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Ambient black carbon reaches the kidneys

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ABSTRACT

Background: Ultrafine particles, including black carbon (BC), can reach the systemic circulation and therefore may distribute to distant organs upon inhalation. The kidneys may be particularly vulnerable to the adverse effects of BC exposure due to their filtration function.
Objectives: We hypothesized that BC particles reach the kidneys via the systemic circulation, where the particles may reside in structural components of kidney tissue and impair kidney function.
Methods: In kidney biopsies from 25 transplant patients, we visualized BC particles using white light generation under femtosecond-pulsed illumination. The presence of urinary kidney injury molecule-1 (KIM-1) and cystatin c (CysC) were evaluated with ELISA. We assessed the association between internal and external exposure matrices and urinary biomarkers using Pearson correlation and linear regression models.
Results: BC particles could be identified in all biopsy samples with a geometric mean (5th, 95th percentile) of 1.80×10^3 (3.65×10^2, 7.50×10^3) particles/mm^3 kidney tissue, predominantly observed in the interstitium (100 %) and tubules (80 %), followed by the blood vessels and capillaries (40 %), and the glomerulus (24 %). Independent from covariates and potential confounders, we found that each 10 % higher tissue BC load resulted in 8.24 % ($p = 0.03$) higher urinary KIM-1. In addition, residential proximity to a major road was inversely associated with urinary CysC (+10 % distance: −4.68 %; $p = 0.01$) and KIM-1 (+10 % distance: −3.99 %; $p < 0.01$). Other urinary biomarkers, *e.g.*, the estimated glomerular filtration rate or creatinine clearance showed no significant associations.
Discussion and conclusion: Our findings that BC particles accumulate near different structural components of the kidney represent a potential mechanism explaining the detrimental effects of particle air pollution exposure on kidney function. Furthermore, urinary KIM-1 and CysC show potential as air pollution-induced kidney injury biomarkers for taking a first step in addressing the adverse effects BC might exert on kidney function.

1. Background

Human kidneys may be vulnerable target to exposure to toxic environmental substances due to their filtration function, as they filter 180 L of fluid per day (Xu et al., 2018). One such substance includes fine particulate matter ($PM_{2.5}$) from ambient air pollution, of which higher levels of $PM_{2.5}$ were already associated with an increased risk of adverse health outcomes, including cardiovascular disease (Hayes et al., 2019), diabetes (Bowe et al., 2018), and all-cause mortality (Josey et al., 2022). Furthermore, $PM_{2.5}$ is also associated with known regulators of kidney function, including insulin resistance (Wolf et al., 2016) and systemic hypertension (Fuks et al., 2011; Fuks et al., 2014). Moreover, increased levels of $PM_{2.5}$ have already been associated with an increased risk for decline in kidney function, including a lower estimated glomerular filtration rate (eGFR) (An and Liu, 2021; Mehta et al., 2016; Li et al., 2021); a faster decline in the glomerular filtration rate (An and Liu, 2021; Mehta et al., 2016; Li et al., 2021), and a higher rate of chronic kidney disease and end-stage kidney disease (Bowe et al., 2018; Bowe

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et al., 2018).

Black carbon (BC) particles, being part of the ultrafine particulate mixture, are able to reach the deepest regions of the lungs and may even reach the circulatory system (Nemmar et al., 2002) to spread to distant organs (Bové et al., 2019; Bongaerts et al., 2022), such as *i.e.*, the placenta (Bongaerts et al., 2019). Previously, we have shown that at low levels of ambient air pollution, the amount of BC particulates in the urine of children related to their residential ambient long-term air pollution exposure. (Saenen et al., 2017) Here, we postulate that BC particles are able to translocate from the lungs through the systemic circulation and reach the kidneys.

A higher exposure to $PM_{2.5}$ could already be associated with increased rates of all-cause mortality, graft failure, and graft rejection in kidney transplant recipients. (Rasking et al., 2022; Chang et al., 2021) Indirectly, kidney transplant recipients may be more susceptible to the detrimental effects of $PM_{2.5}$ and BC, through the development of *e.g.*, cardiovascular disease (Rangaswami et al., 2019), which has already been extensively linked to elevated $PM_{2.5}$ and BC exposure levels. (Du et al., 2016; Sommar et al., 2021; Bell et al., 2009; Brook, 2008; Peters et al., 2004).

Over the years, ample biomarkers have been studied as potential prognostic and diagnostic markers of kidney injury, both in healthy individuals and kidney transplant recipients. Kidney injury molecule-1 (KIM-1) is a type 1 transmembrane protein which is distinctly upregulated in the proximal tubule after kidney damage, such as *e.g.*, nephrotoxic injury (Bonventre, 2009) or transplant rejection (Szeto et al., 2010). It has been shown to be a useful prognostic urinary biomarker for renal function decline. (Szeto et al., 2010) Another example includes cystatin C (CysC), a protein produced by all cells that contain a nucleus, and thus can be found in almost all tissue and body fluids. CysC gets effectively filtered by the glomerulus and completely catabolized by the renal tubules. (Li et al., 2002) Therefore, raised plasma or urinary CysC levels correlate closely to GFR, and reflect glomerular (Madero et al., 2006; Murty et al., 2013) or tubular (Conti et al., 2006) dysfunction, respectively. Moreover, CysC is not affected by *e.g.*, age, sex, and ethnicity, as opposed to the clinically relevant biomarker serum creatinine. (Murty et al., 2013) To our knowledge, our study is the first to show the presence of BC particles in human kidney tissue and to investigate a direct association between these biomarkers of kidney injury and the accumulation of black carbon in the kidney.

2. Methods

2.1. Study population

All adult recipients of a single kidney transplant performed from October 2019 to November 2020 at the University Hospital of Leuven (UZ Leuven, Belgium) were eligible for this study. At the hospital, renal allograft protocol biopsies are routinely performed by a trained physician at the time of transplantation, and 3, 12, and 24 months after transplantation, in addition to clinically indicated biopsies. During this period, 131 kidney transplantations were performed at the hospital. However, due to the COVID-19 pandemic, a general halt was placed on all one year protocol biopsies and predominantly, only clinically indicated biopsies were performed during this time period. In this study, the first 25 patients with a protocol biopsy and 24-hour urine sample one year post-transplant were included for BC detection in tissue and evaluation of urinary biomarkers. The ethical committee of the University Hospital of Leuven approved the secondary use after primary routine care (S64649).

2.2. Recipient clinical data collection

For the kidney transplant recipients, the following data was collected: age at the time of transplantation, sex, weight and length, body mass index (BMI), new-onset diabetes mellitus after transplantation (defined as the need to start insulin treatment or oral anti-diabetic medication after transplantation), smoking after transplantation, and 24-hour urinary creatinine clearance levels at the one-year routine follow-up visit. Additionally, the GFR was estimated using the chronic kidney disease Epidemiology Collaboration (CKD-EPI) equation: $eGFR\ (mL/min/1.73\ m^2) = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black], where S_{cr} is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1, and age is expressed in years. (Levey et al., 2009).

2.3. Residential exposure measurements

The ambient exposure to BC of kidney transplant recipients was determined based on their residential address using a validated high-resolution spatial and temporal interpolation method. (Bongaerts et al., 2019; Saenen et al., 2017; Janssen et al., 2008) This method employs land cover data obtained from satellite images (CORINE land cover data set) and pollution data of fixed monitoring stations. This model chain provides daily exposure values in a high-resolution receptor grid, coupled with a dispersion model that uses emissions from point and line sources. Overall model performance was evaluated by leave-one-out cross-validation including 16 monitoring points for BC. Ambient exposure to BC was calculated for various time points: (i) during the follow-up period (from the day of transplantation up to the day of one year post-transplant sampling), (ii) one month before the one year post-transplant biopsy sampling (medium-term exposure) (iii) one week before the one year post-transplant biopsy sampling (recent exposure), and (iv) each day of the week leading up to the one year post-transplant biopsy sampling (contemporary exposure). Residential proximity to a major road from the transplant recipient's home was calculated using official digitized maps and are represented in meters.

2.4. Black carbon detection in kidney biopsy samples

BC particles present in the kidney were detected using a specific and sensitive detection technique based on the non-incandescence-related white light generation of the particles under femtosecond illumination, as described elsewhere (Supplemental Fig. 1). (Bongaerts et al., 2019; Saenen et al., 2017; Bové et al., 2016) In brief, 5 tile scans of 3 × 3 of paraffin-embedded kidney tissue, sectioned at 4 μm, were collected at room temperature using a Zeiss LSM510 (Carl Zeiss, Jena, Germany) confocal microscope, equipped with a two-photon femtosecond-pulsed laser (150 fs, 80 MHz, MaiTai DeepSee, Spectra-Physics, USA) tuned to a central wavelength of 810 nm with a 5 to 10 mW radiant power on average at the sample, using a 10×/0.30 (Plan-Neofluar, Carl Zeiss) objective. Captured images were analyzed according to a peak-finding algorithm with MatLab (2017b) software (MathWorks, the Netherlands) to count the number of black carbon particles and with ImageJ free software (Fiji version 1.53c, USA) to determine the focal volume of each image.

To validate the presence of BC, BC fingerprinting was performed (Supplemental Methods). The emission fingerprint of black carbon particles alongside the fluorescence-lifetime imaging microscopy (FLIM) decay showed similar behavior between the identified BC particles and reference carbonaceous carbon black (CB) particles (Supplementary Fig. 2).

2.5. Black carbon scoring in histologic regions

The aforementioned images of kidney tissue sections were evaluated for BC bioaccumulation in different structural components of the kidney tissue. BC particles present were affixed onto the image through ImageJ free software, and all five tile scan images of 3 × 3 captured per participant were scored according to a scoring system based on the

presence or absence of BC particles near structural components. In brief, this system appoints a yes or no score when BC particles are found in major structural components of the kidney: the glomerulus, tubules, blood vessels or capillaries and/or the smooth muscle encompassing them, and the interstitial regions surrounding these renal structures.

2.6. Kidney damage-related biomarkers

Collected 24-hour urine samples were immediately stored after receival at −20 °C until further processing. Urinary KIM-1 and CysC levels were evaluated and quantified according to human KIM-1 (ab235081, Abcam, Cambridge, United Kingdom) and CysC (ab119589, Abcam) colorimetric enzyme-linked immune sorbent assays (ELISA), respectively. For the KIM-1 and CysC ELISA, samples were diluted 1:4 and 1:100, respectively, prior to following the manufacturer's protocol. The 96-well plates were colorimetrically visualized with the FLUOstar® Omega microplate reader (BMG Labtech, Ortenberg, Germany) and processed with the Omega software (Software version 1.20, BMG Labtech).

2.7. Statistical analysis

All data were analyzed and/or visualized with RStudio software (RStudio 2022.02.3, USA) and GraphPad (GraphPad Prism 8, GraphPad Software Inc., USA). The normality of data was evaluated and non-normally distributed variables (tissue BC, residential proximity to major road, KIM-1 levels, and CysC levels) were logarithmically transformed (log 10) and described by the geometric mean (5th, 95th percentile). Associations between covariates and outcomes of interest were evaluated with a two-sided T-test. Pearson correlation coefficient was used to assess the correlation between average tissue BC, or modelled BC, and urinary biomarkers including KIM-1, CysC, eGFR, and creatinine clearance. To determine significant differences in the above biomarkers, linear regression models were employed. The transplant recipients' residence was used to estimate the median neighborhood income based on personal tax declarations per statistical sector (1.55 km2) of the 2020 income year as disclosed by the Belgian statistical office (Statbel), which includes taxable professional income, replacement income, pensions, dividends, cadastral income and maintenance payments, but excludes non-taxable income (*e.g.*, child benefits and integration income). (Alfano et al., 2023) The adjusted model included the following covariates: age (years), sex, BMI, socio-economic status (SES), and smoking status (either never, former, current smoker, or no data available).

Additionally, several sensitivity analyses were performed to assess the robustness of our findings. Therefore, we adjusted the model separately for the onset of diabetes post-transplantation (n = 25, yes/no), the need for dialysis in the first week post-transplantation (n = 25, yes/no), donor age (n = 25, years), smoking status of the donor (n = 25, yes/no), estimated glomerular filtration rate of the donor (n = 23), and BMI of the donor (n = 25).

3. Results

3.1. Kidney transplant recipient characteristics

The study population of patients (n = 25) is described in Table 1. The average ± SD age of participants (32.0 % women) was 60.3 ± 9.0 years. Overall, the study population was slightly overweight, with an average ± SD BMI score of 27.1 ± 4.6. The average ± SD eGFR amounted to 48.24 ± 16.01 mL/min/1.73 m^2, where 84.0 % had an eGFR < 60 mL/min/1.73 m^2, and the average ± SD creatinine clearance amounted to 66.11 ± 18.05 mL/min. The time between the kidney transplantation and the day of biopsy sampling (*i.e.*, the follow-up period) amounted to an average ± SD of 397.08 ± 37.45 days. The median (interquartile range, IQR) value of income per declaration amounted to 30,661 (7994) euros.

Table 1
Recipient Characteristics.

Recipients (n = 25)	
Age at time of transplantation	60.3 ± 9.0
Sex	
Male	17 (68)
Female	8 (32)
Weight, kg	83.5 ± 15.6
Height, m	174.4 ± 9.7
BMI	27.1 ± 4.6
Smoking	
Never	13 (52)
Former Smoker	7 (28)
Current Smoker	2 (8)
Unknown	3 (12)
Follow-up period, days	397.1 ± 37.5
Serum Creatinine, mg/dL	1.58 ± 0.63
eGFR, mL/min/1.73 m^2	48.24 ± 16.01
<60 mL/min/1.73 m^2	21 (84)
>60 mL/min/1.73 m^2	4 (16)
Urinary KIM-1, pg/mL	176.8 (54.8, 583.3)
Urinary cystatin c, ng/mL	602.01 (95.55, 3,370.83)
Urinary creatinine clearance, mL/min	66.11 ± 18.05
Tissue BC load, no. of particles/mm^3	1.80×10^3 (3.65×10^3, 7.50×10^3)
Residential proximity to major road, m	340.75 (34.86, 2,665.85)
Residential BC exposure, μg/m^3	
Follow-up period	0.63 ± 0.16
Average one month before sampling	0.61 ± 0.23
Average one week before sampling	0.65 ± 0.36

Abbreviations: BC, black carbon; BMI, body mass index; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule-1; SD, standard deviation.
Statistics are represented as arithmetic mean ± SD, geometric mean (5th, 95th percentile interval), or number of subjects (%).

The average ± SD BC exposure during the follow-up period amounted to 0.63 ± 0.16 μg/m^3 (Table 1); the corresponding IQR was 0.26 μg/m^3. Shorter exposure periods did not differ much from the yearly average (p > 0.05) and are provided in Table 1 and Supplementary Table 1. The geometric average (5th, 95th percentile) residential proximity to a major road was 340.75 (34.86, 2,665.85) meters.

3.2. Black carbon detection in kidney biopsy tissue

We were able to detect BC particles from ambient air pollution exposure in all screened kidney biopsies from transplant recipients one year post-transplant (Fig. 1). The kidney BC load, the number of BC particles in the tissue, did not differ between men and women (p = 0.67). Furthermore, no association was observed between kidney BC load and the transplant recipient's age (p = 0.64), weight (p = 0.44), height (p = 0.79), BMI (p = 0.21), smoking status (p = 0.57), the new-onset of diabetes post-transplantation (p = 0.16), or delayed graft function (characterized by the need of dialysis in the first week post-transplantation, p = 0.20).

The number of BC particles amount to a geometric mean (5th, 95th percentile) of 1.80×10^3 (3.65×10^2, 7.50×10^3) particles per cubic millimeter kidney tissue.

In our study, the kidney BC load was positively but not significantly associated with modelled BC exposure at the residential address during the follow-up period (r = 0.20; p = 0.35) and tended to be inversely associated with residential proximity to major road (r = -0.33; p = 0.10).

The bioaccumulation of BC particles in human kidneys is summarized in Table 2. BC particles could be found in the interstitium of all included biopsy samples (100.0 % of patients), where BC particles were mainly observed surrounding the tubules (84.0 % of patients; Fig. 2A), followed by surrounding the blood vessels (36.0 % of patients), the glomeruli (28.0 % of patients) and capillaries (28.0 % of patients). The second most common site of BC bioaccumulation is the tubule system,

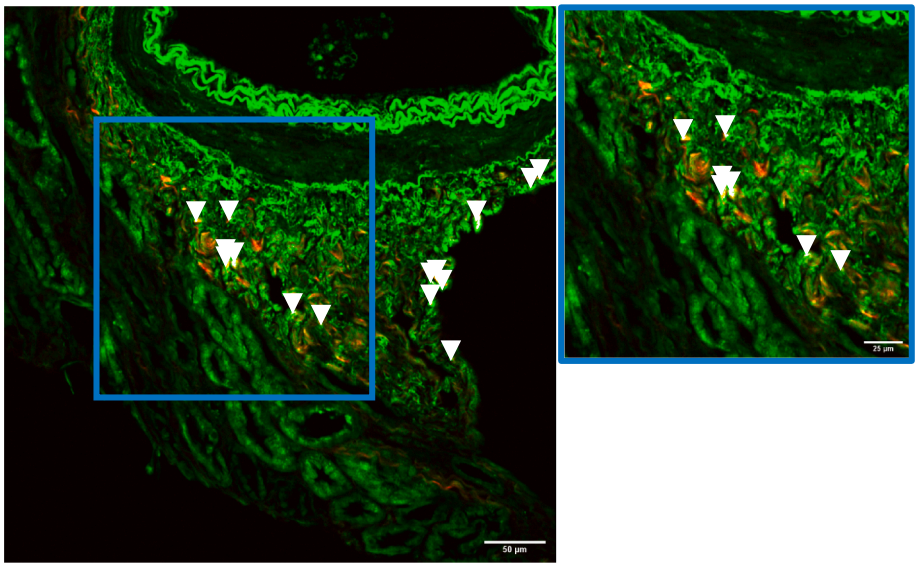

Fig. 1. Evidence of BC particles in kidney biopsy tissue from transplant recipients one-year post-transplant. The white light generation originating from the BC particles (depicted in white and indicated with white arrowheads) under femtosecond-pulsed laser illumination (ex. 810 nm) can be observed. Two-photon autofluorescence of the tissue (green, em. 450 – 650 nm), mainly caused by flavin (em. 530 nm) and lipofuscin (em. 570 nm), and second harmonic generation from collagen (red, em. 400 – 410 nm) are detected simultaneously. Scale bar: 50 µm. The blue box on the right indicate BC particles present in kidney biopsy tissue at a greater magnification. Scale bar: 25 µm. ***Abbreviations:*** *BC, black carbon; em., emission; ex., excitation.* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Overview of the histologic scoring of black carbon bioaccumulation in one-year post-transplant kidney biopsy tissue (n = 25).

	Presence, yes*	Percentage of patients (%)
Glomerulus	6	24.0
Tubules	20	80.0
Blood Vessels and Capillaries including smooth muscle	10	40.0
Interstitium	25	100.0
surrounding glomerulus	7	28.0
surrounding tubules	21	84.0
surrounding blood vessels	9	36.0
surrounding capillaries	7	28.0

* The employed system appoints a yes or no score when BC particles are found in major structural components of the kidney: the glomerulus, tubules, blood vessels or capillaries and/or the smooth muscle encompassing them, and the interstitial regions surrounding these renal structures.

where in 20 of 25 biopsy samples, BC particles were observed in the epithelial cells of the tubules (Fig. 2B). Furthermore, the blood vessels and predominantly the smooth muscle harbored BC particles (40.0 % of patients; Fig. 2C), with the smallest number of particles observed in the glomeruli (24.0 % of patients), where they were mainly observed in Bowman's capsule (66.67 %) or the glomerular capillary tuft (50.0 %; Fig. 2D).

3.3. Kidney function in transplant patients with kidney black carbon load

The protein quantification of KIM-1 and CysC in 24-hour urine collected the day before kidney biopsy sampling amounted to a geometric mean (5th, 95th percentile) of 176.82 pg/mL (54.76, 583.30) and 602.01 ng/mL (95.55, 3,370.83), respectively. The average ± SD eGFR, estimated according to the CKD-EPI equation, was 48.24 ± 16.01 mL/min/1.73 m^2 (Table 1). Both before (Fig. 3A) and after (Table 3) adjustment for age, sex, BMI, SES, and smoking status, a 10 % higher kidney tissue BC load was associated with a 7.06 % (95 % CI 0.38 to 14.19) and 8.24 % (95 % CI 0.88 to 16.13) higher urinary KIM-1 level in the unadjusted and adjusted model, respectively. Creatinine clearance was significantly inversely associated with tissue BC, where each 10 % increase in tissue BC was associated with a 1.63 mL/min (95 % CI −2.99 to −0.28) lower clearance in the unadjusted model; however, after adjusting for age, sex, BMI, SES, and smoking status (Table 3), the inverse association lost its significance, where each 10 % increase in tissue BC was associated with a 1.33 mL/min lower clearance (95 % CI −2.94 to 0.26; p = 0.09). Furthermore, no signification association could be observed between tissue BC and urinary CysC or eGFR.

3.4. Kidney function in transplant patients with external exposure matrices

Both before (Fig. 3C and 3F, respectively) and after (Table 3) adjustment, significant inverse associations were observed for KIM-1 and CysC with residential proximity to a major road. Each 10 percent increase in distance amounted to a 3.99 percent (95 % CI −5.73 to −2.22) and 4.68 percent (95 % CI −8.00 to −1.24) lower urinary KIM-1 and CysC protein expression levels, respectively. At the same time, we did not find a significant result for eGFR or creatinine clearance in relation to residential proximity to a major road.

When evaluating the association between the average BC exposure during the follow-up period, both before (Fig. 3B and 3E, respectively) and after (Table 3) adjustment, urinary KIM-1 and CysC levels were increased. For each IQR (0.26 µg/m^3) increase in modelled BC, an increase of 113.95 percent (95 % CI 15.50 to 296.11, p = 0.02) and 145.02 percent (95 % CI 13.42 to 593.79, p = 0.08) was observed for KIM-1 and CysC after adjusting for covariates, respectively. Furthermore, when evaluating modelled BC exposure in the month before biopsy sampling, a 50.45 percent (95 % CI −1.81 to 130.55, p = 0.05) increase in urinary KIM-1 was observed for each IQR (0.30 µg/m^3) increase in modelled BC in the month before biopsy sampling, which remained after adjustment for covariates (data not shown). Additionally, CysC showed a significant increase of 86.60 percent (95 % CI 20.54 to 188.89 p < 0.01) with the one week BC exposure, but other kidney biomarkers were not associated with recent exposure (Supplementary Table 2).

3.5. Sensitivity analyses

The sensitivity analysis confirmed the robustness of our findings. The main model was additionally adjusted for donor age (n = 25), donor BMI (n = 25), donor eGFR (n = 23), smoking status of the donor (n = 25), the need for dialysis in the first week post-transplant (n = 25), and the onset of diabetes mellitus post-transplant (n = 25) (Supplemental Table 3). Most of the associations were robust in the sensitivity analysis, but for some, the p-values were borderline nonsignificant (*e.g.*, adjusting for donor age in regards to associations for urinary KIM-1 and kidney BC load; p = 0.05).

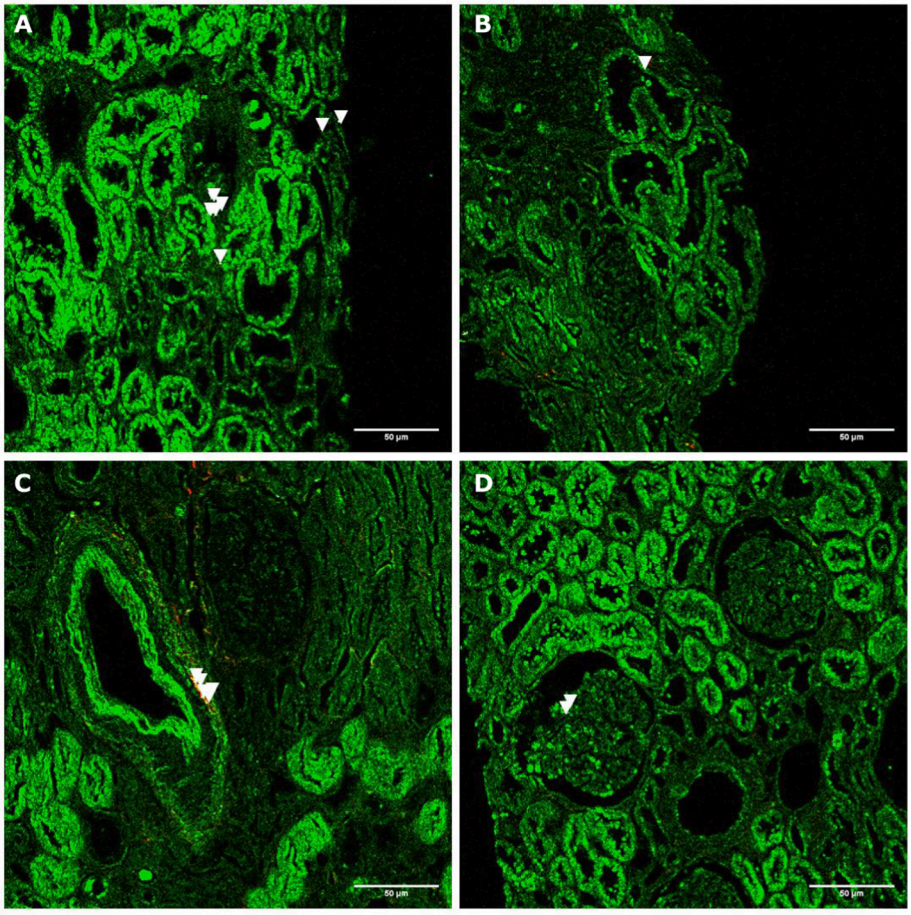

Fig. 2. BC particles are observed in major structural components of kidney biopsy tissue from transplant recipients one-year post-transplant. The white light generation originating from the BC particles (depicted in white and indicated with white arrowheads) under femtosecond-pulsed laser illumination can be observed in multiple renal structures: **A)** in the interstitial region surrounding tubule(s), **B)** in the epithelial lining of the tubule(s), **C)** in the smooth muscle surrounding a blood vessel, and **D)** in the capillaries of the glomerular tuft. *Scale bar:* 50 µm. ***Abbreviations:*** *BC, black carbon.*

4. Discussion

In this current study, we evaluated whether naturally present BC particles translocated to and biodistributed into the kidney tissue upon inhalation. Firstly, BC particles translocate to and biodistribute into the kidney tissue. Secondly, the kidney BC load depended on the long-term ambient black carbon exposure at the residence. Lastly, we examined urinary KIM-1 in kidney transplant recipients one year post-transplant as promising a biomarker to evaluate potential tubular kidney damage in relation to BC exposure.

As the kidneys receive roughly 25 % of cardiac output (Skorecki et al., 2016), BC particles entering the systemic circulation presumably translocate towards the kidneys. Despite the fact that a fraction of BC particles is excreted via the urine after passing the filtration system of the kidneys, our results indicate that a considerable fraction of particles is retained in structural components of the kidney. BC particles could be identified inside kidney biopsy tissue, based on the white light generation by the particles under femtosecond-pulsed illumination. (Bové et al., 2016) Furthermore, the signals originating from BC particles were fingerprinted and equaled the carbonaceous characteristics of reference CB particles.

Moreover, our results demonstrate that BC particles are predominantly observed in the interstitial regions, mainly surrounding the tubules, followed by preferential bioaccumulation in the tubules, blood vessels and/or capillaries, and glomeruli, respectively. There is a possibility that BC particles reach the kidneys through the renal artery after entering systemic circulation, which branches into smaller blood vessels as it enters the kidney. The presence of the BC particles near the vascular components of the kidney suggests migration into the kidney tissue either before filtration by the glomerulus, or partial reabsorption by the tubules. In this regard, further investigation towards the biodistribution of BC particles is required.

To evaluate whether the accumulated BC particles might influence kidney function and/or damage, urinary biomarkers previously established as promising biomarkers to evaluate kidney damage were included in this study. KIM-1 is a type I transmembrane protein with an immunoglobulin and mucin domain. (Bonventre, 2009; Han et al., 2002) A recent study has indicated high(er) urinary KIM-1 levels and extensive expression in kidney biopsies of the proximal tubule of patients with acute tubular necrosis (Han et al., 2002) and has been shown to serve as a urinary biomarker of acute kidney tubular injury (Han et al., 2008). Furthermore, research has also indicated urinary KIM-1 as a biomarker for kidney injury possibly caused by the exposure to these environmental pollutants, including cadmium (Pennemans et al., 2011) or lead (Cabral et al., 2021) exposure. In this study, we found that elevated urinary levels of KIM-1 positively correlated with both modelled BC over the follow-up period and tissue BC in kidney biopsy tissue. These results indicate that even low levels of BC exposure, either modelled or measured in kidney biopsy tissue, might influence urinary KIM-1 expression levels and quantifying urinary KIM-1 levels might allow early detection of cellular stress in proximal tubular cells as a result of BC exposure (Wu and Parikh, 2008; Vaidya et al., 2006; Prozialeck et al., 2009).

CysC is a member of the family of cysteine protease inhibitors, and its function is believed to regulate proteases secreted from lysosomes from dying and/or diseased cells. When the kidneys function appropriately, CysC is effectively filtered by the glomerulus, completely reabsorbed, and broken down by the renal tubules for recycling. Urinary CysC concentrations in healthy populations are reported to be low, ranging from 30.0 to 300.0 ng/mL. (Uchida and Gotoh, 2002) For example, Conti *et al.*

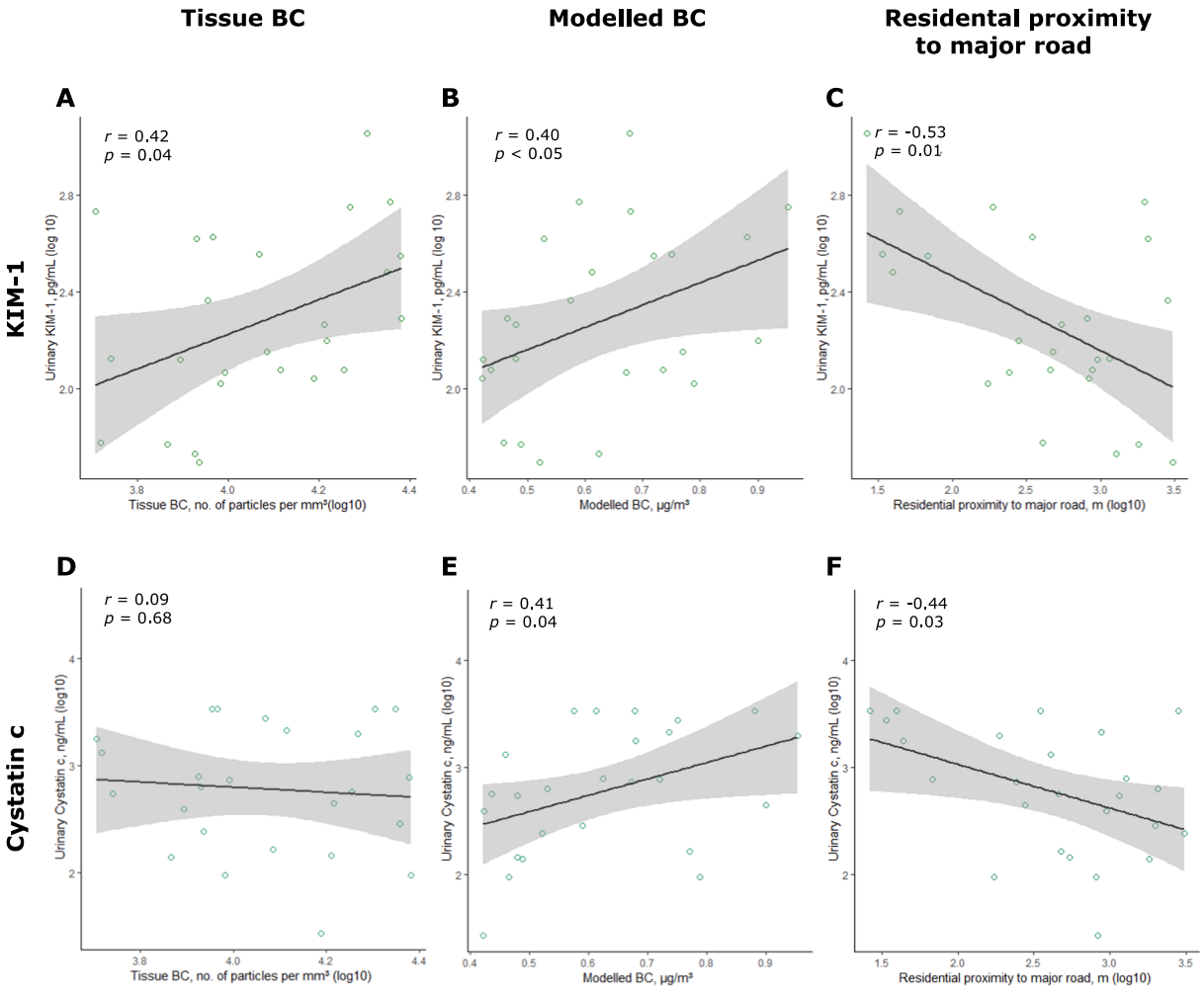

Fig. 3. Correlations between tissue BC, modelled BC, or residential proximity to major road and urinary biomarkers KIM-1 and cystatin c. Pearson correlation between A) tissue BC and urinary KIM-1, B) modelled BC and urinary KIM-1, C) residential proximity to a major road and urinary KIM-1, **D)** tissue BC and urinary cystatin c, **E)** modelled BC and urinary cystatin c, and **F)** residential proximity to a major road and urinary cystatin c. The black line represents the unadjusted regression line with a 95 % confidence interval (grey area). ***Abbreviations:*** *BC, black carbon; KIM-1, kidney injury molecule-1.*

(Conti et al., 2006) found a reference value for freshly collected urine samples ranging from 30.0 to 180.0 ng/mL. (Conti et al., 2006) In this study, the geometric mean (5th, 95th percentile) of urinary CysC levels amount to 602.01 (95.55, 3,370.83) ng/mL, which is two-fold higher the higher limit reference values Uchide *et al.* and Conti *et al.* indicated for a healthy population. A study investigating various renal disorders by Herget-Rosenthal *et al.* showed that increased urinary cystatin C levels reflect structural and functional tubular (function) impairment in the kidney. (Herget-Rosenthal et al., 2007) Furthermore, elevated levels of urinary CysC are associated with interstitial fibrosis and tubular atrophy in kidney transplant recipients, which are terminal consequences of chronic inflammation in the kidney. (Oberbauer, 2016) We found associations with urinary CysC and ambient BC exposure, as well as with residential proximity to a major road, but not with the individual kidney BC load. It might be interesting to also evaluate serum CysC as opposed to urinary CysC levels in relation to BC exposure, as elevated urinary CysC levels indicate tubular dysfunction (Conti et al., 2006), whereas elevated serum CysC levels might indicate early glomerular dysfunction (Madero et al., 2006). Moreover, research has already indicated the importance of serum CysC as a biomarker of kidney function in the early stages of kidney damage (Murty et al., 2013) and serum CysC has been found to be positively correlated to an average daily dose of air pollutants (Wang et al., 2020).

No significant correlations or associations could be observed for eGFR in relation to either investigated pollution exposure or residential proximity to a major road. Albeit non-significant, our results show a trend of decline in eGFR with an increase in tissue BC and modelled BC. Previous studies have found contradicting associations of $PM_{2.5}$ and eGFR, both in healthy participants (Mehta et al., 2016; Li et al., 2021; Li et al., 2021) as well as in subpopulations with chronic kidney-related illnesses, including *e.g.*, chronic kidney disease (Chen et al., 2018; Yang et al., 2017; Feng et al., 2021) or end-stage kidney disease (Bowe et al., 2018). The eGFR is affected by physiological and pathological conditions as opposed to *e.g.*, CysC, including diet, exercise, age, and obesity. (Levey et al., 2014) Furthermore, eGFR is not always decreased in the early stages of kidney function impairment. It has been shown that the estimated GFR detects functional impairments (Stevens et al., 2008; Thomas and Thomas, 2009), rather than provide an early detection of renal (function) impairment, as to the early detection urinary biomarkers KIM-1 (Bonventre, 2009; Vaidya et al., 2006) and CysC (Hall et al., 2011; Koyner et al., 2008; Bagshaw and Bellomo, 2010), which may explain why we could not observe any associations with eGFR. In addition, studies addressing modelled BC exposure and eGFR are scarce (Gao et al., 2019; Zhao et al., 2020), and no personalized BC exposure data has been linked to a decline in eGFR before. In the Boston area, Lue *et al.* (Lue et al., 2013) observed that ischemic stroke patients who lived within 50 m from a major road had a 3.9 (95 % CI 1.0 to 6.7) mL/min/1.73 m^2 lower eGFR ($p < 0.01$) compared to those living further than

Table 3
Association between internal and external exposure matrices or residential proximity to a major road and urinary biomarkers in kidney transplant recipients (n = 25).

		Personalized tissue BC		Distance to major road		Modelled BC (follow-up period)	
		% difference (95 % CI)	p value	% difference (95 % CI)	p value	Estimate (95 % CI)	p value
KIM-1†	unadjusted	7.06 (0.38, 14.19)	0.04	−2.89 (−4.86, −0.88)	<0.01	72.37 (0.75, 194.90)	<0.05
	adjusted	8.24 (0.88, 16.13)	0.04	−3.99 (−5.73, −2.22)	<0.01	113.95 (15.50, 296,11)	0.02
Cystatin C†	unadjusted	−2.26 (−12.68, 9.41)	0.68	−3.81 (−7.08, −0.42)	0.03	145.22 (4.61, 474.86)	0.04
	adjusted	−0.80 (−12.55, 12.53)	0.90	−4.68 (−8.00, −1.25)	0.01	145.02 (−13.42, 593.79)	0.08
eGFR* mL/min/1.73 m^2	unadjusted	−0.44 (−1.78, 0.91)	0.51	0.13 (−0.33, 0.58)	0.57	−1.66 (−12.84 to 9.52)	0.76
	adjusted	−0.61 (−2.09, 0.87)	0.40	0.11 (−0.39, 0.62)	0.64	−7.81 (−20.81, 5.19)	0.22
Creatinine Clearance* mL/min	unadjusted	−1.63 (−2.99, −0.28)	0.02	0.04 (−0.47, 0.56)	0.86	−6.04 (−18.39, 6.32)	0.32
	adjusted	−1.34 (−2.94, 0.26)	0.09	0.20 (−0.38, 0.78)	0.48	−21.90 (−27.08, 1.28)	0.07

The adjusted model adjusts for age, sex, BMI, socio-economic status, and smoking status. **Abbreviations**: BC, black carbon; CysC, cystatin c; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule-1.

† Estimates were log transformed and represent the percentage increase in urinary biomarker with a 95 % confidence interval for a 10 % increase in tissue BC or residential proximity to a major road or an IQR increase in modelled BC during the follow-up period.

* Estimates represent the change in unit for the marker (*e.g.*, creatinine clearance, expressed in mL/min) with a 95 % confidence interval for a 10 % increase in tissue BC or residential proximity to a major road or an IQR increase in modelled BC during the follow-up period.

1000 m from a major road. In another study performed by the same research group, a similar trend was shown, where a decrease of 1.4 (95 % CI −4.7 to 2.0) mL/min/1.73 m^2 in eGFR was observed when participants were living < 150 m from a major road, albeit nonsignificant (Weaver et al., 2019). The authors state that effects may be stronger when persons live near major roads, which may also be extrapolated to this study, as only 4 kidney transplant recipients lived < 50 m from a major road, while most of transplant recipients (n = 17) lived further than 250 m from a major road.

To our knowledge, this study is the first to assess naturally present BC particles from air pollution in kidney tissue on an individual level, which does not require extensive sample preparation or labelling and has already been established in other biological samples (Bové et al., 2019; Saenen et al., 2017). Secondly, we confirmed the carbonaceous characteristics of the kidney tissue BC particles and excluded external contamination through FLIM, emission fingerprinting, and orthogonal projections showing BC particle embedment in kidney tissue. Additionally, multiple sensitivity analyses confirmed the robustness of our findings. Nevertheless, the results should be interpreted with probable limitations, predominantly due to the small sample size. It is of note that kidney transplant recipients may be particularly susceptible to environmental toxicants, such as $PM_{2.5}$ or BC in comparison to healthy adults. Chang *et al.* indicated that fine particulate matter exposure was an independent risk factor for acute rejection, graft failure, and mortality among kidney transplant recipients; furthermore, their results suggest that $PM_{2.5}$ exposure might lead to increased systemic inflammation, which may activate both the innate and adaptive immune system in kidney transplant recipients (Chang et al., 2021). Components of fine particulate matter, such as BC, may be associated with increased oxidative stress, as well as gene and protein expression of proinflammatory mediators, such as *e.g.*, tumor necrosis factor-alpha (TNF-α) (Chang et al., 2021). Possibly, individual lifestyle factors of the kidney donor and means of kidney collection before transplantation might influence kidney function, even one year post-transplant, as it has been shown that living donor kidneys function far superior to those of a deceased individual post-transplant. (Matas et al., 2013) Furthermore, the kidney is exposed to BC particles prior to transplantation through the donor, which might influence kidney function; regardless, this baseline BC load is present at the moment of transplantation and can exert effects on the transplantation and kidney function (outcome).

The ability to determine a personalized BC exposure window for kidney transplant recipients in relation to kidney function post-transplant provides a novel method to address a population-based perspective towards kidney function, (potentially delayed) graft function, and other renal outcomes. In the future, this personalized BC exposure determination might be individualizable in a clinical setting, where tissue BC particles can be a systemic indicator of exposure to air pollution and its influence on kidney function.

5. Conclusion

In conclusion, we were able to demonstrate, under real-life exposure conditions, the translocation of inhaled BC particles into the kidneys of kidney transplant recipients. Furthermore, urinary biomarkers, such as KIM-1, a biomarker to assess kidney damage, were linked to higher accumulation of kidney BC load, as well as with ambient BC exposure at the transplant recipients' residential address and the residential proximity to a major road. More research towards the effects of accumulated BC particles on the kidney and its functioning is warranted and we show that direct visualization of particles in the kidney might add to exposure effects on the kidneys.

Authors' Contributions

L.R., H.B., K.D.V., and T.S.N. designed the current study. L.R. performed all measurements. P.K. provided insight in the translocation and biodistribution of black carbon in kidney tissue. T.S.N. and M.P. assisted in statistical analysis. E.B. provided assistance and feedback in black carbon measurements and fingerprinting. M.A. and H.B. developed the black carbon measurement technique and provided technical support. All authors contributed to important intellectual content during manuscript drafting or revision. All authors read and approved the final manuscript.

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Data Sharing

The data used in the findings of this study are not publicly available as they contain information which may compromise research participant privacy, but are available upon reasonable request from the corresponding author (T.S.N.).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: H.B., M.A., and T.S.N. declare that aspects of the work are subject of a patent application (Method for detecting or quantifying carbon black and/or black carbon particles, US20190025215A1) filed by Hasselt University (Hasselt, Belgium) and KU Leuven (Leuven, Belgium). The remaining authors declare no competing interests. None of the funding agencies had a role in the design and conduct of the study, in the collection, analysis and interpretation of the data, or in the preparation, review, or approval of the manuscript.

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Appendix A. Supplementary material

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