

Original Article



OPEN ACCESS

Received: Nov 28, 2022
1st Revised: Jan 24, 2023
2nd Revised: Feb 8, 2023
Accepted: Feb 9, 2023
Published online: Mar 15, 2023

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Abbreviations

BMI: body mass index; CI: confidence
interval; eGFR: estimate glomerular
filtration rate; HbA1c: hemoglobin A1c;

The association of perfluoroalkyl substances (PFAS) exposure and kidney function in Korean adolescents using data from Korean National Environmental Health Survey (KoNEHS) cycle 4 (2018–2020): a cross-sectional study

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ABSTRACT

Background: Perfluoroalkyl substances (PFAS) are chemicals widely used in various products in everyday life. Due to its unique strong binding force, the half-life of PFAS is very long, so bioaccumulation and toxicity to the human body are long-standing concerns. In particular, effects on kidney function have recently emerged and there are no studies on the effect of PFAS on kidney function through epidemiological investigations in Korea. From 2018 to 2020, the Korean National Environmental Health Survey (KoNEHS) cycle 4, conducted an epidemiological investigation on the blood concentration of PFAS for the first time in Korea. Based on this data, the relationship between PFAS blood concentration and kidney function was analyzed for adolescents.

Methods: We investigated 5 types of PFAS and their total blood concentration in 811 middle and high school students, living in Korea and included in KoNEHS cycle 4, and tried to find changes in kidney function in relation to PFAS concentration. After dividing the concentration of each of the 5 PFAS and the total concentration into quartiles, multivariable linear regression was performed to assess the correlation with kidney function. The bedside Schwartz equation was used as an indicator of kidney function.

Results: As a result of multivariable linear regression, when observing a change in kidney function according to the increase in the concentration of each of the 5 PFAS and their total, a significant decrease in kidney function was confirmed in some or all quartiles.

Conclusions: In this cross-sectional study of Korean adolescents based on KoNEHS data, a negative correlation between serum PFAS concentration and kidney function was found. A well-designed longitudinal study and continuous follow-up are necessary.

Keywords: Perfluoroalkyl substances (PFAS); Kidney function; KoNEHS

KoNEHS: Korean National Environmental Health Survey; LOD: limit of detection; NHANES: National Health and Nutrition Examination Survey; PFAS: perfluoroalkyl substances; PFDeA: perfluorodecanoic acid; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctansulfonate; ROS: reactive oxidative species.

Funding

This work was supported by the Soonchunhyang University Research Fund.

Competing interests

The authors declare that they have no competing interests.

Authors contributions

Conceptualization: Yun JS, Lee YJ; Data curation: Yun JS, Jang EC, Kwon SC, Min YS; Formal analysis: Yun JS, Lee YJ, Jang EC, Kwon SC, Min YS; Investigation: Yun JS, Lee YJ, Jang EC, Kwon SC, Min YS; Writing - original draft: Yun JS; Writing - review & editing: Lee YJ.

BACKGROUND

Due to the development of civilization, we are using various chemicals for the convenience of daily life, and the amount and frequency of exposure to chemicals is proportionally increasing. Among the many chemicals, perfluoroalkyls, a group of synthetic fluorine-containing chemicals, the so-called “forever chemicals”, have been widely used for diverse applications. Due to special hydrophobic and oleophobic properties, perfluoroalkyl substances (PFAS) can generally be found in consumer products such as disposable food packaging, cookware, outdoor gear, furniture, and carpet.^{1,2} PFAS have a well-documented long half-life and do not readily decompose due to the presence of a unique, strong carbon-fluorine bond, which in turn creates large problems due to bioaccumulation.³ In Korea, various types and concentrations of PFAS are detected in rivers and sediments,⁴ and PFAS are continuously detected, even in purified tap water.^{5,6}

Overseas literature has continuously suggested the negative effects of PFAS on the human body through various animal experiments as well as epidemiological studies,⁷ and recently, PFAS have emerged as a threat to kidney health,^{8,9} especially focusing on the effects on kidney function.⁹ It is widely known that PFAS induces the production of reactive oxidative species (ROS), which has a toxic effect on the kidneys, decreasing kidney function.^{10,11} The risks of PFAS have increased steadily over time. The Stockholm Convention specifically noted that these substances could have toxic effects on health, such as immunotoxicity, developmental toxicity, and reproductive toxicity, by bioaccumulation over a long period of time. Therefore, perfluorooctansulfonate (PFOS) and perfluorooctanoic acid (PFOA) were listed as persistent organic pollutants in 2009 and 2019, respectively, and many countries control their production and use in various ways.¹² However, PFAS are still detectable globally in the bio-specimens of humans due to their unique persistence and bioaccumulation.¹³ The National Health and Nutrition Examination Survey (NHANES) which is an annual national survey conducted in the United States has been measuring blood PFAS concentrations since 1999, and it was reported that PFAS was detected in the blood of more than 98 percent of the population.¹⁴

As a result of continuous warnings about the negative effects on the human body, regulations on production and use have continued, and thanks to this, the concentration of PFAS in the blood has decreased significantly during NHANES follow-up over the past 20 years.¹⁵ Recently, in Korea, the Ministry of Environment and the National Institute of Environmental Research conducted the Korean National Environmental Health Survey (KoNEHS) cycle 4, from 2018 to 2020. The 4th KoNEHS conducted from 2018 to 2020 is the first national health survey conducted in Korea that includes data on the blood concentration of PFAS. Five types of PFAS were investigated; PFOA, PFOS, perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDeA), respectively. It is the first population-based epidemiological survey of PFAS in Korea, and to our knowledge, no other study has investigated the blood concentration of PFAS and their association with the kidneys based on Korean raw data. This study was designed from this perspective. We targeted the pediatric population, in the 4th cycle KoNEHS data to better understand the effect on kidney function. Children are generally known to be more vulnerable to toxicity due to their relatively low weight and immature metabolic pathways compared to adults.¹⁶ Based on this data, the relationship between blood PFAS concentration and kidney function in middle and high school students residing in Korea was analyzed.

METHODS

Study population

This study is a secondary analysis study based on the 4th KoNEHS raw data collected by the National Institute of Environmental Research from 2018 to 2020. The 4th KoNEHS used a sampling method to present representative results for all middle and high school students living in Korea, with an age distribution between 12 and 17 years, and 67 middle and high schools were selected as sampling institutions. Guidelines were given to the person in charge of at the sampling institution to avoid selecting a specific target. The person in charge used the guidelines to select an appropriate number of students of different ages and sexes. The 4th KoNEHS survey consists of a survey on environmental exposure, clinical tests (21 types including a general clinical examination), and evaluation of exposure levels in the body to harmful substances in the environment (33 types including heavy metals). Biological samples were collected by medical institutions (hospitals, clinics, etc.) located adjacent to educational institutions, and medical staff took bodily measurements such as blood pressure, and collected biological samples (blood and urine) for analysis. Afterwards, a field survey team visited a sample education institution, reconfirmed the identity of the participants, collected the biological samples for transport, and surveyed the questionnaire through a one-on-one interview method. Finally, if a value was missing among the variables of a study subject, the subject was excluded from the study.

Kidney function measurement

Several clinical laboratory tests are useful in investigating and evaluating kidney function. Clinically, the most practical test to assess kidney function is to estimate glomerular filtration rate (eGFR) and to check for proteinuria (albuminuria).^{17,18} However, since the subjects of this study were not tested for urine albumin, eGFR was used as an indicator of kidney function. eGFR applied the Creatinine-based Bedside Schwartz equation (2009) formula, which is useful for measuring eGFR in children, based on guidelines from the National Kidney Foundation.¹⁹ The eGFR is obtained using serum creatinine concentration and height, the formula is as follows: $eGFR_{Cr} (\text{mL}/\text{min}/1.73 \text{ m}^2) = 0.413 \times \text{Height (cm)} \div \text{SCr (mg/dL)}$. Serum creatinine was measured using the Jaffe reaction method. Serum creatinine was analyzed by an ADVIA 1800 Auto Analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA).

PFAS

There are more than 14,000 PFAS known to date.²⁰ The compounds subject to this study are PFOA, PFOS, PFHxS, PFNA, and PFDeA which are the most widely known PFAS. The 5 types of compounds were detected using a high-performance liquid chromatograph/mass spectrometer of Q-Sight Triple Quad (Perkin-Elmer, Waltham, MA, USA). As for the reporting the limit of detection (LOD) of PFAS in serum in accordance with this test method, PFOA was 0.050 $\mu\text{g}/\text{L}$, PFOS was 0.056 $\mu\text{g}/\text{L}$, PFHxS was 0.071 $\mu\text{g}/\text{L}$, PFNA was 0.019 $\mu\text{g}/\text{L}$, and PFDeA was 0.017 $\mu\text{g}/\text{L}$. Serum PFAS concentrations were measured in this way and the results are presented. We also observed changes in serum PFAS concentrations in adolescents in the United States based on the public data released by the NHANES and compared it with the results of KoNEHS cycle 4.

Potential confounders

We included age, sex, body mass index (BMI), household income, blood pressure, diabetes, total cholesterol, and urinary cotinine, which are widely known to affect kidney function,²¹ as potential confounders to analyze the association between blood PFAS concentration and

kidney function. The study subjects ranged from 12 to 17 years old, and age was used as an ordinal variable in statistical analysis. The BMI (kg/m^2) was classified as less than $18.5 \text{ kg}/\text{m}^2$, $18.5 \text{ kg}/\text{m}^2$ to less than $25 \text{ kg}/\text{m}^2$, and $25 \text{ kg}/\text{m}^2$ or more. Household income was surveyed through a prepared questionnaire, and over the past year, the average monthly income was categorized into 7 categories: less than 1 million won (803 dollars), 1 million won (803 dollars) to less than 2 million won (1,606 dollars), 2 million won (1,606 dollars) to less than 3 million won (2,409 dollars), 3 million won (2,409 dollars) to less than 5 million won (4,014 dollars), 5 million won (4,014 dollars) to less than 7 million won (5,620 dollars), over 7 million won (5,620 dollars), and unknown. According to the clinical practice guidelines of the American Academy of Pediatrics in 2017, stage 2 hypertension is defined as a systolic blood pressure higher than 140 mmHg or a diastolic blood pressure higher than 90 mmHg.²² In this study, 'abnormal blood pressure' was defined as any subject with stage 2 hypertension or currently taking anti-hypertensive drugs. Blood pressure not falling into this category was considered as 'normal.' No subject in this study were classified as having diabetes or taking anti-diabetic drugs through a preliminary questionnaire. However, according to the Korean Diabetes Association 2021 guidelines, if hemoglobin A1c (HbA1c) was 6.5% or higher, it was treated as diabetes.²³ Since exposure to tobacco smoke is thought to be a risk factor for kidney disease in adolescents, urinary cotinine was also included in the analyses.²⁴ Urinary cotinine was detected using a gas chromatograph/mass spectrometer of Clarus 600T (Perkin-Elmer). The LOD of urinary cotinine by this test method was $0.2 \mu\text{g}/\text{L}$. Cotinine concentrations were categorized into tertiles.²⁵ Total cholesterol was considered as a potential covariate as a lowering cholesterol has been shown to reduce the rate of kidney function loss.²⁶ Total cholesterol was divided into less than $170 \text{ mg}/\text{dL}$ and more than $170 \text{ mg}/\text{dL}$, the starting point of being classified as borderline according to the 2017 Clinical Practice Guidelines for Dyslipidemia of Korean Children and Adolescents.²⁷

Statistical analysis

The numbers and percentages of the general characteristics of the study subjects were investigated. In addition, the average eGFR and 95% confidence interval (CI) according to general characteristics were shown, and the average eGFR difference was statistically verified through a t-test and analysis of variance. Multivariable linear regression was used to analyze the relationship between serum PFAS concentration and kidney function, and a method of complex sample analysis with weights was applied. The method of calculating and applying the weight is presented in the original publicly available final dataset with the KoNEHS analysis guidelines.²⁸ Since individual PFAS concentrations and the total concentrations were right-skewed, they were transformed into a natural logarithm, and then categorized into quartiles. For each PFAS and its total, the change in eGFR according to the increase in the quartile was shown, and the beta coefficient and 95% CI were presented. Multivariable linear regression was used to analyze the relationship between blood PFAS concentration and kidney function, which was analyzed by adjusting for age, sex, BMI, household income, abnormal blood pressure, diabetes, total cholesterol, and urinary cotinine. Additional stratified analyses were also performed for sex, age, BMI, urinary cotinine, total cholesterol, and abnormal blood pressure.

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) program and p-values of less than 0.05 were considered as statistically significant.

Ethics statement

The Institutional Review Board (IRB) of Soonchunhyang University Cheonan Hospital approved this study (IRB No. 2022-10-016).

RESULTS

The general characteristics of the subjects of this study are summarized in **Table 1**. A total of 811 subjects were selected as the final subjects for this study. Exclusions included 578 infants, 736 elementary school students, 4,239 adults aged 19 years or older, and 17 subjects with missing data out of a total of 6,381 in the 4th KoNEHS (2018–2020). Of the total 811 participants, 379 (46.7%) were male and 432 (53.3%) were female. The age of the study participants was 12–17 years, which was relatively evenly distributed. The average monthly

Table 1. General characteristics and mean eGFR of the study population

Characteristics	Unweighted sample size (n = 811)	eGFR (mL/min/1.73 m ²)	p-value ^a
Sex		94.67 (93.49–95.85)	< 0.001***
Male	379 (46.7)	85.35 (83.94–86.76)	
Female	432 (53.3)	102.84 (101.38–104.31)	
Age (years)			< 0.001***
12	122 (15.0)	104.82 (102.05–107.59)	
13	113 (13.9)	99.21 (96.50–101.87)	
14	128 (15.8)	97.03 (94.16–99.89)	
15	154 (19.0)	90.74 (88.30–93.19)	
16	156 (19.2)	89.17 (86.87–91.47)	
17	138 (17.0)	90.38 (86.90–93.87)	
Household income (million won) ^b			0.253
< 1 (803 \$)	10 (1.2)	89.32 (77.47–101.17)	
1–2 (803–1,606 \$)	42 (5.2)	97.93 (92.64–103.23)	
2–3 (1,606–2,409 \$)	100 (12.3)	95.18 (91.06–99.29)	
3–5 (2,409–4,014 \$)	269 (33.2)	95.90 (93.88–97.93)	
5–7 (4,014–5,620 \$)	196 (24.2)	92.65 (90.39–94.92)	
≥ 7 (5,620 \$)	147 (18.1)	93.59 (90.86–96.31)	
unaware	47 (5.8)	96.51 (91.81–101.21)	
BMI (kg/m ²)			< 0.001***
< 18.5	106 (13.1)	100.82 (97.78–103.85)	
18.5–25	540 (66.6)	93.98 (92.59–95.38)	
≥ 25	165 (20.3)	92.96 (89.97–95.94)	
HbA1c (%)			0.533
< 6.5	808 (99.6)	94.74 (93.55–95.87)	
≥ 6.5	3 (0.4)	88.50 (64.28–109.89)	
Urinary cotinine (ng/mL)			< 0.001***
< 1.93	270 (33.3)	98.37 (96.20–100.53)	
1.94–3.43	271 (33.3)	93.95 (91.88–96.01)	
≥ 3.44	270 (33.3)	91.69 (89.84–93.5)	
Total cholesterol (mg/dL)			0.734
< 170	598 (73.7)	94.55 (93.17–95.97)	
≥ 170	213 (26.3)	95.01 (92.69–97.57)	
Abnormal blood pressure ^c			< 0.001***
No	635 (78.3)	95.74 (94.54–97.13)	
Yes	176 (21.7)	90.82 (88.09–93.58)	

Values are presented as number (%) or mean (95% confidence interval).

BMI: body mass index; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c.

^aThe p-value calculated by t-test or analysis of variance.

^bAn exchange rate of 1,245.5 won per dollar was applied.

^cAbnormal blood pressure was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or currently taking anti-hypertensive drugs.

***p < 0.001.

household income showed a relatively normal distribution pattern, with the largest number of people, 269 (33.2%), distributed in the range of 3 million won (2,409 dollars) to 5 million won (4,014 dollars) or less. Regarding BMI distribution, 106 participants (13.1%) were in the less than 18.5 kg/m² group, 540 (66.6%) were in the more than 18.5 kg/m² and less than 25 kg/m² group, and 165 (20.3%) were in the more than 25 kg/m² group. In the HbA1c survey to distinguish diabetes, 808 people (99.6%), the majority of the participants, were non-diabetes. When measuring the total cholesterol, the group below 170 was 598 (73.7%), more than twice as much as the group above 170. In blood pressure measurement, the number of people classified with normal blood pressure was 635 (78.3%), approximately 3 times more than the number of 176 (21.7%) classified with abnormal blood pressure.

The average eGFR according to the general characteristics of the study subjects is shown in **Table 1**. The average eGFR of women was higher than that of men, and the result was statistically significant. There was a significant difference in mean eGFR according to age, and approximately, the higher the age, the lower the mean eGFR. There was no statistically significant difference in average eGFR according to household income, concentrations of HbA1c and total cholesterol. The BMI showed a significant difference in the mean eGFR in the 3 groups, and the mean eGFR tended to decrease with increasing BMI. Finally, urinary cotinine and blood pressure also showed a significant difference in the mean eGFR according to classification. Urinary cotinine showed a significantly lower mean eGFR in the high group and blood pressure in the abnormal blood pressure group. **Table 2** shows a significant difference in mean eGFR according to the quartile of each variable, and in general, the higher the quartile, the lower the mean eGFR.

To adjust for potential confounders, multivariable linear regression results are presented in **Table 3**. In the case of total PFAS, which is the mixture of all 5 PFASs, which are the subjects of this study, compared to the reference value, in quartile 2, eGFR decreased by -4.04 (95% CI: -7.45, -0.59), in quartile 3, by -5.13 (95% CI: -7.98, -2.27), and the last in quartile 4, by -5.17 (95% CI: -8.61, -1.73), all statistically significant. PFHxS similarly showed significant eGFR reductions of -3.85 (95% CI: -6.78, -0.93) in quartile 2, -3.63 (95% CI: -6.61, -0.65) in quartile 3, and -5.24 (95% CI: -8.59, -1.88) in quartile 4 based on reference values. PFNA also showed significant eGFR reductions of -3.77 (95% CI: -6.49, -1.05), -3.32 (95% CI: -5.80, -0.83), and -4.20 (95% CI: -7.35, -1.04) compared to the reference value with the increase in quartile. In PFOA and PFOS, a statistically significant decrease in eGFR was shown only in quartile 3 and quartile 4 compared to the reference value. PFOA showed significant eGFR reductions by -3.96 (95% CI: -6.68, -1.23) and -4.16 (95% CI: -7.44, -0.87) in the third and fourth quartiles, respectively, while PFOS showed significant reductions by -3.39 (95% CI: -5.84, -0.94) and -3.13 (95% CI: -5.64, -0.61) respectively. Finally, in PFDeA, only quartile 4 showed a statistically significant reduction in eGFR by -3.79 (95% CI: -6.74, -0.84) based on the reference value. **Table 4** in the appendix presents the change in eGFR when the natural logarithm of the serum PFAS concentration increased by 1. Total PFAS and PFOS in model 1 and total PFAS, PFOA, PFOS, and PFDeA in model 2 showed statistically significant decreases in eGFR.

Table 5 in the appendix presents the change in eGFR when the natural logarithm of the serum PFAS concentration increased by 1 according to confounders. For each confounder, the change in the mean eGFR according to a change in serum PFAS was inconsistent and showed various patterns.

Table 2. Mean eGFR according to quartile of PFAS

Serum perfluoroalkyl chemical level (µg/L)	Unweighted sample size (n = 811)	eGFR (mL/min/1.73 m ²)	p-value ^a
Total PFAS			
Quartile 1 (< 11.92 µg/L)	203	99.37 (96.84–101.90)	< 0.001***
Quartile 2 (11.92 to 15.89 µg/L)	201	93.65 (91.30–96.00)	
Quartile 3 (15.89 to 21.94 µg/L)	205	93.11 (91.01–95.22)	
Quartile 4 (> 21.94 µg/L)	202	92.56 (90.16–94.96)	
PFOA			
Quartile 1 (< 2.70 µg/L)	203	98.31 (95.64–100.97)	< 0.001***
Quartile 2 (2.70 to 3.44 µg/L)	203	95.50 (93.35–97.66)	
Quartile 3 (3.44 to 4.76 µg/L)	204	93.21 (90.90–95.52)	
Quartile 4 (> 4.76 µg/L)	201	91.69 (89.41–93.96)	
PFOS			
Quartile 1 (< 5.71 µg/L)	202	97.04 (94.71–99.37)	0.022*
Quartile 2 (5.71 to 7.61 µg/L)	204	95.96 (93.41–98.52)	
Quartile 3 (7.62 to 11.08 µg/L)	203	92.80 (90.65–94.95)	
Quartile 4 (> 11.08 µg/L)	202	92.88 (90.46–95.29)	
PFHxS			
Quartile 1 (< 1.42 µg/L)	202	98.98 (96.45–101.51)	< 0.001***
Quartile 2 (1.42 to 2.16 µg/L)	204	94.64 (92.28–96.99)	
Quartile 3 (2.16 to 3.47 µg/L)	203	92.05 (89.78–94.32)	
Quartile 4 (> 3.47 µg/L)	202	93.04 (90.79–95.28)	
PFNA			
Quartile 1 (< 0.70 µg/L)	203	99.63 (96.91–102.35)	< 0.001***
Quartile 2 (0.70 to 0.93 µg/L)	202	93.65 (91.51–95.79)	
Quartile 3 (0.93 to 1.22 µg/L)	204	94.03 (91.97–96.10)	
Quartile 4 (> 1.22 µg/L)	202	91.39 (88.99–93.78)	
PFDeA			
Quartile 1 (< 0.36 µg/L)	204	97.54 (94.93–100.16)	0.003**
Quartile 2 (0.36 to 0.45 µg/L)	201	94.48 (92.36–96.60)	
Quartile 3 (0.46 to 0.56 µg/L)	203	95.31 (92.96–97.66)	
Quartile 4 (> 0.56 µg/L)	203	91.36 (89.04–93.69)	

Values are presented as number or mean (95% confidence interval).

PFAS: perfluoroalkyl substances; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonate; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFDeA: perfluorodecanoic acid; eGFR: estimated glomerular filtration rate.

^aThe p-value calculated by analysis of variance.

*p < 0.05; **p < 0.01; ***p < 0.001.

Fig. 1 is a table comparing serum PFAS concentrations in 1999–2000 and the last 4 years based on the NHANES results. As mentioned before, the median serum PFAS concentration decreased steadily since the investigation began, and in particular, PFOS decreased by more than 85% compared to the most recent results.¹⁵

Fig. 2 is a table comparing the survey results of KoNEHS (2018–2020) and NHANES (2017–2018). For all compounds, Korean adolescents showed blood concentrations approximately twice as high or more than American adolescents based on median values.

DISCUSSION

Through this study representing Korean adolescents, we found that each of the 5 PFAS substances (PFOA, PFOS, PFHxS, PFNA, and PFDeA) and their sum were significantly associated with decreased kidney function. It is very interesting that statistically significant changes in kidney function were observed in quartile 2, which had relatively low concentrations of some PFAS compared to quartile 1. Our findings support other studies that

Table 3. Multivariable regression of PFAS with outcome measure of kidney function

Serum perfluoroalkyl chemical level ($\mu\text{g/L}$)	Unweighted sample size (n = 811)	Multivariable adjusted change in eGFR ^a (mL/min/1.73 m ²)
Total PFAS		
Quartile 1 (< 11.92 $\mu\text{g/L}$)	203	Reference
Quartile 2 (11.92 to 15.89 $\mu\text{g/L}$)	201	-4.04 (-7.45, -0.59)**
Quartile 3 (15.89 to 21.94 $\mu\text{g/L}$)	205	-5.13 (-7.98, -2.27)***
Quartile 4 (> 21.94 $\mu\text{g/L}$)	202	-5.17 (-8.61, -1.73)*
PFOA		
Quartile 1 (< 2.70 $\mu\text{g/L}$)	203	Reference
Quartile 2 (2.70 to 3.44 $\mu\text{g/L}$)	203	-1.57 (-4.04, 0.90)
Quartile 3 (3.44 to 4.76 $\mu\text{g/L}$)	204	-3.96 (-6.68, -1.23)**
Quartile 4 (> 4.76 $\mu\text{g/L}$)	201	-4.16 (-7.44, -0.87)*
PFOS		
Quartile 1 (< 5.71 $\mu\text{g/L}$)	202	Reference
Quartile 2 (5.71 to 7.61 $\mu\text{g/L}$)	204	-1.46 (-4.51, 1.59)
Quartile 3 (7.62 to 11.08 $\mu\text{g/L}$)	203	-3.39 (-5.84, -0.94)**
Quartile 4 (> 11.08 $\mu\text{g/L}$)	202	-3.13 (-5.64, -0.61)*
PFHxS		
Quartile 1 (< 1.42 $\mu\text{g/L}$)	202	Reference
Quartile 2 (1.42 to 2.16 $\mu\text{g/L}$)	204	-3.85 (-6.78, -0.93)*
Quartile 3 (2.16 to 3.47 $\mu\text{g/L}$)	203	-3.63 (-6.61, -0.65)*
Quartile 4 (> 3.47 $\mu\text{g/L}$)	202	-5.24 (-8.59, -1.88)**
PFNA		
Quartile 1 (< 0.70 $\mu\text{g/L}$)	203	Reference
Quartile 2 (0.70 to 0.93 $\mu\text{g/L}$)	202	-3.77 (-6.49, -1.05)**
Quartile 3 (0.93 to 1.22 $\mu\text{g/L}$)	204	-3.32 (-5.80, -0.83)**
Quartile 4 (> 1.22 $\mu\text{g/L}$)	202	-4.20 (-7.35, -1.04)*
PFDeA		
Quartile 1 (< 0.36 $\mu\text{g/L}$)	204	Reference
Quartile 2 (0.36 to 0.45 $\mu\text{g/L}$)	201	-1.45 (-4.25, 1.35)
Quartile 3 (0.46 to 0.56 $\mu\text{g/L}$)	203	-2.28 (-5.09, 0.54)
Quartile 4 (> 0.56 $\mu\text{g/L}$)	203	-3.79 (-6.74, -0.84)*

Values are presented as mean (95% confidence interval).

PFAS: perfluoroalkyl substances; PFOA: perfluorooctanoic acid; PFOS: perfluorooctansulfonate; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFDeA: perfluorodecanoic acid; eGFR: estimated glomerular filtration rate.

^aAdjusted for sex, age, household income, body mass index, urinary cotinine, hemoglobin A1c, total cholesterol, abnormal blood pressure

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4. Mean change in eGFR (mL/min/1.73 m²) per 1 ln-serum PFAS using multivariable regression

Serum perfluoroalkyl chemicals	Multivariable adjusted change in eGFR (mL/min/1.73 m ²)	
	Model 1 ^a	Model 2 ^b
Total PFAS	-2.81 (-5.50, -0.12)*	-3.31 (-5.98, -0.64)*
PFOA	-2.62 (-5.40, 0.17)	-3.09 (-5.80, -0.38)*
PFOS	-2.24 (-3.96, -0.53)*	-2.50 (-4.20, -0.80)**
PFHxS	-1.20 (-3.06, 0.67)	-1.53 (-3.35, 0.29)
PFNA	-2.21 (-4.73, 0.31)	-2.45 (-4.91, 0.02)
PFDeA	-2.50 (-5.26, 0.25)	-3.05 (-5.77, -0.32)*

Values are presented as mean (95% confidence interval).

PFAS: perfluoroalkyl substances; PFOA: perfluorooctanoic acid; PFOS: perfluorooctansulfonate; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFDeA: perfluorodecanoic acid; eGFR: estimated glomerular filtration rate.

^aAdjusted for sex and age.

^bAdjusted for sex, age, household income, body mass index, urinary cotinine, hemoglobin A1c, total cholesterol and abnormal blood pressure.

* $p < 0.05$; ** $p < 0.01$.

have shown a negative correlation between PFAS and kidney function.²⁹⁻³¹ However, since this study is a cross-sectional study, attention should be paid to interpretation, and the problem of reverse causation must be considered.

Association between serum PFAS concentration and kidney function

Table 5. Mean change in eGFR (mL/min/1.73 m²) per 1 ln-serum PFAS using multivariable regression according to confounders

Characteristics	Multivariable adjusted change in eGFR ^a (mL/min/1.73 m ²)					
	Total PFAS	PFOA	PFOS	PFHxS	PFNA	PFDeA
Sex						
Male	-2.27 (-4.84, 0.31)	-2.45 (-5.58, 0.68)	-1.68 (-3.57, 0.20)	-1.50 (-3.76, 0.76)	-2.23 (-5.30, 0.84)	-2.57 (-5.70, 0.57)
Female	-4.50 (-8.79, -0.20)*	-3.75 (-7.85, 0.35)	-3.44 (-6.31, -0.57)*	-1.60 (-3.85, 0.64)	-3.02 (-6.95, 0.92)	-3.72 (-8.37, 0.92)
Age (years)						
< 15	-1.66 (-4.81, 1.49)	0.38 (-2.78, 3.54)	-1.51 (-3.90, 0.88)	-1.14 (-3.63, 0.35)	0.89 (-3.19, 4.97)	0.82 (-3.22, 0.41)
≥ 15	-3.79 (-7.84, 0.26)	-6.30 (-10.56, -2.04)**	-2.80 (-5.11, -0.49)*	-1.25 (-4.19, 1.70)	-4.80 (-8.17, -1.43)**	-5.76 (-9.46, -2.06)**
BMI (kg/m ²)						
< 18.5	-3.98 (-0.83, 0.32)	-2.20 (-8.18, 3.77)	-5.27 (-8.52, -2.03)**	-0.11 (-2.46, 2.25)	-4.35 (-11.16, 2.47)	-1.75 (-8.42, 4.93)
18.5-25	-2.23 (-5.14, 0.68)	-2.19 (-4.80, 0.42)	-2.05 (-4.05, -0.05)*	-0.55 (-2.41, 1.30)	-2.22 (-5.02, 0.57)	-3.14 (-6.46, 0.19)
≥ 25	-6.53 (-12.72, -0.34)*	-7.40 (-14.17, -0.62)*	-2.00 (-7.21, 3.21)	-6.26 (-10.00, -2.52)**	-4.63 (-10.77, 1.51)	-4.31 (-10.05, 1.43)
Urinary cotinine (ng/mL)						
< 1.93	-3.33 (-8.50, 1.84)	-3.23 (-8.91, 2.45)	-1.63 (-5.44, 2.17)	-2.85 (-5.51, -0.19)*	-2.84 (-8.02, 2.35)	-4.34 (-10.56, 1.89)
1.94-3.43	-3.58 (-7.97, 0.82)	-3.74 (-7.69, 0.20)	-3.06 (-6.29, 0.18)	-0.69 (-3.28, 1.90)	-4.12 (-8.36, 0.13)	-1.05 (-5.26, 3.17)
≥ 3.44	-2.37 (-4.79, 0.04)	-1.31 (-4.65, 2.04)	-2.20 (-4.01, -0.38)*	-1.31 (-3.97, 1.34)	-0.67 (-4.02, 2.69)	-2.91 (-6.37, 0.57)
Total cholesterol (mg/dL)						
< 170	-2.30 (-5.00, 0.39)	-3.69 (-6.55, -0.82)*	-1.43 (-3.25, 0.39)	-1.09 (-3.04, 0.86)	-3.55 (-6.31, -0.79)*	-3.66 (-6.69, -0.64)*
≥ 170	-5.72 (-11.24, -0.21)*	-1.79 (-8.47, 4.89)	-4.51 (-8.34, -0.68)*	-3.01 (-5.78, -0.23)*	-0.59 (-6.48, 5.31)	-0.93 (-7.68, 5.82)
Abnormal blood pressure ^b						
No	-1.97 (-4.98, 1.04)	-2.08 (-5.06, 0.90)	-1.58 (-3.46, 0.30)	-0.87 (-2.84, 1.09)	-1.38 (-4.19, 1.42)	-1.68 (-4.93, 1.58)
Yes	-6.37 (-11.21, -1.53)*	-5.57 (-11.72, 0.58)	-4.85 (-9.06, -0.65)*	-3.39 (-7.36, 0.59)	-6.42 (-13.20, 0.36)	-9.27 (-16.42, -2.11)*

Values are presented as mean (95% confidence interval).

PFAS: perfluoroalkyl substances; PFOA: perfluorooctanoic acid; PFOS: perfluorooctansulfonate; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFDeA: perfluorodecanoic acid; eGFR: estimated glomerular filtration rate; BMI: body mass index.

^aAdjusted for sex, age, household income, body mass index, urinary cotinine, hemoglobin A1c, total cholesterol, abnormal blood pressure

^bAbnormal blood pressure was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or currently taking anti-hypertensive drugs. **p* < 0.05; ***p* < 0.01.

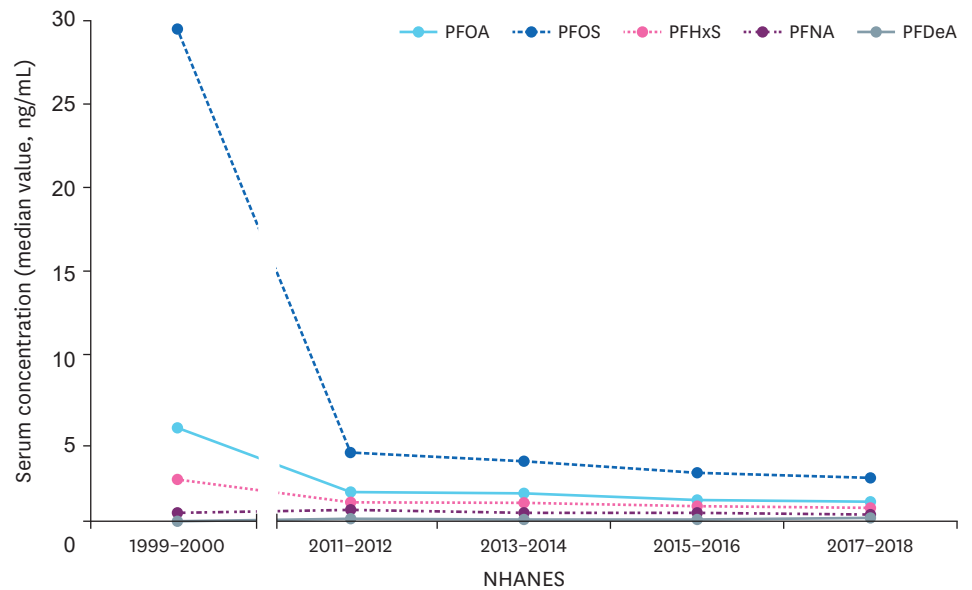


Fig. 1. Changes in serum perfluoroalkyl substances concentration of adolescents in 1999-2000 and in the last 4 years in the USA.

PFOA: perfluorooctanoic acid; PFOS: perfluorooctansulfonate; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFDeA: perfluorodecanoic acid; NHANES: National Health and Nutrition Examination Survey.

When PFAS reaches the body through various routes (dietary, inhalation, skin, etc.),³² it is distributed to diverse organs such as the liver and kidneys.^{33,34} Since the main excretion route of PFAS from the body are the kidneys,¹⁰ the effect of PFAS on kidney function is important.

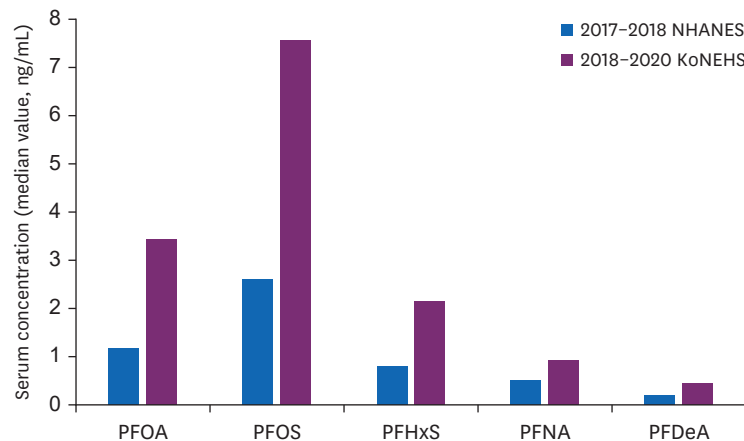


Fig. 2. Comparison of recent study results in Korean and USA adolescents. PFOA: perfluorooctanoic acid; PFOS: perfluorooctansulfonate; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFDeA: perfluorodecanoic acid; NHANES: National Health and Nutrition Examination Survey; KoNEHS: Korean National Environmental Health Survey.

PFAS is removed from the kidneys through active secretion in the proximal tubule, which is excreted from the blood into urine, and reabsorbed from urine back into the blood, without going through separate biotransformation in the kidneys.³⁵⁻³⁷ In addition, many molecular biological studies have also been reported on organic anion transport proteins that mediate the renal tubular secretion or reabsorption process involved in the renal elimination process of PFAS.³⁶⁻³⁸ The main toxic effects of PFAS on the kidneys are renal hypertrophy and histologic changes due to increased production of ROS,^{10,11} which change the permeability of microvascular endothelial cells, resulting in decreased kidney function.¹¹

There are many epidemiologic studies suggesting a negative association between PFAS and decreased kidney function.²⁹⁻³¹ In particular, Watkins et al.³⁰ and Kataria et al.³¹ are noteworthy. They found that an increase in serum PFAS concentrations was associated with decreased eGFR in a non-adult population. However, since all of these studies are cross-sectional studies, the problem of reverse causation remains. On this issue, Moon,³⁹ by using causal inference in statistics, recently stated that the possibility of reverse causation might be low. Moon also performed cross-sectional studies and used not only the linear regression method used in previous studies but additional methods (the generalized additive model and regression discontinuity model). To study the possibility of reverse causation, he applied these statistical models to reversed independent and dependent variables. He found that when the eGFR decreased below 60 mL/min/1.73 m², the concentration of each PFAS did not increase but rather decreased.

Blake et al.⁴⁰ and Lin et al.⁴¹ reported that PFAS was associated with a decrease in eGFR through well-designed longitudinal studies. This study can tentatively rule out the possibility of reverse causation from the following points of view. First, because kidney function decreases with age,⁴² all the study subjects are adolescents with superior kidney function compared to adults. Second, the prevalence and duration of chronic diseases that can affect kidney function is very low compared to adults. Third, there were no patients with congenital or recognized kidney disease through a preliminary questionnaire.

This study has great significance as basic data in determining public health policy in the future from a long-term perspective. In the United States, a survey of blood PFAS

concentrations began in 1999, and **Fig. 1** shows traces in blood the results of the initial survey and the last 4 years from the NHANES. Overall, from 1999–2000 to the latest study in 2017–2018, PFOA, PFOS, and PFHxS decreased significantly, but PFNA and PFDeA showed no significant change. Since PFAS were classified as persistent organic pollutants according to the Stockholm Convention on Persistent Organic Pollutants, their use and production are restricted in Korea. However, due to the long half-life and bioaccumulation of residual PFAS in nature, exposure is unavoidable.^{4-6,43} In addition to PFOA and PFOS, which have been studied the most among PFAS, the exposure of other substitutes, for which there are no restrictions on use, should be noted.⁴⁴ According to the 2021 Environmental Movement Federation investigation, as a result of investigating 20 types of cosmetics sold in the country, more than one type of PFAS was detected in 10 products, and up to 5 types, with a maximum concentration of 105.50 ng/g.⁴⁵ The blood concentration of PFAS in adolescents in the KoNEHS survey conducted from 2018 to 2020 was approximately twice as high or more in all 5 PFAS based on median values compared to the 2017 to 2018 NHANES (**Fig. 2**). Even if kidney function is normal during adolescence, a history of kidney damage during that period is associated with an increased risk of chronic kidney disease in the long term.⁴⁶ Therefore, considering the persistency, bioaccumulation, toxicity and wide distribution of PFAS in wildlife, it is easy to infer that exposure to PFAS in adolescence may have far greater long-term adverse effects than in adults.

This study has the following limitations. First, since the urine albumin concentration was excluded in this study, only eGFR was used as an index of kidney function. If the albumin-to-creatinine ratio, another index of kidney function, could be investigated, more diverse results could be obtained. Second, since the bedside Schwartz equation was originally created to estimate eGFR in children with CKD, it might be inaccurate in a healthy population, as in this study.⁴⁷ Third, there were many practical limitations. Because it was an epidemiological study, guidelines for measuring blood pressure were not well applied, and many other factors were not considered when diagnosing diabetes due to the lack of diversity in clinical blood tests. In addition, the failure to consider other risk factors that may affect kidney function, such as heart (cardiovascular) disease, a family history of kidney disease, and the frequent use of medications that can damage the kidneys, is clear limitations of using secondary data. Fourth, more diverse statistical methods, such as the relative potency factor approach, could be used to analyze the relationship between serum PFAS concentration and kidney function. Finally, due to the inherent limitations of cross-sectional studies, care must be taken in interpretation, and the direction of the relationship between serum PFAS concentration and decreased kidney function is unclear.

Nevertheless, this study has the following strengths. For the first time in Korea, the relationship between PFAS, an environmentally harmful substance, and kidney function was derived from representative results of Korean adolescents. In particular, it is very noteworthy that the median serum PFAS concentration in Korean adolescents is significantly higher than that of American adolescents. Based on this, it is expected that it will be used as basic data when identifying and analyzing the health threats of PFAS and as a basis for establishing health policies.

CONCLUSIONS

The association between kidney function and PFAS is one of the major environmental concerns in recent years. In this cross-sectional study, which was conducted for the first time among Korean adolescents, it was found that there was a negative correlation between the 5 types of PFAS (PFOA, PFOS, PFHxS, PFNA, and PFDeA) and their combinations, and kidney function. Long-term, well-designed longitudinal studies and continuous follow-up are needed.

ACKNOWLEDGEMENTS

Thanks to the National Institute of Environmental Research for willingly providing data. To many people, including Lee and reviewers, thanks them for their helpful advice. And above all, I would like to express my greatest gratitude to my wife for her encouragement and advice.

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