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Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: A cohort study

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Summary

Background Experimental evidence and preliminary clinical evidence suggest that environmental air pollution adversely effects kidney health. Previous work has examined the association between fine particulate matter and risk of kidney disease; however, the association between ambient coarse particulate matter (PM_{10}; ≤10 μm in aerodynamic diameter), nitrogen dioxide (NO_2), and carbon monoxide (CO) and risk of incident chronic kidney disease, chronic kidney disease progression, and end-stage renal disease is not clear.

Methods We merged multiple large databases, including those of the Environmental Protection Agency and the Department of Veterans Affairs, to build a cohort of US veterans, and used survival models to evaluate the association between PM_{10}, NO_2, and CO concentrations and risk of incident estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m², incident chronic kidney disease, eGFR decline of 30% or more, and end-stage renal disease. We treated exposure as time-varying when it was updated annually and as cohort participants moved.

Findings Between Oct 1, 2003, and Sept 30, 2012, 2 010 398 cohort participants were followed up over a median of 8·52 years (IQR 8·05–8·80). An increased risk of eGFR of less than 60 mL/min per 1·73 m² was associated with an IQR increase in concentrations of PM_{10} (hazard ratio 1·07, 95% CI 1·06–1·08), NO_2 (1·09, 1·08–1·10), and CO (1·09, 1·08–1·10). An increased risk of incident chronic kidney disease was associated with an IQR increase in concentrations of PM_{10} (1·07, 1·05–1·08), NO_2 (1·09, 1·08–1·11), and CO (1·10, 1·08–1·11). An increased risk of an eGFR decline of 30% or more was associated with an IQR increase in concentrations of PM_{10} (1·08, 1·07–1·09), NO_2 (1·12, 1·10–1·13), and CO (1·09, 1·08–1·10). An increased risk of end-stage renal disease was associated with an IQR increase in concentrations of PM_{10} (1·09, 1·06–1·12), NO_2 (1·09, 1·06–1·12), and CO (1·05, 1·02–1·08). Spline analyses suggested a monotonic increasing association between PM_{10}, NO_2, and CO concentrations and risk of kidney outcomes.

Interpretation Environmental exposure to higher concentrations of PM_{10}, NO_2, and CO is associated with increased risk of incident chronic kidney disease, eGFR decline, and end-stage renal disease.

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See **Comment** page e261

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Introduction

Experimental evidence and observations from several small clinical research studies suggest that exposure to higher amounts of air pollution adversely affects kidney function. Higher kidney disease mortality in coal mining regions of the Appalachian Mountains (USA) has been ascribed to environmental exposure to air pollutants.[1] Residential proximity to major roads, which in large part is an indirect measure of exposure to air pollutants (and other possible factors, including noise pollution), is associated with a reduced estimated glomerular filtration rate (eGFR).[2] In a large cohort of US veterans,[3] higher amounts of fine particulate matter were associated with increased risk of incident chronic kidney disease, eGFR decline, and end-stage renal disease.

Major air pollutants include fine particulate matter of smaller than 2·5 μm in aerodynamic diameter ($PM_{2·5}$), coarse particulate matter of smaller than 10 μm in aerodynamic diameter (PM_{10}), nitrogen dioxide (NO_2), carbon monoxide (CO), and others. Previous work has focused on the evaluation of the association between $PM_{2·5}$ and kidney disease outcomes.[3] Much less is known about the association of other major pollutants and the risk of development of kidney disease and kidney function decline.

Identification of specific air pollutants as potential drivers of adverse kidney outcomes might inform targeted mitigation strategies and will possibly contribute to the national and global discussion on the importance of curbing air pollution on health and disease. We aimed to investigate whether exposure to higher amounts of air pollutants, including PM_{10}, NO_2, and CO, is associated with increased risk of development and progression of kidney disease. To address this question, we built a national cohort of US veterans and followed up these veterans to examine the association between PM_{10}, NO_2, and CO and risk of incident eGFR of less than 60 mL/min per 1·73 m²,

Research in context

Evidence before this study

Experimental and epidemiological evidence suggests that environmental exposure to fine particulate matter smaller than 2·5 μm in aerodynamic diameter adversely effects kidney function. The associations between other major air pollutants, including ambient coarse particulate matter (PM_{10}), nitrogen dioxide (NO_2), and carbon monoxide (CO), and the risk of incident chronic kidney disease, chronic kidney disease progression, and end-stage renal disease have not been previously investigated.

Added value of this study

This Article provides evidence that higher concentrations of PM_{10}, NO_2, and CO are associated with increased risk of chronic kidney disease development, kidney function decline, and end-stage renal disease. The findings show a monotonic increasing association between exposure concentrations of PM_{10}, NO_2, and CO and risk of adverse kidney outcomes. The study also provides a quantitative assessment of the burden of incident kidney disease and incident end-stage renal disease attributable to PM_{10}, NO_2, and CO in the USA.

Implications of all the available evidence

The findings suggest that elevated concentrations of ambient PM_{10}, NO_2, and CO are important, yet unrecognised, environmental risk factors for kidney disease and its progression. The results will also inform estimates of the global burden of kidney disease attributable to air pollution, and serve to inform policy makers and the public about the hazards of specific pollutants on the kidneys. The findings might explain some of the geographical variation in the burden of kidney disease in the USA and globally. Since the burden of kidney disease of unknown origin is increasing in multiple geographies worldwide, especially those countries with significant air pollution from agricultural sources, this report might serve as a blueprint to investigate the contribution of air pollution to this rising—so far elusive—disease entity when identification of specific air pollutants as potential drivers of adverse kidney outcomes might inform targeted mitigation strategies.

incident chronic kidney disease, eGFR decline of 30% or more, and end-stage renal disease.

Methods

Study design and participants

For more on the **CDC CKD Surveillance Project** see http://www.cdc.gov/ckd

We selected users of the Veterans Affairs Health Care System from the US Department of Veterans Affairs' datasets. Participants were required to have at least one outpatient eGFR measurement between Oct 1, 2003, and Sept 30, 2004, and no previous history of end-stage renal disease; the date of the last eGFR measurement in this time period was designated as time zero (T_0; n=2 751 717). We further selected participants who had at least one outpatient eGFR measurement after T_0 (n=2 680 431), and followed up these participants until Sept 30, 2012, or death. We then limited participants to those individuals who at any timepoint during follow-up were within 48 km of an air monitoring station that measured at least one of the studied pollutants, yielding a final cohort of 2 010 398. The study was approved by the Institutional Review Board of the Veterans Affairs Saint Louis Health Care System, Saint Louis, MO, USA.

Data sources

For more on the **County Health Rankings' dataset** see http://www.countyhealthrankings.org/rankings/data

See Online for appendix

We used the Department of Veterans Affairs' datasets to procure participants' demographics, inpatient and outpatient data, laboratory information, vital signs, and prescriptions. We obtained zip code and county of residence at time of receipt of care from inpatient and outpatient encounter data. Data from the US Renal Database System (USRDS) were used to augment end-stage renal disease status information.[4–10] Environmental Protection Agency's (EPA) annual air quality data from 2003 to 2012, provided data on all pollutants and the latitude and longitude of the data's corresponding monitoring station collection points. National US estimates of the incident rates of chronic kidney disease were obtained from the CDC CKD Surveillance Project and treated end-stage renal disease were obtained from the 2016 USRDS Annual Data Report.[11] We obtained county-level data on metropolitan statistical areas (MSA), zip code centroid, population, population density, and poverty from the US Census Bureau. We used data from the 2014 County Health Rankings' dataset to obtain information on county-level variables.[12,13] A more detailed description of data sources is provided in the appendix.

For more on the **Environmental Protection Agency's annual air quality data** see http://www.epa.gov/ttn/airs/aqsdatamart

Exposure assessment

The primary predictor variables for analyses were annual mean concentrations of 24-h local condition particulate matter of 10 μm or smaller in aerodynamic diameter (μg/m³), 1-h observed NO_2 (parts per billion [ppb]), and 8-h running average CO (parts per million [ppm]). Participants were assigned exposure, as time-varying, on the basis of the nearest air monitoring station, within 48 km, to the centroid of the participant's zip code of residence. Air monitoring station measures were selected for inclusion in these analyses when they met EPA quality control conditions of completeness and certification, as appropriate. We assessed distance from the air monitoring station to the participant's residential zip code's centroid with the haversine formula. We assigned cohort participants' geographical location, which might have varied over time, on the basis that their zip code contained in outpatient or inpatient data closest, but before, a given timepoint. Pollutant exposure was updated as cohort participants moved, in which average annual exposure

was matched to their updated geographical locations at any specific time. In all primary analyses, unless otherwise indicated, measures correspond to an IQR increase in the pollutant.

Ascertainment of outcomes

Outcomes were comprised of the risk of incident eGFR of less than 60 mL/min per 1·73 m²; the risk of incident chronic kidney disease, with chronic kidney disease defined as two eGFR measurements less than 60 mL/min per 1·73 m² at least 90 days apart and time of event was set at the second eGFR measurement;[6] time until a decline of eGFR of 30% or more from eGFR at T_0; and time until end-stage renal disease.[14] Participants were censored following inception of end-stage renal disease, for all outcomes other than end-stage renal disease, and at time of death or end of study follow-up. We determined the date of first end-stage renal disease service (dialysis or kidney transplant) by linking the databases of the Department of Veterans Affairs and USRDS. Outpatient eGFR measurements were used in the evaluation of all outcomes except for end-stage renal disease, in which inpatient eGFR data were also used. We estimated eGFR using the four-variable abbreviated Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation on the basis of age, race, sex, and serum creatinine concentrations.[15]

Covariates

We based covariate selection on factors that could conceivably confound the association of air pollutants and kidney disease outcomes, and this assessment was informed by previous studies.[4,12,16–19] Baseline covariates were ascertained from Oct 1, 1999, until cohort entry (T_0). Covariates included age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidaemia, hypertension, T_0 eGFR, body-mass index, smoking status, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, number of outpatient eGFR measurements, number of hospital admissions, county population density, and percentage of the county in poverty. Details of covariate definitions are presented in the appendix. We treated covariates as continuous variables when relevant, unless otherwise indicated.

Statistical analysis

Demographic and clinical characteristics of the overall cohort are presented as frequency (percentage) for categorical variables, and as mean (SD) or median (IQR) for continuous variables. We present the distribution of pollutants in the cohort in 2004, and the IQRs were used in subsequent analyses. Age, race, sex, and eGFR-adjusted incidence of each adverse kidney outcome are presented by pollutant category, in which categories are defined as less than the 25th percentile for category 1, 25–75th percentile for category 2, and more than the 75th percentile for category 3. We used Cox proportional hazards survival models to assess the association between pollutants, as a time-varying exposure, and outcomes, and adjusted for covariates. We used a robust sandwich variance estimator to account for intra-county correlation. As the exposure definition was dependent on proximity to an air monitoring station, patients were not included in analyses at time t if, at time t, they were not within 48 km of an air monitoring station measuring the pollutant of interest; participants were included at all other times as appropriate. Additionally, we did analyses with exposure defined by pollutant category, as previously defined. Restricted cubic spline analyses were undertaken,[20] and we included distribution histograms of the pollutants in the background of these graphs (appendix). We analysed exposure to assess within-city effects in those participants who lived within 8 km of an air monitoring station, in which city was defined by MSA, using a within-city model with a city-wide mean parameter (for between-city effects) and a difference from city mean parameter (for within-city effects; appendix).[16] As a negative control,[21,22] we examined the association of sodium concentration, in which exposure was assigned in the same method as that of the primary pollutants of interest, with kidney disease outcomes, and also with mortality.

Population attributable fractions (PAFs) are presented as a measure of the proportion of the outcome in the population attributable to each air pollutant exposure above the theoretical minimum exposure risk level (TMREL), and a PAF was additionally calculated for the joint effect of the three pollutants to account for possible overlap in effect.[23,24] For all pollutants, we used the fifth percentile of the distribution of all air monitoring stations nationally in 2004, intended to be representative of a realistically obtainable low pollutant amount, as the TMREL, and any exposure amount under the TMREL was considered not to contribute any risk. We calculated PAF with the exposure distribution at T_0 (appendix). We calculated attributable burden of disease for incident eGFR of less than 60 mL/min per 1·73 m² and end-stage renal disease (appendix).[11,25]

We did not impute missing data. In analyses, a 95% CI of a hazard ratio (HR) that did not include unity was considered statistically significant. In all analyses, a p value of 0·05 or less was considered statistically significant. All statistical analyses were done using SAS Enterprise Guide version 7.1. To test the robustness of the study findings, we undertook a number of sensitivity analyses (appendix).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 1, 2003, and Sept 30, 2012, 2 010 398 cohort participants were followed up for a median of 8·52 years (IQR 8·05–8·80; figure 1). Overall, cohort participants were mostly white and male (table 1). In 2004, among those individuals in the cohort, the median concentration for PM_{10} was 20·45 μg/m³ (IQR 14·64–24·81), NO_2 was 14·54 ppb (9·69–17·91), and CO was 0·51 ppm (0·40–0·64). Adjusted incident rate of eGFR of 60 mL/min per 1·73 m², chronic kidney disease, eGFR decline of 30% or more, and end-stage renal disease gradually increased across ordinal categories of increasing PM_{10}, NO_2, and CO concentrations (figure 2, appendix).

In a cohort of participants who had no history of eGFR of less than 60 mL/min per 1·73 m² before time of cohort entry, an IQR increase in concentrations of PM_{10} (10·17 μg/m³), NO_2 (8·22 ppb), and CO (0·24 ppm) was associated with an increased risk of eGFR of less than 60 mL/min per 1·73 m² (table 2). Spline analyses suggested a monotonic increasing association between PM_{10}, NO_2, and CO concentrations and risk incident eGFR of less than 60 mL/min per 1·73 m² (figure 3). Because variation in regional characteristics might confound the association between environmental air pollutants and kidney disease, we developed analyses to estimate risk within a city (appendix). Results of the within-city models suggested that higher concentrations of PM_{10}, NO_2, and CO within the same MSA were associated with an increased risk of eGFR of less than 60 mL/min per 1·73 m² (table 3).

We assessed the risk of incident chronic kidney disease in a subcohort of participants with no less than two eGFR measurements separated by at least 90 days during follow-up and no history of eGFR less than 60 mL/min per 1·73 m² before time of cohort entry. The results were consistent with the results showing an increased risk of eGFR less than 60 mL/min in that an IQR increase in concentrations of PM_{10}, NO_2, and CO was associated with an increased risk of incident chronic kidney disease (table 2). Spline analyses showed a monotonic increasing association between concentrations of PM_{10}, NO_2, and CO and risk of incident chronic kidney disease (figure 3). Results of the within-city models suggested that higher concentrations of PM_{10}, NO_2, and CO within the same MSA were associated with an increased risk of incident chronic kidney disease (table 3).

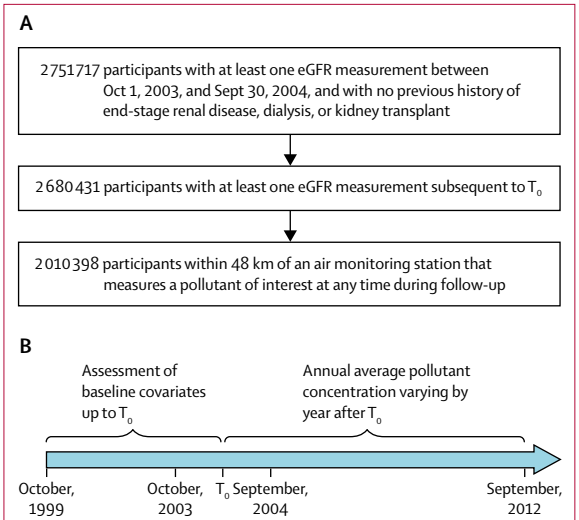

Figure 1: **Study design**
(A) Flow diagram of cohort participant inclusion. (B) Data assessment timeline. eGFR=estimated glomerular filtration rate. T_0=time zero.

	Overall cohort
Zip codes	22 098
Participants	2 010 398
Age (years)	62·15 (54·39–71·72)
Race	
White	1 623 247 (80·74%)
Black	315 025 (15·67%)
Other	72 126 (3·59%)
Sex	
Male	1 909 206 (94·97)
Female	101 192 (5·03%)
Cancer	235 223 (11·70%)
Cardiovascular disease	589 321 (29·31%)
Chronic lung disease	381 764 (18·99%)
Diabetes mellitus	559 470 (27·83%)
Hyperlipidaemia	1 134 687 (56·44%)
Hypertension	1 342 771 (66·79%)
Peripheral artery disease	52 968 (2·63%)
Smoking status	
Current	516 116 (25·67%)
Former	435 632 (21·67%)
Never	1 058 650 (52·66%)
Body-mass index	
Underweight	20 990 (1·04%)
Normal weight	399 402 (19·87%)
Overweight	791 783 (39·38%)
Obese	798 223 (39·70%)
ACEI or ARB use	936 555 (46·59%)
Follow-up time (years)	8·52 (8·05–8·80)
eGFR at T_0 (mL/min per 1·73 m²)	76·52 (20·06)
Number of outpatient eGFR measurements	
Before T_0	4 (2–7)
After T_0	13 (8–20)
Participants with one or more hospital admissions	338 857 (16·86%)
Percentage of county in poverty	12·7 (10·1–15·3)
Population density (per km²)	138·4 (44·1–447·1)

Data are n, median (IQR), n (%), or mean (SD). Covariates were measured at T_0, unless otherwise stated. ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin receptor blockers. eGFR=estimated glomerular filtration rate. T_0=time zero.

Table 1: **Characteristics of overall study cohort**

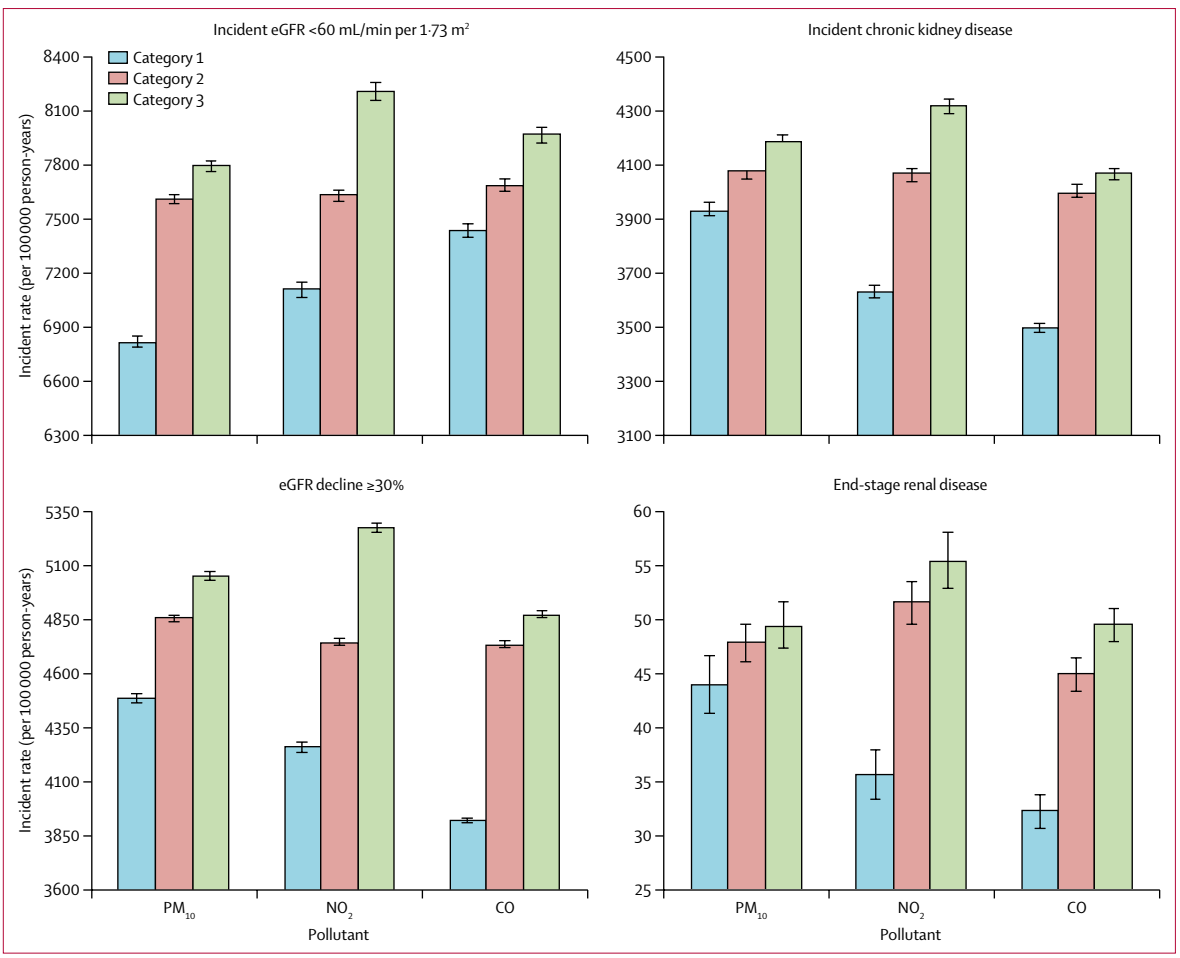

Figure 2: **Adjusted incident rates of kidney disease outcomes by pollutant category**
Adjusted for age, race, sex, and T_0 eGFR. Categories are defined by the cohort distribution in 2004: less than the 25th percentile is category 1, 25–75th percentile is category 2, and more than the 75th percentile is category 3. Error bars represent 95% CIs. T_0=time zero. eGFR=estimated glomerular filtration rate. CO=carbon monoxide. NO_2=nitrogen dioxide. PM_{10}=ambient course particulate matter (≤10 μm).

An IQR increase in PM_{10}, NO_2, and CO concentrations was associated with increased risk of eGFR decline of 30% or more (table 2). Spline analyses suggested a monotonic increasing association between PM_{10}, NO_2, and CO concentrations and risk of eGFR decline of 30% or more (figure 3). Risk estimates from within-city analyses showed an association of PM_{10}, NO_2, and CO with eGFR decline of 30% or more (table 3). The results were consistent in analyses considering the outcome of end-stage renal disease in that an IQR increase in concentrations of PM_{10}, NO_2, and CO was associated with an increased risk of end-stage renal disease (table 2). Spline functions depicted a consistent monotonic increasing association (figure 3). Risk estimates from within-city analyses showed an association of PM_{10}, NO_2, and CO with end-stage renal disease (table 3).

We considered exposure to ambient air sodium concentration as a negative control. No biological or clinical evidence supports an association between

	Incident eGFR <60 mL/min per 1·73 m²*	Incident chronic kidney disease†	eGFR decline ≥30%	End-stage renal disease
PM_{10}	673 230; 1·07 (1·06–1·08)	674 905; 1·07 (1·05–1·08)	964 688; 1·08 (1·07–1·09)	1 034 488; 1·09 (1·06–1·12)
NO_2	983 744; 1·09 (1·08–1·10)	958 051; 1·09 (1·08–1·11)	1 426 272; 1·12 (1·10–1·13)	1 452 755; 1·09 (1·06–1·12)
CO	1 029 175; 1·09 (1·08–1·10)	997 700; 1·10 (1·08–1·11)	1 490 023; 1·09 (1·08–1·10)	1 510 545; 1·05 (1·02–1·08)
Sodium	1 084 437; 0·99 (0·99–0·99)	1 053 333; 0·99 (0·98–0·99)	1 564 530; 0·99 (0·99–0·99)	1 588 470; 1·01 (1·00–1·01)

Data are n; hazard ratio (95% CI). Models are adjusted for baseline age, race, sex, T_0 eGFR, hypertension, diabetes, cancer, cardiovascular disease, chronic lung disease, body-mass index, smoking, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use, number of hospital admissions, number of eGFR measurements, county population density, and percentage of county in poverty. eGFR=estimated glomerular filtration rate. PM_{10}=ambient course particulate matter (≤10 μm). NO_2=nitrogen dioxide. CO=carbon monoxide. T_0=time zero. *Incident eGFR of less than 60 mL/min per 1·73 m² was evaluated in a subcohort of people with no previous history of eGFR less than 60 mL/min per 1·73 m² at the time of cohort entry. †Incident chronic kidney disease was evaluated in a subcohort of people with at least two eGFR measurements taken at least 90 days apart and who had no previous history of eGFR less than 60 mL/min per 1·73 m² at the time of cohort entry.

Table 2: **Risk of kidney disease outcomes for every IQR increase in air pollutant and sodium concentration**

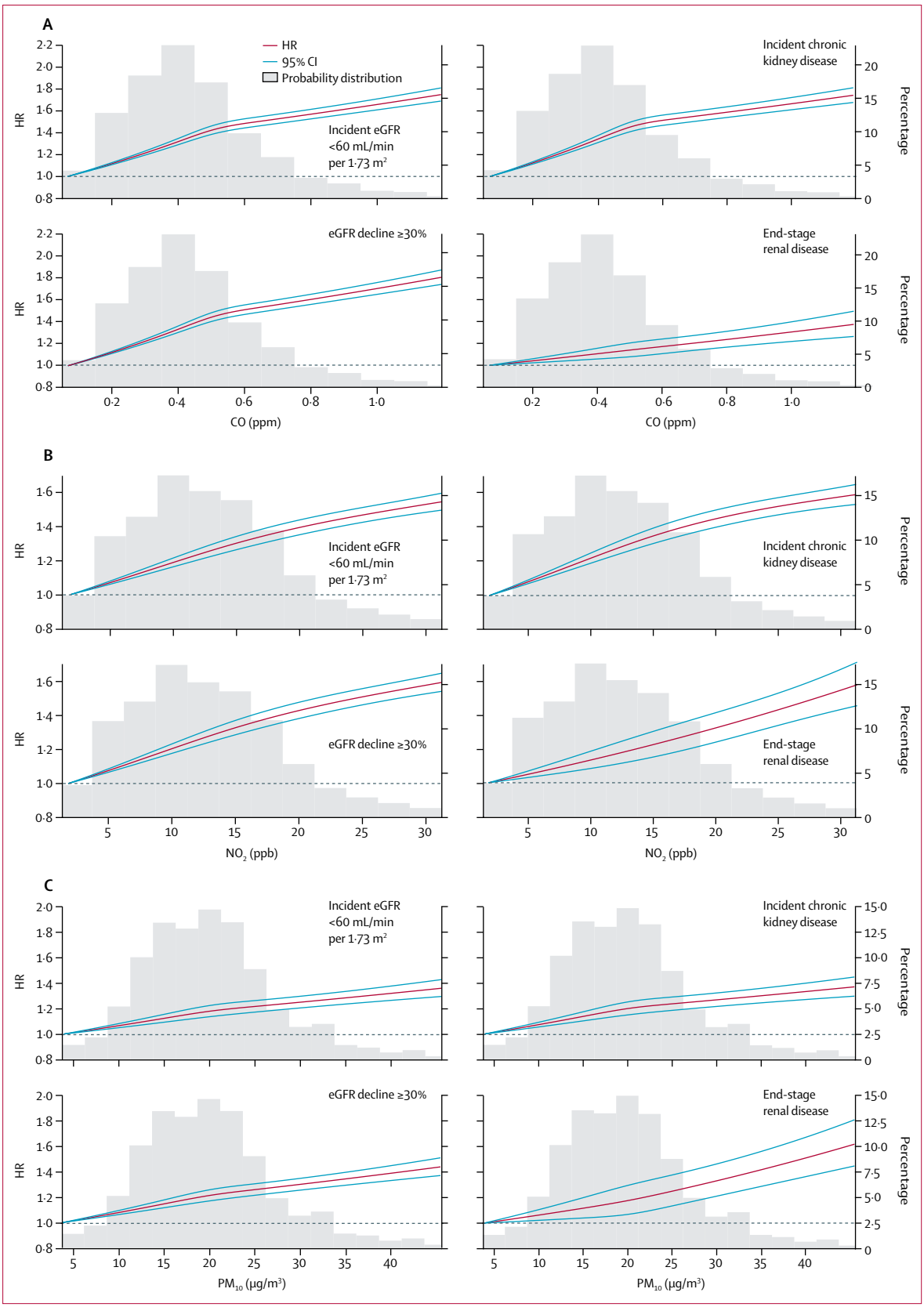

***Figure 3*: Spline analyses of risk of kidney outcomes by pollutant concentrations with pollutant probability distribution**

Models are adjusted for age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidaemia, hypertension, T_0 eGFR, body-mass index, smoking, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, county population density, number of outpatient eGFR measurements, number of hospital admissions, and percentage of the county in poverty for CO (A), NO_2 (B), and PM_{10} (C). The minimum pollutant concentration included in analyses served as the referent value. T_0=time zero. eGFR=estimated glomerular filtration rate. CO=carbon monoxide. ppm=parts per million. NO_2=nitrogen dioxide. ppb=parts per billion. PM_{10}=ambient course particulate matter (≤10 μm). HR=hazard ratio.

different sodium concentrations in the air and risk of adverse kidney outcomes; thus, ambient air sodium is a suitable negative control.[22] We therefore tested the association between ambient air sodium concentrations and the risk of kidney outcomes, and the results indicated no significant association (table 2). Air sodium concentrations were not associated with the risk of death (HR 1·00, 95% CI 1·00–1·01).

PAF represents the proportional reduction in population disease that would occur if exposure to pollutants was reduced to the TMREL. The PAFs of PM_{10}, NO_2, and CO considered separately for each kidney disease outcome are provided in table 4. In analyses in which the pollutants were considered jointly, the PAF for each kidney disease outcome exceeded that of any one pollutant alone (table 4).

The national burden of kidney disease attributable to concentrations of PM_{10} exceeding the TMREL in the contiguous USA was 340757·4 incident cases (95% CI 283964·5–397550·2) of eGFR less than 60 mL/min per 1·73 m² per year and 15223·7 incident cases (9674·8–20772·7) of end-stage renal disease per year. The national burden of kidney disease attributable to excess NO_2 was 366297·3 incident cases (321266·3–414688·9) of eGFR less than 60 mL/min per 1·73 m² per year and 12796·1 incident cases (8490·9–17 101·3) of end-stage renal disease per year. Our estimate of the national burden of kidney disease attributable to excess CO was 349494·7 incident cases (308160·2–390829·2) of eGFR less than 60 mL/min per 1·73 m² per year and 7091·7 incident cases (6613·3–7330·8) of end-stage renal disease per year. When considered jointly, the national burden of kidney disease attributable to PM_{10}, NO_2, and CO was 765863·9 incident cases (656982·9–875081·0) of eGFR less than 60 mL/min per 1·73 m² per year and 29227·7 incident cases (19899·7–38855·7) of end-stage renal disease per year.

To test the sensitivity of our results, we did the following sensitivity analyses. We considered exposure in ordinal categories. We observed a graded association in that the risk was increased with increasing ordinal category; compared with the lowest category, the highest category of PM_{10}, NO_2, and CO was associated with increased risk of kidney outcomes (appendix). To test different spatial resolutions for exposure definition, exposure levels were assigned by nearest air monitoring station within 8 km and 16 km (appendix); the results were consistent in that an IQR increase in exposure to pollutants (PM_{10}, NO_2, and CO) was associated with significant increased risk of kidney outcomes. To account for local conditions that might confound the association of PM_{10}, NO_2, and CO and risk of kidney outcomes,[12] we also did analyses in which we controlled for several US county-level characteristics (in several domains capturing health outcomes, health behaviours, clinical care, social and economic factors, physical environment, and demographics) obtained from the County Health Ranking's dataset (appendix),[13] and results were consistent in that an IQR increase in exposure to pollutants was associated with an increased risk of kidney outcomes. We then considered additional kidney outcomes of doubling of serum creatinine concentrations and the composite outcome of end-stage renal disease or eGFR decline of 50% or more, and the results were consistent (appendix).

We examined the association of PM_{10}, NO_2, and CO and risk of death. This analysis served as a positive control in which a-priori observations suggested that an association is expected.[25,26] Our results showed a significant association between PM_{10}, NO_2, and CO concentrations and risk of death (appendix). Results of sensitivity analyses for the competing risk of death were consistent with those shown in primary analyses[27] (appendix).

	Incident eGFR <60 mL/min per 1·73 m²*	Incident chronic kidney disease†	eGFR decline ≥30%	End-stage renal disease
PM_{10}				
Sample size	589691	593101	844356	912032
Between-city difference	1·44 (1·34–1·54)	1·32 (1·21–1·44)	1·40 (1·30–1·50)	1·62 (1·36–1·94)
Within-city difference	1·06 (1·05–1·08)	1·06 (1·05–1·08)	1·07 (1·06–1·08)	1·09 (1·05–1·12)
NO_2				
Sample size	932504	907188	1351258	1375128
Between-city difference	1·29 (1·24–1·34)	1·32 (1·26–1·39)	1·31 (1·25–1·36)	1·28 (1·16–1·42)
Within-city difference	1·07 (1·06–1·08)	1·07 (1·05–1·09)	1·10 (1·08–1·11)	1·06 (1·03–1·10)
CO				
Sample size	985200	954656	1426391	1445056
Between-city difference	1·10 (1·09–1·11)	1·11 (1·09–1·12)	1·10 (1·09–1·11)	1·05 (1·02–1·08)
Within-city difference	1·09 (1·08–1·10)	1·10 (1·08–1·11)	1·09 (1·08–1·10)	1·04 (1·02–1·07)

Data are n or hazard ratio (95% CI). Models are adjusted for baseline age, race, sex, T_0 eGFR, hypertension, diabetes, cancer, cardiovascular disease, chronic lung disease, body-mass index, smoking, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use, number of hospital admissions, number of eGFR measurements, county population density, and percentage of county in poverty. eGFR=estimated glomerular filtration rate. PM_{10}=ambient course particulate matter (≤10 μm). NO_2=nitrogen dioxide. CO=carbon monoxide. T_0=time zero. *Incident eGFR of less than 60 mL/min per 1·73 m² was evaluated in a subcohort of people with no previous history of eGFR less than 60 mL/min per 1·73 m² at the time of cohort entry. †Incident chronic kidney disease was evaluated in a subcohort of people with at least two eGFR measurements taken at least 90 days apart and who had no previous history of eGFR less than 60 mL/min per 1·73 m² at the time of cohort entry.

Table 3: **Risk of kidney outcomes for every IQR increase in pollutant concentration for between-city and within-city analyses**

Discussion

In this study, we aimed to characterise the association between ambient concentrations of PM_{10}, NO_2, and CO and risk of incident chronic kidney disease, eGFR decline of 30% or more, and end-stage renal disease. The results suggest a consistent graded and monotonically increasing association in which exposure to higher concentrations of these pollutants is associated with increased risk of development of kidney disease and progression to end-stage renal disease. The results were consistent across a range of kidney outcomes, and were robust to challenges

	Theoretical minimum risk exposure concentration	Incident eGFR <60 mL/min per 1·73 m² (%)*	Incident chronic kidney disease (%)†	eGFR decline ≥30% (%)	End-stage renal disease (%)
PM_{10}	4·56 μg/m³	10·14 (8·45–11·83)	9·97 (7·96–11·98)	11·62 (9·88–13·36)	12·73 (8·09–17·37)
NO_2	3·09 ppb	10·90 (9·56–12·34)	10·99 (9·25–12·73)	13·70 (12·22–15·19)	10·70 (7·10–14·30)
CO	0·18 ppm	10·40 (9·17–11·63)	11·37 (9·83–12·91)	10·68 (9·43–11·93)	5·93 (5·53–6·13)
Joint effect‡	PM_{10} 4·56 μg/m³, NO_2 3·09 ppb, and CO 0·18 ppm	265 206; 22·79 (19·55–26·04)	253 095; 23·91 (20·10–27·71)	381 379; 23·94 (20·62–27·26)	381 379; 24·44 (16·64–32·24)

Data are HR (95% CI) or n; HR (95% CI). Models are adjusted for baseline age, race, sex, T_0 eGFR, hypertension, diabetes, cancer, cardiovascular disease, chronic lung disease, body-mass index, smoking, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use, number of hospital admissions, number of eGFR measurements, county population density, and percentage of county in poverty. eGFR=estimated glomerular filtration rate. PM_{10}=ambient course particulate matter (≤10 μm). NO_2=nitrogen dioxide. ppb=parts per billion. CO=carbon monoxide. ppm=parts per million. HR=hazard ratio. T_0=time zero. *Incident eGFR of less than 60 mL/min per 1·73 m² was evaluated in a subcohort of people with no previous history of eGFR less than 60 mL/min per 1·73 m² at the time of cohort entry. †Incident chronic kidney disease was evaluated in a subcohort of people with at least two eGFR measurements taken at least 90 days apart and who had no previous history of eGFR less than 60 mL/min per 1·73 m² at the time of cohort entry. ‡Done in participants who were within 48 km of stations measuring the three pollutants.

Table 4: **Population attributable fraction for kidney outcomes by air pollutant**

in sensitivity analyses, including analyses which considered exposure in ordinal categories, varying spatial resolution for exposure definition, and—to account for potential regional variation—within-city estimates. Our analytic strategies also included testing a negative control, which showed that ambient air sodium concentrations (routinely collected by air monitoring stations) were not associated with higher risk of adverse kidney outcomes. Taken together, the findings suggest that environmental exposure to elevated concentrations of PM_{10}, NO_2, and CO is a novel risk factor for the development and progression of kidney disease.

Few experimental and clinical studies[1,2,12,28–36] have examined the effect of environmental air pollution on the kidney. Air pollution has been cited as a potential explanation of the geographical variation in burden of kidney disease in the USA, Europe, and globally.[12,34–36] We previously observed clusters of geographical areas in the USA with high prevalence for increased odds of rapid eGFR decline that were not explained by traditional drivers, including diabetes mellitus and hypertension. Our report on the association between specific air pollutants (PM_{10}, NO_2, and CO) and risk of kidney outcomes might explain some of these geographical disparities in the USA, can inform targeted mitigation strategies, and, most importantly, contributes to the broader national and global discussion on the hazardous effect of air pollution on kidney health.

We used the Global Burden of Disease methodologies and developed analyses to estimate the national burden of disease attributable to excess concentrations of environmental air pollutants including PM_{10}, NO_2, and CO.[23,25,37,38] The findings provide a quantitative assessment—to inform the public and policy makers—of the potential reduction in the burden of kidney disease that is likely to be achievable with targeted reduction of specific environmental pollutants. These estimates might also inform global estimates of the burden of kidney disease attributable to excess concentrations of PM_{10}, NO_2, and CO.

The biological mechanism or mechanisms underpinning the reported associations is not entirely clear. Several hypotheses have been proposed to explain the extrapulmonary effects of air pollution. One hypothesis suggests that inhaled pollutants might lead to pulmonary inflammation, which could then trigger systemic inflammation. The second hypothesis posits that pollutants might provoke the lung autonomic nervous system. The third (and most widely accepted) hypothesis postulates that air pollutants might traverse the alveolar space and enter the bloodstream where they can produce an untoward effect on remote organs.[31,39–51]

Our study has a number of limitations. Our cohort included US veterans who were mostly older, white men; therefore, the findings might not be generalisable to other populations. We accounted for known confounders, but cannot exclude the possibility of residual confounding (either unmeasured or unknown). Our datasets did not contain information on time spent in traffic or outdoors, which can result in misclassification of exposure.

The study has a number of strengths. We built a large national cohort of US veterans (17 128 591 person-years) who are recipients of care in a single integrated network of health-care systems. Our analytic strategies included the use of time-varying exposure (to reflect changes in concentrations of exposure with time and as participants moved from one area to another). We evaluated a range of well defined chronic kidney outcomes across the continuum of the chronic kidney disease evolution spectrum, including the development of chronic kidney disease (incident eGFR <60 mL/min per 1·73 m² and incident chronic kidney disease), chronic kidney disease progression (eGFR decline >30%), and the terminal outcome of end-stage renal disease. We tested the robustness of the results in multiple sensitivity analyses including within-city analyses, which reduces concern about confounding due to variation in regional characteristics. Finally, we applied both a positive control

and a negative control. In summary, our results show a significant association between concentrations of PM_{10}, NO_2, and CO and risk of development of kidney disease, and its progression to end-stage renal disease. The national burden of kidney disease attributable to these pollutants is not trivial and an effort to improve air quality might alleviate the burden of kidney disease in the USA and globally.

Contributors

All authors researched and designed the study and analysed and interpreted the data. BB and YX acquired and statistically analysed the data. ZA-A provided supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work were appropriately investigated and resolved. ZA-A takes responsibility that this study has been reported honestly, accurately, and transparently, and that no important aspects of the study have been omitted.

Declaration of interests

We declare no competing interests.

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