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Varied effects of sweeteners on pediatric hypertension: A multicenter study

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SUMMARY

Background & aims: The link between sugar-sweetened beverage consumption and metabolic syndrome has prompted the use of non-nutritive sweeteners(NNS). However, emerging evidence links NNS to elevated cardiovascular risk in children. This study examines the association between sweetener consumption and pediatric hypertension to guide cardiovascular health recommendations for children.
Methods: The Taiwan Pubertal Longitudinal Study, initiated in July 2018, is a multicenter, prospective cohort study involving 1696 patients aged 7–17 years. Baseline dietary exposures were collected using the validated NNS Food Frequency Questionnaire covering acesulfame potassium(AceK), aspartame, sucralose, glycyrrhizin, steviol glycosides, sorbitol, and added sugars. Spot urine samples were collected concurrently. Anthropometric and blood pressure measurements were recorded every 3 months. Pediatric hypertension was defined as systolic or diastolic blood pressure at or above 95th percentile for age, sex, and height, using the measurement closest to dietary assessment. Multivariate generalized linear mixed models were used to examine associations between sweetener exposure and pediatric hypertension, adjusting for age, sex, z-BMI, family history of hypertension, total calorie intake, sodium intake, physical activity, parental education, and household income. Participants were recruited on an ongoing basis, and data collected from July 2018 to September 2022 were analyzed.
Results: Aspartame and added sugars were dose-dependently associated with increased pediatric hypertension risk (aspartame: OR = 1.69, 95%CI:1.03–2.75; p = 0.04; added sugar: OR = 2.63, 95% CI:1.50–4.60; p < 0.001), while steviol glycosides showed borderline protective effects (p for trend = 0.05). AceK was negatively associated with hypertension in girls (OR = 0.30, 95%CI:0.09–0.98; p = 0.05), whereas aspartame was positively associated with hypertension risk in boys (OR = 3.13, 95%

Abbreviations: NNS, Non-nutritive sweetener; CVDs, Cardiovascular diseases; SSB, sugar-sweetened beverages; BMI, Body mass index; TPLS, Taiwan Pubertal Longitudinal Study; AceK, Acesulfame potassium; OR, odds ratio; CI, confidence interval; NNS-FFQ, Nutritive Sweetener Food Frequency Questionnaire; SES, socioeconomic status; NTD, New Taiwan Dollar; ADI, Acceptable daily intake; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

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CI:1.30–7.54; p = 0.01). The association between added sugar intake and hypertension was stronger in overweight children. Substituting added sugars with NNS was associated with lower hypertension risk. Urinary biomarker analysis further supported the inverse association between AceK and hypertension, particularly in girls.

Conclusion: This study demonstrated that aspartame and added sugars were associated with a higher pediatric hypertension risk, while steviol glycosides were linked to lower hypertension risk. Replacing added sugar with NNS was associated with lower pediatric hypertension risk. These findings emphasize the need for tailored dietary guidelines and further investigation on sweetener use in children.

1. Introduction

The increased prevalence of obesity, metabolic syndrome, and cardiovascular diseases (CVDs) in adults has been closely linked to the consumption of sugar-sweetened foods and beverages [1]. In response, strategies to reduce sugar and limit caloric consumption have prompted the use of non-nutritive sweeteners (NNSs), which provide high sweetness with little or no additional energy. However, emerging evidence suggests that NNS consumption may still carry risks for adverse metabolic outcomes.

In animal studies, NNS intake has been associated with weight gain and features of metabolic syndrome. One proposed mechanism suggests that NNSs interact with sweet taste receptors, creating a perceived fasting state. This may trigger the release of appetite-stimulating neuropeptides such as neuropeptide Y, potentially leading to increased food consumption [2]. Additionally, NNSs has been shown to alter gut microbiota composition, increasing Firmicutes and decreasing Bacteroidetes. These changes have been linked to glucose intolerance and metabolic dysregulation [3].

Human studies have yielded mixed results. Some research reports associations between NNSs consumption and elevated fasting glucose and triglyceride levels [4], though the link to metabolic syndrome remains inconclusive. One potential explanation is that NNSs may disrupt metabolic regulation through altered gut microbiota composition, impaired glucose homeostasis, and reduced secretion of metabolic hormones such as glucagon-like peptide-1(GLP-1) [5,6]. Further evidence suggests that NNSs may influence calorie intake by modulating taste perception and appetite regulation [2,6], potentially counteracting their intended role in calorie reduction. These metabolic disruptions may contribute to an increased risk of CVD. A large cohort study demonstrated that habitual NNS consumption was associated with an increased risk of CVD in adults [7]. Moreover, several epidemiological studies have reported a potential positive association between NNS consumption and elevated blood pressure [8], raising public health concerns that NNSs may be a modifiable risk factor for CVD in adults.

Dietary habits established during childhood have long-term health implications. Sweetener consumption in early life may therefore exert lasting effects [9]. Childhood consumption of sugar-sweetened beverages (SSBs) is directly linked to increased body fat, higher body mass index (BMI), and greater waist circumference over time. Replacing SSBs with water, coffee, or tea is associated with improvements in these anthropometric measures [10]. Although NNSs are commonly introduced to reduce total SSB intake, concerns have emerged regarding their potential metabolic impact in children. Evidence suggests a possible relationship between NNS consumption and increased BMI in childhood [11].

Animal models provide potential mechanisms to explain these findings. Early-life exposure to NNSs through maternal milk has been shown to raise the sweet taste threshold. As a result, higher concentrations of sweeteners are required to achieve the same perceived sweetness. The reduced sensitivity to sweetness may lead to a preference for highly sweetened products and contributes to excessive caloric intake, obesity, and related metabolic disorders [12].

Pediatric hypertension is an emerging public health concern [13]. Prevalence rates have reached 19.2 % in boys and 12.6 % in girls in the United States [14]. In China, rates are similarly high, with 20.2 % in boys and 16.3 % in girls [15]. Pediatric hypertension not only contributes to metabolic disturbances in youth but also increases the risk of developing metabolic syndrome and hypertension in adulthood [16,17]. Moreover, children with pediatric hypertension have a 35 % higher risk of developing hypertension in adulthood compared to their normotensive peers [18].

Despite these concerns, few studies have specifically examined the relationship between sweetener consumption and pediatric hypertension. In our study, we investigated the association between sweetener consumption and pediatric hypertension, as well as sex differences in this association. We collected urine samples from patients to analyze the association between urinary NNS levels, questionnaire assessments, and their link to pediatric hypertension. These findings can enhance our understanding of the effects of sweeteners on blood pressure in children, address the existing literature gap, and inform dietary recommendations for pediatric cardiovascular health.

2. Materials & methods

2.1. Study design and data collection

Data were obtained from the Taiwan Pubertal Longitudinal Study (TPLS), a multicenter, population-based prospective cohort study initiated in July 2018. The study was conducted at 4 pediatric departments within medical centers in Taiwan: Taipei Medical University Hospital, Taipei Municipal Wanfang Hospital, Cathay General Hospital in Taipei, and National Cheng Kung University Hospital (Supplementary Figs. 1 and 2). Participants aged 7–17 years were enrolled through physician referrals during routine clinical visits, in-hospital recruitment posters, and outreach efforts, including direct invitations from healthcare providers. Informed consent was obtained from parents or guardians, and adolescents provided assent before participation. Detailed information is provided in the Supplementary Material, Supplementary Figs. 1 and 2.

The participants were followed up prospectively. Those with metabolic disorders or congenital conditions, such as diabetes, hyperlipidemia, maple syrup urine disease, or phenylketonuria, were excluded. Follow-up assessments were conducted every 3 months, recording body weight, body height and blood pressure. Demographic information and 24-h dietary records were collected

during the recruitment phase. Participants were administered the Non-Nutritive Sweetener Food Frequency Questionnaire (NNS-FFQ) to investigate the consumption of the most commercially used sweeteners in Taiwan, including acesulfame potassium (AceK), aspartame, sucralose, glycyrrhizin, steviol glycosides, sorbitol, and added sugars. Urine samples were also collected to assess NNS exposure.

This study was approved by the Institutional Review Boards of Taipei Medical University (N201802018), Cathay General Hospital (CGH-P108107), and National Cheng Kung University Hospital (B-BR-108-076) and adhered to the ethical principles outlined in the Helsinki Declaration.

2.2. Exposure assessment

Demographic data, namely sex, age, anthropometric data, family history of hypertension and CVDs, household secondhand smoke exposure, parental education level, household income, sleep duration, and physical activity records, were collected during the recruitment phase. Socioeconomic status (SES) was assessed via a self-reported questionnaire. Parental education was categorized as senior high school or below, college, and graduate school or above. Household income was grouped into three categories: less than 70,000 New Taiwan Dollar (NTD), 70,000–100,000 NTD, and greater than 100,000 NTD per month. Body height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI values were calculated and converted into age- and sex-specific z-scores (z-BMI) using the World Health Organization (WHO) 2007 AnthroPlus R package (version 0.9.0) [19].

Dietary intake data, including daily food components, caloric and sodium intake, were collected by trained dietitians using mobile software (Nutritionist edition, COFIT Pro, Version 1.0.0) with reference to a Taiwanese food composition table validated in a pilot study [20]. The NNS-FFQ, delivered online, was previously validated for reproducibility in our prior research [21]. It assessed the frequency and portion sizes of food and beverage items containing NNSs consumed in the past month. Detailed validation methods and questionnaires are provided in the Supplementary Materials.

The NNS-FFQ included items such as hand-shaken drinks, sparkling drinks, caffeine/tea beverages, dairy drinks, soy/rice milk, potato chips, sweet snacks (e.g., biscuits, cookies, desserts), candies (e.g., chewing gum, fudge, hard candy, jelly), processed frozen foods, dried fruits, instant noodles, and nutritional supplements. A separate item captured the use of tabletop sugar substitutes. Brand examples were provided for each item to enhance recall accuracy and ensure comprehensive NNS exposure assessment. NNS intake was calculated as a proportion of the daily intake relative to the WHO-recommended acceptable daily intake (ADI) [22]. Since there is no recommended ADI for sorbitol, the maximum observed intake in the population was used as a reference.

Urine samples were analyzed according to established protocols [23], reflecting NNS intake by the participants within 24–48 h [21]. Detailed methods are provided in the Supplementary Materials.

2.3. Outcome assessment

Blood pressure were measured using electronic (oscillometric) devices by trained technicians. Children were comfortably seated for at least 10 min before assessment. Blood pressure was measured 3 times on the right arm with an appropriate cuff size during a single visit, and the average was calculated for each child.

Hypertension was defined as an average systolic blood pressure (SBP) or diastolic blood pressure (DBP) at or above the 95th percentile for sex, age, and height, based on a large cross-sectional study involving children aged 7–17 years in the Chinese National Survey on Students' Constitution and Health [24]. Advanced hypertension was defined as SBP or DBP at or above the 99th percentile.

2.4. Statistical analysis and data management

Participants were continuously recruited and followed, and data collected from July 2018 to September 2022 were used in this study. For each participant, the blood pressure measurement closest in time to the dietary record assessment was used to ensure temporal alignment between exposure and outcome.

Data integrity and logical consistency were verified. Blood pressure values were examined to ensure that SBP exceeded DBP, and extreme values (those exceeding 5 standard deviations from the sex- and age-specific mean [24]) were excluded.

T-tests and chi-square tests were used to compare continuous and categorical demographic variables between boys and girls. The participants were divided into two groups (M1 and M2) based on the median intake of each NNS, and compared to a non-exposure group. A multivariate generalized linear mixed model was introduced to examine the relationship between sweetener exposure and pediatric hypertension. Statistical models were adjusted for potential confounders, including sex, age, z-BMI, family history of hypertension, total caloric intake, total sodium intake, physical activity, parental education, and household income. Secondary analyses explored the association between NNS consumption and pediatric hypertension in greater detail. Dose–response relationships were analyzed using NNS consumption as a continuous variable to assess the trend of hypertension risk across increasing exposure levels, adjusted for the same potential confounders as in the primary analysis. Subgroup analyses were carried out by stratifying participants based on sex, using a multivariate generalized linear mixed model adjusting for age, z-BMI, family history of hypertension, total calorie intake, total sodium intake, physical activity, parental education, and household income. Furthermore, subgroup analysis stratifying participants based on BMI categories (non-overweight and overweight), defined according to WHO recommendations (overweight: z-BMI$\geq$1; non-overweight: z-BMI<1) [19].

Although dietary and lifestyle variables, including 24-h dietary records, NNS-FFQ, physical activity and sleep duration, were collected repeatedly during follow-up, this analysis utilized the values closest in time prior to the blood pressure measurement as baseline sweetener intake and lifestyle variables. This approach ensured temporal alignment between exposure and outcomes, minimized reverse causality and promoted data consistency across participants, as not all individuals completed repeated assessments at the same intervals.

To evaluate the substitution effect of replacing added sugars with NNSs, both added sugars and NNSs were categorized into three levels: non-consumers, low (below-median), and high (above-median) intake groups. For each NNS, a substitution variable was constructed to compare the "Low Sugar, High NNS" group with the "High Sugar, Low/No NNS" group. Logistic regression was used to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) for hypertension, adjusting for sex, age, z-BMI, family history of hypertension, total calorie intake, total sodium intake, and physical activity. Although this approach does not represent a standardized serving size, it reflects a relative shift in consumption patterns, specifically by substituting higher added sugar intake with relatively higher NNS intake. This allows us to explore the potential impact of dietary substitutions on pediatric hypertension risk.

For the urine sample analysis, t-tests and chi-square tests were used to compare continuous and categorical demographic variables between participants with and without urine samples. Sweetener urinary levels were categorized into two groups (M1 and M2) based on median NNS levels, compared to a non-exposure group. Associations with hypertension were evaluated using the same adjusted generalized linear models.

The "mice" package was used to impute missing values [25]. All statistical tests were two-sided with a significance threshold of 0.05. Analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing).

3. Results

A total of 1696 children, including 1157 girls and 539 boys, were included in the study. The overall prevalence of hypertension in our study was 14.4 %, with advanced hypertension observed in 6.3 % of the participants. Table 1 lists the baseline characteristics of these participants. Boys had higher SBP than girls, while DBP was comparable between sexes. Boys also had a higher average daily caloric intake (1780.26 kcal) compared to girls (1491.01 kcal). Girls were more frequently from higher-income households. There were no significant sex differences in family history of CVDs or hypertension, household secondhand smoke exposure, total sodium intake, parental education levels, or z-BMI.

3.1. Association between sweetener consumption and pediatric hypertension

Table 2 and Table 3 summarize the association between sweetener consumption and pediatric hypertension. Steviol consumption was not significantly association with hypertension risk in either the M1 or M2 group, though a borderline inverse dose–response trend was observed (p for trend = 0.05). In contrast, higher added sugar consumption was associated with greater odds of hypertension. The OR was 1.67 (95 % CI: 1.16–2.43; p = 0.006) in the M1 group and 1.99 (95 % CI: 1.38–2.87; p < 0.001) in the M2 group, with a significant dose–response relationship (p for trend <0.001).

For advanced hypertension, aspartame consumption in the M2 group was associated with greater odds of hypertension (OR = 1.69, 95 % CI: 1.03–2.75; p = 0.04), with a significant dose-dependent effect (p for trend = 0.03). Furthermore, added sugars consumption showed a positive association with advanced hypertension. The OR was 2.04 (95 % CI: 1.14–3.63; p = 0.02) in the M1 group and 2.63 (95 % CI: 1.50–4.60; p < 0.001) in the M2 group, with a significant dose-dependent effect (p for trend<0.001).

Positive correlations were observed between added sugars intake and both systolic and diastolic hypertension with dose-dependent effect. Steviol intake was inversely associated with diastolic hypertension in the M2 group (OR = 0.49, 95 % CI: 0.25–0.96; p = 0.04), with a significant dose-dependent effect (p for trend = 0.01). Though aspartame consumption showed a borderline association with advanced diastolic hypertension in the M2 group (OR = 1.70, 95 % CI: 1.0–2.89; p = 0.05), dose–response trend was observed (p for trend = 0.04). Other sweeteners did not show significant association with hypertension.

Figure 1 illustrates the relationships between sweetener consumption and pediatric hypertension. Added sugar consumption showed positive association with systolic and diastolic hypertension (Figures 1A and 1B). However, steviol consumption was negatively associated with diastolic hypertension.

Table 1
Baseline participant characteristics.

Characteristics	Girls	Boys	*P* value
	Mean or N (SD or %)	Mean or N (SD or %)	
N	1157 (68.22 %)	539 (31.78 %)	NA
Age	9.81 (1.80)	11.64 (1.82)	**<0.001**
SBP (mmHg)	95.67 (12.84)	101.34 (12.86)	**<0.001**
DBP (mmHg)	67.69 (10.20)	67.43 (8.79)	0.61
Family history[a]	263 (22.73 %)	100 (18.56 %)	0.29
Exposure to household secondhand smoke	254 (21.95 %)	108 (20.04 %)	0.84
Daily total calories (kcal)	1491.01 (421.08)	1780.26 (488.92)	**<0.001**
Daily total sodium (mg)	2415.15 (1851.67)	2477.29 (1860.97)	0.59
Parental education			
Senior high school or below	82 (7.09 %)	31 (57.51 %)	0.11
College	604 (52.20 %)	241 (44.71 %)	
Graduate school or above	324 (28.00 %)	165 (30.61 %)	
Household income (NTD)			
<70,000	282 (24.37 %)	95 (17.63 %)	**0.04**
70,000–100,000	484 (41.83 %)	215 (39.89 %)	
>100,000	240 (20.74 %)	121 (22.45 %)	
z-BMI	0.248 (1.37)	0.35 (1.56)	0.18
Sleep (h)	8.77 (1.36)	8.5 (1.18)	**0.05**
Physical activity[b]	148 (12.79 %)	96 (17.81 %)	0.17
ADI_AceK (mg/kg)[c]	0.0012 (0.006)	0.0028 (0.016)	**0.03**
ADI_Aspartame (mg/kg)[c]	0.0006 (0.003)	0.0015 (0.011)	0.07
ADI_Sucralose (mg/kg)[c]	0.0029 (0.011)	0.0058 (0.020)	**0.002**
ADI_Glycyrrhizin (mg/kg)[c]	0.0012 (0.003)	0.0013 (0.004)	0.73
ADI_Steviol (mg/kg)[c]	0.0012 (0.007)	0.0038 (0.026)	**0.02**
ADI_Sorbitol (mg/kg)[c]	0.0003 (0.001)	0.0004 (0.001)	0.18
ADI_Added sugar (mg/kg)[c]	0.0040 (0.007)	0.0040 (0.008)	0.68

Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; NTD, New Taiwan Dollar; BMI, Body Mass Index; ADI, acceptable daily intake; AceK, acesulfame potassium; CVDs, cardiovascular diseases.

[a] Positive family history defined as any family history of hypertension or CVDs.

[b] Physical activity was defined as exercising for 30 min daily.

[c] The sweetener exposure dose was estimated as the proportion of daily intake relative to the acceptable daily intake recommended by the WHO. Sorbitol was estimated as the proportion of daily intake relative to maximal intake level in the population.

Table 2
Association between sweetener consumption and pediatric hypertension.

Sweeteners	Exposure dose[a,b]	95[c]					99[d]				
		OR	95 % CI		*P*	*P* for trend	OR	95 % CI		*P*	*P* for trend
AceK	0 (N = 1120)	ref				0.56	ref				0.09
	M1 (N = 253)	0.65	0.41	1.03	0.07		0.48	0.23	1.01	0.05	
	M2 (N = 254)	1.01	0.67	1.51	0.98		0.69	0.36	1.33	0.27	
Aspartame	0 (N = 976)	ref				0.79	ref				**0.03**
	M1 (N = 339)	0.91	0.63	1.32	0.63		1.34	0.80	2.24	0.26	
	M2 (N = 326)	0.97	0.67	1.41	0.89		1.69	1.03	2.75	**0.04**	
Sucralose	0 (N = 917)	ref				0.59	ref				0.38
	M1 (N = 387)	1.18	0.84	1.65	0.35		1.36	0.86	2.16	0.19	
	M2 (N = 338)	1.06	0.74	1.53	0.75		0.64	0.35	1.17	0.15	
Glycyrrhizin	0 (N = 984)	ref				0.48	ref				0.21
	M1 (N = 317)	0.69	0.47	1.02	0.07		0.66	0.37	1.19	0.17	
	M2 (N = 336)	0.96	0.67	1.38	0.84		0.77	0.45	1.32	0.34	
Steviol	0 (N = 1273)	ref				0.06	ref				0.05
	M1 (N = 157)	0.70	0.42	1.17	0.18		0.59	0.27	1.29	0.19	
	M2 (N = 160)	0.65	0.37	1.14	0.13		0.48	0.19	1.21	0.12	
Sorbitol	0 (N = 708)	ref				0.19	ref				0.13
	M1 (N = 481)	0.61	0.43	0.87	**0.006**		0.76	0.47	1.22	0.26	
	M2 (N = 452)	0.87	0.62	1.22	0.43		0.70	0.42	1.17	0.17	
Added sugars	0 (N = 483)	ref				**<0.001**	ref				**<0.001**
	M1 (N = 586)	1.67	1.16	2.43	**0.006**		2.04	1.14	3.63	**0.02**	
	M2 (N = 592)	1.99	1.38	2.87	**<0.001**		2.63	1.50	4.60	**<0.001**	

Abbreviation: OR, odds ratio; CI, confidence interval; AceK, acesulfame potassium; BMI, Body Mass Index.
[a] The exposure dose was estimated as the proportion of daily intake relative to the acceptable daily intake and was categorized into two groups (M1 and M2) on the basis of the median, with a reference to the no intake group. The models were adjusted for age, sex, family history, z-BMI, total calorie intake, total sodium intake, physical activity, parental education, and household income.
[b] Sample sizes vary slightly across sweeteners due to missing exposure data for specific sweetener types. Participants without valid intake data for a particular sweetener were excluded from that specific analysis.
[c] 95 means hypertension, using cutoff at 95th percentile of blood pressure, either systolic or diastolic hypertension.
[d] 99 means advanced hypertension, using cutoff at 99th percentile of blood pressure, either systolic or diastolic hypertension.

3.2. Sex-specific association between sweetener consumption and pediatric hypertension

Figure 1C and 1D illustrate sex-specific analysis of sweetener consumption in relation to advanced hypertension. In girls, added sugar consumption was associated with greater odds of hypertension, whereas AceK consumption was associated with lower odds of hypertension. In boys, both added sugars and aspartame consumption showed positive association with pediatric hypertension.

Supplementary Tables 1–4 provide a detailed breakdown of these associations. The association between added sugar and hypertension or advanced hypertension was consistent across both sexes. Aspartame consumption was linked to greater odds of hypertension in boys. In contrast, AceK consumption was negatively associated with hypertension in girls. Collectively, these associations appeared more pronounced for diastolic hypertension.

3.3. Stratified analysis of sweetener consumption and pediatric hypertension by BMI

Supplementary Table 5 presents the association between sweetener consumption and pediatric hypertension stratified by BMI. Among overweight children, added sugar intake showed a stronger association with hypertension than in non-overweight children. Among non-overweight children, a borderline significant association was observed in the M2 group (OR = 1.61, 95 % CI: 1.00–2.57; p = 0.05), with a dose-dependent effect (p for trend = 00.04). Although steviol intake did not show a statistically significant inverse association with hypertension risk, but dose-dependent trend was observed (p for trend = 00.02). No significant association were observed for other sweeteners, including AceK, aspartame, and sucralose.

3.4. Dose–response analysis

Figure 2 displays β-values for each sweetener intake group for dose-dependent effects. Significant dose-dependent effects were observed for the aspartame, added sugars, and steviol in relation to hypertension. Higher added sugars consumption was associated with greater odds of hypertension and advanced hypertension, while aspartame intake showed a similar trend for advanced hypertension. Conversely, higher steviol intake was linked to lower hypertension risk, though this pattern was not observed for advanced hypertension.

3.5. Substitution analysis

To explore the potential impact of replacing added sugars with NNS, we conducted a substitution analysis (Fig. 3). Substituting added sugars with AceK (OR = 0.27, 95 % CI: 0.06–0.76, p = 0.013), sucralose (OR = 0.36, 95 % CI: 0.15–0.75, p = 0.007), glycyrrhizin (OR = 0.37, 95 % CI: 0.15–0.80, p = 0.011), steviol (OR = 0.26, 95 % CI: 0.04–0.86, p = 0.028) and sorbitol (OR = 0.31, 95 % CI: 0.13–0.65, p = 0.002) was associated with lower odds of advanced hypertension. Aspartame substitution showed a trend toward lower hypertension risk, but the association was not statistically significant. These findings suggest that replacing added sugars with specific NNS may be associated with a lower likelihood of advanced hypertension.

3.6. Urinary biomarker validation and sensitivity analysis

To validate self-reported NNS intake, we analyzed urinary sweetener levels in participants with available urine samples. The correlation between NNS-FFQ sweetener consumption and urinary biomarkers was strong, with AceK ($\rho = 0.903$, $p < 0.001$) and steviol ($\rho = 0.996$, $p < 0.001$), supporting the validity of the dietary

Table 3
Association between sweetener consumption and pediatric hypertension at various cutoffs.

Sweeteners	Exposure dose[a,b]	SBP95[c]					SBP99[d]					DBP95[c]					DBP99[d]				
		OR	95 % CI		*P*	*P* for trend	OR	95 % CI		*P*	*P* for trend	OR	95 % CI		*P*	*P* for trend	OR	95 % CI		*P*	*P* for trend
AceK	0 (N = 1120)	ref				0.05	ref				0.13	ref				0.47	ref				0.19
	M1 (N = 253)	0.54	0.26	1.14	0.11		0.74	0.25	2.13	0.57		0.62	0.37	1.02	0.06		0.50	0.23	1.10	0.09	
	M2 (N = 254)	0.55	0.26	1.17	0.12		0.34	0.08	1.47	0.15		0.98	0.63	1.52	0.92		0.76	0.38	1.52	0.44	
Aspartame	0 (N = 976)	ref				0.18	ref				0.41	ref				0.77	ref				**0.04**
	M1 (N = 339)	0.62	0.33	1.16	0.13		0.88	0.33	2.37	0.80		1.12	0.77	1.64	0.55		1.48	0.86	2.54	0.16	
	M2 (N = 326)	0.74	0.41	1.34	0.32		1.48	0.66	3.31	0.34		1.03	0.69	1.53	0.89		1.70	1.00	2.89	0.05	
Sucralose	0 (N = 917)	ref				0.92	ref				0.18	ref				0.55	ref				0.70
	M1 (N = 387)	1.22	0.73	2.03	0.45		0.96	0.42	2.20	0.93		1.00	0.69	1.45	0.99		1.36	0.82	2.24	0.23	
	M2 (N = 338)	0.90	0.50	1.62	0.73		0.45	0.15	1.33	0.15		0.87	0.58	1.31	0.51		0.77	0.41	1.43	0.41	
Glycyrrhizin	0 (N = 984)	ref				0.33	ref				0.40	ref				0.31	ref				0.55
	M1 (N = 317)	0.51	0.26	1.01	0.05		0.46	0.14	1.55	0.21		0.73	0.48	1.11	0.14		0.77	0.41	1.43	0.41	
	M2 (N = 336)	0.88	0.50	1.53	0.64		0.78	0.33	1.83	0.56		0.88	0.59	1.30	0.51		0.89	0.51	1.56	0.68	
Steviol	0 (N = 1273)	ref				0.50	ref				0.31	ref				**0.01**	ref				0.14
	M1 (N = 157)	0.52	0.21	1.30	0.16		0.54	0.13	2.33	0.41		0.63	0.35	1.13	0.12		0.63	0.27	1.49	0.30	
	M2 (N = 160)	0.94	0.44	2.01	0.88		0.56	0.13	2.39	0.43		0.49	0.25	0.96	**0.04**		0.57	0.23	1.45	0.24	
Sorbitol	0 (N = 708)	ref				0.12	ref				0.16	ref				0.22	ref				0.16
	M1 (N = 481)	0.49	0.28	0.87	**0.01**		0.47	0.19	1.18	0.11		0.68	0.47	0.98	**0.04**		0.74	0.44	1.24	0.25	
	M2 (N = 452)	0.74	0.44	1.26	0.27		0.61	0.26	1.40	0.24		0.85	0.59	1.23	0.38		0.70	0.40	1.21	0.20	
Added sugars	0 (N = 483)	ref				**0.01**	ref				0.19	ref				**0.003**	ref				**<0.001**
	M1 (N = 586)	1.60	0.88	2.91	0.12		1.88	0.75	4.75	0.18		1.62	1.09	2.40	**0.02**		1.86	0.98	3.52	0.06	
	M2 (N = 592)	2.20	1.24	3.89	**0.01**		1.91	0.76	4.80	0.17		1.84	1.24	2.73	**0.002**		2.98	1.63	5.45	**<0.001**	

Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; AceK, acesulfame potassium; OR, odds ratio; CI, confidence interval; BMI, Body Mass Index.

[a] The exposure dose was estimated as the proportion of daily intake relative to the acceptable daily intake and was categorized into two groups (M1 and M2) on the basis of the median, with a reference to the no intake group. The models were adjusted for age, sex, family history, z-BMI, total calorie intake, total sodium intake, physical activity, parental education, and household income.

[b] Sample sizes vary slightly across sweeteners due to missing exposure data for specific sweetener types. Participants without valid intake data for a particular sweetener were excluded from that specific analysis.

[c] 95 means hypertension, using cutoff at 95th percentile of blood pressure, either systolic or diastolic hypertension.

[d] 99 means advanced hypertension, using cutoff at 99th percentile of blood pressure, either systolic or diastolic hypertension.

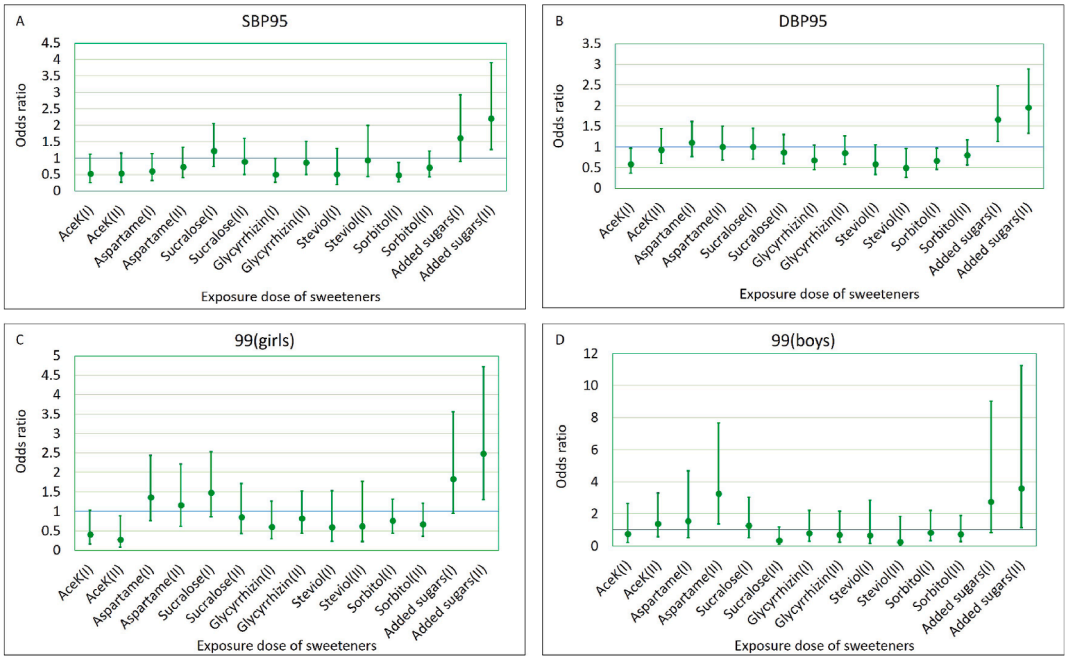

Fig. 1. Effect of sweetener consumption on hypertension risk. The exposure dose was categorized into two groups (I and II) on the basis of the median, with a reference to the no intake group. The models were adjusted for age, sex, family history, z-BMI, total calorie intake, total sodium intake, and physical activity. **A,** Effect on systolic hypertension using cutoffs at 95th percentile in children. **B,** Effect on diastolic hypertension using cutoffs at 95th percentile in children. **C** and **D**, We conducted sex-specific analysis using cutoff at 99th percentile of blood pressure, either systolic or diastolic hypertension. **C,** Effect on hypertension using cutoff at 99th percentile in girls. **D,** Effect on hypertension using cutoff at 99th percentile in boys. Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; AceK, acesulfame potassium.

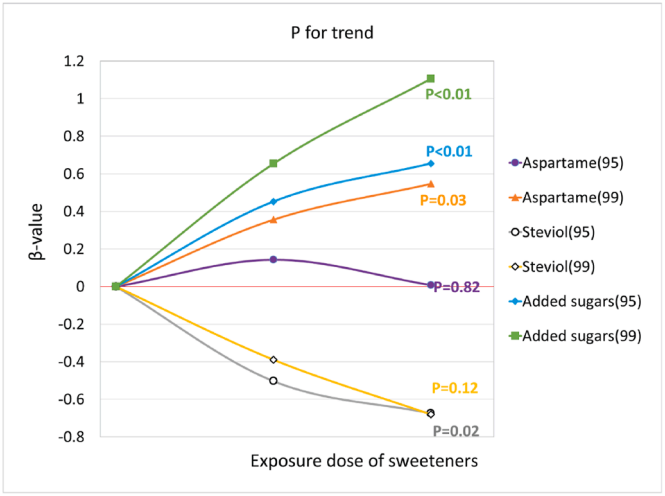

Fig. 2. Dose-dependent effect of sweetener consumption on diastolic hypertension. P for trend was analyzed for dose-dependent effect of sweeteners on blood pressure with logistic regression models. The models were adjusted for age, sex, family history, z-BMI, total calorie intake, total sodium intake, physical activity, parental education, and family income. 95 means using cutoff at the 95th percentile of diastolic blood pressure. 99 means using cutoff at the 99th percentile of diastolic blood pressure.

questionnaire assessment. Supplementary Table 6 compares baseline characteristics of the participants with and without urine samples. Girls were more likely to provide urine samples. Participants with urine samples had higher DBP and z-BMI, while SBP and other variables did not differ significantly.

Table 4 demonstrates the relationship between urinary sweetener levels and pediatric hypertension. The urinary AceK level was inversely associated with hypertension risk. The OR was 0.59 (95 % CI: 0.35–0.99; p = 0.05) in the M1 group and 0.37 (95 % CI: 0.22–0.63; p < 0.001) in the M2 group, with a strong dose-dependent effect (p for trend<0.001). Conversely, urinary steviol level were not significantly associated with hypertension risk in either the M1 or M2 group. In advanced hypertension, urinary AceK were inversely associated with hypertension risk in the M2 group (OR = 0.39, 95 % CI: 0.19–0.79; p = 0.009; p for trend = 0.01), while no significant association was observed in the M1 group or for urinary steviol.

In sex-specific analyses, urinary AceK levels were inversely associated with hypertension in girls. The OR was 0.34 (95 % CI: 0.18–0.66; p = 0.001) in the M1 group and 0.22 (95 % CI: 0.12–0.43; p < 0.001) in the M2 group. These associations remained significant for advanced hypertension. The OR was 0.28 (95 % CI: 0.11–0.70; p = 0.006) in the M1 group and 0.30 (95 % CI: 0.13–0.68; p = 0.004) in the M2 group. No significant associations were observed in boys.

4. Discussion

Our study revealed that added sugar consumption was associated with a higher hypertension risk in a dose-dependent manner, with this relationship consistent across both sexes and notably stronger in overweight children. Regarding NNS, aspartame consumption was linked to higher diastolic hypertension risk, especially in boys. Conversely, steviol intake showed an inverse dose-dependent relationship with diastolic hypertension, although the effect appeared subtle in cases of advanced hypertension. AceK consumption was negatively correlated with hypertension risk, particularly diastolic hypertension, with a more pronounced association observed in girls. Importantly, substitution analysis indicated that replacing added sugars with certain NNSs was associated with a reduced risk of hypertension. These findings from the NNS-FFQ was further supported by urinary biomarker analysis, which revealed a consistent inverse association observed between urinary AceK levels and hypertension risk.

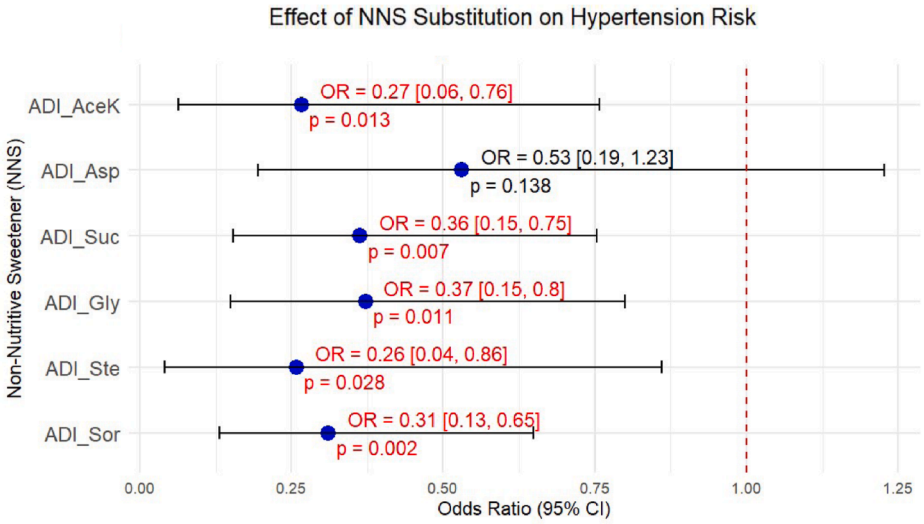

Fig. 3. Substitution Analysis of Added Sugars with Non-Nutritive Sweeteners for Pediatric Hypertension. The substitution analysis examines the association between substituting added sugars with NNS and pediatric hypertension risk. The exposure dose was estimated as the proportion of daily intake relative to the acceptable daily intake, and participants were categorized as non-consumers or further stratified by median intake. The substitution model compared the "Low Sugar, High NNS" group with the "High Sugar, Low/No NNS" group, adjusting for age, sex, family history, z-BMI, total calorie intake, total sodium intake, and physical activity. This model reflects relative differences in consumption patterns rather than standardized serving sizes. Abbreviation: NNS, Non-Nutritive Sweeteners; ADI, acceptable daily intake; AceK, acesulfame potassium; Asp, aspartame; Suc, sucralose; Gly, glycyrrhizin; Ste, steviol; Sor, sorbitol; BMI, body mass index.

Table 4
Association between levels of urinary sweetener and pediatric hypertension.

Group	Sweeteners	Urine level[a,b]	95[c]					99[d]				
			OR	95%CI		*P*	*P* for trend	OR	95%CI		*P*	*P* for trend
Total group	**AceK**	0 (N = 152)	ref				**<0.001**	ref				**0.01**
		M1 (N = 194)	0.59	0.35	0.99	**0.05**		0.52	0.25	1.08	0.08	
		M2 (N = 229)	0.37	0.22	0.63	**<0.001**		0.39	0.19	0.79	**0.009**	
	Steviol glycosides	0 (N = 142)	ref				0.42	ref				0.51
		M1 (N = 255)	0.93	0.54	1.59	0.78		1.04	0.49	2.21	0.92	
		M2 (N = 163)	1.24	0.71	2.18	0.45		1.29	0.59	2.81	0.53	
Girls	**AceK**	0 (N = 112)	ref				**<0.001**	ref				**0.004**
		M1 (N = 134)	0.34	0.18	0.66	**0.001**		0.28	0.11	0.70	**0.006**	
		M2 (N = 171)	0.22	0.12	0.43	**<0.001**		0.30	0.13	0.68	**0.004**	
	Steviol glycosides	0 (N = 101)	ref				0.36	ref				0.27
		M1 (N = 190)	0.69	0.36	1.32	0.26		0.87	0.35	2.18	0.77	
		M2 (N = 118)	1.33	0.68	2.60	0.41		1.60	0.64	4.00	0.32	
Boys	**AceK**	0 (N = 40)	ref				0.34	ref				0.47
		M1 (N = 60)	3.31	1.11	9.86	**0.03**		8.16	0.88	75.72	0.07	
		M2 (N = 58)	1.97	0.64	6.05	0.24		3.32	0.31	36.02	0.32	
	Steviol glycosides	0 (N = 41)	ref				0.59	ref				0.40
		M1 (N = 65)	2.60	0.81	8.33	0.11		1.41	0.28	7.20	0.68	
		M2 (N = 45)	1.66	0.49	5.64	0.42		0.44	0.06	3.19	0.42	

Abbreviation: OR, odds ratio; CI, confidence interval; BMI, Body Mass Index; AceK, acesulfame potassium.

[a] Urine level was categorized into two groups (M1 and M2) on the basis of the median, with a reference to the no intake group. The models were adjusted for age, sex, family history, z-BMI, total calorie intake, total sodium intake, physical activity, parental education, and household income.

[b] Sample sizes vary slightly across sweeteners due to missing exposure data for specific sweetener types. Participants without valid intake data for a particular sweetener were excluded from that specific analysis.

[c] 95 means hypertension, using cutoff at 95th percentile of blood pressure, either systolic or diastolic hypertension.

[d] 99 means advanced hypertension, using cutoff at 99th percentile of blood pressure, either systolic or diastolic hypertension.

These findings carry important public health implications in the Taiwanese dietary context, where added sugars are widely consumed through processed foods and popular beverages such as hand-shaken drinks (e.g., bubble tea). Aspartame is commonly found in diet sodas and sugar-free gum. Steviol is frequently used in low-sugar drinks and health foods, while AceK appears in sugar-free beverages, candies, and dairy products. These consumption patterns highlight the need to shape dietary guidelines. Educating parents and caregivers to monitor children's intake of added sugars and NNSs may be a valuable strategy for mitigating the risk of pediatric hypertension.

4.1. Added sugar and pediatric hypertension

Excessive added sugar consumption in children is a well-established contributor to adverse health outcomes, including obesity, metabolic syndrome, and type 2 diabetes. These conditions are recognized risk factors for elevated blood pressure [26]. Several biological mechanisms may explain how added sugars contributes to hypertension. High sugar intake can induce insulin resistance, which activates the renin-angiotensin-aldosterone system and upregulate angiotensin II type 1 receptor expression. These changes lead to endothelial dysfunction and promote hypertension [27,28].

Moreover, excessive sugar consumption has been shown to increase reactive oxygen stress, which may stimulate sympathetic nervous system and further raise pediatric hypertension risk [29,30]. Evidence from adult studies, such as the PREMIER trial, demonstrated that reducing SSB consumption by just one serving per day over 18 months significantly lowered both systolic and diastolic blood pressure [31]. These findings support the biological plausibility of the impact of added sugar intake on blood pressure. However, more pediatric-specific investigation is needed to confirm these effects in younger populations.

4.2. NNS and pediatric hypertension

The association between NNSs consumption and cardiovascular health, particularly pediatric hypertension, remains complex and is still under debate. Some research, including a randomized controlled trial in young adults, have reported that reducing both naturally and artificially sweetened beverages intake led to lower blood pressure [32]. Systematic reviews have raised concerns that NNS consumption may lead to lasting adverse cardiometabolic outcomes. These include increased weight gain, larger waist circumference, and a higher risk of developing obesity, hypertension, metabolic syndrome, type 2 diabetes, and cardiovascular events [8]. However, the mechanisms underlying these association, and whether they differ across specific NNS types, remain unclear and warrant further clarification.

Aspartame is metabolized into phenylalanine, aspartic acid, and methanol, which can elevate oxidative stress and impair mitochondrial function [33]. Emerging research suggests that phenylalanine might impair nitric oxide availability and endothelial function [34]. These alternations could contribute to vascular remodeling, such as smooth muscle cell proliferation, hypertrophy, and collagen deposition, ultimately leading to vascular thickening and narrowing. In addition, elevated oxidative stress may damage endothelial cells, impair vascular relaxation, and increase vascular contractility [35]. These mechanisms may collectively promote the development of hypertension. In our study, aspartame consumption was positively associated with diastolic hypertension, especially among boys.

The evidence regarding AceK and cardiovascular risk is inconclusive. While one animal study reported that AceK consumption was associated with increased atherosclerosis risk [36], the mechanisms remain uncertain. Interestingly, our findings showed an inverse association between AceK consumption and hypertension risk, particularly among girls. One possible explanation for this finding is AceK's antiglycation effect [37], which may reduce the accumulation of advanced glycation end-products and limit free radical activity. Both processes contribute to biomolecular damage and are implicated in the development of hypertension [38]. Notably, sex-specific differences have been observed in animal studies. For instance, AceK consumption led to weight gain in male rats but not in females [39]. Another study revealed that AceK modulated gut microbiota and the expression of metabolic genes differently in male and female mice. In males, AceK intake altered gut bacteria related to carbohydrate metabolism and increased body weight. In contrast, in females, AceK intake shifted microbial composition and downregulated genes involved in carbohydrate absorption [40]. Although these observations are noteworthy, the relevance of these animal model findings to human physiology remains uncertain and necessitates additional validation.

AceK is not metabolized and excreted unchanged in urine [41], making it an accurate urinary biomarker for dietary exposure [42]. In our study, urinary AceK levels were inversely associated with hypertension risk, supporting the questionnaire-based findings and providing objective evidence for the observed associations.

Steviol glycosides, natural sweeteners derived from the Stevia plant, have demonstrated antihypertensive effects in both experimental and clinical settings. In animal models, steviol consumption has been shown to reduce glucose accumulation in the liver and kidneys, lower blood glucose levels, and decrease insulin resistance [43]. Moreover, steviol consumption induces systemic and renal vasodilation, diuresis, and natriuresis, contributing to blood pressure reduction in hypertensive rats [44,45]. Human studies have reported similar effects, showing significant reductions in both systolic and diastolic blood pressure following steviol consumption [46]. These effects are linked to vasorelaxation mediated by inhibition of calcium influx [45,47], similar to the action of calcium-channel blockers such as verapamil [48]. Prostaglandin-mediated enhancement of diuretic and natriuretic effects may also play a role in reducing plasma volume and vascular resistance [49]. These mechanisms align with our findings of an inverse association between steviol intake and hypertension, although the effect appeared less pronounced in advanced hypertension cases.

Steviol glucuronide, a urinary metabolite of steviol glycosides [50], serves as valid biomarkers for detecting oral steviol consumption [23]. However, in our study, urinary steviol levels were not significantly associated with hypertension risk. This discrepancy may be attributed to relatively low steviol intake within our cohort or to other unmeasured confounding factors that warrant further exploration.

4.3. Strengths and limitations

To the best of our knowledge, this is the first prospective cohort study to examine the association between NNS consumption and pediatric hypertension. By evaluating commonly consumed sweeteners and their relationship with hypertension risk, our findings offer valuable information for clinicians, caregivers, and public health policymakers. In addition, we conducted a subanalysis for both SBP and DBP outcomes. Systolic hypertension is widely recognized as a major predictor of cardiovascular events [51]. However, diastolic hypertension plays a more significant role in driving coronary risk among younger individuals, whereas systolic hypertension becomes the dominant indicator in older populations [52].

A major strength of our study is the comprehensive adjustment for multiple confounding factors, including age, sex, family history of hypertension, z-BMI, calorie and sodium intake, physical activity, parental education, and household income. Each of these factors critically influence blood pressure regulation. For instance, age reflects a child's stage of biological maturation. As children grow, changes in height, weight, and body composition naturally affect blood pressure [53]. By adjusting for age, we aimed to ensure that the associations we observed were not merely artifacts of normal developmental processes.

Sex also influences pediatric hypertension risk through hormonal changes during puberty. Boys typically have higher blood pressure than girls, primarily due to differences in gonadal and adrenal steroids, growth hormones, and growth factors. These physiological differences impact blood pressure regulation independently of body fat [54]. A family history of hypertension further increases pediatric hypertension risk, driven by both shared genetic susceptibility and lifestyle factors within households [55]. Moreover, physical activity is a well-documented protective factor against pediatric hypertension, with evidence showing a 33 % reduction in risk, particularly for elevated DBP. The protective effect is mediated through mechanisms such as reduced excess visceral fat, which mitigates systemic inflammation, improves insulin sensitivity, and promotes endothelial function [56]. These

changes contribute to better blood pressure regulation. Sodium intake is another crucial dietary factor. A systematic review found that each additional grams of daily sodium intake was associated with a 0.8 mmHg increase in SBP and a 0.7 mmHg increase in DBP among children and adolescents [57].

Importantly, we identified BMI as a key confounding factor that often overlooked in previous studies on blood pressure. Childhood obesity is strongly associated with elevated blood pressure [58]. Higher BMI in early childhood are linked to an increased hypertension risk later in life [59]. Furthermore, obesity correlates with increased NNS intake and higher BMI, both of which are linked to a greater likelihood of developing pediatric hypertension over time [60]. Since NNS use may be linked to both BMI and blood pressure, we performed a stratified analysis. Results revealed a stronger impact of added sugar on hypertension among overweight children.

SES, reflected by parental education and household income, is another essential determinant of pediatric cardiometabolic health. Adolescents from lower SES households are more likely to engage in unhealthy lifestyle behaviors, such as poor dietary habits, reduced physical activity, and excessive screen time, all of which contribute to obesity and elevated blood pressure [61]. These disparities are often driven by environmental factors, including limited access to nutritious foods and physical activity opportunities, and greater exposure to SSB [62]. In our study, both parental education and household income were included as covariates in the multivariate models to account for potential confounding. Notably, the associations between sweetener consumption and pediatric hypertension remained significant after SES adjustment, suggesting that these dietary exposures exert effects on blood pressure beyond the influence of socioeconomic context. Nevertheless, SES may still interact with other unmeasured environmental or behavioral factors, which warrants further exploration in future studies.

We also conducted a substitution analyses, which modeled the theoretical impact of replacing added sugars with NNS. This approach provides practical insights for dietary recommendations aimed at improving cardiovascular health in pediatric populations.

Despite these strength, our study still has several limitations. Participants were recruited during clinical visits for growth or pubertal evaluation, which may potentially introduce selection bias. This cohort may differ from the general pediatric population in health status, parental health awareness, or lifestyle factors. Such differences could limit the generalizability of our findings. Although the prevalence of pediatric hypertension in our study (14.4 %) was comparable to national data from China and Japan [15,63], subtle differences might still exist, even after excluding children with known medical conditions.

Recall biases is another limitation, particularly in 24-h dietary recalls and food frequency questionnaires. Although the validity and accuracy of the NNS-FFQ was confirmed when establishment [21], caregivers might overlook condiments containing sweeteners during meal preparation and underestimating sweeteners intake. To mitigate this problem, we collected urine samples and measured AceK and steviol levels through liquid chromatography tandem mass spectrometry [64]. These biomarkers showed strong agreement with questionnaire-based data in our study and provided objective validation of associations with hypertension. However, urinary biomarkers only reflect recent exposure, and do not eliminate the recall bias for other sweeteners.

Pediatric hypertension resulted from multifaceted interactions between genetic, environmental, and lifestyle factors. While our analysis adjusted for key confounders, residual confounding from unmeasured variables cannot be entirely excluded. For example, while NNS is generally used to reduce total energy intake, NNS consumption may lead to compensatory eating behaviors [2,6]. Additionally, NNS consumption might indicate broader dietary patterns, such as dieting or frequent intake of processed, high-calorie foods, which can influence overall caloric intake. Since total energy intake impacts weight and metabolic health regardless of sweetener type [1], these dietary patterns may partly explain the observed variations of blood pressure. To account for this condition, we included total calorie intake in all statistical models. Notably, the associations between NNS and pediatric hypertension remained consistent after this adjustment, supporting the robustness of our findings.

In addition, our analysis did not specifically exclude secondary hypertension, which accounts for approximately 14.3 % of pediatric hypertension cases in Taiwan [65]. Nonetheless, given its rarity and the exclusion of known metabolic or congenital diseases, the impact on our results is likely minimal. Lastly, although most participants consumed sweeteners below the WHO-recommended ADI, we still observed significant associations with hypertension risk. This suggests that even moderate consumption of sweeteners may have cardiovascular implications in pediatric populations.

5. Conclusion

This study provides evidence of the association between sweetener consumption and pediatric hypertension. Added sugars and aspartame were positively associated with hypertension risk in a dose-dependent manner, while steviol glycosides and AceK showed negative correlation with hypertension risk, particularly in diastolic hypertension. Furthermore, substitution modeling suggested that replacing added sugars with certain NNSs was associated with a lower pediatric hypertension risk.

Early identification of dietary factors contributing to pediatric hypertension is crucial for preventing long-term metabolic complications. While our findings suggest potential dietary targets, definitive causal statements cannot be made due to the limitations. However, our findings underscore the importance of limiting added sugar intake in children and highlight that the effects of NNS may vary significantly by type and potentially by sex. Further rigorous research is crucial for clarifying the specific roles of sweeteners in blood pressure and for the development of dietary recommendations. Ultimately, such efforts may help reduce the incidence of cardiovascular complications and mitigate the associated medical and societal burden.

Author contributions

Dr Yuan-Jen Tsai carried out the statistical analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Professor Yang-Ching Chen conceptualized and designed the study, and critically reviewed and revised the manuscript. Professor Hsien-Yu Fan and Shih-Yuan Hsu advised on data analyses. Yung-Feng Lin, Huang-Ren Lin, and Professor Chien-Tien Su contributed to the data interpretation and critically revised the manuscript for intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. No one eligible for authorship has been excluded from the list of authors.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request and subject to institutional and ethical regulations.

Ethical approval, study registration, and permissions

This study was approved by the Institutional Review Boards of Taipei Medical University (N201802018), Cathay General Hospital (CGH-P108107), and National Cheng Kung University Hospital (B-BR-108-076) and adhered to the ethical principles outlined in the Helsinki Declaration. Written informed consent was obtained from all participants and/or their legal guardians. The Taiwan Pubertal Longitudinal Study is a registered, ongoing cohort study, and all data collection followed approved institutional guidelines.

Declaration of generative AI and AI-assisted technologies in the writing process

Generative AI-assisted technologies (e.g., ChatGPT) were used to improve language clarity during manuscript revision. All content was reviewed and approved by the authors.

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Conflict of interest

The authors declare no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.08.034.

References

[1] Keller A, Heitmann BL, Olsen N. Sugar-sweetened beverages, vascular risk factors and events: a systematic literature review. Public Health Nutr 2015;18:1145–54.
[2] Green CH, Syn WK. Non-nutritive sweeteners and their association with the metabolic syndrome and non-alcoholic fatty liver disease: a review of the literature. Eur J Nutr 2019;58:1785–800.
[3] Wang QP, Browman D, Herzog H, Neely GG. Non-nutritive sweeteners possess a bacteriostatic effect and alter gut microbiota in mice. PLoS One 2018;13:e0199080. https://doi.org/10.1371/journal.pone.0199080.
[4] Hess EL, Myers EA, Swithers SE, Hedrick VE. Associations between nonnutritive sweetener intake and metabolic syndrome in adults. J Am Coll Nutr 2018;37:487–93.
[5] Shearer J, Swithers SE. Artificial sweeteners and metabolic dysregulation: lessons learned from agriculture and the laboratory. Rev Endocr Metab Disord 2016;17:179–86.
[6] Schiano C, Grimaldi V, Scognamiglio M, Costa D, Soricelli A, Nicoletti GF, et al. Soft drinks and sweeteners intake: possible contribution to the development of metabolic syndrome and cardiovascular diseases. Beneficial or detrimental action of alternative sweeteners? Food Res Int 2021;142:110220.
[7] Debras C, Chazelas E, Sellem L, Porcher R, Druesne-Pecollo N, Esseddik Y, et al. Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort. BMJ 2022;378:e071204. https://doi.org/10.1136/bmj-2022-071204.
[8] Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, et al. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. CMAJ (Can Med Assoc J) 2017;189:E929–39.
[9] Fidler Mis N, Braegger C, Bronsky J, Campoy C, Domellöf M, Embleton ND, et al. Sugar in infants, children and adolescents: a position paper of the European society for paediatric gastroenterology, hepatology and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr 2017;65:681–96.
[10] Zheng M, Rangan A, Olsen NJ, Andersen LB, Wedderkopp N, Kristensen P, et al. Substituting sugar-sweetened beverages with water or milk is inversely associated with body fatness development from childhood to adolescence. Nutrition 2015;31:38–44.
[11] Karalexi MA, Mitrogiorgou M, Georgantzi GG, Papaevangelou V, Fessatou S. Non-nutritive sweeteners and metabolic health outcomes in children: a systematic review and meta-analysis. J Pediatr 2018;197:128–33.
[12] Li WL, Chen ML, Liu SS, Li GL, Gu TY, Liang P, et al. Sweet preference modified by early experience in mice and the related molecular modulations on the peripheral pathway. J Mol Neurosci 2013;51:225–36.
[13] Swithers SE. Artificial sweeteners are not the answer to childhood obesity. Appetite 2015;93:85–90.
[14] Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988-2008. Hypertension 2013;62:247–54.
[15] Zhai Y, Li WR, Shen C, Qian F, Shi XM. Prevalence and correlates of elevated blood pressure in Chinese children aged 6-13 years: a nationwide school-based survey. Biomed Environ Sci 2015;28:401–9.
[16] Litwin M, Kułaga Z. Obesity, metabolic syndrome, and primary hypertension. Pediatr Nephrol 2021;36:825–37.
[17] Agirbasli M, Tanrikulu AM, Berenson GS. Metabolic syndrome: bridging the gap from childhood to adulthood. Cardiovasc Ther 2016;34:30–6.
[18] Kelly RK, Thomson R, Smith KJ, Dwyer T, Venn A, Magnussen CG. Factors affecting tracking of blood pressure from childhood to adulthood: the childhood determinants of adult health study. J Pediatr 2015;167:1422–8.
[19] de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660–7.
[20] Wang JS, Hsieh RH, Tung YT, Chen YH, Yang C, Chen YC. Evaluation of a technological image-based dietary assessment tool for children during pubertal growth: a pilot study. Nutrients 2019;11:2527.
[21] Chu YY, Chen YH, Hsieh RH, Hsia SM, Wu HT, Chen YC. Development and validation of the Chinese version non-nutritive sweetener FFQ with urinary biomarker in children and adolescents. Public Health Nutr 2022;25:2056–63.
[22] World Health Organization. Evaluation of certain food additives: sixty-ninth report of the Joint FAO/WHO expert committee on food additives, 69. World Health Organization; 2009.
[23] Logue C, Dowey LRC, Strain JJ, Verhagen H, McClean S, Gallagher AM. Application of liquid chromatography–tandem mass spectrometry to determine urinary concentrations of five commonly used low-calorie sweeteners: a novel biomarker approach for assessing recent intakes? J Agric Food Chem 2017;65:4516–25.
[24] Dong Y, Ma J, Song Y, Dong B, Wang Z, Yang Z, et al. National blood pressure reference for Chinese Han children and adolescents aged 7 to 17 years. Hypertension 2017;70:897–906.
[25] Zhang Z. Multiple imputation with multivariate imputation by chained equation (MICE) package. Ann Transl Med 2016;4:30.
[26] Gidding SS, Lichtenstein AH, Faith MS, Karpyn A, Mennella JA, Popkin B, et al. Implementing American heart association pediatric and adult nutrition guidelines: a scientific statement from the American heart association nutrition committee of the council on nutrition, physical activity and metabolism, council on cardiovascular disease in the young, council on arteriosclerosis, thrombosis and vascular biology, council on cardiovascular nursing, council on epidemiology and prevention, and council for high blood pressure research. Circulation 2009;119:1161–75.
[27] Hahn K, Rodriguez-Iturbe B, Winterberg B, Sanchez-Lozada LG, Kanbay M, Lanaspa MA, et al. Primary aldosteronism: a consequence of sugar and Western diet? Med Hypotheses 2022;160:110796.
[28] Zhou MS, Schulman IH, Zeng Q. Link between the renin-angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med 2012;17:330–41.
[29] Prasad K, Dhar I. Oxidative stress as a mechanism of added sugar-induced cardiovascular disease. Int J Angiol 2014;23:217–26.
[30] Campese VM. Oxidative stress and sympathetic activity in hypertension. Am J Hypertens 2010;23:456.
[31] Chen L, Caballero B, Mitchell DC, Loria C, Lin PH, Champagne CM, et al. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. Circulation 2010;121:2398–406.
[32] Vázquez-Durán M, Orea-Tejeda A, Castillo-Martínez L, Cano-García Á, Téllez-Olvera L, Keirns-Davis C. A randomized control trial for reduction of caloric and non-caloric sweetened beverages in young adults: effects in weight, body composition and blood pressure. Nutr Hosp 2016;33:1372–8.
[33] Griebsch LV, Theiss EL, Janitschke D, Erhardt VKJ, Erhardt T, Haas EC, et al. Aspartame and its metabolites cause oxidative stress and mitochondrial and lipid alterations in SH-SY5Y cells. Nutrients 2023;15:1467.
[34] Ashok I, Sheeladevi R. Oxidant stress evoked damage in rat hepatocyte leading to triggered nitric oxide synthase (NOS) levels on long term consumption of aspartame. J Food Drug Anal 2015;23:679–91.

[35] Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative stress and hypertension. Circ Res 2021;128:993–1020.
[36] Lin CH, Li HY, Wang SH, Chen YH, Chen YC, Wu HT. Consumption of non-nutritive sweetener, acesulfame potassium exacerbates atherosclerosis through dysregulation of lipid metabolism in ApoE−/− mice. Nutrients 2021;13:3984.
[37] Ali A, More TA, Hoonjan AK, Sivakami S. Antiglycating potential of acesulfame potassium: an artificial sweetener. Appl Physiol Nutr Metabol 2017;42:1054–63.
[38] Zgutka K, Tkacz M, Tomasiak P, Tarnowski M. A role for advanced glycation end products in molecular ageing. Int J Mol Sci 2023;24:9881.
[39] Bian X, Chi L, Gao B, Tu P, Ru H, Lu K. The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. PLoS One 2017;12:e0178426. https://doi.org/10.1371/journal.pone.0178426.
[40] Basson AR, Rodriguez-Palacios A, Cominelli F. Artificial sweeteners: history and new concepts on inflammation. Front Nutr 2021;8:746247.
[41] Renwick AG. The metabolism of intense sweeteners. Xenobiotica 1986;16:1057–71.
[42] Wilson LA, Wilkinson K, Crews HM, Davies AM, Dick CS, Dumsday VL. Urinary monitoring of saccharin and acesulfame-K as biomarkers of exposure to these additives. Food Addit Contam 1999;16:227–38.
[43] Myint KZ, Chen JM, Zhou ZY, Xia YM, Lin J, Zhang J. Structural dependence of antidiabetic effect of steviol glycosides and their metabolites on streptozotocin-induced diabetic mice. J Sci Food Agric 2020;100:3841–9.
[44] Orellana-Paucar AM. Steviol glycosides from Stevia rebaudiana: an updated overview of their sweetening activity, pharmacological properties, and safety aspects. Molecules 2023;28:1258.
[45] Mélis MS. Influence of calcium on the blood pressure and renal effects of stevioside. Braz J Med Biol Res 1992;25:943–9.
[46] Hsieh MH, Chan P, Sue YM, Liu JC, Liang TH, Huang TY, et al. Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. Clin Ther 2003;25:2797–808.
[47] Lee CN, Wong KL, Liu JC, Chen YJ, Cheng JT, Chan P. Inhibitory effect of stevioside on calcium influx to produce antihypertension. Planta Med 2001;67:796–9.
[48] Melis MS, Sainati AR. Effect of calcium and verapamil on renal function of rats during treatment with stevioside. J Ethnopharmacol 1991;33:257–62.
[49] Melis MS, Sainati AR. Participation of prostaglandins in the effect of stevioside on rat renal function and arterial pressure. Braz J Med Biol Res 1991;24:1269–76.
[50] Geuns JM, Buyse J, Vankeirsbilck A, Temme EH, Compernolle F, Toppet S. Identification of steviol glucuronide in human urine. J Agric Food Chem 2006;54:2794–8.
[51] Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. Am J Cardiol 2000;85:251–5.
[52] Li Y, Wei FF, Wang S, Cheng YB, Wang JG. Cardiovascular risks associated with diastolic blood pressure and isolated diastolic hypertension. Curr Hypertens Rep 2014;16:489.
[53] Werneck AO, Silva DR, Souza MF, Christofaro DG, Tomeleri CM, Fernandes RA, et al. Correlates of blood pressure according to early, on time, and late maturation in adolescents. J Clin Hypertens 2016;18:424–30.
[54] Shen W, Zhang T, Li S, Zhang H, Xi B, Shen H, et al. Race and sex differences of long-term blood pressure profiles from childhood and adult hypertension: the bogalusa heart study. Hypertension 2017;70:66–74.
[55] Zhao W, Mo L, Pang Y. Hypertension in adolescents: the role of obesity and family history. J Clin Hypertens 2021;23:2065–70.
[56] Tozo TA, Pereira BO, Menezes Junior FJ, Montenegro CM, Moreira CMM, Leite N. Hypertensive measures in schoolchildren: risk of central obesity and protective effect of moderate-to-vigorous physical activity. Arq Bras Cardiol 2020;115:42–9.
[57] Leyvraz M, Chatelan A, da Costa BR, Taffé P, Paradis G, Bovet P, et al. Sodium intake and blood pressure in children and adolescents: a systematic review and meta-analysis of experimental and observational studies. Int J Epidemiol 2018;47:1796–810.
[58] Jeong SI, Kim SH. Obesity and hypertension in children and adolescents. Clin Hypertens 2024;30:23.
[59] Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140:e20171904.
[60] Reid AE, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, et al. Early exposure to nonnutritive sweeteners and long-term metabolic health: a systematic review. Pediatrics 2016;137:e20153603.
[61] Kaczmarek M, Stawińska-Witoszyńska B, Krzyżaniak A, Krzywińska-Wiewiorowska M, Siwińska A. Who is at higher risk of hypertension? Socioeconomic status differences in blood pressure among Polish adolescents: a population-based ADOPOLNOR study. Eur J Pediatr 2015;174:1461–73.
[62] Seum T, Meyrose AK, Rabel M, Schienkiewitz A, Ravens-Sieberer U. Pathways of parental education on Children's and Adolescent's body mass index: the mediating roles of behavioral and psychological factors. Front Public Health 2022;10:763789.
[63] Shirasawa T, Shimada N, Ochiai H, Ohtsu T, Hoshino H, Nishimura R, et al. High blood pressure in obese and nonobese Japanese children: blood pressure measurement is necessary even in nonobese Japanese children. J Epidemiol 2010;20:408–12.
[64] Logue C, Dowey LRC, Verhagen H, Strain JJ, O'Mahony M, Kapsokefalou M, et al. A novel urinary biomarker approach reveals widespread exposure to multiple low-calorie sweeteners in adults. J Nutr 2020;150:2435–41.
[65] Hsu WF, Kao YW, Chen M, Chiang HC, Chen SY, Lu MC, et al. A reappraisal of the prevalence of pediatric hypertension through a nationwide database in Taiwan. Sci Rep 2021;11:4475.