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Per- and polyfluoroalkyl substances and kidney function: Follow-up results from the Diabetes Prevention Program trial

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are ubiquitously detected in populations worldwide and may hinder kidney function. The objective of the study was to determine longitudinal associations of plasma PFAS concentrations with estimated glomerular filtration rate (eGFR) and evaluate whether a lifestyle intervention modify the associations. We studied 875 participants initially randomized to the lifestyle or placebo arms in the Diabetes Prevention Program (DPP, 1996–2002) trial and Outcomes Study (DPPOS, 2002–2014). We ran generalized linear mixed models accounting *a priori* covariates to evaluate the associations between baseline PFAS concentrations and repeated measures of eGFR, separately, for six PFAS (PFOS, PFOA, PFHxS, EtFOSAA, MeFOSAA, PFNA); then used quantile-based g-computation to evaluate the effects of the six PFAS chemicals as a mixture. The cohort was 64.9% female; 73.4% 40–64 years-old; 29.4% with hypertension; 50.5% randomized to lifestyle intervention and 49.5% to placebo and had similar plasma PFAS concentrations as the general U.S. population in 1999–2000. Most participants had normal kidney function (eGFR > 90 mL/min/1.73 m^2) over the approximately 14 years of follow-up. We found that plasma PFAS concentrations during DPP were inversely associated with eGFR during DPPOS follow-up. Each quartile increase in baseline plasma concentration of the 6 PFAS as a mixture was associated with 2.26 mL/min/1.73 m^2 lower eGFR (95% CI: −4.12, −0.39) at DPPOS Year 5, approximately 9 years since DPP randomization and PFAS measurements. The lifestyle intervention did not modify associations, but inverse associations were stronger among participants with hypertension at baseline. Among prediabetic adults, we found inverse associations between baseline plasma PFAS concentrations and

Abbreviations: BMI, Body mass index; CDC, Centers for Disease Control and Prevention; DAGs, directed acyclic graphs; DASH, Dietary Approaches to Stop Hypertension; DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcomes Study; eGFR, Estimated glomerular filtration rate; EtFOSAA, N-ethyl-perfluorooctane sulfonamido acetic acid; FDR, False-discovery rate; FP, Fractional polynomials; GAM, Generalized additive models; IRB, institutional review board; LOD, limit of detection; MeFOSAA, N-methyl-perfluorooctane sulfonamido acetic acid; NHANES, National Health and Nutrition Examination Survey; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; n-PFOA, n-perfluorooctanoic acid; n-PFOS, n-perfluorooctane sulfonic acid; PFAS, Per- and polyfluoroalkyl substances; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexane sulfonic acid; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctane sulfonic acid; Sb-PFOA, branched perfluorooctanoic acid isomers; Sm2-PFOS, Perfluorodimethylhexane sulfonic acid isomers; Sm-PFOS, Perfluoromethylheptane sulfonic acid isomers.

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measures of eGFR throughout 14 years of follow-up. The lifestyle intervention of diet, exercise and behavioral changes did not modify the associations, but persons with hypertension may have heightened susceptibility.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large group of nonbiodegradable synthetic chemicals ubiquitously detected in the environment worldwide. First manufactured in 1950s, PFAS are widely used in industrial and consumer products, including firefighting foams, non-stick cookware, food packaging, stain-, grease- and water-resistant products (ATSDR, 2018). PFAS are ubiquitously detected in human populations and many also have long elimination half-lives in humans, e.g., 5.3 years for perfluorohexanesulfonic acid (PFHxS), 3.4 years for perfluorooctanesulfonic acid (PFOS), 2.7 years for perfluorooctanoic acid (PFOA) (Li et al., 2018). More than 98% of blood samples collected from participants in the U.S. National Health and Nutrition Survey (NHANES) contained detectable concentrations of select PFAS (Calafat et al., 2007; Kato et al., 2011a, 2011b). Exposure to PFAS has been linked with obesity, diabetes, hyperlipidemia and microvascular disease, conditions that are themselves associated with poorer kidney function (Cardenas et al., 2017a, 2019; Lin et al., 2019; Smurthwaite et al., 2018). Furthermore, the kidney is a primary route for PFAS elimination (Kjølholt and Warming, 2015). Once certain PFAS enter the human body, it may take up to several years to eliminate them (Olsen et al., 2007) and continued exposure leads to bioaccumulation. PFAS have been shown to cause renal hypertrophy and histopathologic changes (Cui et al., 2009) and alter renal microvascular endothelial-cell permeability through increased production of reactive oxidative species. The proximal tubules have been shown to actively secrete and reabsorb PFAS (Stanifer et al., 2018).

Systematic reviews of the PFAS literature found evidence that PFAS is an emerging environmental threat to kidney health (Ferrari et al., 2019; Stanifer et al., 2018). Currently, most epidemiological evidence from population-based studies on PFAS biomarkers and kidney diseases is cross-sectional (Dhingra et al., 2017; Kataria et al., 2015; Shankar et al., 2011; Watkins et al., 2013), and reverse causation has been a main concern, i.e. that PFAS concentration in blood increases as kidney function declines. More findings from longitudinal data are needed to address the potential gap causal link between PFAS and kidney health (Ferrari et al., 2019; Stanifer et al., 2018; Wang et al., 2019). The two available studies that used longitudinal data showed contradictory findings. Blake et al. found that higher serum PFHxS, perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were associated with lower prospective measures of eGFR but N-methyl-perfluorooctane sulfonamido acetic acid (MeFOSAA) was associated with higher eGFR. However, Dhingra et al. concluded reduced eGFR was the cause rather than the result of elevated serum PFOA level (Blake et al., 2018; Dhingra et al., 2017). Both studies used community-exposed cohorts which had higher PFAS exposure than the U.S. general population.

In this study, we used a longitudinal cohort of prediabetic adults to test the relationship between commonly detected PFAS and kidney function over 14 years of follow-up. We implemented directed acyclic graphs (DAGs) to assess variables that may confound the relationship and used multiple approaches to address the issue of reverse causation in this association. Our study question was whether baseline PFAS concentrations, as individual exposure and as a mixture, were associated with repeated measures of estimated glomerular filtration rate (eGFR) over time, and whether lifestyle intervention could modify this association. We hypothesized higher baseline PFAS concentrations would be associated with lower eGFR over time. We also hypothesized that an initial lifestyle intervention of diet, exercise and behavioral changes could reduce this detrimental effect.

2. Methods

2.1. Study population

The Diabetes Prevention Program (DPP) was a randomized controlled trial to prevent or delay the onset of type 2 diabetes using lifestyle or pharmacological intervention, relative to medication placebo (Diabetes Prevention Program Research Group, 1999, 2000). The trial recruited obese and overweight adults $\geq$ 25 years with elevated fasting glucose from 27 clinical centers across the United States between 1996 and 1999, and randomized participants into three arms: a pharmacological intervention (metformin), a medication-placebo control, or a lifestyle intervention (Knowler et al., 2002). The lifestyle intervention arm contained a goal-based behavioral intervention to achieve 7% weight loss and maintenance of weight loss; each participant had a personal lifestyle coach or case manager who delivered the intervention and provided frequent follow-up and contacts to ensure achievement and maintenance of weight and physical activity goals (Diabetes Prevention Program Research Group, 2002a,b). Both the lifestyle and metformin interventions demonstrated effectiveness in preventing type 2 diabetes (Knowler et al., 2002). All participants were offered a modified version of the lifestyle intervention after DPP ended (Diabetes Prevention Program Research Group, 2009, 2012) and were offered follow up in Diabetes Prevention Program Outcome Study (DPPOS) which started in 2002 (Diabetes Prevention Program Research Group, 2015). For this analysis, we captured the exposure (plasma PFAS) during the DPP phase (from baseline recruitment to DPP intervention) and the outcome (eGFR) from DPPOS follow-up (after the DPP intervention phase ended) to allow for the prospective temporal order between exposure and outcome (**eFigure 1**). Participants enrolled in the DPP intervention phase for an average (standard deviation, SD) of 3.1 (0.7) years (for this sub-cohort), and had up to 11 annual visits during DPPOS; the total follow-up time since DPP baseline randomization was 13.9 (2.6) years (**eTable 1**).

This prospective analysis was restricted to participants initially randomized to the lifestyle and placebo arms; 957 (46.6%) had enough blood volume remaining in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Repository for plasma PFAS measurements. We did not measure PFAS among participants in the metformin arm given the unknown interaction between metformin and PFAS and the protective effect of metformin on diabetic kidney disease. Both DPP and DPPOS study phases have little missing data (only N = 1 missing all eGFR measures among those with PFAS measurements) so we used complete case analysis in this study (Diabetes Prevention Program Research Group, 2015). After excluding participants with missing covariates and removing extreme values for eGFR, the final longitudinal analysis included 875 participants (see study flow chart in **eFigure 1**).

All DPP/DPPOS protocols were approved by the institutional review board (IRB) at each clinical center and Harvard Pilgrim Health Care IRB reviewed and approved the protocol for this current analysis. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research.

2.2. Plasma PFAS concentrations

We retrieved plasma samples stored at the NIDDK repository (https://repository.niddk.nih.gov) for analyses at the CDC laboratory. The modified on-line solid-phase extraction-high performance liquid chromatography-isotope dilution-tandem mass spectrometry method (Cardenas et al., 2017a, Kato et al., 2011a, 2011b), also used to analyze NHANES PFAS samples, yielded limit of detections (LOD) of 0.1 ng/mL

for all PFAS. Measurements < LOD were imputed as LOD/$\sqrt{2}$ (Hornung and Reed, 1990). This analysis included 6 PFAS with detection frequency > 80% [PFOS, PFOA, PFHxS, N-ethyl-perfluorooctane sulfonamido acetic acid (EtFOSAA), MeFOSAA, and PFNA]. Concentrations of PFOS and PFOA were calculated as the sum of their respective isomers: linear perfluorooctanesulfonic acid PFOS (n-PFOS), sum of perfluoromethylheptane sulfonic acid isomers (Sm-PFOS), and sum of perfluorodimethylhexane sulfonic acid isomers (Sm2-PFOS) for PFOS; and linear perfluorooctanoic acid (n-PFOA) and sum of perfluoromethylheptanoic and perfluorodimethylhexanoic acids (Sb-PFOA) for PFOA; we performed imputation for concentrations < LOD before summing which was consistent with the method used in the Fourth National Report on Human Exposure to Environmental Chemicals (Centers for Disease Control and Prevention, 2019). We calculated the average concentrations of baseline and the DPP Year 2 measures (referred to as baseline PFAS from now on), which had been shown to adequately reflect the relative PFAS body burden considering the relatively long half-lives of many PFAS (Cardenas et al., 2017a; Cardenas et al., 2019; Lin et al., 2020a). The year of blood collection ranged between 1996 and 1999 for baseline and 1998 to 2001 for DPP Year 2. The concentrations between the two measurements did not change significantly for all participants, which was expected considering the relatively long biological half-lives of most PFAS. The temporal pattern and geometric means of all 6 PFAS were comparable to those observed in US NHANES adults (Cardenas et al., 2017a).

2.3. Kidney function

As previously reported, DPP/DPPOS used Roche reagents on the Hitachi 917 autoanalyzer (Boehringer Mannheim, Mannheim, Germany) to measure serum creatinine (Kim et al., 2019). We extracted annual laboratory results of serum creatinine for DPPOS years 1 to 11 annual visits for our analysis; 62% of the 875 participants had all 11 annual measures and more than 90% had more than 5 measures (**eTable 2**). We used the 2009 Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) serum creatinine equation (Levey et al., 2006) to calculate eGFR. Due to privacy protection, we did not have participants' actual age, so we used the following "mid-point" for each age category: 38 for <40 years; 42 for 40–44 years; 47 for 45–49 years; 52 for 50–54 years; 57 for 55–59 years; and 62 for 60–64 years; 67 for 65+ years). We recognize the use of 67 for the 65+ age group may introduce bias considering accelerating declines in eGFR with age, so we also performed sensitivity analyses using 70 and 75 as the imputed age for this oldest group. To avoid healthy participant bias, we included eGFR data only for DPPOS Years 1 to 8 annual visits for the final longitudinal analysis so more than 90% of the participants had eGFR measures at all annual follow-up visits; this covered approximately 4.5 to 11.4 years since baseline (time point of PFAS measurements). We also included all available DPPOS follow-up data (up to 11th annual visits) in the sensitivity analysis (**eTable 1**). Although eGFR is not a perfect measure of kidney function, due to data availability, we decided to use eGFR which can also produce comparable results with previous studies. We also had measures urine albumin-to-creatinine ratios (ACRs), but only at DPP baseline. We defined elevated ACR, or microalbuminuria, as ACR ≥ 30 mg/g.

2.4. Covariates

We selected covariates *a priori* based on study questions and used DAGs to identify potential confounders as well as mediators that could be in the causal pathway between plasma PFAS concentration and eGFR (**eFigure 2**). The following information was extracted directly from the NIDDK data repository: age category, sex, race/ethnicity, education, marital status, income, smoking status, treatment arm, baseline microalbuminuria, hypertension status, menopause status, diabetes status at the end of DPP phase, and time (years since randomization) of each outcome assessment. Hypertension status was defined as self-reported hypertension diagnosis, use of anti-hypertensive medications or systolic/diastolic BP ≥ 140/90 mmHg. We modeled time and age (using the "mid-point" age described in the previous section) as continuous variables and the rest as categorical variables (see categorization in Table 1). We evaluated dietary habits using the Dietary Approaches to Stop Hypertension (DASH) score, which we previously found to be associated with plasma PFAS concentrations (Lin et al., 2020b). We evaluated uses of kidney medications [angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers] based on self-reported prescriptions.

2.5. Statistical analyses

We used descriptive analysis to report participants' characteristics, applied visual inspection to detect outliers, and used normality tests to assess the distributions of each variable. Plasma PFAS concentrations were right-skewed, thus we log-2 transformed them. In the main analysis we examined differences in the eGFR during DPPOS by baseline PFAS plasma concentrations. Because Sm2-PFOS concentrations were <LOD in more than 50% of the samples and the median concentration was close to the LOD (0.1 ng/mL), we also treated Sm2-PFOS as a binary variable (detected vs non-detected) in the analysis. We applied

Table 1
Baseline characteristics of study participants.

Characteristics	N(%), or mean ± SD
Sample size, N	875
Group assignment	
Lifestyle	442 (50.5)
Placebo	433 (49.5)
Sex	
Male	307 (35.1)
Female	568 (64.9)
Race/ethnicity	
Non-Hispanic White	502 (57.4)
African American	171 (19.5)
Hispanic of any race	163 (18.6)
All others	37 (4.5)
Age at DPP enrollment (years)	
<40	95 (10.9)
40–44	100 (11.4)
45–49	196 (22.4)
50–54	155 (17.7)
55–59	130 (14.9)
60–64	97 (11.1)
>65	102 (11.7)
Educational attainment	
<High school	41 (4.7)
High school/GED	183 (20.9)
College	427 (48.8)
Graduate school	224 (25.6)
Marital Status	
Married/Cohabitating	590 (67.4)
Single	107 (12.2)
Divorced	138 (15.8)
Widowed	40 (4.6)
Income	
<$20,000	107 (12.2)
$20,000 - <$35,000	159 (18.2)
$35,000 - <$50,000	173 (19.8)
$50,000 - <$75,000	166 (19.0)
≥75,000	196 (22.4)
Refused to answer	74 (8.5)
Current smoker	52 (5.9)
Menopausal, % among female participants	307 (54.0)
Hypertension diagnosis	262 (29.4)
Use of kidney medication[a]	72 (8.2)
DASH Diet Score (0–9 range)	2.5 ± 1.6
Microalbuminuria at baseline (ACR ≥ 30 mg/g)	41 (4.7)
Developed diabetes during DPP	483 (55.2)

[a] Kidney medication: ACE-inhibitor, ARBs, beta-blockers.

generalized linear mixed models with random intercepts and slopes and used restricted maximum likelihood for estimation to estimate the longitudinal association between baseline PFAS and annual measures of eGFR during DPPOS (approximately 3–16 years after the baseline PFAS measurement, see **eFigure 1** and **eTable 1** for DPP/DPPOS timeline). We tested models with different correlation structures, added quadratic and cubic terms for the follow-up time based on visual inspection of scatter plot and eGFR trajectories, and evaluated interactions between parameters. We selected the final model based on study questions and model fit using the likelihood ratio test for nested models (see detailed information in **Appendix A**). We reported parameter estimates of the fixed effect that estimated the differences in mean eGFR per doubling of plasma PFAS concentrations across the study period adjusted for covariates; evaluated potential effect modification of the longitudinal associations by sex, treatment arm, and baseline hypertension status, by adding a multiplicative term between plasma PFAS concentrations and each effect modifier in the model; and conducted additional stratified analyses if the multiplicative term had $p < 0.10$. We tested reverse causation of effect by using baseline eGFR at DPP as the exposure and repeated measures of plasma PFAS concentrations (measured at baseline, DPP Year 2 annual visit and DPPOS Year 10 annual visits) as outcomes in the longitudinal models (see detailed equation of the model in **Appendix A**).

We performed mixture analysis using quantile-based g-computation (Keil et al., 2020) to estimate the effect of the 6 PFAS as a mixture with eGFR measured at the DPPOS Year 5 (mean 8.4 years since randomization) as the outcome, a timepoint when outcome measures were available for more than 90% of the study participants (**eTable 1**). Quantile g-computation (Keil et al., 2020) estimates the effect of an exposure mixture index that is a weighted average of all exposure after transforming PFAS concentrations into quartiles, and produces effect estimates that can be interpreted as mean difference in eGFR across quantile range of the plasma PFAS concentrations as a mixture. We evaluated both linear and nonlinear effects and present the mixture slope with overall model confidence bounds (estimated by 1000 bootstraps) as well as pointwise comparison of the expected difference in eGFR at each quartile of PFAS concentration with respect to the 2nd quartile using the *gqcomp* R package (https://cran.r-project.org/web/packages/qgcomp/vignettes/qgcomp-vignette.html version 1.3 defaults).

As a sub-analysis, we performed cross-sectional analyses of plasma PFAS concentrations with eGFR and ACR at DPP baseline using linear regression to compare with most previous literature. We assessed the linearity using generalized additive models. For sensitivity analyses, we accounted for additional variables in the longitudinal models and mixtures analysis, including baseline eGFR level, diabetic status at the beginning of DPPOS, and elevated ACR at baseline. However, since these variables were likely mediators between the associations of plasma PFAS concentrations and kidney function (**eFigure 2**), we did not include them in the main analysis. We also ran sensitivity analyses using 70 and 75 as the imputed age for estimating the eGFR for the 65 + age group. We performed the statistical modeling using SAS Studio and R version 3.6.0. Reporting of the manuscript follows the guidelines and checklist for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Von Elm et al., 2007).

3. Results

3.1. Participant characteristics and plasma PFAS concentrations

We included 875 DPP/DPPOS participants in this analysis: 442 (50.5%) from the lifestyle arm and 433 (49.5%) from the placebo arm. At baseline, participants were 64.9% female; 57.4% non-Hispanic White, 66.4% 40–59 years old; 74.4% college graduates; 67.4% married/cohabitating; 41.4% with annual income >$50,000; 5.9% smokers; 29.4% with hypertension.; 8.2% used kidney medication, 4.7% had microalbuminuria at baseline, and 55.2% developed diabetes at the start of DPPOS follow-up (Table 1). Average plasma PFAS concentrations were comparable to the general U.S. population concentrations during 1999–2000 (Centers for Disease Control and Prevention, 2019) and did not differ across the two treatment arms. Concentrations of all PFAS were positively correlated (**eFigure 3**). PFOS [median (interquartile range, IQR): 27.6 ng/mL (19.2, 38.9)] and PFOA [5.5 ng/mL (3.8, 7.4)] were the two PFAS detected at the highest concentrations (Table 2).

Most participants had normal eGFR (>90 mL/min/1.73 m^2) throughout DPP/DPPOS (Table 2). At baseline, the mean (STD) eGFR was 111.05 (38.0) mL/min/1.73 m^2 and 87.2% had normal eGFR (Table 2).

3.2. Longitudinal associations of PFAS with eGFR

We used DAGs to evaluate the appreciate covariates to adjust for in assessing the longitudinal relationship between baseline PFAS and repeated measures of eGFR (**eFigure 2A**) and described the model evaluation and selection process in detail in **Appendix A**. After controlling for baseline covariates including age, sex, race/ethnicity, education, marital status, income, smoking status, menopause status, DASH diet score, hypertension status, and use of kidney medication, we observed inverse associations of PFOS and PFOA isomers with eGFR; each doubling of plasma total PFOS concentrations were associated with 1.50 mL/min/1.73 m^2 lower eGFR (95% CI: −2.81, −0.19) ; and each doubling of n-PFOA and Sb-PFOA were associated with 1.49 (95% CI: −2.97, 0.00) and 0.85 (95% CI: −1.58, −0.12) mL/min/1.73 m^2 lower eGFR, respectively (Table 3). The effect estimates were robust with additional adjustment for diabetic status (**eTable 3**). When adjusting for baseline eGFR, which was a potential mediator between plasma PFAS

Table 2
Plasma concentrations of PFAS and kidney function during study follow-up.

Exposure (PFAS)[a]	N	Median (IQR) (ng/mL)	
Total PFOS	875	27.6 (19.2, 38.9)	
n-PFOS	875	19.9 (13.6, 28.2)	
Sm-PFOS	875	7.5 (5.2, 10.9)	
Sm2-PFOS	875	0.1 (0.1, 0.3)	
Total PFOA	875	5.5 (3.8, 7.4)	
n-PFOA	875	4.7 (3.4, 6.2)	
Sb-PFOA	875	0.6 (0.4, 1.0)	
PFHxS	875	2.4 (1.6, 3.8)	
EtFOSAA	875	1.2 (0.7, 2.0)	
MeFOSAA	875	1.1 (0.7, 1.7)	
PFNA	875	0.6 (0.4, 0.9)	
Outcome eGFR	N	Mean (STD) (mL/min/1.73 m^2)	Percent of participants with normal eGFR (>90 mL/min/1.73 m^2)
DPPOS Year 1	811	111.0 (40.2)	79.4
DPPOS Year 2	868	106.7 (24.4)	79.2
DPPOS Year 3	845	105.3 (22.7)	77.6
DPPOS Year 4	826	100.9 (18.6)	71.2
DPPOS Year 5	843	101.2 (19.1)	71.4
DPPOS Year 6	814	102.1 (22.0)	70.4
DPPOS Year 7	780	99.4 (19.4)	67.4
DPPOS Year 8	788	98.0 (19.2)	63.3
DPPOS Year 9	773	96.9 (18.9)	61.7
DPPOS Year 10	771	96.7 (19.6)	58.8
DPPOS Year 11	748	96.8 (19.7)	56.0

[a] Average of baseline and DPP Year 2.

Table 3
Associations between PFAS plasma concentration and mean change in eGFR during DPPOS follow-up estimated using generalized mixed models[a], overall and stratified according to baseline hypertension status.

Log-2 PFAS analyte	Full	Stratified		
	(N = 875) β (95% CI)	Hypertension[b] (N = 262) β (95% CI)	No hypertension (N = 613) β (95% CI)	p_{int}[c]
Total PFOS	**−1.50 (−2.81, −0.19)**	−2.19 (−4.92, 0.53)	−1.44 (−2.96, 0.06)	0.68
n-PFOS	**−1.34 (−2.62, −0.06)**	−1.98 (−4.62, 0.66)	−1.30 (−2.79, 0.17)	0.72
Sm-PFOS	**−1.56 (−2.85, −0.28)**	−2.15 (−4.89, 0.57)	−1.49 (−2.96, −0.02)	0.72
Sm2-PFOS[d]	**−1.87 (−2.88, −0.86)**	−2.66 (−4.73, −0.60)	−1.58 (−2.75, −0.41)	0.24
Total PFOA	−1.35 (−2.73, 0.02)	−3.18 (−5.85, −0.51)	−0.65 (−2.30, 0.99)	0.16
n-PFOA	**−1.49 (−2.97, −0.01)**	−3.16 (−5.98, −0.35)	−0.83 (−2.63, 0.96)	0.24
Sb-PFOA	**−0.85 (−1.58, −0.12)**	−1.66 (−3.11, −0.21)	−0.55 (−1.41, 0.29)	0.20
PFHxS	0.21 (−0.79, 1.21)	**−2.35 (−4.46, −0.25)**	**1.24 (0.09, 2.39)**	**0.01**
EtFOSAA	−0.15 (−0.97, 0.65)	0.02 (−1.63, 1.68)	−0.31 (−1.27, 0.64)	0.53
MeFOSAA	−0.62 (−1.71, 0.45)	−1.56 (−3.82, 0.69)	−0.15 (−1.40, 1.09)	0.33
PFNA	0.18 (−0.90, 1.27)	**−1.85 (−4.20, 0.49)**	**0.90 (−0.33, 2.14)**	**0.06**

[a] The generalized mixed model include random intercept and random slope for year since enrollment, the crude model used repeated measures of eGFR from the 1st to the 8th annual visit during DPPOS follow-up as the dependent variable and used baseline PFAS concentration (average between baseline and year 2 measures during DPP, log-2 transformed), treatment arm, and year since randomization as the independent variables, the model also included a second and a third order spline term for year (year*year and year*year*year); the adjusted model adjusted for baseline covariates including age, sex, race/ethnicity, education, marital status, income, smoking status, menopause status, DASH diet score, hypertension status, and use of kidney medication. N = 875. The beta coefficient is interpreted as the mean difference in eGFR (mL/min/1.73 m^2) during DPPOS follow-up per doubling of baseline PFAS concentration.
[b] Hypertension was defined as self-reported hypertension diagnosis, use of anti-hypertensive medications, or systolic/diastolic BP ≥ 140/90 mmHg.
[c] p_{int}: p-value of the interactive term between PFAS and baseline hypertension status ($p < 0.1$ suggests effect modification).
[d] β (95% CI) = −3.75 (−5.83, −1.68) for detected vs non-detected Sm2-PFOS.

concentration and longitudinal decline in kidney function (see **eFigure 2 for DAG**), significant longitudinal associations remained for Sm2-PFOS and Sb-PFOS (**eTable 3**). Controlling for elevated ACR at baseline strengthened the magnitude of inverse association between some plasma PFAS and eGFR (**eTable 3**) which suggested potential negative confounding by microalbuminuria (see **eFigure 2 for DAG**). We did not find evidence of effect modification by sex or the initial lifestyle intervention (**eTable 4**), but participants with baseline hypertension had greater decreases in eGFR per doubling of plasma PFAS concentrations (Table 3). The test for potential difference in the slope of eGFR decline by adding an interaction term between time and PFAS yield statistically insignificant result (**Appendix A**). Evaluation for reverse causation showed that repeated measures of plasma PFAS concentrations did not differ significantly by baseline eGFR level (data not shown). Analysis using all eGFR data from Year 1 to Year 11 shows comparable findings with associations of the same direction and similar magnitude, however, most of the 95% confidence interval were wider and crossed the null (data not shown). Sensitivity analyses using different imputed ages in estimating the eGFR for the oldest age group (65+ years) showed comparable estimates (beta changed less than 0.1), and all the statistically significant findings remained excepted for the borderline significant n-PFOA (**eTable 5**).

3.3. PFAS as a mixture

Quantile g-computation estimated a one quartile increase in PFAS mixtures to be associated with 2.26 (95% CI: −4.12, −0.39) mL/min/1.73 m^2 lower eGFR at year 5 in DPPOS, conditional on covariates. Sm2-PFOS and Sb-PFOA contributed to most of the weight of the mixtures (**eTable 6**). Estimated eGFR decreased linearly by quartile of PFAS mixture concentrations (Fig. 1), and test of nonlinearity did not show significant deviation from linear effect. Controlling for baseline eGFR reduced the magnitude of the estimate but the effect remained statistically significant [Ψ: −1.81 (95% CI: −3.57. −0.04,) mL/min/1.73 m^2 eGFR at DPPOS Year 5 per quartile increase) (**eTable 6**).

3.4. Cross-sectional association at baseline

We evaluated cross-sectional associations of plasma PFAS concentrations with eGFR and ACR at baseline using data from 925 participants who had available data (**eFigure 1**); participants' characteristics were comparable with study population of the main longitudinal analysis (**eTable 7**). Most PFAS were not cross-sectionally associated with eGFR at baseline, except for Sm2-PFOS [-4.66 (-8.29, −1.04) mL/min/1.73 m^2 per doubling or −2.90 (-4.94, −0.85) mL/min/1.73 m^2 comparing detectable vs non-detectable, **eTable 8**]. Consistent with longitudinal findings, we detected effect modification by hypertension status (**eTable 8**). There was no evidence of effect modification by sex or nonlinearity of effect. As a mixture, baseline plasma concentrations of these 6 PFAS were not associated with baseline eGFR in this population [ψ: −3.26 (95% CI: −1.63, 0.64) mL/min/1.73 m^2 eGFR per quantile increase]. Baseline ACR was inversely associated with baseline PFOA and EtFOSAA, and there was no evidence of effect modification by hypertension status (**eTable 9**) or baseline eGFR (data not shown).

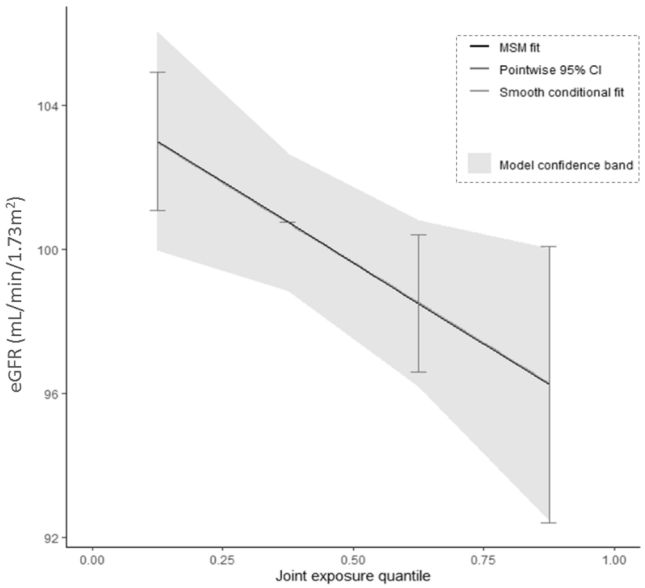

Fig. 1. Mixture effect of 6 plasma PFAS concentrations on eGFR at DPPOS Year 5.

4. Discussion

In this prospective analysis incorporating approximately 14 years of kidney function data from prediabetic adults enrolled in the lifestyle and placebo arms of the DPP trial, we observed that plasma concentrations of select PFAS, individually and as a mixture, were associated with lower mean eGFR over time, or declining kidney function. These results support our initial hypothesis. However, we did not find evidence that higher baseline PFAS was associated with greater slope of eGFR decline, which could be due to the fact that most participants had normal kidney function throughout the follow-up and our data was underpowered to detect the difference in slope. Additionally there presumably was decreasing PFAS exposure after baseline (1996–1999) due to manufactures' phasing out of PFOS and PFOA (US EPA, 2016) which may have attenuated the effect. While there is evidence on the adverse effect of PFAS on kidney function (Ferrari et al., 2019; Stanifer et al., 2018; Zhao et al., 2020), most prior epidemiological studies were cross-sectional, thus limiting inferences on causality (Stanifer et al., 2018; Wang et al., 2019), and the two available studies using longitudinal data showed inconsistent results. Specifically, Black et al. observed repeated measures of higher serum PFNA, PFHxS and PFDA and lower MeFOSAA were significantly associated with lower longitudinal measures of eGFR, but found null association between PFOA and eGFR (Blake et al., 2018). Dhingra et al., on the other hand, observed significant association between PFOA and eGFR, but only when using PFOA concentration measured in the serum (cross-sectional analysis only). When they evaluated the longitudinal data with modelled PFOA serum concentrations based on external exposure, such association did not exist which led them to conclude the observed association between higher serum PFOA and reduced eGFR was a result of reverse causation (Dhingra et al., 2017). While we cannot perform a randomized intervention to examine the causal effect of PFAS exposure on kidney function, our study utilized a prospective study design and implemented multiple tests of reverse causation to establish the temporality of the relationship in order to provide a more definitive evidence of the causal influence of PFAS on kidney function. We estimated that each doubling of baseline PFOS concentrations were associated with 1.50 mL/min/1.73 m^2 (95% CI: −2.81, −0.19) lower eGFR during the study follow-up; and as a mixture, each quartile increase in baseline PFAS was associated with 2.26 mL/min/1.73 m^2 (95% CI: −4.12, −0.39) lower eGFR at the 5th annual follow-up visits of DPPOS controlling for age, sex, race/ethnicity, education, marital status, income, smoking status, baseline menopause status, baseline diet score, treatment arm, and baseline blood pressure. When additionally controlled for baseline eGFR, the effect estimates attenuated somewhat but still stayed statistically significant. While this effect may not translate to immediate clinical manifestation on kidney health, over time and at the population level, PFAS exposure may negatively affect the kidney and compound the effects of other risk factors. Contrary to our hypothesis, we did not find evidence that the PFAS-associated decreases in eGFR were modified by an initial lifestyle intervention targeting diet, exercise and behavioral changes. However, all participants were offered a modified lifestyle intervention after the unblinding of the DPP intervention (Diabetes Prevention Program Research Group, 2015; Diabetes Prevention Program Research Group et al., 2009; Goldberg et al., 2017), thus, the differential effect across the lifestyle and placebo arm might be diluted, and additional investigation is needed.

Our study observed comparable findings with some previous studies (Shankar et al., 2011; Zhao et al., 2020). Cross-sectional analyses using U.S. NHANES data (1999–2008, N = 4857 adults) showed those with the highest quartile of serum PFOS and PFOA concentration (PFOS > 29.5 ng/mL, PFOA: >5.9 ng/mL) had 6.7 and 5.7 mL/min/1.73 m^2 lower eGFR compared to those with the 1st quartile concentrations (PFOS: <11.7 ng/mL, PFOA: <2.8 ng/mL); and the odds of CKD were 82% and 73% higher, respectively (Shankar et al., 2011). Consistently, the China C8 Study [N = 1612, median (IQR) PFOS 24.2 (14.6, 37.2) ng/mL] estimated a −0.91 (-1.83, 0.00) mL/min/1.73 m^2 lower eGFR per natural-log (~2.7-fold) increase in serum PFOS (Wang et al., 2019); and the US C8 Health Project (Mid-Ohio Valley, N = 29,641) estimated −0.98 (SE: 0.274, p = 0.0003) mL/min/1.73 m^2 lower eGFR comparing the 5th (>88 ng/mL) to the 1st quintile (<11.1 ng/mL) of serum PFOA, cross-sectionally (Dhingra et al., 2017). The only available longitudinal estimates were a study from 210 community residents living close to a uranium processing site in Fernald, Ohio who also had high risk of exposure of PFAS due to residential location (Blake et al., 2018). The study had repeated measures of serum PFAS and eGFR over approximately 10 years of follow-up (1999–2008). The latent models they applied were comparable to the longitudinal model we used in this analysis as both evaluated the longitudinal trend of eGFR in relation to a baseline eGFR measurement. They found −1.72 (−3.29, −0.15) mL/min/1.73 m^2 lower eGFR per quartile increase (approximately 30% absolute increase) in serum PFOS adjusting for age, year of measurement, sex, education, income, BMI and marital status, which was comparable to our finding [−1.50 (−2.81, −0.19) mL/min/1.73 m^2 lower eGFR per doubling of PFOS]. Compared to Blake et al., our study had a larger sample size and a narrower age range, therefore our estimates had higher precision, which was evident by the narrower 95% confidence interval. However, since our participants had fewer measures of blood PFAS and eGFR, we did not apply the repeated measures approach as done by Blake et al., thus, we cannot confirm their findings on the inverse associations of PFHxS, PFNA, PFDA and the positive association of MeFOSAA with eGFR. We should note that while this repeated measure approach applied by Black et al. can gain more power, findings from this method was also more likely to be biased by time-varying confounding so care should be taken in interpreting the results. Similar to one previous report (Wang et al., 2019), we observed stronger effects of the branched PFOS and PFOA which have higher renal clearance rates compared to linear isomers (Gao et al., 2015; Olsen et al., 2007; Russell et al., 2015; Shi et al., 2016; Worley et al., 2017; Zhang et al., 2013). The uptake of PFAS by organic anion transporters into the proximal renal tubules regulates the active secretion and reabsorption of PFAS (Weaver et al., 2010; Worley et al., 2017; Yang et al., 2010; Zhang et al., 2013). The reabsorption of PFAS is hypothesized to alter normal kidney function.

Impaired kidney function can also disrupt the balance of renal secretion and reabsorption of PFAS which in term alters blood PFAS concentrations (Olsen et al., 2007; Stanifer et al., 2018). Previous cross-sectional study from US NHANES had shown an inverted U-shaped relationship between PFAS and eGFR (Jain and Ducatman, 2019a), suggesting that the level of absorption and secretion activities may be differentially affected during progressive renal decline. Thus, caution should be taken when using blood PFAS concentrations as a proxy of PFAS exposure as it may underestimate the effect of PFAS on kidney function, especially at the stage of advanced renal failure. In our study, most participants had normal kidney function, so we may have been unable to detect this inverted U-shape association. However, when we additionally adjusted for baseline microalbuminuria or elevated ACR, which often precede eGFR decline, the inverse association between blood PFAS and eGFR strengthened, confirming the potential negative confounding effect. The inverse relationship between blood PFAS concentration and ACR was previously reported in NHANES (Jain and Ducatman, 2019b). The study hypothesized that elevated ACR could directly cause PFAS excretion, or that elevated ACR could also be a result of a process that also reverses the reabsorption of PFAS by the kidney, leading to higher PFAS excretion from urine and lower blood PFAS concentrations. The role of protein-binding had been noted to alter PFAS excretion (Beesoon and Martin, 2015); and a recent study also showed that albumin is the major protein carrier for many long-chain PFAS including PFOS, PFOA, PFHxS, PFDA and PFNA (Forsthuber et al., 2020). Together this evidence shows that adjustment for albumin level and stages of glomerular filtration function may have important implications and further investigations are warranted.

Unreported in previous literature, we observed differential effect by hypertension status. Hypertension may accelerate renal damage and increase the susceptibility of CKD for patients with diabetes (Mennuni et al., 2014). Our previous analysis showed plasma PFAS concentrations were not associated with blood pressure (Lin et al., 2020a), thus hypertension was unlikely an intermediate variable in the causal pathway. In the hypertensive state, the kidney experiences alteration of vascular structure, change in glomerular permeability to macromolecules, and increase in glomerular, tubular and interstitial injuries (Folkow et al., 1977; Mennuni et al., 2014) which could intensify the damage of PFAS on kidney function. Hypertensive patients often experienced microalbuminuria (Palatini, 2003; Rodicio et al., 1998), and the severity of microalbuminuria correlates with the severity of hypertension and responses to lowering of blood pressure levels (Parving et al., 1974). Other mechanisms that may promote renal damage include oxidative stress, endothelial dysfunction, and genetic and epigenetic factors. Additional studies are needed to better understand this differential effect.

Important strengths of our current study included the long follow-up time, prospective assessments of exposure and eGFR, multiple sensitivity analyses and tests of reverse causation to ensure the internal validity and robustness of detected associations. The current longitudinal findings fill a significant gap in the current literature (Stanifer et al., 2018). The g-computation approach provided a framework to estimate the overall effect of the multiple PFAS chemicals.

Limitations include: limited generalizability because of participants' characteristics (all had overweight/obesity and prediabetes); potential unmeasured confounders, such as blood iron level, genetics and epigenetic variants; and findings from the 6 PFAS we examined in this study may not be generalizable to other, newer PFAS. Renal clearance of PFAS vary by carbon-chain length, side-chain functional groups and isomeric structure, and continued monitoring of the potential adverse effects of PFAS on kidney health is needed.

5. Conclusions

Among adults with prediabetes enrolled in the long-term DPP/DPPOS studies who had plasma PFAS concentrations comparable to those of the general U.S. population, higher baseline plasma concentrations were associated with lower eGFR over approximately 14 years of follow-up. An initial intensive lifestyle intervention of diet and exercise did not modify this adverse effect. However, individuals with hypertension may experience a more detrimental effect.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106375.

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