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Original Research Article

Fried food consumption-related gut microbiota is associated with obesity, fat distribution, and cardiometabolic diseases: results from 2 large longitudinal cohorts with sibling comparison analyses

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ABSTRACT

Background: In prospective cohort studies, the relationship between fried food consumption, gut microbiota, obesity, and cardiometabolic diseases remains unknown.

Objectives: We aimed to explore associations of fried food consumption with gut microbiota and associations of fried food consumption-related microbiota with obesity and related disorders.

Methods: We analyzed 6637 individuals from the Wellness Living Laboratory China cohort (baseline 2016–2019) and 3466 from the Lanxi cohort (baseline 2017–2019), with follow-up until 24 June, 2024. Face-to-face interviews provided data on fried food consumption and other covariates. Analysis of 16S ribosomal ribonucleic acid data from fecal samples collected at baseline identified microbial genera. Body composition was evaluated using dual-energy x-ray absorptiometry. The microbiome multivariable associations with linear models helped identify genera associated with the frequency of fried food consumption in the cross-sectional analysis. Cox regression models examined the relationship of fried food consumption-related microbiota with cardiometabolic diseases during follow-up. Sibling comparison analyses were used to control for unmeasured familial confounders using the between-within model.

Results: Twenty-five microbial genera were dramatically associated with fried food consumption frequency. Using these genera, we constructed a fried food consumption-related microbiota index. Meta-analysis of both cohorts found a positive relationship of this index with overall adiposity measures [body mass index (kg/m^2)] [β coefficient: 0.26; 95% confidence interval (CI): 0.19, 0.32] and central fat distribution parameters [including android-gynoid fat ratio (β: 1.48; 95% CI: 1.14, 1.82)]. Longitudinal analyses indicated that a higher fried food consumption-related microbiota index was linked to a higher risk of developing cardiometabolic diseases, with adjusted hazard ratios (95% CI) of 1.16 (1.07, 1.27) for diabetes and 1.16 (1.06, 1.26) for major adverse cardiovascular events. Sibling comparison analyses yielded similar results.

Conclusions: Fried food consumption-related microbiome is associated with a higher risk of obesity, central fat distribution, and cardiometabolic diseases, emphasizing the importance of dietary choices in the management and prevention of chronic diseases.

Keywords: fried food consumption, gut microbiota, obesity, central fat distribution, cardiometabolic disease

Abbreviations: AOI, android-gynoid fat ratio; CI, confidence interval; FFQ, food frequency questionnaire; FMI, fried food consumption-related microbiota index; HbA1c, glycated hemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease; MetS, metabolic syndrome; OR, odds ratio; WELL-China, Wellness Living Laboratory China.

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Introduction

Fried food, a ubiquitous component of many diets worldwide, has garnered considerable attention in the realm of public health due to its potential negative impact on human health [1]. It is reported that 25–36% of adults in North America have food from fast food restaurants on a daily basis, usually fried food [1]. Multiple studies have provided evidence about the relationships between fried foods and risk of central fat accumulation, metabolic syndrome (MetS), as well as cardiometabolic diseases [2–4]. Understanding the complex interplay of fried food with health outcomes is crucial for developing effective strategies to reduce the diet-associated diseases burden and promote healthier dietary habits on a global scale.

Diet is a vital source of nutrients not only for humans but also for the gut microbiota, which consists of trillions of microbes located in the gastrointestinal tract [5]. The different components of our diet—fibers, proteins, fats, and micronutrients—shape the diversity, population, and activity of these microbial communities [6–8]. Research indicated that fried foods influence the presence of certain microbial genera [9–11]. For instance, a study with 117 overweight participants revealed that consuming fried meat reduced Flavonifractor and Lachnospiraceae prevalence, whereas increasing that of Veillonella, Dorea, and Dialister [9]. However, population-based studies have provided inconsistent evidence about the relationship between fried foods and gut microbiota α-diversity [9,10,12], and little is known about the association of fried food consumption-related microbiome with obesity and cardiometabolic diseases.

To address these knowledge gaps, we utilized both cross-sectional and longitudinal methods to analyze data from 2 Chinese cohorts: the Wellness Living Laboratory China (WELL-China) cohort (Hangzhou City, Zhejiang Province) [13] and the Lanxi cohort (Lanxi City, Zhejiang Province) [14]. The primary aim of our study was to investigate 3 key questions: *1*) Is there a relationship between fried food consumption and gut microbiota composition? *2*) Is the fried-food-related microbiota associated with obesity and body fat distribution? *3*) Is fried-food-related microbiota associated with the incidence rate of cardiometabolic diseases?

As a secondary aim, considering that gut microbiota, obesity, and cardiometabolic diseases often cluster within families [15], we examined whether genetic factors and shared early life environments might play a role in these associations. We performed sibling comparison analyses to take genetic and early life environment factors into consideration and obtain more reliable and robust results.

Methods

Data sources

This study used data from 2 prospective cohorts: the WELL-China cohort and the Lanxi cohort. Comprehensive details about the WELL-China cohort [13] and the Lanxi cohort [14] have been published previously. In brief, the WELL-China cohort included 10,268 individuals aged 18–80 y recruited from 3 districts of Hangzhou, China. The WELL-China cohort recruited 3069 participants from Xihu district from November 2016 to April 2017, 3055 participants from Shangcheng district from August 2017 to March 2018, and 4144 participants from Gongshu district from September 2018 to May 2019. The Lanxi cohort, including Lanxi urban cohort and Lanxi rural cohort, included 4503 participants aged 18–80 y from urban (N = 2698) and rural (N = 1805) areas of Lanxi, China. The recruitment periods for the Lanxi urban cohort and Lanxi rural cohort were from June 2019 to August 2019 and from July 2017 to August 2017, respectively. The baseline investigation of the WELL-China cohort and Lanxi cohort both included a questionnaire survey, physical examination, dual-energy x-ray absorptiometry scan, and fecal and blood sample collection. The subsequent health conditions, including diabetes, cardiovascular diseases, cancer, and mortality, of all participants in the 2 cohorts were monitored through the disease registry system.

The institutional review boards of Zhejiang University (number ZGL201507-3) and Stanford University (institutional review board-35020) approved the protocol for the WELL-China cohort study. The Lanxi cohort study obtained approval from the ethics committee of the School of Public Health, Zhejiang University (number ZGL201905-1). All participants in both cohorts provided written informed consent.

Study population

The participant selection process for both cohorts is shown in Figure 1. After excluding individuals with abnormal energy intake (<500 kcal or >4000 kcal), inflammatory bowel diseases, baseline cancers, or missing information on gut microbiota, 6637 individuals from the WELL-China cohort were included for the final analyses. The selection process for the Lanxi cohort was similar to the above, with 3466 participants included in the final analyses.

For sibling comparison analyses, we restricted to 431 participants from 175 families (Lanxi urban cohort: 151 siblings from 66 families; Lanxi rural cohort: 280 siblings from 109 families) where >2 siblings were involved in the Lanxi cohort. Sibling information was collected through a questionnaire survey.

Frequency of fried food consumption

In the WELL-China cohort, the information on habitual dietary consumption was evaluated through a validated food frequency questionnaire (FFQ) consisting of 26 items through face-to-face interviews, as previously described [16,17]. The test-retest reliability of FFQ26 was assessed by comparing food intake measurements at 2 time points separated by a 2-wk interval. The validity of FFQ26 was evaluated through comparative and correlational analyses of food intake, and energy and nutrient intake between FFQ26 and a comprehensive dietary frequency questionnaire (FFQ146), as well as between FFQ26 and a 3-d 24-h dietary record [16,17]. The question about the frequency of consumption of fried foods [fried breadstick (Youtiao), Chinese oil pancake, French fries, etc.] had 9 choices of responses, which ranged from never to daily. In the Lanxi urban cohort, habitual dietary consumption was evaluated through the China Health and Nutrition Survey (CHNS) 2002 FFQ, consisting of 46 items, which was obtained from the China Health and Nutrition Survey [18]. This FFQ has been widely used in the literature [19,20]. Participants were requested to recall how many times they had fried wheat-based foods in the past year: _____ times/day; _____ times/week; _____ times/month; _____ times/year. In final analyses, the frequency of consumption in the 2 cohorts was divided into 3 categories: <1 time/mo; 1~3 times/mo, and ≥4 times/mo, based on previous publications [21]. Dietary assessment and fecal and blood sample collection were all conducted at baseline.

Fried food consumption-related microbiota index

In baseline surveys in both cohorts, fecal samples were self-collected by participants with guidance from cohort staff and placed in dry ice within 4 h and then transferred to long-term storage at

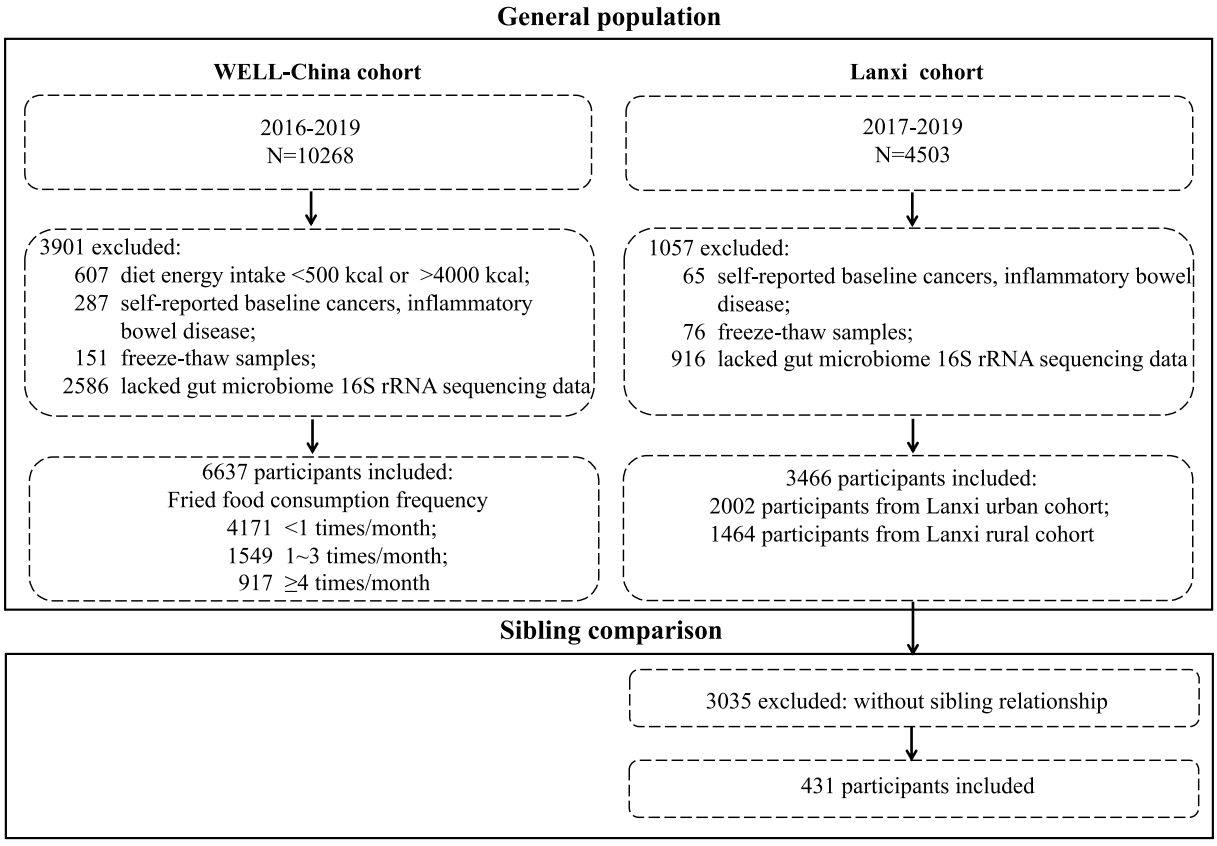

FIGURE 1. Flow diagram in the WELL-China cohort, the Lanxi cohort, and the Lanxi sibling subcohort. In the Lanxi urban cohort, after excluding 191 participants with diet energy intake <500 kcal or >4000 kcal, 1811 participants were included in the final analyses, including 1069 participants with fried food consumption frequency <1 times/mo, 437 participants with fried food consumption frequency 1~3 times/mo, and 305 participants with fried food consumption frequency ≥4 times/mo. We did not collect the fried food consumption frequency in the Lanxi rural cohort. rRNA, ribosomal ribonucleic acid; WELL-China, wellness living laboratory China.

–80°C. Microbial DNA was extracted from each sample using the DNeasy PowerSoil kit (Qiagen) following the manufacturer's instructions. DNA concentrations were determined using the NanoDrop 1 spectrophotometer (NanoDrop Technologies) and Qubit 3.0 fluorometer (Life Technologies). The V3-V4 hypervariable region of the 16S rRNA gene was amplified from genomic DNA using primers 341F (5'-CCTACGGGNGGCWGCAG-3') and 805R (5'-GACTACHVGGGTATCTAATCC-3').

Amplicon sequencing was performed on the Illumina NovaSeq6000 (Illumina). Fastq files were demultiplexed, merge-paired, and quality filtered by 64-bit ultra-fast sequence analysis software (version 7.0.1234) [22]. To obtain effective reads, marker gene Illumina sequence data, chimeric sequences, and low-quality regions of the sequences were detected and filtered. Filtered sequences were clustered into amplicon sequence variants with 97% similarity. Amplicon sequence variants were annotated to the genus level using the SILVA ribosomal RNA database (version 138) [23].

After obtaining gut microbial genera for each participant, based on the 25 identified microbial genera, we created the fried food consumption-related microbiota index (FMI), which offers a comprehensive view of gut bacterial profiles linked to the frequency of fried food consumption (Supplemental Method 1).

Obesity data at baseline

Body weight, height, waist circumference, and hip circumference were assessed by trained personnel for both cohorts. BMI was calculated as weight (kilogram)/height (meter)^2. Waist-to-hip ratio was calculated as waist circumference (centimeters)/hip circumference (centimeters). Body fat mass and regional fat mass were evaluated via dual-energy x-ray absorptiometry scans (software version 11.40.004, GE Lunar Prodigy; GE Healthcare) [14]. For the android fat region, the upper boundary was a horizontal line drawn 20% of the way between the pelvis and the head, and the lower boundary was at the pelvis. For the gynoid fat region, the upper boundary begins slightly below the pelvic line, extending down 1.5 times the android region's height [24]. Android fat mass percentage and gynoid fat mass percentage were calculated as android fat mass/total fat mass and gynoid fat mass/total fat mass, respectively. Additionally, the android-gynoid fat ratio (AOI) was calculated as android fat mass/gynoid fat mass.

Cardiometabolic conditions at baseline

Blood pressure, lipid profiles, fasting glucose, and glycated hemoglobin (HbA1c) were examined at baseline. Glucose, total triglycerides, HDL cholesterol, and total cholesterol in serum were measured on an automated analyzer (Roche cobas 8000 c701). LDL cholesterol and HbA1c were measured on an automated analyzer (Roche cobas 8000 c502). Hypertension was defined as having a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or currently taking antihypertensive medications. Dyslipidemia was defined as having HDL cholesterol concentrations <1.0 mmol/L, LDL cholesterol concentrations ≥4.1 mmol/L, triglyceride concentrations ≥2.3 mmol/L, total cholesterol

TABLE 1
Baseline characteristics of the participants according to frequency of fried food consumption in the wellness living laboratory China cohort and the Lanxi urban cohort[1].

	All participants	Fried food consumption frequency, times/month		
		<1	1~3	≥4
WELL-China cohort				
Participants, *n* (%)	6637 (100.0)	4171 (62.8)	1549 (23.3)	917 (13.8)
Age, years	56.0 (12.5)	58.5 (11.0)	52.3 (13.5)	50.7 (13.9)
Sex, *n* (% of males)	2724 (41.0)	1721 (41.3)	593 (38.3)	410 (44.7)
Marital status, *n* (%)				
Married	5930 (89.3)	3777 (90.6)	1365 (88.1)	788 (85.9)
Others	707 (10.7)	394 (9.4)	184 (11.9)	129 (14.1)
Education level, *n* (%)				
≤6 y	1377 (20.7)	1013 (24.3)	233 (15.0)	131 (14.3)
6–12 y	3873 (58.4)	2505 (60.1)	851 (54.9)	517 (56.4)
≥ 12 y	1383 (20.8)	651 (15.6)	463 (29.9)	269 (29.3)
Income level (Chinese yuan/year/person), *n* (%)				
≤50000	4307 (64.9)	2884 (69.1)	881 (56.9)	542 (59.1)
50001–109999	1921 (28.9)	1078 (25.8)	541 (34.9)	302 (32.9)
≥110000	404 (6.1)	206 (4.9)	125 (8.1)	73 (8.0)
Smoking status, *n* (%)				
Nonsmokers	4876 (73.5)	3067 (73.5)	1171 (75.6)	638 (69.6)
Former smokers	514 (7.7)	344 (8.2)	113 (7.3)	57 (6.2)
Current smokers	1243 (18.7)	758 (18.2)	263 (17.0)	222 (24.2)
Alcohol intake, *n* (%)				
Nondrinker	3630 (54.7)	2346 (56.2)	828 (53.5)	456 (49.7)
Occasional	1646 (24.8)	940 (22.5)	443 (28.6)	263 (28.7)
Regular	1361 (20.5)	885 (21.2)	278 (17.9)	198 (21.6)
Physical activity level, *n* (%)[2]				
Low activity	1085 (16.3)	638 (15.3)	281 (18.1)	166 (18.1)
Moderate activity	3228 (48.6)	2044 (49.0)	753 (48.6)	431 (47.0)
High activity	2319 (34.9)	1487 (35.7)	512 (33.1)	320 (34.9)
Diet energy intakes, kcal[3]	1354.7 (531.1)	1325.7 (510.6)	1320.5 (500.4)	1544.4 (625.8)
Living area, *n* (%)				
Xihu district	1176 (17.7)	726 (17.4)	278 (17.9)	172 (18.8)
Shangcheng district	2279 (34.3)	1382 (33.1)	569 (36.7)	328 (35.8)
Gongshu district	3182 (47.9)	2063 (49.5)	702 (45.3)	417 (45.5)
BMI, kg/m^2	23.9 (3.2)	23.7 (3.1)	24.0 (3.4)	24.3 (3.5)
Waist circumference, cm	83.9 (9.8)	83.6 (9.6)	83.9 (10.1)	85.2 (10.4)
Waist-hip ratio, %	90.3 (7.6)	90.4 (7.4)	89.8 (7.5)	90.9 (8.4)
Android fat percentage, %	10.9 (1.8)	11.0 (1.8)	10.7 (1.8)	11.0 (1.8)
Gynoid fat percentage, %	16.6 (3.0)	16.5 (3.0)	16.9 (3.2)	16.7 (3.1)
Android-gynoid fat ratio, %	69.2 (21.5)	69.9 (21.3)	67.2 (21.7)	69.1 (22.0)
16S rRNA Sequencing batch, *n* (%)				
First	779 (11.7)	503 (12.1)	178 (11.5)	98 (10.7)
Second	4648 (70.0)	2908 (69.7)	1081 (69.8)	659 (71.9)
Third	1148 (17.3)	721 (17.3)	277 (17.9)	150 (16.4)
Fourth	62 (0.9)	39 (0.9)	13 (0.8)	10 (1.1)
16S rRNA sequencing depth	150,590.7 (59,494.0)	150,586.7 (60,650.4)	151,080.7 (56,845.8)	149,780.7 (58,602.2)
Lanxi urban cohort				
Participants, *n* (%)	1811 (100.0)	1069 (59.0)	437 (24.1)	305 (16.8)
Age, years	57.3 (11.5)	59.4 (10.7)	55.6 (12.0)	51.9 (11.8)
Sex, *n* (% of males)	651 (35.9)	358 (33.5)	157 (35.9)	136 (44.6)
Marital status, *n* (%)				
Married	1646 (90.9)	973 (91.0)	396 (90.6)	277 (90.8)
Others	165 (9.1)	96 (9.0)	41 (9.4)	28 (9.2)
Education level, *n* (%)				
≤6 y	555 (30.6)	366 (34.2)	125 (28.6)	64 (21.0)
6–12 y	982 (54.2)	584 (54.6)	229 (52.4)	169 (55.4)
≥12 y	274 (15.1)	119 (11.1)	83 (19.0)	72 (23.6)
Income level (Chinese yuan/year/family), *n* (%)				
≤50000	568 (31.4)	352 (32.9)	143 (32.7)	73 (23.9)
50001–109999	630 (34.8)	380 (35.5)	149 (34.1)	101 (33.1)
≥110000	613 (33.8)	337 (31.5)	145 (33.2)	131 (43.0)
Smoking status, *n* (%)				
Nonsmokers	1462 (80.7)	898 (84.0)	339 (77.6)	225 (73.8)
Former smokers	113 (6.2)	67 (6.3)	27 (6.2)	19 (6.2)
Current smokers	236 (13.0)	104 (9.7)	71 (16.2)	61 (20.0)
Alcohol intake, *n* (%)				

(*continued on next page*)

TABLE 1 (*continued*)

	All participants	Fried food consumption frequency, times/month		
		<1	1~3	≥4
Nondrinker	1136 (62.7)	713 (66.7)	260 (59.5)	163 (53.4)
Occasional	417 (23.0)	212 (19.8)	120 (27.5)	85 (27.9)
Regular	258 (14.2)	144 (13.5)	57 (13.0)	57 (18.7)
Physical activity level, *n* (%)[2]				
Low activity	459 (25.3)	268 (25.1)	113 (25.9)	78 (25.6)
Moderate activity	984 (54.3)	596 (55.8)	224 (51.3)	164 (53.8)
High activity	366 (20.2)	205 (19.2)	100 (22.9)	61 (20.0)
Diet energy intakes, kcal[3]	2209.9 (605.6)	2,173.8 (612.8)	2201.4 (576.4)	2348.4 (603.4)
BMI, kg/m^2	23.6 (3.2)	23.3 (2.9)	23.7 (3.5)	24.4 (3.6)
Waist circumference, cm	83.9 (9.6)	83.3 (9.3)	84.2 (10.2)	85.8 (9.9)
Waist-hip ratio, %	91.4 (7.7)	91.3 (7.9)	91.4 (7.6)	92.0 (7.2)
Android fat percentage, %	10.9 (1.6)	10.8 (1.5)	10.9 (1.5)	11.0 (1.6)
Gynoid fat percentage, %	16.2 (2.9)	16.3 (2.8)	16.2 (2.9)	15.9 (2.9)
Android-gynoid fat ratio, %	70.3 (20.3)	69.5 (20.0)	70.4 (20.1)	72.6 (21.5)
16S rRNA Sequencing depth	198,688.9 (58,289.7)	197,969.9 (57,780.5)	198,366.4 (62,322.7)	201,668.7 (54,027.6)

Abbreviations: BMI, body mass index; rRNA, ribosomal ribonucleic acid; SD, standard deviation; WELL-China, wellness living laboratory China.

[1] Data were presented as means (SDs) for continuous variables and numbers (percentage) for categorical variables. The missing data (normally ≤5) were not presented in the table.

[2] Physical activity was classified into 3 groups according to the international physical activity questionnaire.

[3] Diet energy intakes in the WELL-China cohort were measured via a 26-item validated food frequency questionnaire (FFQ). The 46-item validated FFQ was used in the Lanxi urban cohort.

concentrations ≥6.2 mmol/L, or using lipid-lowering medications. MetS was defined according to revised criteria set by the International Diabetes Federation [25]. Specifically, MetS is diagnosed based on a waist circumference of ≥90 cm in males and ≥80 cm in females, along with the presence of any 2 of the following criteria: elevated triglycerides (>150 mg/dL or 1.7 mmol/L), decreased HDL cholesterol (<40 mg/dL or 1.03 mmol/L in males, <50 mg/dL or 1.29 mmol/L in females), specific treatment for triglycerides or HDL cholesterol abnormality, elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg), treatment of previously diagnosed hypertension, elevated fasting plasma glucose (≥100 mg/dL or 5.6 mmol/L), and previously diagnosed type 2 diabetes. Diabetes was diagnosed based on fasting blood glucose concentrations ≥7.0 mmol/L, HbA1c concentrations ≥6.5% (48 mmol/mol), or currently using diabetes medications. Metabolic dysfunction-associated steatotic liver disease (MASLD) was identified based on a consensus review of ultrasound images conducted by skilled operators. The detailed methodology of the ultrasound image consensus review has been previously published [26,27].

Cardiometabolic diseases during the follow-up

The deaths and hospitalizations of the participants were monitored through an established disease registration system, including the inpatient system and the outpatient system. Participants were monitored from baseline (2016–2019) until the occurrence of cardiometabolic disease, mortality, or 24 June, 2024, whichever came first. The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) diagnostic codes were used to define cardiometabolic diseases, such as incident diabetes (E11–E14) and major adverse cardiovascular events (MACE), including death, myocardial infarction (I20–I25), heart failure (I50), or stroke (I60–I64, I69) [28].

Covariates

Data on age (years), sex (male or female), residential area (Xihu district, Shangcheng district, or Gongshu district), physical activity levels (low, moderate, or high), smoking status (nonsmokers, former smokers, or current smokers), alcohol intake (nondrinker, occasional, or regular), antibiotic use (yes or no), annual income (≤50000 CNY, 50000–109999 CNY or ≥110000 CNY), marital status (married or others), and education level (≤6 y, 6–12 y, or ≥12 y) were gathered through standardized structured questionnaires [29,30]. Dietary energy consumption was evaluated via a validated FFQ consisting of 26 items in the WELL-China cohort [16] and a validated FFQ consisting of 46 items in the Lanxi urban cohort [18].

For categorical covariates, missing data were assigned to a separate "Missing" category, as detailed in Table 1 and Supplemental Table 1. For the continuous covariate 16S rRNA sequencing depth, 1 missing sample each in the WELL-China cohort and the Lanxi cohort was imputed using the mean value. Diet energy intake in the Lanxi rural cohort was imputed using the mean value from the Lanxi urban cohort due to the unavailability of dietary data.

Statistical analysis

Microbiome analyses

To explore the relationships of fried food consumption frequency with gut microbiota α-diversity, multivariable linear regression was employed. Permutational multivariate analysis of variance with 999 permutations was used to investigate the relationship of fried food consumption frequency with gut microbiota β-diversity [31]. Microbiome multivariable associations with linear models [32] were utilized to identify potential gut microbial genera linked to fried food consumption frequency. To mitigate false discoveries from multiple tests, the Benjamini-Hochberg method was employed, setting a Q value (false discovery rate-adjusted *P* value) below 0.25 as statistically significant. To validate the collective effects of genera (FMI) constructed by the above-identified gut microbial genera, the association between fried food consumption frequency and FMI was investigated through multivariable linear regression.

Cross-sectional analyses

Multivariable linear regression was utilized to explore the relationship of FMI with obesity and fat distribution. In addition, multivariable logistic regression was applied to explore the association of FMI with cardiometabolic conditions, including hypertension, MetS, dyslipidemia, diabetes, and MASLD.

Longitudinal analyses

Longitudinal analyses were performed using a Cox regression model to examine the association of FMI with the onset of cardiometabolic diseases, such as diabetes and MACEs. The Schoenfeld residual test was used to test the proportional assumption of the Cox regression (in the WELL-China cohort, the *P* values corresponding to the diabetes model, MACE model, and diabetes-MACE combined model were 0.741, 0.236, and 0.533, respectively. In the Lanxi cohort, the *P* values for the 3 models were 0.035, 0.287, and 0.025, respectively.). To investigate the role of adiposity in the relationship between FMI and cardiometabolic diseases, we additionally controlled for BMI and AOI on the basis of the fully adjusted model.

Meta-analyses

We conducted meta-analyses using the Mantel-Haenszel method to derive combined effect estimates from the WELL-China cohort and the Lanxi cohort. Cochran's Q test was utilized to assess heterogeneity within the meta-analysis. A fixed-effects model was utilized.

Sibling comparison analyses

To address confounding factors common within families, sibling comparison analyses were conducted. The analyses of FMI with obesity and cardiometabolic conditions were repeated using the between-within model [33]. This was implemented through the lmer and glmer functions in the "lme4" package (version 1.1.27) in R. The between-within model divides the covariate effect into 2 independent components: the between-cluster effect and the within-cluster effect to eliminate the bias caused by the generalized linear mixed model [33,34].

We used R version 4.1.2 for statistical analysis, and a 2-sided *P* value <0.05 was considered statistically significant.

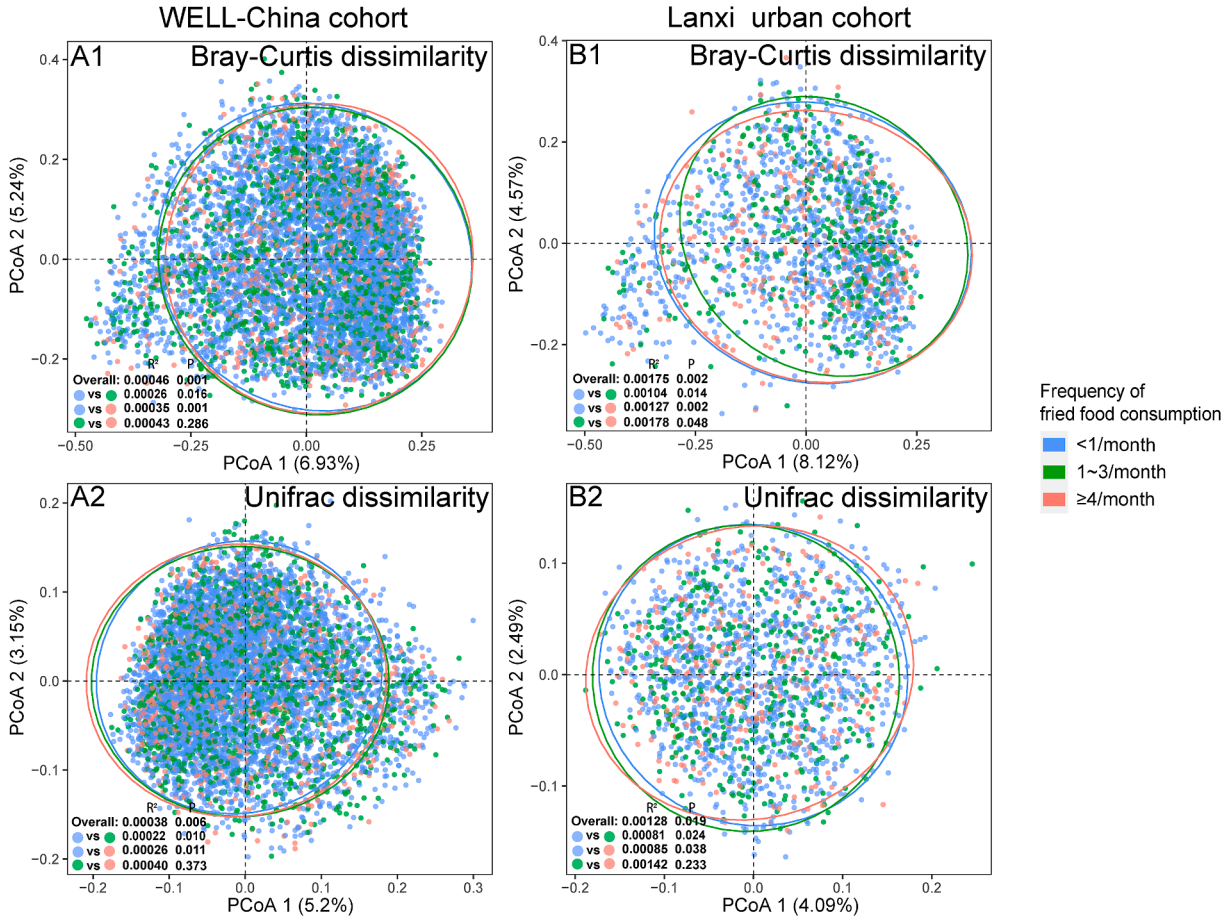

FIGURE 2. Fried food consumption and β-diversity in the participants of the WELL-China cohort and the Lanxi urban cohort. Dietary assessment and fecal samples collection were all conducted at baseline. Principal coordinates analysis(PCoA) was conducted on the WELL-China cohort ($N = 6637$) and the Lanxi urban cohort ($N = 1811$) using Bray-Curtis dissimilarity for (A_1 and B_1), and weighted Unifrac dissimilarity for (A_2 and B_2). A PERMANOVA test was employed, utilizing 999 permutations, to explore the relationship of the frequency of fried food consumption with β-diversity, whereas controlling for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth. PERMANOVA, permutational multivariate analysis of variance; WELL-China, wellness living laboratory China.

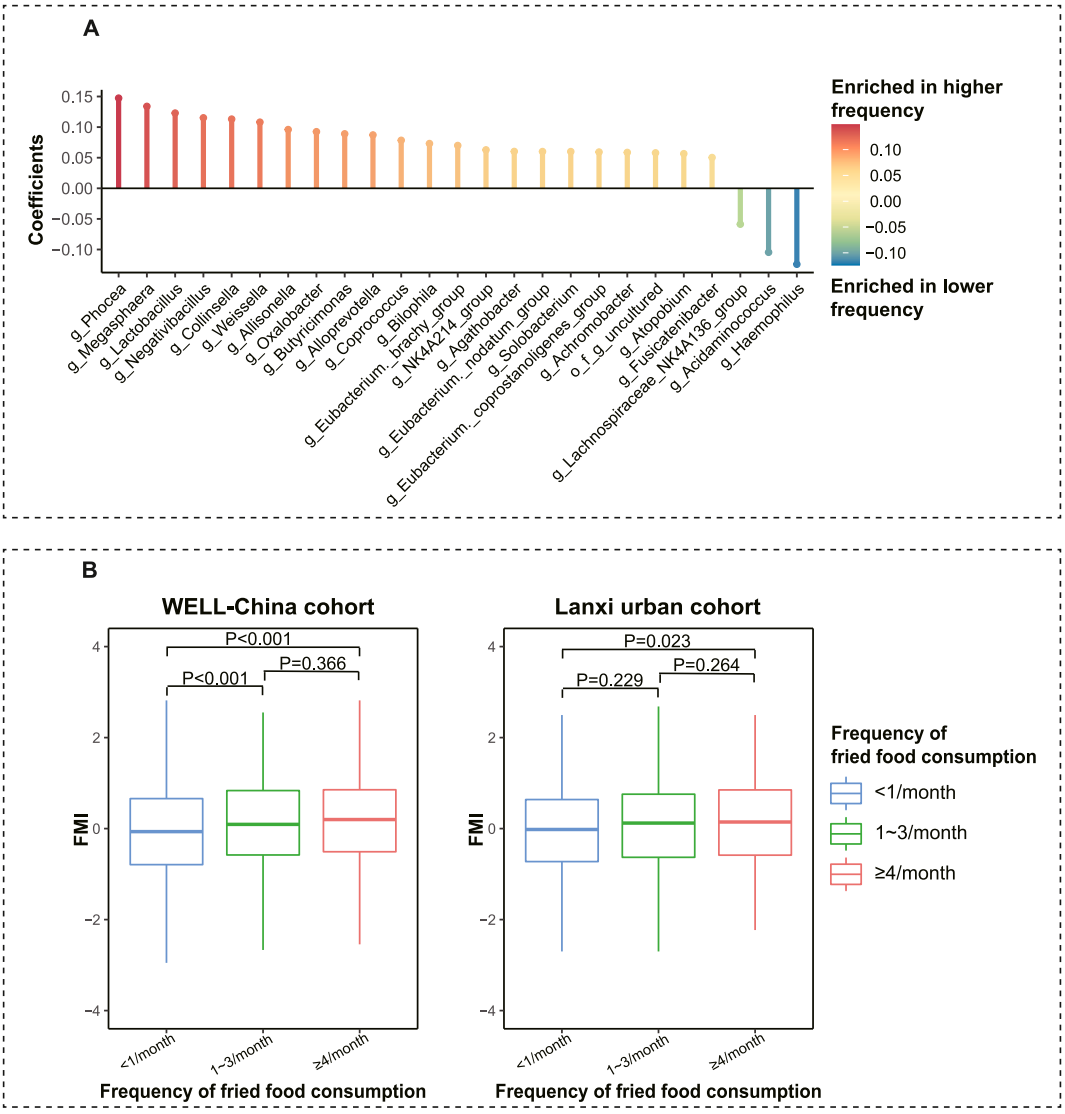

FIGURE 3. Fried food consumption and identified microbial genera in the participants of the WELL-China cohort. Dietary assessment and fecal sample collection were all conducted at baseline. (A) Multivariate analysis by linear models were used to identify microbial genera associated with frequency of fried food consumption in the WELL-China cohort ($N = 6637$), adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use, sequencing batch, and sequencing depth. The Q values (false discovery rate-adjusted P value) were calculated using the Benjamini-Hochberg method (Q value <0.25). (B) Multivariable linear regression models were utilized to explore the relationship of Fried food consumption-related microbiota index (FMI) (per SD unit increase) with frequency of fried food consumption in participants of the WELL-China cohort (left) and the Lanxi urban cohort (right), adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth. In the WELL-China cohort ($N = 6637$), compared with participants whose consumption frequency of fried food was <1 time/mo, participants whose consumption frequency of fried food were 1~3 times/mo and ≥4 times/mo had higher FMI, respectively (1~3 times/mo: β = 0.18; 95% CI: 0.12, 0.24; ≥4 times/mo: β = 0.21; 95% CI: 0.14, 0.29). In the Lanxi urban cohort ($N = 1811$), compared with the <1 time/mo group, β (95% CI) for the 1~3 times/mo group and the ≥4 times/mo group were 0.07 (–0.04, 0.18) and 0.15 (0.02, 0.29), respectively. CI, confidence interval; SD, standard deviation; WELL-China, wellness living laboratory China.

Results

Population characteristics

Table 1 presents the baseline characteristics by frequency of fried food consumption in the WELL-China cohort and the Lanxi urban cohort. Supplemental Table 1 presents the baseline characteristics for the Lanxi rural cohort and the Lanxi sibling subcohort (both part of the Lanxi cohort).

Fried food consumption and gut microbiota

When comparing lower to lower frequency of fried food consumption, a significant difference in β-diversity (gut microbial composition) was observed in both the WELL-China cohort ($R^2 = 0.00035$, $P < 0.001$) and the Lanxi urban cohort ($R^2 = 0.00127$, $P = 0.002$) (Figure 2A_1 and B_1). Analysis of β-diversity, considering phylogenetic relationships using weighted Unifrac distances, supported these findings (Figure 2A_2 and B_2). Twenty-five microbial genera were

statistically significantly linked to the fried food consumption frequency (false discovery rate <0.25) in the WELL-China cohort (Figure 3A, Supplemental Table 2). After adjusting for the frequency of fruit intake and vegetable intake, only 1 unannotated genus-level bacterium was removed, demonstrating the reliability of our results (Supplemental Table 3). However, associations of the 3 groups categorized by fried food consumption frequency with α-diversity (gut microbial richness) were not significant (Supplemental Figure 1).

FMI

The FMI, comprising 25 identified microbial genera, was associated with the fried food consumption frequency in the WELL-China cohort (Figure 3B). Compared with participants whose consumption frequency of fried food was <1 time/mo, participants whose consumption frequency of fried food were 1~3 times/mo and ≥4 times/mo had higher FMI, respectively [1~3 times/mo: β: = 0.18; 95% confidence interval (CI): 0.12, 0.24; ≥4 times/mo: β = 0.21; 95% CI: 0.14, 0.29] (Figure 3B). This association was also observed in the Lanxi urban cohort, underscoring the robustness of the FMI (Figure 3B).

FMI and obesity

Table 2 presents the relationship of FMI with obesity measures. No significant heterogeneity was found between the cohorts. A meta-analysis found a strong positive relationship of FMI with obesity indicators including BMI (β: 0.26; 95% CI: 0.19, 0.32), waist circumference (β: 0.79; 95% CI: 0.61, 0.97), waist-to-hip ratio (β: 0.43; 95% CI: 0.29, 0.56), android fat percentage (β: 0.09; 95% CI: 0.06, 0.11), and AOI (β: 1.48; 95% CI: 1.14, 1.82), whereas a negative relationship with gynoid fat percentage (β: –0.23; 95% CI: –0.28, –0.17). Similarly, in sibling comparisons, significant associations were observed across these obesity measures.

TABLE 2

Fried food consumption-related microbiota index and prevalent obesity in the participants of the wellness living laboratory China cohort, Lanxi cohort, and Lanxi sibling subcohort.

Prevalent	Total cohort analysis[1]						Sibling comparison analysis[2]	
	WELL-China cohort		Lanxi cohort		Meta-analyzed		Lanxi sibling subcohort	
	N	β (95% CI)	*N*	β (95% CI)	β (95% CI)	$P_{heterogeneity}$	*N*	β (95% CI)
BMI (kg/m^2)	6629	0.23 (0.15, 0.31)	3446	0.31 (0.20, 0.42)	0.26 (0.19, 0.32)	0.249	431	0.39 (0.12, 0.66)
Waist-circumference (cm)	6628	0.81 (0.59, 1.03)	3451	0.74 (0.43, 1.05)	0.79 (0.61, 0.97)	0.718	431	1.17 (0.37, 1.98)
Waist-hip ratio (%)	6627	0.47 (0.31, 0.64)	3451	0.34 (0.11, 0.57)	0.43 (0.29, 0.56)	0.368	431	0.89 (0.35, 1.43)
Android percentage (%)	6568	0.09 (0.06, 0.13)	3408	0.08 (0.03, 0.12)	0.09 (0.06, 0.11)	0.731	430	0.10 (−0.02, 0.22)
Gynoid percentage (%)	6568	–0.22 (–0.28, –0.15)	3408	–0.24 (–0.33, –0.15)	–0.23 (–0.28, –0.17)	0.724	430	–0.39 (–0.61, –0.16)
Android-gynoid ratio (%)	6568	1.43 (1.01, 1.85)	3408	1.58 (0.98, 2.18)	1.48 (1.14, 1.82)	0.688	430	2.32 (0.69, 3.94)

Abbreviations: BMI, body mass index; CI, confidence interval; FMI, fried food consumption-related microbiota index; SD, standard deviation; WELL-China, wellness living laboratory China.

[1] Multivariable linear regression models were utilized to explore the relationship of FMI (per SD unit increase) with obesity in the total cohort analysis, adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth.

[2] Between-within models were employed to assess the association between FMI (per SD unit increase) and obesity in a sibling comparison analysis, adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth.

TABLE 3

Fried food consumption-related microbiota index and prevalent cardiometabolic conditions in the participants of the wellness living laboratory China cohort, Lanxi cohort, and Lanxi sibling subcohort[1].

Prevalent	Total cohort analysis[2]						Sibling comparison analysis[3]	
	WELL-China cohort		Lanxi cohort		Meta-analyzed		Lanxi sibling subcohort	
	N	OR (95% CI)	*N*	OR (95% CI)	OR (95% CI)	$P_{heterogeneity}$	*N*	OR (95% CI)
Hypertension	6605	1.11 (1.05, 1.18)	3461	1.07 (0.99, 1.15)	1.09 (1.05, 1.15)	0.449	429	1.37 (1.09, 1.71)
Dyslipidemia	6628	1.08 (1.02, 1.14)	3461	1.18 (1.10, 1.27)	1.12 (1.07, 1.17)	0.056	430	1.21 (0.97, 1.51)
Metabolic syndrome	6620	1.21 (1.14, 1.28)	3448	1.21 (1.12, 1.30)	1.21 (1.16, 1.27)	1.000	428	1.27 (1.01, 1.60)
Diabetes	6629	1.29 (1.19, 1.40)	3462	1.27 (1.13, 1.42)	1.28 (1.20, 1.37)	0.827	430	1.48 (1.03, 2.12)
MASLD[4]	2547	1.16 (1.07, 1.26)	3466	1.25 (1.16, 1.34)	1.21 (1.15, 1.28)	0.113	431	1.18 (0.94, 1.47)

Abbreviations: CI, confidence interval; FMI, fried food consumption-related microbiota index; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; SD, standard deviation; WELL-China, wellness living laboratory China.

[1] Prevalent cardiometabolic conditions were defined using baseline data.

[2] Multivariate logistic regression models were employed to assess the relationships between FMI (per SD unit increase) and prevalent cardiometabolic conditions in the total cohort, adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth. The estimates were subjected to meta-analysis using a fixed-effect model.

[3] Between-within models were utilized to evaluate the relationship between FMI (per SD unit increase) and prevalent cardiometabolic conditions in sibling comparison analysis, adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth.

[4] The diagnosis of MASLD was conducted exclusively in the Gongshu district of the WELL-China cohort.

TABLE 4
Fried food consumption-related microbiota index and incident cardiometabolic diseases in the participants of the wellness living laboratory China cohort and Lanxi cohort[1].

Incident	WELL-China cohort		Lanxi cohort		Meta-analyzed	
	Case/*N*	HR (95% CI)[2]	Case/*N*	HR (95% CI)[2]	HR (95% CI)[3]	$P_{heterogeneity}$
Diabetes[4]	419/5751	1.14 (1.03, 1.26)	140/3039	1.23 (1.04, 1.46)	1.16 (1.07, 1.27)	0.450
Major adverse cardiovascular events	356/6637	1.14 (1.02, 1.27)	209/3412	1.19 (1.03, 1.36)	1.16 (1.06, 1.26)	0.635
Diabetes and major adverse cardiovascular events	620/5724	1.13 (1.04, 1.22)	285/3011	1.21 (1.07, 1.36)	1.15 (1.08, 1.23)	0.352

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation; WELL-China, wellness living laboratory China.

[1] Cardiometabolic disease incidents were identified based on the disease register data from the inpatient system and the outpatient system.

[2] Cox models were utilized to explore the relationship of per SD unit increase in FMI with risk of diabetes, major adverse cardiovascular events, and cardiometabolic diseases (diabetes and major adverse cardiovascular events), adjusted for age, sex, residential area, annual income, marital status, education level, alcohol consumption, physical activity levels, smoking habits, diet energy intakes, antibiotics use (specific to the WELL-China cohort), sequencing batch, and sequencing depth. Patients were monitored from the beginning of the study until the occurrence of cardiometabolic diseases, death, or the end of the follow-up on 24 June, 2024, whichever came first. The median follow-up time was 6 y in the WELL-China cohort and 5 y in the Lanxi cohort.

[3] Estimates were meta-analyzed using a fixed-effect model.

[4] Diabetes: In the longitudinal analysis of the onset of diabetes, we excluded participants with diabetes at baseline. The exclusion criteria were self-reported use of diabetes medication or a baseline fasting blood glucose concentration >7.0 mmol/L or a baseline diagnosis of diabetes in the disease registry system.

FMI and prevalent cardiometabolic conditions

Table 3 presents the relationship between FMI and prevalent cardiometabolic conditions. No significant heterogeneity was found between the 2 cohorts. A meta-analysis found a positive relationship of FMI with cardiometabolic conditions, with each SD unit increase in FMI associated with higher risk of hypertension [odds ratio (OR): 1.09; 95% CI: 1.05, 1.15], dyslipidemia (OR: 1.12; 95% CI: 1.07, 1.17), MetS (OR: 1.21; 95% CI: 1.16, 1.27), diabetes (OR: 1.28; 95% CI: 1.20, 1.37), and MASLD (OR: 1.21; 95% CI: 1.15, 1.28). Second, we did gather extensive details on the specific type of oil Consistent results were found in sibling analyses for hypertension (OR: 1.37; 95% CI: 1.09, 1.71), MetS (OR: 1.27; 95% CI: 1.01, 1.60), and diabetes (OR: 1.48; 95% CI: 1.03, 2.12).

FMI and incident cardiometabolic diseases

Table 4 presents the relationship of FMI with incident cardiometabolic diseases. No significant heterogeneity was found between the 2 cohorts. A meta-analysis found a positive relationship of FMI with incident cardiometabolic diseases, with each SD unit increase in FMI associated with higher risk of incident diabetes [hazard ratio (HR): 1.16; 95% CI: 1.07, 1.27] and MACEs (HR: 1.16; 95% CI: 1.06, 1.26). The association of FMI with cardiometabolic diseases diminished after adjusting for obesity (BMI) and central fat distribution (AOI), suggesting that part of the association between FMI and cardiometabolic diseases may be mediated through fat and fat distribution (Supplemental Figures 2 and 3). Fried food consumption-related microbiota was independently associated with incident cardiometabolic diseases after controlling for diet energy intake or dietary diversity score (Supplemental Tables 4 and 5).

Discussion

In this study involving 2 population-based cohorts in China, we observed a significant association between gut microbiota β-diversity and fried food consumption frequency. We detected no associations between fried food consumption frequency and gut microbiota α-diversity. Further analyses identified 25 genera related to the fried food consumption frequency in the WELL-China cohort. FMI, based on these 25 genera, was linked to the fried food consumption frequency in the WELL-China cohort, and the association was validated in the Lanxi urban cohort. We found that FMI had a strong association with obesity, central fat distribution, and various cardiometabolic conditions in both cross-sectional and longitudinal analyses. Results of sibling comparison analyses provided consistent evidence, confirming that gut microbiomes associated with fried food consumption are associated with obesity and cardiometabolic diseases, independent of genetic and early life environmental factors.

Several limitations should be considered. First, residual confounding still persists despite adjustment for multiple covariates. (vegetable or animal oil) used for frying, the method (deep or pan) used for frying, and other details about fried food consumption that could potentially affect results. Third, in our microbial analysis, the exclusive use of 16S rRNA sequencing rather than metagenomic sequencing may have limited functional insights into the microbiome. Fourth, in the prospective analysis, the statistical power was constrained by insufficient incident case numbers, precluding robust assessment of specific MACE endpoints (such as stroke, heart failure). Fifth, the observational design used to investigate the association between fried food consumption and gut microbiota precludes robust causal inference. Last, as both of our cohorts are Chinese, caution needs to be taken when generalizing our findings.

Three previous studies, limited by small sample sizes, have examined the link between fried foods and gut microbiota α-diversity, and have shown inconsistent results [9,10,12]. A randomized controlled trial in 117 adults revealed no changes in Chao1/Shannon diversity indices between high fried meat intake and control groups [9], whereas a cross-sectional analysis of 862 adults revealed an inverse link between fried food consumption and α-diversity indices [10]. The inconsistent findings could stem from short trial durations and/or limited sample sizes. Our observational study on gut microbiota in nearly 10,000 individuals has greater statistical power compared to previous studies, suggesting that our findings of no relationship of frequency of fried food consumption with the overall richness of gut microbiota are reliable.

Our findings of significant variations in gut microbe β-diversity associated with fried food consumption are in line with prior studies [10,11], implying that fried food consumption is significantly related to the gut microbiota overall structure. We identified 25 genera associated with fried food consumption, suggesting selective associations between fried food consumption and specific gut microbiota genera. Although the mechanisms by which fried foods alter gut microbiota remain unclear, frying-induced chemical reactions (e.g., polymer

formation, *trans*-fatty acid) [35] may affect the health and abundance of some microbiota. A clinical trial has shown that the intake of fried meat not only affects the abundance of some bacteria but also causes significant changes in fecal metabolites [9]. In an association analysis of 19 dietary variables with gut microbiota β-diversity, fried products explained the second-highest proportion of variation in gut microbiota composition, surpassed only by raw fruit intake, suggesting its potential microbial impacts [10].

Since the effect of individual microbial genera is limited, we constructed an index representing the fried food consumption-related gut microbiota, termed FMI, to quantify the cumulative effect of variation across multiple identified genera. We found that FMI was linked to overall obesity and central fat accumulation, with the latter showing a stronger association with cardiometabolic risk compared to overall obesity [36]. Fried food consumption-related microbiota were independently associated with central fat distribution after controlling for overall obesity (BMI) (Supplemental Table 6), suggesting fried food consumption-related microbiota may contribute to the accumulation of abdominal fat, and, by extension, greater cardiometabolic risk, independent of BMI.

In our cross-sectional and longitudinal analyses, we found a positive association between FMI and cardiometabolic diseases, including MACEs and diabetes. Identifying new gut microbiota related to fried food consumption may help elucidate the mechanism determining the relationship of fried food consumption with cardiometabolic risk. Notably, the association between FMI and cardiometabolic diseases was reduced when controlled for BMI and AOI, as indicated in Supplemental Figures 2 and 3. This suggests that overall obesity and central fat distribution may play a mediating role in the relationship of fried food consumption-associated gut microbiota with cardiometabolic diseases.

The sibling comparison design reinforced our results. Recent studies have found extensive sharing of bacterial strains among individuals, with patterns of intrahousehold and intrapopulation transmission [15]. Obesity and cardiometabolic diseases are affected by common environmental and genetic factors that are difficult to capture in cohort studies. The sibling comparison design is a powerful method for mitigating these confounding factors [37], thereby boosting the reliability of our results. Given the limited sample size in our study, investigating whether siblings discordant in fried food consumption exhibit differences in their gut microbiota composition also presents a valuable direction for future research.

In conclusion, our research identifies measurable associations between fried food consumption frequency and specific gut microbiota profiles that link to higher adiposity, central fat distribution, and a higher likelihood of cardiometabolic diseases. These observations call for further investigation into microbial mediators of metabolic outcomes and emphasize the potential value of monitoring dietary patterns in population health strategies.

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Author contributions

The authors' responsibilities were as follows – YD, YL, WH, SZ: designed the study; YD, YL: performed the data analyses and prepared the figures; YD, YL, WH, SZ: wrote the paper; CX, WW, XW, WZ, JCH, JW, AM, AWH: provided constructive analytical suggestions; WH, SZ: was primarily responsible for the final content; and all authors: read and approved the final manuscript.

Conflict of interest

WH reports financial support was provided by the National Key R&D Program of China. WH reports financial support was provided by Pioneer and Leading Goose R&D Program of Zhejiang. SZ reports financial support was provided by the National Key R&D Program of China. SZ reports financial support was provided by grants from the Nutrilite Health Institute Wellness Fund. SZ reports financial support was provided by the Cyrus Tang Foundation. SZ reports financial support was provided by the China Medical Board (CMB) and the Hsun K. Chou Fund of Zhejiang University Education Foundation. All other authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval by the corresponding authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2025.06.025.

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