

treatment of patients with CKD and should be anticipated and integrated with pharmacologic therapies.^{S25} In Australia, CKD knowledge remains inadequate for standard nephrology outpatient care.^{S26} In Brazil, patients in intermediate stages of CKD do not receive follow-up with a multidisciplinary team at the recommended frequency.^{S27} Anemia in CKD is very prevalent. Although it has been treated with red blood cell transfusion, epoetins, and intravenous iron, the best approaches to anemia management in CKD are still unknown.^{S28}

In conclusion, hypertension and diabetes preceded most of our ESKD cases. Hypertension was prevalent among our young ESKD population, which makes glomerulonephritides likely underlying causes, although kidney biopsies are rarely performed. Follow-up in diabetes and hypertension clinics has not translated into better CKD care ([Supplementary Study Limitations](#)). Communication about the disease between patients and healthcare providers is not satisfactory. A multidisciplinary approach by various specialties needs to be embraced when caring for these patients. Patient factors need to be considered when planning healthcare delivery.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary Methods.](#)

[Supplementary Results.](#)

Table S1. Characteristics of patients who previously attended the diabetes clinic only and those who previously attended both the diabetes and hypertension clinics.

Figure S1. Patient recruitment flowchart.

Supplementary Study Limitations.

Supplementary References.

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Association Between Perfluoroalkyl Substance Exposure and Renal Function in Children With CKD Enrolled in H3Africa Kidney Disease Research Network



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The prevalence of chronic kidney disease (CKD) is increasing at an accelerated pace in countries with limited health resources compared to developed countries.¹ There is a need for more studies of the epidemiology and clinical characteristics of CKD in pediatric populations in sub-Saharan Africa, where risk factors are common.²

Perfluoroalkyl substances (PFASs), a group of synthetic chemicals with a fluorinated hydrophobic linear carbon chain attached to hydrophilic heads, are characterized by resistance to thermal, chemical, and biological degradation.³ They are used in household products such as cookware, clothing, sofas, and carpets to make them stain resistant, waterproof, and non-stick.^{3,S1} Exposure occurs through diet, dust, tap or bottled drinking water, and inhalation.^{3,4,S2-S5} PFASs are detected in serum from over 98% of a studied sample of the US population aged 12 to 60 years.^{4,S6} Children have elevated serum PFAS concentrations compared to adults.^{4,S6,S7}

Although the use of environmental industrial chemicals including PFASs is increasing in Africa, few studies have assessed exposure in populations residing on this continent compared to developed countries such as the United States.^{S8,S9} One investigation measured PFASs in matched maternal serum and cord blood samples, and another compared PFAS levels in pregnant women from sub-Saharan Africa to women in Nordic countries, where serum levels of PFASs are the highest.^{S10,S11} Shankar *et al.* demonstrated a positive association between serum PFAS concentration and CKD in adults.⁵ Kataria *et al.* documented a reduction in kidney function in association with increasing serum PFAS levels in healthy children and adolescents enrolled in the National Health and Nutrition Survey (NHANES) from 2003 to 2010.^{3,4} Other reports did not confirm an adverse effect of PFAS exposure on kidney function.^{S12-S15} This underscores the need to conduct additional studies of PFAS exposure and renal function outcomes in diverse patient populations. Therefore, we performed the following study to test the hypotheses

that: (i) because of different consumer habits, manufacturing practices, and environmental regulation, exposure to PFASs in children and adolescents with CKD enrolled in the H3Africa Kidney Disease Research Network (KDRN) would be lower than in participants of comparable age in the US-based NHANES⁶; and (ii) higher levels of exposure to PFAS would be associated with a lower estimated glomerular filtration rate (eGFR) in African children and adolescents with CKD.

RESULTS

There were 89 children and adolescents selected, of whom 8 were excluded because of missing data, yielding a cohort of 81 participants. The mean age was 13.4 years, and 53.1% were boys. The median body mass index was 17.5 kg/m²⁷ (interquartile range, 16.5–21.7), systolic blood pressure (SBP) 109 mm Hg (interquartile range, 99–123), and diastolic blood pressure 64 mm Hg (interquartile range, 55–80). The median and interquartile range for serum creatinine concentration, eGFR, and albumin:creatinine ratio are summarized in Table 1.

Table 1. Demographic and clinical characteristics of participants with serum perfluoroalkyl substance measurements, H3Africa 2013 to 2017, N = 81

Characteristic	Result
Sex, n (%)	
Male	43 (53.1%)
Female	38 (46.9%)
Age, yr, mean ± SD	13.4 ± 2.7
Median serum creatinine, mg/dl (IQR)	0.8 (0.6, 1.1)
Median eGFR min/ml per 1.73 m ² (IQR)	74.3 (49.7, 102.5)
Median albumin:creatinine ratio (IQR)	2.0 (0.6, 11.5)
Median height cm (IQR)	149.6 (134.4, 169.8)
Median weight kg (IQR)	41.1 (30.1, 49.0)
Median body mass index	17.5 (16.5, 21.7)
Median systolic blood pressure, mm Hg	109 (99, 123)
Median diastolic blood pressure, mm Hg	64 (55, 80)

IQR, interquartile range.

Table 2. PFAS concentrations in H3Africa and NHANES cohorts

Chemical	H3Africa data 2013–2017 (ng/ml) N = 81		NHANES data 2013–16 (ng/ml) N = 4158	
	Median (IQR)	% Detection	Median (IQR)	% Detection
PFOS	1.9 (0.8, 2.9)	92.6	3.3 (1.9, 5.9) ^a	99.3
PFOA	0.4 (0.2, 0.6)	87.7	1.6 (1.0, 2.5) ^a	99.2
PFHxS	0.2 (0.1, 0.4)	82.7	1.2 (0.7, 2.2) ^a	98.7
PFHxA	0.2 (0.1, 0.4)	69.1	—	—
PFNA	0.1 (0.1, 0.3)	46.9	0.6 (0.4, 1.0) ^a	98.8
PFDA	0.2 (0.1, 0.2)	87.7	0.2 (0.07, 0.3)	72.8

IQR, interquartile range; LOD, limit of detection; NHANES, National Health and Nutrition Survey; PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexane sulfonate; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid. PFOS LOD, 0.2 ng/ml; PFOA LOD, 0.08 ng/ml; PFHxS LOD, 0.08 ng/ml; PFHxA LOD, 0.08 ng/ml; PFNA LOD, 0.2 ng/ml; PFDA LOD, 0.08 ng/ml. PFHxA measurements were not included in NHANES data.

^a $P < 0.0001$ versus H3Africa. Median and IQR were converted to mean \pm SD, and the levels in the 2 groups were compared with a t -test.

In the African cohort, perfluorooctane sulfonic acid (PFOS) had the highest median serum concentration level (1.9 ng/ml) and perfluorononanoic acid (PFNA) the lowest (0.14 ng/ml) (Table 2). PFOS also had the highest rate of detection at 92.6%, whereas PFNA had the lowest at 46.9%. The serum concentrations of all chemicals except perfluorohexanoic acid (PFHxA) had high correlation coefficients with one another (>0.5). The median level and the rate of detection for all PFASs except PFDA were higher for children enrolled in NHANES ($n = 4158$) than those enrolled in H3Africa (Table 2). When PFAS concentrations were categorized by CKD stage, there were no differences in the level of exposure to any of the chemicals among the various CKD-stage subgroups (<60 , $60-90$, and >90 ml/min per 1.73 m^2) and the healthy controls (Supplementary Table S1).

Analyses of eGFR against concentration of individual PFASs demonstrated inverse associations with eGFR for all PFASs except PFHxA (Table 3), and that was significant for PFNA and PFDA. In adjusted models, per natural log increase in serum PFNA concentration, there was a -21.2 min/ml decrease in eGFR (95%

confidence interval [CI], -41.6 to -0.8), and for PFDA, per natural log increase in serum level, there was a -18.3 min/ml lower eGFR (95% CI, -35.3 to -1.3). When the analyses were stratified by sex, the inverse association between PFNA and eGFR was more prominent in boys. Per log-based increase in serum PFNA, there was a 32.4 min/ml lower (95% CI, -57.8 to -7.1) eGFR for boys versus -4.9 min/ml (95% CI, -39.5 to 29.8) for girls (Supplementary Table S2).

Adjusted models of SBP z score against serum PFAS concentration demonstrated a trend toward a positive relationship for all chemicals except PFHxA (Table 3). Because of a possible interaction between blood pressure and eGFR, we performed a stratified analysis and found that the inverse association between eGFR and PFDA and PFNA was more pronounced at higher SBP (Table 4).

Multivariable analyses with the outcome variable albumin:creatinine ratio showed no associations with PFAS concentrations and eGFR and albumin:creatinine ratio—stratified models demonstrated no associations with the serum PFAS concentrations (data not shown).

DISCUSSION

In our sample of 81 African children and adolescents with CKD, serum concentrations of all PFASs were lower compared to those in NHANES participants of similar age. Nonetheless, the lower serum PFAS levels were still associated with a significantly lower eGFR, especially in boys. There was a significant association between exposure to PFNA and PFDA and lower eGFR and a trend for perfluorooctanoic acid (PFOA), PFOS, and perfluorohexane sulfonate (PFHxS). The latter observations reflect the limited sample size. There was a trend toward an increase in SBP in association with PFAS exposure. There was no association between albuminuria and PFAS exposure.

Countries in Africa have different consumer product patterns, and only in recent years has PFAS use been increasing. Therefore, we anticipated that PFAS serum concentrations would be lower in the African children

Table 3. Regression analyses of PFASs with outcome measures of kidney function ($N = 81$)

Chemical	eGFR (min/ml per 1.73 m^2) coefficient (95% CI)		Systolic blood pressure z score coefficient (95% CI)	
	Unadjusted	Adjusted for age, sex, and BMI	Unadjusted	Adjusted for age, sex, and BMI
PFOA	-3.7 ($-14.0, 6.7$)	-5.3 ($-16.6, 6.1$)	0.04 ($0.3, 0.4$)	0.07 ($-0.3, 0.4$)
PFOS	-7.5 ($-17.0, 2.0$)	-10.1 ($-20.4, 0.1$)	0.2 ($-0.2, 0.5$)	0.2 ($-0.1, 0.5$)
PFHxS	-8.0 ($-20.3, 4.26$)	-10.3 ($-23.6, 3.0$)	0.3 ($-0.1, 0.6$)	0.3 ($-0.1, 0.7$)
PFHxA	4.9 ($-3.4, 13.2$)	5.9 ($-2.6, 14.4$)	0.0 ($-0.2, 0.2$)	-0.1 ($-0.3, 0.2$)
PFNA	-17.4 ($-36.6, 1.8$)	-21.2 ($-41.6, -0.8$) ^a	0.4 ($-0.3, 1.0$)	0.4 ($-0.2, 1.1$)
PFDA	-16.3 ($-32.6, 0.04$)	-18.3 ($-35.3, -1.3$) ^a	0.3 ($-0.2, 0.8$)	0.4 ($-0.2, 0.9$)

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexane sulfonate; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid.

^a $P < 0.05$.

All chemical values were log transformed for normality.

Table 4. Regression analyses of PFASs with eGFR stratified by SBP z score

Chemical	Lower SBP, z score <0, N = 33		Higher SBP, z score ≥0, N = 48	
	eGFR (min/ml per 1.73 m ²) coefficient (95% CI)		eGFR (min/ml per 1.73 m ²) coefficient (95% CI)	
	Unadjusted	Adjusted for age, sex, and BMI	Unadjusted	Adjusted for age, sex, and BMI
PFOA	-0.04 (-14.3, 14.3)	-2.3 (-23.5, 19.0)	-11.4 (-23.9, 1.1)	-8.0 (-22.3, 6.26)
PFOS	1.4 (-16.1, 19.0)	-3.5 (-20.1, 13.3)	-6.1 (-18.9, 6.6)	-13.6 (-27.2, 0.01)
PFHxS	-6.3 (-26.0, 13.3)	-9.9 (-31.6, 11.7)	-6.2 (-22.1, 9.8)	-8.8 (-26.9, 9.2)
PFHxA	4.5 (-9.5, 18.4)	7.4 (-8.20, 23.0)	6.1 (-4.1, 16.4)	6.2 (-5.1, 17.5)
PFNA	-3.6 (-31.6, 24.4)	-6.3 (-37.7, 25.1)	-25.3 (-51.3, 0.7)	-29.0 (-56.8, -1.1) ^a
PFDA	0.08 (-23.9, 24.1)	-0.6 (-27.9, 26.8)	-25.0 (-47.2, 2.8) ^a	-26.5 (-49.6, -3.4) ^a

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; PFAS, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexane sulfonate; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid; SBP, systolic blood pressure.

^a*P* < 0.05.

All chemical values were log transformed for normality. The adjusted models were adjusted for age and BMI.

and adolescents compared to pediatric participants in NHANES and that the potential for adverse renal effects would be less. Interestingly, American and African children and adolescents had similar concentrations of PFDA. This correlates with changes in manufacturing and production practices in which PFOS and PFOA use is decreasing and PFNA and PFDA use is increasing. In the United States, serum concentrations of PFOS and PFOA have decreased over the past 10 to 15 years, whereas serum concentrations of PFNA and other replacement PFASs increased.^{S16,S17}

Our findings in African children and adolescents are consistent with reports that PFASs are associated with reduced kidney function in the study by Kataria *et al.* of 1960 Americans of comparable age enrolled in NHANES 2003 to 2010, and that elevated PFAS levels are associated with CKD in American adults.^{4,5,S17} Among boys, specifically for PFNA, the effect on eGFR was more pronounced compared to that in girls. There has been no evidence of a differential effect of PFASs on kidney function based on sex in NHANES studies.⁴

Although past studies have often focused on the impact of PFOS and PFOA, we found that PFNA and PFDA, at lower concentrations than PFOS and PFOA, had an adverse effect on eGFR. There is little literature focusing on the biological effects of PFNA and PFDA, and there is a need to investigate these replacement chemicals as the use of PFOS and PFOA is phased out.^{S8}

No effect on BP was documented in the Kataria *et al.* study of healthy American children and adolescents enrolled in NHANES.⁴ Similarly, PFAS exposure was not significantly associated with SBP in the H3Africa participants. However, at higher blood pressure levels, there was a larger reduction in eGFR. CKD may enhance the susceptibility to the changes in blood pressure induced by exposure to the PFASs. No effect of the PFASs on albumin:creatinine ratio was noted in either healthy American participants in NHANES or African participants in H3Africa with CKD.⁴

Given the small sample size and cross-sectional nature of our study, there are limitations to the generalizability of the results. We were unable to assess whether site of residence or urban *versus* rural status had an impact on the extent of exposure to the PFASs among the African children, because this information was not captured in the database. There is a question of reverse causation in which serum PFAS concentration may be increased because of lower kidney function or severity of CKD.⁴ However, there was no relationship between CKD stage and serum PFAS levels. In addition, serum PFAS concentrations were lower in the H3Africa participants with impaired kidney function compared to participants in NHANES, and yet we confirmed an association between exposure and lower eGFR. Finally, PFASs accumulate in the kidney, and intrarenal levels are more likely to be linked to nephrotoxicity than serum or urinary concentrations.³ Taken together, these considerations make reverse causation less plausible.

In conclusion, our cross-sectional study of children and adolescents enrolled in the H3Africa study demonstrates that African participants have lower PFAS exposure compared to Americans of comparable age. Nonetheless, increased exposure to PFASs was associated with kidney dysfunction, namely reduced GFR, with a more pronounced decrease in eGFR among boys and those with higher SBP.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(Word\)](#)

Supplementary Methods.

Supplementary References.

Table S1. Comparison of perfluoroalkyl substances concentrations in H3Africa subgroups based chronic kidney disease stage.

Table S2. Regression analyses of perfluoroalkyl substances with estimated glomerular filtration rate stratified by sex.

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