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Causal inference for the effect of environmental chemicals on chronic kidney disease

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ABSTRACT

The impacts of environmental chemicals on the decline of kidney function have been suggested by a limited number of statistical and animal studies. Thus, those exposures may be modifiable risk factors for chronic kidney disease. Some of the chemicals, such as Perfluoroalkyl acid (PFA), are pervasive throughout our environment, determining their health effects is an important public health concern. In this study, we examined cross-sectional data from the 2009–2010 cycle of the National Health and Nutrition Examination Survey (NHANES) using a statistical causal inference method-generalized propensity score method, to determine the links between concentrations of several major environmental chemicals and kidney function measured by the estimated glomerular filtration rate (eGFR). Various generalized propensity score estimation methods including Hirano-Imbens, additive spline, and a generalized additive model were compared. Among the examined environmental chemicals, each of the statistical models used associated an increase in PFA concentration with a decline in eGFR. We conclude that PFA is a modifiable risk factor for chronic kidney disease and the statistical causal method produces credible results in estimating the effect of chemical exposures on a continuous measure of kidney functions with an observational dataset.

1. Introduction

The prevalence of Chronic Kidney Disease (CKD) continues to increase and is present in more than 10% of the adult US population [1]. The presence of CKD raises the risk of other diseases including cardiovascular disease and kidney failure (associated with increased morbidity and mortality) [2]. Early intervention in kidney disease would alleviate patient suffering and the economic burden of treating the disease incurred by kidney transplant operations and dialysis required to treat ESRD. However, the early stages of CKD often go unrecognized clinically and therefore remain under-diagnosed. Hence, it is a big challenge to Identify individuals most at risk for the disease and benefit from a preventive and therapeutic intervention [3].

To intervene, we need to identify those individuals most at risk for the disease. An individual's genetic and phenotypic characteristics both affect their risk in developing CKD, including genetic mutations, a family history, gender, ethnicity, age, obesity, socioeconomic status, smoking, nephrotoxins, acute kidney injury, diabetes mellitus, and hypertension [4–8]. The negative impact of environmental chemicals on human health has drawn much attention, with liver and kidney being the two major organs harmed by environmental chemicals [9]. A brief overview of research studying the health impacts of several major environmental chemicals is given below.

Perfluoroalkyl acids (PFAs) are synthetic chemicals that have been detected in the blood of most people in the United States [10]. PFAs are of concern because they are persistent environmental contaminants that bioaccumulate in organisms and are biomagnified along food chains [11]. PFAs are found in a variety of products, including food packaging, surfactants, lubricants, sealants, stain-resistant sprays for textiles, and fire-retarding foams. Animal studies suggest that there may be an association between PFAs and CKD, but human research studies on the topic are scarce. PFA levels in the blood have been positively associated with CKD but more evidence are needed to support this point [10]. Two PFAs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), bioaccumulate in the kidneys, as kidneys are the primary

Abbreviations: PFAs, perfluoroalkyl acids; CKD, chronic kidney disease; GPS, generalized propensity score; eGFR, estimated glomerular filtration rate.

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route of elimination of PFAs. PFAs are associated with changes in the permeability of endothelial cells, which is considered a mechanism of renal failure based on rat models [9]. PFOA and PFOS have been previously associated with increased cholesterol levels, insulin resistance and risk of metabolic syndrome, which has been linked independently to an increased risk of CKD [10]. Increased serum levels of PFOA linked to decreased renal function and increased risk of having CKD, but reverse causality cannot be ruled out. Elevated serum PFA levels may be caused by decreased kidney function, instead of PFA causing a decline in kidney function [12]. PFAs have also been associated with hyperuricemia, insulin resistance, diabetes risk, and metabolic syndrome, each of which is an additional risk factor for CKD [12].

Bisphenol A (BPA) is a synthetic estrogen used in the production of polycarbonate plastics and epoxy resins, which are used in many consumer and industrial products [13]. Polycarbonate plastics are used in food packaging, safety equipment, and medical devices. Epoxy resins are used to coat metal surfaces, such as cans, water supply pipes, and bottle tops. BPA is a possible endocrine disruptor [14]. Dialysis patients have increased BPA exposure due to the use of BPA in dialysis tubing [9]. Increased levels of urinary BPA were associated with higher levels of albuminuria. Lower levels of urinary BPA excretion were associated with a decreased GFR, but the same study found no association between BPA excretion and BPA [13]. BPA is cleared rapidly by the kidneys [13]. Animal studies found an association between serum BPA and albuminuria and suggest that BPA negatively affects the glomerulus [9]. Few studies have looked exclusively at the relationship between BPA and estimated glomerular filtration rate (eGFR). One study found that a decrease in BPA and triclosan excretion was associated with a lowered GFR using data from the National Health and Nutrition Examination Survey (NHANES) 2003–2006 [13]. Elevated urinary BPA levels may increase the risk of hypertension and diabetes mellitus, two risk factors also associated with renal function [9].

Phthalates are separated into two categories based on molecular weight: low or high. Low molecular weight (LMW) phthalates are found in personal hygiene items such as shampoo, lotion, and cosmetics, while phthalates of high molecular weight (HMW) phthalates are involved in the production of vinyl plastics found in flooring, intravenous tubing, and food packaging [9]. Phthalates are possible endocrine disruptors, and infants and children may be more affected by phthalates because of the increased food consumed-to-body weight ratio. Diethyhexyl phthalate (DEHP) is an HMW phthalate used in medical supplies to administer blood and nutrition intravenously and respiratory gases to patients. Patients with CKD are at a high exposure risk to phthalates due to the number of medical treatments they undergo, such as dialysis, and the prevalence of phthalates in equipment used to complete such procedures. Albuminuria, the presence of albumin in the urine, is a symptom of kidney disease and a risk factor for cardiovascular disease. An increase in DEHP metabolites in the urine was associated with an increase in the albumin concentration in the urine, though LMW phthalates did not affect albuminuria [15]. An increase in DEHP metabolites in urine was associated with an increase in the systolic blood pressure, but phthalates of LMW had no effect [15].

Polyaromatic hydrocarbons are produced from burning coal, oil, or gas, from grilling meat over charcoal, or in tobacco. Oxidized PAHs may be mutagenic. PAH exposure increases the risk of Balkan endemic nephropathy, a disease also associated with urothelial cancer [9]. PAHs also have a direct relationship with systolic and pulse pressure, but further studies are needed to confirm the hypertension risk associated with PAH exposure [9].

Statistical methods, including both non-causal and causal inference models, have been revealing associations between environmental chemicals and renal functions. Multiple linear regression identified significant associations between increases in phthalate metabolites and in albumin/creatinine ratio in a cross-sectional study with 667 children participating NHANES [16]. An age and sex adjusted multiple regression investigated the relationship between serum PFA levels and eGFR and found that PFA and eGFR were negatively correlated with each other, even after adjusting for confounders in Shankar et al. [10]. A positive association was found between urinary BPA level and renal function measured by eGFR in NHANES data using regression models [17]. Univariate, bivariate, and weighted multiple regression models were applied in associating high serum levels of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), two PFAs with decreased eGFR in children and adolescents [18]. This study also found differences in PFA concentration and eGFR by social and behavioral characteristics, emphasizing the need for confounding adjustment. The main limitation in the current literature examining the effect of environmental chemicals on renal function using linear regression is the cross-sectional nature of the data used. Results may also have been hindered by the lack of availability of potential confounders, such as lifestyle choices and concentrations of other environmental chemicals in the serum [19]. Reverse causation may also play a part as suggested by Watkins et al. that an inverse association between eGFR and serum PFA concentration existed in a cross-sectional study of children and adolescents [12]. Many of the risk factors that likely contribute to kidney disease are associated with one another, and it is difficult to determine if kidney disease is a direct or indirect consequence of a specific risk factor. For example, socioeconomic status does not directly cause chronic kidney disease, but factors associated with lower socioeconomic status, like lack of health care, poor dietary choices, substance abuse, and behavioral patterns increase the risk of developing and/or dying from CKD [8]. Addressing the ancestral causes of risk factors may have a greater positive effect on the treatment and outcome of patients with chronic kidney disease than each risk factor individually. In this study, we are aiming to elucidate the causal impact of environmental chemicals on kidney functions by controlling confounding factors using data from NHANES. The data collection, data manipulation, and statistical methods are demonstrated in the Materials and Methods section. Data description and results for the comparison between linear regression methods and generalized propensity score methods are showcased in the Results section. The achievements and limitations of this study are discussed in the last section.

2. Material and methods

2.1. Data collection

We used the 2009–2010 cycle of NHANES [20] to study the statistical causal association between kidney function and the environmental chemicals including PFAs, BPA, phthalates, and PAHs. The amount of a chemical in an individual was measured using the sum of the urinary concentration of each chemical's respective metabolites. We converted the concentration of each urinary metabolite to nanomoles per liter (nmol/L). The components included in the calculation of each of the chemicals were listed in Table 1.

Kidney function is measured by the GFR clinically as a comprehensive index. Instead of directly being measured, GFR is estimated from serum creatinine and adjusted by age, gender, and race [21]. Thus, in this study, the kidney function of participants was represented by eGFR values, which were estimated using the CKD-EPI creatinine equation (2009) [21]:

$$eGFR = 141 \times \min(S_{Cr}/K, 1)^{\alpha} \times \max(S_{Cr}/K, 1)^{-1.209} \times 0.993^{age} \times 1.018[\textit{if female}] \times 1.159[\textit{if African American}].$$

Table 1
The components used in calculating the total concentration of environmental chemicals PFAs, PAH and phthalates.

Environmental Chemicals	Components
PFAs	perfluorooctanoic acid, perfluorooctane sulfonic acid, perfluorohexane sulfonic acid, 2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid, 2-(N-Methyl-perfluorooctane sulfonamido) acetic acid, pefluorodecanoic acid, perfluorobutane sulfonic acid, perfluoroheptanoic acid, perfluorononanoic acid, perfluorooctane sulfonamide, perfluoroundecanoic acid, and perflurododecanoic acid
PAH	2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 1-hydroxpyrene, 1-naphthol, 2-naphthol, and 4-hydroxyphenanthrene
HMW phthalates	Mono (carboxynonyl) phthalate, mono (carboxyoctyl) phthalate, mono-2-ethyl-5-carboxypentyl phthalate, mono-(2-ethyl-5-hydroxyhexyl), mono-(2-ethyl)-hexyl phthalate, mono-(2-ethyl-5-oxohexyl), and mono-benzyl phthalate
LMW phthalates	mono-n-butyl phthalate, mono-(3-carboxypropyl) phthalate, mono-ethyl phthalate, mono-n-methyl phthalate, and mono-isobutyl phthalate

To establish the causal relationship between chemicals and kidney function, we extracted the confounding factors, including age, gender, race, systolic and diastolic blood pressure, income-to-poverty level ratio, BMI, diabetes status, smoking status, and alcohol consumption habits. We excluded subjects with missing data for chemicals or confounding factors from our study.

2.2. Descriptive and univariate analysis

The concentrations of environmental chemicals including PFA, BPA, PAH, LMW phthalates, and HMW phthalates were log-transformed to reduce the skewness of their distribution. The log-transformed chemical concentrations were analyzed as continuous variables. A univariate analysis was performed using *t*-test or chi-square test as appropriate to compare each of the characteristics from two groups defined by the first and fourth quartiles of the chemical level. Descriptive and univariate analyses were conducted using R version 3.6.0.

2.3. The generalized propensity score method

In the study, we further examined the causal effect of PFA on renal function using a generalized propensity score (GPS) method, since PFA is the only environmental chemical that demonstrated a significant statistical association with eGFR from the univariate analysis. We then compared the performance of this method with linear regression models. The GPS is a continuation of the propensity score method and is the probability of an individual having a certain chemical level in urine, given their baseline covariates. This removes bias introduced by the imbalance of baseline covariates, and differences in eGFR can be solely attributed to differences in PFA concentrations.

The GPS was first introduced in Hirano and Imbens 2004 [22]. The Hirano and Imbens method give a parametric estimator that first estimates the GPS by regressing on the covariates and then estimates the eGFR based on the observed PFA concentration and fitted GPS [22]. The additive spline estimator estimates the ADRF is a two-step semiparametric process as outlined in Bia et al. [23]. The first step is to parametrically model the GPS based on the covariates and create additive spline bases for the GPS and PFA. The eGFR is regressed on PFA, PFA bases, GPS, and GPS bases. The second step is to calculate the eGFR based on each PFA value and corresponding covariates, and then to average the eGFR to get the ADRF at that treatment value. The generalized additive model (GAM) estimator uses a treatment formula to estimate and model the GPS, and then the eGFR is estimated based on the treatment and the spline base terms from fitting the GPS [24]. The formulation of the Hirano and Imbens method in this study is outlined below:

For each unit $i = 1, \cdots, N$, there exists a set of potential eGFR values, $Yi(c)$, namely outcome variable, for some $c \epsilon C$, the concentration level, which is the treatment variable in the causal model. This gives the unit-level chemical dose-response function. The average dose–response function (ADRF) is given by $\mu = E[Y_i(c)]$. Each unit i is associated with a vector of variables that serve as covariates, $\boldsymbol{X_i}$, and the corresponding concentration level, $c_i \epsilon [c_0, c_1]$.The variables $\boldsymbol{X_i}, c_i,$ and $Y_i(c_i)$ are observed.

The unconfoundedness assumption made by Rosenbaum and Rubin in 1983 is generalized for the GPS by Hirano and Imbens [22], which means if we condition on covariates, response to treatment level is independent of the treatment assignment, and bias due to varying covariate distributions for different PFA levels is reduced. This allows us to make comparisons in the eGFR between subjects with similar covariate values at different PFA levels.

As has been defined in [22], the conditional density function of the treatment given the covariates is $r(c,x) = f_{C|X}(c,x)$ and the generalized propensity score is $R = r(C,X)$.

The GPS has a balancing property, and the probability of concentration level does not depend on $\boldsymbol{X}$. Combining the balancing property with the unconfoundedness assumption, the level of PFA is unconfounded based on the GPS.

The GPS model was implemented and the average dose–response function (ADRF) was estimated using the *causaldrf* package. A variety of causal estimators for the ADRF in the *causaldrf* package were tested, including Hirano and Imbens (H-I), generalized additive model (GAM), and additive spline. The covariates adjusted for in the estimation of the ADRF were the diabetes status, systolic blood pressure (SBP), diastolic blood pressure (DBP), the ratio of family income-to-poverty level (social-economic status), body mass index (BMI), number of weekly drinks, and smoker status. These estimators were compared to two regression models. One model regressed eGFR on the log-transformed PFA concentration and the above-mentioned covariates with interaction terms considered. A step-wise variable selection procedure was performed. The other model was a simple linear regression of eGFR on log PFA concentration.

3. Results

3.1. Baseline characteristics and univariate analysis

Characteristics of the 1607 participants in NHANES with laboratory test results available on PFA, PAH, LMW Phthalates and HMW Phthalates are shown in Fig. 1. The summary statistics for BPA is shown in Appendix Fig. A1.

Each of the chemical concentrations was summarized over demographic features, clinical measurements as well as CKD. The first and fourth quartiles of concentration levels were also compared against these covariates. As showcased in Fig. 1, there is a statistically significant decrease in the renal function measured by eGFR of patients of the fourth quartile of urine PFA concentration (mean = 84.88) compared to those in the first quartile (mean = 101.79). This indicated that a decrease in renal function might be associated with an increased urinary PFA concentration. This observation was further validated by the fact that patients in the fourth quartile of PFA level had significant higher CKD prevalence (14.96%) than those in the first quartile (5.21%). People with

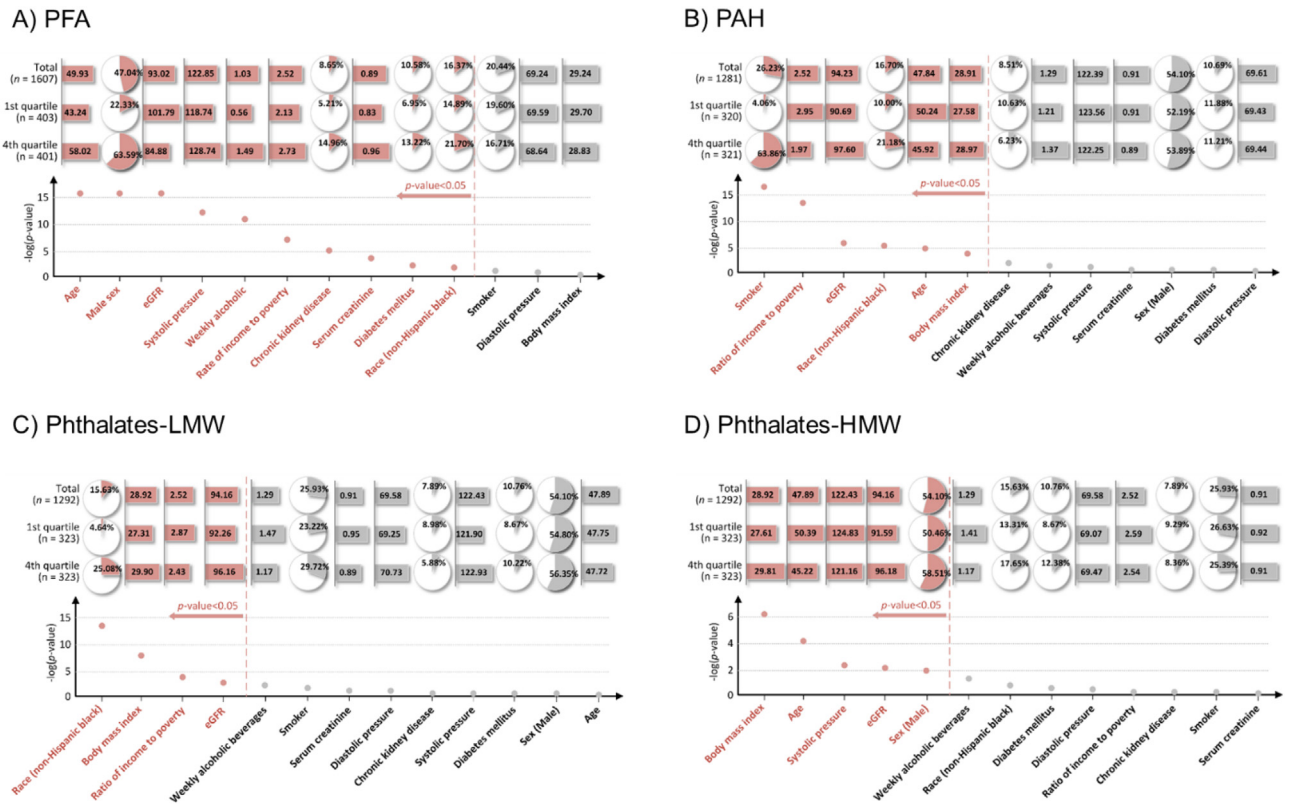

Fig. 1. Baseline characteristics and univariate analysis.

higher PFA concentration (who were in the fourth quartile of PFA concentration) tended to be older, male, non-Hispanic black, have a lower income-to-poverty level ratio, consume more alcoholic beverages, have diabetes, and have higher systolic blood pressure than those with lower PFA concentration (who were in the first quartile).

There were significant inverse associations between eGFR and the urinary concentrations of PAH, LMW and HMW Phthalates. However, the CKD prevalence in the first and fourth quartiles of urinary concentrations of these chemicals was not statistically different. This may be due to unconsidered confounders or interactions with other chemicals. As shown in Fig. A1, the urinary BPA level was neither significantly associated with eGFR nor CKD. Therefore we were focusing on elucidating the causal association between PFA and eGFR using statistical causal methods.

3.2. Association between PFA concentration and eGFR using GPS and regression methods

The propensity scores were calculated from the variables that were highly correlated with both PFA level and eGFR. The common support plot for the propensity scores was shown in Fig. 2, which demonstrates that there were distinct overlaps in the range of propensity scores across different PFA concentration levels. The extents of overlap between each pair of level 1 vs. level 6, level 2 vs level 5, and level 3 vs. level 4 were satisfactory.

Both non-causal (regression) and causal methods (GPS) were applied in estimating the effect of PFA on eGFR. Table 2 contains diagnostic statistics for three different causal estimators of the dose-response function of the PFA concentration of eGFR. The models based on a GPS and the regression models all show a significant relationship between eGFR and the regressor variables, including PFA. The adjusted R^2 values for each of the five models are relatively low, with the simple linear regression model having the lowest (adjusted R^2 = 0.053) and the multiple regression having the highest (adjusted R^2 = 0.21).

We further estimated eGFR corresponding to the value of the log PFA for the three GPS causal estimators (GAM, H-I, and additive spline) and two regression models (simple linear and multiple regressions). GAM was compared to univariate and multiple regressions as described in Fig. 3. The estimated response curves of eGFR to log PFA using additive spline and H-I were shown in Fig. A2. The univariate regression model shows a similar trend to the GPS models, but predicts lower eGFR at lower log PFA values and slighter higher eGFR as log PFA increases. The multiple regression model was plotted using the estimated coefficient for log PFA. The multiple regression model estimates much higher eGFR values across log PFA values. The three GPS models are qualitatively similar in shape, slightly increasing with log PFA before reaching a peak, decreasing, and then beginning to plateau. The accuracy of the estimated curves from GPS outperforms the regression models with much smaller confidence intervals.

4. Discussion and conclusions

Some of the environmental chemicals are hypothesized to have negative effects on renal function and supported by animal studies. But evidence from human studies are very rare in suggesting that those chemicals are linked to a decline in kidney function. In this study, observational data from the 2009–2010 cycle of NHANES were used in assessing the associations between urinary PFA, PAH, Phthalates and PAH concentrations and eGFR. Quartile analysis was firstly performed to examine the data quality as well filtering the chemicals that will feed the following causal analysis. Then PFA was selected out of the four chemicals examined and subject to three GPS estimators and two regression models. The fitted eGFR values over PFA concentration demonstrate an increase in PFA concentration with a decline in eGFR. Thus we conclude that PFA is a

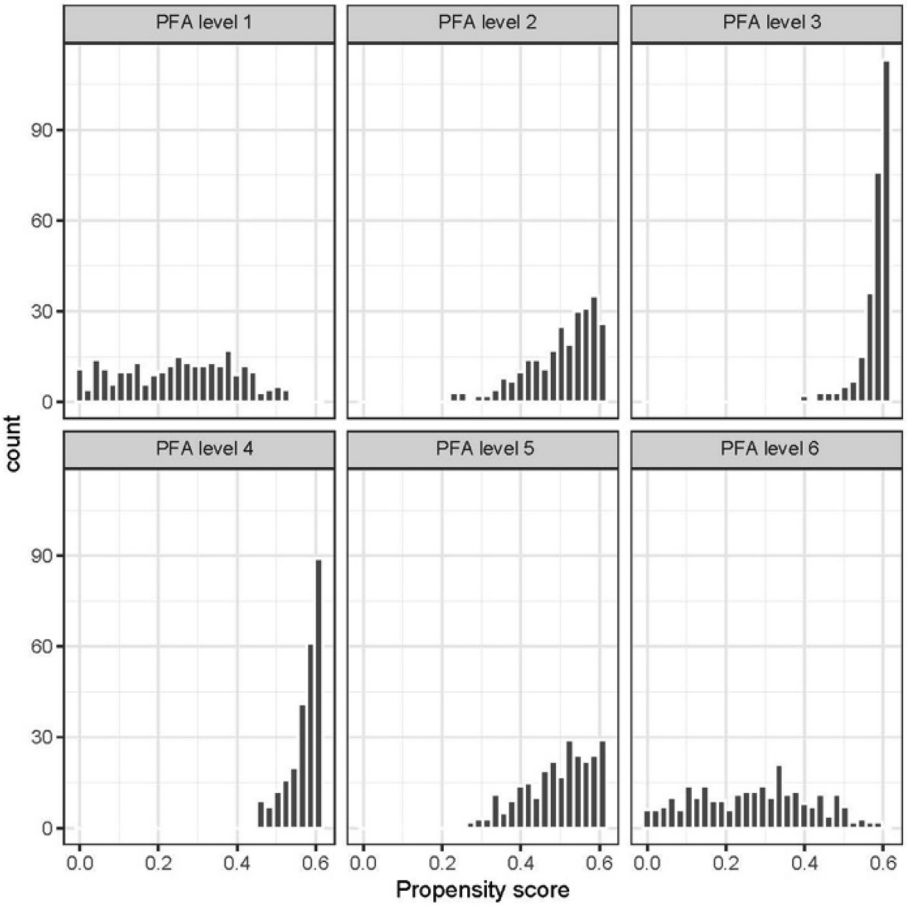

Fig. 2. Distribution of propensity score across treatment Groups: PFA levels were ordered as concentration ranges from low to high.

Table 2
Diagnostic statistics of ADRF estimators and regression models.

Estimator	Predictors	Adjusted R^2	F-value	p-value
H-I				
	LogPFA, Diabetes, SBP, DBP, socioeconomic status, smoker, BMI, weekly drinks	0.0996	36.53	<0.0001
GAM				
	LogPFA, Diabetes, SBP, DBP, socioeconomic status, smoker, BMI, weekly drinks	0.0930	27.12	<0.0001
Additive spline				
	LogPFA, Diabetes, SBP, DBP, socioeconomic status, smoker, BMI, weekly drinks	0.0752	17.32	<0.0001
Linear regression				
Multiple regression	LogPFA, diabetes, SBP, DBP, socioeconomic status, smoker, logPFA*SBP, logPFA* socioeconomic status	0.2087	53.93	<0.0001
Simple linear regression	LogPFA	0.0534	91.60	<0.0001

modifiable risk factor for CKD and GPS analysis produces credible results in estimating the effect of chemical exposures on a continuous measure of kidney functions such as eGFR.

This study has significant impacts on determining the health effects of environmental chemicals. Environmental chemicals such as PFA are invading human life in an unobservable manner and experiments in evaluating the health effects of these chemicals are impractical to implement in clinical settings. Thus advanced statistical techniques such as GPS methods provide us with a way of causing no additional risks to patients while eliminating the biases introduced by unbalanced covariates in observational studies. Results from causal methods as GPS also facilitate biomedical researchers formulating more solid hypotheses in examining the health-related environmental chemicals.

However, limitations still exist in the current study. One of the limitations was the lack of availability of data. We were unable to investigate potential interaction effects on kidney function between PFA and other chemicals, including BPA, PAH, and phthalates, as the subset of individuals in NHANES 2009–2010 with recorded PFA levels did not have levels measured for these other chemicals. Also, as NHANES data is cross-sectional in nature, we could not evaluate the effect of PFA on individuals over time, which would be ideal when studying a chronic disease such as CKD. Besides, although the GPS methods used in this study have satisfactory common support which means most of the participants' data were used in the analysis, some of the data has been discarded due to no matched sample in the comparison group. To overcome these limitations, we are planning to use methods such as inverse probability weighting which can improve the efficiency and reduce the bias of unweighted estimators. We will also reach out and request access to databases that have paired and longitudinal data sets.

We have shown that GPS-based methods can be used to identify a causal relationship between two continuous variables, and has

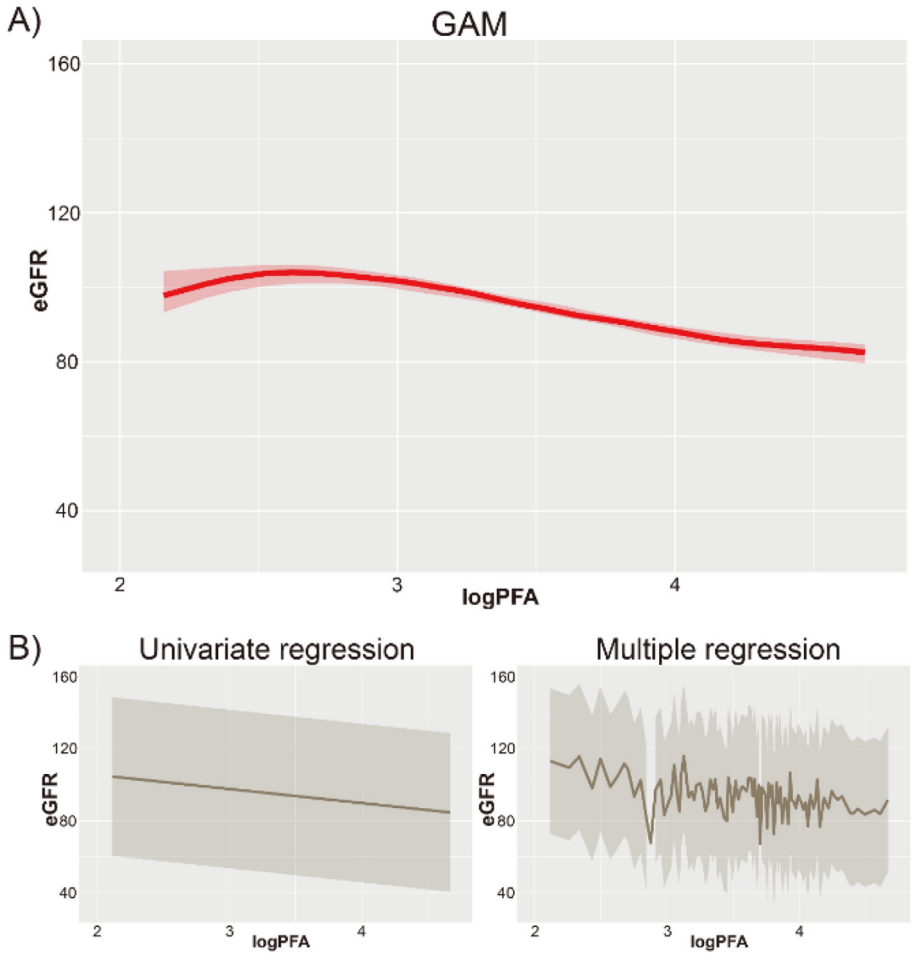

Fig. 3. Estimated eGFR corresponding to log PFA concentration levels using GAM and regression models.

theoretical advantages over regression models. Future work entails the investigation of the effect of interaction between PFA and other chemicals on CKD, and the application of causal inference methods to longitudinal studies, which would make an even stronger case for the negative effect of PFA on kidney function.

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.

Appendix

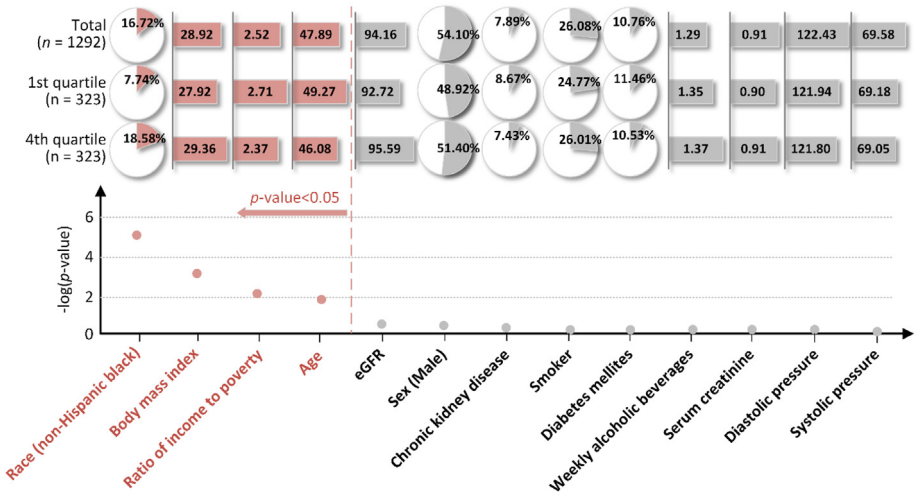

Fig. A1. Summary statistics and comparison between BPA level defined groups of baseline characteristics.

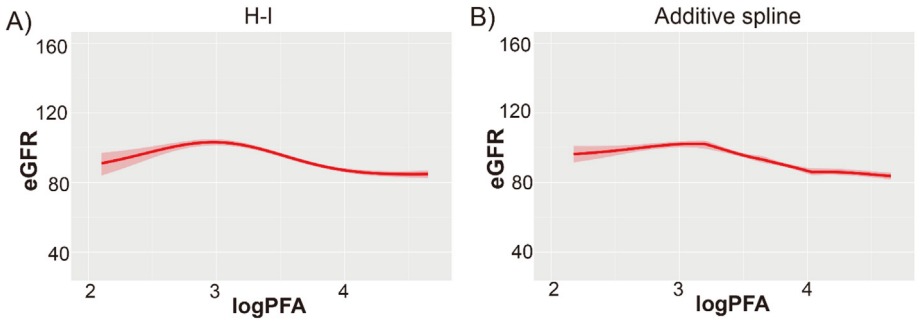

Fig. A2. Estimated eGFR corresponding to log PFA concentration levels using H-I and additive spline estimators.

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