Critical windows of perinatal particulate matter (PM$_{2.5}$) exposure and preadolescent kidney function

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A R T I C L E   I N F O

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Prenatal exposure
Bayesian distributed lag interaction models

A B S T R A C T

Air pollution exposure, especially particulate matter ≤2.5 μm in diameter (PM$_{2.5}$), is associated with poorer kidney function in adults and children. Perinatal exposure may occur during susceptible periods of nephron development. We used distributed lag nonlinear models (DLNMs) to examine time-varying associations between early life daily PM$_{2.5}$ exposure (periconceptional through age 8 years) and kidney parameters in preadolescent children aged 8–10 years. Participants included 427 mother-child dyads enrolled in the PROGRESS birth cohort study based in Mexico City. Daily PM$_{2.5}$ exposure was estimated at each participant’s residence using a validated satellite-based spatio-temporal model. Kidney function parameters included estimated glomerular filtration rate (eGFR), serum cystatin C, and blood urea nitrogen (BUN). Models were adjusted for child’s age, sex and body mass index (BMI) z-score, as well as maternal education, indoor smoking report and seasonality (prenatal models were additionally adjusted for average first year of life PM$_{2.5}$ exposure). We also tested for sex-specific effects. Average perinatal PM$_{2.5}$ was 22.7 μg/m$^3$ and ranged 16.4–29.3 μg/m$^3$. Early pregnancy PM$_{2.5}$ exposures were associated with higher eGFR in preadolescence. Specifically, we found that PM$_{2.5}$ exposure between weeks 1–18 of gestation was associated with increased preadolescent eGFR, whereas exposure in the first 14 months of life after birth were associated with decreased eGFR. Specifically, a 5 μg/m$^3$ increase in PM$_{2.5}$ during the detected prenatal window was associated with a cumulative increase in eGFR of 4.44 mL/min/1.73$^2$ (95%CI: 1.37, 7.52), and during the postnatal window we report a cumulative eGFR decrease of $-10.36$ mL/min/1.73$^2$ (95%CI: $-17.68$, $-3.04$). We identified perinatal windows of susceptibility to PM$_{2.5}$ exposure with preadolescent kidney function parameters. Follow-up investigating PM$_{2.5}$ exposure with peripubertal kidney function trajectories and risk of kidney disease in adulthood will be critical.

1. Introduction

Chronic kidney disease (CKD) affects 10%–15% of the population worldwide, with rising prevalence due to global epidemics of major risk factors for CKD including hypertension, obesity, and diabetes (Hill et al., 2016). However, the increasing prevalence of CKD cannot be fully

Abbreviations: BDLIM, Bayesian distributed lag interaction model; BP, Blood pressure; BUN, Blood urea nitrogen; CI, confidence interval; DLNM, Distributed lag nonlinear models; eGFR, Estimated glomerular filtration rate; GPS, global positioning system; PM$_{2.5}$, Particulate matter less than or equal 2.5 μm in diameter.

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attributed to these risk factors, and exposure to environmental pollutants is increasingly recognized as a potential contributor to the rising prevalence (Xu et al., 2018). Moreover, rates of CKD and hypertension among children and young adults are increasing (Collaboration, 2020; Kim et al., 2006) furthering the need to examine early life determinants of disease.

Exposure to particulate matter (PM) air pollution has been associated with adverse cardiorenal outcomes including decreased kidney function and elevated blood pressure (BP) in children and adolescents (Rosa et al., 2020; Sanders et al., 2018). Long-term PM exposure contributes to the incidence and progression of chronic kidney disease (CKD) and hypertension (HTN) in adults (Blum et al., 2020; Bowe et al., 2018). Inhaled particles can rapidly trigger changes in BP and stimulate an inflammatory response of activated immune cells and cytokines leading to imbalance of vascular homeostatic responses. Increased demand on the kidney, may in turn lead to compromised glomerular function or acute kidney injury (Matsumura et al., 2018). Given the growing body of evidence that air pollution (i.e. PM$_{2.5}$) may cross the placenta to disrupt normal homeostatic responses, it is possible that perinatal exposure to air pollution may occur during a particularly vulnerable period of nephron development and maturation, priming the kidney for subsequent CKD (Sanders et al., 2018; Zheng et al., 2017).

Indeed, the perinatal period comprises key susceptible windows of kidney development. In the developing fetus, metanephric kidney development begins around week 4 gestational age (GA). By the second trimester (11–14 weeks GA) the majority of branching morphogenesis is complete (Sampogna et al., 2015), with 90% of nephron formation accomplished in the third trimester (26–36 weeks GA) (Hinchcliffe et al., 1991). After birth, renal blood flow, glomerular filtration rate (GFR) and renal homeostatic processes continue to mature and are also processes susceptible to environmental insults (Gubbaju et al., 2014; Veille et al., 1998). Environmental insults during these critical developmental periods may program adverse health outcomes in adulthood such as CKD or HTN (Solhaug et al., 2004). These events experienced in utero can lead to a higher risk for cardiovascular diseases and metabolic abnormalities observed in children with CKD who have GFR decline (Furth et al., 2011; Luyckx et al., 2013). Even minor changes in GFR within a normal or mildly reduced range can predict CKD or mortality later in life (Matsumita et al., 2009; Turin et al., 2013). As Mexico has one of the highest prevalence of CKD worldwide (Collaboration, 2020) as well as elevated ambient PM$_{2.5}$ concentrations in Mexico City (Just et al., 2015), we sought to examine perinatal windows of susceptibility to PM$_{2.5}$ exposure on preadolescent eGFR and kidney function parameters among a high risk population. We additionally examined potential effect modification by child sex, given evidence of sex-specific differences in studies of PM exposure and children’s eGFR as well as CKD risk (Carrero et al., 2018; Liu et al., 2020). Our a priori hypothesis was that developmental PM$_{2.5}$ exposure was associated with declines in eGFR, and an increase in serum cystatin C, serum creatinine, and blood urea nitrogen (BUN).

2. Methods

2.1. Study population

Between July 2007 and February 2011, pregnant women who were receiving prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social –IMSS) were recruited into the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study. Participants’ eligibility criteria included: less than 20 weeks’ gestation, at least 18 years of age, had completed primary education, planned to stay in Mexico City for the next 3 years, had access to a telephone, had no medical history of heart or kidney disease, did not consume alcohol daily, and did not use any steroid or anti-epilepsy medications. Procedures were approved by institutional review boards at the Brigham and Women’s Hospital, Icahn School of Medicine at Mount Sinai (protocol number –00751), and the Mexican National Institute of Public Health (project #560). After a detailed explanation of the project protocols, during each study visit women provided written informed consent and at the preadolescent visit children provided assent. Of 948 mothers who delivered a live birth, a total of 571 children were followed longitudinally and presented at the 8-10 year-old visit. Our analysis excluded children born preterm (<37 weeks gestation; n = 64) and post term (>42 weeks gestation; n = 3), missing kidney parameter measures (n = 73), missing daily PM$_{2.5}$ estimates (n = 1), and missing child characteristics (n = 3). Derivation of gestational age was previously reported elsewhere (Sanders et al., 2015). Thus, study participants for this analysis were restricted to the 427 dyads who had at least one kidney parameter measure, daily PM$_{2.5}$ estimates, and were born term.

2.2. PM$_{2.5}$ levels

Daily exposure to PM$_{2.5}$ at each participant’s residence was estimated during pregnancy through age 8 years using a previously described spatio-temporal model that incorporates Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Depth (AOD) measurements at a 1 × 1 km spatial resolution (Just et al., 2015). Briefly, remote sensing data were calibrated with municipal ground level monitors of PM$_{2.5}$, meteorological data and land use regression variables to generate estimates of daily ambient PM$_{2.5}$ concentrations for each participant at their residential location as recorded by research staff using handheld GPS devices. Mixed effect models with spatial and temporal predictors and day-specific random effects were used to account for temporal variations in the PM$_{2.5}$–AOD relationship. The model was fit with a seasonal smooth function of latitude and longitude and time-varying average incorporating local monitoring for days without AOD data. We refer the reader to (Just et al., 2015) for additional details of the model methods and performance. In trimester-specific analyses, PM$_{2.5}$ levels were averaged over clinically defined trimesters (in gestational weeks). In these trimester-specific analyses, we calculated the average PM$_{2.5}$ over the first trimester defined as weeks 1–13 gestation, the second trimester defined as weeks 14–27 gestation, and the third trimester defined as 28 weeks’ gestation to delivery. Average postnatal PM$_{2.5}$ was also estimated for the first year after delivery.

2.3. Serum collection details

At children’s arrival to the study clinic, fasting venous blood samples were collected in red top vacutainer tubes during the morning between 8 and 11 a.m. Samples were centrifuged and serum was separated, aliquoted and stored at −70 °C until subsequent analyses.

2.4. Kidney function parameters

Serum cystatin C was measured using the Quantikine Enzyme-Linked Immunosorbent Assay (ELISA) Human Cystatin C Immunoassay (R&D Systems, Minneapolis, MN) with intra- and inter-assay coefficient of variation below 5%. Optical density was measured by a microplate reader (Synergy HT, BioTek Instruments, Inc., Winooski, VT) set to 450 nm with a limit of detection of 31 pg/mL. Serum creatinine was measured using creatinine FS reagent and response910 (DiaSys, Holzheim, Germany), based on Jaffe’s kinetic method without deproteinization, with a detection limit of 0.2 mg/dL and coefficient of variation $<5%$. BUN was calculated with the following formula: Serum urea (mg/dL)/2.14; serum urea was determined through the Urease-GLDH enzymatic UV test (Sarkar, 2013).

2.5. Estimated glomerular filtration rate (eGFR)

eGFR was calculated according to cystatin C–based formula: and
approach the null value. A sensitive window was identified when the models, ridge penalties (Gasparrini et al., 2017) were applied under the with penalties for overall smoothness. Additionally, for the prenatal exposure and outcome and a penalized spline basis for the lag structure on a generalized additive model with linear terms for the association of weeks gestation. A postnatal model included an exposure period starting nonlinear models (DLNMs) using (a) prenatal and (b) postnatal expo

GFR in pediatric populations (Aggarwal et al., 2012; Ng et al., 2018). Cystatin C is produced by all mononucleated cells and freely filtered at the glomerulus. Compared to serum creatinine, cystatin C is not as subject to variation with muscle mass, BMI and delayed sensitivity to kidney damage (Gerchman et al., 2009). For sensitivity analysis, eGFR was also calculate using the validated serum creatinine eGFR

\[ eGFR_{Schwartz} = \frac{k \times \text{height}}{\text{weight}^{0.55}} \]

where \( k = 0.55 \) for children <13 years (the preferred equation for serum creatinine measured by the Jaffe method) and creatinine-cystatin C-based CKID formula eGFR

\[ = 39.8 \times \frac{\text{height}}{\text{serum creatinine}}^{0.456} \times \frac{1.8}{\text{serum cystatin C}}^{0.418} \times \frac{30}{\text{BUN}}^{0.079} \times \frac{1.076}{\text{female}}^{1.0179} \] (Schwartz et al., 2009).

2.6. Covariates

Covariates were selected a priori based on previous literature (Aris et al., 2019) and included child’s sex, age, and body mass index (BMI) z-score at blood draw, average first postnatal year PM2.5 (prenatal models only), seasonality of conception, maternal educational attainment at enrollment (categorized as < high school, some high school or high school graduate, > high school), and prenatal environmental tobacco smoke exposure. Children were weighed with the least amount of clothing possible and without footwear using an InBody 230, and height was measured with a SECA stadiometer without footwear. BMI z-score was estimated according to WHO guidelines (Group, 2006): underweight, normal weight, overweight, and obesity were defined as < −2SD, −2SD to ≤ +1SD, > +1SD to −2SD, and > +2SD, respectively. As there was one underweight child, this observation was excluded from the analyses. Prevalence of maternal smoking was very low in the cohort; in our sample, only 2 mothers reported smoking in pregnancy, therefore only prenatal exposure to environmental tobacco smoke (ETS) was considered in the models. Prenatal exposure to ETS was defined as report of any smoker in the home during the second or third trimester of pregnancy. Seasonality of PM2.5 exposure was defined as sine and cosine of time of year (Stolwijk et al., 1999; van Rossem et al., 2015). In linear regression models, where no time series data were used, season of conception was used to account for seasonality and was defined according to weather patterns in Mexico City as dry cold (January–February; November–December), dry warm (March–April) and rainy (May–October). Postnatal models included adjustment for season of kidney function assessment.

2.7. Statistical analyses

Kidney outcomes of interest included eGFR\textsubscript{Cyst C} 2012, cystatin C, creatinine and BUN. First, traditional linear regression models with adjustment for covariates listed above were run using clinically defined trimesters and average PM\textsubscript{2.5} over pregnancy in separate models. In order to avoid bias in estimates (Wilson et al., 2017b), average exposure from all three trimesters were included in a single model.

To estimate the time-variation association between estimated daily PM\textsubscript{2.5} levels and each kidney parameter, we then fitted distributed lag nonlinear models (DLNMs) using (a) prenatal and (b) postnatal exposures. The prenatal models included a 390-day exposure period starting 60 days prior to last menstrual period (LMP) and ending 50 days after 40 weeks gestation. A postnatal model included an exposure period starting one month prior to birth and ending at 8 years. The DLNMs were based on a generalized additive model with linear terms for the association of exposure and outcome and a penalized spline basis for the lag structure with penalties for overall smoothness. Additionally, for the prenatal models, ridge penalties (Gasparrini et al., 2017) were applied under the assumption that the associations at earliest lags (preconception period) approach the null value. A sensitive window was identified when the
dpointwise 95% confidence bands did not contain zero. In sensitivity analyses, we additionally examined the consistency of our detected windows to the use of alternative smoothers over the lag period and compared our results using b-splines, natural splines and penalized cubic regression splines. We also additionally adjusted for temperature by including a separate cross-basis for daily mean temperature (for prenatal models) and monthly mean temperatures (for postnatal models) covering the same lags. DLNMs were implemented using the dlm package version 2.4.2 (Gasparrini, 2011) in R Version 3.5.1 (R Development Core Team) and other analyses were performed in SPSS version 24 (Chicago, IL).

Exploratory Bayesian distributed lag interaction models (BDLIM) were employed to examine effect modification by child sex using weekly average PM\textsubscript{2.5}. In addition to sensitive windows, BDLIM estimates the cumulative effect of PM\textsubscript{2.5} exposure over the entire pregnancy for each sex-specific subgroup, accounting for identified sensitive windows and within-window effects (Wilson et al., 2017b). In these models, each stratum can have either the same or different sensitive windows or the same or different within-window effects (Wilson et al., 2017b). The model quantifies the likelihood of each pattern of heterogeneity and estimates the association between exposure and outcome under the effect modification pattern that is best supported by the data.

3. Results

Children in our study were an average of 9 years of age, equally distributed between males and females, and over a third experienced prenatal exposure to ETS (Table 1). More than half (53%) were normal weight, and 24% and 22% were overweight or obese, respectively. Nearly all eGFR measures were within normal range, only 4 participants had an eGFR < 60 mL/min/1.73\textsuperscript{2}, a level associated with adult CKD

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics for mother-child dyads participating in the PROGRESS study at age 8-10 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>N = 427</td>
</tr>
<tr>
<td>Child sex</td>
<td>213 (49.9)</td>
</tr>
<tr>
<td>Female</td>
<td>214 (50.1)</td>
</tr>
<tr>
<td>Maternal age at enrollment (years)</td>
<td>38.8 ± 1.13</td>
</tr>
<tr>
<td>High school</td>
<td>170 (39.8)</td>
</tr>
<tr>
<td>Some high school or high school graduate</td>
<td>161 (37.7)</td>
</tr>
<tr>
<td>&gt; High school</td>
<td>96 (22.5)</td>
</tr>
<tr>
<td>Maternal age at enrollment (years)</td>
<td>38.8 ± 1.13</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>22.7 ± 2.51</td>
</tr>
<tr>
<td>Average prenatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>22.7 ± 2.21</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>22.0 ± 2.33</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>23.0 ± 1.85</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>22.2 ± 1.93</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>21.6 ± 2.00</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>21.2 ± 1.91</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>20.8 ± 1.78</td>
</tr>
<tr>
<td>Average postnatal PM\textsubscript{2.5} (μg/m\textsuperscript{3})</td>
<td>20.8 ± 1.82</td>
</tr>
<tr>
<td>At preadolescence study visit (8-10 years)</td>
<td>9.65 ± 0.65</td>
</tr>
<tr>
<td>Child BMI z-score</td>
<td>0.92 ± 1.24</td>
</tr>
<tr>
<td>Normal weight, n (%)</td>
<td>228 (53.2)</td>
</tr>
<tr>
<td>Overweight, n (%)</td>
<td>104 (24.4)</td>
</tr>
<tr>
<td>Obese, n (%)</td>
<td>95 (22.2)</td>
</tr>
<tr>
<td>Child kidney markers</td>
<td>99.4 ± 22.4</td>
</tr>
<tr>
<td>eGFR\textsubscript{Cyst C} 2012 (mL/min/1.73\textsuperscript{2})</td>
<td>0.73 ± 0.17</td>
</tr>
<tr>
<td>Serum Cystatin C (mg/L)</td>
<td>0.43 ± 0.09</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>12.3 ± 3.05</td>
</tr>
<tr>
<td>Missing</td>
<td>81</td>
</tr>
</tbody>
</table>
First, we assessed associations between averaged PM$_{2.5}$ across pregnancy, each trimester, and one year postnatally with each outcome in generalized linear models (Table 2). We found that each 5 µg/m$^3$ increase in PM$_{2.5}$ exposure averaged across the pregnancy period was associated with a statistically significant 4.57 mL/min/1.73 m$^2$ increase in eGFR$_{\text{cysC}}$ 2012 (95% CI: 0.13, 9.00). Correspondingly, each 5 µg/m$^3$ increase in average PM$_{2.5}$ exposure during pregnancy was associated with a decrease in $-0.05$ (95% CI: $-0.08$, $-0.01$) mg/dL and $-0.02$ (95% CI: $-0.05$, $-0.002$) mg/dL in serum cystatin C and serum creatinine, respectively. In models using the average PM$_{2.5}$ exposure in each trimester, we observed that 5 µg/m$^3$ increase in first trimester PM$_{2.5}$ exposure was associated with a 3.44 mL/min/1.73$^2$ increase in eGFR$_{\text{cysC}}$ 2012 (95% CI: 0.35, 6.52). Additionally, average PM$_{2.5}$ exposure in the first postnatal year was associated with a 5 min/ml (95% CI: $-9.87$, $-0.19$) decrease in eGFR$_{\text{cysC}}$ 2012, and corresponding increased serum cystatin C (β: $0.05$; 95% CI: $0.01$, $0.08$) and serum creatinine (β: $0.04$; 95% CI: $0.02$, $0.06$). No significant relationships were observed with BUN (Table 2). Sensitivity analyses using the creatinine-cystatin C-based equation showed similar results (Table S1, Supplemental Fig. S1), whereas derived results with the “old” Schwartz equation showed a similar shape, but did not reach statistical significance (results not shown).

In DLNM with daily resolution PM$_{2.5}$ estimates, we observed several non-linear relationships in the timing of the association between PM$_{2.5}$ exposure and kidney parameters (Fig. 1 a-d). We identified a window of susceptibility to PM$_{2.5}$ exposure early during gestation with higher eGFR$_{\text{cysC}}$ 2012. Specifically, we found that first trimester PM$_{2.5}$ exposure between weeks 1–18 of gestation (days 1–129) was associated with increased preadolescent eGFR$_{\text{cysC}}$ 2012. In contrast, a 5 µg/m$^3$ increase in PM$_{2.5}$ throughout this critical window would predict a cumulative increase in eGFR$_{\text{cysC}}$ 2012 of 4.44 mL/min/1.73$^2$ (95% CI: 1.37, 7.52). In DLNs examining monthly postnatal PM$_{2.5}$ averages, we observed that PM$_{2.5}$ exposure in the first 14 months of life was associated with a cumulative decrease in eGFR$_{\text{cysC}}$ 2012 (β: $10.36$; 95% CI: $-17.68$, $-3.04$) (Fig. 2).

Correspondingly, we also report that PM$_{2.5}$ exposure between weeks 2–15 of gestation (days 15–108) was associated with decreased (β: $0.04$; 95% CI: $-0.07$, $-0.01$) cystatin C. Among the monthly postnatal PM$_{2.5}$ averages, we found that PM$_{2.5}$ exposure in the first 8 months of life was associated with a slight cumulative increase in cystatin C (β: $0.038$; 95% CI: $0.005$, 0.071). For serum creatinine, we detected a susceptibility window at 5–19 weeks of gestation in which PM$_{2.5}$ was associated with lower creatinine (β: $0.008$; 95% CI: $-0.002$, $-0.0007$), although the observed magnitude of effect was close to zero. There was a small cumulative increase (β: $0.05$; 95% CI: $0.01$, $0.09$) in creatinine among the first 18 months of life. For BUN the susceptibility window was estimated later (approximately third trimester), from gestational weeks 25–34 (days 176–240) (β: $0.70$; 95% CI: $0.23$, 1.18). The postnatal analysis examining BUN did not find a susceptibility window. Sensitivity analyses using of alternative smoothers over the lag period (Table S2, Figs. S2–S5) or additionally adjusting for temperature showed similar results (Table S3). In BDILM analysis, there was no evidence of sex-modification between PM$_{2.5}$ and kidney parameters (data not shown).

4. Discussion

In this study, we found that children exposed perinatally to PM$_{2.5}$ had altered kidney parameters at approximately 9 years of age. Exposure to PM$_{2.5}$ early in pregnancy was associated with higher eGFR, lower cystatin C and lower creatinine. We also report that PM$_{2.5}$ in late pregnancy was associated with higher BUN. We observed that early postnatal exposure was associated with lower eGFR and higher cystatin C and creatinine. Our findings suggest that PM$_{2.5}$ exposure in the first trimester and first 14 months of life may have implications for kidney health in adolescence. While several prior studies have examined time-specific PM exposure and children’s kidney function or BP (Liu et al., 2020, 2021; Sanders et al., 2018), time-varying relationships of perinatal PM exposure with preaduls eGFR have not yet been reported. As adolescent kidney function is a predictor of kidney health across the life course, the findings may have important public health implications for mitigating the risk of CKD and HTN.

There are several important observations from this work. First, one important interpretation is that in utero PM$_{2.5}$ exposure may account for some portion of later-life kidney dysfunction, observable as early as 9 years of age. Our data suggest that the first trimester is an important window of susceptibility for increased preadolescent eGFR. Indeed, this overlaps with a critical developmental window of nephron progenitor development prior to branching morphogenesis (Sampogna et al., 2015). Importantly, loss of nephron progenitor cells affects uterine branching and nephron endowment (Cebrian et al., 2014). Our data also suggest that postnatal PM$_{2.5}$ exposure is associated with lower eGFR, as suggested in prior studies (Liu et al., 2020, 2021). Postnatal kidney development and maturation is characterized by increased renal blood flow and GFR as renal homeostatic processes continue to mature (Veille et al., 1998). The opposite directionality of the two observed windows may seem counterintuitive, however, this is in-line with the sequelae of nephron damage and initially presenting as overcompensation by hyperfiltration followed by eGFR decline (Orr and Bridges, 2017). Additionally, several mechanisms have hypothesized potential developmental or teratogenic effects of PM exposure, including placental inflammation, oxidative stress and coagulation changes, which may occur during embryogenesis in the first trimester, leading to potential DNA damage in cells and future disruptions in cell activity in adolescence and adulthood (Kamnan et al., 2006; Vrijheid et al., 2011). Additionally, experimental animal studies suggest that exposure to diesel and deep exhaust particles may lead to changes in renal hemodynamics, DNA damage in renal tissue, and further worsens acute kidney injury and chronic renal injury (Nemmar et al., 2010, Nemmar et al., 2016). Future research is needed to examine the opposite directionally of the two observed windows, including unmeasured or residual confounding, when examining the prenatal versus postnatal time periods.

Evidence from animal models supports in utero biological programming of kidney dysfunction and disease. There are several biologically

Table 2
Association of average PM$_{2.5}$ levels calculated during across pregnancy, each trimester, and the first postnatal year with kidney parameters assessed at pre-adolescence (ages 8–10 years).

<table>
<thead>
<tr>
<th></th>
<th>eGFR$_{\text{cysC}}$ 2012 (mL/min/1.73$^2$)</th>
<th>Serum Cystatin C (mg/L)</th>
<th>Serum Creatinine (mg/dL)</th>
<th>BUN (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pregnancy</td>
<td>4.57* (0.13, 6.52)</td>
<td>$-0.05^*$</td>
<td>$-0.02^*$</td>
<td>0.04</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>9.00</td>
<td>(-0.08, -0.05)</td>
<td>(-0.70)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>3.44* (0.35, 6.52)</td>
<td>$-0.03^*$</td>
<td>$-0.15$ (-0.03, 0.18)</td>
<td></td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>(-0.05, -0.01)</td>
<td>(-0.00, -0.03)</td>
<td>(-0.33, -0.68)</td>
<td></td>
</tr>
<tr>
<td>Second trimester</td>
<td>-$0.09$ (-3.16, 2.97)</td>
<td>$-0.01$</td>
<td>$-0.01$ (-0.02, -0.41)</td>
<td></td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>(-0.03, -0.00)</td>
<td>(-0.00, -0.08)</td>
<td>(-0.89, -0.08)</td>
<td></td>
</tr>
<tr>
<td>Third trimester</td>
<td>1.46 (-1.50, 4.43)</td>
<td>$-0.01$</td>
<td>0.00 (-0.02, 0.41)</td>
<td></td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>(-0.03, 0.01)</td>
<td>0.00 (-0.02, 0.41)</td>
<td>(-0.07, 0.09)</td>
<td></td>
</tr>
<tr>
<td>First Postnatal year</td>
<td>-$5.00^*$ (-9.87, -0.19)</td>
<td>0.05* (0.01, 0.08)</td>
<td>0.04* (0.02, -0.49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-12.3, 0.25)</td>
<td>(-0.19, 0.06)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimates shown for a 5 µg/m$^3$ increase in PM$_{2.5}$. Linear models adjusted for child’s age, sex and BMI z-score, maternal education, prenatal ETS exposure, season of conception, other trimester PM$_{2.5}$ concentrations (Model 1) and first postnatal year average PM$_{2.5}$ (Models 1 and 2).

*p < 0.05, |p| < 0.01.
plausible mechanisms by which PM$_{2.5}$ could result in lower nephron endowment coupled with alterations in the renin-angiotensin-aldosterone system (RAS). For example, prenatal PM exposure can affect the RAS pathways in animal models, interfering with placental angiogenesis and nutrient transfer at the maternal-fetal interface (Soto et al., 2017). Oxidative stress and inflammation are the predominant unifying mechanisms that underlie PM$_{2.5}$-associated kidney damage in animal models (Zhang et al., 2018). Fetal nephrogenesis is subject to
Prenatal PM$_{2.5}$ exposure can disrupt mitochondrial energy production potentially resulting in decreased nephron number at birth, which carries an increased risk for CKD later in life (Chevalier, 2020). Notably, our prior work showed that third trimester PM$_{2.5}$ levels were associated with decreased mitochondrial copy number in cord blood (Rosa et al., 2017). Longitudinal assessment of cumulative mitochondrial DNA damage is needed in future studies to better understand effects of renal-accumulated oxidative stress across the life course.

Prior studies of time-varying PM exposure and children’s kidney function have omitted the perinatal exposure period. In a study of 105 children aged 4–13-year-old in China, real-time PM$_{2.5}$ was measured at three time points in childhood, prior to serum creatinine collection (Liu et al., 2020). The authors showed that personal exposure to PM$_{2.5}$ was associated with a decrease in serum creatinine-based eGFR with a potential 2-day lag, showing acute changes in kidney function (Liu et al., 2020). In a subsequent study, the same group reported on real-time size-fractionated particle number counts (PNG) and 13 p.m. constituents, reporting greater reductions in eGFR in association with PNGC and PNGC$_{2.5}$ (with an aerodynamic diameter ≤1 μm and ≤2.5 μm, respectively) than PNGC$_{0.5}$ (with an aerodynamic diameter ≤0.5 μm) in this panel of children (Liu et al., 2021).

While we did not find any sex-specific effects with the kidney biomarkers assessed herein, Liu et al. reported greater reductions in eGFR with short-term exposure to PM$_{2.5}$ in boys when compared to girls (Liu et al., 2020). Recent data support male sex as an important risk factor for primary HTN in children (Theodore et al., 2015; Wang et al., 2006). Moreover, boys have been previously shown to be more susceptible to particulate matter exposure in utero, including higher risk of adverse fetal outcomes (Lakshmanan et al., 2015), differences in body composition (Chiu et al., 2017) and measures of oxidative stress (Song et al., 2019). As gender-associated risk disparities exist in CKD, sex-specific models will be important at later life stages (Carrero et al., 2018).

The PROGRESS cohort is an established prospective birth cohort with well-characterized demographic and covariate data. Strengths of fine-resolution satellite models include the ability to reconstruct ambient exposure estimates for the early pregnancy period based on residential locations and prospectively collected ground stations and remote sensing data. Furthermore, these modelled ambient exposure metrics are less susceptible to biases than personal exposure measurements, which risk confounding by individual behaviors (Weisskopf and Webster, 2017). We assessed multiple kidney parameters at age 9, prior to adolescence - a stage with hormone-associated growth spurts which affect kidney function. Our primary statistical approach included traditional linear regression models using averaged PM$_{2.5}$ across pregnancy, each trimester, and one year postnatally as well as fine-resolution DLNMs using daily PM$_{2.5}$ estimates of exposure. Advantages of our approach using different modeling methods (simple linear regression, DLNMs with different smoother specifications) enables comparison of the consistency of identified critical windows as well as overall shape of time-varying associations. Standard techniques wherein average PM during prenatal periods are assessed by linear regression models are unable to capture the distinct windows of susceptibility that may lie within or across trimesters.

PROGRESS is an urban disadvantaged population and our results may translate to other disadvantaged populations who face similar urban pollution, stressors and poverty. Similar studies conducted in other regions may help elucidate whether these results generalize to other populations. In our study, daily PM$_{2.5}$ measures were used in the prenatal analysis, with a standard deviation between 7 and 8.5 μg/m$^3$, and monthly measures were used in the postnatal analysis with a standard deviation of 1.67–7.81 μg/m$^3$. In a recent study, a 1 μg/m$^3$ interquartile range increase in PM$_{2.5}$ concentration was associated with a 2% reduction in eGFR (Kuzma et al., 2021). Therefore, we believe there was substantial exposure variability in our study area to support the observed associations with kidney function. Our reliance on ambient exposure estimates do not capture indoor sources (although the ventilation patterns in Mexican homes let outdoor pollution indoors), nor did we include estimates of humidity, and thus may not completely reflect personal exposure. PM$_{2.5}$ is attributed as the largest component of the global burden of disease due to air pollution (Cohen et al., 2017) and has an established association with adult kidney disease (Bowe et al., 2018). However, air pollution is a complex mixture and our analysis may be leaving out the potential contribution of other toxicants found in the study region. We cannot rule out residual confounding due to unmeasured factors or incomplete adjustment for measured factors related to PM$_{2.5}$ that may also influence kidney function in childhood (e.g., socioeconomic factors related to residential location). Nevertheless, our findings were limited to specific perinatal time periods, thus unmeasured confounders would need to co-vary with PM$_{2.5}$ and time-invariant characteristics, such as diet, would not explain these associations (Weisskopf et al., 2015). It is possible that BDLIM analyses of sex differences with kidney parameters were underpowered. Kidney function was assessed at a single time point and future analyses will include longitudinal follow-up. We assessed eGFR using both cystatin C and creatinine-based equations. Decrements in kidney function are traditionally assessed by biomarkers such as serum creatinine and urea (Khan et al., 2010); however, changes in these biomarkers may not manifest until substantial kidney impairment is present or clinical kidney disease is apparent. Thus, future work will examine biomarkers such as validated urinary proteins (i.e. beta-2-microglobulin, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin) that capture subclinical kidney damage including potential tubular dysfunction. We note that comparison of serum creatinine vs. cystatin C findings showed greater variance and wider confidence intervals observed with creatinine and supports prior observations that cystatin C may be an improved biomarker for estimating GFR in children (Schwartz et al., 2012). We acknowledge that debate remains in the ideal equation for estimating GFR. Use of existing formulae requires careful selection considering the biomarker analyzed, type of molecular assay employed, as well as demographics of the study population (e.g., children vs. adult). Given the inequities in CKD across different racial/ethnic groups which are compounded by socioeconomic disparities, examining potential health disparities will be important considerations in future studies (Norris and Nissenson, 2008).

Mexico has one of the highest prevalence of CKD worldwide (Collaboration, 2020) and our research in PROGRESS children is directly relevant for understanding the role that early life environment plays in HTN and CKD etiology. Understanding regional causes for CKD and HTN are key factors for developing and maintaining effective disease care models (Stanièr et al., 2018) and furthermore can help inform public health strategies for disease prevention (Joshi et al., 2017; Luyckx et al., 2021). Longitudinal assessments of at-risk populations during adolescence and early adulthood will be an important next step.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112062.

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