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Recent ambient temperature and fine particulate matter ($PM_{2.5}$) exposure is associated with urinary kidney injury biomarkers in children

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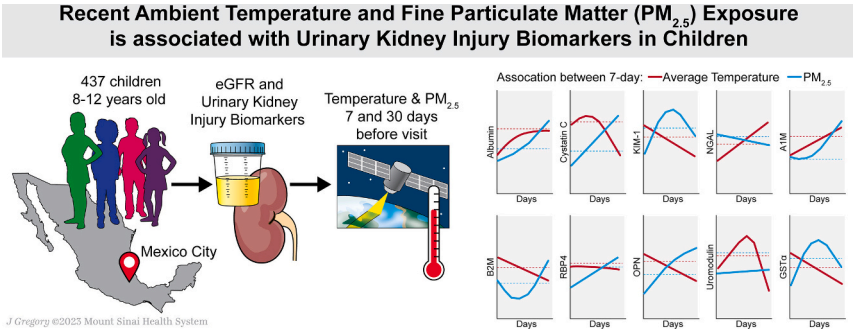
HIGHLIGHTS

- Short-term $PM_{2.5}$ exposure was associated with higher eGFR, and increased urinary A1M and cystatin C.
- Ambient temperature seven days prior to date of visit was associated with decreased urinary cystatin C and osteopontin.
- Short-term ambient temperature and $PM_{2.5}$ exposure may lead to subclinical glomerular or tubular injury.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Limited research has examined associations between exposure to ambient temperature, air pollution, and kidney function or injury during the preadolescent period. We examined associations between exposure to ambient temperature and particulate matter with aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$) with preadolescent estimated glomerular filtration rate (eGFR) and urinary kidney injury biomarkers.
Methods: Participants included 437 children without cardiovascular or kidney disease enrolled in the Programming Research in Obesity, Growth, Environment and Social Stressors birth cohort study in Mexico City. eGFR and urinary kidney injury biomarkers were assessed at 8–12 years. Validated satellite-based spatio-temporal models

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Kidney injury biomarkers
Distributed lag models

were used to estimate mean daily temperature and $PM_{2.5}$ levels at each participant's residence 7- and 30-days prior to the date of visit. Linear regression and distributed lag nonlinear models (DLNM) were used to examine associations between daily mean temperature and $PM_{2.5}$ exposure and kidney outcomes, adjusted for covariates.

Results: In single linear regressions, higher seven-day average $PM_{2.5}$ was associated with higher urinary alpha-1-microglobulin and eGFR. In DLNM analyses, higher temperature exposure in the seven days prior to date of visit was associated with a decrease in urinary cystatin C of −0.56 ng/mL (95 % confidence interval (CI): −1.08, −0.04) and in osteopontin of −0.08 ng/mL (95 % CI: −0.15, −0.001). $PM_{2.5}$ exposure over the seven days prior to date of visit was associated with an increase in eGFR of 1.77 mL/min/1.73m^2 (95 % CI: 0.55, 2.99) and urinary cystatin C of 0.19 ng/mL (95 % CI: 0.03, 0.35).

Conclusions: Recent exposure to ambient temperature and $PM_{2.5}$ were associated with increased and decreased urinary kidney injury biomarkers that may reflect subclinical glomerular or tubular injury in children. Further research is required to assess environmental exposures and worsening subclinical kidney injury across development.

1. Introduction

Globally, the prevalence of chronic kidney disease (CKD) is estimated to be 11 %–15 % (Hill et al., 2016; Lv and Zhang, 2019). Many comorbidities, such as obesity, hypertension, and diabetes, are risk factors for CKD and end-stage renal disease (Chang et al., 2021; Kazancioğlu, 2013). Although these risk factors play a role in the increasing prevalence of CKD, research suggests that warming global temperatures and concomitant exposure to environmental pollutants contributes to disease burden. Similarly, ambient temperature has been associated with increased risk of cardiovascular diseases (Bhatnagar, 2017), and occupational data from agricultural workers in Central America, Sri Lanka, and the United States have linked heat exposure to higher incidence and prevalence of acute kidney disease and CKD or CKD of unknown origin (CKDu) in these populations (Correa-Rotter et al., 2014; Jayasekara et al., 2019; Moyce et al., 2017). While studies have reported associations between environmental exposures and kidney disease, particularly in older adults, there is limited research examining these associations earlier in life (e.g., childhood, adolescence).

Research examining the environmental effects of ambient temperature on kidney disease often uses hospital admissions data, when individuals may have pre-existing or progressed kidney disease, which may be worsened by extreme temperatures. Potential heat-related kidney disease is hypothesized to be caused by dysregulated body temperature, water loss through sweating, and subsequent dehydration, with rising ambient temperatures (Ó Flatharta et al., 2019). Among children, the incidences of kidney disease and electrolyte imbalance increase significantly during heat waves (Xu et al., 2012). Further, higher exposure to air pollution has been linked to increased blood pressure in both adults (Yang et al., 2018) and children (Huang et al., 2021), and has been associated with higher incidence of hypertension and CKD later in life (Bo et al., 2019; Sanders et al., 2018). A recent meta-analysis reported that both short- and long-term exposure to ambient air pollutants were associated with increased systolic and diastolic blood pressure among children and adolescents (Huang et al., 2021). We previously reported that exposure to in utero particulate matter $\leq$ 2.5 μm in diameter ($PM_{2.5}$) was associated with higher estimated glomerular filtration rate (eGFR) and blood pressure in pre-adolescents in Mexico City (Rosa et al., 2020; Rosa et al., 2022), an area with mild ambient temperature, elevated $PM_{2.5}$, and higher incidence of kidney disease (GBD Chronic Kidney Disease Collaboration, 2020; Gutiérrez-Avila et al., 2022).

To improve upon prior cross-sectional studies of temperature and kidney outcomes, we aimed to assess associations of short-term ambient temperature and $PM_{2.5}$ exposure on eGFR and kidney injury biomarkers in healthy preadolescent children in Mexico City. Since serum creatinine and eGFR have limitations for diagnosing pre-clinical CKD and may not be an ideal early indicator of disease, we assessed soluble kidney injury biomarkers in urine which may provide a more sensitive indication of kidney damage (Zsom et al., 2022).

2. Methods

2.1. Study design and population

We used data from the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study, which is a longitudinal cohort study based in Mexico City, Mexico. Briefly, women who were in their second trimester of pregnancy were recruited into the study through the Mexican Social Security Institute (Instituto Mexicano del Seguro Social) between July 2007 and February 2011. Eligibility of the participants included at least 18 years of age, <20 weeks' gestation, no medical history of kidney or heart disease, no daily alcohol consumption, and no use of anti-epilepsy drugs or steroids. A total of 948 women delivered a live child into the cohort, and 571 children attended the 8–12 year visit. In this analyses, we excluded children with missing data on exposure assessment and covariate data. We excluded participants with missing ambient temperature and $PM_{2.5}$ values (n = 63), gestational age <37 weeks and >42 weeks (n = 57), missing BMI (n = 2), and missing indoor smoke exposure during the 8–12 year visit (n = 12). Our final study population consisted of 437 Mexican children aged 8 to 12 years. These children were free of kidney or cardiovascular disease, assessed through maternal questionnaire as of the 8–12 year study visit. Written informed consent from the children's mothers and children's assent were obtained prior to the collection of samples and all data collection methods were completed in accordance with the appropriate guidelines and regulations. PROGRESS study protocols were approved by the institutional review boards of the Icahn School of Medicine at Mount Sinai, Brigham and Women's Hospital, and the Mexican National Institute of Public Health.

2.2. Ambient temperature and $PM_{2.5}$ measurements

Daily predictions of ambient temperature and $PM_{2.5}$ with 1 × 1 km spatial resolution came from the novel satellite-based models developed for the Mexico City Metropolitan Area and were used to estimate exposures at each participant's residence. Briefly, both models utilized a combination of data from NASA satellites Terra and Aqua [Land Surface Temperature (LST) to predict ambient air temperature, and aerosol optical depth to predict $PM_{2.5}$], and other spatiotemporal predictors of ambient temperature and $PM_{2.5}$ including meteorology and land use information among others. Our temperature models leveraged satellite-hybrid mixed-effects modeling, regressing air temperature measurements from ground monitoring stations against land use terms, day-specific random intercepts, and fixed and random LST slopes. We assessed model performance using 10-fold cross-validation at withheld stations. The root-mean-square error ranged from 0.92 to 1.92 K and the R^2 ranged from 0.78 to 0.95. The daily mean $PM_{2.5}$ model used Extreme Gradient Boosting with inverse-distance weighted surfaces and

spatiotemporal predictors, and it was evaluated using leave-one-station-out cross-validation, and the model exhibited good performance, with an overall cross-validated mean absolute error (MAE) of 3.68 μg/m^3, and R^2 ranging from 0.64 to 0.86. Detailed methods employed in the satellite-based models were published in prior studies (Gutiérrez-Avila et al., 2021; Just et al., 2015).

Exposure estimates of ambient temperature and $PM_{2.5}$ were assigned to study participants based on their geocoded home addresses using the corresponding ambient temperature and $PM_{2.5}$ 1 × 1 km grid cells from our satellite-based models.

2.3. Child urinary creatinine, specific gravity, and protein biomarker measurements

At the 8–12 year visit, spot urine samples were collected from the children and stored at −80 °C until shipment to the Icahn School of Medicine at Mount Sinai for subsequent analysis. The Arbor Assay's Urine Creatinine Detection Kit was used to quantify urine creatinine. Samples were analyzed on a SpectraMax Plus 385 plate reader (Molecular Devices, California), diluted at a 1:100 dilution with water and pipetted into a 96-microwell plate with creatinine reagent. Urine specific gravity was measured using a Rudolph J157HA+ Automatic Refractometer (Rudolph Research, New Jersey).

Urinary protein concentrations were determined for nine proteins, grouped by primarily glomerular or tubular segment-specific proteins, based on their sites of expression and the pathophysiologic mechanisms that correspond to clinical acute kidney injury (Gunasekara et al., 2020; Murray et al., 2014). Glomerular proteins included albumin and cystatin C, tubular proteins included kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), alpha-1-microglobulin (A1M), beta-2-microglobulin (B2M), retinol-binding protein 4 (RBP4), osteopontin (OPN), uromodulin and glutathione S-transferase alpha (GSTα). Protein concentrations have been previously described (Politis et al., 2022). Briefly, protein concentrations were assayed using the Luminex-multiplex system at the Mount Sinai Human Immune Monitoring Core. Absolute quantification levels, based on linear internal standard curves, were obtained from the mean fluorescence intensity (MFI) values measured for each analyte. The subsequent analyses used the absolute quantification values after normalization for each protein. Protein concentrations that were below the lower limit of detection (LLOD) were replaced with the value of the LLOD divided by the square root of two. Protein concentrations higher than the quantifiable range were excluded from analyses. This included albumin (n = 3), NGAL (n = 1), OPN (n = 1), and B2M (n = 1). Nearly 33 % (n = 144) of uromodulin MFI values were higher than the quantifiable range, thus we performed exploratory analyses using uromodulin MFI values without imputation.

2.4. Serum cystatin C and eGFR

Fasting blood samples were collected at the study visit by a trained phlebotomist and serum was separated. Serum samples were stored at −80 °C until subsequent analysis. Measurements of serum cystatin C were obtained using the Quantikine® human cystatin C immunoassay (R&D Systems, Minneapolis, MN, USA). The serum cystatin C measurements were then used to derive the eGFR values using the following formula: $eGFR = 70.69 \times (\text{serum cystatin C})^{-0.931}$, where serum cystatin C is in mg/L (Ng et al., 2018).

2.5. Covariates

Demographic information, including child age, sex, body mass index (BMI), maternal report of indoor smoke exposure at the time of visit, and socioeconomic status (SES) during pregnancy was collected from the participants. SES was assessed utilizing 13 variables derived from prenatal questionnaire results which were used to classify study participant families into six levels based on the SES index created by the Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública (AMAI) (Carrasco, 2002). These levels were then collapsed into lower, medium, and higher SES. Prenatal SES was used because it was reported for majority participants and it did not change over time for participants at the time of visit. Children's BMI was measured at the same time as the collection of urine for the kidney injury biomarkers and the estimation of the BMI z-scores were based on the World Health Organization guidelines for children (WHO Multicentre Growth Reference Study Group, 2006). BMI was categorized into 3 levels: normal weight (BMI z-score ≤ 1), overweight (1 < BMI z-score ≤ 2), and obese (BMI z-score > 2). Indoor smoke exposure at the time of visit reports of any smoker in the home. Season of date of visit was used to account for seasonality and defined according to weather patterns in Mexico City as dry cold (January–February; November–December), dry warm (March–April), and rainy (May–October).

2.6. Statistical analysis

The kidney outcomes of interest in our study included eGFR and nine urinary kidney injury biomarkers. All protein concentrations were $\log_2$ transformed. We first conducted linear regression models using seven-day mean temperature averages and seven-day mean $PM_{2.5}$ averages in separate models. The seven-day exposure prior to kidney assessment was selected because $PM_{2.5}$ and ambient temperature can affect the kidneys within days to weeks time (Johnson et al., 2019); a secondary analysis examined exposure over a period of 30 days. Covariates in adjusted models included child age, child sex, child BMI, SES, season of visit and child urine specific gravity to account for urinary dilution. Models for temperature were also adjusted for smoking inside at the time of visit. To estimate the time-varying association between estimated daily mean temperature and $PM_{2.5}$ levels and each kidney parameter, we fitted distributed lag nonlinear models (DLNMs). Models included both cross-basis for temperature and $PM_{2.5}$ for an exposure period starting 7 days prior to the date of visit and ending on the date of visit. The DLNMs utilized a generalized additive model that used linear terms to examine the association between exposure and outcome, and a penalized spline basis was used to model the lag structure, with penalties for overall smoothness. In sensitivity analyses, we additionally examined the association between temperature and $PM_{2.5}$ and the kidney injury biomarkers for an exposure period starting 30 days prior to the date of visit and ending on the date of visit. We also examined associations between 7-day measures of temperature and $PM_{2.5}$ using the concentrations of uromodulin and excluding values above the quantifiable range. For all analyses we considered an alpha level of 0.05 for statistical significance. DLNMs analyses were ran using dlnm package version 2.4.5 (Gasparrini et al., 2010) in R Version 4.0.3 (R Development Core Team) and all other analyses were conducted using SAS v9.4 (SAS Corporation, Cary, NC).

3. Results

3.1. Characteristics of the study participants

The study population's sociodemographic characteristics and exposure measurements are displayed in Table 1. The average age of our study population was 9.6 years, and males and females were evenly distributed. The majority of children were lower SES (52 %). Over half of the children (55 %) were normal weight, 24 % and 21 % were overweight or obese, respectively. About 10 % of the children had exposure to indoor tobacco smoke at the time of visit. The majority of participants' (66 %) study visit occurred during the rainy season, with 25 % occuring during the cold dry season and 9 % during the warm dry season. Four participants had an eGFR <60 mL/min/1.73^2, which is the level associated with adult CKD (Levin et al., 2013). The average seven-day temperature was 16.2 °C and ranged 10.8–21.8 °C. The average seven-day $PM_{2.5}$ was 18.7 μg/m^3 and ranged 7.5–55.7 μg/m^3. Among each

Table 1
Demographic information and descriptive statistics for PROGRESS subjects (n = 437) in the study.

	N (%)
Child sex	
Male	221 (50.57)
Female	216 (49.43)
Socioeconomic status at pregnancy	
Lower	228 (52.17)
Medium	164 (37.53)
Higher	45 (10.30)
Child body mass index	
Normal	241 (55.15)
Overweight	104 (23.80)
Obese	92 (21.05)
Indoor tobacco smoke exposure at time of visit	
No	394 (90.16)
Yes	43 (9.84)
Season at 8–12 year visit	
Cold-dry	107 (24.49)
Rainy	289 (66.13)
Warm-dry	41 (9.38)

	Mean (range)
eGFR (mL/min/1.73 m^2)	99.61 (46.76–201.33)
Serum cystatin C (mg/L)	0.73.73 (0.32–1.56)
Urinary creatinine (mg/dL)	102 (15.8–322)
Body mass index z-score	0.86 (−3.00–3.98)
Age at urine collection (years)	9.64 (8.08–11.87)
Average seven-day $PM_{2.5}$ (μg/m^3)	18.79 (7.51–58.29)
Average 30-day $PM_{2.5}$ (μg/m^3)	18.83 (11.40–37.64)
Average seven-day temperature (°C)	16.26 (10.75–21.79)
Average 30-day temperature (°C)	16.29 (10.99–21.29)
Urinary kidney injury biomarkers at 8–12 years of age	Median (25th–75th percentile)
Albumin (mg/dL)	22.71 (12.11–45.23)
Cystatin C (ng/mL)	11.61 (4.61–21.57)
KIM-1 (ng/mL)	0.44 (0.20–0.80)
NGAL (ng/mL)	8.22 (3.36–23.08)
A1M (ng/mL)	169.63 (106.55–263.62)
B2M (ng/mL)	205.01 (75.49–455.99)
RBP4 (ng/mL)	1372.85 (587.50–2682.94)
OPN (ng/mL)	731.32 (236.23–1399.90)
Uromodulin (MFI)	3837.98 (2390.00–5592.93)
GSTα (ng/mL)	0.54 (0.08–4.53)

eGFR: estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin; KIM-1: kidney injury molecule-1; A1M: alpha-1-microglobulin; B2M: beta-2-microglobulin; RBP4: retinol-binding protein 4; OPN: osteopontin; MFI: mean fluorescence intensity; GSTα: glutathione S-transferase alpha.

season, the average seven-day temperature was 16.7 °C for the rainy season, 14.5 °C for the cold-dry season, and 17.7 °C for the warm-dry season. The kidney injury biomarker concentrations normalized by urine creatinine are shown in Supplemental Table 1.

3.2. Associations of individual exposures with individual kidney injury biomarkers

We assessed the associations between daily mean temperature and $PM_{2.5}$ averaged across 8 days (seven days prior to date of visit plus the day of the visit) with each kidney parameter in generalized linear models shown in Table 2. In single linear regressions, seven-day average $PM_{2.5}$ μg/m^3 was associated with 0.52 mL/min/1.73m^3 (95 % confidence interval [CI]: 0.22, 0.83) higher eGFR. Seven-day average $PM_{2.5}$ was also associated with a 7 % increase in urinary A1M, and a 7 % decrease in uromodulin (MFI) per every 5 μg/m^3 increase of in the exposure using back-transformed values. We did not find evidence of an association between ambient temperature and kidney injury biomarkers.

Table 2
Linear regressions of one-week average temperature and $PM_{2.5}$ with eGFR and individual urinary kidney biomarkers assessed at age 8–12 years.

	Temperature[a]		$PM_{2.5}$[b]	
	Beta	95 % confidence interval	Beta	95 % confidence interval
Glomerular				
eGFR (mL/min/1.73 m^2)	−0.23	−1.47–1.02	**0.52**	**0.22–0.83**
Albumin (mg/dL)	−0.07	−0.15–0.01	0.002	−0.02–0.02
Cystatin C (ng/mL)	−0.07	−0.15–0.01	0.02	−0.004–0.03
Tubular				
KIM1 (ng/mL)	−0.03	−0.10–0.03	0.003	−0.01–0.02
NGAL (ng/mL)	0.05	−0.13–0.24	0.004	−0.05–0.04
A1M (ng/mL)	0.00	−0.05–0.05	**0.02**	**0.004–0.03**
B2M (ng/mL)	−0.02	−0.11–0.08	−0.01	−0.03–0.01
RBP4 (ng/mL)	−0.05	−0.13–0.03	−0.01	−0.03–0.004
OPN (ng/mL)	−0.06	−0.16–0.03	0.02	−0.01–0.04
Uromodulin (MFI)	−0.06	−0.12–0.01	**−0.02**	**−0.04 to −0.01**
GSTα (ng/mL)	0.03	−0.15–0.20	0.02	−0.02–0.06

KIM-1: kidney injury molecule-1; NGAL: neutrophil gelatinase-associated lipocalin; A1M: alpha-1-microglobulin; B2M: beta-2-microglobulin; RBP4: retinol-binding protein 4; OPN: osteopontin; MFI: mean fluorescence intensity; GSTα: glutathione S-transferase alpha. Results in bold denote p-value < 0.05.

[a] Adjusted for child age, child sex, child body mass index z-score, socioeconomic status, season of visit, specific gravity.

[b] Adjusted for child age, child sex, child body mass index z-score, socioeconomic status, season of visit, smoking inside, specific gravity.

3.3. Joint temperature and $PM_{2.5}$ exposure DLNMs

We assessed the DLNMs of temperature and $PM_{2.5}$ with eGFR (Fig. 1). We did not find evidence of an association between ambient temperature and eGFR, however, there was an increase in eGFR of 1.77 mL/min/1.73m^2 (95 % CI: 0.55, 2.99) associated with $PM_{2.5}$ exposure between day 1 and day 4. We did not observe any associations between temperature and albumin, KIM-1, NGAL, A1M, B2M, RBP4, and GSTα (Fig. 2). Higher ambient temperature was associated with a decrease in urinary cystatin C of −0.56 (95 % CI: −1.08, −0.04) from day 6 to day 7, in OPN of −0.08 ng/mL (95 % CI: −0.15, −0.001) on day 5, and a nonlinear relationship with uromodulin [an increase in uromodulin of

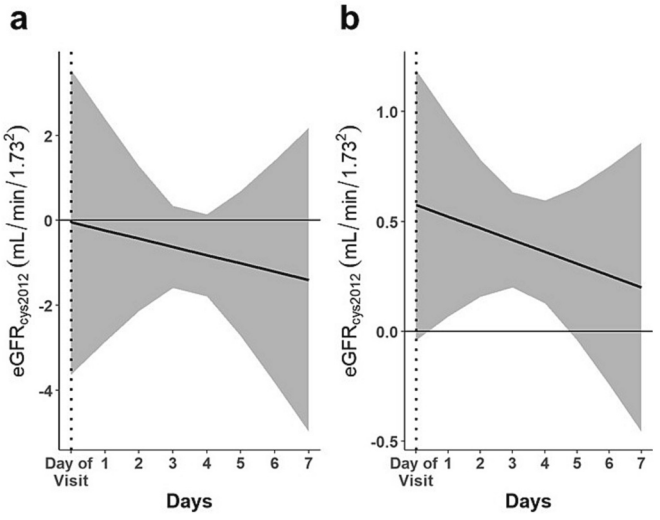

Fig. 1. Association between seven-day average a) daily temperature and b) $PM_{2.5}$ and eGFR assessed at 8–12 years. Models adjusted for child's age, sex, BMI z-score and urine specific gravity, socioeconomic status, smoking exposure, and seasonality. Dotted lines represent date of visit.

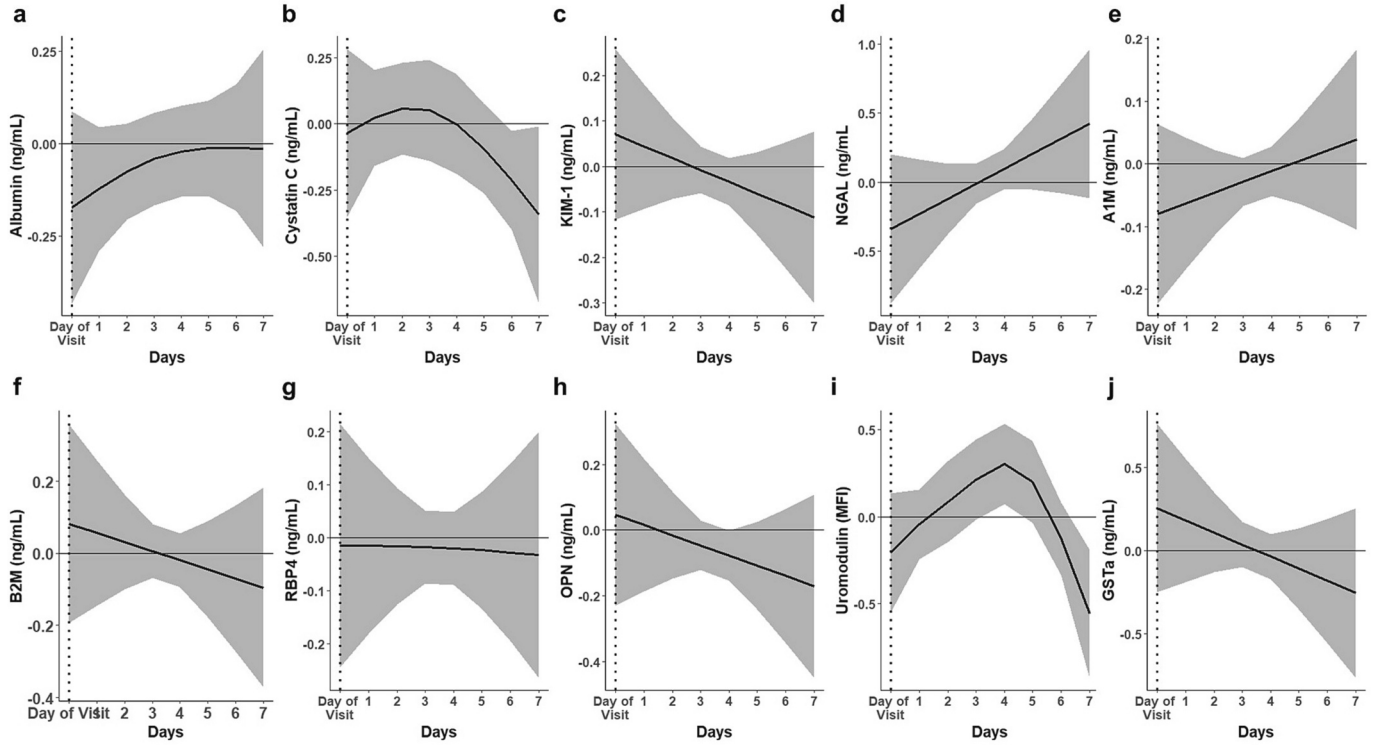

Fig. 2. Associations between seven-day average daily temperature and a) albumin, b) cystatin C, c) KIM-1, d) NGAL, e) A1M, f) B2M, g) RBP4, h) OPN, i) uromodulin, and j) GSTα at 8–12 years. Models adjusted for child's age, sex, BMI z-score and urine specific gravity, socioeconomic status, smoking exposure, and seasonality. Dotted lines represent date of visit.

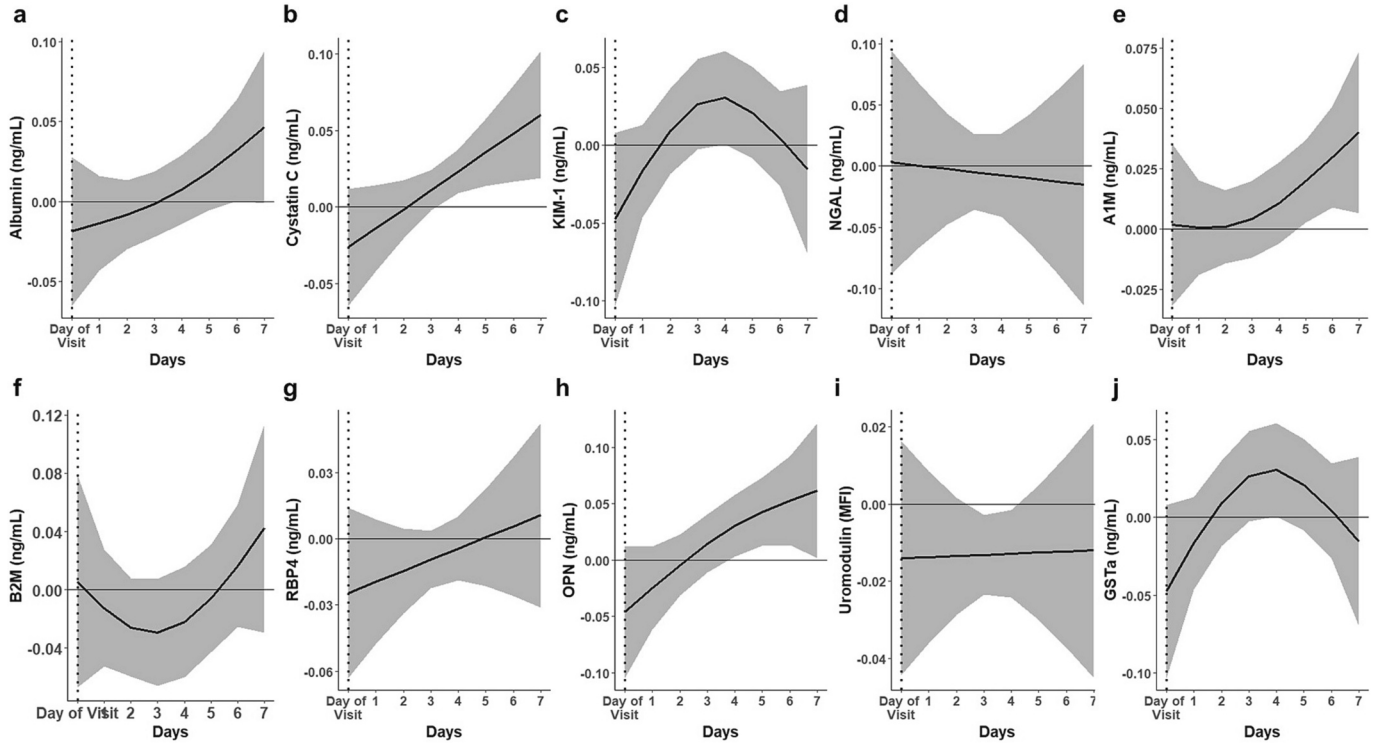

Fig. 3. Associations between seven-day average daily $PM_{2.5}$ and a) albumin, b) cystatin C, c) KIM-1, d) NGAL, e) A1M, f) B2M, g) RBP4, h) OPN, i) uromodulin, and j) GSTα at 8–12 years. Models adjusted for child's age, sex, BMI z-score and urine specific gravity, socioeconomic status, smoking exposure, and seasonality. Dotted lines represent date of visit.

0.30 MFI (95 % CI: 0.07, 0.53) on day 5 but a decrease of −0.56 (95 % CI: −0.93, −0.19) on day 7] (Fig. 2). Among the DLNMs with $PM_{2.5}$ (Fig. 3), we observed specific associations with kidney injury biomarkers including albumin, cystatin C, KIM-1, A1M, OPN, uromodulin, and GSTα. $PM_{2.5}$ exposure was associated with an increase in albumin of 0.03 ng/mL (95 % CI: 0.0001, 0.06) on day 7, an increase in cystatin C of 0.19 ng/mL (95 % CI: 0.03, 0.35) from day 4 to 7, an increase in KIM-1 of 0.03 ng/mL (95 % CI: 0.001, 0.06) on day 5, an increase in A1M of 0.09 ng/mL (95 % CI: 0.02, 0.16) from day 5 to 7, an increase in OPN of 0.19 ng/mL (95 % CI: 0.03, 0.34) from day 5 to 8, a decrease in uromodulin of −0.03 MFI (95 % CI: −0.05, −0.004) from day 3 to 4, and an increase in GSTα of 0.03 ng/mL (95 % CI: 0.001, 0.06) on day 5. In sensitivity analyses, we reran our uromodulin analysis using the quantified concentrations and we see similar results to those reported with MFI values in linear regression and DLNM models (see Supplemental Table 2 and Supplemental Fig. 1). We note that when these values are excluded, the sample size is reduced by 1/3 and we observe similar findings with wider confidence intervals.

3.4. 30-day sensitivity analyses

Results of 30-day daily mean averages of temperature and $PM_{2.5}$ linear regression associations with kidney injury biomarkers is shown in Supplementary Table 3. In single linear regressions, 30-day average temperature was associated with lower urinary albumin (β: −0.13), cystatin C (β: −0.14), OPN (β: −0.12), and uromodulin (β: −0.08). Thirty-day average $PM_{2.5}$ was associated with higher eGFR (β: 0.51), cystatin C (β: 0.03), A1M (β: 0.03), and GSTα (β: 0.06), and associated with lower uromodulin (β: −0.14).

Among the 30-day lags in DLNMs, we observed a decrease in eGFR of −4.38 mL/min/1.73 m^2 (95 % CI: −8.06, −0.70) associated with temperature exposure between day 14 and day 23, and an increase in eGFR of 4.67 mL/min/1.73 m^2 (95 % CI: 2.49, 6.84) associated with $PM_{2.5}$ exposure from the date of visit to day 16 (Supplementary Fig. 2). Among the 30-day average daily temperature DLNMs, we observed specific associations with kidney injury biomarkers including albumin, cystatin C, KIM-1, A1M, OPN, uromodulin, and GSTα (Supplementary Fig. 3). Higher temperature in the 7 days prior to date of visit was associated with an increase in KIM-1 of 0.40 ng/mL (95 % CI: 0.05, 0.74) and in the first 15 days a decrease of −0.88 ng/mL (95 % CI: −1.36, −0.40). Temperature exposure was associated with a decrease in albumin of −0.75 ng/mL (95 % CI: −1.36, −0.14) from day 14 to day 30, in cystatin C of −1.24 ng/mL (95 % CI: −1.88, −0.59) from day 15 to day 30, in A1M of −0.41 ng/mL (95 % CI: −0.76, −0.06) from day 24 to day 30, in OPN of −1.02 ng/mL (95 % CI: −1.72, −0.32) from day 23 to day 31, in uromodulin of −0.35 MFI (95 % CI: −0.69, −0.03) from day 10 to day 14, and in GSTα of −1.41 (95 % CI: −2.68, −0.15) from day 17 to day 30. We did not find evidence of any associations between $PM_{2.5}$ and albumin, KIM-1, NGAL, B2M, RBP4, and OPN (Supplementary Fig. 4). $PM_{2.5}$ exposure was associated with an increase in cystatin C of 0.13 ng/mL (95 % CI: 0.03, 0.22) from day 7 to day 22, in A1M of 0.13 ng/mL (95 % CI: 0.03, 0.22) from day 4 to day 19, in GSTα of 0.34 (95 % CI: 0.05, 0.62) from day 15 to day 30, and a decrease in uromodulin of −0.15 MFI (95 % CI: −0.25, −0.05) from the date of visit to day 14 (Supplementary Fig. 4).

4. Discussion

We investigated the associations between ambient temperature and $PM_{2.5}$ exposure with eGFR and urinary kidney injury biomarkers in healthy children aged 8–12 years of age. We observed that exposure to both short-term (7 days) and longer-term (30 days) $PM_{2.5}$ was associated with higher eGFR closer to the date of visit. Seven-day $PM_{2.5}$ exposure had specific associations with kidney injury biomarkers including cystatin C, A1M, OPN, and uromodulin. We also report that ambient temperature exposure 30 days before the date of visit was associated with decreased albumin, cystatin C, KIM-1, A1M, OPN, uromodulin, and GSTα. Our findings suggest that ambient temperature and $PM_{2.5}$ exposure may have implications for kidney health in adolescence.

Ambient temperature was associated with fluctuations in urinary kidney injury biomarkers in healthy children. Some prior research on the association of kidney injury biomarkers and ambient temperature has been limited to the use of hospital and emergency department admissions data. In a study conducted in Brazil among 2,726,886 hospitalizations for renal diseases, the estimated risk of hospitalization over a seven-day lag increased by 0.9 % for every 1 °C increase in daily mean temperature, with the associations being the largest at lag 0 (day of hospitalization), but remaining for a lag of 1–2 days (Wen et al., 2022). Another study found that the risk of hospitalization for acute renal failure increased about 7 % per 10 °F (5.56 °C) increase in temperature, with typical summer temperatures in the state of California (Green et al., 2010). Increases in ambient temperatures may play a role in the development of dehydration and kidney volume loss, which in turn has led to increased hospitalizations for renal diseases (Borg et al., 2017).

Limited studies have examined the associations of kidney biomarker levels and ambient temperature. One cross-sectional study conducted in the United States among 3377 participants older than 57 years of age observed that for every 1 °C increase in daily average temperature (restricted to temperatures >10 °C), NGAL levels increased by 1.89 % (95 % CI: 0.77, 3.91) (Honda et al., 2019). In a prior study of agricultural workers exposed to extreme temperatures, an increase of urinary NGAL, a protein released by damaged nephron tubular cells at the onset of inflammation, 200–400 % above baseline was a strong predictor of acute kidney injury (Wesseling et al., 2016). Lastly, a study conducted among Nicaraguan sugarcane cutters found that levels of NGAL and *N*-acetyl-β-D-glucosaminidase (NAG) were increased near the end of the harvest season, a period from March to May (Laws et al., 2016). However, these studies were limited to adult and agricultural worker populations who are at risk for CKDu. Although our results for NGAL were null for prior seven-day and 30-day temperature exposure periods, we observed that the association with KIM-1 became more positive closer to the date of visit when examining the 30-day lag exposure in temperature, but were null when examining the seven-day lag exposure. Both NGAL and KIM-1 are biomarkers of tubulointerstitial damage, and have been associated with heat stress symptoms or heat-related illnesses in population-based studies (Goto et al., 2022; Kulasooriya et al., 2021; Kuwabara et al., 2009; van Timmeren et al., 2007). Here, we also identified that five other tubular kidney biomarkers (KIM-1, A1M, OPN, GSTα, and uromodulin) were associated with 30-day temperature exposure, which may suggest that increasing ambient temperature may have a role in short-term tubular changes in the kidneys. These findings may inform future studies of children in CKDu-endemic areas, where a majority of current research is conducted with adult participants.

Prior research has examined children's kidney function and time-varying PM exposure. A study conducted in China among 105 children aged 4–13 years old reported that personal exposure to $PM_{2.5}$ was associated with a decrease in serum creatinine-based eGFR with a potential 2-day lag (Liu et al., 2020). This differed from our study, which observed that $PM_{2.5}$ was associated with an increase in serum cystatin C-based eGFR among 2 to 5-day lag. However, we did observe a decrease in serum cystatin C-based eGFR among 21–31 day lag in our sensitivity analyses. This may be due to differences in exposure assessment or eGFR biomarker (serum creatine vs. cystatin C), since participants in the prior study carried personal monitoring devices to measure personal exposure and the current study used residential assessments to estimate ambient exposure. An 18-year longitudinal study conducted of 10,942 children and adolescents in Taiwan and Hong Kong (median age: 19 years) found that each 10 $\mu g/m^3$ increase in yearly mean $PM_{2.5}$ concentration was associated with decreased eGFR (β: −0.45; 95 % CI: −0.63 to −0.28), after adjusting for ambient temperature and seasonality (Guo et al., 2022). In an adult rat model study, urinary NGAL and EGF were increased with $PM_{2.5}$ exposure in the second week of exposure, and

urinary B2M and cystatin C were increased with exposure to $PM_{2.5}$ in the first, second, sixth, and eight weeks of exposure (Aztatzi-Aguilar et al., 2016). Our study found that the association with A1M, a tubular kidney biomarker, became more positive closer to the date of visit when examining the thirty-day lag exposure to $PM_{2.5}$. These results, as well as results from prior studies, may indicate that short-term exposure to $PM_{2.5}$ might negatively affect tubular kidney function in children and adults.

Our study had many strengths. The PROGRESS study is an established prospective birth cohort with well-characterized demographic and covariate data. We were able to reconstruct exposure to ambient temperature and $PM_{2.5}$ and concurrently examine their impact on kidney function. However, repeated exposure to high ambient temperatures can cause harmful kidney effects which can be challenging to assess with traditional clinical measures, such as eGFR and serum creatinine (Hsu and Powe, 2017). It is important to note that debate exists regarding the use of cystatin C and/or serum creatinine when calculating eGFR and appropriateness of the various estimating equations (Farrington et al., 2023; Ferguson et al., 2015; Inker et al., 2021). For example, acknowledged differences of eGFR equations commonly applied in clinical settings led to overestimation of eGFR among Black and Hispanic individuals and therefore equations that include race as a variable are no longer recommended (Delgado et al., 2021; Powe, 2020; Spencer et al., 2023). Caution should be taken when applying estimating equations (e.g., were equations derived from data generated among diverse or predominantly White study populations) and whether the equations are most effective among individuals with extant CKD or renally 'healthy' individuals. Regardless of the estimating equation used, limitations of eGFR includes that it only reflects one of the physiological kidney functions, it cannot detect kidney damage at earlier stages, as the kidney injury biomarkers can, and lastly can be affected by disease conditions and factors that are not kidney-related (Zsom et al., 2022). Additionally, we used a panel of multiple proteins that have been established as early indicators of kidney injury. Many biomarkers of kidney injury, such as NGAL, are able to assess subclinical kidney injury, and are more sensitive than the common clinical diagnostic measurements (Schinstock et al., 2013). Additionally, using customized panels, as well as urinary proteomics, with specific biomarkers for each functional region of the nephron may be more informative to determine damage sites in the kidney (Øvrehus et al., 2015). These kidney injury biomarkers, measured in the urine, are also less invasive compared to serum-derived markers, such as serum creatinine for eGFR.

A potential limitation of this work is that timing of urine collection and whether it was the first urine of the day was not collected. Subsequent PROGRESS study visits are collecting information on urine collection time, since time of urine collection is a predictor of specific gravity and urine creatinine concentration (Gaines et al., 2010). To account for hydration status in our analyses we adjusted for urine specific gravity. Prior studies have reported that urine specific gravity is a preferred indicator to account for hydration status compared to creatinine normalized kidney injury biomarkers (Kuiper et al., 2021; White et al., 2010). Another limitation of our study is the lack of data on humidity. Accounting for humidity would be important to address confounding and modification effects, especially since it can influence heat stress and dehydration as well as provide an account for the geographical region. We also did not evaluate time spent outdoors/physical activity which might impact exposure to both $PM_{2.5}$ and temperature.

5. Conclusions

We found that among children in the PROGRESS longitudinal birth cohort study, ambient temperature and $PM_{2.5}$ exposure were associated with selected urinary kidney injury biomarkers. Recent short-term environmental exposures such as heat stress and air pollution may lead to subclinical glomerular or tubular injury in adolescents. Future studies are needed to further assess ambient temperature and $PM_{2.5}$ and kidney injury biomarkers in children and adolescents, especially since nephrotoxic contributions to subclinical acute kidney injury can exacerbate chronic kidney injury at later life stages.

CRediT authorship contribution statement

Maria D. Politis: Methodology, Formal analysis, Writing-Original draft preparation, Writing-Reviewing and editing; **Iván Gutiérrez-Avila**: Data curation, Writing-Reviewing and editing; **Allan Just**: Data curation, Writing-Reviewing and editing; **María Luisa Pizano-Zárate**: Writing-Reviewing and editing; **Marcela Tamayo-Ortiz**: Writing-Reviewing and editing; **Jason H Greenberg**: Writing-Reviewing and editing; **Martha M. Téllez-Rojo**: Data curation, Funding acquisition, Writing-Reviewing and editing; **Alison P. Sanders**: Conceptualization, Methodology, Writing-Original draft preparation, Funding Acquisition, Writing-Reviewing and editing, Supervision; and **Maria José Rosa**: Conceptualization, Methodology, Writing-Original draft preparation, Funding acquisition, Writing-Reviewing and editing, Supervision. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maria Jose Rosa reports financial support was provided by National Institute of Environmental Health Sciences. Alison P. Sanders reports financial support was provided by National Institute of Environmental Health Sciences. Allan Just reports financial support was provided by National Institute of Environmental Health Sciences. Martha M. Tellez-Rojo reports financial support was provided by National Institute of Environmental Health Sciences. Maria D. Politis reports financial support was provided by National Institutes of Health.

Data availability statement

The data that were used in this study can be made accessible to researchers upon appropriate request with restrictions to ensure the privacy of human subjects. Note that access to the data is limited due to a data sharing agreement approved by the IRB at Mount Sinai.

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Appendix A. Supplementary data

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