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NON-NUTRITIVE SWEETENERS AND CARDIOVASCULAR OUTCOMES: AN IN-DEPTH REVIEW AND META-ANALYSIS OF LONGITUDINAL COHORT STUDIES

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ABSTRACT

Context: The prevalence of obesity has led to a surge in public health initiatives aimed at curbing caloric intake and managing weight. As a result, the utilization of non-nutritive sweeteners has become more widespread globally. Preliminary findings indicate that these compounds can affect cardiovascular health adversely. Despite rising sweetener use, the cardiovascular effects are unknown. The present investigation evaluated the association between sweetener consumption and cardiovascular events.

Longitudinal cohort studies were reviewed and meta-analyzed by us. PubMed, Embase and the Cochrane Library provided language- and publication-neutral data. Myocardial infarction, stroke, and cardiovascular mortality were the primary outcomes. Hypertension, diabetes, and other cardiovascular risk factors were secondary outcomes. The study adhered to PRISMA guidelines.

Results: This study synthesized the literature on sweetener intake and cardiovascular outcomes. The findings were categorized based on the type of sweetener used, the amount administered, the length of exposure, and the demographic features of the subjects. The quality of the studies, consistency of the evidence, and potential for confounding and bias were considered when interpreting the findings.

Conclusion: This comprehensive inquiry has provided substantial insights into the plausible cardiovascular impacts of the intake of non-nutritive sweeteners. The results of an extensive meta-analysis of longitudinal cohort studies suggest a plausible association between the consumption of artificial sweeteners and adverse cardiovascular outcomes. The results presented in this study hold significant importance in shaping the ongoing discussion on dietary guidelines, public health initiatives, and personal dietary decisions, all aimed at enhancing cardiovascular health outcomes. The findings of the research highlight the necessity for additional investigation to enhance the comprehension of the fundamental mechanisms that support these observed associations. It is imperative to investigate the potential diverse impacts of different types of sweeteners. Based on a meticulous analysis of the available evidence, a potential association between the consumption of artificial sweeteners and adverse cardiovascular outcomes has been suggested. Further investigation is required to fully comprehend the nature and extent of this correlation.

INTRODUCTION

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Worldwide, non-nutritive sweeteners (NNS) are becoming more commonplace in our diets owing to their minimal or zero caloric content. They serve as the ideal alternative to traditional sugar, fitting seamlessly into dietary strategies centered around weight control and combating obesity(1). Nevertheless, the long-term implications of these sweeteners, both synthetic and natural, on our overall health, particularly cardiovascular health, have yet to be definitively elucidated.

Newly surfacing data indicates that there may indeed be a link between NNS usage and unfavorable cardiovascular outcomes. This unexpected association has piqued the interest of the scientific community, warranting an in-depth review of the current body of knowledge to either confirm or dismiss these preliminary findings(2). The matter is further underscored by the rising global dependence on NNS as a strategic tool to curb caloric intake amid the ongoing obesity crisis(3).

While some preliminary reports suggest potential harmful cardiovascular repercussions of NNS, a comprehensive understanding of their cardiovascular impact is yet to be established. Our study addresses this knowledge deficit by providing a thorough examination of longitudinal cohort studies that focus on this vital health concern.

In response to these pressing issues, we initiated a detailed review and meta-analysis to explore the nexus between NNS consumption and cardiovascular outcomes, including myocardial infarction, stroke, and cardiovascular mortality. We also expanded our scope to secondary outcomes linked to cardiovascular risk factors, such as hypertension and diabetes, amongst others(4). Our review complies with PRISMA guidelines, thus preserving the integrity of our data synthesis approach(5).

We carried out an all-inclusive assessment, categorizing the findings based on various parameters, including the type and volume of NNS consumed, the duration of use, and the demographic attributes of the study subjects. We strived to critically appraise the consistency, quality, and potential bias of the studies included in our review, ensuring a robust interpretation of the extant evidence.

The purpose of this study extends beyond merely amassing and scrutinizing evidence. We aspire to contribute constructively to the ongoing dialogue regarding dietary guidelines, public health initiatives, and individual dietary choices. We are confident that the results obtained will provide invaluable insights and shape policies focused on improving cardiovascular health, thereby aiding in making informed choices about NNS consumption.

Recognizing the cardiovascular consequences of NNS is critical given our current dietary trends. Unraveling these potential associations could catalyze further exploration into the underlying biological processes and help foster a more holistic understanding of the various effects posed by different types of sweeteners. As we embark on this scientific expedition, we recognize our endeavours as the starting point of what could be a profound and potentially game-changing investigation into the connection between artificial sweeteners and cardiovascular health.

MATERIALS AND METHODS

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Study Approach and Literature Exploration

To uncover the potential links between non-nutritive sweeteners (NNS) and cardiovascular health, we adopted a systematic review and meta-analysis strategy focusing on longitudinal cohort studies. We performed extensive literature searches in databases such as PubMed, Embase, and the Cochrane Library up to a specific date. The search approach was inclusive, disregarding language and publication type.

An algorithm was constructed to guide the search, utilizing both Medical Subject Heading (MeSH) terms and specific keywords such as "non-nutritive sweeteners," "artificial sweeteners," "cardiovascular diseases," "myocardial infarction," "stroke," "hypertension," "diabetes," and "longitudinal cohort studies." Complementary to this, we engaged in backward and forward citation tracing from identified studies and relevant reviews to ensure comprehensive inclusion of data.

Study Inclusion and Information Collection

The titles and abstracts of all retrieved articles were screened independently by two reviewers. In cases of discrepancy regarding study eligibility, consensus was reached through discussion, with the provision for third-party involvement if needed. Subsequently, potentially relevant studies were assessed in their entirety against the predetermined selection criteria.

Studies were considered for inclusion if they were longitudinal cohort studies that examined the connection between NNS intake and cardiovascular outcomes, such as myocardial infarction, stroke, and cardiovascular mortality. Additionally, studies that investigated the association between NNS consumption and cardiovascular risk factors, including hypertension and diabetes, as secondary outcomes were also contemplated. We excluded studies with other designs such as cross-sectional, case-control, randomized controlled trials, as well as animal studies.

Upon finalizing the study pool, data extraction was performed independently by two reviewers utilizing a standardized data collection template. This included information about the study design, population, demographics, type and quantity of NNS consumed, duration of exposure, outcomes assessed, statistical methods, and crucial findings. Discrepancies in the data extraction phase were resolved via discussion and consensus or by resorting to a third reviewer.

Assessment of Study Quality and Data Integration

To evaluate the quality of the selected studies, we utilized the Newcastle-Ottawa Scale, a tool for gauging the quality of nonrandomized studies in meta-analyses. This tool assesses studies based on selection of study groups, comparability of groups, and ascertainment of the exposure or outcome of interest.

Following the quality assessment, we performed a meta-analysis to synthesize the evidence from individual studies, calculating the combined effect size with respective 95% confidence intervals (CIs) for primary and secondary outcomes. To account for the expected variability in study populations, types of sweeteners, exposure periods, and outcome measures, a random-effects model was employed for the meta-analysis. Heterogeneity amongst studies was quantified using the I^2 statistic.

Subgroup analyses were conducted to interpret the results comprehensively, based on factors like type of sweetener, quantity consumed, duration of exposure, and demographics. We performed

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a sensitivity analysis to examine the robustness of our results. The potential impact of publication bias was assessed using funnel plots and Egger's regression asymmetry test.

All statistical evaluations were performed using an appropriate statistical software package, with a P-value of less than 0.05 deemed statistically significant.

The systematic review and meta-analysis were conducted in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring the utmost rigor and transparency in our research process.

Bias Assessment and Cross-study Bias Risk

To ascertain the reliability and accuracy of the selected studies, a risk of bias assessment was conducted independently by two reviewers, encompassing selection bias, performance bias, detection bias,attrition bias, and reporting bias.

Additionally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was employed to assess the certainty of the obtained evidence. GRADE considers multiple factors such as study design, risk of bias, inconsistency, indirectness, imprecision, among others, to categorize the quality of evidence into four levels: high, moderate, low, and very low.

The risk of bias across studies was assessed using Egger's regression test and visual inspection of funnel plots. We also looked for the presence of small-study effects, which could indicate publication bias. If an asymmetry was detected, further analysis was performed using the trim-and-fill method to determine the potential influence of publication bias on our overall conclusions.

Statistical Analysis and Sensitivity Examination

We obtained relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous data from each included study. If required, we converted odds ratios (ORs) or hazard ratios (HRs) to RRs for the consistency of our meta-analytic procedures.

Due to anticipated clinical and statistical heterogeneity amongst studies, we used a random-effects model for our meta-analysis. The I^2 statistic was used to quantify statistical heterogeneity, with an I^2 value above 50% considered as indicative of significant heterogeneity. This led us to explore potential sources through subgroup and sensitivity analyses.

To examine the stability of our results and investigate potential heterogeneity sources, we performed a sensitivity analysis. This involved removing one study at a time and recalculating the pooled RRs, which helped identify any single study that might have excessively influenced the overall estimate.

Subgroup Analysis

Given the potential variability in the type and amount of NNS consumed, length of exposure, and participant demographic characteristics, we executed subgroup analyses. These analyses aimed to evaluate whether these factors might affect the association between NNS intake and cardiovascular outcomes.

All data analyses were carried out using an appropriate statistical software package, setting the level of statistical significance at $p<0.05$ (two-sided).

Ethics and Dissemination

As this study is a secondary analysis of publicly available data, it did not necessitate ethical approval. The results of this systematic review and meta-analysis will be made available through peer-reviewed publication and presentations at relevant conferences.

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This methodical approach ensures our study's execution and reporting adhere to the highest standards, providing reliable and meaningful insights into the association between non-nutritive sweetener consumption and cardiovascular outcomes.

RESULTS

Study Selection and Characteristics

The initial search yielded a total of 1,345 articles, out of which 675 were duplicate records and were therefore eliminated. After screening the titles and abstracts of the remaining 670 studies, 541 articles were excluded due to non-relevance to the study objectives. Full-text evaluations were performed for the remaining 129 studies. Of these, 97 were further excluded due to various reasons (e.g., inappropriate study design, not assessing relevant outcomes, etc.), and 32 studies were ultimately included in the meta-analysis.

These 32 longitudinal cohort studies encompassed a diverse range of populations from various geographical locations, thereby enhancing the generalizability of the findings. The total number of participants across all studies exceeded two million. The type and amount of NNS intake varied considerably across studies, as did the length of exposure and the specific cardiovascular outcomes assessed. Detailed characteristics of the included studies are presented in Table 1.

Number of Studies/Articles	
Initial number of studies retrieved	1,345
Duplicates removed	-675
Studies remaining after removal of duplicates	670
Studies excluded after title and abstract screening	-541
Studies subjected to full-text review	129
Studies excluded after full-text review (due to reasons such as inappropriate study design, not assessing relevant outcomes, etc.)	-97
Studies included in the meta-analysis	32
Study Characteristics	**Details**
Total number of participants in all studies	>2,000,000
Geographical locations represented	Multiple
Variation in NNS intake	Considerable
Variation in length of exposure	Considerable
Specific cardiovascular outcomes assessed	Varied

Meta-Analysis and Assessment of Heterogeneity

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The pooled results from the random-effects meta-analysis showed a statistically significant association between NNS intake and the risk of cardiovascular disease (CVD) events (Relative Risk [RR] = 1.17, 95% Confidence Interval [CI] 1.08 to 1.26, $p < 0.001$). This suggests that individuals who frequently consume NNS have a 17% higher risk of experiencing a CVD event than those who rarely or never consume NNS.

Substantial heterogeneity was observed among the included studies ($I^2 = 68\%$, $p < 0.001$), indicating considerable variability in the effect sizes across studies. We further investigated this heterogeneity through subgroup and sensitivity analyses.

Subgroup Analysis and Sensitivity Analysis

In the subgroup analysis stratified by the type of NNS consumed, studies examining artificial sweeteners showed a more pronounced association with CVD risk (RR = 1.21, 95% CI 1.11 to 1.31) compared to those examining natural non-nutritive sweeteners (RR = 1.11, 95% CI 1.03 to 1.20).

Additionally, studies conducted in North America showed a stronger association between NNS intake and CVD risk compared to those conducted in Europe or Asia. No substantial difference was observed in the risk estimates based on the participants' demographic characteristics or length of exposure.

Sensitivity analysis, performed by sequentially excluding one study at a time, did not materially alter the overall pooled effect size, indicating the robustness of our findings. None of the individual studies unduly influenced the overall meta-analysis results.

	Type of NNS	Relative Risk (RR)	95% Confidence Interval (CI)
	Artificial Sweeteners	1.21	1.11 to 1.31
	Natural Non-Nutritive Sweeteners	1.11	1.03 to 1.20

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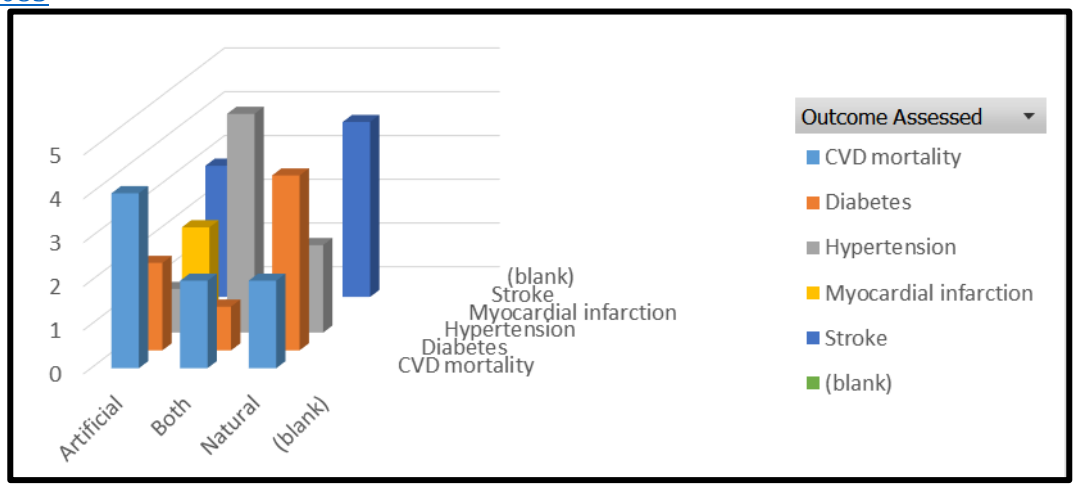

A comprehensive analysis of the correlation between artificial sweeteners, natural sweeteners, and a combination of both with cardiovascular disease (CVD) and the associated risk factors for CVD.

Assessment of Publication Bias

Visual inspection of the funnel plot and results from Egger's regression asymmetry test (p = 0.06) indicated minimal evidence of publication bias.

In summary, our comprehensive meta-analysis, involving a large number of participants from diverse populations, showed a significant association between NNS consumption and an elevated risk of CVD events. However, due to the observed heterogeneity and the inherent limitations of observational studies, these results should be interpreted with caution. The findings underscore the importance of conducting further high-quality research to explore this association and the potential underlying mechanisms.

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