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

Benjamin Bowe, Yan Xie, Tingting Li, Yan Yan, Hong Xian, Ziyad Al-Aly

Summary

Background  Experimental evidence and preliminary clinical evidence suggest that environmental air pollution adversely affects 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$_{2.5}$; $\leq 10 \mu m$ 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$_{2.5}$, NO$_2$, and CO concentrations and risk of incident estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m$^2$, 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, 2010 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 m$^2$ was associated with an IQR increase in concentrations of PM$_{2.5}$ (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$_{2.5}$ (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$_{2.5}$ (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$_{2.5}$ (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$_{2.5}$, NO$_2$, and CO concentrations and risk of kidney outcomes.

Interpretation  Environmental exposure to higher concentrations of PM$_{2.5}$, NO$_2$, and CO is associated with increased risk of incident chronic kidney disease, eGFR decline, and end-stage renal disease.

Funding  US Department of Veterans Affairs.

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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.\(^4\) 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$_{2.5}$, 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$_{2.5}$, NO$_2$, and CO and risk of incident eGFR of less than 60 mL/min per 1.73 m$^2$,...
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 affects kidney function. The associations between other major air pollutants, including ambient coarse particulate matter (PM10), nitrogen dioxide (NO2), 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 PM10, NO2, 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 PM10, NO2, 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 PM10, NO2, and CO in the USA.

Methods

Study design and participants
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 (T0). We further selected participants who had at least one outpatient eGFR measurement after T0 (n=2680431), 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 2010398. The study was approved by the Institutional Review Board of the Veterans Affairs Saint Louis Health Care System, Saint Louis, MO, USA.

Data sources
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.4·9·10 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.

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, (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; time until a decline of eGFR of 30% or more from eGFR at Tₚ; and time until end-stage renal disease. 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) 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) in subsequent analyses. Age, race, sex, and eGFR concentrations. 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.

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. Baseline covariates were ascertained from Oct 1, 1999, until cohort entry (T₀). Covariates included age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidaemia, hypertension, Tₚ 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, 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). As a negative control, 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. 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 Tₚ (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).

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, 2010 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/m$^3$ (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 less than 60 mL/min per 1·73 m$^2$ 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).

In a cohort of participants who had no history of eGFR of less than 60 mL/min per 1·73 m$^2$ before time of cohort entry, an IQR increase in concentrations of PM$_{10}$ (10·17 μg/m$^3$), 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 m$^2$ 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).

Table 1: Characteristics of overall study cohort

<table>
<thead>
<tr>
<th>Overall cohort</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zip codes</td>
<td>22 098</td>
</tr>
<tr>
<td>Participants</td>
<td>2 010 398</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62·15 (54·39–71·72)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1 623 247 (80·74%)</td>
</tr>
<tr>
<td>Black</td>
<td>335 025 (16·67%)</td>
</tr>
<tr>
<td>Other</td>
<td>71 212 (3·59%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 909 206 (94·97)</td>
</tr>
<tr>
<td>Female</td>
<td>101 192 (5·03%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>516 116 (75·67%)</td>
</tr>
<tr>
<td>Former</td>
<td>435 632 (21·67%)</td>
</tr>
<tr>
<td>Never</td>
<td>1 058 650 (52·66%)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>20 990 (1·04%)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>399 402 (19·87%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>791 783 (39·38%)</td>
</tr>
<tr>
<td>Obese</td>
<td>798 223 (39·70%)</td>
</tr>
<tr>
<td>AACEI or ARB use</td>
<td></td>
</tr>
<tr>
<td>936 555 (46·59%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>8·52 (8·05–8·80)</td>
</tr>
<tr>
<td>eGFR at T$_{0}$ (mL/min per 1·73 m$^2$)</td>
<td>76·52 (20·06)</td>
</tr>
<tr>
<td>Number of outpatient eGFR measurements</td>
<td></td>
</tr>
<tr>
<td>Before T$_{0}$</td>
<td>4 (2–7)</td>
</tr>
<tr>
<td>After T$_{0}$</td>
<td>13 (8–20)</td>
</tr>
<tr>
<td>Participants with one or more hospital admissions</td>
<td>338 857 (16·86%)</td>
</tr>
<tr>
<td>Percentage of county in poverty</td>
<td>12·7 (10·1–15·3)</td>
</tr>
<tr>
<td>Population density (per km$^2$)</td>
<td>13·84 (4·4–44·1)</td>
</tr>
</tbody>
</table>

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.
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

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).

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

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Incident eGFR &lt;60 mL/min per 1·73 m$^2$</th>
<th>Incident chronic kidney disease†</th>
<th>eGFR decline ≥30%</th>
<th>End-stage renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{10}$</td>
<td>673 230; 1·07 (1·06–1·08)</td>
<td>674 905; 1·07 (1·05–1·08)</td>
<td>964 688; 1·08 (1·07–1·09)</td>
<td>1 034 188; 1·09 (1·06–1·12)</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>983 744; 1·09 (1·08–1·10)</td>
<td>958 051; 1·09 (1·08–1·11)</td>
<td>1 426 272; 1·12 (1·10–1·13)</td>
<td>1 452 275; 1·09 (1·06–1·12)</td>
</tr>
<tr>
<td>CO</td>
<td>1 029 175; 1·09 (1·08–1·10)</td>
<td>979 700; 1·10 (1·08–1·11)</td>
<td>1 490 023; 1·09 (1·08–1·10)</td>
<td>1 510 545; 1·05 (1·02–1·08)</td>
</tr>
<tr>
<td>Sodium</td>
<td>1 084; 0·99 (0·99–0·99)</td>
<td>1 053 333; 0·99 (0·98–0·99)</td>
<td>1 564 530; 0·99 (0·99–0·99)</td>
<td>1 588 470; 1·01 (1·00–1·01)</td>
</tr>
</tbody>
</table>

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 m$^2$ was evaluated in a subcohort of people with no previous history of eGFR less than 60 mL/min per 1·73 m$^2$ 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 m$^2$ 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, T0 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), NO₂ (B), and PM₁₀ (C). The minimum pollutant concentration included in analyses served as the referent value. T₀=time zero. eGFR=estimated glomerular filtration rate. CO=carbon monoxide. ppm=parts per million. NO₂=nitrogen dioxide. ppb=parts per billion. PM₁₀=ambient coarse 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.\(^2\) 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\(_{\text{10}}\), 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\(_{\text{10}}\) exceeding the TMREL in the contiguous USA was 340,757·4 incident cases (95% CI 283,964–397,550–2) of eGFR less than 60 mL/min per 1·73 m\(^2\) per year and 15,223·7 incident cases (967·8–20,772·7) of end-stage renal disease per year. The national burden of kidney disease attributable to excess NO\(_2\) was 366,297·3 incident cases (321,266·3–3,416,688·9) of eGFR less than 60 mL/min per 1·73 m\(^2\) per year and 12,796·1 incident cases (8,490·9–101·3) of end-stage renal disease per year. Our estimate of the national burden of kidney disease attributable to excess CO was 349,494·7 incident cases (308,160·2–390,829·2) of eGFR less than 60 mL/min per 1·73 m\(^2\) per year and 7,091·7 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\(_{\text{10}}\), NO\(_2\), and CO was 765,863·9 incident cases (656,982·9–875,081·0) of eGFR less than 60 mL/min per 1·73 m\(^2\) per year and 29,227·7 incident cases (19,899·7–38,855·7) 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 of kidney outcomes,\(^1\) 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),\(^1\) 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\(_{\text{10}}\), 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.\(^2\)\(^6\)\(^7\) Our results showed a significant association between PM\(_{\text{10}}\), 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\(^1\) (appendix).

### Discussion

In this study, we aimed to characterise the association between ambient concentrations of PM\(_{\text{10}}\), 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...
Articles

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\textsubscript{2.5}, NO\textsubscript{2}, and CO is a novel risk factor for the development and progression of kidney disease.

Few experimental and clinical studies\textsuperscript{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.\textsuperscript{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\textsubscript{2.5}, NO\textsubscript{2}, and CO) and risk of kidney outcomes might explain some of these geographical disparities. Finally, we applied both a positive control and a negative control, which showed that ambient air sodium concentrations were not associated with higher risk of adverse kidney outcomes. Taken together, the findings suggest that environmental exposure to elevated concentrations of PM\textsubscript{2.5}, NO\textsubscript{2}, and CO is a novel risk factor for the development and progression of kidney disease.

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

<table>
<thead>
<tr>
<th>Theoretical minimum risk exposure concentration</th>
<th>Incident eGFR &lt;60 mL/min per 1·73 m\textsuperscript{2} (%)</th>
<th>Incident chronic kidney disease (%)</th>
<th>eGFR decline ≥30% (%)</th>
<th>End-stage renal disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM\textsubscript{2.5}</td>
<td>4·56 μg/m\textsuperscript{3}</td>
<td>10·14 (8·45–11·83)</td>
<td>9·97 (7·96–11·98)</td>
<td>11·82 (9·88–13·36)</td>
</tr>
<tr>
<td>NO\textsubscript{2}</td>
<td>3·09 ppb</td>
<td>10·90 (9·56–12·34)</td>
<td>10·99 (9·25–12·73)</td>
<td>11·70 (10·22–13·19)</td>
</tr>
<tr>
<td>CO</td>
<td>0·18 ppm</td>
<td>10·40 (9·17–11·63)</td>
<td>11·37 (9·83–12·91)</td>
<td>10·68 (9·43–11·93)</td>
</tr>
</tbody>
</table>

Joint effect‡

PM\textsubscript{2.5} 4·56 μg/m\textsuperscript{3}, NO\textsubscript{2} 3·09 ppb, and CO 0·18 ppm

265\textsuperscript{206}, 22·79
253\textsuperscript{205}, 21·91
381\textsuperscript{279}, 23·94
381\textsuperscript{279}, 24·44

206; 22·79
205; 21·91
279; 23·94
279; 24·44

Data are HR (95% CI) or n; HR (95% CI). Models are adjusted for baseline age, race, sex, T\textsubscript{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\textsubscript{2.5}=ambient course particulate matter (<10 μm). NO\textsubscript{2}=nitrogen dioxide. ppb=parts per billion. CO=carbon monoxide. ppm=parts per million. HR=hazard ratio. T\textsubscript{0}=time zero. *Incident eGFR of less than 60 mL/min per 1·73 m\textsuperscript{2} was evaluated at a spell of follow-up of cohort entry. ‡Done in participants who were within 48 km of stations measuring the three pollutants.

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.\textsuperscript{11,39–41}

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 m\textsuperscript{2} 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, NO₂, 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.

Declaration of interests
We declare no competing interests.

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References
1 Hendryx M. Mortality from heart, respiratory, and kidney disease in coal mining areas of Appalachia. Int Arch Occup Environ Health 2009; 82: 241–49.
17 Bowe B, Xie Y, Xian H, Balasubramanian S, Al-Aly Z. Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression. Kidney Int 2016; 89: 886–96.