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Associations of artificial sweetener intake with cardiometabolic disorders and mortality: a population-based study

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Abstract

Artificial sweeteners are generally used and recommended to alternate added sugar for health promotion. However, the health effects of artificial sweeteners remain unclear. In this study, we included 6371 participants from the National Health and Nutrition Examination Survey with artificial sweetener intake records. Logistic regression and Cox regression were applied to explore the associations between artificial sweeteners and risks of cardiometabolic disorders and mortality. Mendelian randomisation was performed to verify the causal associations. We observed that participants with higher consumption of artificial sweeteners were more likely to be female and older and have above medium socio-economic status. After multivariable adjustment, frequent consumers presented the OR (95 % CI) for hypertension (1·52 (1·29, 1·80)), hypercholesterolaemia (1·28 (1·10, 1·50)), diabetes (3·74 (3·06, 4·57)), obesity (1·52 (1·29, 1·80)), congestive heart failure (1·89 (1·35, 2·62)) and heart attack (1·51 (1·10, 2·04)). Mendelian randomisation confirmed the increased risks of hypertension and type 2 diabetes. Moreover, an increased risk of diabetic mortality was identified in participants who had artificial sweeteners ≥ 1 daily (HR = 2·62 (1·46, 4·69), $P = 0·001$). Higher consumption of artificial sweeteners is associated with increased risks of cardiometabolic disorders and diabetic mortality. These results suggest that using artificial sweeteners as sugar substitutes may not be beneficial.

Keywords: **National Health and Nutrition Examination Survey: Artificial sweetener: Type 2 diabetes mellitus: CVD: Diabetic mortality**

Artificial sweeteners have been widely employed as sugar substitutes in the food industry[1]. Because of their strong sweetness and low-calorie characteristics, artificial sweeteners were generally considered safe and highly appreciated by consumers for weight loss and glycaemic control[2–4]. Hence, artificial sweeteners are frequently introduced to patients with metabolic or CVD to replace added sugar within a balanced diet[5]. In fact, several basic researches and clinical trials have focused on the associations between artificial sweetener consumption with physiological index, gut microbiota and disease risks[6,7]. Though substantial attention from scientific and public fields has been paid, the long-term health effects of artificial sweeteners remained controversial.

Over the past few decades, sweeteners such as aspartame, acesulfame potassium and sucralose have been approved by the US Food and Drug Administration. Meanwhile, with the accumulation of continuous cross-sectional studies and the initiation of large prospective cohorts, it has been made possible to study the long-term health effects of artificial sweeteners. A recent prospective study, which enrolled health professionals with type 2 diabetes, suggested that artificial sweetener consumption did not influence all-cause mortality, CVD incidence and CVD mortality and favoured replacing sugar with artificial sweeteners[8]. These results were confirmed in a recent cohort study based on the general population by Pacheco[9]. Moreover, evidence from the Strong Heart Family Study indicated no significant associations of artificial sweetener consumption with incident diabetes, fasting insulin or glucose levels[10]. However, results from the NutriNet-Santé cohort suggested that higher consumers of artificial sweeteners confronted higher risks of developing CVD, type 2 diabetes and cancer[11–13].

In this context, we aimed to study the associations of artificial sweetener consumption with cardiometabolic risk factors and

Abbreviations: HR, hazard ratios; MR, Mendelian randomisation; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio.

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mortality based on the National Health and Nutrition Examination Survey (NHANES). Moreover, Mendelian randomisation (MR) was performed to back up our results.

Methods

Study population

The NHANES (https://www.cdc.gov/nchs/nhanes/index.htm) is a continuous programme designed to assess the health and nutritional status of adults and children in the USA. Since 1999, the NHANES has examined nationally representative individuals every 2 years. Detailed information on demographic, socio-economic, dietary and health status were normatively collected. Meanwhile, examination and laboratory tests were administered by skilled medical personnel. In this study, we enrolled two cycles (2003–2006) of the NHANES with artificial sweetener consumption records. Participants meeting the following criteria were excluded: less than 20 years old, being pregnant and without complete information on artificial sweetener consumption (Fig. 1). After exclusion, a total of 6371 participants were included for further analysis.

Assessment of artificial sweetener consumption

The frequency of artificial sweetener intakes was fetched from the 'FFQ – Raw Questionnaire Responses' data file in the dietary data section. Participants were asked, 'How often did you add artificial sweetener to your coffee or tea?', without detailed artificial sweetener types. Answers from participants were encoded with twelve values, including ten frequencies (never, less than 1 time per month, 1–3 times per month, 1 time per week, 2–4 times per week, 5–6 times per week, 1 time per d, 2–3 times per d, 4–5 times per d, 6 or more times per d), blank and error. Thereinto, data representing blank and error were treated as missing values. Then, the frequency of artificial sweetener consumption was merged into three levels: less than 1 time per month was deemed as 'rare', more than or equal to 1 time per d was considered as 'frequent' and the middle was defined as 'moderate'.

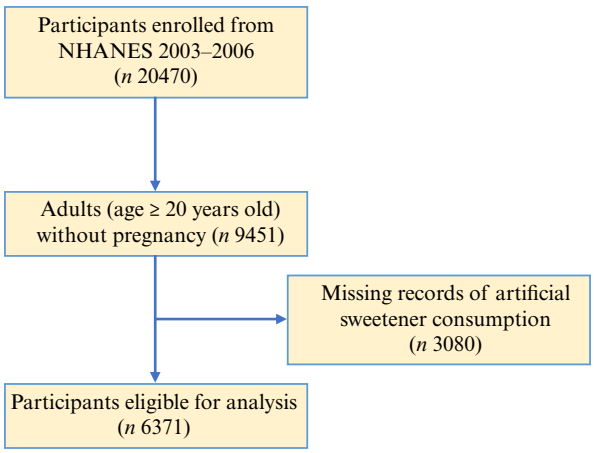

Fig. 1. Flow chart of study participants selection.

Assessment of covariates

In the NHANES, demographic data and standardised questionnaires were collected by trained interviewers. The definition and categorisation of baseline characteristics, health status and medical conditions have been described previously[14]. Briefly, we included age, sex, race/ethnicity, family poverty income ratio (PIR), employment status, marital status, education, smoking status, drinking status, body measurement index and several CVD at baseline. Family PIR was calculated by dividing family income by poverty guidelines specific to the survey year, deemed as a measure of socio-economic status. In addition, intakes of cold cereal, coffee and hot tea were considered. The frequency of their consumption was divided by once per month, once per week and once daily.

Assessment of outcomes

The corresponding follow-up information of the NHANES participants is available from the National Center for Health Statistics. Currently, available mortality data are updated to 31 December 2019. The underlying cause of death records were derived from UCOD_113, which could be recoded into comparable ICD-10 (International Classification of Diseases-10th Revision) based groups[15]. We examined all-cause mortality, death from CVD (I00-I09, I11, I13, I20-I51) and diabetes mellitus (E10-E14) as outcomes.

Statistical analyses

After participant selection, covariates with more than 30 % missing values were removed. Missing values were complemented using multiple imputations with five times iterations. The imputed data were evaluated with box-and-whisker plots.

The Shapiro–Wilk test was performed to assess the distribution of continuous variables for normality. Non-normally distributed variables were described as medians (interquartile ranges), and Kruskal–Wallis tests were applied for comparisons. Categorical variables were reported using counts (percentages) and compared using Pearson's χ^2 tests.

In the cross-sectional analysis, logistic regression models were computed to evaluate the associations between artificial sweetener consumption and the prevalence of hypertension, hypercholesterolaemia, diabetes, obesity, congestive heart failure, coronary artery disease (CAD), angina pectoris, myocardial infarction and stroke. We defined the rare artificial sweetener consumers as the reference group in the primary three-category model to obtain OR and 95 % CI for moderate consumers and frequent consumers. Furthermore, potential confounders such as age, sex, race, education, family PIR, smoking, alcohol usage and cereal, coffee and hot tea intakes were considered in the adjusted models.

Kaplan–Meier method with log-rank test was employed to analyse the three-categorised survival curves (rare, moderate, frequent) of all-cause mortality and cause-specific mortality from CVD and diabetes mellitus. Then, we tested the proportional hazards assumption by calculating Schoenfeld residuals. Associations between frequency of artificial sweetener addition and all-cause, CVD and diabetic mortality risks were assessed by

Table 1. Baseline characteristics of study population
(Median values and interquartile ranges; numbers and percentages)

	Overall, *n* 19 741		Rare, *n* 4691		Moderate, *n* 849		Frequent, *n* 831		*P*-value
	n	%	*n*	%	*n*	%	*n*	%	
Female (%)	3268	51·3	2333	49·7	468	55·1	467	56·2	<0·001
Age									
Median	51·00		50·00		51·00		60·00		<0·001
IQR	37·00, 68·00		35·00, 68·00		37·00, 65·00		46·00, 71·00		<0·001
Race/ethnicity (%)									
Mexican	1131	17·8	771	16·4	181	21·3	179	21·5	
Hispanic	178	2·8	137	2·9	21	2·5	20	2·4	
White	3544	55·6	2648	56·4	419	49·4	477	57·4	
Black	1261	19·8	929	19·8	208	24·5	124	14·9	
Others	257	4·0	206	4·4	20	2·4	31	3·7	
Education (%)									0·001
Less than high school	1647	25·9	1214	25·9	191	22·5	242	29·1	
High school or equivalent	1646	25·8	1255	26·8	207	24·4	184	22·1	
More than high school	3078	48·3	2222	47·4	451	53·1	405	48·7	
Marital status (%)									<0·001
Married	3951	62·0	2899	61·8	540	63·6	512	61·6	
Separated	1514	23·8	1068	22·8	198	23·3	248	29·8	
Never married	906	14·2	724	15·4	111	13·1	71	8·5	
Family PIR (%)									<0·001
<1·3	1628	25·6	1252	26·7	197	23·2	179	21·5	
1·3–3·5	2549	40·0	1884	40·2	313	36·9	352	42·4	
>3·5	2194	34·4	1555	33·1	339	39·9	300	36·1	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
BMI (median (IQR))	27·58	24·10, 31·89	27·01	23·70, 31·30	28·84	25·34, 33·56	29·21	25·58, 33·38	<0·001
Waist circumference (median (IQR))	97·30	87·10, 108·00	96·00	86·00, 106·50	100·00	89·60, 110·50	101·20	91·70, 111·40	<0·001
Glycated Hb (median (IQR))	5·40	5·20, 5·80	5·40	5·10, 5·70	5·50	5·20, 5·90	5·60	5·30, 6·20	<0·001
Total cholesterol (median (IQR))	5·04	4·40, 5·77	5·02	4·37, 5·74	5·09	4·37, 5·77	5·17	4·53, 5·92	<0·001
HDL-cholesterol (median (IQR))	1·32	1·09, 1·63	1·32	1·06, 1·60	1·32	1·09, 1·60	1·34	1·09, 1·66	0·262
	n	%	*n*	%	*n*	%	*n*	%	
Drinking (%)	4370	68·6	3231	68·9	569	67·0	570	68·6	0·563
Smoking (%)	3163	49·6	2348	50·1	388	45·7	427	51·4	0·037
Hypertension (%)	2361	37·1	1611	34·3	352	41·5	398	47·9	<0·001
Hypercholesterolaemia (%)	2639	41·4	1851	39·5	376	44·3	412	49·6	<0·001
Diabetes (%)	820	12·9	428	9·1	158	18·6	234	28·2	<0·001
Obesity (%)									<0·001
Normal weight	2013	31·6	1636	34·9	199	23·4	178	21·4	
Overweight	2183	34·3	1599	34·1	286	33·7	298	35·9	
Obesity	2175	34·1	1456	31·0	364	42·9	355	42·7	
Congestive heart failure (%)	260	4·1	165	3·5	37	4·4	58	7·0	<0·001
CHD (%)	350	5·5	247	5·3	41	4·8	62	7·5	0·025
Angina pectoris (%)	275	4·3	197	4·2	33	3·9	45	5·4	0·227
Heart attack (%)	356	5·6	242	5·2	46	5·4	68	8·2	0·002
Stroke (%)	277	4·3	179	3·8	47	5·5	51	6·1	0·002

Continued variables are presented as the median and interquartile range, compared with Kruskal–Wallis tests. Category variables are presented as count and proportion, compared using Pearson's χ^2 tests. PIR, poverty income ratio.

Cox proportional hazards models. Respectively, we calculated hazard ratios (HR) and 95 % CI with the rare consumer group as the reference category in univariate and multivariate models. Potential covariates such as age, sex, race, education, family PIR, smoking, alcohol usage and cereal, coffee and hot tea intakes were adjusted in the multivariate Cox model.

Subgroup analyses were conducted to test the sensitivity of the above results, exploring potential interactions with clinical features. Diabetic mortality risk was tested between the frequent group and rare group with stratified factors, including sex, age brackets ($< 65, \geq 65$ years old), ethnicity, family PIR, drinking, smoking, diabetes and obesity. Interaction effects between artificial sweetener consumption and these variables were statistically assessed. All analyses were performed using R version 4.2.2. All statistical tests were two-sided, with a pre-set significance threshold of $P < 0{\cdot}05$.

Mendelian randomisation

The two-sample MR study was conducted to provide causal evidence[16]. The summary-level genome-wide association studies data were retrieved from the IEU OpenGWAS data portal (https://gwas.mrcieu.ac.UK/)[17]. Exposure factors were sourced from the UK Biobank[18],

Table 2. OR (95% CI) for cardiometabolic disorders according to the frequency of artificial sweetener intake (Percentages; odds ratios and 95 % confidence intervals)

			Model 1			Model 2			Model 3		
	Events	%	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
Hypertension											
Rare	1611	34·3	Reference			Reference			Reference		
Moderate	352	41·5	1·35	1·17, 1·57	<0·001	1·45	1·23, 1·71	<0·001	1·44	1·22, 1·71	<0·001
Frequent	398	47·9	1·76	1·51, 2·04	<0·001	1·47	1·25, 1·74	<0·001	1·52	1·29, 1·80	<0·001
Hypercholesterolaemia											
Rare	1851	39·5	Reference			Reference			Reference		
Moderate	376	44·3	1·22	1·05, 1·41	0·008	1·26	1·08, 1·47	0·003	1·26	1·08, 1·47	0·004
Frequent	412	49·6	1·51	1·30, 1·75	<0·001	1·29	1·11, 1·50	0·001	1·28	1·10, 1·50	0·002
Diabetes											
Rare	428	9·1	Reference			Reference			Reference		
Moderate	158	18·6	2·28	1·86, 2·77	<0·001	2·42	1·96, 2·99	<0·001	2·44	1·96, 3·03	<0·001
Frequent	234	28·2	3·90	3·26, 4·68	<0·001	3·58	2·95, 4·34	<0·001	3·74	3·06, 4·57	<0·001
Obesity											
Rare	1456	30·6	Reference			Reference			Reference		
Moderate	364	42·9	1·67	1·44, 1·94	<0·001	1·62	1·39, 1·89	<0·001	1·64	1·40, 1·91	<0·001
Frequent	355	42·7	1·66	1·42, 1·93	<0·001	1·76	1·51, 2·05	<0·001	1·90	1·62, 2·23	<0·001
Congestive heart failure											
Rare	165	3·5	Reference			Reference			Reference		
Moderate	37	4·4	1·25	0·86, 1·78	0·230	1·50	1·01, 2·17	0·037	1·47	0·99, 2·16	0·051
Frequent	58	7·0	2·06	1·50, 2·79	<0·001	1·80	1·30, 2·47	<0·001	1·89	1·35, 2·62	<0·001
CHD											
Rare	247	5·3	Reference			Reference			Reference		
Moderate	41	4·8	0·91	0·64, 1·27	0·598	1·18	0·82, 1·68	0·354	1·20	0·82, 1·71	0·329
Frequent	62	7·5	1·45	1·08, 1·92	0·012	1·31	0·96, 1·76	0·086	1·32	0·96, 1·79	0·082
Angina pectoris											
Rare	197	4·2	Reference			Reference			Reference		
Moderate	33	3·9	0·92	0·62, 1·32	0·674	1·14	0·76, 1·67	0·500	1·10	0·73, 1·62	0·626
Frequent	45	5·4	1·31	0·93, 1·80	0·116	1·09	0·77, 1·52	0·617	1·07	0·75, 1·51	0·688
Heart attack											
Rare	242	5·2	Reference			Reference			Reference		
Moderate	46	5·4	1·05	0·75, 1·44	0·754	1·39	0·97, 1·95	0·062	1·38	0·96, 1·95	0·074
Frequent	68	8·2	1·64	1·23, 2·15	<0·001	1·47	1·08, 1·97	0·012	1·51	1·10, 2·04	0·009
Stroke											
Rare	179	3·8	Reference			Reference			Reference		
Moderate	47	5·5	1·48	1·05, 2·04	0·020	1·73	1·21, 2·43	0·002	1·87	1·30, 2·65	<0·001
Frequent	51	6·1	1·65	1·19, 2·25	0·002	1·37	0·97, 1·89	0·066	1·35	0·95, 1·88	0·087

Model 1: Logistic regression model without adjustment. Model 2: adjusted for age, sex, race, education, family poverty income ratio, drinking and smoking status. Model 3: adjusted for variables in model 2 and cold cereal, coffee and hot tea intakes.

including artificial sweetener intake in cereal/coffee/tea in the European population (64 949 individuals), South Asian population (1469 individuals) and African American or Afro-Caribbean population (1207 individuals). We included ischaemic heart disease, hypertension and type 2 diabetes as outcome factors according to the corresponding populations. The included genome-wide association studies datasets were summarised in online Supplementary Table S1. The 'TwoSampleMR' package was employed to perform the MR analysis. A relatively relaxed threshold ($P < 1 \times 10^{-5}$) was applied to select instrumental variables from the common SNP sites. Then linkage disequilibrium clumping ($r2 < 0{\cdot}01$, clumping distance = 5000 kb) was performed to prove the dependence of the chosen SNP. Five models (MR Egger, Weighted median, inverse variance weighted, simple mode, weighted mode) were utilised by default to eliminate potential bias from the heterogeneity of MR methods. In addition, certain tests were performed to guarantee reliability: leave-one-out test for sensitivity, Steiger test for directionality, heterogeneity test and pleiotropy test. The 'MR-PRESSO' package was utilised to test for horizontal pleiotropy as well[19].

Results

Baseline characteristics

Of the total 6371 participants, 4691 (73·6 %) participants added artificial sweetener < 1 monthly, 849 (13·3 %) ≥ 1 monthly and < 1 daily, 831 (13·0 %) ≥ 1 daily (Table 1). Compared with participants who rarely consumed artificial sweeteners, higher consumers were more likely to be female, older, non-Hispanic, separated, have a higher education level and middle-to-high annual income and with metabolic disorders (hypercholesterolaemia, diabetes) and CVD (hypertension, congestive heart failure, CHD, angina pectoris, heart attack and stroke). In addition, participants who had more artificial sweeteners reported higher BMI, glycated Hb and total cholesterol.

Association of artificial sweetener intake and cardiometabolic disorders

As demonstrated in Table 2, frequent artificial sweetener consumers might confront increased risks of hypertension

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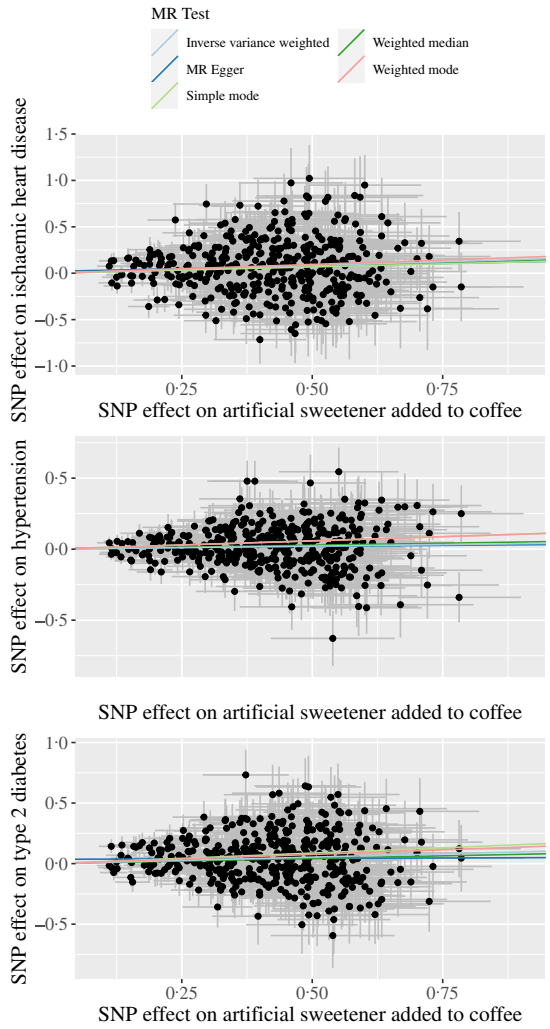

Fig. 2. Scatter plots for the associations between artificial sweeteners added to coffee and the risk of ischaemic heart disease (above), hypertension (middle) and type 2 diabetes (below). MR, Mendelian randomisation.

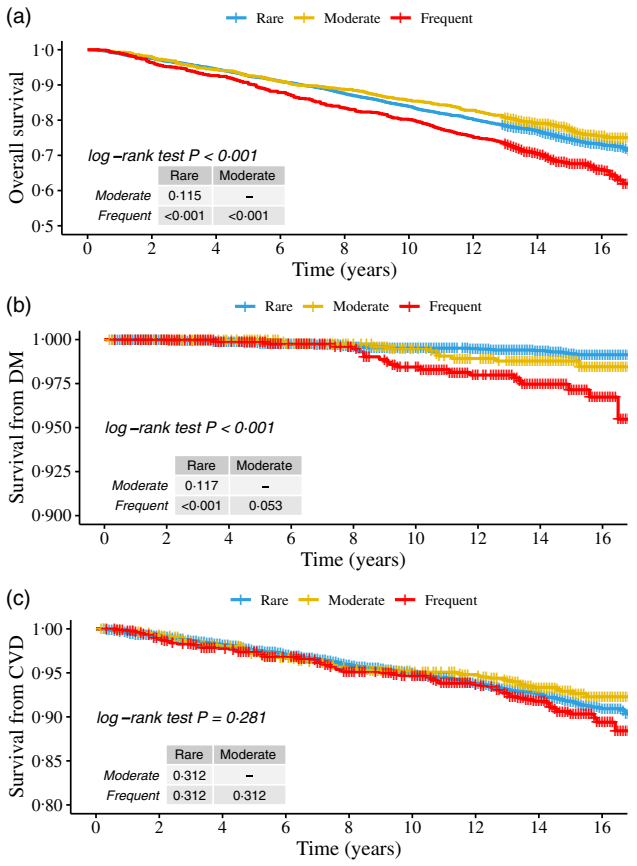

Fig. 3. Kaplan–Meier survival plots of artificial sweetener consumption and all-cause mortality, diabetes mortality and cardiovascular mortality. Kaplan–Meier analyses showed that participants consuming artificial sweeteners more than one time per d had higher rates of all-cause death (a) and diabetic death (b), but not cardiovascular death (c). DM, diabetes mellitus.

(OR = 1·52 (1·29, 1·80), $P < 0·001$), hypercholesterolaemia (OR = 1·28 (1·10, 1·50), $P = 0·002$), diabetes (OR = 3·74 (3·06, 4·57), $P < 0·001$), obesity (OR = 1·52 (1·29, 1·80), $P < 0·001$), congestive heart failure (OR = 1·89 (1·35, 2·62), $P < 0·001$) and heart attack (OR = 1·51 (1·10, 2·04), $P = 0·009$).

However, the causal effect of the above results was limited due to the cross-sectional design of the NHANES programme. Thus, MR was applied for verification. As shown in Fig. 2, our IVW models indicate a positive correlation between artificial sweetener added to coffee with ischaemic heart disease (OR = 1·18 (1·10, 1·26), $P < 0·001$), hypertension (OR = 1·04 (1·01, 1·08), $P = 0·011$) and type 2 diabetes (OR = 1·11 (1·06, 1·16), $P < 0·001$) among African population. Similar results were obtained in other models like MR Egger and so forth. Moreover, these results were steady with leave-one-out analysis, and the direction of these causal associations was tested and consolidated. Notably, MR-PRESSO global analysis also indicated a potential pleiotropy for ischaemic heart disease ($P = 0·008$), but not for hypertension ($P = 0·822$) and type 2 diabetes ($P = 0·302$).

However, causal associations were not found from artificial sweetener intake in cereal or tea nor in European and South Asian populations (online Supplementary Table S2).

Association of artificial sweetener intake and mortality

Kaplan–Meier curves and log-rank tests showed that participants who consumed the highest levels of artificial sweeteners were exposed to significantly higher risks of all-cause ($P < 0·001$) and diabetic mortality ($P < 0·001$) (Fig. 3(a) and (b)). While mortality due to CVD was not significantly influenced (Fig. 3(c)). In Cox proportional hazard regression, compared with the rare consumers, participants who reported the highest levels of artificial sweetener consumption had substantially increased risks of all-cause (HR = 1·34 (1·17, 1·53), $P < 0·001$) and diabetic mortality (HR = 3·83 (2·18, 6·72), $P < 0·001$) (Table 3). After controlling for demographic, behavioural and dietary factors, the risk of diabetic mortality remained significant (HR = 2·62 (1·46, 4·69), $P = 0·001$). Consistently, a positive association between artificial sweeteners and diabetic mortality was observed to hold among subgroups, without potential interaction effect (Fig. 4).

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Table 3. HR (95% CI) for all-cause, CVD and diabetic mortality according to the frequency of artificial sweetener intake (Percentages; hazard ratios and 95 % confidence intervals)

			Model 1			Model 2			Model 3		
	Events	%	Hazard ratio	95 % CI	*P*	Hazard ratio	95 % CI	*P*	Hazard ratio	95 % CI	*P*
All-cause mortality											
Rare	1188	25·3	Reference			Reference			Reference		
Moderate	193	22·7	0·88	0·76, 1·03	0·114	1·12	0·96, 1·31	0·136	1·13	0·97, 1·33	0·123
Frequent	270	32·5	1·34	1·17, 1·53	<0·001	1·03	0·90, 1·18	0·669	1·01	0·89, 1·16	0·837
CVD mortality											
Rare	353	7·5	Reference			Reference			Reference		
Moderate	56	6·6	0·86	0·65, 1·15	0·311	1·17	0·88, 1·55	0·290	1·167	0·872, 1·563	0·300
Frequent	69	8·3	1·15	0·89, 1·49	0·288	0·88	0·68, 1·15	0·355	0·879	0·674, 1·145	0·338
Diabetic mortality											
Rare	31	0·7	Reference			Reference			Reference		
Moderate	10	1·2	1·75	0·86, 3·57	0·124	2·06	1·00, 4·25	0·050	2·08	0·99, 4·37	0·053
Frequent	20	2·4	3·83	2·18, 6·72	<0·001	2·85	1·61, 5·03	<0·001	2·62	1·46, 4·69	0·001

Model 1: Cox proportional hazards model without adjustment. Model 2: adjusted for age, sex, race, education, marital status, family poverty income ratio, drinking and smoking status. Model 3: adjusted for variables in model 2 and cold cereal, coffee, hot tea, total energy intakes (kcal).

Discussion

Results from the current study indicated positive associations between artificial sweetener intake and higher risks of several cardiometabolic disorders, especially for hypertension and type 2 diabetes. Moreover, higher artificial sweetener consumers confronted an increased risk of mortality from diabetes, but not CVD.

To our knowledge, this study for the first time linked artificial sweetener intake with diabetic mortality. Previous large-scale cohort studies have revealed positive associations between artificial sweeteners with risks of several cardiometabolic disorders and all-cause and CVD mortality. Results from the Women's Health Initiative cohort suggested that participants who had more than one serving per d had a greater likelihood of stroke, CHD and all-cause mortality[20]. Despite the counterpart results in our study were not statistically significant, they shared the same tendency. Similar results were reported in the UK Biobank cohort[21] and NutriNet-Santé cohort[11]. Interestingly, the NutriNet-Santé cohort further suggested the specific effects of artificial sweeteners on individuals, like aspartame towards cerebrovascular events, acesulfame potassium and sucralose towards CHD. What's more, Malik *et al.* reported that CVD mortality was significantly higher in the highest artificial sweetener intake category[22]. Malik's work included two large prospective cohorts, the Nurses' Health Study and the Health Professionals Follow-up Study, whereas the significant results were merely seen in the pooled analysis. The weak association hinted the existence of residual confounding.

Comparatively, the relationship between artificial sweetener consumption and diabetes is much more intricate. People with diabetes or at high risk of developing diabetes tend to use artificial sweeteners to prevent or manage diabetes[2,23]. However, two prospective studies and an MR study recently have identified that higher consumers of artificial sweeteners had higher risks of developing type 2 diabetes, regardless of sex and artificial sweetener types[12,24,25]. Our work verified this result and further indicated that artificial sweetener consumption might contribute to diabetes-related adverse outcomes. Notably, the inference from MR by Zhang *et al.* is similar, but not the same, with our results. We merely identified causal associations between artificial sweetener intake in coffee and type 2 diabetes among the African population, rather than the European population. This difference may result from the parameter setting of instrumental variable selection.

Meanwhile, the underlying mechanism of how artificial sweeteners influence cardiovascular and endocrine systems remained unclear. Pham *et al.* performed intraduodenal administration of sucralose in healthy older subjects and found no significant changes in blood pressure or superior mesenteric artery blood flow[6]. A prospective study reported that consumption of artificial sweeteners during pregnancy and at follow-up increased glycated Hb, insulin, TAG and liver fat and lowered HDL[26]. Moreover, artificial sweetener was found to lower β-cell glucose sensitivity, total insulin secretion and β-cell rate sensitivity in the Maastricht Study[27]. These clinical trials provide insights into the effective targets of artificial sweeteners. In addition, basic research into the biological effect has been launched. For example, early research focused on the influence of artificial sweeteners on apo A-I and HDL, indicating a pro-atherogenic property in artificial sweetener-treated apo A-I[28]. Interestingly, Bian *et al.* reported a 4-week acesulfame potassium consumption could perturb the gut microbiome of CD-1 mice, activating genes related to carbohydrate absorption, metabolism and lipopolysaccharide synthesis[7]. Similarly, sucralose was reported to change the composition of mice gut microbiota as well and affect the intestinal barrier function[29]. In addition, sucralose regulates endothelial barrier function by activating the sweet taste receptor T1R3[30]. These studies suggested the multiple physiological effects of artificial sweeteners. Considering the incremental consumption of artificial sweeteners worldwide, further study is needed to elucidate its health effects.

Though this study had the advantages of comprehensive baseline information and long follow-up, certain limitations

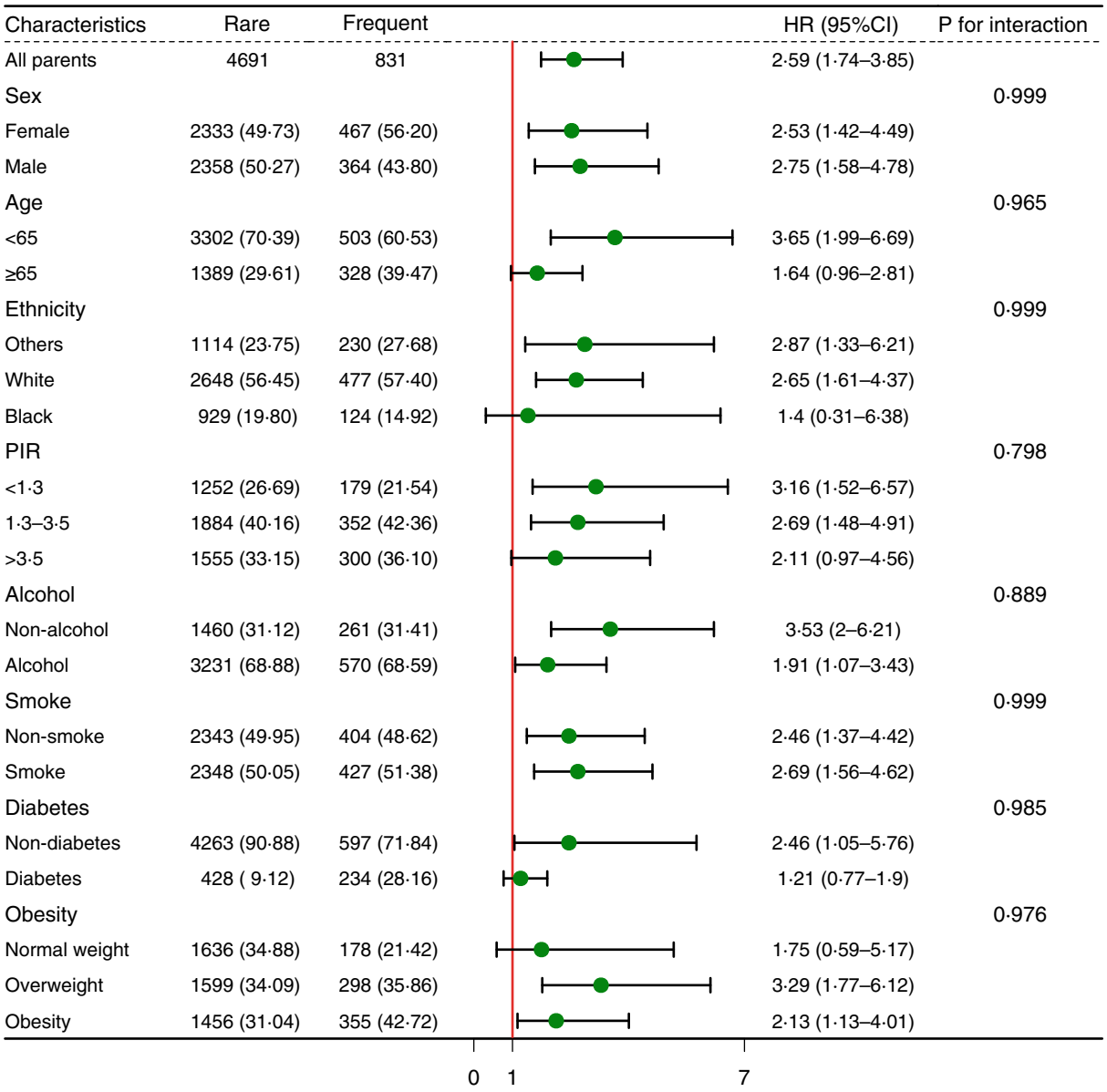

Fig. 4. Adjusted diabetes mortality in subgroups with artificial sweetener consumption more than one time per d and less than one time per month. PIR, poverty income ratio.

should be acknowledged. First, the artificial sweetener usage habits recorded in this study were based on cross-sectional studies, participants may change their frequency of artificial sweetener intake during follow-up. Meanwhile, there is a lack of information regarding artificial sweeteners in other food items and detailed artificial sweetener types. Second, the sample size is relatively small, considering the low incident rate of death due to diabetes. The number of events in some subgroups was too small for analysis. Third, SNP sites strongly associated with artificial sweetener intake are scarce. Thus, we employed a relaxed threshold in MR analysis. Additionally, using artificial sweetener intake as exposure might not well satisfy the gene-environment equivalence during MR analysis. The results should be interpreted with great caution.

Conclusions

In summary, we reported that greater consumers of artificial sweeteners are confronted with a higher risk of cardiometabolic disorders (hypertension, type 2 diabetes) and diabetic mortality. People who use artificial sweeteners to prevent and manage diabetes may not benefit from these sugar substitutes. Our results support public outreach to limit artificial sweetener consumption to avoid its adverse health effects.

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Yue Gu and Ming-xing Chen conceived the study design and are responsible for the overall content. Jun-yan Kan and Dong-chen Wang analysed and interpreted the data. Yu Chang and Zi-hao Jiang wrote the manuscript. Xiao-min Jiang, Hao Xie and Xin-xin Jia edited the manuscript. All authors read and approved the final manuscript.

The authors declare that they have no competing interests.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452400223X.

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