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Determinants of Serum PFOA Concentrations Among Residents in the Industrially Contaminated Area 11 Years After PFOA Production Cessation in Osaka, Japan

Tamiki Oshima [1], Kunio Kanetani [2], Kouji H. Harada [3,4], Hideaki Akihisa [5], Hiromi Ogata [6], Kenji Nakamura [7], Yasunobu Shiota [8], Takeshi Sekiguchi [8] and Akio Koizumi [3,9,*]

1 Aikawa Clinics, Suita 564-0025, Japan; tamioshima@gmail.com
2 Ueni Seikyo Clinics, Chuoku, Osaka 540-0004, Japan; kukinkoku.516@gmail.com
3 Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine, Kyoto 606-8501, Japan; kharada-hes@umin.ac.jp
4 Graduate School of Life and Environmental Sciences, Kyoto Prefectural University, Kyoto 606-8522, Japan
5 Himejima Clinics, Nishiyodogawaku, Osaka 555-0033, Japan; hakihisa2004@s2.dion.ne.jp
6 Mimihara Takasago Clinics, Sakaiku, Sakai 590-0820, Japan; wankoinko@gmail.com
7 Department of Occupational Medicine, Nozato Clinics, Nishiyodogawaku, Osaka 555-0024, Japan; nakamura-kenji@yodokyo.or.jp
8 Faculty of Information Science, Tohoku Gakuin University, Sendai 980-8511, Japan; yasunobu.shiota@jcom.home.ne.jp (Y.S.); johmo@jcom.home.ne.jp (T.S.)
9 Public Health Institute, Public Interest Associations, Kyoto Hokenkai, Ukyoku, Kyoto 616-8141, Japan
* Correspondence: koizumi@kyoto-hokenkai.or.jp

Abstract

Background: In 2023, community-initiated biomonitoring was conducted among residents near the Daikin Industries Yodogawa Plant (DIYP), where PFOA contamination had previously been identified. **Methods:** Serum PFOA and questionnaire data were analyzed in 1174 participants; 1084 had complete data for 15 prespecified variables. Log_{10}(PFOA) was modeled using multivariable regression, with model selection by AIC and Bonferroni correction. A sensitivity analysis excluded six consumers of self-grown agricultural products. We also theoretically examined the relationship between serum concentration and time-weighted average exposure using a one-compartment model with a lognormal Ornstein–Uhlenbeck exposure process. **Results:** Residence, age, fish consumption, drinking habit, laxative use, and tap-water use were significant determinants. Residents nearest DIYP had a geometric mean PFOA concentration of 5.95 ng/mL and adjusted concentrations 18–21% higher than other areas. Predicted and observed stratum means were strongly correlated ($r = 0.927$). Results remained significant in sensitivity analysis. The theoretical analysis showed that the white-noise limit provides a global lower bound for the serum–exposure correlation; for averaging over three biological half-lives, $\rho \geq 0.858$. **Conclusions:** Elevated PFOA near DIYP suggests that local exposure may have persisted after production ceased in 2012. Continued biomonitoring is warranted.

Keywords: PFOA-producing plant; PFOA biomonitoring; Ornstein–Uhlenbeck process; lower-bound theorem; time-weighted average; residence area; drinking habit; laxatives; fish consumption; local vegetable consumption

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1. Introduction

Perfluorooctanoic acid (PFOA) is a representative member of the more than 10,000 per- and polyfluoroalkyl substances (PFAS) and, together with perfluorooctane sulfonate

(PFOS), is classified as a legacy PFAS. PFOA has been called a 'forever chemical' because of its exceptional chemical stability and useful properties, including heat resistance, water repellency, and amphiphilicity. It was manufactured worldwide beginning in the 1960s. By the 2000s, however, concerns had increased regarding environmental persistence and bioaccumulation, and production was discontinued in many countries during the 2010s. By then, environmental contamination had already occurred, and community contamination had been documented in the United States [1], European countries [2], China [3], and elsewhere.

In Japan, environmental contamination attributable to PFOA production at the Daikin Industries Yodogawa Plant (DIYP) was identified in the early 2000s in the Yodo and Ai River basins of Osaka Prefecture, with substantial contamination extending through the Yodo River system to Osaka Bay [4]. Subsequent investigations documented contamination of groundwater [5], soil, and locally grown agricultural products [6].

PFOA is now listed under the Stockholm Convention on Persistent Organic Pollutants and is regulated in Japan, where its manufacture, sale, and import are prohibited. The US Environmental Protection Agency (EPA) has cited epidemiological evidence concerning immunotoxicity, impaired fetal and neonatal growth, altered lipid metabolism, and kidney cancer. With particular emphasis on prevention of immune effects, while also addressing carcinogenicity and developmental effects, the EPA established a stringent drinking-water maximum contaminant level of 4 ng/L for PFOA [7]. In 2023, the International Agency for Research on Cancer (IARC) reclassified PFOA from Group 2B to Group 1, carcinogenic to humans [8]. In Japan, because epidemiological evidence for human health effects was considered insufficiently definitive, a tolerable daily intake of 20 ng/kg/day was established primarily on the basis of reduced fetal body-weight gain in animal studies [9].

The US National Academies have recommended a combined serum or plasma PFAS concentration of 20 ng/mL for seven PFAS, including PFOA and PFOS, as a level at which clinical follow-up should be considered [10]. Serum PFAS concentrations integrate exposure from multiple pathways, including drinking water, outdoor and indoor environments, and food, and have therefore been widely used for exposure assessment. Serum concentrations can vary not only with contamination of community drinking-water sources but also with demographic factors such as age, sex, and BMI and with behavioral or dietary factors such as consumption of local vegetables and fish, use of local fishery resources, and use of personal-care products [11–14].

One-compartment models have been applied for dosimetry to quantitatively relate adult serum concentrations to external exposure [15]. In contrast, physiologically based pharmacokinetic (PBPK) models have been developed to investigate more detailed toxicokinetic mechanisms, including target-organ concentrations [16]. Studies in contaminated drinking-water areas along the Ohio River [17] and in Veneto [12] showed that serum PFOA concentrations declined according to biological half-life after exposure reduction, supporting the utility of one-compartment models for dosimetric evaluation of remediation effects.

The first objective of this study was to characterize current serum PFOA concentrations among residents living around DIYP in Settsu City, Osaka Prefecture, where PFOA contamination has been documented. PFOA had been produced at DIYP since the 1970s, and production ceased in 2012. Although elevated exposure among nearby residents had been reported before production cessation [18–20], serum concentrations 11 years after cessation had not been characterized.

Serum concentration is widely used as an index of PFOA exposure, but the duration of time-weighted average (TWA) exposure represented by a serum measurement has not been established theoretically. Multiplying a TWA concentration by its averaging duration yields cumulative exposure over that period; therefore, the correlation between serum

concentration and TWA exposure is important for interpreting exposure intensity. The Koizumi–Sekiguchi theorem [21] addresses this correlation, but it was originally developed for occupational exposure over an 8 h workday. Our second objective was therefore to establish a more general toxicokinetic framework applicable to exposure scenarios extending over years. This framework provides a theoretical basis for interpreting serum concentrations in relation to the persistence of community contamination around DIYP after production ceased.

2. Subjects and Methods

2.1. Study Design and Participants

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine and Kyoto University Hospital (Approval No. R1478) and the Ethics Committee of the Yodogawa Workers' Welfare Association (Approval No. 2023-Rin-31). Written informed consent was obtained from all participants.

In 2023, a community-initiated serum PFAS biomonitoring campaign was conducted in northern Osaka Prefecture, including Settsu City and Higashiyodogawa Ward, where DIYP is located, in collaboration with Kyoto University and Osaka Min-iren, a social movement organization comprising public-interest entities that operate hospitals, 47 clinics, and medical, nursing, and long-term-care facilities in Osaka Prefecture [6].

The campaign was conducted from September through December 2023 and primarily targeted current residents of northern Osaka Prefecture and people working in the area. Because the campaign was broadly publicized through local mass media, a participation rate could not be calculated. Accordingly, the number of individuals who actually provided blood samples was used as the denominator for the analytical population. Blood collection was conducted at 39 sites, most of which were community clinics or hospitals. Current and former DIYP employees were excluded from the present analysis.

At blood collection, 12–15 mL of venous blood was obtained from the median cubital vein using vacuum blood collection tubes (Venoject VP-AS076K50; Terumo, Tokyo, Japan). To evaluate potential PFAS contamination from sample collection and analytical procedures, distilled water was processed as a procedural blank, and no target PFAS were detected. Participants were also asked to complete a self-administered questionnaire.

The questionnaire collected date of birth, height, weight, residential history, medical history (including thyroid disease, dyslipidemia, heart disease, liver disease, diabetes, hypertension, ulcerative colitis, allergy, testicular cancer, kidney cancer, and pregnancy-related disorders), laxative use, smoking history, drinking habits, tap-water use, use of well water for drinking, water-filter use, consumption of locally produced agricultural products, use of well water to grow consumed produce, seafood consumption, consumption of fish from Osaka Bay, shellfish consumption frequency, and history of aqueous film-forming foam (AFFF) use. Age was calculated from date of birth at the time of blood collection. Questionnaires were checked on site when received, and participants were asked to correct obvious errors or complete omitted items whenever possible.

2.2. Measurement of Serum PFOA Concentrations

Serum was separated from whole blood by centrifugation at 1500× g for 15 min at room temperature. The serum supernatant was transferred into polypropylene cryogenic tubes (Nalgene Cryogenic Tube, 1.8 mL, Cat. No. 5011-0020; Thermo Fisher Scientific, Waltham, MA, USA) prior to storage at −20 °C and analysis. Serum PFOA concentrations (ng/mL) were measured by gas chromatography–mass spectrometry (GC-MS) as previously described [22].

For GC-MS analysis, 0.10 mL of serum was mixed with 0.4 mL acetonitrile and 1 ng of surrogate standard mixture (EPA-533ES; Wellington Laboratories, Guelph, ON, Canada). Precipitated proteins were removed by centrifugation at approximately 12,900× g for 1 min. The supernatant was evaporated to dryness under a nitrogen stream.

Bis(4-tert-butylphenyl)iodonium hexafluorophosphate (BtBPI; Tokyo Chemical Industry, Tokyo, Japan) was used as the in-port derivatization reagent. Each sample extract was dissolved in 1% (w/v) BtBPI in acetone and transferred to a glass vial. A 1-uL aliquot was injected into an Agilent 6890N GC at an inlet temperature of 300 °C under splitless conditions.

PFOA was separated on a DB-5MS column (30 m × 0.25 mm internal diameter, 0.25 um film thickness).

PFOA was detected using an Agilent 5973 N inert mass spectrometer (Agilent Technologies, Inc., Wilmington, DE, USA) with methane negative chemical ionization [22]. The analytical value used in this study was the sum of linear and branched PFOA isomers.

2.3. Statistical Analysis

Statistical analyses were performed using Spotfire Statistica v14.4 [23] and the statsmodels library for statistical analyses in Python v3.14 [24]. Serum PFOA concentrations were log10-transformed for regression analyses. If a PFOA concentration was below the limit of detection (0.1 ng/mL), one-half the detection limit (0.05 ng/mL) was assigned. Medical-history outcomes were not included as explanatory variables in the present determinant analysis.

Determinants of serum PFOA concentration were evaluated using linear regression models with $\log_{10}$(PFOA) (log(PFOA), hereafter) as the dependent variable. The following explanatory variables were prespecified.

Continuous or ordinal variables were (1) BMI; (2) AgeClass (<50 years = 1, 50–59 = 2, 60–69 = 3, 70–79 = 4, ≥80 = 5); (3) drinking habit (Drink: never = 1, occasional = 2, habitual = 3); (4) fish consumption (FishCons); and (5) shellfish consumption (ShellCons). FishCons and ShellCons were each coded in six frequency categories: <1 time/month = 1, 1–3 times/month = 2, 1–2 times/week = 3, 3–4 times/week = 4, 5–6 times/week = 5, and daily or more = 6.

Categorical variables were (6) Residence (Residence 1: Settsu City plus Higashiyodogawa Ward; Residence 2: Toyonaka, Ikeda, Minoh, Suita, Ibaraki, Takatsuki, Shimamoto, Moriguchi, and Neyagawa; Residence 3: Osaka City excluding Higashiyodogawa Ward; Residence 4: other areas of Osaka Prefecture); (7) Sex (male = 1, female = 2); (8) Laxative use (yes = 1, no = 2); (9) Tobacco use (never = 1, former = 2, current = 3); (10) TapWater use for drinking (yes = 1, no = 2); (11) WellUse, use of well water for drinking (yes = 1, no = 2); (12) VegWell, use of well water for vegetable farming (yes = 1, no = 2, do not know = 3); (13) WaterFilter, water-filter use (yes = 1, no = 2); (14) Veg, consumption of locally produced vegetables (yes = 1, no = 2); (15) OsakaFish, consumption of fish caught in Osaka Bay (yes = 1, no = 2); and (16) history of AFFF use (yes = 1, no = 2, do not know = 3). Variables with valid responses from at least 80% of participants were retained for regression analysis. Significance of each variable was evaluated using a likelihood-ratio chi-square test (LRT-Chi2), with a Bonferroni-corrected alpha of 0.05 divided by the number of retained variables. Regression analyses were restricted to complete cases; no imputation was performed.

First, Model 1 assumed a common residual variance across residence groups:

$$\text{Model 1: logPFOA} = c + \sum a_i(\text{continuous or ordinal variables}) + \sum b_j(\text{categorical variables}) + \varepsilon$$

The analysis was then repeated using Model 2, which allowed residual variance to differ by residence group:

$$\text{Model 2: logPFOA} = c + \sum a_i(\text{continuous or ordinal variables}) + \sum b_j(\text{categorical variables other than Residence}) + \varepsilon_1 + [b_r(\text{Residence category} + \varepsilon_2)]$$

These two models were fitted to the data. Model selection was based primarily on the Akaike information criterion (AIC), with the lower AIC indicating the preferred model [25]. AIC was also used to compare normal and log-normal distributional fits for serum PFOA. Log-likelihood values were calculated as supporting information, but AIC was the primary model-selection criterion.

Differences among residence groups in age, BMI, PFOA, and log (PFOA) were evaluated by one-way analysis of variance (ANOVA). When the overall test was significant at $p < 0.05$, pairwise comparisons were performed using the Scheffé post hoc test with a significance level of 0.05. Comparisons of geometric mean PFOA concentrations were conducted on the log10-transformed scale.

To evaluate potential selection associated with questionnaire completeness, age, BMI, PFOA, and log (PFOA) were compared between complete and excluded participants using Welch's *t*-test, and sex distributions were compared using the chi-square test.

As a sensitivity analysis, participants who consumed self-grown agricultural products were excluded to assess whether these participants influenced the residence effect.

To evaluate the interrelationships among prespecified variables, multicollinearity was assessed using variance inflation factors (VIFs).

3. Results

3.1. Demographic Characteristics

A total of 1190 individuals initially participated. After excluding 12 nonresidents of Osaka Prefecture and four current or former Daikin workers, 1174 participants remained (Figure 1). Table 1 summarizes their demographic characteristics. The overall sex distribution was approximately 30–40% male and 60–70% female. Mean age was 63.3 years overall, ranging from 66.8 years in Residence 1 to 56.4 years in Residence 4. Mean BMI was 23.0 kg/m^2 and was similar across the four residence groups. Overall serum PFOA had an arithmetic mean (SD) of 5.93 (6.04) ng/mL and a geometric mean (GSD) of 4.80 (1.86) ng/mL (Table 1).

The difference in AIC between the normal and log-normal models was 1656.6 in favor of the log-normal model, which also had the higher log-likelihood (Figure S1, Table S1). Therefore, subsequent analyses used log(PFOA). PFOA was detected in 100% of participants. Serum PFOA differed significantly among residence groups; Residence 1 had significantly higher arithmetic and geometric mean concentrations than each of Residences 2–4 (overall ANOVA and Scheffé post hoc comparisons, $p < 0.0001$; Table 1). The coefficient of variation was <1.3 in each residence group.

The questionnaire item on use of well water for vegetable farming had only 469 valid responses and did not meet the prespecified ≥ 80% response-rate criterion; it was therefore excluded. The remaining 15 variables were analyzed, giving a Bonferroni-corrected significance threshold of 0.05/15 = 0.0033. After excluding 90 participants with missing data for one or more required variables, 1084 complete cases were included in the main regression analysis. The 1084 complete cases and the 90 excluded participants did not differ significantly in age, sex, BMI, or serum PFOA concentration (Table S2). Questionnaire completion rates across the four residence groups ranged from 90.3% to 93.9% and did not differ significantly (chi-square = 2.30, df = 3, $p = 0.512$).

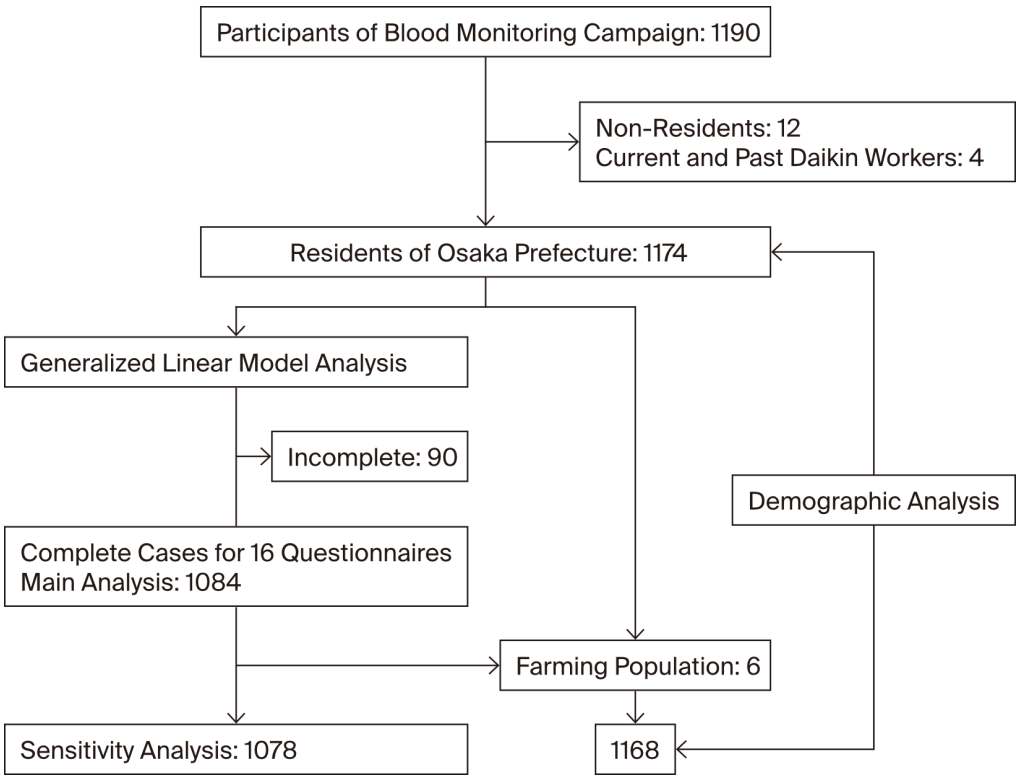


Figure 1. Participant flow and analytical populations. The blood-monitoring campaign included 1190 participants. Twelve nonresidents and four current or former Daikin workers were excluded, leaving 1174 residents of Osaka Prefecture. Of these, 1084 participants with complete data for the 16 questionnaire items entered the main regression analysis, whereas 90 participants had incomplete questionnaire data. For the sensitivity analysis, six participants who owned agricultural land were excluded from the 1174 residents, leaving 1168 participants; 1078 complete cases were included in the sensitivity regression analysis. Demographic analyses were conducted in the corresponding full analytical populations.

Table 1. Demographic characteristics and serum PFOA concentrations by residence area.

Population	Overall	Residence 1	Residence 2	Residence 3	Residence 4	ANOVA, p Value
No. of participants	1174	311	196	448	219	-
No. of women/men	813/361	200/111	131/65	335/113	147/72	-
Women (%)	69.25	64.31	66.84	74.78	67.12	-
Age, mean	63.34	66.79	61.52	65.15	56.38	$p < 1.00 \times 10^{-4}$
Age, SD	15.01	15.21	15.70	14.10	13.37	-
BMI, mean [#]	23.00	22.86	23.26	22.85	23.26	$p = 0.33$
BMI SD	3.61	3.35	3.65	3.68	3.76	-
Serum PFOA (ng/mL)						
Arithmetic mean	5.93	8.11 *	5.04	5.45	4.61	$p < 1.00 \times 10^{-4}$
PFOA SD	6.04	10.48	3.10	2.87	2.18	-
PFOA GM	4.80	5.95 *	4.33	4.68	4.10	$p < 1.00 \times 10^{-4}$
PFOA GSD	1.86	2.02	1.73	1.82	1.67	-

Note: Values are shown for all 1174 participants. Overall differences among the four residence groups were evaluated by one-way analysis of variance (ANOVA). When the overall test was significant, pairwise comparisons were performed using the Scheffé post hoc test with a family-wise significance level of 0.05 (*). Comparisons of geometric mean PFOA concentrations were performed on logPFOA values. GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation. [#] For BMI, data were available for 1153 for overall, 306 for Residence 1, 190 for Residence 2, 440 for Residence 3 and 217 for Residence 4.

3.2. Application of Generalized Least-Squares Models

Model 1 was first fitted with log(PFOA) as the dependent variable (Table S3). Seven variables were significant at the Bonferroni-corrected level: AgeClass, FishCons, Residence, Drink, Laxative, TapWater, and WaterFilter. BMI, ShellCons, Sex, Tobacco, WellUse, Veg, OsakaFish, and AFFF were not significant.

Model 2, which allowed residence-specific residual variances, was then fitted (Table S4). Six variables were significant: AgeClass, FishCons, Residence, Drink, Laxative, and TapWater. The AIC decreased from −138.79 for Model 1 to −151.32 for Model 2, and Model 2 also had the higher log-likelihood (Table S5). Model 2 was therefore selected for the main analysis.

Using the selected Model 2, the effects of the six significant determinants on serum log(PFOA) were estimated (Table 2). Residence 1 was associated with approximately 18–21% higher PFOA concentrations than the other residence groups. Laxative use was associated with an approximately 18% lower concentration, and avoiding tap-water use for drinking was associated with an approximately 13% lower concentration. Each one-category increase in AgeClass was associated with an approximately 21% increase, each category increase in FishCons with an approximately 11% increase, and each category increase in Drink with an approximately 7% increase.

Table 2. Adjusted effect sizes of significant determinants of serum PFOA concentration in the selected main-analysis model.

Parameter	Adjusted β	SE	p Value	Adjusted PFOA Ratio (10^{β})	Adjusted Ratio 95% CI Lower	Adjusted Ratio 95% CI Upper
const	0.25	0.04	0.00	1.77	1.48	2.11
AgeClass	0.08	5.72×10^{-3}	5.03×10^{-49}	1.21	1.18	1.25
Drink	0.03	8.55×10^{-3}	5.22×10^{-4}	1.07	1.03	1.11
FishCons	0.05	7.25×10^{-3}	1.14×10^{-10}	1.11	1.08	1.15
Residence_2	−0.10	0.02	2.38×10^{-6}	0.79	0.72	0.87
Residence_3	−0.10	0.02	4.74×10^{-8}	0.79	0.72	0.86
Residence_4	−0.09	0.02	7.45×10^{-5}	0.82	0.74	0.90
Laxative_2.0	0.07	0.02	4.77×10^{-4}	1.18	1.08	1.30
TapWater_2.0	−0.06	0.02	5.20×10^{-4}	0.87	0.81	0.94

Note: The analysis included 1084 complete cases. Model 2, which allows residence-specific heteroscedasticity, was selected by AIC. The table presents coefficients for terms that were significant by likelihood-ratio chi-square testing at the Bonferroni-corrected significance level (0.05/15 = 0.0033). β is the regression coefficient for log(PFOA); SE, standard error; CI, 95% confidence interval. The PFOA ratio is 10^{β}. For categorical variables (Residence, Laxative, and TapWater), ratios are relative to category 1. For ordinal variables (AgeClass, Drink, and FishCons), the ratio represents the multiplicative change per one-category increase. Effect sizes are adjusted estimates from the multivariable regression model, conditional on the other covariates included in that model. Adjusted PFOA ratios were calculated as 10^{β}, with 95% confidence intervals obtained by exponentiating the corresponding coefficient limits. The p values shown in this table are two-sided coefficient-level Wald tests, computed from adjusted β/SE using a standard normal approximation. They are distinct from the variable-level likelihood-ratio test p values used for variable selection (Table S4).

Using the significant predictors (AgeClass, FishCons, Residence, Drink, Laxative, and TapWater), individual predicted values were calculated and summarized together with observed values by age class and residence. Across the 20 residence-by-age-class strata, predicted and observed mean log(PFOA) values were strongly correlated (Pearson r = 0.927, $p = 4.46 \times 10^{-9}$; Figure 2A). Figure 2B shows age-class profiles of observed mean log(PFOA) +/− 1 SD and predicted mean log(PFOA) for each residence group. Agreement was particularly strong in Residences 1–3. In Residence 4, the correlation was high (approximately 0.80) but was not statistically significant. Stratum-specific observed values, SDs, and predicted values are presented in Table S6.

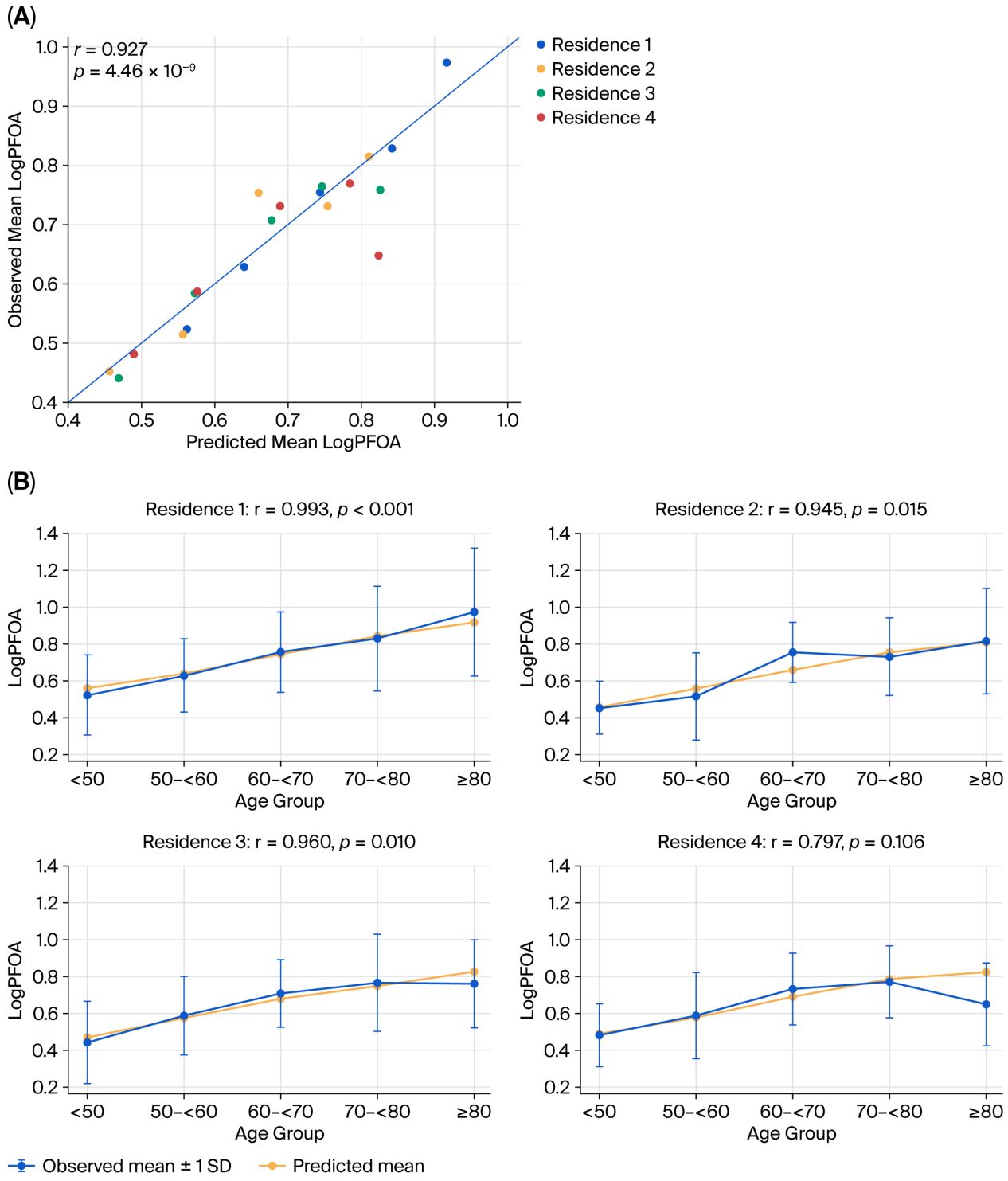


Figure 2. Agreement between observed and model-predicted serum PFOA concentrations in the main analysis. (**A**) Mean predicted versus observed log(PFOA) across 20 residence-by-age-class strata (four residence groups × five age classes). Pearson $r = 0.927$, $p = 4.46 \times 10^{-9}$. The analysis included 1084 complete cases and used the selected Model 2. (**B**) Age-class profiles of observed mean log(PFOA) ± 1 SD (blue) and predicted mean log(PFOA) (orange) for each residence group. Pearson correlation coefficients and *p* values are shown for each residence group.

3.3. Sensitivity Analysis

A sensitivity analysis was then conducted after excluding six prespecified participants who consumed self-grown agricultural products. Among the remaining 1168 participants,

the arithmetic mean (SD) and geometric mean (GSD) serum PFOA concentration in Residence 1 decreased from 8.11 (10.48) and 5.95 (2.02) ng/mL to 6.85 (4.54) and 5.67 (1.86) ng/mL, respectively (Table S7), but Residence 1 remained significantly higher than the other residence groups by ANOVA. Regression analyses were performed among 1078 complete cases using Model 1 (Table S8) and Model 2 (Table S9). The AIC values were −237.4 for Model 1 and −237.0 for Model 2; although Model 2 had a slightly higher log-likelihood, Model 1 had the slightly lower AIC and was selected for the sensitivity analysis (Table S10). In both models, the same six variables identified in the main analysis remained significant: AgeClass, FishCons, Residence, Drink, Laxative, and TapWater; WaterFilter was additionally significant. In the selected Model 1, the Residence 1 effect was approximately 14–18%, and WaterFilter use was associated with an approximately 13% reduction in serum PFOA (Table 3).

Table 3. Adjusted effect sizes of significant determinants of serum PFOA concentration in the sensitivity analysis.

Parameter	Adjusted β	SE	p Value	Adjusted PFOA Ratio (10^{β})	Adjusted Ratio 95% CI Lower	Adjusted Ratio 95% CI Upper
const	0.22	0.04	2.48×10^{-8}	1.65	1.38	1.96
AgeClass	0.08	5.59×10^{-3}	2.06×10^{-41}	1.20	1.17	1.23
Drink	0.03	8.27×10^{-3}	5.27×10^{-4}	1.07	1.03	1.11
FishCons	0.04	6.99×10^{-3}	1.01×10^{-9}	1.10	1.07	1.14
Residence_2	−0.08	0.02	1.24×10^{-4}	0.83	0.76	0.91
Residence_3	−0.08	0.02	5.93×10^{-7}	0.82	0.76	0.89
Residence_4	−0.07	0.02	1.20×10^{-3}	0.86	0.78	0.94
Laxative_2.0	0.08	0.02	1.09×10^{-4}	1.20	1.09	1.32
TapWater_2.0	−0.06	0.02	1.75×10^{-4}	0.86	0.80	0.93
WaterFilter_2.0	0.05	0.01	1.60×10^{-4}	1.13	1.06	1.21

Note: The sensitivity analysis excluded six prespecified participants who consumed self-grown agricultural products and included 1078 complete cases. Model 1 (homoscedastic model) was selected by AIC. The table presents coefficients for terms that were significant by likelihood-ratio chi-square testing at the Bonferroni-corrected significance level (0.05/15 = 0.0033). b is the regression coefficient for log(PFOA); SE, standard error; CI, 95% confidence interval. The PFOA ratio is 10^{b}. For categorical variables, ratios are relative to category 1; for ordinal variables, ratios represent the multiplicative change per one-category increase. Effect sizes are adjusted estimates from the multivariable regression model, conditional on the other covariates included in that model. Adjusted PFOA ratios were calculated as 10^{β}, with 95% confidence intervals obtained by exponentiating the corresponding coefficient limits. The p values shown in this table are two-sided coefficient-level Wald tests, computed from adjusted b/SE using a standard normal approximation. They are distinct from the variable-level likelihood-ratio test p values used for variable selection (Table S8).

Predicted and observed mean values across the 20 residence-by-age-class strata remained strongly correlated ($r = 0.925$, $p = 5.68 \times 10^{-9}$; Figure 3A), and the residence-specific age profiles showed close agreement between observed and predicted values (Figure 3B). The Residence 4 correlation was not statistically significant. Stratum-specific observed values, SDs, and predicted values are shown in Table S11.

Multicollinearity among prespecified variables was assessed using variance inflation factors (VIFs). For categorical variables, dummy coding was applied, and the maximum VIFs among the corresponding prespecified variables were reported (Tables S3, S4, S8 and S9). All VIF values were below 5 in both the main and sensitivity analyses, with maximum values of 3.664 and 3.663, respectively. These findings indicate that substantial multicollinearity was absent among the prespecified variables, ensuring that correlation did not disturb the explanatory analyses.

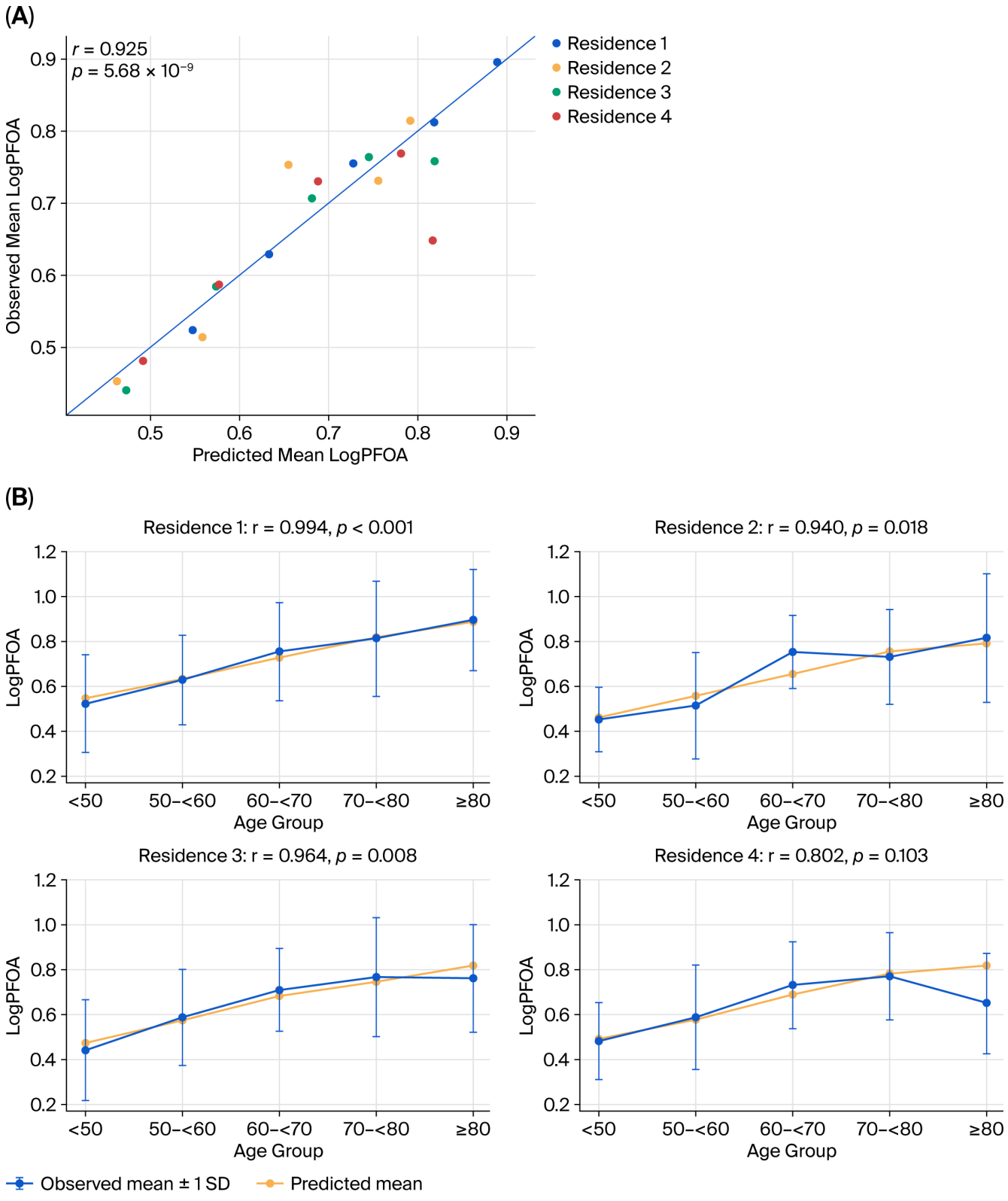


Figure 3. Agreement between observed and model-predicted serum PFOA concentrations in the sensitivity analysis. (**A**) Mean predicted versus observed log(PFOA) across 20 residence-by-age-class strata after exclusion of six participants who owned agricultural land. Pearson $r = 0.925$, $p = 5.68 \times 10^{-9}$. The analysis included 1078 complete cases and used the selected Model 1. (**B**) Age-class profiles of observed mean log(PFOA) ± 1 SD (blue) and predicted mean log(PFOA) (orange) for each residence group. Pearson correlation coefficients and p values are shown for each residence group.

4. Theoretical Analysis

An important question in biomonitoring is the duration of exposure for which a serum concentration is strongly correlated with the time-weighted average exposure concentration. Multiplying a TWA concentration by the averaging duration gives cumulative exposure over that period. Thus, when blood is used for exposure monitoring, it is important to know the period of TWA exposure—and therefore cumulative exposure—for which the serum concentration can serve as an indicator.

The Koizumi–Sekiguchi (KS) theorem [21] theoretically predicts the correlation between a TWA exposure and the concentration in a compartment when exposure concentration is modeled as a stochastic process. The original theorem assumes that exposure follows a normally distributed Ornstein–Uhlenbeck (OU) process, that fluctuations in airborne concentration occur on a time scale much shorter than the biological half-life, and that the process is stationary. Under those assumptions, a TWA over approximately two biological half-lives can have a correlation >0.9 with the compartment concentration. Environmental PFAS concentrations, however, are often approximately log-normally distributed, and their correlation time may not be negligible relative to biological half-life. We therefore retained stationarity but derived a new exact solution under more general conditions.

The exact mathematical results are summarized below as the Koizumi–Sekiguchi–Shiota (KSS) Theorem 1, two corollaries, and the global lower-bound theorem.

4.1. Koizumi–Sekiguchi–Shiota (KSS) Theorem 1: Exact Correlation Between Serum Concentration and Time-Weighted Average Exposure Under Lognormal OU Exposure

The concept of treating temporally varying exposure concentration as a stochastic process was introduced into occupational health by Roach (1966) [26]. Mathematically, the OU process is a classical Gaussian–Markov process related to Brownian motion [27]. The discrete-time stochastic process considered by Roach corresponds, in continuous time, to an OU process, as previously shown [21]. Here we use this continuous-time representation to analyze the relationship between exposure concentration and serum concentration.

Let the exposure concentration be

$$C(t) = \exp\{X(t)\} \tag{1}$$

where $X(t)$ is a stationary Gaussian OU process satisfying

$$E[X(t)] = \mu, \qquad \mathrm{Var}[X(t)] = \sigma^2, \tag{2}$$

$$\mathrm{Cov}[X(s), X(t)] = \sigma^2 \exp\left(-\frac{|t-s|}{T_e}\right) \tag{3}$$

Here, $T_e > 0$ is defined as the exposure correlation time: the autocorrelation of log exposure decays exponentially with time lag T_e, at which the autocorrelation equals e^{-1} and decreases to $\frac{1}{2}$ at $T_e \ln 2$. Let the biological half-life be $T_{1/2}$ and define

$$k = \frac{\ln 2}{T_{1/2}} \tag{4}$$

Under a one-compartment model, we define serum concentration as

$$B(t) = \int_0^\infty e^{-ku} C(t-u)\, du \tag{5}$$

and define the time-weighted average exposure over the preceding interval of length S as

$$A_S(t) = \frac{1}{S}\int_0^S C(t-u)\, du \tag{6}$$

For each $n \geq 1$, we define

$$\lambda_n = \frac{n}{T_e} \tag{7}$$

and let

$$I_{AA}^{(n)} = \frac{1}{S^2}\int_0^S \int_0^S e^{-\lambda_n|u-v|}\,du\,dv, \tag{8}$$

$$I_{AB}^{(n)} = \frac{1}{S}\int_0^S \int_0^\infty e^{-kv}e^{-\lambda_n|u-v|}\,dv\,du, \tag{9}$$

$$I_{BB}^{(n)} = \int_0^\infty \int_0^\infty e^{-ku}e^{-kv}e^{-\lambda_n|u-v|}\,du\,dv \tag{10}$$

Then

$$\rho = \mathrm{Corr}(A_S(t), B(t)) = \frac{\sum_{n=1}^{\infty} \frac{(\sigma^2)^n}{n!} I_{AB}^{(n)}}{\sqrt{\left(\sum_{n=1}^{\infty} \frac{(\sigma^2)^n}{n!} I_{AA}^{(n)}\right)\left(\sum_{n=1}^{\infty} \frac{(\sigma^2)^n}{n!} I_{BB}^{(n)}\right)}}. \tag{11}$$

Furthermore, each integral can be written explicitly in terms of T_e

$$I_{AA}^{(n)} = \frac{2\{\lambda_n S - 1 + e^{-\lambda_n S}\}}{S^2\lambda_n^2}, \tag{12}$$

$$I_{BB}^{(n)} = \frac{1}{k(k+\lambda_n)}, \tag{13}$$

$$I_{AB}^{(n)} = \frac{1}{S}\left[\frac{\frac{1-e^{-\lambda_n S}}{\lambda_n} - \frac{1-e^{-kS}}{k}}{k-\lambda_n} + \frac{1-e^{-kS}}{k(k+\lambda_n)}\right] \tag{14}$$

For the exceptional parameter value $\lambda_n = k$, at which a denominator vanishes, the corresponding continuous limit is used. The coefficient of variation of the lognormal exposure distribution is

$$CV = \sqrt{e^{\sigma^2} - 1}, \qquad \sigma^2 = \ln\left(1 + CV^2\right) \tag{15}$$

Also, if we define

$$M = \frac{S}{T_{1/2}} \tag{16}$$

then, the correlation coefficient is independent of the parameter μ and is determined only by M, $\frac{Te}{T_{\frac{1}{2}}}$ and CV. We denote it compactly below as $\rho(M, T_e, CV)$, with dependence on T_e occurring through the relevant dimensionless ratio $T_e/T_{1/2}$. See Supplement 1 for the proof.

4.2. Corollary 1: White-Noise Limit

Keeping $M = \frac{S}{T_{\frac{1}{2}}}$ constant, let the exposure correlation time tend to zero $T_e \downarrow 0$. Then

$$\lim_{T_e \downarrow 0} \rho(M, T_e, CV) = \rho_{\mathrm{WN}}(M) = \left(1 - 2^{-M}\right)\sqrt{\frac{2}{M\ln 2}} \tag{17}$$

This limit is independent of exposure variability CV. Thus, in the white-noise limit, the correlation coefficient is determined only by M, the ratio of averaging duration S to biological half-life $T_{1/2}$. See Supplement 2 for the proof.

In particular,

$$\rho_{\mathrm{WN}}(2) = \frac{3}{4\sqrt{\ln 2}} \approx 0.90084, \tag{18}$$

$$\rho_{\mathrm{WN}}(3) = \frac{7}{8}\sqrt{\frac{2}{3\ln 2}} \approx 0.85812. \tag{19}$$

4.3. Corollary 2: Limit of Extremely Slowly Varying Exposure

Keep M and CV constant and let $T_e \to \infty$. Then, for every finite time lag τ

$$\exp\left(-\frac{|\tau|}{T_e}\right) \to 1, \tag{20}$$

and therefore

$$\lim_{T_e \to \infty} \rho(M, T_e, CV) = 1. \tag{21}$$

Thus, when exposure varies sufficiently slowly relative to both the biological half-life $T_{1/2}$ and averaging duration S, $A_S(t)$ and $B(t)$ are governed by essentially the same slowly varying exposure level, and their correlation approaches 1. See Supplement 3 for the proof.

4.4. Koizumi–Sekiguchi–Shiota (KSS) Theorem 2: Global Lower-Bound Theorem

Under the assumptions of Theorem 1, for any

$$M > 0, \qquad T_e > 0, \qquad 0 < CV < \infty \tag{22}$$

we have

$$\rho(M, T_e, CV) > \rho_{\mathrm{WN}}(M) = \left(1 - 2^{-M}\right)\sqrt{\frac{2}{M \ln 2}}. \tag{23}$$

Moreover, by Corollary 1, equality is approached in the white-noise limit $T_e \downarrow 0$. Therefore, including that limiting case,

$$\rho_{\mathrm{WN}}(M) \le \rho(M, T_e, CV) \le 1. \tag{24}$$

This lower bound is independent of exposure variability CV. In other words, within the class of lognormal OU exposures, the correlation for any finite exposure correlation time cannot be lower than the white-noise-limit correlation. See Supplement 4 for the proof.

For an averaging duration equal to three biological half-lives, Corollary 1 gives a lower bound of 0.85812 (Equation (19)). This high lower bound indicates that cumulative exposure over approximately three biological half-lives is strongly reflected in the current serum concentration.

5. Discussion

5.1. Major Findings and Contributions

Many studies have investigated determinants of serum PFAS concentrations [11–14]. In the present study, age, fish consumption, residence, drinking habit, laxative use, and tap-water use for drinking were identified as significant determinants of serum PFOA; WaterFilter use was additionally identified in the sensitivity analysis. Age, fish consumption, and drinking habit have been reported previously [11–14] and were confirmed here. Laxative use was a newly identified determinant. We also found that living near DIYP remained associated with higher serum PFOA concentrations more than a decade after PFOA production ceased in 2012. This raises the question of whether the elevated concentrations reflect continuing local exposure, residual body burden from historical exposure, or both.

We therefore considered theoretically how far back in time the serum concentration at blood collection represents exposure. Both one-compartment and PBPK models have been used for PFOA toxicokinetics [15]. PBPK models can provide valuable information for toxicity assessment, including target-organ concentrations. However, tissue uptake and elimination of PFOA involve active transport processes [28], and the complete organ-specific transporter system remains incompletely characterized. For dosimetry, where serum concentration is treated as the response to external exposure, one-compartment

models have been shown to provide useful approximations [12,17]. Under this framework, the KSS theorem derived here can be applied.

The KSS theorem evaluates the correlation between two different linear filters of a lognormal OU exposure process: the one-compartment serum concentration and the TWA exposure, indicating that the mathematical operation is elementary once the covariance structure is specified. Given that one-compartment models are widely used in chemical exposure assessment, an exact stochastic-process formulation directly linking biomonitoring to TWA exposure has been lacking. We therefore formulate the result as the KSS theorem to emphasize the theoretical basis of one-compartment biomonitoring. When biological half-life is used as the time scale, the theorem proves that the white-noise limit—the most rapidly fluctuating exposure considered—provides a global lower bound for the correlation. For an averaging duration of three biological half-lives, the correlation is at least 0.858. If the PFOA biological half-life is approximately 2.2–3 years [6,12,17], current serum PFOA is therefore strongly correlated with TWA exposure over approximately 7–9 years. For blood collected in 2023, this interval extends back to roughly the early-to-mid 2010s, overlapping the period when DIYP ceased PFOA production. The higher serum PFOA in Residence 1 is therefore consistent with greater cumulative exposure during the post-cessation period, although serial follow-up is needed to determine the temporal trajectory.

Tap-water use and water-filter use may reflect continuing contributions from PFOA in drinking water. Drinking habit has previously been considered a possible marker of exposure through beverages produced with contaminated water [12]. However, the C8 study also observed a longer PFAS biological half-life among habitual drinkers after contaminated water exposure had been reduced [17], suggesting that biological mechanisms may also contribute. Animal studies have identified the apical sodium-dependent bile acid transporter (ASBT) as a transporter involved in intestinal handling of PFAS [29], and ASBT-related enterohepatic bile-acid transport can be altered by alcohol exposure [30]. These observations raise the hypothesis that PFAS exposure and habitual alcohol consumption could enhance intestinal reabsorption of both bile acid [31] and PFOA and thereby influence serum PFOA kinetics. This mechanism remains speculative and requires direct investigation.

Laxative use was a novel determinant associated with lower serum PFOA. One possible mechanism is enhanced fecal elimination through interruption of enterohepatic recirculation, analogous in principle to the effect of bile-acid-binding resins. Anion-exchange treatment has been reported to substantially reduce serum PFAS concentrations [32]. Laxatives can increase fecal output and, depending on their type, may alter bile-acid excretion [33]; dietary fiber interventions have also reduced PFAS body burden in animal experiments [34]. Because PFOA and PFOS are excreted into bile and can undergo intestinal reabsorption and enterohepatic circulation in humans [35], enhanced fecal elimination is biologically plausible. However, the questionnaire did not identify the specific laxative products used, so the mechanism cannot be established from the present data.

Several local exposure pathways could contribute to the Residence 1 effect. As previously reported, some residents consume agricultural products grown in PFOA-contaminated soil, including water-rich vegetables such as Chinese cabbage, eggplant, and daikon radish [6]. Excluding six clearly identified consumers of self-grown agricultural products reduced both the mean and variability of serum PFOA in Residence 1, but the residence difference remained. Thus, self-grown produce explains only part of the observed geographic pattern, and exposure through locally produced and marketed vegetables cannot be excluded. Atmospheric dispersion of PFOA has also been documented in this area [20]. PFOA transported from outdoor air may have accumulated indoors, and our previous study found higher PFOA concentrations in household dust near the plant [36]. There are several reports on local contamination episodes worldwide. The current serum PFOA levels in the

present study are comparable to those reported in the USA [1], Italy [11], and Germany [12], but are substantially lower than those in China [37]. Given the extremely high exposure cases observed in China [37], the potential contribution of local ecological bioconcentration through the food chain warrants further investigation. Detailed investigation of exposure from local foods and the indoor environment is therefore warranted.

5.2. Limitations and Strengths

This study has several important limitations. First, because the questionnaire was self-administered, omissions and recall errors regarding past and current lifestyle factors are possible. Second, a participation rate could not be calculated for the community blood-monitoring campaign. Third, the determinant analysis assumed linear relationships with log(PFOA), and possible nonlinear associations were not examined. Fourth, the questionnaire did not identify specific laxative products or detailed information on alcoholic beverages, limiting evaluation of the mechanisms underlying these associations. Fifth, although observed and predicted values agreed well in Residences 1–3, the Residence 4 correlation was not statistically significant, indicating a limitation of the prediction model in that group. Sixth, given that the study participants were recruited through community-initiated biomonitoring, the possibility of selection bias cannot be ruled out. Future studies could also benefit from recruitment strategies designed to obtain a more representative sample. Finally, residential history could not be incorporated into the present determinant analysis. Therefore higher serum PFOA levels in Residence 1 do not necessarily establish a causal relationship between the plant and elevated serum PFOA levels. Nevertheless, several lines of evidence—including historical drinking-water contamination [4], simulated inhalation exposure [20], the exclusion of dietary exposure as a contributing route [19], and elevated serum PFOA levels observed in former DIYP workers [6]—collectively support the conclusion that DIYP is the local source of PFOA.

This study also has several strengths. Participation from residents throughout Osaka Prefecture enabled confirmation of biological and lifestyle determinants of serum PFOA, including age and fish consumption, within a broad regional population. The main and sensitivity analyses consistently identified a Residence 1 effect even after exclusion of six participants with clearly documented consumption of self-grown agricultural products, supporting the robustness of the geographic finding. In addition, the KSS theorem provides a stochastic-process basis for interpreting current serum concentrations in relation to cumulative exposure over a period on the order of several biological half-lives. Applied to the present findings, this framework supports the interpretation that residents of Residence 1 experienced greater cumulative PFOA exposure during the years following production cessation. The observed associations with drinking habit and laxative use also generate hypotheses concerning enterohepatic transport that merit further biological investigation.

6. Conclusions

Among residents of Osaka Prefecture, serum PFOA concentrations were significantly associated with six determinants in the main analysis: age class, fish consumption, residence, drinking habit, laxative use, and tap-water use for drinking. Water-filter use was additionally significant in the sensitivity analysis. After exclusion of six participants who consumed self-grown agricultural products, the mean and variance of serum PFOA in Residence 1 decreased, but the residence difference persisted, suggesting that locally grown produce may contribute to exposure while other area-specific pathways also remain possible. Serum PFOA concentrations were higher in Residence 1, the area nearest DIYP. The KSS lower-bound theorem indicates that current serum concentrations are strongly correlated with TWA exposure over a period of approximately three biological half-lives. Accordingly,

the Residence 1 finding is consistent with greater cumulative exposure during the years after DIYP ceased PFOA production. However, the current analyses are exploratory, and continued biomonitoring is warranted to confirm these findings.

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Abbreviations

The following abbreviations are used in this manuscript:

AFFF	Aqueous Film-Forming Foam
AgeClass	Age Class
AIC	Akaike's Information Criteria
ANOVA	Analysis of Variance
ASBT	Apical Sodium-dependent Bile Acid Transporter
BMI	Body Mass Index
CV	Coefficient of variation
DIYP	Daikin Industry Yodogawa Plant
EPA	Environmental Protection Agency
FishCons	Fish Consumption
GC-MS	Gas Chromatography–Mass Spectrometry
IARC	International Agency of Research on Cancer
LRT-Chi2	Likelihood ratio chi-square test
OsakaFish	Fish caught in the Osaka Bay
OU process	Orstein–Uhlenbeck Process
PBPK	Physiologically based pharmacokinetic modeling
PFAS	Perfluoroalkyl and Polyfluoroalkyl Substances
PFOA	Perfluorooctanoic Acid
PFOS	Perfluorooctane sulfonate

POPs	Persistent organic pollutants
ShellCons	Shell Consumption
TapWater	Tap-water use for drinking water
TDI	Tolerable Daily Intake
TWA	Time-Weighted Average
VegWell	Well water use for Vegetable farming

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