Associations of sugar- and artificially sweetened soda with nonalcoholic fatty liver disease: a systematic review and meta-analysis

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Summary

Background/Objectives: Nonalcoholic fatty liver disease (NAFLD) is the major concern of public health worldwide. The risk of NAFLD in subjects who regularly drink soda is controversial. The aim of this study was to assess the association between consumption of sugar-sweetened soda and NAFLD.

Methods: A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from inception through June 2015. Studies that reported relative risks, odd ratios, or hazard ratios comparing the risk of NAFLD in patients consuming a significant amount of either sugar or artificially sweetened soda vs. those who did not consume soda were included. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Seven observational studies were included in our analysis to assess the association between consumption of sugar-sweetened soda and NAFLD. The pooled RR of NAFLD in patients consuming sugar-sweetened soda was 1.53 (95% CI: 1.34–1.75, I² = 0). When meta-analysis was limited only to studies with adjusted analysis, the pooled RR of NAFLD was 1.55 (95% CI: 1.36–1.78, I² = 0). The data on association between consumption of artificially sweetened soda and NAFLD were limited; one observational study reported no significant increased risk of NAFLD in artificially sweetened soda consumption.

Conclusions: Our study demonstrates statistically significant association between sugar-sweetened soda consumption and NAFLD. This finding may impact clinical management and primary prevention of NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western industrialized countries and one of serious public health problems worldwide. The spectrum of NAFLD ranging from hepatic steatosis without evidence of inflammation, which called nonalcoholic fatty liver, to the condition that have significant hepatic inflammation or nonalcoholic steatohepatitis. A number of studies have previously identified

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risk factors for NAFLD including diabetes mellitus, metabolic syndrome, older age, elevated serum aminotransferase and higher visceral adiposity index. Despite the effort to prevent NAFLD, its prevalence has been reported ranging from 6% to 35%.1,2,4

Sugar-sweetened soda consumption has recently been demonstrated as a risk factor for a number of medical conditions such as diabetes, obesity, chronic kidney disease, hypertension, gout, kidney stones and metabolic syndrome.5–9 In addition, the consumption of sugar-sweetened soda has also risen dramatically.10,11 The reported risk of NAFLD in patients consuming either sugar-sweetened soda, however, is still conflicting. A few studies suggested the association between sugar-sweetened soda consumption and NAFLD.12–15 Conversely, several studies demonstrated no significant association between sugar-sweetened soda consumption and NAFLD.14,16 Thus, we conducted this meta-analysis to assess the association between sugar-sweetened soda consumption and NAFLD.

Materials and Methods

Search strategy

Two investigators (K.W. and W.C.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception through June 2015 using the search strategy described in Item S1 in Supplementary Material. A manual search for additional relevant studies using references from retrieved articles was also performed. To assess the quality and publication bias of all studies, conference abstracts, and unpublished studies were excluded.

Inclusion criteria

The inclusion criteria were as follows: (i) randomized controlled trials (RCTs) or observational studies (case–control, cross-sectional or cohort studies) published as original studies to evaluate the risk of NAFLD in patients consuming either sugar or artificially sweetened soda; (ii) odds ratios, relative risks, hazard ratios or standardized incidence ratio with 95% confidence intervals (CI) were provided; and (iii) a reference group composed of participants who did not consume soda. No limits were applied to language.

Study eligibility was independently determined by the two investigators noted above. Differing decisions were resolved by mutual consensus. The quality of each study was independently evaluated by each investigator using Newcastle-Ottawa quality assessment scale.17

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, study design, year of study, country of origin, year of publication, sample size, characteristics of included participants, definition of significant amount of soda consumption, method used to diagnose NAFLD, confounder adjustment and adjusted effect estimates with 95% CI. The two investigators mentioned above independently performed this data extraction.

Statistical analysis

Review Manager 5.3 software from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird.18 Given the high likelihood of between study variances, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran’s Q-test. This statistic is complemented with the I²-statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I² of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and >75% high heterogeneity.19 The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios vs. their standard errors.20

Results

Our search strategy yielded 162 potentially relevant articles. In total, 135 articles were excluded based on title and abstract for not fulfilling inclusion criteria on the basis of the type of article, study design, population or outcome of interest. Twenty-seven articles underwent full-length article review. Twenty articles were excluded (11 articles were not observational studies or RCTs and 9 articles did not report the outcomes of interest). Seven articles were identified and included in the data analysis.2,12,14,16,21–23 Item S2 outlines our search methodology and selection process. Table 1 describes the detailed characteristics and quality assessment of the included studies.

The risk of NAFLD in patients consuming sugar-sweetened soda

Seven studies (six cross-sectional studies1,12,14,16,21–23 and a cohort study25) with 4639 patients were included in the data analysis for the risk of NAFLD. The pooled risk ratio (RR) of NAFLD in individuals consuming sugar-sweetened soda was 1.53 (95% CI: 1.34–1.75). There was no significant heterogeneity with an I² of 0%. Figure 1 shows the forest plot of the included studies.

We performed a sensitivity analysis excluding the studies without adjusted analysis for confounder.24 The association between sugar-sweetened soda consumption and NAFLD remained significant (RR = 1.55 [95% CI: 1.36–1.78, I² = 0]), as shown in Figure 2.

The risk of NAFLD in patients consuming artificially sweetened soda

Data regarding association between consumption of artificially sweetened soda and NAFLD were limited; one cross-sectional study14 reported no significant increased risk of NAFLD in artificially sweetened soda consumption with odds ratio of 0.91 (0.66–1.24).

Evaluation of publication bias

Funnel plot to evaluate publication bias for the risk of NAFLD in patients consuming sugar-sweetened soda is summarized in Figure S1. The graph provides a suggestion for insignificant publication bias of the risk of NAFLD in patients with sugar-sweetened soda consumption.

Discussion

This study is the first systematic review and meta-analysis of published studies assessing the association between sugar-sweetened soda and NAFLD. We demonstrated a statistically
<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Year</th>
<th>Total number</th>
<th>Study sample</th>
<th>Exposure definition</th>
<th>Exposure measurement</th>
<th>Outcome definition</th>
<th>Outcome ascertainment</th>
<th>Adjusted OR</th>
<th>Confounder adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelber-Sagi et al.</td>
<td>Cross-sectional study</td>
<td>2007</td>
<td>349</td>
<td>Israeli adults (aged 24–70 years) randomly sampled from national population registry and interviewed in the First Israeli National Health and Nutrition Survey</td>
<td>Soft drink</td>
<td>Interviewer-administered food frequency questionnaire</td>
<td>A diffuse hyperechoic echo texture, bright liver compared with kidneys, vascular blurring and deep attenuation</td>
<td>Abdominal ultrasound</td>
<td>1.45 (1.13–1.85)</td>
<td>Age, gender, BMI, total calories intake of carbohydrates from soft drinks and protein from all type of meat</td>
</tr>
<tr>
<td>Abid et al.</td>
<td>Cross-sectional study</td>
<td>2009</td>
<td>90</td>
<td>NAFLD patients with and without risk for metabolic syndrome and similar age and gender-matched healthy individual without NAFLD from general population</td>
<td>Soft drink: &gt;50 g/day (&gt;500 cm³/day or &gt;12 teaspoons/day of added sugar)</td>
<td>Self-administered food frequency questionnaire</td>
<td>Combination of brightness, liver–kidney contrast with vascular blurring, and deep attenuation</td>
<td>Abdominal ultrasound</td>
<td>&gt;6 sweetened beverages/week</td>
<td>Age, sex, smoking habits, physical activity, dietary composition, BMI, metabolic syndrome, triglyceride, homeostasis model assessment and metabolic markers</td>
</tr>
<tr>
<td>Vos et al.</td>
<td>Cross-sectional study</td>
<td>2012</td>
<td>149</td>
<td>Children 2–17 years old in multicenter NASH Clinical Research Network</td>
<td>Soft drink: 2 cans soda/week</td>
<td>Self-administered food frequency questionnaire</td>
<td>Definite NASH (&gt;5 NAFLD activity score)</td>
<td>Liver biopsy</td>
<td>2.0 (1.0–5.0)</td>
<td>None</td>
</tr>
<tr>
<td>Oddy et al.</td>
<td>Cohort study</td>
<td>2013</td>
<td>995</td>
<td>Pregnant women in Western Australian Pregnancy Cohort Study</td>
<td>Soft drink: &gt;6 sweetened beverages/week</td>
<td>Physician-administered food frequency questionnaire</td>
<td>Fourth quartile of soft drinks</td>
<td>Liver ultrasound 17-year follow up</td>
<td>None</td>
<td>Western dietary pattern, healthy dietary pattern, sex, misreporting, TV viewing, frequency of physical activity and family income</td>
</tr>
</tbody>
</table>

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(continued)
significant association between sugar-sweetened soda and NAFLD, with 1.53-fold increased risk of developing NAFLD compared with those who did not regularly consume sugar-sweetened soda.

There are several plausible explanations for the significant association between sugar-sweetened soda consumption and NAFLD in individuals who consume sugar-sweetened soda. First, fructose corn syrup, the main sweetener in many sugar-sweetened soda in the majority of included studies has been shown to promote NAFLD. Fructose can induce lipogenesis via upregulation of sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response elementary (ChREBP), which regulate several lipogenic genes. These can lead to increase free fatty acid in hepatic pool. In addition, according to ‘two hits’ hypothesis theory of NAFLD pathophysiology that proposed by Day and James, the progression from steatosis to NAFLD is associated with the factors (second hit), such as lipid peroxidation, advanced glycation end product (AGEs), inflammatory process, oxidative stress and insulin resistance. Thus, it is possible that the consumption of sugar-sweetened soda results in the second hit in the pathogenesis of NAFLD development. Second, fructose has been well demonstrated to link with

Table 1. Continued

<table>
<thead>
<tr>
<th>Adjusted OR</th>
<th>Koch et al.</th>
<th>Mollard et al.</th>
<th>Ma et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft drink:</td>
<td>1.56 (1.29–1.88)</td>
<td>1.10 (0.26–4.67)</td>
<td>1.61 (1.04–2.50)</td>
</tr>
<tr>
<td>Soda:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet soda:</td>
<td>0.91 (0.66–1.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSB:</td>
<td>1.61 (1.04–2.50)</td>
<td></td>
<td></td>
</tr>
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</table>

Confounder adjustment

| Age, sex, BMI, type 2 DM, Alcohol consumption, years of education, smoking status and duration, physical activity total energy intake | Age, sex, BMI, z-score, ethnicity, cardiorespiratory fitness | Age, sex, smoking status, Framingham cohort, energy intake, alcohol, dietary fiber, fat, protein, diet soda intake and BMI |

Quality assessment (Newcastle-Ottawa scale)

<table>
<thead>
<tr>
<th>Selection: 4</th>
<th>Selection: 3</th>
<th>Selection: 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity: 2</td>
<td>Comorbidity: 2</td>
<td>Comorbidity: 2</td>
</tr>
<tr>
<td>Outcome: 3</td>
<td>Outcome: 3</td>
<td>Outcome: 3</td>
</tr>
</tbody>
</table>

NASH, nonalcoholic steatohepatitis; DM, diabetes mellitus; SSB, sugar-sweetened beverages; MDCT, multiple detector computer tomography.

Figure 1. Forest plot of the included studies comparing risk of NAFLD in patients who consumed sugar-sweetened soda and those who did not; square data markers represent RRs, horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV, inverse variance; SE, standard error.

Figure 2. Forest plot of the included studies with adjusted analysis comparing risk of NAFLD in patients who consumed sugar-sweetened soda and those who did not; square data markers represent RRs, horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV, inverse variance; SE, standard error.

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obesity, insulin resistance, metabolic syndrome and diabetes mellitus, major causes of NAFLD.31 However, most of the included studies in our meta-analysis included diabetes and body mass index (BMI) as confounders in the adjusted analysis.2,12,14,16,21 Recently, a few studies have shown that sugar-sweetened soda consumption can lead to NAFLD without the evidence of metabolic syndrome suggesting that high sugar-sweetened soda consumption may directly contribute to NAFLD via lipogenesis and hepatic inflammation related to fructose-induced ATP depletion.12,13,30 It has been shown that NAFLD is induced ATP depletion.12,13,30 It has been shown that NAFLD is associated with NAFLD.34 Thus, further studies are needed to address the impact of artificially sweetened soda consumption and the risk of NAFLD.

Although most of the included studies have good quality, there are some limitations of this study. First, there was no studies comparing between sugar-sweetened soda and artificially sweetened soda consumption in this meta-analysis. Second, this is a meta-analysis of observational studies with its inherent limitations because most of the included are cross-sectional studies. It can at best demonstrate an association but not a causal relationship. Most studies also lacked information regarding types of soda and color of soda; therefore, we cannot determine whether there is any particular soda that may be associated with NAFLD. However, there was no significant heterogeneity or publication bias in our final analysis.

In summary, this meta-analysis demonstrates a significant association between sugar-sweetened soda consumption and NAFLD. Data regarding association between consumption of artificially sweetened soda and NAFLD were limited. The finding of this study may impact clinical management and primary prevention of NAFLD.

Supplementary material

Supplementary material is available at QMED online.

Conflict of interest: None declared.

References


