

Five-Year Longitudinal Changes and Determinants of Serum PFAS Exposure Profiles in a Community-Based Cohort from Southern China

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Abstract

Background

Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants widely detected in human populations. Although regulatory actions have restricted several legacy PFAS, longitudinal evidence on changes in human PFAS exposure and their determinants remains limited, particularly in rapidly urbanizing regions. This study aimed to characterize five-year changes in serum legacy PFAS concentrations and identify demographic and geographic determinants of longitudinal exposure among community residents in Guangzhou, southern China.

Methods

We conducted a prospective community-based cohort study of 958 residents from three communities representing distinct residential environments: an urban commercial area, an industrial/livestock/fishery area, and an ecological conservation area. Participants were examined at baseline (2018–2019) and follow-up (2023–2024). Serum legacy PFAS concentrations were measured using ultra-performance liquid chromatography–tandem mass spectrometry. Temporal changes were assessed using paired analyses, and longitudinal determinants were evaluated using linear mixed-effects models with false discovery rate correction.

Results

Six legacy PFAS with detection frequencies approaching 100% were included in longitudinal analyses. Over five years, total PFOS, PFNA, PFDA, and total PFHxS concentrations decreased from 14.129 to 11.262, 0.998 to 0.871, 0.692 to 0.532, and 0.771 to 0.598 ng/mL, respectively, whereas PFOA increased from 5.534 to 9.789 ng/mL and PFHpA from 0.024 to 0.034 ng/mL. Older age was consistently associated with higher concentrations of all six PFAS. Residential location was also an important determinant, with higher PFAS concentrations observed among residents of the urban commercial and industrial/livestock/fishery communities than among those in the ecological conservation community.

Conclusions

Serum legacy PFAS exposure showed heterogeneous five-year trajectories in this community-based population in Guangzhou, with divergent temporal patterns across individual PFAS. The contrasting trends and persistent demographic and geographic differences highlight the complexity of human PFAS exposure following regulatory changes. Continued biomonitoring and identification of populations with elevated exposure are warranted to support targeted exposure reduction and public health surveillance.

1 Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large group of synthetic fluorinated compounds that have been widely used in industrial and consumer applications since the 1950s, including firefighting foams, food packaging, electronics, and textile treatments(1). Due to their strong carbon–fluorine bonds, PFAS exhibit exceptional chemical stability and resistance to environmental degradation, resulting in their widespread occurrence in environmental matrices and biological systems(2). Among the diverse PFAS compounds, legacy long-chain perfluorocarboxylic acids (PFCAs) and perfluorosulfonic acids (PFSAs), particularly perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS), have attracted considerable attention because of their environmental persistence, bioaccumulative potential, and potential adverse effects on human health(3).

Human exposure to PFAS occurs primarily through dietary intake, drinking water, and contact with PFAS-containing products(4). After absorption, PFAS can bind to serum proteins and remain in the human body for years due to their long biological half-lives(5). Epidemiological evidence has raised concerns about the potential health effects of PFAS exposure, particularly metabolic alterations, liver dysfunction, immune responses, and disturbances in lipid metabolism(6). Previous studies have consistently reported associations between serum PFAS concentrations and altered lipid profiles, including increased total cholesterol and low-density lipoprotein cholesterol levels(7, 8). Therefore, understanding long-term patterns of human PFAS exposure and identifying populations with elevated exposure burdens remain important for environmental health risk assessment.

In response to growing evidence regarding the persistence and toxicity of PFAS, global regulatory actions have been implemented to restrict the production and use of several legacy PFAS, including PFOS, PFOA, and PFHxS, under the Stockholm Convention on Persistent Organic Pollutants(9). Following these regulatory measures, declines in serum concentrations of some legacy PFAS have been observed in several populations(10). However, temporal patterns of PFAS exposure remain complex because they are influenced by historical emissions, environmental persistence, population characteristics, dietary behaviors, and the emergence of alternative PFAS compounds(11). Although PFOS concentrations have generally decreased after regulatory restrictions, PFOA and other precursor-derived or replacement PFAS may persist or even increase in certain populations(12). Therefore, repeated biomonitoring within populations is essential to determine whether regulatory actions and changes in PFAS use have translated into measurable reductions in human exposure.

Previous biomonitoring studies have demonstrated substantial geographic variability in serum PFAS concentrations worldwide(13, 14). Higher PFAS exposure levels have frequently been observed in populations residing in industrialized regions, suggesting that local emission sources, environmental contamination, and socioeconomic activities may contribute to exposure disparities(15, 16). In China, previous investigations have identified regional differences in PFAS exposure, with elevated concentrations reported in areas affected by industrial activities(17). However, most existing studies

have employed cross-sectional designs, limiting the ability to characterize individual-level changes in PFAS exposure over time(15). Moreover, evidence regarding demographic and geographic determinants associated with longitudinal variations in serum PFAS concentrations remains limited, particularly in rapidly developing urban areas with heterogeneous residential environments and economic activities(18).

Guangzhou, a highly urbanized metropolitan city in southern China, contains diverse communities characterized by distinct environmental and socioeconomic backgrounds, including commercial, industrial/livestock/fishery, and ecological conservation regions. These heterogeneous settings provide a unique opportunity to investigate temporal changes in PFAS exposure across different residential environments and identify potential determinants among the general population. Therefore, we conducted a prospective cohort study with a five-year follow-up among residents of Guangzhou. The objectives of this study were to (1) characterize serum legacy PFAS exposure profiles among community residents; (2) evaluate five-year temporal changes in serum PFAS concentrations; and (3) identify demographic and geographic determinants associated with longitudinal variations in PFAS exposure.

2 Materials and methods

2.1 Study population

This prospective cohort study was conducted within the framework of the Guangzhou Air Pollution and Population Health Impact Monitoring Project in Guangdong Province, China. The baseline survey was conducted between 2018 and 2019. Three representative communities were selected according to economic development level, geographic characteristics, and administrative district type: Community A (a mixed commercial and residential area), Community B (a mixed industrial, livestock, and fishery area), and Community C (a natural ecological and low-density residential area). A multi-stage stratified random sampling strategy was employed. In the first stage, two neighborhood or village committees were randomly selected from each designated monitoring district as survey communities. In the second stage, one community was randomly selected from each previously selected survey community as the study site. In the third stage, households were selected at fixed intervals based on community population registries or family health records, with the requirement that each selected household include both elderly and child members. The sample size was determined in proportion to the population size of each community, and eligible residents meeting the inclusion and exclusion criteria were enrolled. Face-to-face questionnaire interviews (Questionnaire information was collected using standardized questionnaires at baseline (2018–2019) and follow-up (2023–2024). Although different questionnaire versions were used at the two survey waves, the questionnaire items relevant to the present study were consistent across the two waves. The English versions of the baseline and follow-up questionnaires are provided as Supplementary Files 1 and 2, respectively.), health examinations, and blood sample collection were conducted at the community health service centers of the three monitoring sites. Follow-up of the same participants was conducted between 2023 and 2024. After excluding participants with

incomplete questionnaire data and those who were lost to follow-up, had died, or had relocated, a total of 958 community residents were included in the final analysis.

The inclusion criteria were: (1) residence in the local area for at least six months; and (2) no age restriction, provided that participants were ambulatory and free of significant cognitive impairment. The exclusion criteria were: (1) severe mental illness or cognitive impairment precluding participation in the survey; (2) diagnosis of malignant tumors, stroke, severe kidney disease, major organ failure, or other end-stage clinical conditions; (3) non-permanent residency; and (4) severe mobility impairment (high paraplegia) or inability to perform activities of daily living independently. This study was conducted in accordance with the Measures for the Ethical Review of Biomedical Research Involving Humans. The study protocol was reviewed and approved by the Medical Ethics Committee of the Guangzhou Center for Disease Control and Prevention (Approval Nos.: GZCDC-ECHR-2026P0038, GZCDC-ECHR-2026P0039). Written informed consent was obtained from all participants or their guardians/legal representatives after they had been fully informed of the study procedures.

2.2 Sample collection and analysis

2.2.1 Blood sample collection

During both the baseline (2018–2019) and follow-up (2023–2024) surveys, fasting venous blood samples were collected by trained phlebotomists. For participants aged ≥ 12 years, venous blood samples were collected into two purple-top ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes (2.5 mL each) and two red-top non-anticoagulant tubes (2.5 mL each). For children aged < 12 years, venous blood was collected into two tubes: one purple-top EDTA anticoagulant tube (2.5 mL) and one red-top non-anticoagulant tube (2.5 mL). Blood was collected in the following order: red-top non-anticoagulant tubes followed by purple-top anticoagulant tubes. All blood samples were labeled, stored at 4°C, and transported under cold-chain conditions to the laboratory immediately after sample collection for all participants. Samples were centrifuged at 12,000 rpm for 5 minutes at 4°C, after which the supernatant was aliquoted into vials. Samples that were not analyzed immediately were stored at -80°C . Detailed procedures are provided in the Supplementary File 3.

2.2.2 PFAS quantification

Serum concentrations of per- and polyfluoroalkyl substances (PFAS) were quantified using ultra-performance liquid chromatography (Agilent 1290) coupled with an Agilent 6495B triple quadrupole tandem mass spectrometer (UPLC–MS/MS), using 0.2 mL of serum for each analysis. The limit of detection (LOD) and the limit of quantification (LOQ) were defined as the minimum concentrations at which target PFAS could be detected at signal-to-noise ratios of 3:1 and 10:1, respectively(19). PFAS concentrations below the LOD were imputed as $LOD/\sqrt{2}$ (20). A total of 25 PFAS were measured, including 14 perfluorosulfonic acids (PFBS, PFPeS, n-PFHxS, br-PFHxS, 1m-PFOS, $\Sigma 3 + 4 + 5\text{m}$ -PFOS, n-PFOS, 6m-PFOS, Σm_2 -PFOS, PFDS, PFHpS, PFNS, total PFOS, total PFHxS) and 11 perfluorocarboxylic acids (PFHpA, PFHxA, PFBA, PFPeA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTTrDA, PFTeDA). Detailed

information on reference standards and reagents, liquid chromatography–mass spectrometry conditions, PFAS nomenclature, internal standards, and mass spectrometric parameters is provided in the Supplementary File 3 (Tables S1–S3).

2.2.3 Quality assurance/quality control

PFAS were quantified using the internal standard method. To minimize background contamination and endogenous interference, all experimental containers were soaked in methanol for at least 4 hours before use. A nine-point calibration curve covering concentrations from 0.05 to 100 ng/mL was established, and the coefficient of determination (R^2) exceeded 0.99 for all analytes. Method blanks (using calf serum) were extracted with every batch of 22 samples to monitor potential exogenous contamination. Two types of blank analyses were performed. A solvent blank (70% methanol/30% water) was injected after every 12 samples to assess potential instrumental carryover. The first blank consisted of a method blank using commercial calf serum as the matrix to monitor potential contamination introduced during sample extraction. Each sample batch also included two quality control (QC) procedures to evaluate analyte loss during sample preparation, contamination, instrument response, and instrumental drift. The second QC consisted of a standard recovery solution prepared by spiking external standards to achieve a serum pre-treatment concentration of 5 ppb or a 5 ppb standard solution analyzed directly by the instrument without sample pre-treatment.

2.3 Statistical analyses

All statistical analyses were performed using R software (version 4.5.1). Serum concentrations of the 25 legacy PFASs were right-skewed and are therefore presented as geometric means (GMs) with 95% confidence intervals (95% CIs). Categorical variables are presented as frequencies and percentages. Concentrations below the limit of detection (LOD) were imputed as $LOD/\sqrt{2}$ before statistical analyses.

To evaluate temporal changes in PFAS exposure over the five-year follow-up period, paired-sample *t*-tests were performed using natural log-transformed serum PFAS concentrations to compare measurements obtained at baseline (2018–2019) and follow-up (2023–2024).

Longitudinal associations between participant characteristics and PFAS exposure were assessed using linear mixed-effects models (LMMs). Six legacy PFASs with detection frequencies approaching 100% (PFNA, PFDA, PFOA, PFHpA, total PFOS, and total PFHxS) were selected for subsequent analyses. Natural log-transformed serum PFAS concentrations were specified as the dependent variables. Sampling time (baseline and follow-up) was included as the repeated-measures factor, and participant identification number was specified as a random intercept to account for within-subject correlations. Fixed effects included age (< 30, 30–39, 40–49, 50–59, and ≥ 60 years), sex (male or female), residential region (Community A, Community B, and Community C), marital status (single, currently married, divorced, widowed), educational attainment (junior high school or below, senior high school/technical secondary school, and college degree or above), annual household income (≤ 30,000 CNY, 30,001–100,000 CNY, and > 100,000 CNY), body mass index (BMI; underweight, < 18.5 kg/m²; normal weight,

18.5–23.9 kg/m²; overweight, 24.0–27.9 kg/m²; and obese, $\geq$ 28.0 kg/m²), residential distance from a major road (< 50 m, 50–100 m, 101–200 m, 201–300 m, $\geq$ 300 m, and unknown), smoking status (never, current smoker, or former smoker), passive smoking status (never, current exposed, or former exposed), alcohol consumption (never, former, or current drinker), physical activity frequency ($\leq$ 3 days/month or never, 1–4 days/week, and 5–7 days/week), occupation (service worker, industrial worker, farmer, Government employee/professional/technical worker, unemployed, and other), occupational physical workload (light, moderate, and heavy), daily cooking (yes or no), hypertension (yes or no), and diabetes (yes or no). To account for multiple comparisons, *P* values were adjusted using the false discovery rate (FDR) method. A two-sided *P* < 0.05 was considered statistically significant.

3 Results

3.1 Characteristics of the study population

A total of 958 participants who completed both the baseline (2018–2019) and follow-up (2023–2024) surveys were included in the longitudinal analysis. The proportion of older adults ($\geq$ 60 years) increased from 30.48% at baseline to 42.07% at follow-up, representing the largest age group, and females accounted for the majority of the study population (approximately 62.80%). Educational attainment and annual household income both increased over the study period. The proportion of participants with a college degree or above increased from 26.30% to 29.65%, whereas the proportion with a junior high school education or below decreased from 44.15% to 41.65%. The proportion of participants with an annual household income $\geq$ 100,000 CNY increased from 54.59% to 61.9%. Based on BMI categories, the proportions of overweight and obese participants increased, with the prevalence of obesity rising from 8.77% to 11.80%, whereas the proportion of underweight participants decreased from 9.60% to 5.64%. Regarding lifestyle factors, the proportion of never smokers increased from 83.92% to 86.01%, while the proportion of participants exposed to passive smoking decreased from 29.02% to 22.76%. The proportion of participants reporting a high frequency of exercise (5–7 days/week) increased from 57.41% to 61.06%, and the proportion of participants who cooked daily increased from 65.03% to 73.17%. In terms of health status, the prevalence of both hypertension and diabetes increased during follow-up, with hypertension rising from 16.49% to 22.86% and diabetes from 6.05% to 8.04%. Overall, the study population exhibited demographic and lifestyle transitions over the five-year period, which were considered in subsequent analyses of temporal changes and determinants of serum PFAS concentrations. Detailed participant characteristics are presented in Table 1.

Table 1
Characteristics of the study population at baseline (2018–2019) and follow-up (2023–2024)

Characteristics	Baseline (2018–2019)	Follow-up (2023–2024)
	N (%)	N (%)
Age		
< 30 years	135 (14.09)	108 (11.27)
30–40 years	144 (15.03)	106 (11.06)
40–50 years	142 (14.82)	149 (15.55)
50–60 years	245 (25.57)	192 (20.04)
≥ 60 years	292 (30.48)	403 (42.07)
Residential region		
Community C	349 (36.43)	349 (36.43)
Community B	289 (30.17)	289 (30.17)
Community A	320 (33.40)	320 (33.40)
Sex		
Male	356 (37.16)	357 (37.27)
Female	602 (62.84)	601 (62.73)
Marital status		
Single	142 (14.82)	132 (13.78)
Currently married	751 (78.39)	738 (77.04)
Divorced	23 (2.40)	31 (3.24)
Widowed	42 (4.38)	57 (5.95)
Educational attainment		
Junior high school or below	423 (44.15)	399 (41.65)
Senior high school/technical secondary school	283 (29.54)	275 (28.71)
College or above	252 (26.30)	284 (29.65)
Annual household income (CNY)		
< 30,000	59 (6.16)	38 (3.97)
Note: Data are presented as n (%). BMI, body mass index; CNY, Chinese yuan. Baseline and follow-up represent measurements obtained during the 2018–2019 and 2023–2024 surveys, respectively.		

Characteristics	Baseline (2018–2019)	Follow-up (2023–2024)
	N (%)	N (%)
30,000–100,000	376 (39.25)	327 (34.13)
≥ 100,000	523 (54.59)	593 (61.90)
Occupation		
Worker	50 (5.22)	164 (17.12)
Farmer	21 (2.19)	31 (3.24)
Government employee/professional/technical worker	161 (16.81)	169 (17.64)
Service	92 (9.60)	127 (13.26)
Unemployed	503 (52.51)	381 (39.77)
Other	131 (13.67)	86 (8.98)
BMI (kg/m ²)		
Underweight (< 18.5)	92 (9.60)	54 (5.64)
Normal weight (18.5–23.99)	496 (51.77)	503 (52.51)
Overweight (24.0–27.99)	286 (29.85)	288 (30.06)
Obese (≥ 28.0)	84 (8.77)	113 (11.80)
Alcohol consumption		
Never	822 (85.80)	805 (84.03)
Current drinker	124 (12.94)	133 (13.88)
Former drinker	12 (1.25)	20 (2.09)
Smoking status		
Never	804 (83.92)	824 (86.01)
Current smoker	128 (13.36)	114 (11.90)
Former smoker	26 (2.71)	20 (2.09)
Passive smoking status		
Never	583 (60.86)	654 (68.27)
Note: Data are presented as n (%). BMI, body mass index; CNY, Chinese yuan. Baseline and follow-up represent measurements obtained during the 2018–2019 and 2023–2024 surveys, respectively.		

Characteristics	Baseline (2018–2019)	Follow-up (2023–2024)
	N (%)	N (%)
Formerly exposed	97 (10.13)	86 (8.98)
Currently exposed	278 (29.02)	218 (22.76)
Physical activity frequency		
5–7 days/week	550 (57.41)	585 (61.06)
1–4 days/week	272 (28.39)	264 (27.56)
≤ 3 days/month or never	136 (14.20)	109 (11.38)
Daily cooking		
Yes	623 (65.03)	701 (73.17)
No	335 (34.97)	257 (26.83)
Occupational physical workload		
Light	865 (90.29)	854 (89.14)
Moderate	74 (7.72)	97 (10.13)
Heavy	19 (1.98)	7 (0.73)
Residential distance from a major road (m)		
< 50	136 (14.20)	182 (19.00)
50–100	169 (17.64)	167 (17.43)
101–200	145 (15.14)	124 (12.94)
201–300	155 (16.18)	95 (9.92)
≥ 300	315 (32.88)	342 (35.70)
Unknown	38 (3.97)	48 (5.01)
Hypertension		
Yes	158 (16.49)	219 (22.86)
No	800 (83.51)	739 (77.14)
Diabetes		
Yes	58 (6.05)	77 (8.04)
Note: Data are presented as n (%). BMI, body mass index; CNY, Chinese yuan. Baseline and follow-up represent measurements obtained during the 2018–2019 and 2023–2024 surveys, respectively.		

Characteristics	Baseline (2018–2019)	Follow-up (2023–2024)
	N (%)	N (%)
No	900 (93.95)	881 (91.96)

Note: Data are presented as n (%). BMI, body mass index; CNY, Chinese yuan. Baseline and follow-up represent measurements obtained during the 2018–2019 and 2023–2024 surveys, respectively.

3.2 Temporal changes in serum legacy PFAS exposure profiles

Serum concentrations of legacy PFAS were right-skewed and were therefore summarized as geometric means (*GMs*) with 95% confidence intervals (*CI*s). Table 2 presents the geometric means with 95% confidence intervals of serum legacy PFAS concentrations at baseline and follow-up. At baseline, total PFOS had the highest serum concentration, with a geometric mean of 14.129 ng/mL (95% *CI*: 13.350, 14.952), followed by PFOA, with a geometric mean of 5.534 ng/mL (95% *CI*: 5.242, 5.842). At follow-up, serum concentrations of most legacy PFAS exhibited significant declines. Total PFOS decreased to 11.262 ng/mL, PFNA declined from 0.998 ng/mL to 0.871 ng/mL, PFDA declined from 0.692 ng/mL to 0.532 ng/mL, and total PFHxS decreased from 0.771 ng/mL to 0.598 ng/mL. In contrast, several legacy PFAS increased over the study period, most notably PFOA, which increased substantially to 9.789 ng/mL, whereas PFHpA increased from 0.024 ng/mL to 0.034 ng/mL. These divergent temporal patterns indicate heterogeneous changes in legacy PFAS exposure profiles within the study population over the five-year period. Most legacy PFAS compounds showed detection frequencies above 70%. Six compounds, including PFOA, PFNA, PFDA, PFHpA, total PFHxS, and total PFOS, exhibited detection frequencies close to 100% at both time points and were selected for subsequent longitudinal analyses.

Table 2. Serum concentrations of legacy PFAS and their temporal trends

PFAS	Baseline (n=958)		Follow-up (n=958)		Trend	P value
	Quantifiable	GM (95%CI)	Quantifiable	GM (95%CI)		
	percent (%)		percent (%)			
PFNA	100.0	0.998 (0.955, 1.044)	100.0	0.871 (0.830, 0.915)	↓	<0.001
PFDA	100.0	0.692 (0.655, 0.731)	96.3	0.532 (0.488, 0.580)	↓	<0.001
PFUnDA	99.9	0.621 (0.590, 0.653)	99.9	0.566 (0.536, 0.597)	↓	0.012
PFTeDA	78.1	0.014 (0.013, 0.015)	80.4	0.012 (0.012, 0.013)	↓	0.074
PFHpS	99.9	0.269 (0.251, 0.289)	99.2	0.208 (0.195, 0.223)	↓	<0.001
br-PFHxS	94.9	0.014 (0.013, 0.015)	83.3	0.012 (0.010, 0.013)	↓	0.016
n-PFHxS	100.0	0.744 (0.698, 0.794)	99.7	0.560 (0.527, 0.594)	↓	<0.001
Total PFHxS	100.0	0.771 (0.724, 0.821)	100	0.598 (0.565, 0.633)	↓	<0.001
1m-PFOS	100.0	0.387 (0.360, 0.416)	99.4	0.307 (0.284, 0.332)	↓	<0.001
Σm ₂ -PFOS	100.0	0.034 (0.031, 0.037)	87.5	0.018 (0.016, 0.020)	↓	<0.001
Σ3+4+5m-PFOS	92.2	2.102 (1.949, 2.267)	99.8	1.452 (1.356, 1.555)	↓	<0.001
6m-PFOS	100.0	0.720 (0.674, 0.770)	99.8	0.582 (0.545, 0.621)	↓	<0.001
br-PFOS	100.0	3.362 (3.134, 3.606)	100.0	2.437 (2.281, 2.604)	↓	<0.001
n-PFOS	100.0	9.880 (9.334, 10.458)	100.0	8.495 (7.983, 9.040)	↓	<0.001
Total PFOS	100.0	14.129 (13.350, 14.952)	100.0	11.262 (10.608, 11.958)	↓	<0.001
PFPeS	53.7	0.005 (0.005, 0.006)	20.5	0.004 (0.004, 0.005)	↓	<0.001
PFDS	27.8	0.005 (0.005, 0.005)	26.7	0.004 (0.004, 0.004)	↓	<0.001

PFAS	Baseline (n=958)		Follow-up (n=958)		Trend	P value
	Quantifiable	GM (95%CI)	Quantifiable	GM (95%CI)		
	percent (%)		percent (%)			
PFOA	100.0	5.534 (5.242, 5.842)	100.0	9.789 (9.082, 10.551)	↑	<0.001
PFDoDA	95.0	0.055 (0.052, 0.059)	96.9	0.066 (0.062, 0.071)	↑	<0.001
PFTTrDA	98.7	0.235 (0.222, 0.249)	98.8	0.258 (0.242, 0.274)	↑	0.030
PFHpA	94.3	0.024 (0.022, 0.026)	96.9	0.034 (0.032, 0.037)	↑	<0.001
PFBS	59.6	0.014 (0.013, 0.015)	65.4	0.021 (0.019, 0.022)	↑	<0.001
PFBA	28.1	0.038 (0.032, 0.044)	37.8	0.073 (0.059, 0.090)	↑	<0.001
PFPeA	6.0	0.016 (0.015, 0.017)	50.9	0.019 (0.018, 0.020)	↑	0.001
PFNS	31.8	0.007 (0.006, 0.007)	29.8	0.007 (0.007, 0.008)	→	0.494

Note: PFAS concentrations are presented as geometric means (GM) with 95% confidence intervals (CIs). Quantifiable percent refers to the percentage of samples with concentrations above the method quantification limit. Trend indicates the direction of change in serum PFAS concentrations from baseline to follow-up (↓, decrease; ↑, increase; →, no significant change). P values were adjusted for multiple comparisons using the false discovery rate (FDR) method. Statistical significance was defined as a P value < 0.05.

3.3 Population-specific patterns of temporal changes in serum legacy PFAS exposure

Table S4 and Table S5 present the GM with 95% confidence intervals for the six legacy PFAS stratified by population characteristics. Across nearly all population subgroups, PFOA concentrations increased significantly, PFHpA showed a slight increase, whereas total PFOS, total PFHxS, PFNA, and PFDA generally declined over the follow-up period. However, the magnitude of these changes varied according to participant characteristics. Internal exposure to legacy PFAS increased with age. At baseline, the GM concentration of total PFOS in participants aged ≥ 60 years was 18.850 ng/mL, approximately 2.3-fold higher than that in participants aged < 30 years (8.110 ng/mL). Similar age-related patterns were observed for PFNA (1.270 vs. 0.660 ng/mL) and PFDA (0.930 vs. 0.320 ng/mL). Females generally had lower serum PFAS concentrations than males. At baseline, the GM concentration of total PFOS was

15.250 ng/mL in males and 13.500 ng/mL in females. The decline in total PFOS concentrations during follow-up was comparable between males and females (approximately 3.000 ng/mL), whereas the reduction in total PFHxS was more pronounced among males (from 1.060 ng/mL to 0.640 ng/mL) than among females (from 0.640 ng/mL to 0.560 ng/mL). Geographic variation was also evident. At baseline, total PFOS exhibited the highest concentrations across all three communities (Community A: 15.400 ng/mL; Community B: 13.670 ng/mL; Community C: 13.420 ng/mL). During follow-up, PFOA concentrations increased markedly and, in some areas, exceeded those of total PFOS (Community B: 26.050 ng/mL). In addition, participants with an annual household income below 30,000 CNY showed a marked increase in PFAS exposure. Overweight and obese participants generally exhibited higher internal PFAS concentrations than those with normal body weight. Notably, former smokers (baseline: 6.550 ng/mL; follow-up: 19.320 ng/mL) and former drinkers (baseline: 5.060 ng/mL; follow-up: 18.730 ng/mL) experienced substantial increases in PFOA concentrations over the follow-up period. At baseline, participants with hypertension had higher PFOA (7.370 ng/mL) and total PFOS (18.990 ng/mL) concentrations than those without hypertension. These findings highlight that demographic, socioeconomic, and residential characteristics may contribute to heterogeneous patterns of serum PFAS exposure over time.

3.4 Longitudinal determinants of serum legacy PFAS exposure

Table 3 summarizes the longitudinal associations between participant characteristics and serum legacy PFAS concentrations. Only associations that remained significant after false discovery rate (FDR) correction ($P < 0.05$) are presented in the main text, whereas complete association results, including non-significant associations ($P \geq 0.05$), are provided in Tables S6–S11. Age, sex, and residential region were identified as the major determinants of serum legacy PFAS concentrations.

Age was positively associated with all six legacy PFAS examined. For each one-year increase in age, serum concentrations increased by 17.35% for total PFOS (95% CI: 10.52%, 24.74%), followed by PFOA (10.74%, 95% CI: 5.55%, 16.08%), PFDA (8.44%, 95% CI: 5.66%, 11.31%), total PFHxS (7.25%, 95% CI: 4.39%, 10.19%), PFNA (6.93%, 95% CI: 4.29%, 9.64%), and PFHpA (0.80%, 95% CI: 0.30%, 1.21%). Sex differences were also observed. Compared with males, females had significantly lower serum concentrations of PFNA (6.26% lower; 95% CI: -9.89%, -2.46%), PFOA (13.84% lower; 95% CI: -20.07%, -7.11%), total PFHxS (15.06% lower; 95% CI: -18.63%, -11.33%), and total PFOS (17.07% lower; 95% CI: -24.72%, -8.69%). Significant spatial variations were identified across the three communities. Compared with Community C, residents of Community B showed significantly higher concentrations of PFHpA (3.25% increase; 95% CI: 2.43%, 3.98%) and markedly elevated PFOA concentrations (289.23% increase; 95% CI: 261.90%, 318.70%). Residents of Community A also exhibited higher concentrations of PFOA (82.58% increase; 95% CI: 70.24%, 95.78%), total PFHxS (24.32% increase; 95% CI: 19.48%, 29.44%), total PFOS (22.88% increase; 95% CI: 12.31%, 34.43%), and PFNA (5.97% increase; 95% CI: 2.12%, 9.97%) compared with Community C. Regarding lifestyle factors, current alcohol consumption was associated with higher serum PFDA concentrations, with an 8.44% increase (95% CI: 2.84%, 14.34%).

compared with never drinkers. Overall, these findings were generally consistent with the temporal and spatial distribution patterns observed in the descriptive analyses.

Table 3

Associations between participant characteristics and serum legacy PFAS concentrations in the longitudinal cohort (Only associations with P value < 0.05 are presented)

Variable	PFAS	β (95% CI)	Percent change (%)	P value
Age (per year increase)	PFDA	0.082 (0.056, 0.108)	8.57 (5.78, 11.44)	< 0.001
	PFHpA	0.008 (0.003, 0.013)	0.80 (0.30, 1.31)	0.012
	PFNA	0.069 (0.044, 0.094)	7.14 (4.49, 9.86)	< 0.001
	PFOA	0.101 (0.054, 0.147)	10.63 (5.55, 15.84)	< 0.001
	Total PFHxS	0.070 (0.043, 0.097)	7.25 (4.39, 10.21)	< 0.001
	Total PFOS	0.165 (0.105, 0.225)	17.94 (11.08, 25.24)	< 0.001
Sex (Female vs Male)	PFNA	-0.067 (- 0.106, - 0.028)	-6.48 (- 10.05, - 2.76)	0.01
	PFOA	-0.148 (- 0.221, - 0.075)	-13.74 (- 19.81, - 7.22)	0.001
	Total PFHxS	-0.163 (- 0.205, - 0.121)	-15.03 (- 18.55, - 11.40)	< 0.001
	Total PFOS	-0.179 (- 0.273, - 0.086)	-16.39 (- 23.88, - 8.24)	0.002
Alcohol consumption (Current drinker vs Never)	PFDA	0.081 (0.029, 0.132)	8.39 (2.97, 14.09)	0.025
	PFNA	0.072 (0.023, 0.121)	7.47 (2.33, 12.86)	0.046
Residential region (Community B vs Community C)	PFDA	-0.060 (- 0.099, - 0.020)	-5.81 (- 9.43, - 1.96)	0.038
	PFHpA	0.032 (0.025, 0.039)	3.25 (2.53, 3.98)	< 0.001

Notes: β coefficients and 95% confidence intervals (CIs) were estimated using linear mixed-effects models with log-transformed PFAS concentrations as the dependent variables. Percent changes were calculated as $(\exp(\beta) - 1) \times 100\%$. Models were adjusted for age, sex, residential region, marital status, educational attainment, annual household income, body mass index (BMI), residential distance from a major road, smoking status, passive smoking status, alcohol consumption, physical activity frequency, occupation, occupational physical workload, daily cooking, hypertension, and diabetes. Only associations with false discovery rate (FDR)-adjusted P values < 0.05 are shown; complete results are provided in Table S6. Reference groups were: male for sex, never drinker for alcohol consumption, never smoker for smoking, never exposed for passive smoking, and Community C for geographic region.

Variable	PFAS	β (95% CI)	Percent change (%)	<i>P</i> value
	PFOA	1.358 (1.287, 1.430)	288.9 (261.5, 317.6)	< 0.001
Residential region (Community A vs Community C)	PFOA	0.601 (0.532, 0.670)	82.4 (69.9, 101.4)	< 0.001
	Total PFHxS	0.213 (0.174, 0.253)	23.7 (19.0, 28.8)	< 0.001
	Total PFOS	0.203 (0.115, 0.291)	22.5 (12.2, 33.8)	< 0.001
Notes: β coefficients and 95% confidence intervals (CIs) were estimated using linear mixed-effects models with log-transformed PFAS concentrations as the dependent variables. Percent changes were calculated as $(\exp(\beta) - 1) \times 100\%$. Models were adjusted for age, sex, residential region, marital status, educational attainment, annual household income, body mass index (BMI), residential distance from a major road, smoking status, passive smoking status, alcohol consumption, physical activity frequency, occupation, occupational physical workload, daily cooking, hypertension, and diabetes. Only associations with false discovery rate (FDR)-adjusted <i>P</i> values < 0.05 are shown; complete results are provided in Table S6. Reference groups were: male for sex, never drinker for alcohol consumption, never smoker for smoking, never exposed for passive smoking, and Community C for geographic region.				

4 Discussion

4.1 Overview of major findings

To date, prospective studies of PFAS exposure have primarily focused on occupationally exposed populations or residents of highly contaminated areas(21), whereas prospective cohort studies involving general community populations remain limited. In this prospective cohort study, we characterized five-year changes and determinants of serum legacy PFAS exposure among 958 community residents from three environmentally and socioeconomically distinct communities in Guangzhou, southern China. By using repeated biomonitoring measurements collected between 2018–2019 and 2023–2024, this study provides evidence of individual-level transitions in PFAS exposure profiles over time. We observed significant declines in serum concentrations of total PFOS, PFNA, PFDA, and total PFHxS from baseline to follow-up. At the same time, concentrations of PFOA and PFHpA increased over the same period. Furthermore, we evaluated the influence of demographic characteristics, lifestyle factors, and health status on serum PFAS concentrations and identified age, sex, and geographic region as the principal determinants of PFAS exposure.

The highest median serum concentrations were observed for total PFOS and its isomers, PFOA, total PFHxS and its isomers, and PFNA. This exposure profile is broadly consistent with findings reported in other regions of China. For example, a 2021 study of community residents in the Songjiang District of Shanghai identified PFOS and PFOA as the predominant PFAS, with median serum concentrations of 48.61 ng/mL and 37.29 ng/mL, respectively(22), both substantially higher than those observed in the

present study. Compared with international studies, serum PFOA concentrations in our cohort exceeded those reported for the general U.S. population in NHANES 2017–2018 (GM approximately 1.5 ng/mL) (23) but remained lower than those reported among highly exposed populations in the Veneto region of Italy (median PFOA concentration of 49 ng/mL during 2017–2022)(24).

4.2 Declining trends of legacy PFAS and implications of regulatory controls

The follow-up survey demonstrated significant declines in the concentrations of most legacy PFAS, with total PFOS decreasing from 14.129 ng/mL to 11.262 ng/mL, PFNA from 0.998 ng/mL to 0.871 ng/mL, and total PFHxS from 0.771 ng/mL to 0.598 ng/mL. These decreasing trends coincide temporally with the strengthened PFAS regulatory measures implemented in China in recent years. Specifically, since March 26, 2019, China has comprehensively prohibited the production, use, import, and export of PFOS and related substances, except for specific exempted uses(9). While these observational data cannot establish a definitive causal link, the decline observed in our follow-up survey is consistent with the intended population-level effects of such source-control interventions. In December 2022, regulatory controls on PFOS and PFOA were further strengthened. Effective March 1, 2023, the construction of new PFOA production facilities was prohibited, and the processing and use of PFOS, PFOA, and their salts were subject to strict restrictions. Effective January 1, 2024, the import and export of PFOS, and related substances were completely prohibited(25). PFOS and PFHxS exhibit high chemical stability and bioaccumulative potential, with estimated elimination half-lives in humans of 3.4–5.7 years and 2.84–8.5 years, respectively(26). Therefore, the observed declines in serum PFOS and PFHxS concentrations provide epidemiological evidence suggesting that regulatory interventions and source-control measures may contribute to reducing population exposure to certain legacy PFAS.

4.3 Increasing trends of PFOA and other short-chain PFCAs: potential explanations and concerns

In contrast to the declining trends observed for most legacy PFAS, serum PFOA concentrations increased markedly from 5.534 ng/mL to 9.789 ng/mL during the follow-up period, highlighting a pattern that warrants particular attention. This unexpected increase suggests that PFAS exposure patterns may be undergoing transition rather than uniformly declining following regulatory restrictions. One possible explanation is the continued environmental degradation of PFOA precursor compounds, such as fluorotelomer alcohols (FTOHs), which generate PFOA and thereby constitute a secondary source of environmental contamination(27). In addition, PFOA has a relatively long residence time in humans. A systematic review and meta-analysis estimated the elimination half-life of PFOA to range from 1.48 to 5.1 years(26), whereas a study of PFAS-contaminated drinking water in western Tokyo, Japan, reported a PFOA half-life of 8.0 years (95% CI: 6.0, 10.0)(28). Considering the five-year interval between surveys, incomplete elimination and continued exposure may partly explain the observed increase. PFHpA (0.024 ng/mL to 0.034 ng/mL) also exhibited slight increases, which may be related to precursor transformation processes, changes in emission profiles, or shifts in PFAS usage patterns following

restrictions on legacy PFAS(29–31). Although short-chain PFAS generally exhibit lower bioaccumulative potential than long-chain compounds, their environmental mobility and persistence raise concerns regarding long-term exposure. Together, the increasing trends of PFOA and PFHpA highlight the complexity of PFAS exposure transitions. Regulatory actions targeting specific legacy compounds may alter the composition of population exposure profiles rather than result in uniform reductions across all PFAS. Future surveillance should therefore incorporate both regulated legacy PFAS and emerging replacement compounds to better characterize evolving exposure patterns.

4.4 Determinants of PFAS exposure: demographic, geographic, and lifestyle factors

Understanding population characteristics associated with PFAS exposure variability is essential for identifying high-exposure groups and informing targeted biomonitoring strategies. In the present study, age, sex, and residential region were identified as the major determinants of serum legacy PFAS concentrations in longitudinal analyses, whereas lifestyle factors showed relatively limited associations.

Overall, irrespective of whether serum concentrations declined or increased over the follow-up period, all six legacy PFAS were positively associated with age. This finding is consistent with that of Chen et al. (32), who observed positive associations between age and serum PFAS concentrations among populations in industrialized regions of China. Most legacy PFAS have long biological half-lives(26), and cumulative exposure over the lifespan, together with age-related declines in elimination capacity, may contribute to increased PFAS body burdens. Sex-related differences were also evident, with females generally exhibiting lower PFAS concentrations than males, consistent with previous studies conducted in China(33). This sex-specific pattern may partly be attributable to the elimination of certain PFAS through menstrual blood loss, as reported by Pirard et al.(24). In addition, pregnancy and breastfeeding represent important physiological pathways through which women can reduce their PFAS body burden(34). Berg et al.(35) further reported that higher parity was associated with lower serum PFAS concentrations.

The observed geographic variation was consistent with previous reports. Previous research has reported a spatial gradient of PFAS exposure in Guangzhou, characterized by relatively higher concentrations in southern areas and lower concentrations in northern areas(36). Community B, located in the southern suburbs, represents an important industrial area with a high density of electroplating, textile, and electronics manufacturing enterprises. Heydebreck et al. (2016) reported that textile manufacturing processes in China were associated with substantial PFAS emissions, with PFOA identified as one of the predominant compounds(37). Following the progressive phase-out of PFOA and PFOS production and use, PFHpA has been increasingly detected as an alternative compound, which may contribute to changes in PFHpA exposure levels. Community A, located in the northern urban center, represents the old commercial district of Guangzhou and is characterized by a highly developed commercial and service sector and relatively intensive household consumption. Residents predominantly live in high-rise residential buildings, where exposure to PFAS-containing consumer products, including non-stick

cookware, waterproof clothing, and food packaging materials, may represent potential exposure sources(38). Previous studies have identified indoor household dust as a potential source of PFAS exposure(39), and recent studies have suggested that building characteristics and renovation history may influence PFAS concentrations in indoor dust(40). In contrast, Community C is an ecological conservation area and drinking water source protection zone characterized by limited industrial activity and low population density. Therefore, serum PFAS concentrations in residents from this area may be lower than those in central urban districts, consistent with previous studies showing that PFAS exposure varies according to residential environments, industrial activities, and environmental sources(41). Notably, PFDA exhibited a geographic distribution pattern distinct from other PFAS. This finding may reflect differences in local emission sources, environmental transport pathways, or precursor transformation processes, which have been reported to influence the spatial variability of long-chain PFCAs(29). Community A and Community B are both located along the main stream of the Pearl River, with Community B situated downstream within the Guangzhou section. Previous investigations of the Guangzhou section of the Pearl River have shown that PFAS concentrations are generally higher in the main stream than in tributaries, with PFOA identified as the predominant compound during both dry and wet seasons(42). Contaminated drinking water represents one of the important pathways of PFAS exposure among the general population. At the same time, regional differences in wastewater treatment capacity and discharge standards may further contribute to spatial heterogeneity in PFAS contamination.

Alcohol consumption was associated with higher serum PFAS concentrations in the present study. Although the underlying mechanisms remain unclear, previous studies have suggested that lifestyle-related factors may influence PFAS exposure patterns through differences in dietary behaviors, metabolic status, and elimination processes. However, given the observational nature of this study, these findings should be interpreted with caution, and further investigations incorporating detailed dietary information, metabolic biomarkers, and toxicokinetic assessments are needed to clarify the potential pathways linking alcohol consumption to PFAS body burdens. Several lifestyle changes were observed during the follow-up period, including an increase in the proportion of never smokers (from 83.92% to 86.01%), a decrease in passive smoking exposure (from 29.02% to 22.76%), an increase in participants reporting high-frequency exercise (from 57.41% to 61.06%), and an increase in residents who reported daily cooking (from 65.03% to 73.17%). These behavioral changes may have contributed to changes in exposure patterns; however, their direct effects on PFAS concentrations could not be determined in the present study. In particular, the increased frequency of home cooking may reflect changes in dietary habits and reduced reliance on restaurant meals or packaged foods, which could potentially alter exposure to PFAS-containing food-contact materials. Nevertheless, detailed dietary assessments and source-specific exposure measurements are required to confirm this hypothesis. In contrast, several environmental and lifestyle variables, including residential distance from major roads, were not significantly associated with serum PFAS concentrations. This observation suggests that traffic-related exposure may play a limited role in PFAS exposure in this population, consistent with previous evidence indicating that dietary intake and drinking water are generally considered major exposure pathways for PFAS in humans. Overall, our findings indicate that PFAS exposure is influenced by multiple interacting

factors. Identifying these determinants may help prioritize populations and communities for continued PFAS monitoring and targeted exposure reduction interventions.

4.5 Public health implications

This study provides longitudinal evidence of heterogeneous changes in serum legacy PFAS concentrations among community residents in Guangzhou. The declines observed for total PFOS, PFNA, PFDA, and total PFHxS, together with the continued increases in PFOA and PFHpA, indicate that population exposure did not change uniformly across PFAS over the five-year follow-up period. These findings support the value of repeated population-based biomonitoring for evaluating temporal changes in PFAS exposure and identifying compounds that may warrant continued surveillance.

The observed differences across residential communities also have implications for environmental health surveillance. Guangzhou is a highly urbanized and industrialized city with diverse residential environments and complex potential PFAS exposure sources. Residents of the urban commercial and industrial/livestock/fishery communities had higher concentrations of several PFAS than those of the ecological conservation community, while older age was positively associated with concentrations of all six PFAS examined. These findings suggest that demographic and residential characteristics can help identify population groups with relatively higher exposure burdens. However, because the present study did not include detailed source-specific exposure measurements, the observed spatial differences should not be interpreted as evidence of specific environmental sources.

An important implication of these findings is the need for broader and repeated population-based PFAS surveillance. Future monitoring should consider both historically regulated PFAS and compounds showing increasing or persistent concentrations, together with emerging alternatives and precursor substances where feasible. Integrating serum biomonitoring with environmental measurements and information on potential exposure pathways would help clarify the sources underlying temporal and spatial differences in population exposure.

Overall, the findings support a surveillance framework that emphasizes repeated measurement, compound-specific temporal assessment, and identification of populations with relatively higher exposure burdens. Further longitudinal studies integrating repeated PFAS measurements with detailed exposure-source information and health outcomes are needed to determine whether the observed changes in exposure are accompanied by corresponding changes in population health.

4.6 Limitations

Several limitations of this study should be acknowledged. First, linear and branched isomers of legacy PFAS were not included in the linear mixed-effects analyses. Future studies should evaluate the potential influence of individual isomers on exposure estimates. Second, this study relied on serum measurements collected at two discrete time points spanning a 5-year interval. Although this dual-timepoint design cannot resolve individual-level non-linear trajectories, it aligns with established biomonitoring methodological frameworks such as NHANES and is intended to capture the net

population-level change in exposure resulting from regulatory measures. Third, females constituted a higher proportion of the study cohort (62.94%), yet this sex imbalance does not diminish the value of the male subgroup for characterizing legacy PFAS exposure. Males lack physiological excretion pathways such as menstruation, and their serum PFAS concentrations more accurately reflect the upper bound of cumulative environmental exposure. The geometric mean concentrations of baseline PFOA and total PFOS among males in this study both exceeded those reported for adult males in the U.S. NHANES 2017–2018 data, a phenomenon that provides an important basis for assessing the environmental burden of PFAS contamination and identifying populations at elevated exposure risk. Finally, this study focused on characterizing legacy PFAS exposure and did not evaluate associations between PFAS exposure and health outcomes, including liver, renal, or immune function. Future studies should further investigate the health effects associated with PFAS exposure.

5 Conclusions

In this community-based cohort in Guangzhou, serum concentrations of several legacy PFAS, including total PFOS, PFNA, PFDA, and total PFHxS, declined over five years, whereas PFOA and PFHpA increased. Age, sex, and residential region were associated with serum PFAS concentrations, indicating persistent heterogeneity in population exposure. The divergent temporal patterns across PFAS highlight the need for continued population-based biomonitoring that considers both legacy compounds and emerging PFAS and their precursors.

Abbreviations

PFAS

Per- and polyfluoroalkyl substances

PFCAs

perfluorocarboxylic acids

PFSAs

perfluorosulfonic acids

PFOA

perfluorooctanoic acid

PFNA

perfluorononanoic acid

PFBA

Perfluorobutanoic acid

n-PFOS

Linear perfluorooctane sulfonic acid

br-PFOS

Sum of all branched perfluorooctane sulfonic acid isomers

total PFOS

Sum of linear and branched perfluorooctane sulfonic acid isomers

1m-PFOS

1m-Perfluorooctane sulfonic acid

6m-PFOS

Perfluoro-6-methylheptane sulfonic acid

 $\Sigma 3 + 4 + 5m$ -PFOS

Sum of perfluoro-3/4/5-methylheptane sulfonic acid isomers

 Σm_2 -PFOS

Sum of all dimethyl branched perfluorooctane sulfonic acid isomers

PFNS

Perfluorononane sulfonic acid

PFDS

Perfluorodecane sulfonic acid

PFBS

Perfluorobutane sulfonic acid

PFPeS

Perfluoropentane sulfonic acid

n-PFHxS

n-Perfluorohexane sulfonic acid

br-PFHxS

Branched perfluorohexane sulfonic acid

total-PFHxS

Sum of linear and branched perfluorohexane sulfonic acid isomers

PFPeA

Perfluoropentanoic acid

PFDA

Perfluorodecanoic acid

PFUnDA

Perfluoroundecanoic acid

PFDoDA

Perfluorododecanoic acid

PFTTrDA

Perfluorotridecanoic acid

PFTeDA

Perfluorotetradecanoic acid

PFHpS

Perfluoroheptane sulfonic acid

PFHpA

Perfluoroheptanoic acid

BMI

Body mass index

FDR

false discovery rate

LOD

limit of detection

LOQ

limit of quantification

LMMs

linear mixed-effects models

GMs

geometric means

95%CIs

95% confidence intervals

QC

quality control

Declarations

Ethical approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and relevant guidelines and regulations for research involving human participants. The study protocol was reviewed and approved by the Medical Ethics Committee of the Guangzhou Center for Disease Control and Prevention (Approval Nos. GZCDC-ECHR-2026P0038 and GZCDC-ECHR-2026P0039). Written informed consent was obtained from all participants or their legal representatives after they had been informed of the study procedures and potential risks.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

Heng Zhao and Yan Wu contributed equally to this study. Heng Zhao conducted the data curation, formal analysis, and visualization, and drafted and revised the manuscript. Yan Wu contributed to the data curation and formal analysis and revised the manuscript. Weiwei Zhang conceived and supervised the study, coordinated the project, and revised the manuscript. Zhoubin Zhang supervised the study, coordinated the project, and contributed to funding acquisition. Yuling Chen contributed to the investigation, resources, project administration, and supervision. Wenru Feng contributed to the investigation, resources, and project administration. Yijian Yang contributed to the investigation, project administration, and revision of the manuscript. Jie Shi, Chuangwei Weng, Wenjing Liang, and Yongcong Deng contributed to the investigation. Li Bu, Tianji Lin, and Sili Jiang contributed to the investigation and validation. Shujun Fan contributed to project administration, validation, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to ethical restrictions and protection of participant privacy. De-identified data may be available from the corresponding author upon reasonable request and subject to approval by the relevant institutional ethics committee.

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