Newborn glomerular function and gestational particulate air pollution

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Summary

Background Nephron number variability may hold significance in the Developmental Origins of Health and Disease hypothesis. We explore the impact of gestational particulate pollution exposure on cord blood cystatin C, a marker for glomerular function, as an indicator for glomerular health at birth.

Methods From February 2010 onwards, the ENVIRONAGE cohort includes over 2200 mothers giving birth at the East-Limburg hospital in Genk, Belgium. Mothers without planned caesarean section who are able to fill out a Dutch questionnaire are eligible. Here, we evaluated cord blood cystatin C levels from 1484 mother–child pairs participating in the ENVIRONAGE cohort. We employed multiple linear regression models and distributed lag models to assess the association between cord blood cystatin C and gestational particulate air pollution exposure.

Findings Average ± SD levels of cord blood cystatin C levels amounted to 2.16 ± 0.35 mg/L. Adjusting for covariates, every 0.5 μg/m^3 and 5 μg/m^3 increment in gestational exposure to black carbon (BC) and fine particulate matter ($PM_{2.5}$) corresponded to increases of 0.04 mg/L (95% CI 0.01–0.07) and 0.07 mg/L (95% CI 0.03–0.11) in cord blood cystatin C levels ($p < 0.01$), respectively. Third-trimester exposure showed similar associations, with a 0.04 mg/L (95% CI 0.00–0.08) and 0.06 mg/L (95% CI 0.04–0.09) increase for BC and $PM_{2.5}$ ($p < 0.02$). No significant associations were observed when considering only the first and second trimester exposure.

Interpretation Our findings indicate that particulate air pollution during the entire pregnancy, with the strongest effect sizes from week 27 onwards, may affect newborn kidney function, with potential long-term implications for later health.

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Keywords: Air pollution; Fine particulate matter; Black carbon; Cystatin C; Cord blood

Introduction

In 1988, Brenner hypothesized that there is an inverse relationship between the total nephron number at birth, or throughout human life, and the risk of developing hypertension.[1] In this context, the Developmental Origins of Health and Disease (DOHaD) hypothesis postulates that exposure to certain environmental influences during critical periods of development and growth may lead to significant consequences on the individuals' health later in life.[2]

Kidney function is essential for homeostasis in the human body; the kidneys play an important role in the removal of metabolic waste products and the maintenance of the water-electrolyte balance as well as maintaining blood pressure.[3] Unfortunately, investigating kidney function in newborns remains arduous, as there may be an overlay between the ongoing kidney development and any possible kidney damage that has taken place.[4] In newborns at term, the glomerular filtration rate (GFR) has values that are below ten percent of the

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Research in context

Evidence before this study

We searched PubMed and Web of Science for studies published in English up to December 19, 2023, that investigated the effects of particulate air pollution exposure on newborn cystatin C levels. We used the search terms 'newborn' OR 'gestation' AND 'kidney' OR 'cystatin C' AND 'air pollution' OR 'particulate matter'. Although studies have shown the importance of cystatin C for glomerular kidney function, no one evaluated the influence of gestational particulate air pollution exposure on cord blood cystatin C levels.

Fine particulate matter ($PM_{2.5}$) and black carbon (BC) have been demonstrated to penetrate the foetal environment. Given that nephrogenesis continues into the final weeks of pregnancy, maternal exposure to these airborne pollutants may impact the foetal kidney function. Notably, $PM_{2.5}$ exposure during adulthood has previously been linked to a reduction in the glomerular filtration rate in adults, but no studies so far addressed prenatal exposures.

Added value of this study

This study examines a cord blood biomarker to understand prenatal influences on newborns' glomerular kidney function. Our research provides direct evidence linking maternal inhalation of particulate air pollution to neonatal glomerular function, emphasizing crucial exposure periods throughout pregnancy, especially in the third trimester. Aligned with the Brenner hypothesis, on consequences of number of nephrons on future health, our findings might have long-term relevance in the health-disease continuum over life.

Implications of all the available evidence

Our findings suggest that the entire pregnancy, as well as the last trimester, are important time windows where particulate air pollution exposure may influence glomerular kidney function in the newborn. The results may indicate the implementations of early life particulate air pollution exposure-related kidney function as a prognostic biomarker of later life kidney health and might have a role in the developmental origins of health and disease.

normal adult level GFR.[5] Recent evidence has suggested serum cystatin C as a useful marker for glomerular filtration in situations where creatine-based estimations of the GFR are lacking,[6] such as newborns, as it shows no relation to muscle mass and is not affected by inflammatory stimuli.[4,7,8] Cystatin C is a low molecular weight protein belonging to the cysteine protease inhibitors, continuously produced by nucleated cells and constitutively filtered by the glomeruli of the kidney.[3,5] An increase in serum cystatin C indicates a diminished glomerular filtration.[6]

Ambient air pollution is an important environmental contributor to global disease burden, ranked 4th as a risk factor for diseases, such as cardiovascular, respiratory, and kidney diseases.[9] One substantial component of ambient air pollution linked to increased morbidity and mortality is particulate matter (PM), categorized as a mixture of solid and liquid particles suspended in the air.[10] Fine particulate matter ($PM_{2.5}$; particles with a diameter <2.5 μm) is considered a crucial risk factor for adverse cardiovascular effects. Moreover, adverse effects regarding the cardiovascular system have already been extensively linked to subsequent adverse effects on the kidneys.[11–13] Additionally, $PM_{2.5}$ has been indicated as a risk factor for a lower estimated glomerular filtration rate (eGFR) and a faster decline in GFR in adults.[14] It has been hypothesized that $PM_{2.5}$ can reach the deepest regions of our lungs, enter systemic circulation, and cause (in)direct effects. Maternal exposure to $PM_{2.5}$ has already been linked to higher blood pressure[15] and lower birth weight[16] in newborns, which may hold significance in the context of the Brenner hypothesis.[1] Additionally, black carbon (BC), a component of $PM_{2.5}$ formed by the incomplete combustion of e.g., wood and fossil fuels, has been linked to adverse outcomes, including the increase of urinary kidney injury molecule-1, a marker for acute kidney damage.[17] Furthermore, our research group indicated the presence of these harmful particles in crucial structural components of the kidney.[17] In the adult population, outdoor air pollution, including $PM_{2.5}$, has been shown to be associated with increased serum cystatin C levels and decreased estimated GFRs based on cystatin C rather than serum creatinine.[18–20] However, to our knowledge, evidence about the effects of air pollution on the cystatin C levels of newborns is lacking. Therefore, we aim to investigate whether cystatin C levels are elevated in the cord blood plasma of newborns collected within the framework of the ENVIR*ON*AGE birth cohort in relation to ambient air pollution exposure of BC and $PM_{2.5}$.

Methods

Study population

This study is part of the ongoing ENVIR*ON*AGE (ENVIRonmental influence *ON* early AGEing) birth cohort; here, mother–newborn pairs with singleton pregnancies are recruited when they arrive for delivery at the East-Limburg Hospital in Belgium. To date, over 2200 mother–child pairs participate in the ENVIR*ON*-AGE birth cohort. A detailed cohort profile is described elsewhere.[21] After delivery, a comprehensive questionnaire inquired the participants about detailed medical and lifestyle data, including their residential address(es) during pregnancy, age, education, parity, smoking habits, alcohol consumption throughout the pregnancy,

and ethnicity of the newborn. All included newborns were considered healthy and free of any anomalies, as confirmed by prenatal ultrasound examinations and postnatal assessment by paediatricians. In total, 2042 mother–newborn pairs were recruited between February 2nd 2010 until November 23rd 2020. Of all eligible mother–newborn pairs, 191 were excluded as no cord blood plasma was collected after childbirth, 88 were omitted due to too little cord blood plasma sample available to determine cystatin C levels, and of 279 there was missing data in the *a priori* selected covariates (e.g., 15 omitted due to missing smoking habit information). Therefore, this current study included 1484 mother–newborn pairs, for which the cord blood plasma cystatin C measurement and *a priori* selected covariates were available.

Exposure estimates

The BC and $PM_{2.5}$ levels of the mother's residential address(es) during the pregnancy were modelled using a validated high-resolution spatial–temporal interpolation method (kriging).[22–24] in combination with a dispersion model.[25,26] This method employs land cover data obtained from satellite images (CORINE land cover data set) and pollution data of fixed monitoring stations.[26,27] This model chain provides daily exposure values in a high-resolution receptor grid, coupled with a dispersion model that uses emissions from point sources and line sources.[23] These point sources, such as industries, and line sources, such as highways, were calculated on a dense, irregular receptor point grid and interpolated to a 10 × 10 m raster. Overall model performance was evaluated by leave-one-out cross-validation, including 34 and 16 monitoring points for $PM_{2.5}$ and BC, respectively. Validation statistics of the interpolation tool gave a spatiotemporal explained variance of more than 0.80 and 0.74 for $PM_{2.5}$ and BC, respectively.[28,29] We averaged daily BC and $PM_{2.5}$ concentrations for the entire pregnancy and all three pregnancy trimesters, defined as: 1–13 weeks (trimester 1), 14–26 weeks (trimester 2), and 27 weeks to delivery (trimester 3). Additionally, average daily concentrations during the last month (30 days) and last week (7 days) of the pregnancy were considered for analysis.

Cord blood cystatin C levels

Blood samples were taken from the umbilical cord after delivery at the East-Limburg hospital in Genk, Belgium within 10 min after delivery, in BD Vacutainer plastic whole blood tubes, spray-coated with K2EDTA. Samples were processed and aliquoted immediately before storage at –80 °C until further analysis at the hospital. Cord blood plasma cystatin C levels were measured at the hospital through an accredited immune turbidimetry assay (COBAS CcEE, Roche Diagnostics) with antibody-coupled latex particles. In brief, latex particles are coated in anti-cystatin C antibodies. Cystatin C present in the cord blood plasma of the newborn binds to the antibodies and the subsequent agglutination allows quantification of cystatin C levels in plasma.[30]

Statistics

We performed single-pollutant multiple linear regression analyses to assess the association between BC and $PM_{2.5}$ exposure outcomes during the entire pregnancy, all three trimesters, the last month and the last week of pregnancy, and cord blood cystatin C levels. All participants who had a cord blood cystatin C measurement at the time of analysis and no missing covariates were included in the study. The *a priori* selected covariates included sex of the newborn (derived from medical records), birthweight, parity, the season of delivery, gestational duration, maternal age, maternal education, and smoking status during pregnancy. Maternal education was coded as low (no diploma or primary school), middle (high school diploma), and high (college and/or university degree). Smoking habits were allocated as non-smoker, former smoker, and smoker. Pregnancy trimester-averaged $PM_{2.5}$ and BC exposure levels were entered into the same model in order to estimate independent trimester-specific effects.[31] When investigating associations of exposure outcomes during a particular trimester of pregnancy, the model also mutually adjusted for the remaining two trimesters, e.g., when evaluating trimester 1 exposure, the model also adjusted for trimester 2 and 3. The exposure variable was analysed as a continuous measure. Distributed lag models (DLMs; using R package "dlnm" version 2.4.7) were used to estimate gestational week-specific associations between exposure to air pollutants during the entire pregnancy and cord blood cystatin C levels. Here, we used a linear relationship for the exposure-response, and natural cubic splines for the lag-response with three equal knots and five degrees of freedom. We used the date of conception as the lag 0 and counted the lagged response forward through pregnancy (40 weeks), where missing exposure values (due to duration of gestation) were equal to zero. Furthermore, we aimed to evaluate the probability of having higher cord blood cystatin C levels. Here, we dichotomized cord blood cystatin C based on a 10th percentile threshold within the study population. Logistic regression analyses with aforementioned covariates were used to investigate the association between particulate air pollution exposure and the risk of having higher cord blood cystatin C levels than the 10th percentile. Results are expressed as the odds ratio (OR) (95% CI) of cord blood cystatin C for a 0.5 and 5 $\mu g/m^3$ increment in BC and $PM_{2.5}$, respectively.

Additionally, sensitivity analyses were performed to assess the robustness of our findings. Therefore, we adjusted the model separately for the ethnicity (European vs. non-European), maternal pre-pregnancy body mass index (BMI, kg/m^2), alcohol consumption during

pregnancy (yes/no), and the neighbourhood median annual income (in Euros) based on the median annual household income data by sector (2017). For the median annual household income, participants were assigned to statistical sectors (the smallest units for which the Belgian National Institute of Statistics compiles information) based on their residential address. The significance level of 0.05 or confidence level of 95% was used for all estimates through this study.

Ethics

The study protocol for the recruiting phase was approved by the ethical committees of Hasselt University (Diepenbeek, Belgium) and East-Limburg Hospital (Genk, Belgium) (B37120107805). Informed consent was obtained from the mother prior to delivery.

Role of funders

The funders had no role in the conceptualization, study design, data collection, analysis, interpretation of data, in writing the paper, or in the decision to submit the paper for publication.

Results

The characteristics of the mother–child pairs (n = 1484) included in this study are summarized in Table 1. The average ± SD birthweight of newborns (49.60% girls) was 3417.52 ± 474.63 g, where 87.60% were of European descent. The average ± SD gestational age amounted to 39.2 ± 1.43 weeks. The average ± SD cord blood cystatin C levels were 2.16 ± 0.35 mg/L. Mothers were on average 29.61 years old at the time of delivery, with a pre-pregnancy BMI of 24.95 kg/m^2, and 11.11% (n = 165) smoked regularly during pregnancy.

During the entire pregnancy, the average (SD) BC and $PM_{2.5}$ exposure amounted to 1.18 (0.33) μg/m^3 and 12.65 (2.54) μg/m^3 ^{3}, respectively (Table 2). The average BC remained relatively constant throughout the pregnancy, where for trimester 1, 2, and 3 average ± SD concentration levels were observed of 1.21 ± 0.41 μg/m^3, 1.18 ± 0.42 μg/m^3, and 1.17 ± 0.42 μg/m^3, respectively. The average ± SD $PM_{2.5}$ concentrations levels amounted to 12.92 ± 4.55 μg/m^3, 12.59 ± 4.36 μg/m^3, and 12.47 ± 4.70 μg/m^3 during the three consecutive trimesters, respectively (Supplementary Table S1). Average exposures in the last month and last week of the pregnancy did not differ significantly from the trimestral or entire pregnancy exposure outcomes for both investigated exposure outcomes (Table 2, $p \geq 0.11$, two-sided T test).

Both before (Fig. 1b) and after adjusting for newborn covariates or maternal covariates, a significant association between BC exposure during the entire pregnancy and cord blood cystatin C levels was shown. Independent of maternal and newborn characteristics, each 0.5 μg/m^3 increment in gestational BC exposure was associated with a 0.04 mg/L (95% CI 0.01–0.07; $p < 0.01$, linear regression analysis) higher cord blood cystatin C level (Table 3). The corresponding estimate for $PM_{2.5}$ (5 μg/m^3) after adjustment was 0.07 mg/L (95% CI 0.03–0.11; $p < 0.01$, linear regression analysis) (Fig. 1a). Investigating trimester specific exposure (Supplemental Figure S1) revealed significant associations for the third trimester, while none were observed for the second trimester. When evaluating the first trimester, significant associations are observed for BC exposure, but not $PM_{2.5}$ exposure. If trimester 2 was only adjusted for trimester 1 exposure (but not trimester 3) the results were not altered (Table 3, model 3).

As a sensitivity analysis, we additionally adjusted for pre-pregnancy BMI and alcohol consumption during the pregnancy, respectively. While adjusting for ethnicity, pre-pregnancy BMI, alcohol consumption during pregnancy of the mother, or neighbourhood median annual income (Supplementary Table S2), we observed no notable difference in the previously reported effect estimates. Overall, effect estimates and overall confidence intervals remained largely comparable.

Using DLNMs, we investigated gestational week-specific differences in the change in cord blood cystatin C levels for increases in exposure to BC and $PM_{2.5}$ during the entire pregnancy (Fig. 2). The DLM identified the beginning of the third trimester (week 27 onwards) as the most significant exposure window for both investigated exposure outcomes in association with an elevation in cord blood cystatin C levels. Additionally, the last weeks of the first trimester (week 8 onwards) appeared a significant exposure window as well in regards to investigated exposure outcomes in association to cord blood cystatin C levels. In subsequent sensitivity analysis, similar results were obtained for the DLNM models (data not shown).

In addition, we found that higher $PM_{2.5}$ and BC exposure during the entire pregnancy and the last trimester were significantly associated with a higher risk of having higher cord blood cystatin C levels (Table 4). Notably, a 0.5 μg/m^3 increase in BC exposure was associated with a 37% higher risk (95% CI 1.04, 1.80) of having higher cord blood cystatin C levels than the 10th percentile. For each 5 μg/m^3 increase in $PM_{2.5}$ exposure, there was an 80% higher risk (95% CI 1.23, 2.65) of having higher cord blood cystatin C levels than the 10th percentile. Similar results were obtained when only addressing BC or $PM_{2.5}$ exposure during the third trimester (Table 4). No significant associations were found for BC and $PM_{2.5}$ exposure during the first and second trimester and the risk of higher cord blood cy C levels.

Discussion

The Brenner hypothesis, proposed by Dr. Barry Brenner in 1988, suggested that the number of nephrons, the

Characteristics	Mean (SD) or number (%)
Maternal	
Age, years	29·61 (4·54)
Pre-pregnancy BMI, kg/m²	24·95 (11·62)
Maternal education	
Low	176 (11·86%)
Middle	521 (35·11%)
High	787 (53·03%)
Smoking during pregnancy	
No	1,319 (88·88%)
Yes	165 (11·11%)
Alcohol consumption during pregnancy	
No	1,283 (86·46%)
Yes	201 (13·54%)
Parity	
1	778 (52·43%)
2	528 (36·25%)
≥3	178 (11·99%)
Neighbourhood annual income, Euro	25,619.15 (3,377.83)
Newborn	
Sex	
Male	748 (50·40%)
Female	736 (49·60%)
Ethnicity	
European	1300 (87·60%)
Non-European	184 (12·40%)
Gestational age, weeks	39·2 (1·43)
Birthweight, grams	3,417·52 (474·63)
Cord blood plasma cystatin C, mg/L	2·16 (0·35)

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 1: **Study population characteristics (n = 1484).**

functional units of the kidney, established during foetal development, significantly influences kidney function throughout one's life.[1] According to this hypothesis, individuals born with fewer nephrons may have a reduced capacity for kidney function, potentially making them more susceptible to kidney diseases and hypertension later in life. This theory underscores the critical role of early life development in shaping long-term kidney health and highlights the importance of understanding factors that may impact nephron formation during gestation.[1] Inspired by this hypothesis and the role of the prenatal environment, we measured cord blood cystatin C to estimate renal elimination capacity and how this was related to early life exposure to ambient air pollution. The key findings of our study are that higher gestational exposure to ambient air pollution especially during the last weeks of the first trimester (week 8 onwards) and the beginning of the third trimester (week 27 onwards) of gestation was associated with higher cord blood cystatin C levels. This association was independent of various factors including gestational duration, maternal age, pre-pregnancy BMI, as well as socio-economic factors. Furthermore, we also observed that higher particulate air pollution exposure was

Mean (SD)	$PM_{2·5}$ (μg/m³)	BC (μg/m³)
During entire pregnancy	12·65 (2·54)	1·18 (0·33)
Trimester 1	12·92 (4·55)	1·21 (0·41)
Trimester 2	12·59 (4·36)	1·18 (0·42)
Trimester 3	12·47 (4·70)	1·17 (0·42)
Last month of pregnancy	12·41 (5·91)	1·17 (0·50)
Last week of pregnancy	12·59 (8·54)	1·18 (0·65)

Abbreviations: BC, black carbon; $PM_{2.5}$, fine particulate matter <2.5 μm.

Table 2: **Average air pollution prenatal exposure outcomes.**

associated with a higher risk of having higher cord blood cystatin C levels.

Foetal kidneys develop between the 5th and 12th week of foetal life, but nephrogenesis can still be ongoing up until the 38th week.[32] Nonetheless, a variability in cessation of nephron development is noted between week 35 and 37.[33] Danica et al.[33] observed that kidney growth in the latter half of gestation is directly proportional to body weight and gestational age. Subsequently, research previously linked exposure outcomes of air pollution to a decrease in birth weight upon full-term[34–37] and may influence kidney growth prior to delivery. To our knowledge, no research has been performed in regards to associations between trimestral exposure of BC, $PM_{2.5}$, and cord blood cystatin C levels in newborns. The most engaging period of nephrogenesis is during the third trimester; here, harmful substances may influence kidney development.[38] In this

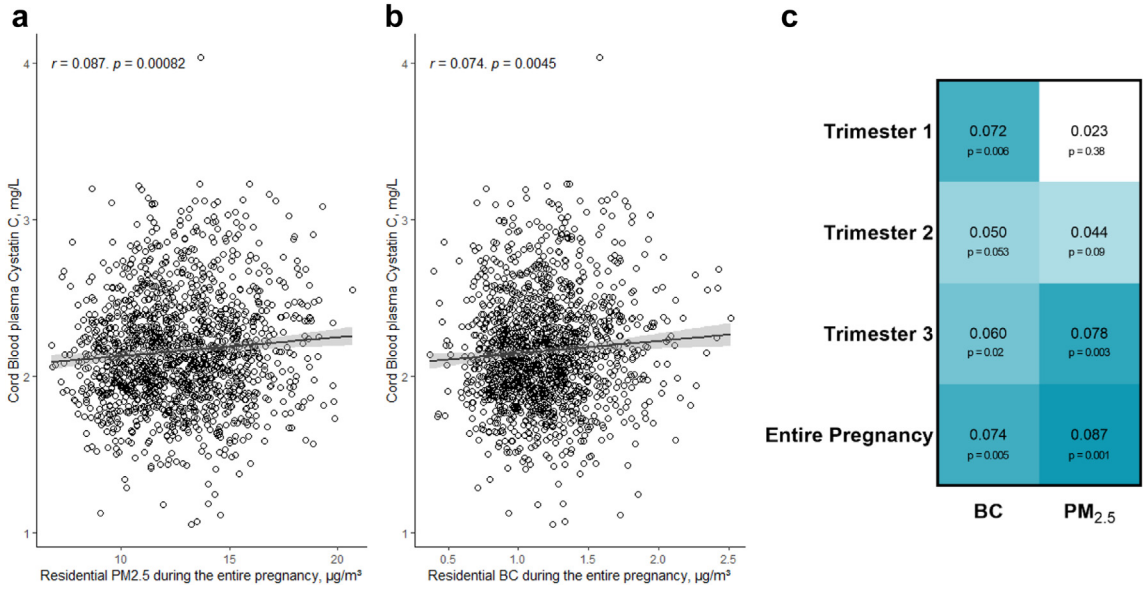

Fig. 1: Correlations between $PM_{2.5}$, BC, and cord blood cystatin C. Pearson correlation during the entire pregnancy between a) $PM_{2.5}$, b) BC, and cord blood cystatin C (n = 1484. The black line represents the unadjusted regression line with a 95% confidence interval (grey area). In c) the heatmap, Pearson correlation values are shown with their respective p values for BC and $PM_{2.5}$ exposures during the three trimesters and the entire pregnancy. Abbreviations: BC, black carbon; $PM_{2.5}$, fine particulate matter <2.5 μm.

	Unadjusted model			Model 1			Model 2			Model 3		
	mg/L change	p-value	95% CI	mg/L change	p-value	95% CI	mg/L change	p-value	95% CI	mg/L change	p-value	95% CI
$PM_{2.5}$												
Entire pregnancy	0·06	< 0·01	0·02, 0·10	0·07	< 0·01	0·03, 0·11	0·07	< 0·01	0·03, 0·11	-	-	-
Trimester 1	0·01	0·38	-0·01, 0·03	0·02	0·23	-0·01, 0·04	0·01	0·34	-0·01, 0·04	0·01	0·37	-0·01, 0·04
Trimester 2	0·02	0·09	0·00, 0·04	0·00	0·76	-0·04, 0·03	0·00	0·80	-0·04, 0·03	0·02	0·18	-0·01, 0·05
Trimester 3	0·03	< 0·01	0·01, 0·05	0·06	< 0·01	0·04, 0·09	0·06	< 0·01	0·04, 0·09	0·06	< 0·01	0·04, 0·09
Last month	0·02	0·04	0·00, 0·03	0·03	< 0·01	0·01, 0·04	0·03	< 0·01	0·01, 0·05	-	-	-
Last week	0·01	0·04	0·00, 0·02	0·02	< 0·01	0·00, 0·03	0·02	< 0·01	0·00, 0·03	-	-	-
BC												
Entire pregnancy	0·04	< 0·01	0·01, 0·07	0·04	< 0·01	0·01, 0·07	0·04	< 0·01	0·01, 0·07	-	-	-
Trimester 1	0·01	< 0·01	0·01, 0·05	0·02	0·18	-0·01, 0·06	0·02	0·27	-0·02, 0·05	0·03	0·01	0·01, 0·06
Trimester 2	0·02	< 0·05	0·00, 0·04	-0·02	0·40	-0·06, 0·02	-0·02	0·46	-0·06, 0·03	0·01	0·51	-0·02, 0·05
Trimester 3	0·03	0·02	0·00, 0·05	0·04	0·02	0·00, 0·08	0·04	0·01	0·00, 0·08	0·04	0·01	0·00, 0·08
Last month	0·01	0·11	0·00, 0·03	0·03	0·02	0·00, 0·05	0·03	0·02	0·00, 0·05	-	-	-
Last week	0·01	0·14	0·00, 0·02	0·02	0·04	0·00, 0·03	0·02	< 0·05	0·00, 0·03	-	-	-

Abbreviations: BC, black carbon; CI, confidence interval; $PM_{2.5}$, fine particulate matter <2.5 μm. Model 1: adjusts for birthweight, sex, parity, season of delivery, and gestational age. The trimester-specific exposure models were mutually adjusted for the other gestational exposure windows to estimate the independent effect of each trimester exposure. Model 2: adjusts for all covariates of model 1 and the age of the mother, maternal education, and smoking during pregnancy. Model 3: adjusts for all covariates of model 2 with exception for the gestational trimestral exposure windows, in which now trimester 2 was mutually adjusted for the exposure during trimester 1 and trimester 3 was mutually adjusted for the exposure of trimester 1 and trimester 2.

Table 3: **Association between an increase in exposure outcomes BC (0.5 μg/m^3), $PM_{2.5}$ (5 μg/m^3), and cord blood cystatin C levels (n = 1484).**

study, DLNM models indicated the third trimester as the most significant exposure window for both BC and $PM_{2.5}$ exposure in relation to cord blood cystatin C levels. As nephrogenesis ceases at approximately gestation week 36, by the end of nephrogenesis, an individual's entire nephron complement is established.[39] Therefore, particulate air pollution exposure may adversely affect kidney development during the third trimester and ultimately affect the number of nephrons or their maturation, thereby increasing the risk of compromised kidney health throughout an individual's lifespan. Furthermore, Sanders et al.[40] also indicated the late third trimester as a critical window of susceptibility associated with kidney function decline to nephrotoxic mixtures, such as e.g., lead exposure.[40]

Our findings at the beginning of life are in line with observations in adults. Wang et al.[20] observed a positive association between an average daily dose of air pollutants and serum cystatin C levels in adults. Furthermore, a study performed in African Americans did observe a significant positive association between $PM_{2.5}$ and serum cystatin C levels in the unadjusted model, but

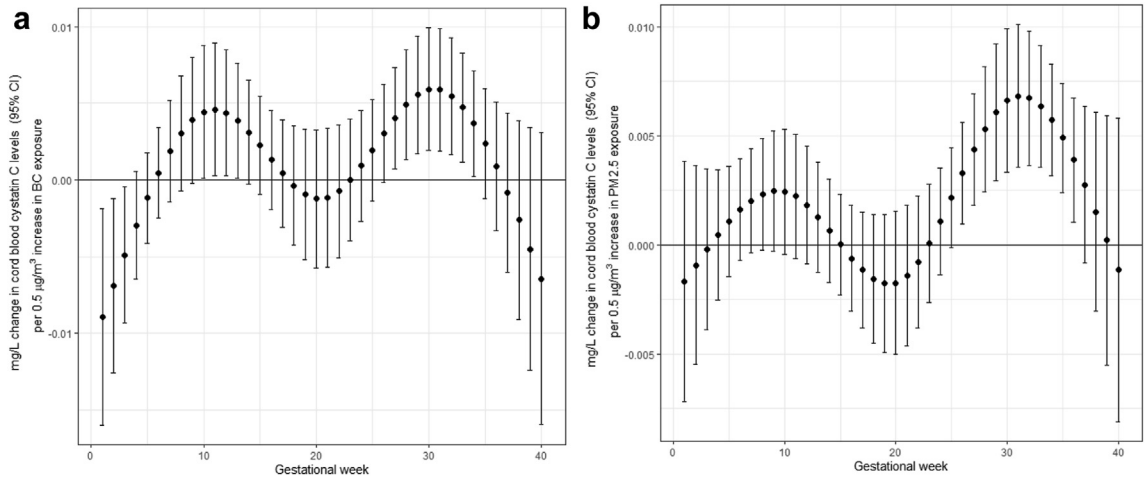

Fig. 2: Gestational week-specific estimates for the association between a) BC exposure, b) $PM_{2.5}$ exposure, and cord blood cystatin C levels (n = 1484). The estimates are represented for a 0.5 μg/m^3 increase in BC and a 5 μg/m^3 increase in $PM_{2.5}$ using distributed lag models. The 95% confidence interval upper and lower limits are shown. All models were adjusted for birthweight, sex, parity, season of delivery, gestational age, maternal age, maternal education, and smoking during pregnancy. Abbreviations: BC, black carbon; CI, confidence interval; IQR, interquartile range; $PM_{2.5}$, fine particulate matter <2.5 μm.

	Odds ratio	95% CI	p value
$PM_{2.5}$			
Entire pregnancy	1.80	1.23, 2.65	< 0.01
Trimester 1	1.13	0.89, 1.43	0.31
Trimester 2	1.07	0.82, 1.42	0.61
Trimester 3	1.76	1.37, 2.27	< 0.01
Last month	1.35	1.14, 1.60	< 0.01
Last week	1.11	0.99, 1.23	0.07
BC			
Entire pregnancy	1.37	1.04, 1.80	0.02
Trimester 1	1.23	0.98, 1.55	0.07
Trimester 2	1.23	0.96, 1.57	0.10
Trimester 3	1.37	1.09, 1.72	< 0.01
Last month	1.28	1.06, 1.54	0.01
Last week	1.15	1.00, 1.33	< 0.05

Abbreviations: BC, black carbon; CI, confidence interval; $PM_{2.5}$, fine particulate matter <2.5 μm. Estimates are presented as the odds ratio (OR) (95% CI) of cord blood cystatin c for a 5 $\mu g/m^3$ or 0.5 $\mu g/m^3$ increment in $PM_{2.5}$ and BC, respectively. The model was adjusted for sex, birthweight, parity, season of delivery, gestational duration, maternal age, maternal education, and smoking status.

Table 4: **Association between the risk of higher cord blood cystatin c and $PM_{2.5}$ (5 $\mu g/m^3$) and BC (0.5 $\mu g/m^3$) exposure (n = 1484).**

lost its significance after adjustment(s).[19] A Mexican study in pregnant women found contradictory results, where each 5 $\mu g/m^3$ increase in $PM_{2.5}$ during pregnancy associated with a –0.05 mg/dL change in serum cystatin C levels.[41] However, it is of note that the first two studies focused on the adult population rather than newborns, while Rosa and colleagues[41] took venous blood samples during a study visit after delivery, rather than use cord blood samples such as in this study. As serum cystatin C levels vary greatly during the first few days after delivery, results might not be comparable between studies.[5]

Differences observed between $PM_{2.5}$ and BC in relation to cord blood cystatin C may be a result of the complexity of the $PM_{2.5}$ fraction; BC is a relevant component of $PM_{2.5}$, which may be partially responsible for the observed cord blood cystatin C levels.[42] However, the presence of other chemical components may influence the observed health effects for the $PM_{2.5}$ fraction, rendering stronger observations when only the BC fraction is considered.

Our study has several strengths and limitations. First, we have a large representative sample of newborns and mothers, which is deeply characterized, with a prospective follow-up.[21] We used high resolution spatial air pollution model, which has been shown that it reflects foetal exposure, as the residential air pollution correlated with maternal, placental, and cord blood exposure.[28,43,44] A limitation of our study is that we do not have other markers of kidney function reflecting tubular function, such as creatinine. However, creatinine levels to estimate renal elimination capacity at birth does not yet reflect neonatal but rather maternal creatinine, and its clearance does not yet fully reflect GFR.[45,46]

We observed significant positive associations between $PM_{2.5}$ and BC exposure and cord blood cystatin C levels in newborns. Our results add to the hypothesis that exposure to air pollutants may negatively influence kidney function, in particular glomerular filtration, even in newborns. Furthermore, these results are relevant for disease tracking over the life course in which kidney function might form a cornerstone.

Contributors

TSN initiated the ENVIRONAGE birth cohort and designed the current study together with LR. TVP MVG, and ER were involved in the recruitment of the mother–child pairs at the hospital. JP advised and was involved with biochemical analysis. LR and TSN wrote the first draft of the paper. LR performed the statistical analysis with guidance of CW, MP, and TSN. LR and TSN have accessed and verified the underlying data. All authors interpreted the data and gave final approval for the final version of the manuscript.

Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declaration of interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105253.

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