JACC: ASIA VOL. 4, NO. 6, 2024

ORIGINAL RESEARCH

Perceived Taste and Olfactory Dysfunctions and Subsequent Stroke Risk

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ABSTRACT

BACKGROUND Taste and olfactory dysfunction are commonly associated with neurodegenerative diseases and cardiovascular risk factors, but their specific associations with stroke risk remain uncertain.

OBJECTIVES The purpose of this paper was to explore whether perceived taste and olfactory dysfunctions were associated with stroke risk.

METHODS Included were 85,656 participants (mean age 51.0 ± 15.3 years) of the Kailuan study. Perceived olfactory and taste dysfunctions were assessed via a questionnaire at baseline (in 2014-2016). Incident stroke cases were confirmed by review of medical records. Cox proportional hazards models were used to investigate associations of perceived olfactory and taste dysfunctions with stroke risk, and mediation analysis was used to estimate the mediating effect of chronic disease statuses.

RESULTS We documented 2,198 incident stroke cases during a mean of 5.6 years of follow-up. Perceived taste dysfunction was associated with a doubled risk of developing total stroke (adjusted HR: 2.03; 95% CI: 1.36-3.04; $P < 0.001$) even with adjustment of lifestyle factors, biomarkers (ie, blood lipids, blood glucose, blood pressure, and uric acid), and other potential confounders. However, perceived olfactory dysfunction (adjusted HR: 1.22; 95% CI: 0.79-1.90; $P = 0.34$) was not significantly associated with a high risk of total stroke. Similar results of both perceived taste and olfactory dysfunctions were observed for ischemic stroke. Presence of chronic diseases, including hypertension, diabetes, chronic kidney disease, and overweight/obesity, mediated 4% to 5% of the association of perceived taste dysfunction with both total stroke and ischemic stroke.

CONCLUSIONS In this large cohort study, perceived taste dysfunction was associated with a high risk of developing stroke. (JACC: Asia 2024;4:483-492) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Stroke is a major public health challenge globally and the leading cause of death in China.[1] Given that approximately 77% of strokes are first events, primary prevention of stroke is crucial[2] and major advances in stroke prevention contributed to a reduced burden of stroke worldwide.[3,4]

Chemosensory functions, commonly referred to as olfactory function and taste function, are the primary

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 18, 2023; revised manuscript received February 2, 2024, accepted February 3, 2024.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.02.001

ABBREVIATION AND ACRONYM

hs-CRP = high-sensitivity C-reactive protein

pathways by which mammals perceive and respond to chemicals in the environment, such as odors, tastes, and stimuli.[5] Alterations in chemosensory functions can dramatically alter eating behavior and profoundly interfere with the quality of life with important clinical implications.[6] Increasing evidence showed that olfactory and taste dysfunctions predicted the risk of neurodegenerative diseases.[7] The association between olfactory dysfunction and high cardiovascular disease mortality was also reported.[8,9] However, the specific associations of olfactory and taste dysfunctions with stroke risk remain unclear. Given the paucity of epidemiological evidence, we hypothesized that individuals with perceived chemosensory dysfunction have a high stroke risk, another common neurological disease. Interestingly we previously reported that individuals with perceived taste/olfactory dysfunction experienced high odds of hyperlipidemia and hypertension,[10,11] providing evidence to support this hypothesis.

In the current study, we prospectively investigated the associations between chemosensory dysfunctions and incident stroke, and explored the potential mediation effect of chronic diseases in such associations, in a community-based cohort encompassing more than 85,000 participants.

METHODS

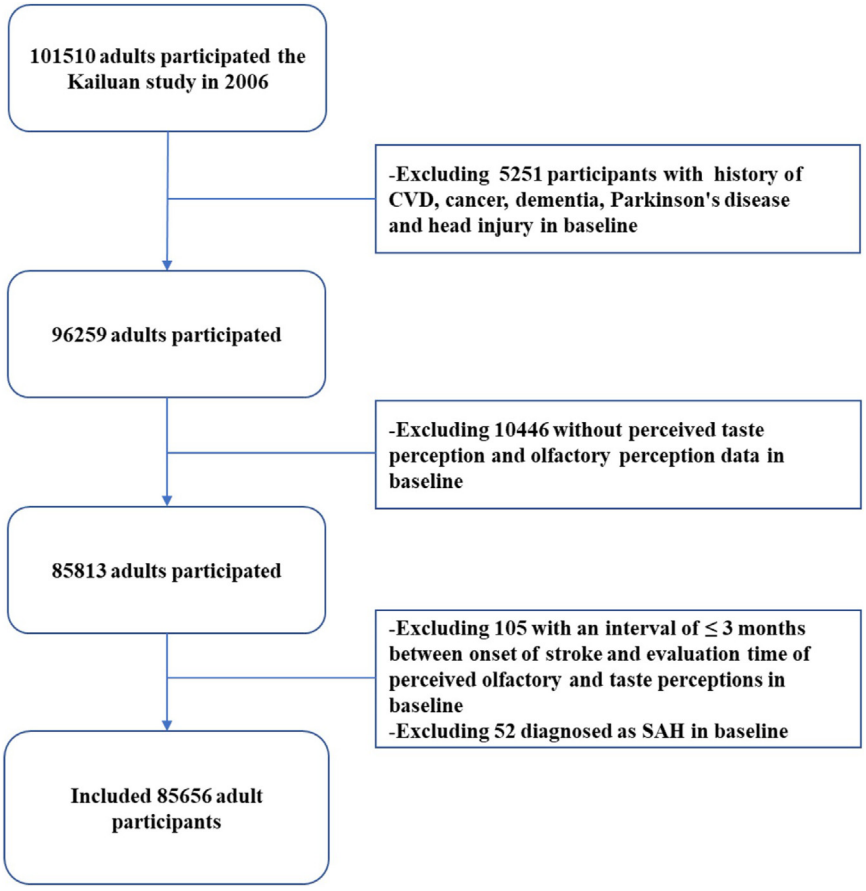
STUDY DESIGN AND PARTICIPANTS. This study was based on an ongoing multicenter Kailuan cohort, which included 101,510 Chinese adults (81,110 men and 20,400 women) aged 18 to 98 years during 2006-2007, and questionnaires and physical examinations were conducted every 2 years thereafter. The covariates in the study were all collected during the 2014-2016 period, as described in detail elsewhere.[12-15] The current community-based study included 85,656 participants (age 51.0 ± 15.3 years) who were free of cardiovascular diseases (myocardial infarction, stroke, and heart failure), cancer, dementia, Parkinson's disease, and head injury at baseline (ie, year 2014 for most participants, and year 2016 for 270 participants who only completed the assessment of perceived chemosensory functions in 2016) (**Figure 1**). This investigation was approved by the Ethics Committee of the Kailuan General Hospital. All the participants gave their written informed consent.

ASSESSMENT OF PERCEIVED OLFACTORY AND TASTE DYSFUNCTIONS. Perceived olfactory and taste perfections information was collected through self-reported questionnaires derived from the National Health Interview Survey in 2014 and 2016.[13-16] All participants were asked the following questions about olfactory/taste: "Do you have any problems with your sense of olfactory/taste, such as not being able to olfactory/taste things or things not smelling/tasting the way they are supposed to for at least 3 months?" Those who answered yes were considered to have perceived olfactory/taste dysfunction.

ASSESSMENT OF INCIDENT STROKE (ISCHEMIC STROKE AND HEMORRHAGIC STROKE). The primary outcome included the initial incidence of stroke, manifesting as either a nonfatal event or culminating in death. The process of identifying incident strokes has been described previously.[13-15] The Municipal Social Insurance Institution database and hospital discharge registries were used to determine stroke incidence among all Kailuan study participants. Potential stroke cases were identified using the International Classification of Diseases-10th Revision (codes 161 and 163). In addition, information regarding the past medical history of stroke was collected via questionnaire biennially since 2006. Data on deaths were obtained from local vital statistics offices. A panel of 3 neurologists and physicians examined the medical records of potential stroke cases discerned through International Classification of Diseases codes and/or questionnaires. Nonfatal strokes were characterized as the abrupt emergence of focal neurological deficits with vascular etiology persisting for more than 24 hours. Fatal strokes were verified by medical records, autopsy reports, and death certificates that indicated stroke as the primary cause. Stroke diagnoses followed the World Health Organization criteria,[17] and were supported by brain computed tomography or magnetic resonance imaging for confirmation. This study concentrated on the 2 principal stroke subtypes: hemorrhagic stroke (excluding subarachnoid and subdural hemorrhages) and ischemic stroke.

ASSESSMENT OF POTENTIAL COVARIATES. Information on sex, age, education level, income level, occupation, daily physical activity (evaluated by the International Physical Activity Questionnaire, and calculated met levels by standard),[18] smoking status, alcohol intake, and disease history was collected at baseline using questionnaires.[12] Anthropometric parameters, such as height and weight were measured by trained nurses. Body mass index was calculated as body weight (kg) divided by the square of height (m^2). Systolic and diastolic blood pressure were measured by a mercury sphygmomanometer in a sitting position, and the mean of the 2 measurements was taken. Hypertension was characterized by systolic blood pressure ≥140 mm Hg or diastolic

FIGURE 1 Flow Chart of Study Participants in the Current Study



Included in the analyses were 85,656 Kailuan study participants (mean age: 51.0 ± 15.3 years), free of cardiovascular diseases, cancer, dementia, Parkinson's disease, or head injury at baseline (2014-2016), when perceived chemosensory functions were assessed.
CVD = cardiovascular diseases (myocardial infarction, stroke, and heart failure); SAH = subarachnoid hemorrhage.

blood pressure ≥90 mm Hg, or the use of antihypertensive medications within the past 2 weeks, regardless of blood pressure status. Prehypertension was defined as systolic blood pressure between 120 and 139 mm Hg or diastolic blood pressure between 80 and 89 mm Hg. Diabetes is defined by a fasting blood glucose concentration of ≥7.0 mmol/L or the use of oral hypoglycemic agents or active insulin therapy, and prediabetes is characterized by a fasting blood glucose concentration ranging from 5.6 to 6.9 mmol/L. Assessment of plasma high-sensitivity C-reactive protein (hs-CRP) concentration was conducted by using high-sensitivity particle-enhanced immunonephelometry assay (Cias Latex CRP-H, Kanto Chemical Co Inc). Concentrations of glucose, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and uric acid were assessed using an autoanalyzer (Hitachi 747, Hitachi) at the central laboratory of the Kailuan General Hospital. Dyslipidemia was defined as total cholesterol ≥6.2 mmol/L or triglyceride ≥2.3 mmol/L.[19] Myocardial infarction cases were confirmed by review of the medical record, as detailed elsewhere.[20]

STATISTICAL ANALYSIS. We used Cox proportional hazards models to estimate HRs and 95% CIs of stroke based on different perceived chemosensory function groups. The proportional hazards (PH) assumption was tested by correlating the scaled Schoenfeld residuals with time and there was evidence that the PH assumption was validated.

Time to events of follow-up was accumulated from baseline until the occurrence of the outcome, death, or the end of follow-up (December 31, 2020), whichever came first. The continuous variables passed the

TABLE 1 Baseline Characteristics by Status of Perceived Taste and Olfactory Dysfunctions

	Perceived Taste Dysfunction			Perceived Olfactory Dysfunction		
	No (n = 85,038)	Yes (n = 618)	*P* Value	No (n = 82,180)	Yes (n = 815)	*P* Value
Age, y	51.0 ± 15.3	48.7 ± 13.2	<0.001	51.0 ± 15.4	49.0 ± 13.2	<0.001
Sex						
Men	68,290 (80.3)	492 (79.6)	0.67	66,304 (80.7)	677 (83.1)	0.09
Education			<0.001			<0.001
Primary	3,418 (4.0)	8 (1.3)		3,388 (4.1)	18 (2.2)	
Middle	69,752 (82.0)	500 (80.9)		67,444 (82.1)	650 (79.8)	
College and higher	11,868 (14.0)	110 (17.8)		11,348 (13.8)	147 (18.0)	
Occupation			0.66			0.042
Blue collar	12,134 (14.3)	92 (14.9)		11,470 (14.0)	134 (16.4)	
White collar	72,904 (85.7)	526 (85.1)		70,710 (86.0)	681 (83.6)	
Average income, RMB/mo			<0.001			0.005
<500	2,364 (2.8)	27 (4.4)		2,300 (2.8)	38 (4.7)	
500-2,999	66,820 (78.6)	442 (71.5)		64,339 (78.3)	619 (76.0)	
≥3,000	15,854 (18.6)	149 (24.1)		15,541 (18.9)	158 (19.4)	
Smoking status			0.003			<0.001
Never	50,510 (59.4)	328 (53.1)		48,420 (58.9)	425 (52.1)	
Past smoker	34,418 (40.5)	288 (46.6)		33,674 (41.0)	388 (47.6)	
Current smoker	110 (0.1)	2 (0.3)		86 (0.1)	2 (0.2)	
Hypertension			0.43			0.18
Normal blood pressure	15,243 (17.9)	123 (19.9)		14,636 (17.8)	164 (20.1)	
Prehypertension	37,053 (43.6)	266 (43.0)		35,995 (43.8)	356 (43.7)	
Yes	32,742 (38.5)	229 (37.1)		31,549 (38.4)	295 (36.2)	
Diabetes			0.45			0.001
Normal glucose	51,098 (60.1)	356 (57.6)		49,269 (60.0)	438 (53.7)	
Prediabetes	24,579 (28.9)	191 (30.9)		23,855 (29.0)	270 (33.1)	
Yes	9,361 (11.0)	71 (11.5)		9,056 (11.0)	107 (13.1)	
Body mass index, kg/m^2	24.8 ± 3.5	25.0 ± 3.7	0.18	24.8 ± 3.5	25.1 ± 3.8	0.05
<24.0	34,980 (41.1)	251 (40.6)	0.54	33,791 (41.1)	317 (38.9)	0.40
24.0-27.9	36,704 (43.2)	260 (42.1)		35,490 (43.2)	361 (44.3)	
≥28.0	13,354 (15.7)	107 (17.3)		12,899 (15.7)	137 (16.8)	
Chronic kidney disease (yes)	485 (0.6)	12 (1.9)	<0.001	476 (0.6)	19 (2.3)	<0.001
Alcohol intake, mL/d	0.0 (0.0, 20.0)	0.0 (0.0, 40.0)	0.026	0.0 (0.0, 20.0)	0.0 (0.0, 39.0)	0.043
Physical activity, METs/d	74 (0.0, 803.0)	520 (0.0, 1040.0)	<0.001	173 (0.0, 803.0)	520 (0.0, 1150.0)	<0.001
Sleep duration, h/d	7.0 (6.0, 8.0)	7.0 (6.0, 7.0)	0.06	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)	0.23
HDL-C, mmol/L	1.3 (1.1, 1.5)	1.3 (1.1, 1.6)	0.040	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	0.42
LDL-C, mmol/L	2.9 (2.4, 3.4)	2.9 (2.4, 3.5)	0.53	2.9 (2.4, 3.4)	2.9 (2.4, 3.4)	0.63
TG, mmol/L	1.3 (0.9, 1.9)	1.3 (0.9, 1.8)	0.76	1.3 (0.9, 1.9)	1.3 (0.9, 2.0)	0.35
Uric acid, μmol/L	323.0 (268.3, 384.0)	329.0 (268.0, 383.0)	0.66	323.0 (268.0, 383.0)	324.0 (262.0, 383.0)	0.13
hs-CRP, mg/L	1.0 (0.5, 2.1)	1.1 (0.4, 2.3)	0.72	1.0 (0.5, 2.1)	1.2 (0.5, 2.4)	0.08

Values are mean ± SD, n (%), or median (25th, 75th percentile). Based on the chi-square test for categorical variables, or Kruskal-Wallis test for continuous variables, $P < 0.05$.
HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

collinearity test (Variance Inflation Factors remained below 5) (Supplemental Table 1). Each outcome was analyzed separately, which resulted in a different follow-up period. We fitted 3 models: model 1 was a crude model with no variables adjusted; model 2 adjusted for age and sex; model 3 further adjusted for occupation (blue collar/white collar), smoking (current, past, or never), alcohol intake (quartile), education (primary, middle, or college and higher), physical activity (METs/d quartile), income (<500, 500-2,999, or ≥3,000 RMB/mo), body mass index (<24, 24-27.9, or ≥28 kg/m^2), triglycerides (quartile), high-density lipoprotein cholesterol (quartile), low-density lipoprotein cholesterol (quartile), uric acid (quartile), hs-CRP (<1, 1-2.9, or ≥3 mg/mL), chronic kidney disease (no, yes), diabetes (normal glucose, prediabetes, yes), incident myocardial infarction (no, yes), hypertension (normal blood pressure, prehypertension, yes), and sleep duration (<6, 6-6.9, 7-7.9, 8-8.9, or ≥9 h/d). In the current

TABLE 2 Association of Perceived Taste and Olfactory Dysfunctions With Stroke Risk

	Perceived Taste Dysfunction			Perceived Olfactory Dysfunction		
	No	Yes	*P* Value	No	Yes	*P* Value
Total stroke						
Cases/N	2,174/85,038	24/618		2,121/82,180	20/815	
Model 1	1.00 (ref.)	1.78 (1.19, 2.66)	0.005	1.00 (ref.)	1.09 (0.70, 1.69)	0.71
Model 2[a]	1.00 (ref.)	2.07 (1.38, 3.10)	<0.001	1.00 (ref.)	1.25 (0.81, 1.95)	0.31
Model 3[b]	1.00 (ref.)	2.03 (1.36, 3.04)	<0.001	1.00 (ref.)	1.22 (0.79, 1.90)	0.34
Ischemic stroke						
Cases/N	2,020/85,038	22/618		1,968/82,180	19/815	
Model 1	1.00 (ref.)	1.76 (1.15, 2.67)	0.009	1.00 (ref.)	1.06 (0.59, 1.52)	0.81
Model 2[a]	1.00 (ref.)	2.05 (1.35, 3.12)	0.001	1.00 (ref.)	1.29 (0.82, 2.03)	0.27
Model 3[b]	1.00 (ref.)	2.02 (1.32, 3.07)	<0.001	1.00 (ref.)	1.26 (0.80, 1.98)	0.34
Hemorrhagic stroke						
Cases/N	205/85,038	3/618		205/82,180	1/815	
Model 1	1.00 (ref.)	2.33 (0.74, 7.27)	0.15	1.00 (ref.)	0.53 (0.07, 3.77)	0.53
Model 2[a]	1.00 (ref.)	2.66 (0.85, 8.31)	0.09	1.00 (ref.)	0.63 (0.09, 4.49)	0.64
Model 3[b]	1.00 (ref.)	2.52 (0.80, 7.94)	0.11	1.00 (ref.)	0.64 (0.09, 4.56)	0.67

Values are n/N or median (25th, 75th percentile). [a]Adjusted for age (y) and sex. [b]Further adjusted for occupation (blue collar/white collar), smoking (current, past, or never), alcohol intake (tertile), education (primary, middle, or college and higher), physical activity (METs/d quartile), income (<500, 500 to 2999, or ≥3000, RMB/mo), body mass index (<24, 24 to 27.9, or ≥28 kg/m^2), triglycerides (quartile), high-density lipoprotein cholesterol (quartile), low-density lipoprotein cholesterol (quartile), uric acid (quartile), high-sensitivity C-reactive protein (<1, 1 to 2.9, or ≥3 mg/mL), chronic kidney disease (no, yes), diabetes (normal glucose, prediabetes, yes), incident myocardial infarction (no, yes), hypertension (normal blood pressure, prehypertension, yes), and sleep duration (<6, 6-6.9, 7-7.9, 8-8.9, or ≥9 h/d).

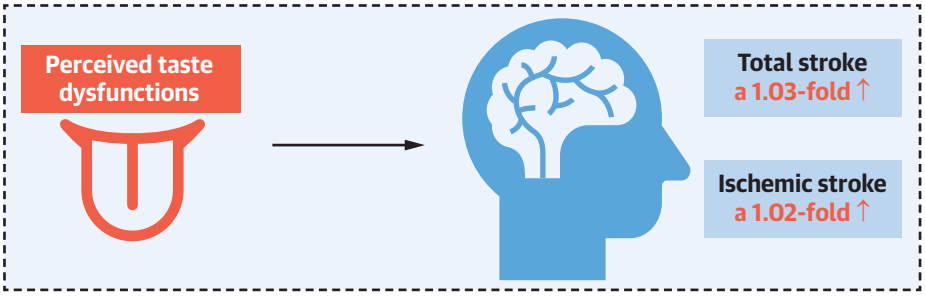
Model 1: Crude model.

study, the selection of covariates combined the results of univariate analysis and reports from previous literature, or clinically meaningful indicators, which showed that these factors are risk factors for stroke and could also be associated with the exposure. Several sensitivity analyses were conducted: 1) excluding the events occurring in the first 2 years of follow-up; 2) excluding participants with a family history of stroke; 3) excluding participants with hs-CRP ≥3 mg/L; 4) excluding cases with 2 subtypes of stroke simultaneously; and 5) using the data without imputation to explore whether the association between different perceived chemosensory dysfunctions and stroke would be affected by a potential allergic reaction or chronic inflammation. We examined potential interactions of different perceived chemosensory dysfunctions with age (<60 or ≥60 years), sex (women/men), smoking status (never/ever), and alcohol intake (quartile), in relation to stroke risk, by including multiplicative terms in the Cox models, with adjustment for other potential confounders in model 3. To explore the mediating role of chronic disease statuses and unhealthy lifestyle in the association between chemosensory dysfunctions and incident stroke, mediation analysis was performed using the "CMAverse" package of R software,[21] adjusted for covariates mentioned previously. It should be noted that time of outcome occurrence corresponded with the primary analysis follow-up time, that is, follow-up event times were recorded from baseline to the earliest of outcome occurrence, death, or follow-up end (December 31, 2020). Chronic disease statuses were assessed by the number of comorbidities, based on hypertension (no, yes), diabetes (no, yes), chronic kidney disease (no, yes), dyslipidemia (no, yes), and overweight/obesity (no, yes). Unhealthy lifestyle was assessed by the number of nonoptimal lifestyle factors, namely smoking (no, yes), alcohol drinking (no, yes), nonoptimal sleep duration (6-8.9 h/d, <6 or ≥9 h/d), and salt intake >6 g (≤6 g, >6 g). Fine-Gray competing risk models (myocardial infarction and death were each considered as competing events) were used to evaluate the associations of perceived chemosensory dysfunctions and stroke risk. Missing covariate data (<20%) were imputed using multiple imputations (the number of imputed datasets was 20). Significance tests were 2-tailed, and a *P* value <0.05 was considered to be statistically significant. All of the analyses were performed by using R software (version 4.0.5, R Foundation).

RESULTS

Individuals with perceived chemosensory dysfunctions typically exhibited younger ages, displayed a propensity for smoking, consumed more alcohol, and possessed a higher educational background (Table 1).

CENTRAL ILLUSTRATION Perceived Chemosensory Dysfunctions and Stroke Risk Analysis



	Perceived Taste Dysfunction		Perceived Olfactory Dysfunction	
	No	Yes	No	Yes
Total stroke				
Cases/total n	2,174/85,038	24/618	2,121/82,180	20/815
Model 1	1.00 (ref.)	**2.03 (1.36, 3.04)**	1.00 (ref.)	1.22 (0.79, 1.90)
Ischemic stroke				
Cases/total n	2,020/85,038	22/618	1,968/82,180	19/815
Model 1	1.00 (ref.)	**2.02 (1.32, 3.07)**	1.00 (ref.)	1.26 (0.80, 1.98)
Hemorrhagic stroke				
Cases/total n	205/85,038	3/618	205/82,180	1/815
Model 1	1.00 (ref.)	2.52 (0.80, 7.94)	1.00 (ref.)	0.64 (0.09, 4.56)

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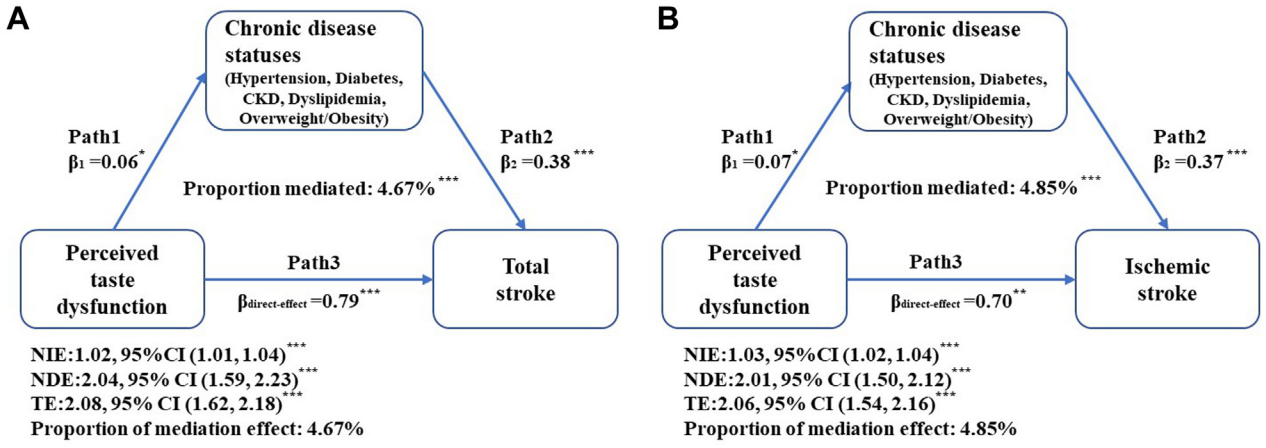
In this large cohort study, perceived taste dysfunction was associated with a high risk of developing stroke, especially the ischemic type.

As of follow-up to 2020 (mean follow-up duration: 5.6 years, IQR: 5.2-6.1 years), we documented 2,198 incident stroke cases.

No significant association between perceived olfactory dysfunction and total stroke was found (adjusted HR: 1.22; 95% CI: 0.79-1.90; $P = 0.34$), whereas perceived taste dysfunction was associated with a higher risk of developing stroke after adjusting for covariates (model 3), with a 1.03-fold increase (adjusted HR: 2.03; 95% CI: 1.36-3.04; $P < 0.001$) (**Table 2**, **Central Illustration**). In addition, the analysis results in the complete, nonimputed database were essentially consistent, indicating perceived taste dysfunctions and total stroke: adjusted HR: 2.08; 95% CI: 1.34-3.25; $P < 0.001$; perceived olfactory dysfunctions and total stroke: adjusted HR: 1.08; 95% CI: 0.65-1.80; $P = 0.77$. Similar results were observed for ischemic stroke, although the results were not significant for hemorrhagic stroke due to the small incident case number (**Table 2**, **Central Illustration**). We further explored the association of subtypes of perceived taste and olfactory dysfunctions with stroke incidence. Relative to participants without perceived taste and olfactory dysfunctions, those with perceived taste loss or olfactory loss had a higher risk of developing stroke (adjusted HR: 2.61; 95% CI: 1.44-4.72; $P < 0.001$; adjusted HR: 1.50; 95% CI: 0.85-2.64; $P = 0.36$), rather than those who reported "wrong" taste/olfactory sensation, regardless of stroke subtypes (Supplemental Table 2).

The interactions of perceived taste dysfunction with other potential stroke risk factors (age, sex, smoking, DASH scores, and alcohol intake) were not significant (P for interaction >0.05 for all) (Supplemental Table 3). **Figure 2** demonstrates the mediation via chronic diseases in the associations of perceived taste dysfunction and risk of total and ischemic stroke; all the mediation effects were

FIGURE 2 Perceived Taste Dysfunction and Stroke, Partially Mediated by Chronic Disease



(A and B) Perceived taste dysfunction (binary exposure)—Chronic disease statuses (the number of comorbidities, namely hypertension, diabetes, chronic kidney disease [CKD], dyslipidemia, and overweight/obesity)—Total stroke/Ischemic stroke (binary outcome). Adjusted for age (y), sex, occupation (blue collar/white collar), smoking (current, past, or never), alcohol intake (tertile), education (primary, middle, or college and higher), physical activity (METs/d quartile), income (<500, 500 to 2,999, or ≥3,000, RMB/mo), uric acid (quartile), high-sensitivity C-reactive protein (<1, 1 to 2.9, or ≥3 mg/mL), incident myocardial infarction (no, yes), and sleep duration (<6, 6-6.9, 7-7.9, 8-8.9, or ≥9 h/d). Path 1: the effect of the independent variable on the mediator. Path 2: the effect of the mediator on the outcome, additionally adjusted for the independent variable. Path 3: the direct effect of the independent variable on the outcome, additionally adjusted for the mediator. βs were regression coefficients with adjustment for covariates. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. NIE = natural indirect effect; NDE = natural direct effect; TE = total effect.

significant. The proportions of mediation by chronic disease statuses from perceived taste dysfunction to total stroke and ischemic stroke were 4.67% and 4.85%, respectively. The mediating effect of unhealthy lifestyle accounted for 3.88%-4.29% (Supplemental Figure 1). In contrast, we did not observe a significant mediating effect of both chronic disease status and unhealthy lifestyle on the association between perceived olfactory dysfunction and the risk of stroke ($P > 0.05$). The main observed results did not materially change in the sensitivity analyses by excluding the cases occurring in the first 2 years of follow-up. Another 4 sensitivity analyses consistently revealed an association between perceived taste dysfunction and stroke, but not for perceived olfactory dysfunction (Supplemental Figure 2). In the Fine-Gray competing risk models, whether myocardial infarction or death was considered as a competing event, the association of perceived taste dysfunction and stroke remained largely stable (competing event: myocardial infarction, adjusted HR: 2.15; 95% CI: 1.43-3.24; $P < 0.001$; competing event: death, adjusted HR: 1.45; 95% CI: 1.01-2.09; $P = 0.048$) (Supplemental Table 4). In summary, the detailed statistical analyses for our primary, mediation, and sensitivity analyses, as well as the analysis of risk factors for total stroke, were comprehensively presented in Supplemental Tables 5 to 8, respectively.

DISCUSSION

In this large-scale prospective population-based study including more than 85,000 adults, we found that perceived taste dysfunction was associated with stroke incidence, and chronic diseases played a mediating role. Our results provided further evidence to support the notion that early recognition of the chemosensory dysfunction might be beneficial, which contributed to our understanding of stroke risk identification and prevention.

Impaired taste and olfactory functions were associated with many diseases, such as neurodegenerative diseases (Alzheimer's disease and Parkinson's disease), cardiovascular diseases (stroke, hypertension, and heart failure), and cancer.[22] Several studies with small sample sizes demonstrated[23-25] that taste dysfunction after a stroke was commonly observed, with hypogeusia being the most frequent taste symptom. However, concerns about taste loss were overwhelmed by other serious life-threatening medical problems in patients, and the sequelae of taste loss were not considered seriously. To the best of our knowledge, this study may be the first to explore the

association between perceived chemosensory function and incident stroke, which may provide clinical implications for future stroke prevention and intervention.

Taste dysfunction could directly affect food and nutrient intake and could be potentially harmful to metabolic capacity and immune function.[26] Mammalian epithelial sodium channels located in taste receptor cells were found to participate in sodium sensing by the tongue and blood pressure regulation,[27,28] and taste dysfunction may be associated with a higher intake of salty food and subsequent high blood pressure,[11] which may help to explain the association between perceived taste dysfunction and stroke incidence. Taste cells in taste buds express different taste receptors, which receive stimuli to form taste signals. Taste receptors exist not only in taste cells but also in the intestinal tract and respiratory tract, which have been shown to be closely related to host metabolism and innate immune function.[29,30] Studies of the microbiota-gut-brain axis showed that gut microbes linked the enteric nervous system to the central nervous system through a variety of mechanisms (eg, gastrointestinal hormones, vagal and ghrelin hormones) that affected taste function,[31-35] which may also be a potential mechanism that needs to be studied in depth. Mechanisms such as inflammation, oxidative stress, protein aggregation, and apoptosis played important roles in the association of chemical senses with neurodegenerative diseases or stroke incidence.[36-39]

Olfactory and taste perceptions are progressively impaired with age. Interestingly, we did not find a significant association between perceived olfactory dysfunction and stroke incidence. However, when we further analyzed the subgroups of perceived taste and olfactory dysfunctions in depth, results demonstrated that olfactory loss was associated with a 50% higher risk of incident stroke. Although the results were not statistically significant, because of the small number of cases, the observed effect size could be still clinically significant. The olfactory loss was common in neurodegenerative processes, and its appearance may be accompanied by olfactory filaments tron (the axons of the olfactory sensory neurons), implying impairment of the neural pathways between the olfactory receptors and the olfactory bulb.[40] Our study also found that perceived taste dysfunction was still associated with stroke risk when participants with perceived olfactory dysfunction were excluded. In addition, some studies showed that the rate of decline in taste function was faster than the rate of decline in olfactory function, and the former could be more closely related to disease than the latter.[41-43] This could be important, given the relatively short follow-up duration in the current analysis. However, the extent of this association manifested differently in different disease types and areas of study, so more studies are needed to better understand the role of taste and olfactory dysfunctions in disease development and treatment.

When taste dysfunction happened, there may be a greater preference for salty or greasy foods, which was associated with cardiovascular risk[44-46] factors such as hypertension, diabetes, chronic kidney disease, and obesity, and led to atherosclerosis and narrowing of blood vessels, thereby increasing the risk of stroke.[47,48] This is consistent with our finding that chronic disease may mediate the association between perceived taste dysfunction and a high risk of stroke. However, we did not observe the mediation effect of salt intake, which may be because salt intake was measured by a questionnaire rather than objective approaches, which inevitably introduced misclassification. The causal association between chemosensory functions and chronic diseases remains to be explored, but our findings may provide implications for understanding the involved pathophysiological mechanisms.

This study has several strengths, including its prospective design with a relatively large sample size, and the comprehensive diagnosis for incident stroke using multiple resources (combination of biochemical examination, medical records, and death registers).

STUDY LIMITATIONS. Participants with perceived taste and olfactory dysfunctions were determined by a self-reported questionnaire, without verification by standards of clinical diagnosis.[49] However, the questionnaire has been commonly used,[16] and it was cost-effective in a large population-based study. Participants' allergic conditions that might affect olfactory and taste perception were not assessed. However, the study investigated olfactory and taste functional states that lasted for at least 3 months, and the transient allergic status may be insufficient to cause a chronic effect. Nevertheless, we still excluded participants with chronic inflammation, as indicated by high hs-CRP concentrations, the results of sensitivity analysis were not materially changed. Given the observational study design, we cannot rule out the potential for residual confounding from unmeasured confounders, such as neurological disorders (eg, dementia, Bell's palsy, and multiple sclerosis), chronic

liver disease, hypothyroidism, gastroesophageal reflux disease, and relevant medication use. Furthermore, due to the absence of data on the severity of stroke events, further exploratory analyses were precluded. Although we followed up for approximately 6 years, the number of incident hemorrhagic stroke cases was relatively small, and the relevant results should thus be interpreted with caution.

CONCLUSIONS

This large-scale community study showed that perceived taste dysfunction was associated with a higher risk of stroke. Prospective cohort studies with long-term follow-up and a larger number of different subtypes of stroke cases can help to better understand this association.

ACKNOWLEDGMENTS The authors appreciate all families for participating in the Kailuan cohort.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by the Startup grant at Fudan University (JIF201015Y) and China Postdoctoral Science Foundation (KLH1322194). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PROFESSIONALISM: Our present findings emphasized the importance of the perceived chemosensory dysfunction in the development of incident stroke, especially the perceived taste dysfunctions.

TRANSLATIONAL OUTLOOK: The earlier the chemosensory dysfunction is recognized, the greater the impact on incident stroke prevention. Raising incident stroke awareness may provide great promise for reducing health disparities and promoting health equity.

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KEY WORDS chronic disease statuses, perceived olfactory dysfunctions, perceived taste dysfunctions, stroke

APPENDIX For supplemental tables and figures, please see the online version of this paper.