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Glomerular function in relation to fine airborne particulate matter in a representative population sample

Short title: Glomerular function and air pollution

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ABSTRACT

Whereas the adverse impact of fine particulate matter on coronary heart disease and respiratory disorders has been clarified, its influence on glomerular function is not well defined in population studies. Serum creatinine levels were quantified in 820 randomly recruited people (50.7% women; mean age 51.1 years). Among them, 653 participants were followed up for a median of 4.8 years. Using multivariable-adjusted mixed model, eGFR (or serum creatinine) both at baseline and follow-up were regressed against long term residential black carbon (BC) or PM_{2.5} (particles with an aerodynamic diameter ≤ 2.5 μm). In longitudinal analysis, the percent change in eGFR was regressed against long term residential exposure to BC or PM_{2.5}. eGFR averaged 80.9 (SD 16.4) mL/min/1.73m² and median long term PM_{2.5} and black carbon amounted 13.1 (SD 0.92) and 1.10 (SD 0.19) $\mu\text{g}/\text{m}^3$, respectively. In multivariable-adjusted cross-sectional analyses, eGFR was unrelated to BC and PM_{2.5} ($P \geq 0.59$). During follow-up, eGFR decreased on average by 1.9 mL/min/1.73m² (95% confidence interval: 1.0-2.8). The percentage decline in eGFR was not significantly associated with either BC or PM_{2.5} ($P \geq 0.75$). In conclusion, long-term residential exposure to PM_{2.5} and black carbon is not associated with eGFR decline in predominantly healthy people drawn from a general semirural population.

Keywords: black carbon; chronic kidney disease; eGFR; PM_{2.5}; population science; renal function

Introduction

According to the report of the Global Burden of Disease Study, renal failure contributed to 0.403 million death in 1990 which increased to 0.736 million in 2010 worldwide¹. Chronic kidney disease (CKD) is the main cause of renal failure and has increased substantially throughout the years². Among all etiological factors, the adverse impact of air pollution on human health has been noted. Airborne fine particulate ($PM_{2.5}$) reaches the smallest airways and alveoli, crosses the blood-air barrier and directly penetrates into the blood stream. Black carbon (BC), a component of $PM_{2.5}$, consists of pure carbon in several bond forms, and finds its origin in the incomplete combustion of fossil fuels, biofuel or biomass. The kidneys clear BC particles from the circulating blood³. The number of carbon particles in urine is measurable and reflects chronic exposure to combustion-related air pollution³.

Several studies reported on the levels of particulate matters in relation to the glomerular filtration rate estimated from serum creatinine (eGFR)⁴⁻⁷, glomerulopathy⁸, prevalent⁶ or incident⁹ CKD, progression to end-stage renal disease⁹, microalbuminuria¹⁰, and the risk of renal cancer in relation to air pollutants¹¹. These studies enrolled population samples^{10,11}, stroke patients⁴, or older male veterans^{5,7,9}. Some studies did not report the level of exposure¹⁰, or estimated exposure from the proximity of major roads⁴, while other findings⁸ were representative for exposure levels far above current air quality standards. Other reports focused on coarse particulate⁶. Of the eight reviewed studies⁴⁻¹¹, none reported on BC exposure. To address this knowledge gap, we analysed data from The Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO¹²).

RESULTS

Baseline characteristics of participants

All 820 participants were White Europeans, of whom 416 (50.7%) were women. Age at baseline (2005-2009) averaged (SD) 51.1 (15.6) years (5th-95th percentile interval, 23.6–75.8 years). Among 820 participants, 341 (41.6%) had hypertension, of whom 211 (61.9%) were on antihypertensive drug treatment, and 32 (3.9%) had diabetes. Among 211 patients on antihypertensive drug treatment, 18 (8.5%) took diuretics, 94 (44.6%) inhibitors of the renin system, 17 (8.1%) vasodilators, 2 (0.9%) centrally acting α_2 adrenergic agonists and 80 (37.9%) were on combination therapy with more than one class of blood pressure lowering medication. Intake of statins was reported by 106 participants (12.9%). Serum creatinine and eGFR averaged 86.4 (15.5) $\mu\text{mol/L}$ and 80.9 (16.4) mL/min/1.73m^2 , respectively. At baseline, 238 people (20.0%) were in CKD stage 1, 503 in CKD stage 2 (61.3%), 63 in CKD stage 3A (7.7%), 14 in CKD stage 3B (1.7%), 2 in CKD stage 4 (0.2%) and none in CKD stage 5. At baseline, the prevalence of microalbuminuria based on the urinary albumin-to-creatinine ratio was 13 (3.3%) in women and 16 (4.2%) in men.

Tables 1 and 2 list the characteristics of the participants by thirds of the distributions of BC and PM_{2.5}, respectively. Most clinical and biochemical characteristics were similar across thirds of the BC and PM_{2.5} distributions, with the exception of plasma glucose which decreased from the lowest to the highest exposure group for both BC ($P = 0.027$) and PM_{2.5} ($P = 0.033$), and the prevalence of smoking ($P = 0.027$) which was higher in the top PM_{2.5} exposure group (Tables 1 and 2).

Ambient air pollution

The median interval between the assessment of renal function and the midpoint assessment of long-term air pollution (30 June 2012) was 5.6 years (5th-95th percentile interval, 3.1–6.9 years)

at baseline (2005–2009) and 0.4 years (–0.6–2.6 years) at follow-up (2009–2013). Of the 820 participants, 231 lived alone, while 165, 33 and 38 shared a home with two, three or more participants. The median long-term air pollution levels (5th–95th percentile interval), to which participants were exposed, amounted to $1.10 \mu\text{g}/\text{m}^3$ ($0.93\text{--}1.55 \mu\text{g}/\text{m}^3$) for BC and $13.1 \mu\text{g}/\text{m}^3$ ($12.4\text{--}15.3 \mu\text{g}/\text{m}^3$) for $\text{PM}_{2.5}$. While accounting for clustering of study participants sharing a residential address, the levels of these two air pollutants were highly correlated ($r = 0.95$).

Cross-sectional analyses

In multivariable-adjusted cross-sectional analyses of all participants, serum creatinine and eGFR were unrelated to BC and $\text{PM}_{2.5}$, irrespective of whether only the baseline data were used, only the follow-up data, or the baseline and follow-up data (Table 3, $P \geq 0.59$). All models accounted for clustering of data among participants living at the same address and were adjusted for sex, age, mean arterial pressure, heart rate, body mass index, fasting plasma glucose, total-to-HDL cholesterol ratio, γ -glutamyltransferase, smoking, socioeconomic class, and antihypertensive treatment (by class). Analyses of baseline combined with follow-up data additionally accounted for the longitudinal correlation between baseline and follow-up measurements within participants.

Renal function changes

Table 4 lists the baseline and follow-up characteristics, and the changes from baseline to follow, in the 653 participants who had a follow-up measurement of renal function. After a median of 4.8 years (5th to 95th percentile interval, 3.7–5.4 years) serum creatinine increased by $3.7 \mu\text{mol}/\text{L}$ ($P < 0.0001$) and eGFR decreased by $1.9 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ($P < 0.0001$). In multivariable-adjusted linear regression analysis, the percent changes in serum creatinine and eGFR were not significantly associated with either BC or $\text{PM}_{2.5}$ (Table 5, $P \geq 0.75$). These findings were confirmed in analyses stratified by age group (Table 5). The multivariable-

adjusted percent changes in eGFR did not correlate with the BC (Figure 1) or PM_{2.5} (Figure 2) air pollution contours either in individual participants or in data aggregated per municipality.

Of the 600 participants with CKD stage ≤ 2 at baseline, 48 progressed to CKD stage ≥ 3 at follow-up. The decline in eGFR to a level below 60 mL/min/1.73 m² was not significantly related to the air pollution indices ($P \geq 0.17$). In multivariable logistic regression analysis, the odds ratio associated with an interquartile increment in the exposure variables amounted to 1.48 (95% CI, 0.84-2.59) for BC and 1.23 (95% CI, 0.70-2.15) for PM_{2.5}.

DISCUSSION

In the current population study, we evaluated the associations of eGFR and change in eGFR with BC and PM_{2.5}. The prospective analyses demonstrated over nearly 5 years a decline in eGFR of approximately 2 mL/min/1.73 m² and a progression from CKD stage 2 or less to CKD stage 3 or higher in 8% of participants. However, findings with regard to the key research question were negative. There was no association of eGFR, change in eGFR or CKD progression with BC or PM_{2.5}.

Particulate matter is a mixture of solid and liquid particles in the air. Most previous studies focused on PM₁₀^{4,6,10}. In 3,901 participants enrolled in the Multi-Ethnic Study of Atherosclerosis, the urinary albumin-to-creatinine ratio was measured at three visits 1.5 to 2 years apart from baseline (2000–2004) and correlated with PM₁₀ as measured by ambient air pollution monitors over 1 month, 2 months and 20 years before the first visit, with adjustments applied for race/ethnicity, sex, age smoking, second-hand smoking, body mass index and dietary protein intake¹⁰. The study did not demonstrate a significant association between prevalent microalbuminuria or accelerated development of microalbuminuria in relation to PM₁₀¹⁰. In contrast, among 1103 consecutive Boston-area patients hospitalised with acute

ischaemic stroke between 1999 and 2004, eGFR was correlated with residential distance to major roadways ranging from 50 meters or less to over 1 kilometre with adjustments applied for race, sex, age, smoking, comorbid conditions, treatment with angiotensin-converting enzyme inhibitors, and neighbourhood-level socioeconomic status⁴. Patients living closer to a major roadway had lower eGFR than patients living farther away (P for trend = 0.01). Patients living at a distance of 50 m vs. 1 kilometre had a 3.9 mL/min/1.73 m² lower eGFR (P = 0.007)⁴. Among 21,656 residents of Taipei (2007–2009)⁶, eGFR and the prevalence of CKD (eGFR <60 mL/min/1.73 m²) were correlated with PM_{coarse}, PM₁₀ and PM_{2.5} with adjustments applied for sex, age, body mass index, hypertension (categorical), fasting blood glucose, serum total cholesterol, smoking and drinking, educational attainment, and distance to a major roads (continuous). eGFR was 0.69 mL/min/1.73 m² lower per 1-IQR increment in PM₁₀ (5.83 µg/m³), while the odds of having CKD were 1.15 times higher for the same increment in PM₁₀⁶. The corresponding estimates for PM_{coarse} (6.59 µg/m³) were –1.07 mL/min/1.73 m² for eGFR and 1.26 for CKD. In contrast to the associations with PM₁₀ and coarse PM, those with PM_{2.5} did not reach statistical significance⁶.

The ultrafine particles within the PM_{2.5} fraction and nano-sized BC particles penetrate the air-blood barrier in the lung alveoli, are dispersed widely throughout the whole human body, as evidenced by the detection of BC particles in the urine³. Human studies relating renal function to exposure to PM_{2.5} reported conflicting results^{5,6,8,9}. In the cross-sectional Taiwanese study reviewed above⁶, there was no association between eGFR or CKD with PM_{2.5} (annual average concentration, 26.6 µg/m³). In a longitudinal analysis of 669 men enrolled in the Veterans Administration Normative Aging Study with up to four visits between 2000 and 2011 (n = 1715 visits)⁵, 1-year exposure to PM_{2.5} prior to each visit was assessed using a validated spatiotemporal model that utilised satellite remote-sensing aerosol optical depth data. In all

person-visits by calendar year, the mean yearly average $\text{PM}_{2.5}$ concentrations increased from $10.5 \mu\text{g}/\text{m}^3$ in 2000 to their highest level of $11.8 \mu\text{g}/\text{m}^3$ in 2002 and later decreased to less than $9.0 \mu\text{g}/\text{m}^3$ in 2010 and 2011. eGFR was modelled by a time-varying linear mixed-effects regression model as a continuous function of 1-year $\text{PM}_{2.5}$ levels, while adjusting for a large number of covariables. A $2.1\text{-}\mu\text{g}/\text{m}^3$ IQR higher 1-year $\text{PM}_{2.5}$ was associated with a $1.87 \text{ mL}/\text{min}/1.73 \text{ m}^2$ lower eGFR [95% CI, 0.76–2.99]. A $2.1 \mu\text{g}/\text{m}^3$ -higher 1-year $\text{PM}_{2.5}$ was also associated with an additional annual decrease in eGFR of $0.60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ per year [95% CI, 0.40–0.79]. A recent study linked the Environmental Protection Agency and the Department of Veterans Affairs databases to build an observational cohort of 2,482,737 United States veterans⁹. It applied survival models to evaluate the association of $\text{PM}_{2.5}$ concentrations and risk of incident CKD and end-stage renal disease⁹. County-level exposure was defined at baseline as the annual average $\text{PM}_{2.5}$ concentrations in 2004, and as time-varying variable updated annually and as cohort participants moved. In analyses of baseline exposure (median, $11.8 \mu\text{g}/\text{m}^3$ [IQR, 10.1–13.7]), a $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration was associated with a 20% to 30% increase in the risk of CKD and end-stage renal dysfunction. The time-varying analyses produced similar results⁹.

A Chinese study of 71,151 renal biopsies involving 282 cities with standardisation for age and region identified IgA nephropathy (28.1%) and membranous nephropathy (23.1%) as the leading causes of nephropathy⁸. Three-year average $\text{PM}_{2.5}$ exposure varied among the 282 cities, ranging from 6 to $114 \mu\text{g}/\text{m}^3$ (mean, $52.6 \mu\text{g}/\text{m}^3$). Each $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration associated with 14% higher odds for membranous nephropathy (odds ratio, 1.14; 95% CI, 1.10–1.18) in regions with $\text{PM}_{2.5}$ concentration in excess of $70 \mu\text{g}/\text{m}^3$ ⁸.

Our study is representative for a Flemish population exposed to low levels of air pollution, includes a longitudinal follow-up and applied a high resolution spatiotemporal interpolation

method to link renal function in individual participants with exposure to BC and PM_{2.5}. Our study therefore did not estimate exposure to air pollutants using bias-prone approaches¹³, such as quantifying individual exposure from summary statistics, such as air pollution aggregated in statistical sectors or from low resolution models.

Limitations

Our study must also be interpreted with its limitations. First, the follow-up study included only 653 of 820 participants assessed at baseline (79.6%). It provided 80% power to detect a 1.1% change in r^2 attributable to the exposure variables on top of the covariables. In our study, the explained variance was only 0.01%. These null findings might not be applicable in patients who already progressed to dialysis or in patients at risk of CKD, for instance as a consequence of diabetes mellitus or severe hypertension. Second, of 653 participants 536 (82.1%) had their serum creatinine measured by different methods at baseline and follow-up. However, the annual decrease in eGFR was of a similar order of magnitude, as reported in other studies of predominantly healthy Caucasian people¹⁴. Third, as in other studies of chronic air pollution^{15,16}, assessment of renal function and collection of the air pollution data was not done at the same point in time. However, studies in the Netherlands¹⁷, Italy (Rome)¹⁸, the UK¹⁹ and Canada (Vancouver)²⁰ demonstrated that particulate air pollution was stable over a decade and that existing land use regression models predicted historic spatial contrast well.

Conclusions

Exposure to polluted air, in contrast to smoking, is unintentional and adversely affects health in multiple ways, and that prevention is of paramount importance, global efforts to improve air quality should continue. What our current study adds is that at current exposure levels in a semirural area of Flanders glomerular renal function is not associated with fine particulate matter in predominantly healthy people, representative of the general population.

METHODS

Study population

FLEMENGHO project started in 1985 and continued until 2004 with 78% initial participation rate. It complies with the Helsinki declaration for research on human subjects and was approved by the Ethics Committee of the University Hospitals of Leuven^{12,21}. From 2005 to 2009, we invited 1031 surviving participants, who still resided in the catchment area of the study (North Limburg, Belgium) and who had not been institutionalised. Of these, 828 renewed informed consent (participation rate, 80.3%). We excluded 8 participants, because their renal function had not been assessed. Of 820 participants examined at baseline, 653 took part in a follow-up assessment of their renal function on average 4.7 years (5th to 95th percentile, 3.7 – 5.4 years) later. Therefore, the number of participants available for the cross-sectional and longitudinal analyses totalled 820 and 653, respectively.

Biochemical measurements

Fasting blood samples were analysed for glucose and total and high-density lipoprotein (HDL) cholesterol, creatinine and γ -glutamyltransferase (biomarker of alcohol intake), using automated methods in a single certified laboratory. Diabetes mellitus was a fasting glucose exceeding 7.0 mmol/L (126 mg/dL) or use of antidiabetic agents. eGFR was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using age, sex and serum creatinine²² and CKD was staged following the National Kidney Foundation (KDOQI) guideline²³. The single laboratory involved in measuring the serum creatinine concentration in our study implemented the IDMS-traceable (isotope-dilution mass spectrometry) creatinine assay²⁴, starting from 18 December 2008. Of the baseline creatinine measurements 703 (85.7%) were done before this date. The remaining 117 baseline measurements and all 653 follow-up measurements were done after 18 December 2008. Participants collected a timed

24-h urine sample for the measurement of microalbumin and creatinine. Microalbuminuria was defined by an albumin-to-creatinine ratio of at least 3.5 mg/mmol in women or 2.5 mg/mmol in men²⁵. A single blood and urine sample were used to define CKD stage in the study as other landmark epidemiological research^{26,27}.

Ambient air pollution

Among all particulate matter that represents the sum of all solid and liquid particles in air²⁸, fine particulate matter (PM_{2.5}) has an aerodynamic diameter of less than 2.5 µm. Black carbon (BC) is a component of PM_{2.5}, consists of pure carbon in several bond forms, and finds its origin in the incomplete combustion of fossil fuels, biofuel or biomass.

In the current study, BC and PM_{2.5} exposure (µg/m³) were calculated using a high resolution spatiotemporal interpolation method²⁹ as described before³⁰. BC and PM_{2.5} data were collected from 2010 till 2014 using the same model^{17-20, 31}. The spatiotemporal explained variance was more than 74% for BC³² and 80% for PM_{2.5}³³.

Other measurements

Blood pressure was the average of five consecutive auscultatory readings obtained with a standard mercury sphygmomanometer. Hypertension was a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. The questionnaires including medical history, smoking, socioeconomic status and etc were obtained as described before³⁴.

Statistical analysis

For database management and statistical analysis, we used the SAS system, version 9.4 (SAS Institute Inc., Cary, NC). Means were compared using the large-sample z-test, ANOVA or the and proportions by Fisher's exact test. We normalised the distributions of

γ -glutamyltransferase and 24-h microalbuminuria by a logarithmic transformation. We rank normalised the distribution of BC and PM_{2.5} by sorting the measurements from the smallest to the largest and then applying the inverse cumulative normal function.

For the cross-sectional analysis, the association of renal function measures with air pollution was assessed by a generalised linear mixed model adjusting for residential clustering of participants (sharing the same address) as random effect and with adjustments applied for covariables of possible physiological relevance^{35,36}, socioeconomic status and different class of antihypertensive drugs. Diuretics included thiazides, loop diuretics and aldosterone antagonists; inhibitors of the renin-angiotensin system comprised β -blockers, angiotensin-converting enzyme inhibitors and angiotensin type-1 receptor antagonists; and vasodilators were calcium-channel blockers and α -blockers.

In longitudinal analyses of 653 participants, we accounted for baseline serum creatinine and baseline eGFR by calculating the percent change between the repeat and the first measurement of these biomarkers, while adjusting the mixed models for the aforementioned covariables measured at baseline. In sensitivity analyses, we stratified the participants according to age (<50, 50–64, ≥ 65 years). The McNemar test was used to analyse the changes in categorical variables. We performed multivariable-adjusted logistic regression analysis, using the covariables as mentioned above, to assess the association between incident CKD stage 3 or higher and air pollution.

The geographical associations between multivariable-adjusted eGFR or change in eGFR from baseline to follow-up and exposure to BC and PM_{2.5} were plotted in individual participants or aggregated per municipality over a map showing the contours of pollution. The midterm (2012) annual BC gradients were interpolated with high resolution, using a spatiotemporal method combined with a dispersion model¹².

Abbreviations

BC, Black carbon; FLEMENGHO, The Flemish Study on Environment, Genes and Health Outcomes; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKD, chronic kidney disease; eGFR, glomerular filtration rate.

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Authors' contribution

YF and JS designed the study, performed the analysis and drafted the manuscript; LT, ZZ, WY, FW, EB, BJ and TN collected the data and participated the analysis. All authors have read and approved the final manuscript.

Additional information

FLEMENGHO complies with the Helsinki declaration for research on human subjects and approved by the Ethics Committee of the University Hospitals of Leuven. Each subject agrees to participate and gave written informed consent to the study. All authors have read and approved the final manuscript.

Data are only available upon formal request to Dr. Ying-Mei Feng (yingmeif13@sina.com) and Dr. Jan A. Staessen (jan.staessen@kuleuven.be).

Competing interests

None declared.

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LEGEND TO FIGURES

Fig. 1: Geographical associations of the multivariable-adjusted percent change in the glomerular filtration rate estimated from serum creatinine (Δ eGFR) at the individual level (A) or aggregated per municipality (B) with black carbon air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlations between percent change in eGFR and exposure to BC was -0.016 ($P = 0.68$) and 0.200 ($P = 0.52$) in individual and aggregated data, respectively.

Fig. 2: Geographical associations of the multivariable-adjusted percent change in the glomerular filtration rate estimated from serum creatinine (Δ eGFR) at the individual level (A) or aggregated per municipality (B) with PM_{2.5} air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlations between percent change in eGFR and exposure to PM_{2.5} was -0.016 ($P = 0.69$) and -0.022 ($P = 0.94$) in individual and aggregated data, respectively.

Table 1. Baseline characteristics of participants by thirds of the black carbon distribution

Characteristic	0.74-1.07 µg/m ³	1.04–1.30 µg/m ³	1.15-1.95 µg/m ³	P
All in category	273	273	274	
Women (n [%])	139 (50.9)	138 (50.6)	139 (50.7)	>0.99
Smokers (n [%])	45 (16.5)	55 (20.2)	68 (24.8)	0.05
Hypertension (n [%])	112 (41.0)	113 (41.4)	116 (42.3)	0.95
Antihypertensive treatment (n [%])	70 (25.6)	67 (24.5)	74 (27.0)	0.80
Statins treatment (n [%])	40 (14.6)	32 (11.7)	34 (12.4)	0.56
Diabetes mellitus (n [%])	17 (6.2)	7 (2.6)	8 (2.9)	0.07
Microalbuminuria (n [%])	6 (2.3)	15 (5.8)	8 (3.1)	0.09
CKD, stage ≥ 3 (n [%])	29 (10.6)	24 (8.8)	26 (9.5)	0.77
Mean of characteristic				
Age (years)	51.4 (15.4)	51.3 (15.6)	50.8 (16.0)	0.90
Body mass index (kg/m ²)	26.7 (4.7)	26.3 (3.9)	26.6 (4.4)	0.63
Systolic pressure (mm Hg)	128.5 (17.6)	129.7 (16.9)	129.9 (17.9)	0.58
Diastolic pressure (mm Hg)	79.4 (9.9)	79.8 (9.0)	79.8 (9.7)	0.80
Mean arterial pressure (mm Hg)	95.7 (11.0)	96.5 (10.2)	96.5 (10.7)	0.63
Heart rate (beats per minute)	63.7 (9.9)	63.0 (9.4)	63.8 (9.9)	0.55
Biochemical data				
Serum creatinine (µmol/L)	86.2 (13.5)	86.4 (18.4)	86.8 (14.3)	0.91
eGFR (mL/min/1.73 m ²)	80.6 (16.1)	80.9 (15.9)	81.3 (17.2)	0.88
Total cholesterol (mmol/L)	5.18 (0.92)	5.37 (1.04)*	5.21 (0.94)	0.06
HDL cholesterol (mmol/L)	1.40 (0.33)	1.45 (0.37)	1.43 (0.35)	0.22
Total-to-HDL cholesterol ratio	3.89 (1.02)	3.90 (1.09)	3.81 (0.99)	0.50
Plasma glucose (mmol/L)	5.05 (1.16)	4.91 (0.55)*	4.87 (0.56)	0.03
γ-glutamyltransferase (units/L)	22 (10–63)	2 (11-95)	22 (10-64)	0.89
Air pollutant exposure				
Black carbon (µg/m ³)	0.99 (0.05)	1.12 (0.06)§	1.39 (0.22)§	<0.0001
PM _{2.5} (µg/m ³)	12.7 (0.27)	13.2 (0.34)§	14.5 (0.74)§	<0.0001

Abbreviations: CKD, chronic kidney disease; eGFR, glomerular filtration rate estimated from serum creatinine by the CKD-EPI formula; HDL, high-density lipoprotein. The black carbon distribution was stratified for sex and age (<50, 50-64, ≥65 years). Blood pressure was the average of five consecutive auscultatory readings. Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or use of antihypertensive drugs. Diabetes mellitus was a fasting glucose exceeding 7.0 mmol/L (126 mg/dL) or a non-fasting glucose exceeding 11.0 mmol/L (200 mg/dl), or use of antidiabetic agents. 24-h albuminuria was not available in 40 subjects. Means are arithmetic mean (SD) or median (5th to 5th percentile interval). *P*-values were derived by Fisher exact test, ANOVA or the Kruskal-Wallis test. Significance of the difference with the adjacent lower third: * *P* ≤ 0.05; § *P* ≤ 0.0001.

Table 2. Baseline characteristics of participants by thirds of the PM_{2.5} distribution

Characteristic	11.0-13.0 µg/m ³	12.9-13.9 µg/m ³	13.3-16.1 µg/m ³	P
All in category	273	273	274	
Women (n [%])	139 (50.9)	137 (50.2)	140 (51.1)	0.98
Smokers (n [%])	48 (17.6)	49 (18.0)	71 (25.9)*	0.03
Hypertension (n [%])	112 (41.0)	118 (43.2)	111 (40.5)	0.79
Antihypertensive treatment (n [%])	72 (26.4)	66 (24.2)	73 (26.6)	0.78
Statins treatment (n [%])	38 (13.9)	37 (13.6)	31 (11.3)	0.63
Diabetes mellitus (n [%])	17 (6.2)	7 (2.6)	8 (2.9)	0.07
Microalbuminuria (n [%])	7 (2.7)	13 (5.1)	9 (3.4)	0.34
CKD, stage ≥ 3 (n [%])	29 (10.6)	26 (9.5)	24 (8.8)	0.75
Mean of characteristic				
Age (years)	51.6 (15.4)	51.7 (15.5)	50.2 (16.1)	0.47
Body mass index (kg/m ²)	26.4 (4.3)	26.6 (4.4)	26.6 (4.4)	0.91
Systolic pressure (mm Hg)	128.2 (18.2)	130.7 (17.3)	129.2 (16.9)	0.26
Diastolic pressure (mm Hg)	79.2 (9.7)	80.0 (9.4)	79.9 (9.5)	0.56
Mean arterial pressure (mm Hg)	95.5 (11.1)	96.9 (10.6)	96.3 (10.2)	0.33
Heart rate (beats per minute)	63.5 (9.8)	63.0 (9.1)	64.0 (10.3)	0.46
Biochemical data				
Serum creatinine (µmol/L)	86.3 (13.4)	86.8 (19.3)	86.2 (13.0)	0.88
eGFR (mL/min/1.73 m ²)	80.3 (15.9)	80.5 (16.1)	81.9 (17.2)	0.44
Total cholesterol (mmol/L)	5.19 (0.94)	5.33 (1.01)	5.24 (0.96)	0.24
HDL cholesterol (mmol/L)	1.40 (0.33)	1.42 (0.38)	1.45 (0.34)	0.40
Total-to-HDL cholesterol ratio	3.86 (1.00)	3.95 (1.09)	3.78 (1.00)	0.17
Plasma glucose (mmol/L)	5.04 (1.11)	4.92 (0.63)	4.86 (0.58)	0.03
γ-glutamyltransferase (units/L)	22 (10-67)	21 (10-95)	22 (11-63)	0.56
Air pollutant exposure				
Black carbon (µg/m ³)	0.99 (0.06)	1.12 (0.07)§	1.39 (0.15)§	<0.0001
PM _{2.5} (µg/m ³)	12.7 (0.25)	13.2 (0.20)§	14.6 (0.70)§	<0.0001

Abbreviations: CKD, chronic kidney disease; eGFR, glomerular filtration rate estimated from serum creatinine by the CKD-EPI formula; HDL, high-density lipoprotein. The PM_{2.5} distribution was stratified for sex and age (<50, 50-64, ≥65 years). Blood pressure was the average of five consecutive auscultatory readings. Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or use of antihypertensive drugs. Diabetes mellitus was a fasting glucose exceeding 7.0 mmol/L (126 mg/dL) or a non-fasting glucose exceeding 11.0 mmol/L (200 mg/dl) or the use of antidiabetic agents. Baseline and/or follow-up 24-h albuminuria was not available in 88 subjects. Means are arithmetic mean (SD) or median (5th to 5th percentile interval). *P*-values were derived by Fisher exact test, ANOVA or the Kruskal-Wallis test. Significance of the difference with the adjacent lower third: * *P* ≤ 0.05; § *P* ≤ 0.0001.

Table 3. Multivariable-adjusted associations of renal function with exposure to black carbon and PM_{2.5}

Pollutant	Baseline only (n=820)		Follow-up only (n=653)		Baseline and follow-up (n=820)	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Black carbon						
Serum creatinine (μmol/L)	0.3 (−0.9, 1.6)	0.59	0.3 (−1.8, 2.4)	0.79	0.4 (−1.1, 1.8)	0.61
eGFR (mL/min/1.73 m ²)	−0.1 (−1.2, 1.1)	0.91	−0.4 (−1.8, 1.1)	0.62	−0.0 (−1.2, 1.1)	0.96
PM _{2.5}						
Serum creatinine (μmol/L)	0.2 (−1.1, 1.5)	0.74	0.1 (−2.0, 2.2)	0.93	0.3 (−1.2, 1.7)	0.72
eGFR (mL/min/1.73 m ²)	0.0 (−1.2, 1.2)	0.97	−0.3 (−1.8, 1.2)	0.70	0.0 (−1.1, 1.2)	0.97

Abbreviations: eGFR, glomerular filtration rate estimated from serum creatinine by the CKD-EPI formula. Associations accounted for clustering of data among participants living at the same address and were adjusted for sex, age (linear and squared term), mean arterial pressure, heart rate, body mass index, plasma glucose, total-to-HDL cholesterol ratio, γ-glutamyltransferase, smoking, socioeconomic class, and antihypertensive (by drug class). Association sizes are expressed for an interquartile range increment in the exposure variables. Baseline and follow-up were combined in mixed models using a random statement.

Table 4. Baseline and Follow-up Characteristics of 653 participants

Characteristic	Baseline 2005-2009	Follow-up 2009-2013	Change 95% CI
Number of subjects (%)			
Women	328 (50.2)	328 (50.2)	...
Smokers	124 (19.0)	98 (15.0)	-4.0 (-5.6, -2.3)§
Hypertension	268 (41.0)	335 (51.3)	10.3 (7.0, 13.5)§
Antihypertensive treatment	163 (25.0)	212 (32.5)	7.5 (5.1, 9.9)§
Diabetes mellitus	23 (3.5)	43 (6.6)	3.1 (1.7, 4.4)§
Microalbuminuria	17 (2.7)	24 (4.0)	1.3 (0.05, 2.6)*
CKD, stage ≥ 3	53 (8.2)	94 (14.4)	6.2 (4.1, 8.5)§
Mean of characteristic			
Age (years)	50.9 (14.7)	55.6 (14.6)	4.7 (4.7, 4.8)§
Body mass index (kg/m ²)	26.5 (4.4)	27.3 (4.4)	0.7 (0.6, 0.9)§
Office blood pressure (mmHg)			
Systolic pressure	128.7 (16.7)	132.2 (16.8)	3.5 (2.4, 4.6)§
Diastolic pressure	79.8 (9.4)	82.3 (9.7)	2.5 (1.8, 3.2)§
Mean arterial pressure	96.1 (10.3)	98.9 (10.1)	2.8 (2.1, 3.5)§
Heart rate (beats per minute)	62.7 (9.4)	62.2 (9.7)	-0.5 (-1.3, 0.3)
Biochemical data			
Serum creatinine (μ mol/L)	86.4 (15.5)	90.0 (22.7)	3.7 (2.6, 4.7)§
eGFR (ml/min/1.73 m ²)	80.9 (15.4)	79.0 (18.1)	-1.9 (-2.8, -1.0)§
Total cholesterol (mmol/l)	5.3 (0.96)	5.0 (0.95)	-0.25 (-0.32, -0.18)§
HDL-cholesterol (mmol/l)	1.43 (0.35)	1.45 (0.38)	0.02 (0.01, 0.04)*
Total-to-HDL cholesterol ratio	3.85 (1.01)	3.68 (1.24)	-0.15 (-0.32, 0.02)
Plasma glucose (mg/dl)	4.94 (0.83)	4.96 (0.79)	-0.00 (-0.08, 0.07)
γ -Glutamyltransferase (units/l)	23.3 (10-69)	24.7 (11-72)	3.7 (0.3, 7.2)*

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate derived from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration equation; HDL, high-density lipoprotein; UACR, urinary albumin-to-creatinine ratio. Reported values are number of participants (%), arithmetic means (\pm SD) or geometric means (5th to 95th percentile interval). UACR thresholds were 3.5 mg/mmol in women and 2.5 mg/mmol in men. Changes are given with 95% confidence interval (CI, in percent for categorical variables and for logarithmically transformed variables). Hypertension was a blood pressure of ≥ 140 mmHg systolic or ≥ 90 mm Hg diastolic or use of antihypertensive drugs. Diabetes mellitus was a self-reported diagnosis, a fasting glucose level of ≥ 126 or a non-fasting glucose exceeding 11.0 mmol/L (200 mg/dl) or the use of antidiabetic agents. Significance of the change: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P < 0.001$; § $P \leq 0.0001$.

Table 5. Multivariable-adjusted associations of percent changes in renal function with average annual exposure to black carbon and PM_{2.5}

Group analysed Outcome variable	Black carbon		PM _{2.5}	
	Estimate (95% CI)	P	Estimate (95% CI)	P
All (n=653)				
Serum creatinine	-0.3 (-2.0, 1.4)	0.72	-0.3 (-2.0, 1.4)	0.75
eGFR	-0.1 (-1.6, 1.4)	0.87	-0.1 (-1.6, 1.4)	0.92
<50 years (n=302)				
Serum creatinine	0.6 (-1.0, 2.2)	0.45	0.4 (-1.1, 2.0)	0.58
eGFR	-0.6 (-2.7, 1.5)	0.56	-0.5 (-2.6, 1.6)	0.66
50–64 years (n=229)				
Serum creatinine	0.3 (-4.2, 4.9)	0.89	0.7 (-3.9, 5.3)	0.77
eGFR	0.0 (-2.7, 2.8)	0.97	-0.1 (-2.9, 2.6)	0.92
≥65 years (n=122)				
Serum creatinine	-2.2 (-5.7, 1.2)	0.19	-2.2 (-5.6, 1.2)	0.19
eGFR	2.5 (-1.5, 6.5)	0.21	2.3 (-1.7, 6.3)	0.24

Abbreviations: eGFR, glomerular filtration rate estimated from serum creatinine by the CKD-EPI formula; ACR, urinary albumin-to-creatinine ratio. Changes were computed as the follow-up minus baseline values and expressed as percentage of the baseline values of the renal function indexes. Associations accounted for clustering of data among participants living at the same address and were adjusted for sex, age (linear and square term), mean arterial pressure, heart rate, body mass index, fasting plasma glucose, total-to-HDL cholesterol ratio, γ -glutamyltransferase, socioeconomic status, smoking and antihypertensive drug intake (by drug class). Association sizes are expressed for an interquartile range increment in the exposure variables.

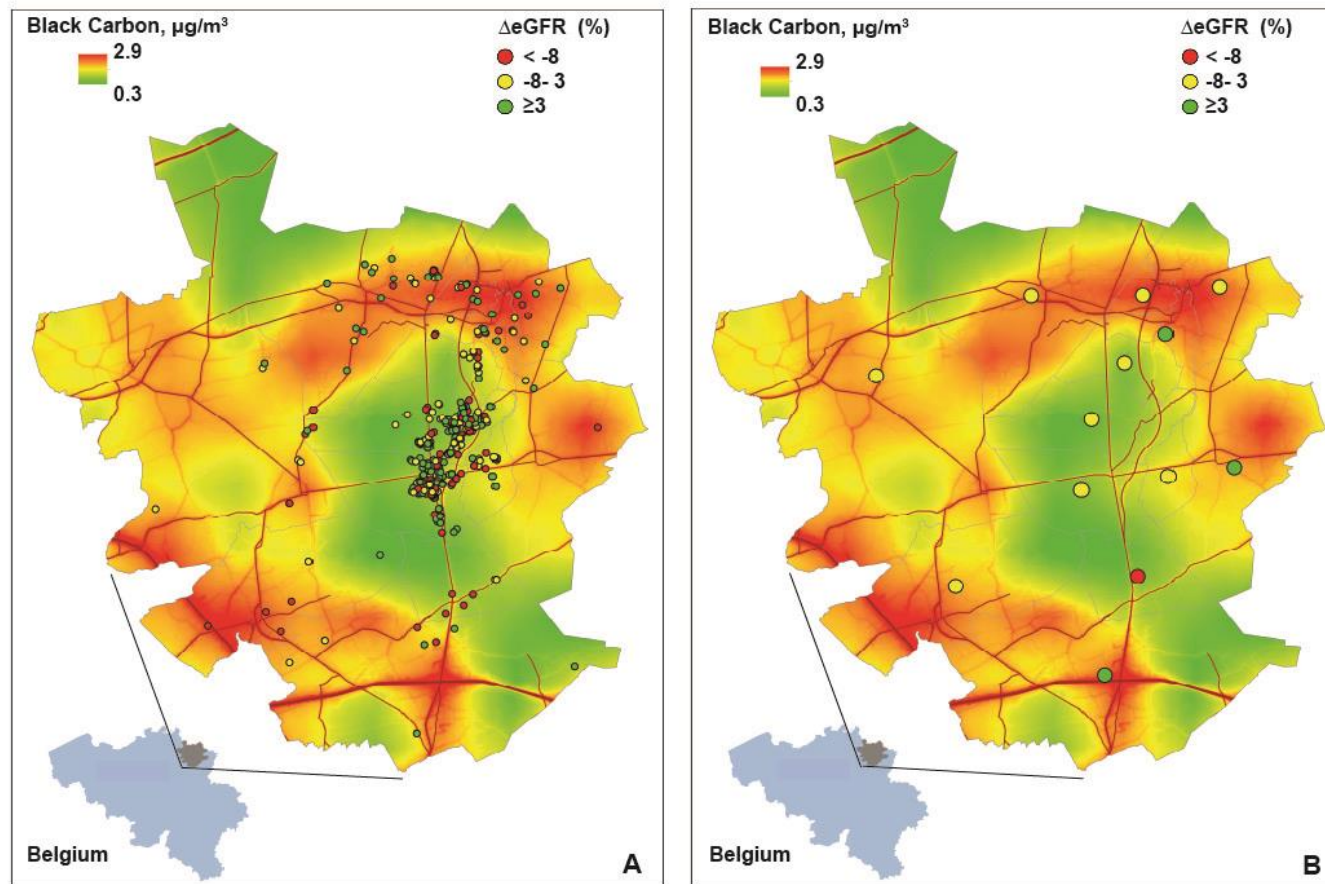


Fig. 1 Geographical associations of the multivariable-adjusted percent change in the glomerular filtration rate estimated from serum creatinine ($\Delta eGFR$) at the individual level (A) or aggregated per municipality (B) with black carbon air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlations between percent change in eGFR and exposure to BC was -0.016 ($P = 0.68$) and 0.20 ($P = 0.52$) in individual and aggregated data, respectively.

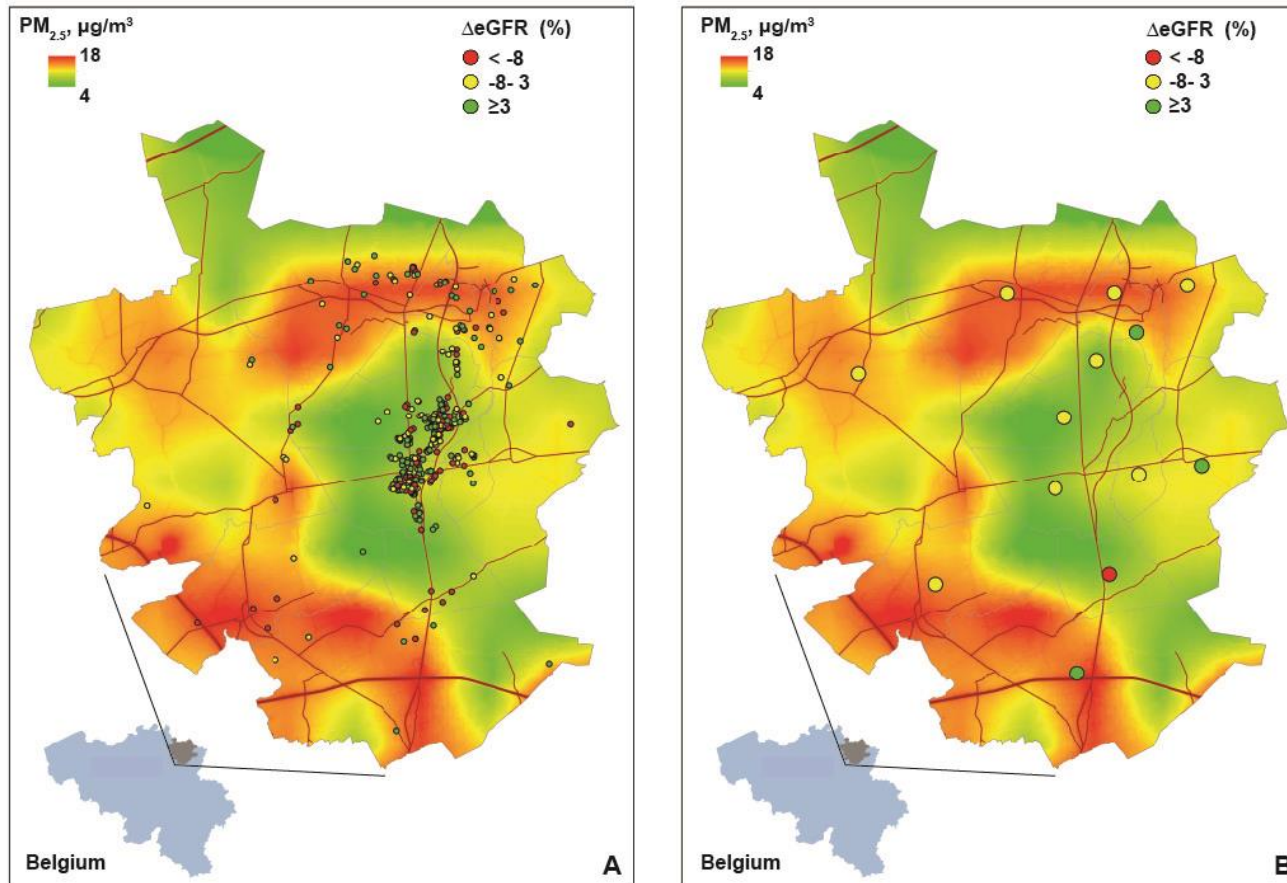


Fig. 2 Geographical associations of the multivariable-adjusted percent change in the glomerular filtration rate estimated from serum creatinine (Δ eGFR) at the individual level (A) or aggregated per municipality (B) with PM_{2.5} air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlations between percent change in eGFR and exposure to PM_{2.5} was -0.016 ($P = 0.69$) and -0.022 ($P = 0.94$) in individual and aggregated data, respectively.

Figures

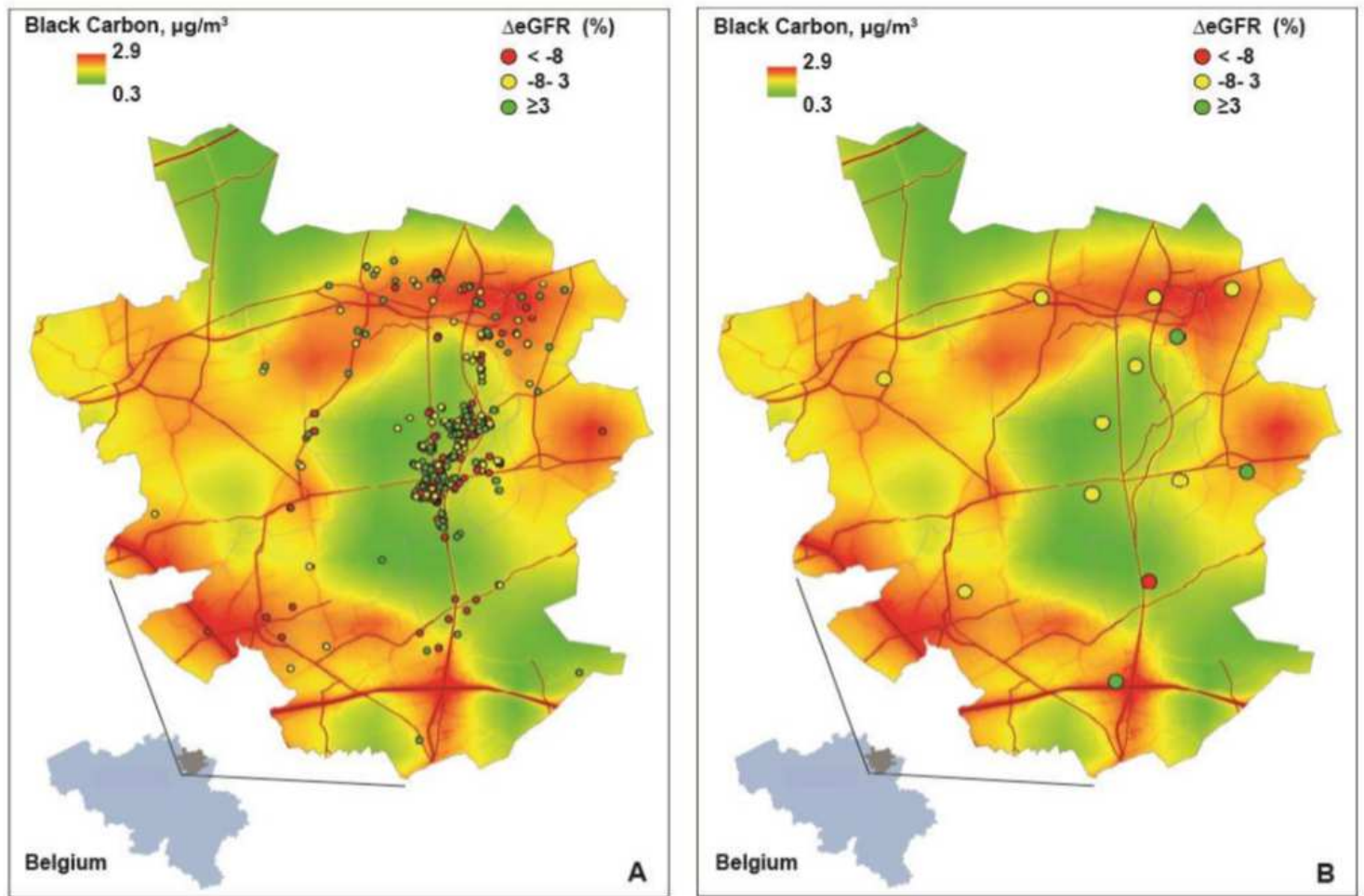


Figure 1

Geographical associations of the multivariable-adjusted percent change in the glomerular filtration rate estimated from serum creatinine (Δ eGFR) at the individual level (A) or aggregated per municipality (B) with black carbon air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlations between percent change in eGFR and exposure to BC was -0.016 ($P = 0.68$) and 0.20 ($P = 0.52$) in individual and aggregated data, respectively.

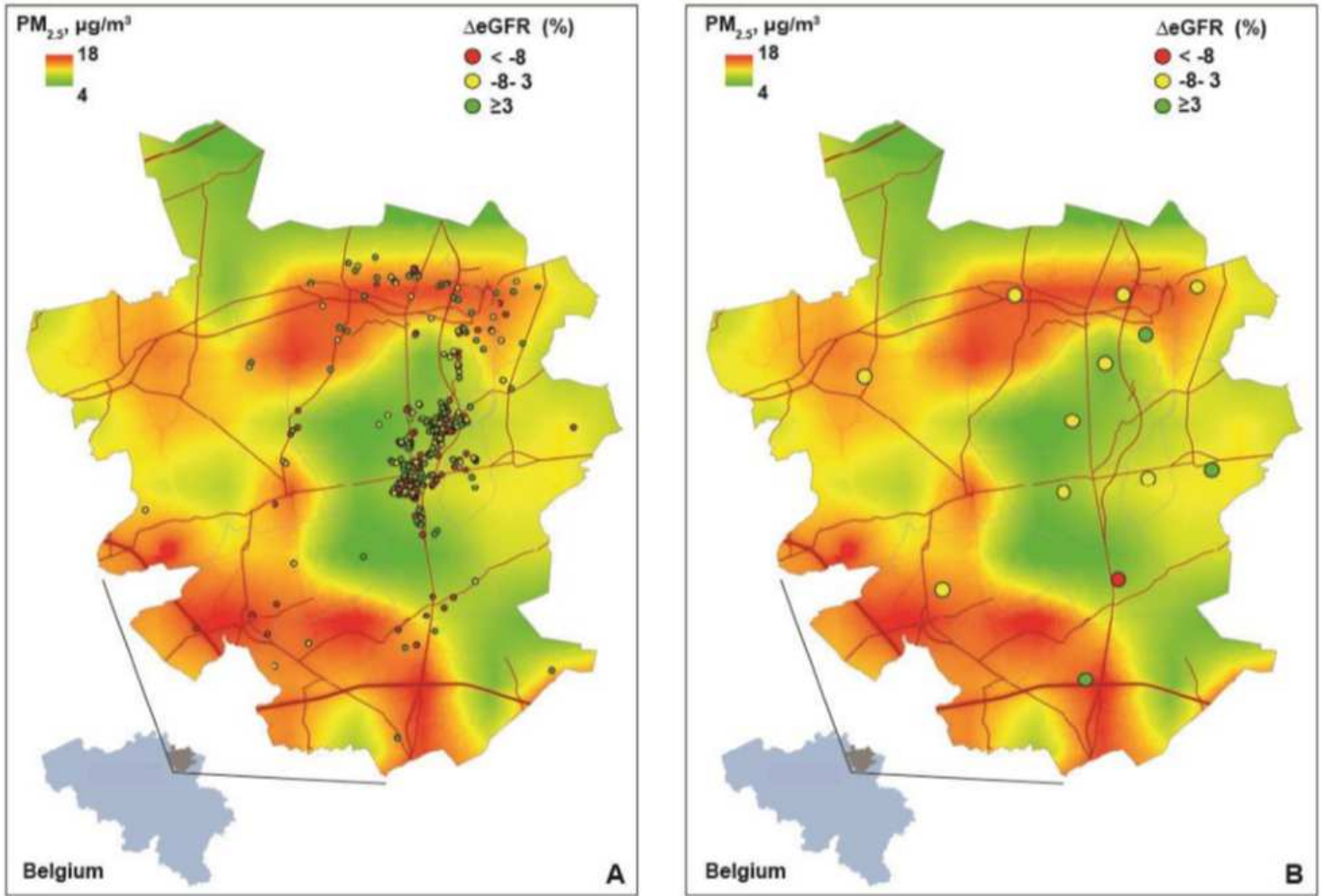


Figure 2

Geographical associations of the multivariable-adjusted percent change in the glomerular filtration rate estimated from serum creatinine ($\Delta eGFR$) at the individual level (A) or aggregated per municipality (B) with PM_{2.5} air pollution contours. Grey lines indicate borders of municipalities. Red lines represent the air pollution contours of major roads. The Spearman rank correlations between percent change in eGFR and exposure to PM_{2.5} was -0.016 ($P = 0.69$) and -0.022 ($P = 0.94$) in individual and aggregated data, respectively.