Dietary patterns and risk of nasopharyngeal carcinoma: a population-based case-control study in southern China

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ABSTRACT

Background: Dietary factors, such as consumption of preserved foods, fresh vegetables, and fruits, have been linked to the risk of nasopharyngeal carcinoma (NPC). However, little is known about associations between dietary patterns and the risk of NPC in NPC-endemic areas.

Objectives: We aimed to evaluate whether dietary patterns are associated with NPC risk.

Methods: We studied 2554 newly diagnosed NPC patients aged 20–74 y living in 3 endemic regions of southern China, and 2648 population-based controls frequency-matched to case patients by age, sex, and region, between 2010 and 2014. Dietary components were derived from food frequency data in adulthood and adolescence using principal component analysis. Four dietary components were identified and highly similar in adulthood and adolescence. We used multivariable unconditional logistic regression to calculate ORs with 95% CIs for the association between dietary patterns and NPC risk.

Results: Compared with the lowest quartile, individuals in the highest quartile of the "plant-based factor" in adulthood had a 52% (OR: 0.48; 95% CI: 0.38, 0.59) decreased risk of NPC, and those in the highest quartile of the "animal-based factor" had a >2-fold (OR: 2.26; 95% CI: 1.85, 2.77) increased risk, with a monotonic dose-response trend (*P*-trend < 0.0001). Similar but weaker associations were found in adolescence. High intakes of the "preserved-food factor" were associated with increased NPC risk in both periods, although stronger associations were found in adolescence. Results from joint analysis and sensitivity analyses indicated that dietary factors in adulthood might be more stable and robust predictors of NPC risk than those in adolescence.

Conclusions: Our results deliver compelling evidence that plant- and animal-based dietary factors are associated with NPC risk, and provide more insights on the associations of diets and cancer risk that may assist healthy diet recommendations. *Am J Clin Nutr* 2021;114:462–471.

Keywords: dietary patterns, nasopharyngeal carcinoma, population-based case-control study, risk factor, plant-based factor, animal-based factor, preserved-food factor

Introduction

Nasopharyngeal carcinoma (NPC), which occurs in the epithelial lining of the nasopharynx, is a rare cancer (0.7% of all cancers globally in 2018) (1) with a unique geographic distribution. Annual incidence rates are ≤20 per 100,000 person-years in southern China, Southeast Asia, and North Africa, compared with 0.5–2 per 100,000 in most of the world, resulting in a heavy public-health burden in endemic areas (1–3). Environmental and lifestyle risk factors are widely thought to play a causal role in the carcinogenesis of NPC: diet, smoking, oral hygiene, and occupational and residential exposures have been reported as risk factors for NPC in endemic areas (3–5).

Specifically, high intake of salted fish and preserved vegetables, and low intake of fresh fruits and vegetables, are associated

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with an increased risk of NPC (3, 6–9). Although numerous studies have shown associations between individual food items or nutrients and NPC risk, research on the impact of dietary patterns accounting for interrelations between food choices is limited. High consumption of some food items is generally related to low intake of other food items, given substitution effects in diet behaviors (10). So far, 1 study has reported a negative association between NPC risk and a vegetable/fruits-rich dietary pattern and a positive association of NPC risk with salted/preserved foods (11). Another study found that a diet rich in fruits, vegetables, milk, fresh fish, eggs, and tea was associated with a reduced risk of NPC (12).

To our knowledge, few, if any, large-scale epidemiological studies of dietary patterns have been undertaken in the NPC-endemic area of China. To this end, we took advantage of a large population-based case-control study conducted in southern China, where NPC is endemic (13), to investigate the potential impact of dietary patterns on NPC risk and provide more insight into the potential protective and harmful aspects of diet.

Methods

Study population

The NPCGEE (Gene-environment Epstein-Barr Virus Interactions in the Etiology of nasopharyngeal carcinoma) project is a collaborative population-based case-control study launched in southern China in March 2010, with completion of enrollment in November 2014. A detailed description of this project has been published previously (13). Persons officially residing in 13 cities/counties in Guangdong Province (Zhaoqing region: Deqing, Fengkai, Gaoyao, Huaiji, Sihui, Zhaoqing, and Guangning) and Guangxi Autonomous Region (Wuzhou region: Wuzhou, Cenxi, Cangwu, and Tengxian; and Guiping/Pingnan region: Guiping and Pingnan) during the study period constituted the study population. The estimated total number of incident NPC cases is ∼850/y (based on data from local cancer registries), with a total population of ∼8 million in the study area (14).

Newly diagnosed and histopathologically confirmed NPC patients aged 20–74 y were identified from 10 hospitals and 2 cancer institutions (13). A total of 3047 eligible NPC cases were identified and contacted between March 2010 and December 2013, which was similar to the estimated number of incident NPC cases expected in the study area. Among them, 2554 cases (83.8%) agreed to participate. Controls were randomly selected every 6–12 mo from regional population registries covering the study population that gave rise to the cases. The controls were frequency-matched on age (in 5-y groups), sex, and residential region. Between 2010 and 2014, 3202 potential controls were identified, of whom 2648 (82.7%) consented to participate.

The study was approved by the institutional review boards of Harvard TH Chan School of Public Health, the Institute for Viral Disease Control and Prevention of the Chinese Center for Disease Control and Prevention, Sun Yat-sen University Cancer Center, and Guangxi Medical University, and the Regional Ethical Review Board in Stockholm, Sweden. All study subjects gave informed consent for participation.

Data collection

A team of trained interviewers performed the interview for each participant, using a computerized questionnaire for data collection (13). Although blinding to disease status was not feasible, interviewers were unaware of the study hypotheses, required to perform interviews in the same manner with both cases and controls, and assigned similar numbers of cases and controls. Information was collected on demographics and known potential NPC risk factors, including a family history of cancer, residential history, occupational history, smoking habits, alcohol drinking, herbal tea consumption, and dietary habits.

Assessment of dietary intake and total energy intake

As part of the electronic questionnaire, an FFQ was used to assess dietary information (15). The FFQ included 77 food items selected from the most commonly consumed foods in the study area and was estimated to cover ∼80% of participants' mean daily total energy intake (TEI—which was estimated at ∼2368 kcal/d for adults in southern China in the year 2000) (16). Participants were asked to recall the frequency (daily, weekly, monthly, yearly, or never) of consumption of each food item 10 y before the interview (i.e., adulthood) and at age 16–18 y (i.e., adolescence, for subjects aged >35 y at the interview), as well as the estimated portion size using local weight units (1 Jin = 500 g; 1 Liang = 50 g). We used an illustrated booklet with pictures of serving sizes of various food items to facilitate correct estimation of the portion size (13). Adulthood represented the dietary habits among all study subjects in the years 2000–2003, whereas adolescence represented several calendar decades from the 1950s to the 1990s.

Approximately 80% of study subjects (1834 cases and 2272 controls) reported household cooking oil consumption in adulthood and their individual cooking oil intakes on average were calculated. Missing values for cooking oil intake were

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Supplemental Tables 1–5 and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: EBV, Epstein-Barr Virus; FA, factor analysis; NPC, nasopharyngeal carcinoma; NPCGEE, Gene-environment Epstein-Barr Virus Interactions in the Etiology of nasopharyngeal carcinoma; PCA, principal component analysis; PLSDA, partial least squares discriminant analysis; RRR, reduced rank regression; TEI, total energy intake.

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imputed using predictive mean matching, with 5 cases in each matched set (17). Alcohol intake in adulthood was also recorded. The daily TEI in adulthood was computed from the energy contributions of the 77 food items, cooking oil, and alcohol intake; daily TEI in adolescence was calculated only from the 77 food items (**Supplemental Table 1**). The energy estimates for individual items were based on Chinese food composition tables (18).

Food groupings

Seventy-seven food items were classified into 20 food groups based on the similarity of their nutrient contents, food group characteristics, and culinary usage (**Supplemental Table 2**) (11, 12). Absolute intake for each food group was calculated as the sum of the corresponding individual food items, in grams.

Exclusion criteria

We excluded participants whose questionnaire data were lost during uploading to the server, who had missing values for >2 food items, were outside the eligible age range, or provided questionnaire information that the interviewer deemed unreliable, leaving 5121 subjects (2528 cases and 2593 controls) in the adulthood data set and 4613 (2271 cases and 2342 controls) in the adolescence data set. We further excluded participants with an extreme daily TEI (<1st percentile or >99th percentile) or an extreme intake of any of the 20 food groups (intake >99.5th percentile). In total, 297 out of 5121 subjects (5.8%) and 231 out of 4613 subjects (5%) were removed, leaving 4824 subjects in the adulthood data set and 4382 subjects in the adolescence data set (**Supplemental Figure 1**).

Identification of dietary patterns

We performed principal component analysis (PCA) using the PROC FACTOR procedure in SAS to characterize major dietary components from the 20 food groups among control subjects in the 2 analytical data sets (19). Dietary components were extracted based on a scree plot of the eigenvalues. A component loading with varimax rotation represented the correlation coefficients between each of the 20 food groups.

We calculated a component score by summing the standardized intakes of each of the 20 food groups with weights that were proportional to their component loadings for each study subject, using the PROC SCORE procedure in SAS. Finally, study subjects were categorized into 4 groups based on quartiles of the component score among controls for each of the dietary components. We compared the similarity of dietary components extracted from the 2 analytical data sets using Tucker's congruence coefficient (20). A congruence value >0.95 indicates good similarity between 2 components, whereas a value ranging from 0.85 to 0.94 suggests fair similarity (21). The extracted components were summarized as dietary factors based on their dominant food groups.

We also performed iterated principal factor analysis (FA) for all data as a sensitivity analysis.

RR estimation

Crude comparisons between cases and controls were conducted using Pearson's χ^2 test for categorical variables and Student's *t* test for continuous variables. We applied unconditional logistic regressions to estimate ORs and the corresponding 95% CIs for quartiles of all adulthood dietary components simultaneously. Adjusted ORs were calculated by including the following potential confounders in the regression models: sex, residential region, BMI, education level, current housing type, current occupation, NPC history among first-degree relatives, frequency of teeth-brushing, number of repaired teeth, smoking status, alcohol drinking, cooking oil intake, frequency of tea consumption, frequency of soup consumption, and frequency of herbal tea consumption, categorized as shown in **Table 1**, as well as age group (5-y groups) and corresponding daily TEI (quartiles). Confounders were selected based on prior knowledge of NPC risk factors in general and in this study population. Approximately 80% of the subjects had their Epstein-Barr Virus (EBV) antibody status measured. Given that EBV is an important risk factor for NPC and might be associated with diet habits (22), we performed a sensitivity analysis by including EBV antibody status (i.e., positivity for Ig A antibodies against the viral capsid antigen) in the models. The same approach was applied to the adolescence dietary components. For all models, tests for linear trend were carried out by scoring the quartiles as ordinal values from 1 to 4.

Further, 4197 subjects (joint analysis) who provided dietary information in both adulthood and adolescence were included in the regression models, with all dietary components from 2 periods simultaneously. Adjusted ORs were computed using the same set of covariates as in the adulthood analysis. Sensitivity analyses were performed to evaluate the influence of data exclusion in the joint analysis by including the dietary components from the adulthood data and adolescence data in separate models. In addition, a variable representing birth before or after the year 1963, according to the median age of the study population, was used to evaluate potential effect modification by age. This variable was included in regression models together with cross-product terms.

As an alternative approach, we also estimated ORs and corresponding 95% CIs using dietary factors generated from iterated principal FAs in the adulthood data and adolescent data. We used SAS software, version 9.4 (SAS Institute, Inc.), for data management and statistical analyses.

Results

Dietary factors in adulthood and adolescence were similar

After exclusion, 4824 study subjects with adulthood diet and 4382 subjects with adolescence diet were analyzed, and 4197 subjects were included in the joint analysis (Supplemental Figure 1). Table 1 and **Supplemental Table 3** show the distribution of demographic characteristics and potential NPC risk factors among cases and controls.

We identified 4 dietary components among controls in both analytical data sets. These components explained ∼37% (36.6% in adulthood; 38% in adolescence) of the variance in intakes

TABLE 1 Characteristics of NPC cases and controls enrolled in NPCGEE[1]

Characteristic	Overall ($n = 4824$)	NPC cases ($n = 2384$)	Controls ($n = 2440$)	P value
Age, y	49.2 ± 10.7	48.6 ± 10.6	49.8 ± 10.8	<0.0001
Sex				0.6718
Male	3528 (73.1)	1737 (72.9)	1791 (73.4)	
Female	1296 (26.9)	647 (27.1)	649 (26.6)	
Geographic area of residence				0.4619
Zhaoqing	2447 (50.7)	1204 (50.5)	1243 (50.9)	
Wuzhou	1294 (26.8)	657 (27.6)	637 (26.1)	
Guiping/Pingnan	1083 (22.5)	523 (21.9)	560 (23.0)	
BMI, 10 y ago				0.7664
Underweight	510 (10.6)	241 (10.1)	269 (11.0)	
Normal	3053 (63.3)	1519 (63.7)	1534 (62.9)	
Overweight	1108 (23.0)	547 (22.9)	561 (23.0)	
Obesity	153 (3.2)	77 (3.2)	76 (3.1)	
Education level, y				0.0047
≤6	1823 (37.8)	947 (39.7)	876 (35.9)	
7–9	1931 (40.0)	955 (40.1)	976 (40.0)	
10–12	841 (17.4)	381 (16.0)	460 (18.9)	
>12	229 (4.8)	101 (4.2)	128 (5.3)	
Current housing type				<0.0001
Building	3608 (74.8)	1714 (71.9)	1894 (77.6)	
Cottage, boat	1216 (25.2)	670 (28.1)	546 (22.4)	
Current occupation				0.0004
Unemployed	164 (3.4)	73 (3.1)	91 (3.7)	
Farmer	1729 (35.8)	806 (33.8)	923 (37.8)	
Blue-collar	1811 (37.5)	959 (40.2)	852 (34.9)	
White-collar	714 (14.8)	331 (13.9)	383 (15.7)	
Other and unknown	406 (8.4)	215 (9.0)	191 (7.8)	
First-degree family history of NPC				<0.0001
No	4414 (91.6)	2081 (87.4)	2333 (95.7)	
Yes	325 (6.7)	258 (10.8)	67 (2.8)	
Unknown	80 (1.7)	41 (1.7)	39 (1.6)	
Missing	5	4	1	
Teeth brushing frequency				<0.0001
Once per day	2956 (61.3)	1589 (66.7)	1367 (56.0)	
Twice per day	1687 (35.0)	712 (29.9)	975 (40.0)	
More than twice per day	181 (3.8)	83 (3.5)	98 (4.0)	
Repaired teeth				0.0029
0	4037 (83.7)	1952 (81.9)	2085 (85.5)	
1–3	621 (12.9)	336 (14.1)	285 (11.7)	
>3	165 (3.4)	95 (4.0)	70 (2.9)	
Missing	1	1		
Smoking status				0.0589
Current smoker	2275 (47.2)	1133 (47.6)	1142 (46.8)	
Former smoker	325 (6.7)	179 (7.5)	146 (6.0)	
Never smoker	2223 (46.1)	1071 (44.9)	1152 (47.2)	
Missing	1	1		
Alcohol drinking				0.6547
Nondrinker	3657 (75.8)	1794 (75.3)	1863 (76.4)	
Lowest	380 (7.9)	187 (7.8)	193 (7.9)	
Medium	374 (7.8)	187 (7.8)	187 (7.7)	
Highest	413 (8.6)	216 (9.1)	197 (8.1)	
Daily cooking oil intake				0.0145
Lowest	1664 (34.5)	785 (32.9)	879 (36.0)	
Medium	1874 (38.9)	923 (38.7)	951 (39.0)	
Highest	1286 (26.7)	676 (28.4)	610 (25.0)	
Tea consumption frequency				<0.0001
Less than daily	2985 (61.9)	1541 (64.7)	1444 (59.2)	
Daily	1838 (38.1)	842 (35.3)	996 (40.8)	
Missing	1	1		
Soup consumption frequency				<0.0001
Once or less per week	1583 (32.8)	779 (32.7)	804 (33.0)	
Twice per week	2016 (41.8)	933 (39.1)	1083 (44.4)	
More than twice per week	1225 (25.4)	672 (28.2)	553 (22.7)	

(*Continued*)

TABLE 1 (*Continued*)

Characteristic	Overall ($n = 4824$)	NPC cases ($n = 2384$)	Controls ($n = 2440$)	*P* value
Herbal tea consumption frequency				0.0307
Once or less per week	448 (9.3)	248 (10.4)	200 (8.2)	
Twice per week	1760 (36.5)	858 (36.0)	902 (37.0)	
More than twice per week	2616 (54.2)	1278 (53.6)	1338 (54.8)	
Energy intake 10 y ago,[2] kcal/d	1657 ± 531	1665 ± 531	1648 ± 531	0.2544
Energy intake in adolescence,[3] kcal/d ($n = 4382$)	1181 ± 497	1183 ± 492	1179 ± 502	0.7814

[1]Values are mean ± SD for continuous variables and *n* (%) for categorical variables; a Student's *t* test was used for comparison of continuous variables and a chi-square test for comparison of categorical variables. NPC, nasopharyngeal carcinoma; NPCGEE, Gene-environment Epstein-Barr Virus Interactions in the Etiology of nasopharyngeal carcinoma.

[2]Energy intake per day 10 y before the recruitment: summarized energy intake from 77 food items, imputed cooking oil, and alcohol (for alcohol drinkers only).

[3]Energy intake per day in adolescence (age 16–18 y): summarized energy intake from 77 food items.

of the 20 food groups (**Figure 1**D; **Supplemental Figure 2**). Loadings after rotation for each extracted component were similar between adulthood and adolescence with congruence values >0.90 (Figure 1). In the iterated principal FAs, the 4 identified factors were identical to the 4 components extracted from PCA. We summarized and labeled the components from both sets as 4 dietary factors (**Table 2**):

1) A "balanced factor" (referring to component 1 in the adulthood data set and component 2 in the adolescence data set) was characterized by high intake of milk and dairy products, fried food and pastries, soybean and its products, processed cereal products, fresh fruits, and processed meats, and low intake of rice, starchy roots, and green leafy vegetables.

2) A "plant-based factor" (referring to component 2 in adulthood and component 3 in adolescence) was specified as high consumption of phytonutrient-rich foods, such as nonleafy and leafy vegetables, fruits, rice, and starchy roots.

3) An "animal-based factor" (referring to component 3 in adulthood and component 1 in adolescence) featured high consumption of animal foods, including red meat (pork, beef, mutton, etc.), poultry, fish and seafood, and organ meats, and low consumption of rice and starchy roots.

4) A "preserved-food factor" (referring to component 4 in adulthood and component 4 in adolescence) was represented by a high intake of foods preserved by salting: salted fish, salted sauce, pickled vegetables, and salted eggs.

Figure 1C presents the congruence coefficients implying similarity between the 4 dietary components derived from adulthood and adolescence. The congruence coefficient of 0.98 suggested that the plant-based factor in adolescence was equal to the same component in adulthood, and a similar result was observed for the preserved-food factor (0.97). The balanced factor and animal-based factor were also fairly similar between the 2 analytical data sets (0.93 and 0.94, respectively).

Dietary factors and NPC risk

Table 3 shows, for both analytical data sets, the ORs of the 4 dietary factors simultaneously included in the fully adjusted models (**Supplemental Table 4** shows the results from the minimal models). We found no evident association between the balanced factor and NPC risk in adulthood or adolescence. We observed strong associations with monotonic trends between increased quartiles of the plant-based factor and reduced risk of NPC in both age periods, with 52% reduced risk in the highest compared with the lowest quartile in adulthood ($OR_{q4\ vs.\ q1}$: 0.48; 95% CI: 0.38, 0.59; $P_{trend} < 0.0001$) and 35% reduced risk in adolescence ($OR_{q4\ vs.\ q1}$: 0.65; 95% CI: 0.51, 0.81; $P_{trend} = 0.005$). The animal-based factor was positively associated with NPC risk in both periods, with consistent trends, although the effect in adulthood ($OR_{q4\ vs.\ q1}$: 2.26; 95% CI: 1.85, 2.77; $P_{trend} < 0.0001$) was larger than in adolescence ($OR_{q4\ vs.\ q1}$: 1.43; 95% CI: 1.17, 1.75; $P_{trend} = 0.0001$). Increasing intake of the preserved-food factor was more convincingly associated with increased NPC risk in adolescence ($OR_{q4\ vs.\ q1}$: 1.44; 95% CI: 1.19, 1.75; $P_{trend} = 0.0004$) than in adulthood ($OR_{q4\ vs.\ q1}$: 1.20; 95% CI: 1.00, 1.43; $P_{trend} = 0.0162$).

Focusing on the 4197 subjects who had available dietary information for both age periods, we included 8 age-specific dietary factors simultaneously (**Table 4**). After adjusting for dietary factors in adolescence, the OR estimates for adulthood dietary factors in association with NPC risk remained largely unchanged, with no evident association for the balanced factor or preserved-food factor. In contrast, the associations between dietary factors in adolescence and NPC risk were attenuated after adjustment for adulthood dietary factors, except the positive association between high intake of the preserved-food factor and NPC risk.

As sensitivity analyses of the adulthood analysis and adolescent analysis, we adjusted for 13 cities/counties instead of 3 regions in the regression models, and the results remained largely unchanged (data not shown); we also adjusted for EBV antibody status and found similar results (data not shown). In the sensitivity analyses of the joint analysis, we regressed the dietary factors from the individual age periods in the fully adjusted models, and the risk estimates were similar to the results shown in Table 3 (**Supplemental Table 5**). No statistical evidence was found for effect modification by age (data not shown). The OR estimates based on factors identified from iterated principal FAs were essentially the same as the results from PCA (data not shown).

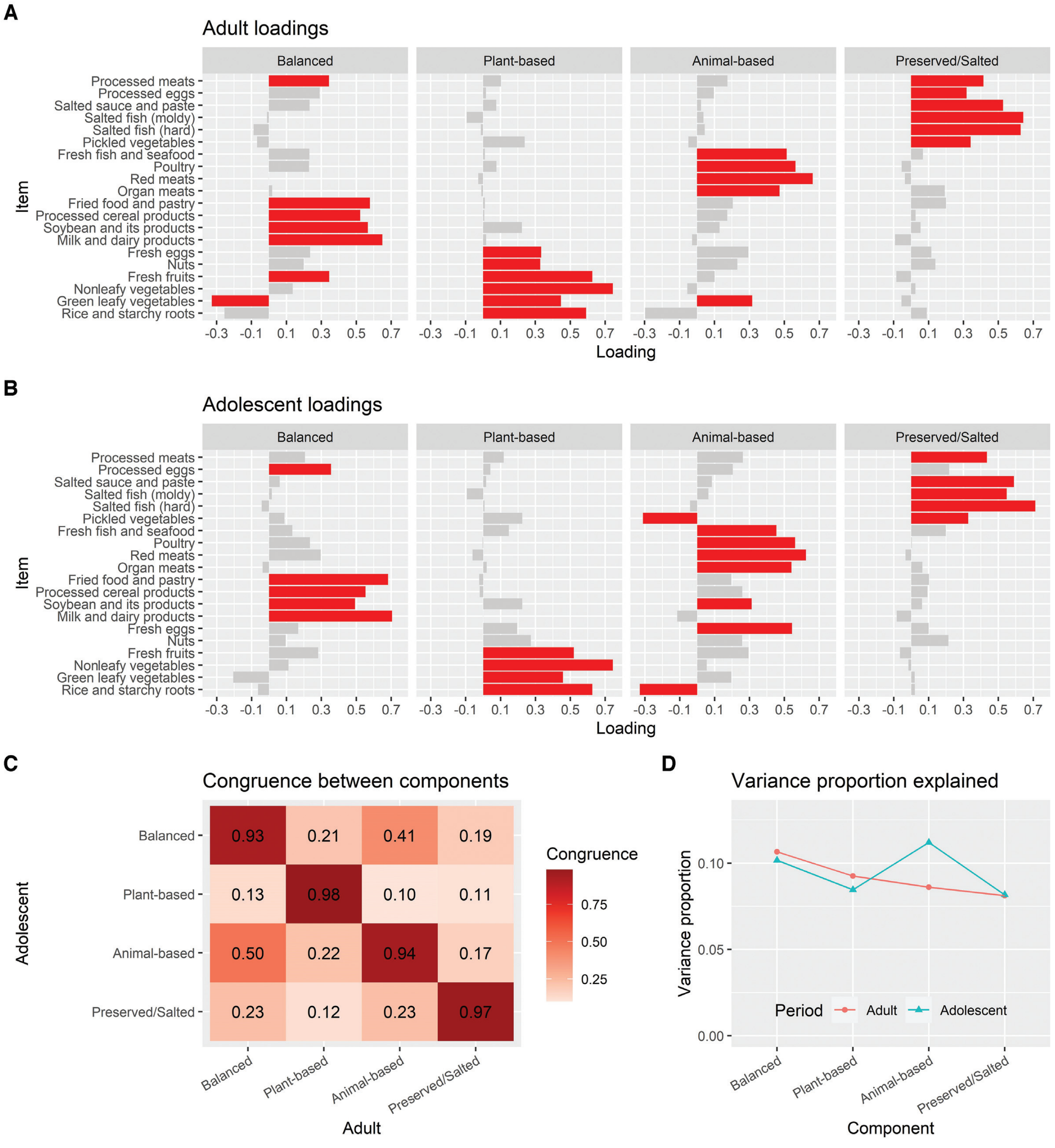

FIGURE 1 Component loadings from adulthood and adolescence, and the congruence between dietary components. Component loadings of 20 food groups after rotation for each component derived from the principal component analysis in (A) adulthood data ($n = 4824$) and (B) adolescence data ($n = 4382$). Food groups with >0.3 in component loading are colored in red, otherwise in grey. The extracted components are summarized and labeled as 4 dietary factors based on their dominant food groups (Table 2). (C) Heatmap visualizing the congruence between dietary components from the 2 periods. A congruence value >0.95 indicates a good similarity between 2 components, which can be treated as equal, whereas a value in the range 0.85–0.94 suggests a fair similarity. The darker the color, the higher the congruence value. (D) The proportions of variance in the 20 food groups explained by the 4 identified components in the 2 periods. The balanced, plant-based, animal-based, and preserved/salted components in adulthood explained 15.3%, 8.3%, 7.1%, and 5.8%, respectively; whereas in adolescence they explained 17.1%, 8.0%, 7.3%, and 5.7%, respectively. The adulthood set is red; the adolescence set is green.

TABLE 2 Dietary factors derived from principal component analysis in adulthood and adolescence

Dietary factors	Eigenvalue[1] adulthood/adolescence	High intake	Low intake
Balanced factor	3.06/1.59	Milk and dairy products; fried food and pastries; soybean and its products; processed cereal products; fresh fruits; processed meats	Green leafy vegetables; rice and starchy roots
Plant-based factor	1.67/1.45	Nonleafy vegetables; fresh fruits; rice and starchy roots; green leafy vegetables	—
Animal-based factor	1.43/3.42	Red meats; poultry; fish and seafood; organ meats	Rice and starchy roots
Preserved-food factor	1.17/1.13	Hard salted fish; moldy salty fish; salty sauce and pastes; processed meats; pickled vegetables; processed eggs	—

[1]Eigenvalue of the correlation matrix of the component analysis.

Discussion

Our large population-based case-control study in southern China demonstrated a strong positive association between higher consumption of the animal-based factor and NPC risk, as well as a strong negative association of NPC risk with higher intake of the plant-based factor. After mutual adjustment for adolescence and adulthood dietary factors, RR estimates for the former were attenuated and no longer statistically significant except for the adolescent preserved-food factor, whereas associations with adulthood dietary factors remained virtually unchanged. This finding suggests adult dietary factors are more stable and robust predictors for NPC risk.

Reported dietary factors remained largely similar during adolescence and adulthood despite rapid economic changes in southern China in the past few decades as previously reported (23). Although the declining intake of traditional preserved/salted foods and rising consumption of animal foods in southern China, with a general trend toward a more westernized diet, has been discussed for years (24), our results might suggest that individual dietary habits have changed little over the last few decades. However, it could also be partially attributed to the possibility that people tend to relate their more recent dietary habits (i.e., 10 y before interview) to the past (i.e., aged 16–18 y).

TABLE 3 ORs of NPC by quartiles of the intake of dietary factors in adulthood and adolescence[1]

	Adulthood[2] ($n = 4824$)				Adolescence[3] ($n = 4382$)			
Dietary factors	Ctrl	Case	OR (95% CI)	P_{trend}	Ctrl	Case	OR (95% CI)	P_{trend}
Balanced factor								
Quartile 1	610	668	1.0 (ref.)	0.2633	554	473	1.0 (ref.)	0.0641
Quartile 2	610	548	0.82 (0.69, 0.98)		555	470	0.95 (0.79, 1.15)	
Quartile 3	610	618	0.93 (0.77, 1.11)		555	572	1.01 (0.84, 1.21)	
Quartile 4	610	550	0.83 (0.68, 1.01)		554	649	0.78 (0.63, 0.95)	
Plant-based factor								
Quartile 1	610	736	1.0 (ref.)	<0.0001	555	563	1.0 (ref.)	0.005
Quartile 2	610	577	0.67 (0.56, 0.80)		554	490	0.75 (0.62, 0.90)	
Quartile 3	610	570	0.61 (0.50, 0.74)		554	604	0.80 (0.66, 0.98)	
Quartile 4	610	501	0.48 (0.38, 0.59)		555	507	0.65 (0.51, 0.81)	
Animal-based factor								
Quartile 1	610	460	1.0 (ref.)	<0.0001	554	605	1.0 (ref.)	0.0001
Quartile 2	610	519	1.18 (0.99, 1.42)		555	496	0.99 (0.82, 1.20)	
Quartile 3	610	566	1.40 (1.16, 1.69)		554	565	1.24 (1.03, 1.50)	
Quartile 4	610	839	2.26 (1.85, 2.77)		555	498	1.43 (1.17, 1.75)	
Preserved-food factor								
Quartile 1	610	628	1.0 (ref.)	0.0162	555	475	1.0 (ref.)	0.0004
Quartile 2	610	514	0.83 (0.70, 0.99)		554	509	1.11 (0.92, 1.33)	
Quartile 3	610	550	0.94 (0.79, 1.12)		554	560	1.28 (1.07, 1.55)	
Quartile 4	610	692	1.20 (1.00, 1.43)		555	620	1.44 (1.19, 1.75)	

[1]Ctrl, control; NPC, nasopharyngeal carcinoma; ref., reference group; TEI, total energy intake.

[2]Adulthood analysis: estimates from the multivariate logistic regression model were adjusted for age (5-y groups), sex, residential area, BMI, education level, current housing type, current occupation, NPC history among first-degree relatives, frequency of teeth-brushing, number of repaired teeth, smoking status, alcohol drinking, cooking oil intake, frequency of tea consumption, frequency of soup consumption, frequency of herbal tea consumption, and quartiles of the daily TEIs in adulthood. All the covariates were considered as categorical. Results referred to the composite model fitting all 4 dietary components simultaneously.

[3]Adolescence analysis: estimates from the multivariate logistic regression model were adjusted for the same set of covariates as in the adulthood analysis, except for alcohol and cooking oil intakes. The quartiles of the daily TEIs in adolescence were used. All the covariates were considered as categorical.

TABLE 4 ORs of nasopharyngeal carcinoma by quartiles of the intake of dietary factors in adulthood and adolescence—joint analysis[1]

	Adulthood (n = 4197)				Adolescence (n = 4197)			
Dietary factors	Ctrl	Case	OR (95% CI)	P_{trend}	Ctrl	Case	OR (95% CI)	P_{trend}
Balanced factor								
Quartile 1	565	615	1.0 (ref.)	0.1834	537	544	1.0 (ref.)	0.1125
Quartile 2	541	498	0.82 (0.68, 1.00)		533	477	1.05 (0.86, 1.28)	
Quartile 3	552	540	0.85 (0.70, 1.04)		529	575	1.10 (0.90, 1.34)	
Quartile 4	465	421	0.85 (0.68, 1.07)		524	478	0.88 (0.70, 1.11)	
Plant-based factor								
Quartile 1	522	641	1.0 (ref.)	<0.0001	529	578	1.0 (ref.)	0.6889
Quartile 2	519	489	0.68 (0.55, 0.83)		540	480	0.85 (0.69, 1.05)	
Quartile 3	544	504	0.59 (0.47, 0.74)		545	548	1.00 (0.79, 1.27)	
Quartile 4	538	440	0.46 (0.34, 0.61)		509	468	0.95 (0.71, 1.26)	
Animal-based factor								
Quartile 1	537	407	1.0 (ref.)	<0.0001	525	444	1.0 (ref.)	0.7276
Quartile 2	536	458	1.12 (0.92, 1.36)		534	451	0.98 (0.80, 1.20)	
Quartile 3	527	488	1.30 (1.04, 1.61)		536	564	1.22 (0.99, 1.49)	
Quartile 4	523	721	2.07 (1.64, 2.62)		528	615	1.20 (0.96, 1.50)	
Preserved-food factor								
Quartile 1	513	525	1.0 (ref.)	0.3108	527	456	1.0 (ref.)	0.0288
Quartile 2	537	464	0.84 (0.69, 1.02)		529	496	1.09 (0.90, 1.32)	
Quartile 3	546	479	0.86 (0.70, 1.05)		538	544	1.25 (1.01, 1.54)	
Quartile 4	527	606	1.12 (0.90, 1.40)		529	578	1.22 (0.97, 1.53)	

[1]Joint analysis: estimates from multivariate logistic regression models including all dietary components from both adulthood and adolescence were adjusted for the same set of covariates as in the adulthood analysis and the quartiles of total energy intake in adulthood and adolescence. Ctrl, control; ref., reference group.

We observed, to our knowledge for the first time in an NPC-endemic area, that an animal-based factor was associated with a ≥2-fold increased risk of NPC, whereas NPC risk decreased by ≤52% in the top quartile of intake of the plant-based factor. These findings are partly in agreement with smaller studies of NPC in Malaysian Chinese and in Italy (11, 25). The 2018 report from the World Cancer Research Fund's Continuous Update Project suggests limited evidence for a positive trend in NPC risk with increasing intake of red meat (9), a conclusion based on a meta-analysis of 7 case-control studies (26). The same report indicates limited evidence that increased consumption of nonstarchy vegetables decreases the risk of NPC, based on 2 meta-analyses of case-control studies (9, 27, 28). One of the 2 meta-analyses also suggested a significantly reduced NPC risk with total or fresh fruit consumption (27). A role of heterocyclic amines, polycyclic aromatic hydrocarbons, and heme iron has been hypothesized; however, potential mechanisms of any effect of meat consumption on cancer risk remain largely unknown (29). On the other hand, antioxidant effects, prevention of nitrosamine formation, and anticarcinogenic effects contributed by numerous plant components, such as dietary fiber, multiple vitamins, selenium, plant sterols, allium compounds, and limonene, have been suggested as potential mechanisms of protective effects on various cancers, including NPC (3, 30). Recent studies on type 2 diabetes and cardiovascular diseases have suggested an overall plant-based diet index (constituted by 18 healthy plant food groups and animal food groups) as a feasible assessment of adherence to different types of plant-based diets (healthy and unhealthy) (31, 32). To assist dietary recommendations, future studies may consider creating and/or utilizing a priori–defined dietary patterns to investigate their associations with cancer risk.

Our study showed weak associations between the preserved-food factor (characterized by salted fish, pickled vegetables, and processed meats) and NPC risk. N-nitroso compounds rich in many preserved foods have been associated with NPC development in animal models (33, 34). We previously analyzed associations of NPC risk with consumption of individual preserved/salted foods as separate items, and found a weak positive association with pickled vegetables (OR for highest quartile compared with lowest: 1.24; 95% CI: 1.02, 1.52), but an inverse association with fermented black beans (OR: 0.67; 95% CI: 0.56, 0.80) (15). Because preserved/salted foods might contribute differently to NPC risk, a weaker association with the broad category of the preserved-food factor was not unexpected when the cumulative contributions of all food components were considered in our study. Our finding suggests that consuming preserved food, such as Cantonese-style salted fish, might not be a strong risk factor for NPC in endemic areas, as has been suggested by the World Cancer Research Fund and the International Agency for Research on Cancer (5, 7–9, 35).

In the joint analysis, markedly, we observed that the associations with adult factors and corresponding risk estimates were robust and stable, whereas the associations with adolescent factors were diminished except the preserved-food factor. These results highlight that, by contrast with adolescent factors, the adult plant-based factor and animal-based factor have more robust and higher predictive value for NPC risk in an endemic area. This phenomenon might be explained by underlying cumulative effects of diets high in plant foods or high in animal foods; it could also be influenced by more accurate recollection of recent than distant-past dietary habits. It is also worth noting that we saw increased NPC risks in association with greater weighting of the adolescent preserved-food factor in both individual and joint analyses. This finding may suggest an earlier susceptible exposure window for a preserved-food factor with respect to NPC risk. In agreement with our findings, a dose-response meta-analysis in the 2007 World Cancer Research Fund report indicated strong dose–response associations between salted fish intake and NPC across different age periods (summary random-effects risk ratio: 1.28; 95% CI: 1.13, 1.44 in adulthood; 1.32; 95% CI: 1.14, 1.60 at age 10 y; 1.42; 95% CI: 1.11, 1.81 at ages 0–3 y) (8). Also, a hospital-based case-control study of NPC in Guangdong Province in China showed a stronger association with earlier consumption of salted fish (ORs for ≥weekly compared with <monthly: 1.58; 95% CI: 1.20, 2.09 in adulthood, and 2.45; 95% CI: 2.03, 2.94 in childhood) (36). Taking these findings together, we suggest that further investigation of early-life exposure to a preserved/salted dietary pattern or individual preserved/salted foods may be warranted, even though it would be difficult, if not impossible, to conduct a birth-cohort study on NPC.

The NPCGEE project is one of the largest case-control studies in an NPC-endemic area with a population-based design, high participation rates, and methodological efforts to minimize biases. Although measurement bias and recall bias are inevitable in case-control studies, we attempted to reduce these biases by developing a structured electronic questionnaire and an illustrated booklet for the interview, audio-recording all interviews for quality checking, and training and monitoring the interviewers for proper conduct of the face-to-face interviews (13, 15). Nevertheless, as in any observational study, control for unmeasured or unknown confounders is impossible. We cannot rule out potential measurement and recall biases. Evaluation of dietary patterns allows us to assess the interaction among synergistic dietary components and potentially detect more substantial effects from the accumulation of many components (10). Although dietary factors might have larger effect sizes than single foods/nutrients, it is unclear which individual constituents contribute to any factor association, which hinders further investigation of potential mechanisms. Usually, only a low to moderate proportion of variation in dietary intake is explained by the principal components, which leaves a large space of possible effects not counted as components of the pattern (10, 37). In nutritional epidemiology, common alternatives to PCA/FA as data reduction methods are partial least squares discriminant analysis (PLSDA) and reduced rank regression (RRR) (38–40). Both PLSDA and RRR aim to identify patterns of predictor variables that are highly predictive for 1 or several outcomes of interest; and for both methods, the resulting patterns are intrinsically linked to the choice of outcome variables. In contrast, the patterns found by PCA/FA are descriptive of the general dietary habits in the underlying population. Given our complementary aims of *1*) describing dietary habits in 2 study periods among participants from the NPCGEE project and *2*) evaluating their associations with NPC risk, we decided to use PCA as the primary analysis, with an iterated principal FA as a sensitivity analysis.

In conclusion, we found that higher intake of an animal-based factor was associated with an increased NPC risk, whereas higher consumption of a plant-based factor was associated with a lower risk of NPC. In addition, we observed a role of the preserved-food factor at younger ages. Our study delivers evidence that dietary patterns are associated with the risk of NPC in an NPC-endemic area, and provides more insights on the associations of diets and cancer risk that may assist healthy diet recommendations.

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The authors' responsibilities were as follows—TH and WY: contributed to the concept and design of the study, are the guarantors of this work, and, as such, had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis; TH: statistically analyzed the data (supervised by AP) and drafted the manuscript; TH, AP, ETC, H-OA, and WY: interpreted the results and provided critical edits; QL, Y Cai, ZZ, GC, QH, SX, SC, WJ, Yuming Z, JL, Y Chen, LL, GH, H-OA, Yi Z, Yixin Z, and WY: were involved in the acquisition of data (investigation, visualization, etc.); and all authors: provided critical revision of the manuscript for important intellectual content and read and approved the final manuscript. The authors report no conflicts of interest.

Data availability

Data described in the article, codebook, and analytic code will be made available upon request, with approval by the principal investigators of the NPCGEE (Gene-environment Epstein-Barr Virus Interactions in the Etiology of nasopharyngeal carcinoma) study.

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