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REVIEW

Sweet Surprises: An In-depth Systematic Review of Artificial Sweeteners and Their Association with Cerebrovascular Accidents

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Abstract

Purpose of Review Artificial sweeteners have become increasingly popular in today's dietary trends as a healthier and sweeter alternative to sugar. As studies emerge regarding artificial sweeteners, concerns are arising about their side effects, particularly linking them to strokes. This systematic review aims to assess the relationship between artificial sweeteners (AS) and cerebrovascular accidents (CVAs). A systematic search of studies indexed in PubMed and Google Scholar was conducted using the keywords "ASB" (artificially sweetened beverage), "Artificial Sweeteners," "Stroke," etc. These studies were screened and filtered according to our exclusion criteria. We reviewed 55 studies published in various journals and further boiled down to finalizing 12 studies for analysis using the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020.

Recent Findings Most studies suggest that there is a positive association between artificial sweetener consumption and CVAs including all types of strokes, particularly ischemic strokes. Poorer outcomes are seen with higher ASB intake. Increased risk is notable among women and black populations. Some studies show no association between ASB consumption and hemorrhagic stroke, however, most suggest a strong link.

Summary The current literature shows a degree of variation so it is crucial to consider possible confounders and eliminate them in future studies. Further research is necessary to determine the underlying mechanisms, especially in individuals with comorbidities. The results obtained play a role in forming dietary guidelines and alarming the public about the possible health implications, prompting caution regarding excessive consumption of artificial sweeteners, in their daily lives.

Keywords Acute stroke · Cerebrovascular accidents (CVAs) · Artificial sweeteners · Aspartame · Artificially sweetened beverages (ASB) · Ischemic stroke · Neurology · Cardiovascular medicine · Emergency medicine · Internal medicine · Nutrition · Health

This systematic review was not registered on PROSPERO, OSF, Cochrane, etc.

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Abbreviations

ASB	Artificially sweetened beverages
SSB	Sugar-sweetened beverages
GRAS	Generally Regarded as Safe
DALY	Disability-adjusted life years

Introduction and Background

Stroke remains a major cause of mortality and a leading contributor to years lost due to disability. From 1990 to 2019, there was a significant increase in the prevalence and impact of stroke. Cases of stroke rose by 70.0%, mortality rates increased by 43.0%, the incidence of stroke saw a 102.0% rise, and there was a staggering rise of 143 in Lost Years. It is important to note that the majority of stroke-related outcomes, including 86.0% of deaths and 89.0% of DALYs (disability-adjusted life years), occur in low- and middle-income countries (LMIC) [1].

In 2021, strokes were responsible for one-sixth of all cardiovascular disease deaths. Shockingly, someone loses their life every 3 min and 14 s to this debilitating condition [2]. In the United States alone, more than 795,000 people suffer a stroke each year, with approximately 610,000 of those cases being first-time occurrences [3].

A stroke is a syndrome characterized by an abrupt onset of neurological deficit resulting from vascular damage (such as infarction or hemorrhage) lasting for more than 24 h within the central nervous system. Stroke can be brought about by several risk factors, disease pathways, and mechanisms [4]. Certain stroke risk factors are non-modifiable, such as age and male gender. It is crucial to note that modifiable risk factors like hypertension, smoking, elevated waist-to-hip ratio, poor dietary habits, poor physical exercise, diabetes mellitus, alcohol usage, psychological elements, cardiac triggers, and the ApoB/Apo1 ratio jointly contribute to over 90% of the stroke risk in the population [5, 6]. In the United States, among the seven markers of cardiovascular well-being, the rating for a healthy diet is the most unfavorable, with a 91.6% rating deemed unfavorable according to the National Health and Nutrition Examination Survey conducted in 2011–2012 [7]. Thus, dietary concerns stand as one of the most serious health challenges in the United States [8].

Artificial sweeteners are synthetic sugar substitutes, which are commonly used by society today as they are comparatively sweeter and contain zero to low calories; thus, they are considered as a healthier alternative to sugar. These artificial sweeteners are categorized into two groups based on their calorie content. Nutritive sweeteners include monosaccharide polyols like xylitol, mannitol, and sorbitol and disaccharide polyols such as lactitol and maltitol. Non-nutritive sweeteners, also called artificial sweeteners, belong to various chemical classes and can be 30–13,000 times sweeter than sugar [9].

Some Food and Drug Administration (FDA) authorized artificial sweeteners include aspartame, acesulfame potassium (Ace-K), sucralose, neotame, advantame, and saccharin.

These sweeteners are commonly used in the beverage industry and are tagged as “diet” soft drinks. Such beverages are usually advertised as being healthy and helpful in weight loss as well. This explains the positive trends in its consumption in recent years all over the world.

The consumption of sweeteners is increasing at a rapid pace in every age group. In the United States, about 25% of children and over 41% of adults consumed artificial sweeteners between 2009 and 2012. If we compare this data to the years 1999–2000, there is an increase of about 54% in consumption in adults and 200% in that of children [10]. During this period, 6000+new products containing artificial sweeteners were introduced in the US alone [11].

Thaumatin and steviol glycosides have been granted Generally Recognized as Safe (GRAS) status by the FDA (Food and Drug Administration). These substances are derived from the leaves of the Stevia plant and Luo Han Guo fruit extracts [12]. In the European Union, the EU Scientific Committee on Food has given the green signal to neohesperidin dihydrochalcone, aspartame-acesulfame salt, and cyclamate [13, 14].

Even after many regulatory bodies have deemed the use of artificial sweeteners as safe, we cannot rule out the possible adverse effects associated with their consumption. While few cohort studies suggest a negative correlation between artificial sweeteners and conditions like type 2 diabetes (T2DM) and obesity, some other observational studies have produced opposite results [15–17]. Cohort studies have shown a positive correlation between artificial sweetener consumption and the risk of conditions such as hypertension, stroke, and cardiovascular events [18].

Hence, while the use of artificial sweeteners appears to be helpful in weight management, there are indeed concerns linking them with various health issues, like obesity and cardiovascular morbidities [19]. The safety of consuming artificial sweeteners continues to be a subject of debate even today. Given the increasing obesity and type 2 diabetes prevalence and the heavy use of such sweeteners, it becomes important to study these sweeteners and their potential contributions to well-being [20, 21]. Nevertheless, it is crucial to understand that the trends identified in these studies might be influenced by the overuse of artificial sweeteners to compensate for an unhealthy dietary pattern (reverse causation).

The increasing trends associated with the prevalence of stroke and associated mortality, heavy consumption of artificial sweeteners, and limited studies focusing on artificial sweeteners’ adverse effects in comparison to sucrose (sugar) necessitate a comprehensive analysis linking artificial sweeteners and their possible connection to stroke.

Review

Methods

This review focuses on available data regarding the consumption of Artificial Sweeteners and their connection to Stroke. We excluded animal studies, paid articles, and papers published in languages other than English. We have adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22] guidelines, as illustrated in Fig. 1, and our data are compiled from previously published papers, thus eliminating the need for ethical approval.

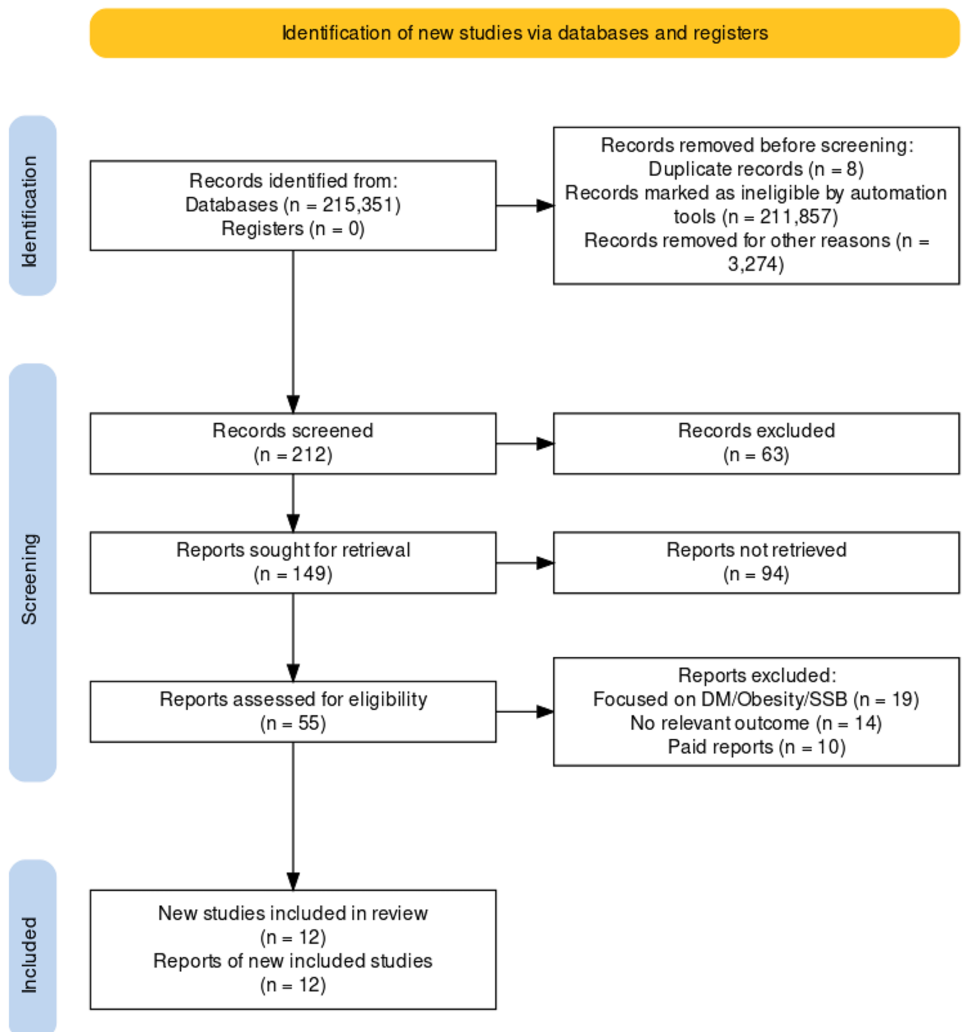

Fig. 1 PRISMA flow diagram illustrating the search strategy and study selection process for the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Systematic Literature Search and Study Selection

We searched for information on artificial sweeteners and possible associations with stroke. We used databases such as PubMed and Google Scholar to find articles related to our study. Eligible outcomes involved strokes including ischemic stroke, hemorrhagic stroke, and TIA. We included all relevant studies but excluded papers related to veterinary studies, papers published in foreign languages, and focusing on other health problems such as obesity or diabetes due to consumption of ASB. These reports were then reviewed by four people independently, and after various discussions, a final consensus was made about the inclusion of studies.

Inclusion and Exclusion Criteria

We established specific criteria for including and excluding reports to achieve our study goals. Our Criteria have been summarized in Table 1.

Search Strategy

We followed a structured approach called PICO (Population, Intervention, Comparison, Outcome) to conduct this systematic review. We searched for studies related to our research question on databases like PubMed and Google Scholar. While searching, we used specific keywords, e.g., "artificial sweeteners," "stroke," "ASB," "Aspartame," and "Sucralose."

Table 1 Inclusion and exclusion criteria adopted during the literature search process

Inclusion criteria	Exclusion criteria
Human studies	Animal studies
From inception till present date	Studies focusing on CHD, DM, SSB, and obesity
English texts	Non-English texts
Free papers	Paid papers

Table 2 Showing the search strategy, search engines used, and the number of results displayed

	Database	Search strategy	Results
A	PubMed	ASB AND Stroke	11
		Artificial Sweeteners AND Stroke	8
		Aspartame OR Sucralose OR Saccharin OR ASB OR Sugar substitutes OR Stevia OR Ischemic Stroke OR Brain TIA OR Acute Stroke	202,732
B	Google Scholar	Artificial Sweeteners and Stroke	12,600

ASB artificially sweetened beverage, *TIA* transient ischemic attack

For PubMed, we used the medical subject heading (MeSH) approach. The method is outlined in Table 2. We limited our study to include the first 20 pages while using Google Scholar.

Quality Appraisal

To ensure that the papers we selected were reliable and of high quality, we employed various tools. A comprehensive table involving various types of studies and the tools applied has been shown in Table 3.

Results

After searching through PubMed and Google Scholar, we found 215,351 articles. We reviewed those records and excluded around 215,139 records. Out of 212 records remaining, we included 149 reports and screened them. We closely examined all reports and 55 of the reports fulfilled our eligibility criteria out of which 43 studies were excluded due to various reasons as stated in Fig. 1 and thus inclusion of 12 studies was made for our systematic review. These 12 studies are summarized in the following Table 4.

Discussions

There has been evidence which links the consumption of artificial sweetening agents like aspartame and sucralose, often an ingredient in various diet sodas, sugar-free soft drinks, non-calorie carbonated drinks, and energy drinks to cerebrovascular insults like stroke.

A systematic review and meta-analysis conducted in China showed a positive correlation between consumption of ASB and stroke which included 5452 participants, incidence of stroke events being 332, and with the RR (relative risk) of 1.54, 95% CI (1.05–2.26). The same study showed a lesser risk of stroke with SSB in comparison to ASB, i.e., sugar-sweetened beverages with RR being 1.09, 95% CI (1.00–1.17) [23••].

Another study done at Harvard University involved a meta-analysis including six prospective studies (16,281,005 person-years of follow-up with 18,077 incident CVD events) concluded that per serving increment of ASBs daily was linked with a 7% higher risk of incidence of CVD (95% CI, 1.05 to 1.10) and was associated with a 9% increased risk of stroke in the future [24•].

If we compare low artificial sweetener consumption with a high consumption subgroup, people who consume higher amounts are associated with worse cardiovascular outcomes HR (hazard ratio) of 1.32, 95% CI (1.12–1.57) [25•].

Consuming ≥ 1 serving/day of ASB was associated with an elevated risk of total stroke 1.24 [1.04, 1.48] in WHI-OS adjusted models and 1.19 [1.04–1.36] in network meta-analysis of 5 prospective cohort studies done by Yang et al. [26••].

A prospective study conducted in Japan over 18 years of follow-up of 39,786 Japanese men and women aged 40–59 years concluded with 1922 incidents of stroke including 859 (454 men and 405 women) cases of hemorrhagic stroke and 1047 (670 men and 377 women) incidents of ischemic stroke. Although the incidence was higher in men, the results showed a significant association

Table 3 Showing quality appraisal tools used

Quality appraisal tools used	Types of studies
Cochrane bias tool assessment	Randomized control trials (RCT)
Newcastle–Ottawa tool	Non-RCT and observational studies
PRISMA Checklist 2020	Systematic reviews and meta-analysis
SANRA checklist	Any other without a clear method section

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis, *SANRA* Scale for Assessment of Non-systematic Review Articles

Table 4 Summary of the results of selected papers

Author/year	Country	Study design	Database used	Conclusion
Li et al. (2023) [23••]	China	Meta-analysis	PubMed	Intakes of SSBs and ASBs were significantly associated with risk of hypertension, stroke, and all-cause mortality
Eshak et al. (2012) [27]	Japan	Prospective cohort	Google Scholar	Soft drink intake was positively associated with risks of total and ischemic strokes for women, whereas a nonsignificant inverse trend was observed for men in this prospective cohort of over 39,786 men and women
Pacheco et al. (2023) [24•]	USA	Prospective cohort	PubMed	Among physically active participants, higher SSB intake, but not ASBs, is associated with a higher cardiovascular risk
Krittanawong et al. (2022) [25•]	USA	Systematic review and meta-analysis	Google Scholar	Compared with low artificially sweetened beverage consumption, higher consumption of artificially sweetened beverages was associated with greater cardiovascular outcomes
Yang et al. (2022) [26••]	USA, China, Canada	Network meta-analysis	PubMed	The consumption of ≥ 1 serving of SSB per day was associated with a slightly elevated risk of total stroke. ASB consumption was also associated with a higher risk of total CVD and total stroke
Rahmani et al. (2019) [28]	USA	Prospective cohort	PubMed	In this study of postmenopausal women in the United States, consumption of ASBs was associated with increased risk of ischemic stroke, CHD, and mortality. Higher risk was associated with the ischemic stroke subtype
Pase et al. (2017) [30]	USA	Prospective cohort	Google Scholar	Artificially sweetened soft drinks were linked with an increased risk of ischemic stroke, dementia, and Alzheimer's disease. When comparing daily cumulative intake to 0 per week (reference), the hazard ratio was 2.96 for ischemic stroke, and SSB was not associated with stroke/dementia
Vyas et al. (2014) [29]	USA	Retrospective cohort	Google Scholar	This analysis demonstrates an association between high diet drink intake and CVD outcomes and mortality in postmenopausal women in the WHI OS
Gardener et al. (2012) [31]	USA	Prospective cohort	Google Scholar	Those who consumed diet soft drinks daily (vs. none) had an increased risk of vascular events, and this persisted after controlling further for metabolic syndrome, peripheral vascular disease, diabetes, cardiac disease, hypertension, etc
Johnson et al. (2018) [32]	USA	Literature review	Google Scholar	Positive association exists between diet soft drinks and stroke
Bernstein et al. (2012) [33]	USA	Prospective cohort	Google Scholar	Greater consumption of sugar-sweetened and low-calorie sodas was associated with a significantly higher risk of stroke
Larsson et al. (2014) [34]	Sweden	Prospective cohort	Google Scholar	High consumption of sweetened beverages, such as soft drinks, may increase the risk of stroke, especially cerebral infarction. Those who consumed > 2 servings/day of sweetened beverages had a 22% higher risk of cerebral infarction compared with those who consumed, on average < 2 servings/week

SSBs sugar-sweetened beverages, *ASBs* artificially sweetened beverages, *CVD* cardiovascular disease, *CHD* coronary heart disease, *WHIOS* Women's Health Initiative Observational Study

between soft drink consumption total and ischemic stroke in women, whereas a non-significant inverse relationship was observed in men. For men who consumed soft drinks almost every day, the multivariable HR ranged from 0.71 to 0.78 for strokes of all types but women on the other hand had HR ranging from 0.70–0.79 for hemorrhagic strokes, but HR was significantly higher ranging from 1.82 to 2.07 for ischemic types [27].

Rahmani et al. observed that individuals who consumed the highest doses of artificial sweeteners compared to those who rarely (less than once a week) or never consumed them were found to have a higher risk of experiencing adverse health outcomes, except hemorrhagic stroke. Even after accounting for several variables, the adjusted models showed hazard ratios of 1.23 95% CI (1.02–1.47) for overall stroke, 1.31 95%CI (1.06–1.63) for ischemic stroke, 1.29 95%CI (1.11–1.51) for coronary heart disease, and 1.16 95%CI (1.07–1.26) for all-cause mortality. Women with no history of diabetes or other cardiovascular diseases had a significant association between high ASB consumption and 2 twofold increased risk of a specific type of ischemic stroke called small artery occlusion ischemic stroke, with a hazard ratio of 2.44 (95%CI 1.47–4.04). Among obese women with a BMI > 30, high ASB intake was associated with an increased risk of ischemic stroke, with an HR of 2.03 95% CI (1.38–2.98) [28].

The WHI OS (Women's Health Initiative Offspring Cohort) included 59,614 women with an average age of 62.8 years, i.e., postmenopausal women. In the initial unadjusted analysis, over a follow-up period of 8.7 ± 2.7 years, the primary outcome was observed in 8.5% of women who consumed 2 or more diet drinks per day. In comparison, this outcome occurred in 6.9%, 6.8%, and 7.2% of women in the groups that consumed diet drinks 5–7 times/week, 1–4 times/week, and 0–3 times/month, respectively. After adjusting risk factors, it was observed that women who consumed 2 or more diet drinks/day had a higher risk of experiencing cardiovascular events HR 1.3 95% CI (1.1–1.5), cardiovascular disease-related mortality HR 1.5 95% CI (1.03–2.3), and overall mortality HR 1.3 95% CI (1.04–1.5) compared to the reference group, which consumed diet drinks 0–3 times per month [29].

A prospective cohort study, popularly known as (FHS) Framingham Heart Study Offspring Cohort (OS), studied 2888 participants and followed them for 10 years. At the end of the study, researchers concluded that artificial sweetener consumption is linked to ischemic stroke (HR = 2.96) 95% CI (1.26–6.97). Additional findings reported in the group adjusted for age, sex, total caloric intake, the dietary guidelines adherence index, self-reported physical activity, and smoking status had an HR (ischemic stroke) 2.47 and 2.27 with a p value of 0.002 and 0.03 for the group of people who consumed recently 0–6 drinks/week and > 1 drink/day, respectively. For chronic consumption, HR for the same adjusted factors was 2.62 and 2.96 with p value being 0.01. Even after being adjusted for HTN, AF, LVH, cholesterol, DM, and waist-to-hip ratio, the HR ranged from 1.59 to 2.59 [30].

In NOMAS (Northern Manhattan Study), a prospective cohort of 2564 people was followed up for 10 years. This study concluded that daily diet drink consumption was associated with an increased risk of vascular events overall, but after diving deep into individual events, there was no elevated risk of stroke per se as the HR was not statistically significant ranging from 0.71 to 2.20; however, significant association with myocardial infarction as much as 59% increased risk of a myocardial infarction was seen among groups who consumed diet drinks daily. A noteworthy result stated that diet soft drink was associated with an increased risk of vascular events in the black population compared to white HR = 1.06 95% CI (1.01–1.11) $p = 0.03$ [31].

Johnson and colleagues synthesized data from various prior studies. The data they gathered indicate that there is a potential link between the prolonged consumption of low-calorie sweetened (LCS) beverages and an increased risk of developing type 2 diabetes mellitus and cardiovascular disease (CVD). However, it is important to note that factors like reverse causation and body fat levels cannot be entirely ignored as contributing factors in these observations. Also, the connection between LCS beverages and the risk of stroke appeared to be elevated across different study groups [32].

Studies show that the more you consume artificial sweeteners, the more the risk of developing hypertension, which in itself is the single most important risk factor for developing stroke. A study done by Bernstein et al. also known as the Nurses' Health Study (NHS) where 84,085 women were followed up for 28 years and the Health Professional Follow-up Study whereby a total of 43,371 men were followed up for 22 years when data from both studies were pooled, it documented that the RR of developing total stroke is 1.16 95% CI (1.05–1.28) for people consuming > 1 low-calorie soda per day. In men, the data were not statistically significant, but the same does not hold in the case of women. In women, low-calorie soda was associated with a higher risk of hemorrhagic stroke RR for 1 serving/day—1.31 95%CI (1.15–1.51) and SSB consumption led to more risk of developing Ischemic Strokes RR for 1 serving/day—1.19 95% CI (1.01–1.39). Also, coffee consumption of 1 serving decreased the risk of developing stroke by around 13%—decaffeinated coffee and about 11%—caffeinated coffee when compared to low-calorie soda (1 serving) [33].

A study done at Karolinska Institutet, Stockholm, Sweden, followed up 32,575 women and 35,884 men for a mean duration of 10.3 years. This study concluded that sweetened beverage consumption was associated with an increased risk of developing total stroke and ischemic stroke but did not show any association with hemorrhagic stroke. Women and men who consumed > 2 servings/day of sweetened beverages had a 19% 95% CI (4–36%) and 22% 95% CI (4–42%) increased risk of total stroke and cerebral infarction, respectively, compared to those who rarely consumed these drinks [34].

The cumulative results of these studies reinforce the negative effects observed from the use of artificial sweeteners and raise concerns about their rapid adoption in today's world as a substance of potent sugar substitute. Although low in calories, sweeteners can initiate inflammation and lead to insulin resistance and gut bacteria damage. Furthermore, it is important to approach results regarding flavorings with caution. This caution arises from the possibility of reverse causation. In simple words, people may have had conditions such as obesity, high blood pressure, and high cholesterol before they started taking ASBs. In other cases, health-conscious individuals may have chosen ASBs to control weight and reduce blood pressure and cholesterol levels.

Limitations

The results generated must be interpreted with potential limitations. We limited our database search to free full texts, thus potentially not taking into consideration another handful of studies with significant information. Individuals who consumed more beverages often exhibited other unhealthy lifestyle choices that could result in possible confounders leading up to the development of stroke. Most of the studies eliminated possible confounders and adjusted their data. But we cannot 100% rule out the possibility of confounders still playing a major role in disease progression. We cannot ascertain any possible additive or synergistic effect of other diet products that may interact with artificial sweeteners and or may play a part in pathogenesis. Also, we limited our search to only English articles and the first 20 pages of the database obtained through Google Scholar as depicted in Table 2.

Conclusion

In conclusion, our research into the consumption of artificial sweeteners and their possible impact on developing stroke is in accordance with previous studies. Although there is a positive association between the consumption of ASB/artificial sweeteners and stroke, it is important that we take into consideration the possible involvement of confounders, including lifestyle choices and pre-existing health conditions. Further research is definitely needed to better draw out the direct causation between the two variables. Such studies must aim to provide a more balanced and unfiltered relationship between the two and eliminate possible confounding and bias.

Individuals with pre-existing health conditions must exercise moderation while consuming artificial sweeteners. We must raise public awareness; this will help individuals make better-informed choices that will eventually support their well-being and reduce the risk of morbidity and mortality due to strokes, thus leading to a better quality of life.

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Author Contribution K.G. substantially contributed to the concept and design of the study; acquisition, analysis, or interpretation of the data; drafting of the manuscript; and critical review of the manuscript and agreed to be accountable for all aspects of the work and will be involved in the final approval of the version to be submitted. I.E. substantially contributed to the conception and design of the study, drafting of the manuscript, and critical review of the manuscript and agreed to be accountable for all aspects of the work and will be involved in the final approval of the version to be submitted. K.S. contributed substantially to the analysis/interpretation of data, critically reviewed the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, and will review the final version to be submitted. B.P. contributed substantially to the concept and design of the study, critically reviewed the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, reviewed the final version to be submitted, and supervised the work.

Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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