjusted BMI (*P* = 0.782) and participants (*P* = 0.394) to explore potential sources of the heterogeneity. But, none of these covariates showed having a significant impact on the between-study heterogeneity. We also conducted influence analysis (Figure S2) to further explore potential sources of the between-study heterogeneity, and the result showed that no individual study had an excessive influence on the pooled effect between SSBs consumption and the risk of depression. A sensitivity analysis was also performed. After excluding the cross-sectional result from Knüppel et al. (Knüppel et al., 2017) and including a combined result from Guo et al. (Guo et al., 2014) on soft drink and fruit drink, the pooled RRs of depression for the highest versus the lowest consumption of SSBs was 1.33 (95% *CI* 1.25–1.41; I^2 = 29.4%; $P_{heterogeneity}$ = 0.193; FEM). The result is very close to the one before the sensitivity analysis (*RR* = 1.31; 95%*CI* 1.24–1.39; I^2 = 29.2%; $P_{heterogeneity}$ = 0.176; FEM).

11. Publication bias

The funnel plot and Egger test showed no significant small-study effect in the analysis of SSBs consumption and the risk of depression (*P* = 0.726; Figure S3).

12. Discussion

To the best of our knowledge, this is the first meta-analysis to explore associations between SSBs consumption and the risk of depression. The results indicated that the consumption of SSBs might be

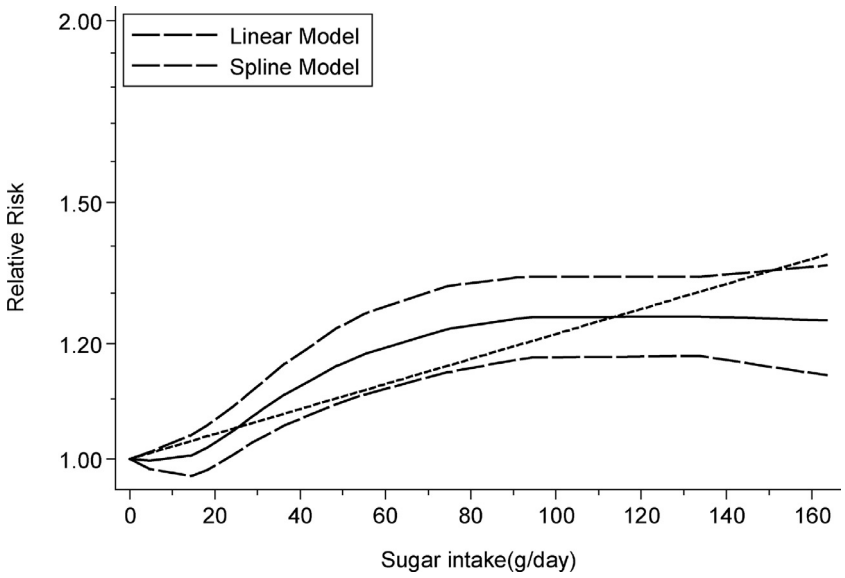

Fig. 2. The dose-response analysis of daily sugar intake and the risk of depression. The solid line and the long dash line represent the estimated relative risks and their 95% *CIs*. The short dash line represents the linear relationship.

associated with an increased risk of depression. This association was statistic significant both in cross-sectional studies (Barros et al., 2017; Knüppel et al., 2017; Shi et al., 2010; Yu et al., 2015; Zahedi et al., 2014) (*RR* = 1.38; 95% *CI* 1.26–1.52) and in cohort studies (Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018) (*RR* = 1.30; 95% *CI* 1.19–1.41). A nonlinear dose-response relationship was found ($P_{\text{nonlinearity}}$ = 0.0103) between SSBs consumption and depression risk. The inflection point was the equivalent of about 2 cups/day of cola. Above that level the risk of depression might be increased greatly.

The association between SSBs consumption and the risk of depression may be related to the following biological explanations. Firstly, SSBs contain a large amount of sugar. Evidence from animal experiment showed that the rats fed a diet high in fructose during peridolescence showed increased anxiety-like behavior and depressive-like behavior in their adulthood, and a higher HPA axis reactivity leading to elevations in glucocorticoids. Adolescents are the largest consumer of added sugar beverages, and adolescence is also critical for maturation of the HPA axis. Overconsumption of high levels of added fructose during adolescence has the potential to promote long-term dysregulation of the stress response (Harrell et al., 2015). Secondly, sugared beverages are in part responsible for the obesity, and obesity may be associated with the development of depression through a stimulation of the HPA axis (Sanchez-Villegas et al., 2018). Moreover, a systematic review and meta-analysis of longitudinal studies showed that there was a bi-directional relationship between depression and obesity (Mannan et al., 2016). Thirdly, consumption of added sugar from liquid rather than solid sources predicts impaired glucose homeostasis and insulin resistance leading to Type 2 diabetes (Wang et al., 2014). And a bi-directional relationship is also present in depression and Type 2 diabetes (Bruce et al., 2018).

Between-study heterogeneity often appears in meta-analysis (Lee, 2015). It is necessary to find the potential sources of heterogeneity among studies. In this meta-analysis, low to moderate heterogeneity was found, and no covariates showed having a significant impact on the between-study heterogeneity by meta-regression analysis. And no individual study had an excessive influence on the pooled effect between SSBs consumption and the risk of depression by influence analysis. The result of sensitivity analysis after excluding the cross-sectional result from Knüppel et al. (2017) and including a combined result from Guo et al. (2014) on soft drink and fruit drink showed almost the same as the one before the sensitivity analysis. That indicated the stability of our results.

The study has several advantages. First, this meta-analysis included a large number of participates, thus reducing small-study effect to a great degree. Second, the studies included in this meta-analysis were with relatively high quality. The quality assessment showed that the Newcastle-Ottawa score of each cohort study and case-control study was no less than 7. The quality score ranged from 7 to 8 in cross-sectional studies. Among the cross-sectional studies, the source of participants and the exclusion criteria were clear. The response rates were more than 80% in most cross-sectional studies except one study performed by Shi et al. (2010). The response rate was 62.1% in that study that would limit universality. However, the weighting of the data in the process of statistical analysis would counteract the non-response bias to a certain degree. The known and assumed confounders for depression were reasonable controlled in all studies included in this meta-analysis. Third, SSBs were assessed by a reliable food frequency questionnaire (FFQ) and semi (SQFFQ) in most studies. In PNS (Barros et al., 2017) and GSHS (Zahedi et al., 2014) questionnaires, the frequency of SSBs consumption was categorized as < 5 or $\geq$ 5times per week, and seldom, weekly, or daily, respectively. In SAMSS questionnaire (Shi et al., 2010), average daily consumption of SSBs was measured. The results were consistent in studies that SSBs consumption was assessed by FFQ and SQFFQ (*RR* = 1.26; 95% *CI* 1.17–1.36; I^2 = 32.4%; $P_{\text{heterogeneity}}$ = 0.181; FEM) and other three methods (*RR* = 1.42; 95% *CI* 1.28–1.58; I^2 = 0.0%; $P_{\text{heterogeneity}}$ = 0.838; FEM). Fourth, in the analysis of dose-response relationship, the problem of different units of SSBs intake in the original studies was solved by taking the sugar intake (g/day) as the exposure. Furthermore, a restricted cubic spline model was used in dose–response meta-analysis, which solved the problem of varied categories of sugar intake levels among studies.

But it has to be admitted that there are still several limitations in our meta-analysis. First, although the potential confounders were adjusted as much as possible in most studies included in our meta-analysis, such as age, sex and physical activity, there are still some studies that did not adjust for potential confounding factors such as smoking and BMI. The pooled *RR* (95% *CI*) of 1.27 (1.18–1.37) for smoking-adjusted studies (Guo et al., 2014; Knüppel et al., 2017; Sanchez-Villegas et al., 2018; Shi et al., 2010; Xia et al., 2017; Yu et al., 2015) were significantly lower than the combined *RR* (95% *CI*) of 1.41 (1.27–1.57) for not smoking-adjusted studies (Barros et al., 2017; Zahedi et al., 2014). While, the pooled *RR* of 1.31 (1.22–1.40) for studies adjusted for BMI (Guo et al., 2014; Sanchez-Villegas et al., 2018; Xia et al., 2017; Yu et al., 2015; Zahedi et al., 2014) was almost the same as the pooled *RR*

of 1.34 (1.18–1.53) for studies not adjusted for BMI (Barros et al., 2017; Knüppel et al., 2017; Shi et al., 2010). Compared to *RRs* for smoking-adjusted, our combined *RR* was overestimated about 3.1%. Moreover, we cannot rule out the possibility that other unmeasured factors and unknown factors may affect the relationship. Second, there are only eleven studies involved in this meta-analysis and more than half of studies were cross-sectional design, which limits the establishment of causal relationship. While the FFQ and SQFFQ were the measurement of SSBs intake in most studies, which can reflect one's diet habit, and therefore the exposure of interest was relatively stable within one's lifetime (Brunner et al., 2001). Moreover, the results of cross-sectional studies were consistent with the results of the cohort studies. These facts could facilitate causal inference. Besides, SSBs might cause depression, in turn, depression might increase consumption of SSBs (Rintamaki et al., 2014; Whitaker et al., 2014), and both directions of causality are important. Third, the measurements of depression assessment were inconsistent, which may raise misclassification bias. However, the *RRs* with their 95%*CIs* were almost identical by both assessment methods from physician (Guo et al., 2014; Sanchez-Villegas et al., 2018; Shi et al., 2010) (*RR* = 1.30; 95% *CI* 1.20–1.41) and self-reported questionnaires (Barros et al., 2017; Knüppel et al., 2017; Xia et al., 2017; Yu et al., 2015; Zahedi et al., 2014) (*RR* = 1.33; 95% *CI* 1.22–1.45). Thus, we infer that there is no extra bias among different measurements of depression.

In summary, findings from the present meta-analysis suggest that the consumption of SSBs might be associated with an increased risk of depression. The threshold of SSBs consumption for depression was the equivalent of about 2 cups/day of cola. Above that level the depression risk might be increased obviously. Findings need to be confirmed further. In future studies, we recommend the use of daily sugar intake from SSBs as the exposure to make exposure measurements more accurate and comparable.

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Author's contribution: DH and WJ designed the study, participated in its design and coordination, interpretation of the data and involved in drafting the manuscript or revising it critically for important intellectual content. DH and LC performed the bibliographical search, data extraction and interpretation of the data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.11.015.

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