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Title

Association of short-term exposure to ambient $PM_{2.5}$ with hospital admissions and 30-day readmissions in end-stage renal disease patients: population based retrospective cohort study

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Abstract

Objectives: To examine the effect of short-term exposure to ambient fine particulate matter ($PM_{2.5}$) on all-cause, cardiovascular, and respiratory related hospital admissions and readmissions among patients receiving outpatient hemodialysis.

Design: Retrospective cohort study.

Setting: Inpatient hospitalization claims identified from the United States Renal Data System in 530 US counties.

Participants: All patients receiving in-center hemodialysis between 2008 and 2014.

Primary and secondary outcome measures: Risk of all-cause, cardiovascular, and respiratory related hospital admissions and 30-day all-cause and cause-specific readmission following an all-cause, cardiovascular, and respiratory related discharges. Readmission risk was

evaluated for early (1-7 days post-discharge) and late (8-30 days post-discharge) readmission time-periods. Relative risk is expressed per 10 μg/m^3 of $PM_{2.5}$.

Results: Same day ambient $PM_{2.5}$ was associated with increased hospital admission risk for cardiovascular causes (0.8%, 95%CI: [0.1, 1.5]). Greater $PM_{2.5}$-related associations were observed with 30-day readmission risk. All-cause readmission risk associated with $PM_{2.5}$ was greater for early-readmissions compared to late-readmissions. Early-readmission risk was increased by 1.4-1.7% following all-cause (1.4%, [0.5, 2.4]), cardiovascular (1.7%, [0.4, 3.1]), and respiratory (1.6%, [0.2, 3.1]) discharges; while late-readmission risk increased by 0.3% following all-cause and cardiovascular discharges. $PM_{2.5}$-related associations with readmission risk were greatest for certain cause-specific readmissions ranging 1.8-7.6% for dysrhythmia and conduction disorder, heart failure, COPD, other non-cardiac chest pain or respiratory syndrome, and pneumonia. Following all-cause discharges, the cause-specific early-readmission risk was increased by 6.1% (3.2, 9.2) for pneumonia, 4.6% (2.1, 7.1) for dysrhythmia and conduction disorder, 3.6% (1.3, 5.9) for heart failure, and 2.7% (1.1, 4.2) for other non-cardiac chest pain or respiratory syndrome related causes.

Conclusions: Daily ambient $PM_{2.5}$ was associated with an increased risk of cardiovascular admissions and 30-day readmissions following cardiopulmonary-related discharges in a vulnerable ESRD population. In the first week following discharge, greater $PM_{2.5}$-related risk of rehospitalization was identified for some diagnoses.

Strengths and limitations of this study

- Hospitalization records for patients undergoing in-center hemodialysis between 2008 and 2014 were identified using the US Renal Data System (> 1.8 million inpatient admissions).
- Fine resolution daily air pollution was linked to the location of the last dialysis visit.

- The time-stratified design in the admissions analysis reduced the potential confounding by factors that very slowly with time and those that are time-invariant.
- Using time-dependent risk factors in the Cox proportional hazard model allowed for readmission risk estimates to reflect the risk associated with daily fluctuations in ambient $PM_{2.5}$ and time-varying confounders.
- This study uses ambient air quality near dialysis centers to estimate individual exposure and diagnosis codes to classify cause-specific hospitalizations, which could contribute to exposure and diagnosis misclassification.

Introduction

Ambient fine particulate matter ($PM_{2.5}$) is a leading risk factor for all-cause mortality [1-4], accounting for millions of premature deaths each year [5]. Daily variation in ambient $PM_{2.5}$ is also associated with increased rates of unplanned hospital admissions, urgent care visits, and medication usage [6 7]. Greater health impacts have been observed consistently in sensitive populations, including the elderly and individuals with chronic health conditions [3 8-10]; however, few studies to our knowledge have examined $PM_{2.5}$-related health impacts on specific chronic health conditions, such as individuals living with chronic kidney disease (CKD).

CKD is a progressive condition that affects 8 to 16% of the population worldwide [11-13], and in the final stage, end-stage renal disease (ESRD), many patients are transitioned to hemodialysis to prolong life. Patients receiving dialysis represent a particularly vulnerable population because of high rates of co-morbidities, including diabetes and cardiovascular disease, which may contribute to the greater likelihood of hospital admission and readmission following PM exposure. In the US, patients on hemodialysis average 1.7 inpatient admissions annually with a 30-day readmission rate twice that of other Medicare beneficiaries [14], contributing to a substantial economic impact [15]. In 2016, $35.4 billion in Medicare fee-for-service costs were attributed to ESRD [14], motivating health promotion and cost-containment efforts to slow the progression of CKD and reduce hospitalizations and readmissions [16]. While many current strategies to reduce hospitalizations focus on care processes and patient-level factors [17-20], there is a knowledge gap on the role of modifiable environmental risk factors - specifically ambient $PM_{2.5}$ [2 21-23].

In this study, we examined the risk of daily hospitalization and subsequent 30-day readmission in relation to daily ambient $PM_{2.5}$ using data from the US Renal Data System (USRDS) over a 7-year period. We focused on all-cause, cardiovascular, and respiratory hospitalizations and

estimated changes in risk for early (1 to 7 days post-discharge) and late (8 to 30 days post-discharge) readmission accounting for the influence of different causal factors (i.e. acute and chronic illness burden) that may influence early versus late-readmissions [24 25].

Methods

Setting and study population

Using patient level data from the USRDS, we constructed an open cohort of individuals receiving in-center hemodialysis between 2008 and 2014. USRDS is a national data registry for dialysis services and includes records of patient demographic characteristics, hospitalizations, and provider information on all patients receiving hemodialysis. Baseline demographic characteristics (sex, birth date, race, and smoking status) recorded at the initiation of dialysis were extracted from the Medical Evidence Form CMS-2728 for each patient. For every inpatient hospital visit, we extracted the admission date, discharge date, discharge diagnoses codes, and discharge status.

For the analysis of 30-day readmission risk, we considered only admissions where patients were discharged alive. Each readmission was counted once as a readmission relative to the prior index admissions and was then considered as a new index admission. Thus, each admission could serve as both an index admission and readmission, consistent with previous studies [26]. An admission that occurred on the same day as a discharge was combined with the previous admission. These readmissions are likely to represent facility transfers for which we were not able to obtain information. Admissions occurring within 30 days of the end of the study period were excluded, as 30 days of follow-up data were not available. For both admissions and readmissions, patients could be represented more than once if they were admitted multiple times during the study period.

Health outcomes

The primary outcomes included daily counts of all-cause, respiratory, and cardiovascular-related admissions and the time to readmission following the cause-specific discharges. All-cause and cause-specific readmissions were examined separately. Readmissions were classified further as early-readmissions, occurring within 1 to 7 days of an index hospitalization discharge, and late-readmissions, occurring 8 to 30 days post-discharge.

International Classification of Diseases, 9th Revision (ICD-9) codes were used to identify cause-specific hospitalizations. Cardiovascular-related diagnoses included hypertension (ICD-9 codes 401-405), myocardial infarction (410), ischemic heart disease (410-411, 413), pulmonary embolism (415), dysrhythmia and conduction disorder (426-427), heart failure (428), and peripheral arterial disease (444). Respiratory-related diagnoses included asthma (493), chronic obstructive pulmonary disease (491-492, 496), pneumonia (480-486), and other non-cardiac chest pain or respiratory syndrome (786).

Environmental data

Daily concentrations of fine particulate matter ($PM_{2.5}$) were estimated using a previously described exposure prediction model [27 28]. Briefly, this model estimates daily $PM_{2.5}$ on a 1 km grid for the entire continental US by incorporating satellite aerosol optical depth measurements, chemical transport model simulations, meteorology, land-use, and other variables. Gridded $PM_{2.5}$ estimates were subsequently converted to population-weighted county-level estimates using 2010 Census tract population values. To enable adjustment for potential confounding by weather conditions, temperature and relative humidity data were obtained from the National Centers for Environmental Information's Global Historical Climatology Network (Global Surface Summary of the Day) [29] and using the Community Multiscale Air Quality model, respectively.

The study area was restricted to all counties containing at least one land surface station from the Global Historical Climatology Network (n = 530).

Daily $PM_{2.5}$ was linked to patient hospitalizations based on the county of their last dialysis visit. Previous work has shown that patients in the USRDS cohort that receive in-center dialysis three times a week have a median travel distance of 5.7 miles to their initial dialysis center [30 31].

Study design and statistical analysis

Daily county hospital admissions. The relative risks of hospital admissions associated with daily $PM_{2.5}$ were estimated using a case-crossover design with conditional Poisson models for each of the three health outcomes separately (all-cause, cardiovascular, respiratory). Aggregated counts of daily admissions were time stratified by county-day, where each county served as its own control. For each county-day strata, $PM_{2.5}$ on the day of admission was compared with $PM_{2.5}$ concentrations on control days. Control days were defined as occurring on the same day of the week in the same month and year. This, by design, enabled us to control for differences in county characteristics, such as population size and risk characteristics, and the influence of day of the week, seasonal, and long-term time trends [32].

The relative risk of hospital admissions related to daily $PM_{2.5}$ for each health outcome was estimated using daily counts with respect to county-time strata, adjusted for meteorological conditions (temperature and humidity). Temperature and humidity effects were averaged over lag days 0, 1, and 2 and modeled using natural splines (df = 3) to allow for non-linear effects [33].

We evaluated immediate (same day) and delayed $PM_{2.5}$ effects on all-cause and cause-specific hospital admissions. Unconstrained distributed lag models were used to assess the delayed effects of short-term exposures to $PM_{2.5}$. Delayed exposure up to 14 days were considered.

Early and late readmissions occurring within 30 days of discharge. Cox proportional hazards models were used to assess the relative risk of early (1 to 7 days post-discharge) and late (8 to 30 days post-discharge) readmission associated with daily $PM_{2.5}$ following all-cause and cause-specific index hospitalizations. Early-readmission models were censored at 7 days and late-readmission models at 30 days.

Models for readmissions incorporated both time-dependent and time-independent risk factors. Time-dependent variables included daily $PM_{2.5}$, daily temperature, daily relative humidity, and day-of-the-week. Time-independent factors included patient-specific and hospitalization event-specific variables. Patient-specific variables included indicator of sex, race, baseline smoking status, whether the patient had three or more previous hospital visits in the year prior, and age at discharge. Event-specific variables included whether the discharge occurred on a holiday and length of stay. Lastly, models were adjusted for patient-specific clusters to account for repeated measures by individual.

Daily county admission and readmission risks were expressed as the rate ratio (RR) per 10-$\mu g/m^3$ increase in $PM_{2.5}$. The proportion hospital admissions and readmissions associated with $PM_{2.5}$ is reported as the attributable fraction (AF), where AF = (RR-1) / RR [34]. All statistical analyses were performed with R software (version 3.6.0) [35].

Results

Characterization of clinical cohort and daily $PM_{2.5}$

Among 361,568 patients who were hospitalized during the study period, 10,274 were excluded due to missing baseline demographic values, with 351,294 patients remaining. Demographic descriptions are in Table 1. Patients had on average 2.97 hospital visits in the year prior to an

admission and more than 70% of patients had at least one hospital admission related to cardiovascular and respiratory causes (Table 2). The average daily county-level $PM_{2.5}$ concentration was 9.3 μg/m^3 (range: 0.05 to 155.16 μg/m^3) (Table S1).

Description of clinical events, hospital admissions, and readmissions

In total, there were 1,801,966 hospital admissions, of which 1,493,795 recorded the patient as alive at discharge. Of admissions that were discharged alive, 11.9% were readmitted within 7 days and 21.4% were readmitted 8 to 30 days post-discharge. The mean length of stay for all-cause, cardiovascular, and respiratory admissions was 7.0, 7.0, and 7.1 days, respectively (Table 2).

Associations between $PM_{2.5}$ and readmission

Early-readmission. Daily $PM_{2.5}$ was positively associated with increased risk for early-readmission following all-cause, cardiovascular, and respiratory related discharges. Same day (lag 0) $PM_{2.5}$ was associated with a 1.4% (95%CI: 0.5, 2.4), 1.7% (95%CI: 0.4, 3.1), and 1.6% (95%CI: 0.2, 3.1) increased risk of an early-readmission for any cause following all-cause, cardiovascular, and respiratory related discharges, respectively (Figure 1, Table S3).

$PM_{2.5}$ associated early-readmission risk was greater for certain cause-specific outcomes. Following all-cause discharges, same day (lag 0) $PM_{2.5}$ was associated with increased early-readmission risk for dysrhythmia and conduction disorder (4.6% [2.1, 7.1]), heart failure (3.6% [1.3, 5.9]), pneumonia 6.1% [3.2, 9.2]), and other non-cardiac chest pain or respiratory syndrome (2.7% [1.1, 4.2]) causes. $PM_{2.5}$ associated early-readmission risk was greatest for pneumonia related readmissions following cardiovascular related discharges (7.6% [3.6, 11.7]). Other cause-specific early-readmission risks following cardiovascular and respiratory related

discharges were similar to estimates observed following discharge for any cause (Figure 2, Table S4).

An average AF at 10 μg/m^3 of $PM_{2.5}$ at lag 0 was 1.4% (95%CI: 0.5, 2.4), 1.7% (95%CI: 0.3, 3.0), and 1.6% (95%CI: 0.2, 3.0) for an early-readmission following all-cause, cardiovascular, and respiratory discharges, respectively (Figure 1). County AF ranged 0.5% to 2.3%, 0.6% to 2.7%, and 0.5% to 2.6% for an early-readmission following all-cause, cardiovascular, and respiratory related discharges, respectively (Figure 2).

Late-readmission. Daily $PM_{2.5}$ was also associated with increased risk of late-readmission following all-cause, cardiovascular, and respiratory related discharges, though the magnitude of risk related to all-cause readmissions was smaller than that observed with early-readmission. Same day $PM_{2.5}$ was associated with a 0.3% (95%CI: 0.1, 0.5) and 0.3% (95%CI: 0.1, 0.6) increased risk of a late all-cause readmission following all-cause and cardiovascular related discharges, respectively (Figure 1, Table S3).

Similar to observations made for early-readmissions, $PM_{2.5}$ associated late-readmission risk was greater for certain cause-specific outcomes. Following all-cause discharges, a 10 μg/m^3 increase in same day (lag 0) $PM_{2.5}$ was associated with increased late-readmission risk for dysrhythmia and conduction disorder (2.5% [1.5, 3.6]), heart failure (3.7% [2.7, 4.7]), COPD (2.2% [0.4, 3.9]), pneumonia (4.6% [3.3, 5.8]), and other non-cardiac chest pain or respiratory syndrome (3.5% [2.9, 4.1]). Other cause-specific early-readmission risks following cardiovascular and respiratory related discharges were similar to estimates observed following discharge for any cause (Figure 2, Table S4).

The average AF at 10 μg/m^3 was 0.3% (95%CI: 0.1, 0.5) and 0.3% (95%CI: 0.1, 0.6) for a late-readmission following all-cause and cardiovascular discharges, respectively (Figure 1). County AF ranged 0.1% to 0.5% for a late-readmission following any cause (data not shown).

Associations between $PM_{2.5}$ and daily admissions

Same day $PM_{2.5}$ was associated with an increase in rate ratio of 0.3% (95%CI: -0.2, 0.9) for all-cause admissions and 0.9% (95%CI: 0.2, 1.7) for cardiovascular admissions (Figure S2, Table S2). We estimated 0.9% (95%CI: 0.1, 1.7) of cardiovascular admissions could be attributed to 10 μg/m^3 ambient $PM_{2.5}$ (Figure 3). Across counties, exposures accounted for 0.3% to 1.5% of cardiovascular admissions when evaluated at the average daily $PM_{2.5}$ for each county (data not shown).

No change in risk of all-cause and cardiovascular admissions was observed related to prior exposure (lags 1-14). Similarly, no change in risk for respiratory admissions was observed with same day exposure (lag 0) or prior exposure (lags 1-14) (Figure S2, Table S2).

Discussion

In a nationwide cohort study of 351,294 patients with ESRD managed with hemodialysis, we evaluated the association between 1.8 million inpatient admissions and nearly 0.5 million corresponding 30-day readmissions and the variation in daily ambient $PM_{2.5}$ in the US over 7 years, 2008-2014. Daily variation in $PM_{2.5}$ was associated with increased risk of hospital admission and even greater risk of rehospitalization. We found that the rehospitalization risk related to readmission for any cause was 4.7-8.0 times greater for readmission in the first week following discharge, compared to late-readmissions (8-30d after discharge). Following all-cause, cardiovascular, and respiratory related discharges, the early-readmission risk for any cause was increased by 1.4, 1.7, 1.6%, respectively per 10 μg/m^3 increase in daily $PM_{2.5}$. Importantly,

readmissions related to some cardiorespiratory diagnoses had the greatest $PM_{2.5}$ attributed readmission risk that was observed to be elevated for both early and late-readmissions. The early-readmission risk following all-cause discharges, was increased by 6.1%, 4.6%, and 3.6% for pneumonia, dysrhythmia and conduction disorder, and heart failure related readmissions, respectively. Most notably for readmissions related to pneumonia and dysrhythmia, the early-readmission risk attributed to $PM_{2.5}$ was nearly twice as large as the late-readmission risk. Overall, these results suggest that at 10 μg/m^3, 1.4-1.7% of early-readmissions for any cause were attributable to short-term exposure. In the context of the daily $PM_{2.5}$ National Ambient Air Quality Standard (35 μg/m^3), this attributable fraction would be 5-6%.

Our findings are consistent with previous studies that observed increased admission risks in elderly populations [6 9 36-40] and patients with cardiovascular health complications [7 41], and increased readmission risk following cardiovascular related admissions [7 41 42]. Studies in the Medicare population similarly observed a 1-2% increase in cardiovascular hospital admissions associated with same-day $PM_{2.5}$ concentrations [6 9 36 38]. Risk appears to vary by diagnosis, as the increased risk was slightly less (0.13%) for ST-elevation myocardial infarction related admissions in a Chinese population [7] and greater (29%) for incident heart failure admissions in an Australian population [41]. Increases in respiratory admissions (1-2%) have been noted in the Medicare population [6 9 36-38], but were not observed in this study. Prior studies provide evidence that air pollution exposure is associated with adverse health outcomes including increased infection rates, acute lung edema, and elevated concentrations of systematic inflammation markers [43-45]. Despite known associations between PM exposure and adverse cardiovascular and respiratory health outcomes, previous studies have not evaluated the impacts on hospital readmissions among individuals with ESRD.

Few studies have examined $PM_{2.5}$-related effects on readmissions, and those that have report on the long-term (>1yr) risk following cardiovascular related admissions. Following cardiovascular hospitalization, $PM_{2.5}$-related rehospitalization risks were greater for cardiac readmissions compared to our observations of all-cause readmissions (1.3-2.6% vs 0.3%) [7 42]. Additionally, one study in an Australian population with very low ambient air pollution concentrations (mean $PM_{2.5}$ = 2.9 μg/m^3) found no relationship between $PM_{2.5}$ and the all-cause readmissions after an incident heart failure hospitalization [41]. Short-term readmission risks were greater in comparison to the long-term readmission risks, suggesting the week following a discharge to be a window of heightened vulnerability. Prior work indicates that factors related to index hospitalizations and acute illness burden were predictive of an early-readmission [24 25]. This may indicate that hospital readmissions related to acute illness burdens may be more susceptible to $PM_{2.5}$ exposure.

Our study contributes to the currently limited literature on the association between air pollution and health impacts among hemodialysis patients and shines a light on the vulnerability in this clinical population related to ambient airborne particulate matter. The 30-day rehospitalization rate is 35% in this population, which is twice that of older Medicare beneficiaries without a kidney disease diagnosis [14]. As many as 70% of readmissions are thought to be unnecessary [46], prompting efforts to improve outcomes. Economic healthcare costs associated with short-term increases in $PM_{2.5}$ are considerable; annual inpatient and post-acute care costs related to a 10 μg/m^3 in daily $PM_{2.5}$ ranges $30-70 million for cardiovascular and respiratory related diseases [47]. $PM_{2.5}$ is a modifiable risk factor and reductions in short-term exposures could contribute to reduced healthcare costs. Our findings suggest that short-term increases in $PM_{2.5}$ contribute to healthcare usage through unplanned admissions and readmissions.

Strengths and Limitations

This study included a nearly complete cohort of US patients undergoing in-center hemodialysis. To our knowledge this is the largest analysis of short-term exposure to air pollution in the US in this highly vulnerable population. The USRDS registry provides a complete registry of all hospitalizations and contains detailed information regarding demographics, dialysis, hospitalization, rehospitalization, and co-morbid conditions. Secondly, ambient $PM_{2.5}$ was estimated using a prediction model with highly resolved spatial and temporal resolution with proven accuracy [27 28]. Thirdly, the time-stratified design allowed for county matching that reduced the potential confounding by factors that very slowly with time and those that are time-invariant. Fourthly, the use of time-dependent risk factors in the Cox proportional hazard model allowed for readmission risk estimates to reflect the risk associated with daily fluctuations in ambient $PM_{2.5}$ and time-varying confounders.

This study also had some limitations. Firstly, there was the potential for exposure misclassification as the location of the last dialysis visit was used to estimate individual level exposures. $PM_{2.5}$ around dialysis centers could differ from concentrations around hospitals and patient residences. However, given that patients generally reside less than 6 miles from their initial dialysis center, differences in temporal variation of exposure should be small and not likely to contribute a systematic bias favoring an association between ambient $PM_{2.5}$ and clinical events [30 31]. Secondly, diagnosis misclassification was possible but was not likely to confound the relationship because it is not likely to vary on the same temporal scale as $PM_{2.5}$. Thirdly, there is the possibility that some unmeasured time variant factors may have confounded our estimates (smoking status, medication usage, behaviors). Data availability restricted the consideration of some patient level confounders, such as smoking status, to values recorded at baseline. Lastly, generalization of the results is limited to the Medicare population with ESRD managed with hemodialysis treatments. Future studies are needed to understand $PM_{2.5}$-related

impacts on specific health conditions, and if health impacts vary based on race, socioeconomic indicators, or other individual and population factors.

Conclusion

In conclusion, this United States wide cohort study identified increased risk in patients receiving in-center hemodialysis associated with short-term increases in ambient air particle pollution. Elevated $PM_{2.5}$ concentrations were found to be associated with increased inpatient hospital admissions related to cardiovascular causes, and an increased likelihood of hospital readmission following cardiovascular and respiratory related hospitalizations. Medicare spending for beneficiaries with ESRD is high. Traditional efforts to reduce the burden of disease focus on patient factors; however, these data suggest that air particle pollution is a factor that contributes to increased risks for hospital admission and subsequent readmission. To reduce $PM_{2.5}$-related morbidities, we echo the recommendations made in the Million Hearts initiative, that healthcare systems, insurers, physicians, and health care professionals should incorporate health risks related to ambient PM into patient care.

Disclaimer

The research described in this article has been reviewed by the Center for Public Health and the Environment, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency, nor does the mention of trade names of commercial products constitute endorsement or recommendation for use.

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Contributors

LHW, AGR conceived and designed the study. TJW, WEC, and AVK provided subject expert input into the study design and interpretation of evidence. AVK, QD, and CWC provided access to the data for the study; LHW managed and analyzed the data and AGR oversaw the analysis. LHW and AGR wrote the first draft of the manuscript. LHW, YX, AVK, CWC, TJW, WEC, and AGR critically contributed to the manuscript and approved the final draft. LHW and AGR are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was reviewed by the institutional review board at the University of North Carolina at Chapel Hill and determined to be exempt based on the study design involving secondary data analysis.

Data sharing

Data access to USRDS data sets is through an internal data use agreement with the University of North Carolina at Chapel Hill's Cecil G. Sheps Center. $PM_{2.5}$ data was obtained through collaboration with Drs. Joel Schwartz (Harvard TH Chan School of Public Health) and Qian Di (Tsinghua University). For general data sharing inquiries, contact rappold.ana@epa.gov or wyatt.lauren@epa.gov.

Transparency

The lead and corresponding authors (LHW and AGR) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient and Public Involvement

This study utilized a deidentified database, thus contact with patients was not possible.

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Table 1. Baseline Demographic Characteristics of the Study Population Between 2008 and 2014 by Hospital Admission Category.

	No. (%)		
	All-cause	Cardiovascular	Respiratory
Characteristic	N = 351,294	n = 262,385	n = 247,829
Age (yr), mean (SD)	64·69 (14.70)	65·58 (14.53)	65·61 (14.48)
Male sex (%)	190,716 (54.3)	140,206 (53.4)	132,288 (53.4)
Race			
White	209,921 (59.8)	155,405 (59.2)	147,204 (59.4)
Black	122,943 (35.0)	93,325 (35.6)	87,831 (35.4)
Other	18,430 (5.2)	13,655 (5.2)	12,794 (5.2)
Smoking status at initiation (no)	330,837 (94.2)	246,634 (94.0)	232,396 (93.8)

Table 2. Hospital Admission Characteristics Among the Study Population Between 2008 and 2014.

Outcome	Number of Events (Number of Unique Patients)		
	All-cause	Cardiovascular	Respiratory
Admissions	1,801,966 (351,294)	832,255 (262,385)	766,447 (247,829)
Discharged alive	1,493,795 (312,521)	685,680 (229,780)	637,250 (217,221)
Early-readmission (1-7d)	177,552 (91,944)	83,533 (52,622)	78,723 (49,576)
Late-readmission (8-30d)	319,058 (130,935)	150,576 (81,149)	142,139 (76,722)
Length of stay, d			
Mean (SD)	6·98 (10.68)	7·05 (10.34)	7·07 (10.38)
Median (IQR)	4 (2-7)	4 (2-8)	4 (2-8)
Hospital visits in prior year			
3+ visits	637,503 (123,949)	307,891 (93,399)	292,803 (89,905)
Mean (SD)	2.97 (3.80)	3.14 (3.95)	3.21 (3.89)
Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)

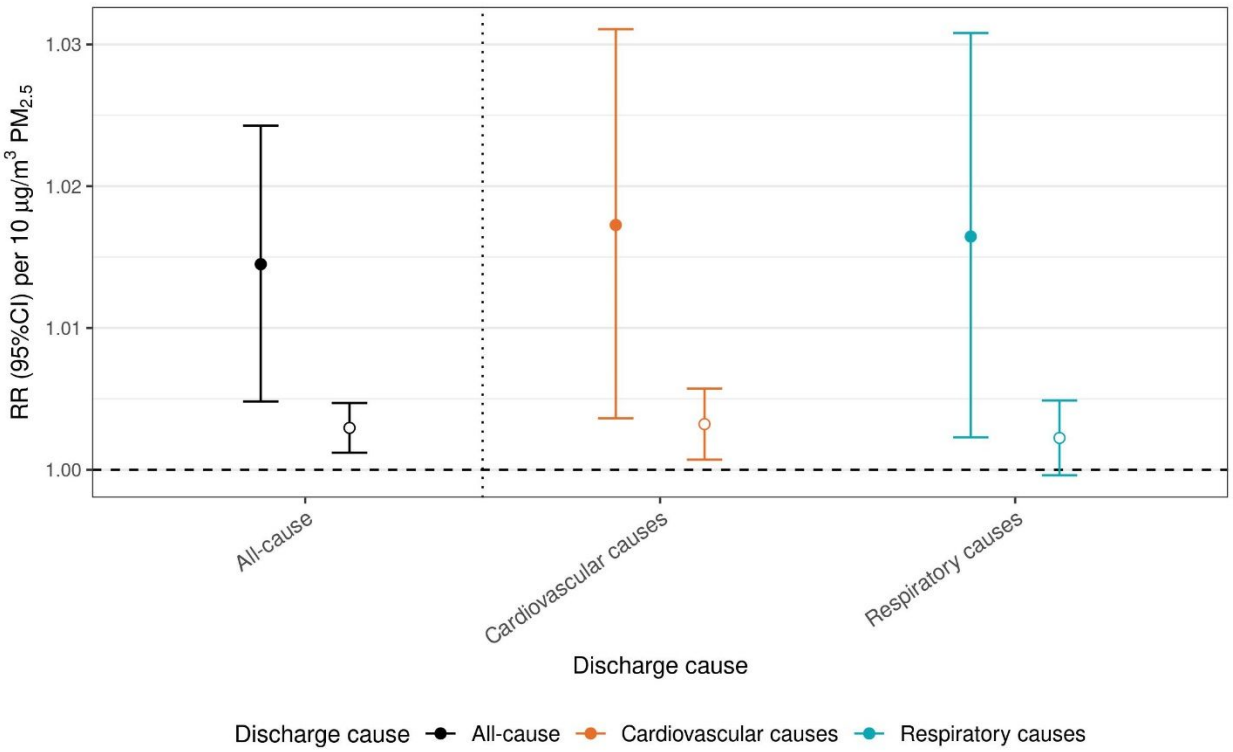

Figure 1. The relative risk (RR, 95%CI) for an all-cause early and late-readmission following all-cause and cause-specific discharges. Discharges are color coded: all-cause discharges are indicated in black, cardiovascular causes in orange, and respiratory causes in blue. Early-readmissions are indicated with filled in circles, late-readmissions with open circles. RR is expressed per 10 µg/m^3 increase in $PM_{2.5}$.

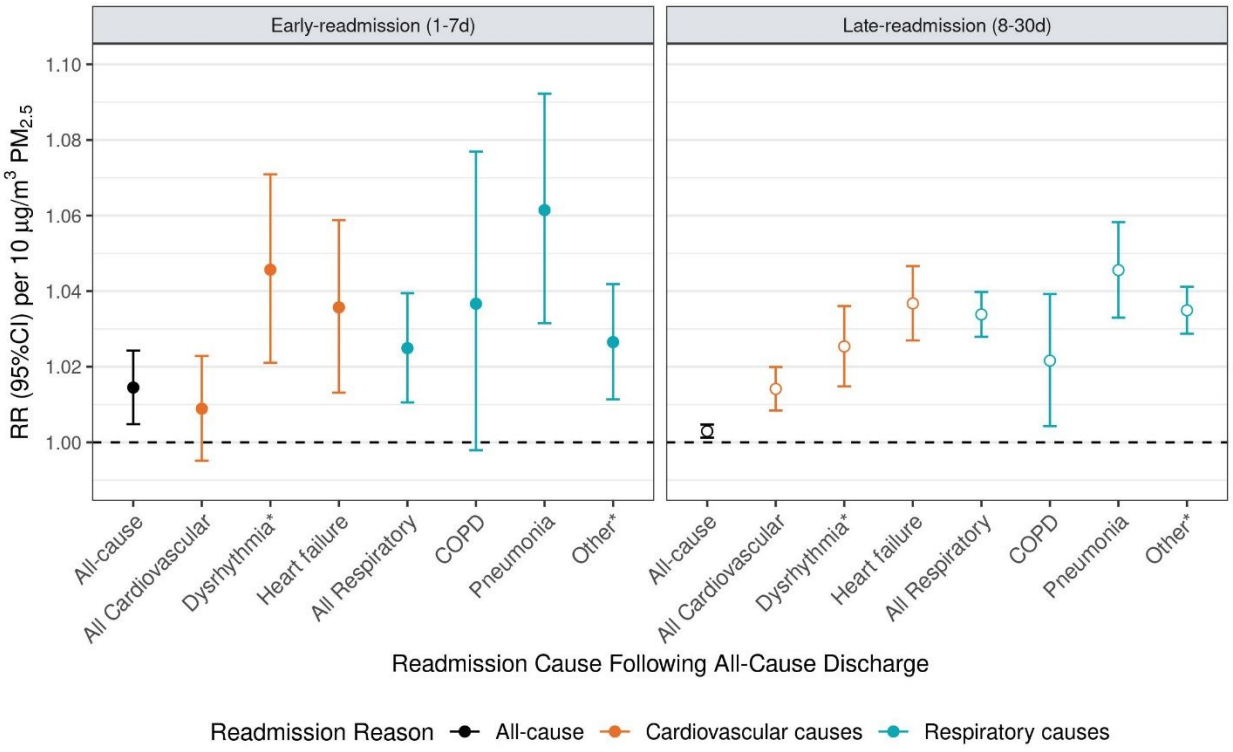

Figure 2. The relative risk (RR, 95%CI) of cause-specific early and late-readmission following all-cause discharge. Readmission causes are color coded: all-cause readmissions are indicated in black, cardiovascular causes in orange, and respiratory causes in blue. RR is expressed per 10 µg/m^3 increase in $PM_{2.5}$.

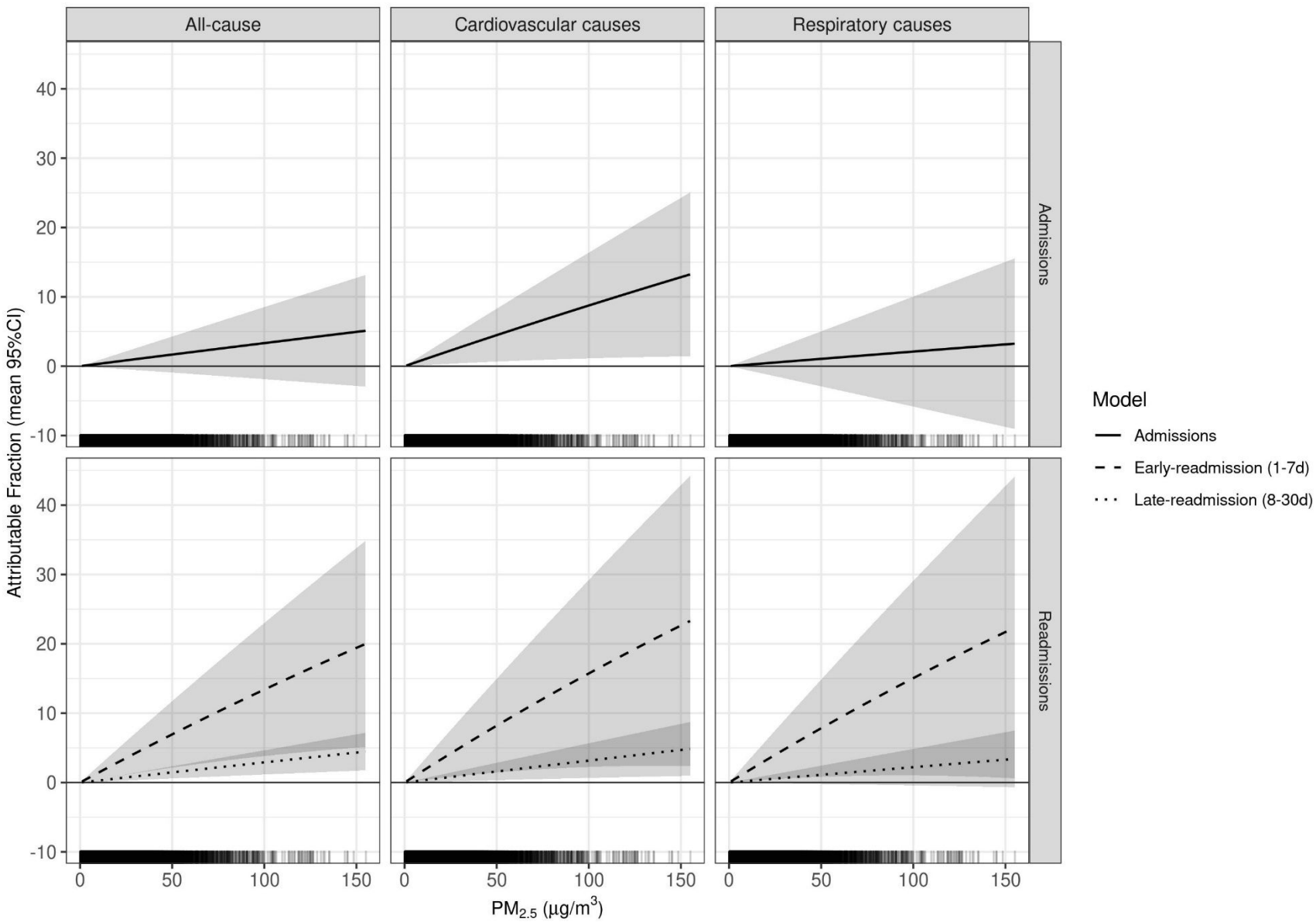

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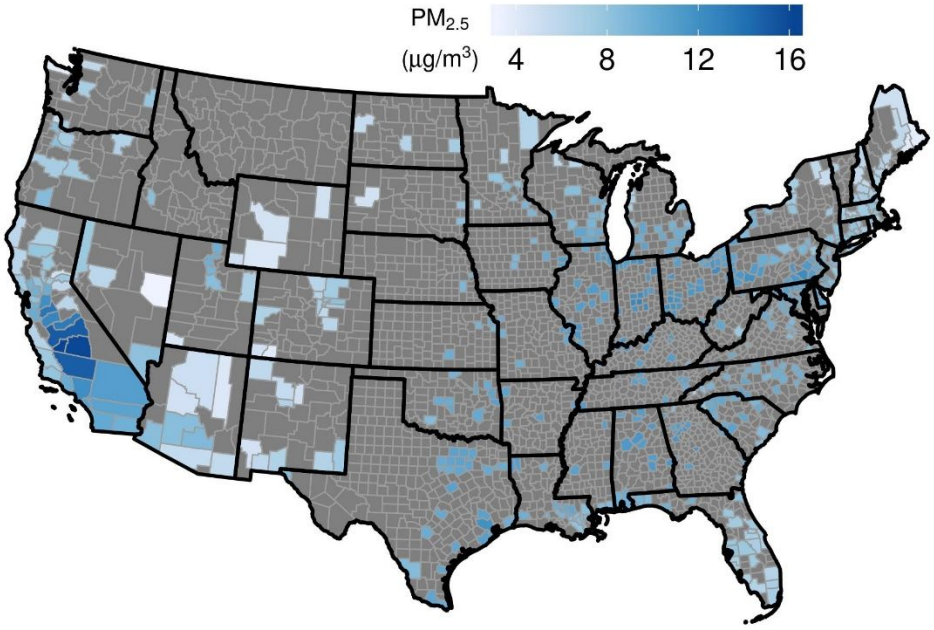
Figure 3. Mean proportion (95%CI) of all-cause and cause-specific hospital admissions, early readmissions (1-7d), and late readmissions (8-30d) with respect to $PM_{2.5}$ ($\mu g/m^3$). Hash marks above the x-axis represent the density of daily county $PM_{2.5}$.

A) Daily county average $PM_{2.5}$ (7yr average)



B) Exposure attributable fraction for early-readmission following an all-cause discharge

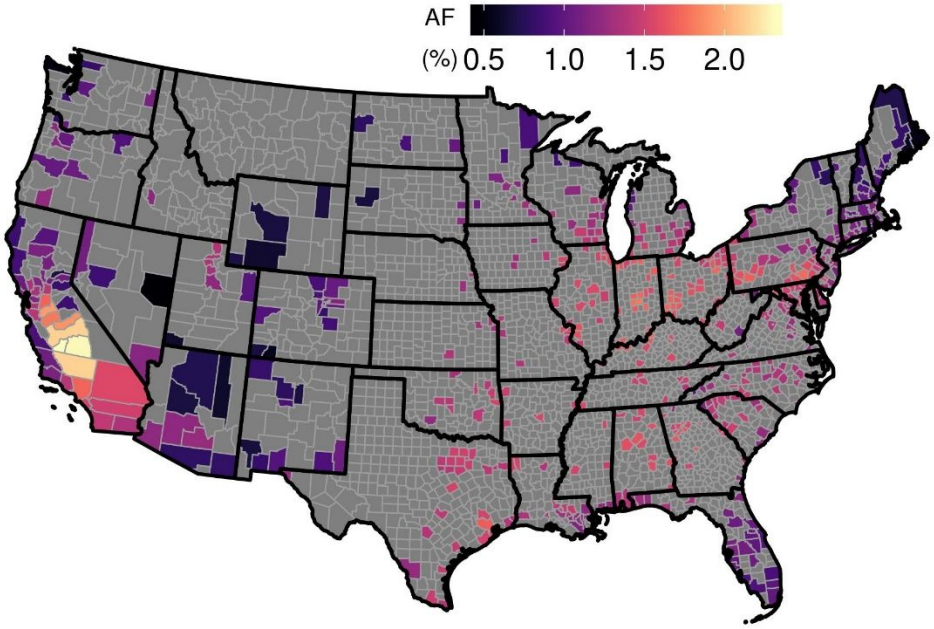


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Figure 4. Average daily county $PM_{2.5}$ ($\mu g/m^3$) between 2008 and 2014 (A) and the attributable fraction for early-readmission following an all-cause discharge based on the average $PM_{2.5}$ (B) for the 530 counties included in the study.

Supplemental Materials

Table S1. Summary statistics of $PM_{2.5}$ and meteorological variables across 530 counties.

Variable	Mean ± SD	Minimum	Maximum
$PM_{2.5}$ (μg/m^3)	9.29 ± 5.39	0.05	155.16
Temperature (°F)	56.37 ± 18.50	-37.30	104.74
Relative humidity (%)	65.24 ± 16.24	0	100

Table S2. Relative risk (RR ± 95% CI) of all-cause and cause-specific daily county admission rates associated with a 10 μg/m^3 increase in $PM_{2.5}$ for exposure lags 0-14 days

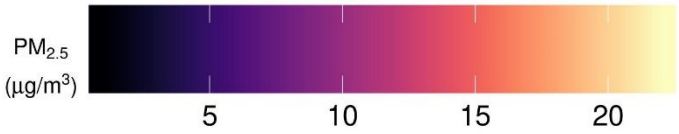
Endpoint	Lag	RR (95% CI)	N
All-cause	0	1.003 (0.998, 1.009)	1,801,966
All-cause	1	0.997 (0.990, 1.003)	1,801,966
All-cause	2	0.999 (0.992, 1.005)	1,801,966
All-cause	3	0.996 (0.990, 1.002)	1,801,966
All-cause	4	1.002 (0.996, 1.008)	1,801,966
All-cause	5	1.001 (0.995, 1.007)	1,801,966
All-cause	6	1.001 (0.995, 1.008)	1,801,966
All-cause	7	1.000 (0.993, 1.006)	1,801,966
All-cause	8	1.004 (0.997, 1.010)	1,801,966
All-cause	9	1.004 (0.998, 1.010)	1,801,966
All-cause	10	0.999 (0.993, 1.005)	1,801,966
All-cause	11	0.996 (0.989, 1.002)	1,801,966
All-cause	12	1.002 (0.996, 1.009)	1,801,966
All-cause	13	0.995 (0.989, 1.001)	1,801,966

All-cause	14	1.000 (0.994, 1.005)	1,801,966
CVD broad definition	0	1.009 (1.002, 1.017)	832,255
CVD broad definition	1	0.995 (0.986, 1.004)	832,255
CVD broad definition	2	0.998 (0.988, 1.007)	832,255
CVD broad definition	3	0.993 (0.984, 1.002)	832,255
CVD broad definition	4	1.003 (0.994, 1.012)	832,255
CVD broad definition	5	1.004 (0.994, 1.013)	832,255
CVD broad definition	6	0.999 (0.990, 1.008)	832,255
CVD broad definition	7	1.005 (0.995, 1.014)	832,255
CVD broad definition	8	1.002 (0.993, 1.011)	832,255
CVD broad definition	9	1.009 (1.000, 1.018)	832,255
CVD broad definition	10	0.992 (0.983, 1.001)	832,255
CVD broad definition	11	0.999 (0.990, 1.008)	832,255
CVD broad definition	12	0.999 (0.990, 1.008)	832,255
CVD broad definition	13	0.996 (0.987, 1.005)	832,255
CVD broad definition	14	1.002 (0.994, 1.009)	832,255
Respiratory broad definition	0	1.002 (0.994, 1.010)	766,447
Respiratory broad definition	1	0.998 (0.989, 1.008)	766,447
Respiratory broad definition	2	0.995 (0.985, 1.004)	766,447
Respiratory broad definition	3	0.995 (0.985, 1.004)	766,447
Respiratory broad definition	4	0.999 (0.989, 1.008)	766,447
Respiratory broad definition	5	1.009 (1.000, 1.019)	766,447
Respiratory broad definition	6	0.999 (0.990, 1.009)	766,447
Respiratory broad definition	7	0.999 (0.989, 1.009)	766,447
Respiratory broad definition	8	1.005 (0.996, 1.015)	766,447

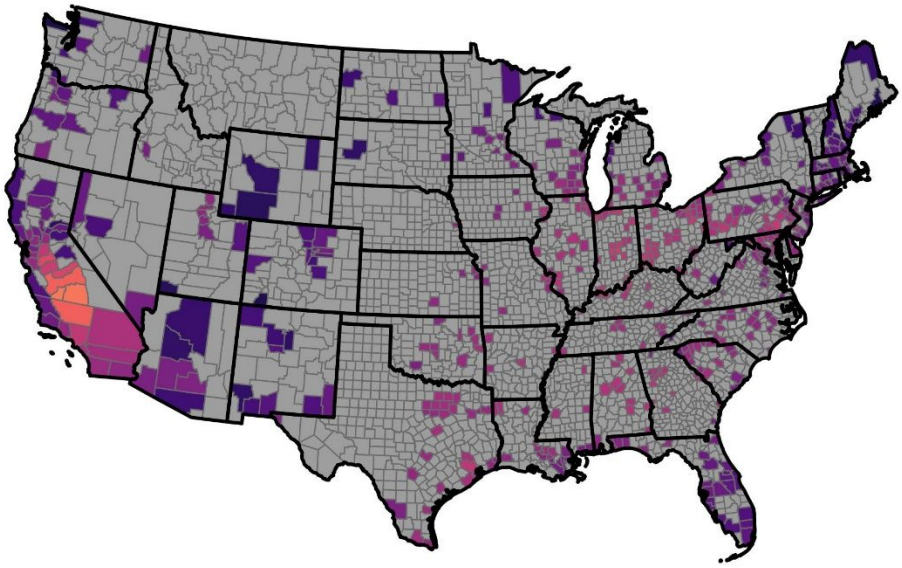
Respiratory broad definition	9	1.008 (0.999, 1.018)	766,447
Respiratory broad definition	10	0.995 (0.985, 1.004)	766,447
Respiratory broad definition	11	0.997 (0.988, 1.007)	766,447
Respiratory broad definition	12	1.002 (0.992, 1.011)	766,447
Respiratory broad definition	13	0.997 (0.987, 1.006)	766,447
Respiratory broad definition	14	1.001 (0.993, 1.009)	766,447

Table S3. The relative risk (RR, 95%CI) for an all-cause early and late-readmission following all-cause and cause-specific discharges. RR is expressed per 10 μg/m^3 increase in $PM_{2.5}$.

Discharge cause	Model	RR (95% CI)	N
All-cause	Early-readmission (1-7d)	1.014 (1.005, 1.024)	177,552
All-cause	Late-readmission (8-30d)	1.003 (1.001, 1.005)	319,058
CVD broad definition	Early-readmission (1-7d)	1.017 (1.004, 1.031)	83,533
CVD broad definition	Late-readmission (8-30d)	1.003 (1.001, 1.006)	150,576
Respiratory broad definition	Early-readmission (1-7d)	1.016 (1.002, 1.031)	78,723
Respiratory broad definition	Late-readmission (8-30d)	1.002 (0.999, 1.005)	142,139



A) Long-term county $PM_{2.5}$ (7yr average)



B) 20% of county days are above $PM_{2.5}$ (80th percentile)

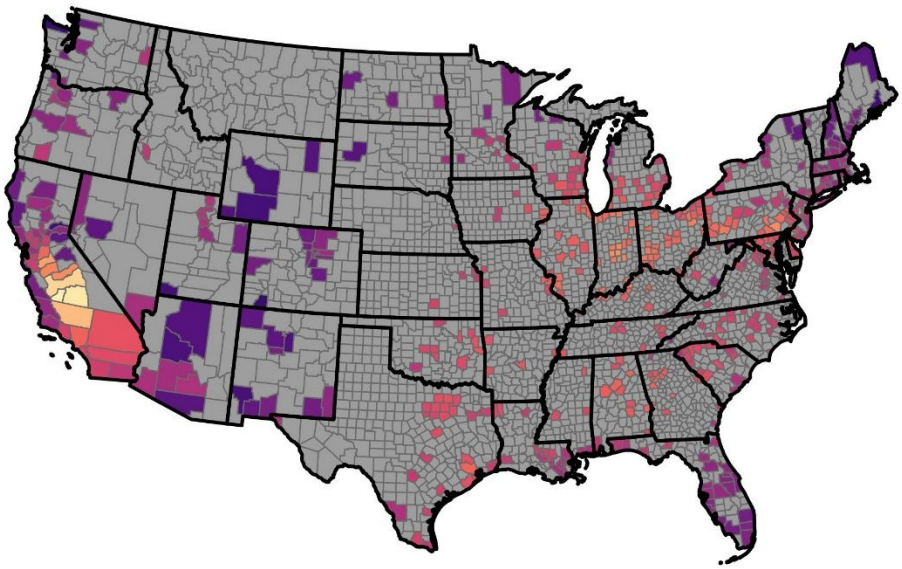


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Figure S1. County $PM_{2.5}$ levels for the 530 counties included in the study. $PM_{2.5}$ levels shown include the A) long-term average and B) 80th percentile (indicating that 20% of county days are at or above this $PM_{2.5}$ level) for the years 2008-2014.

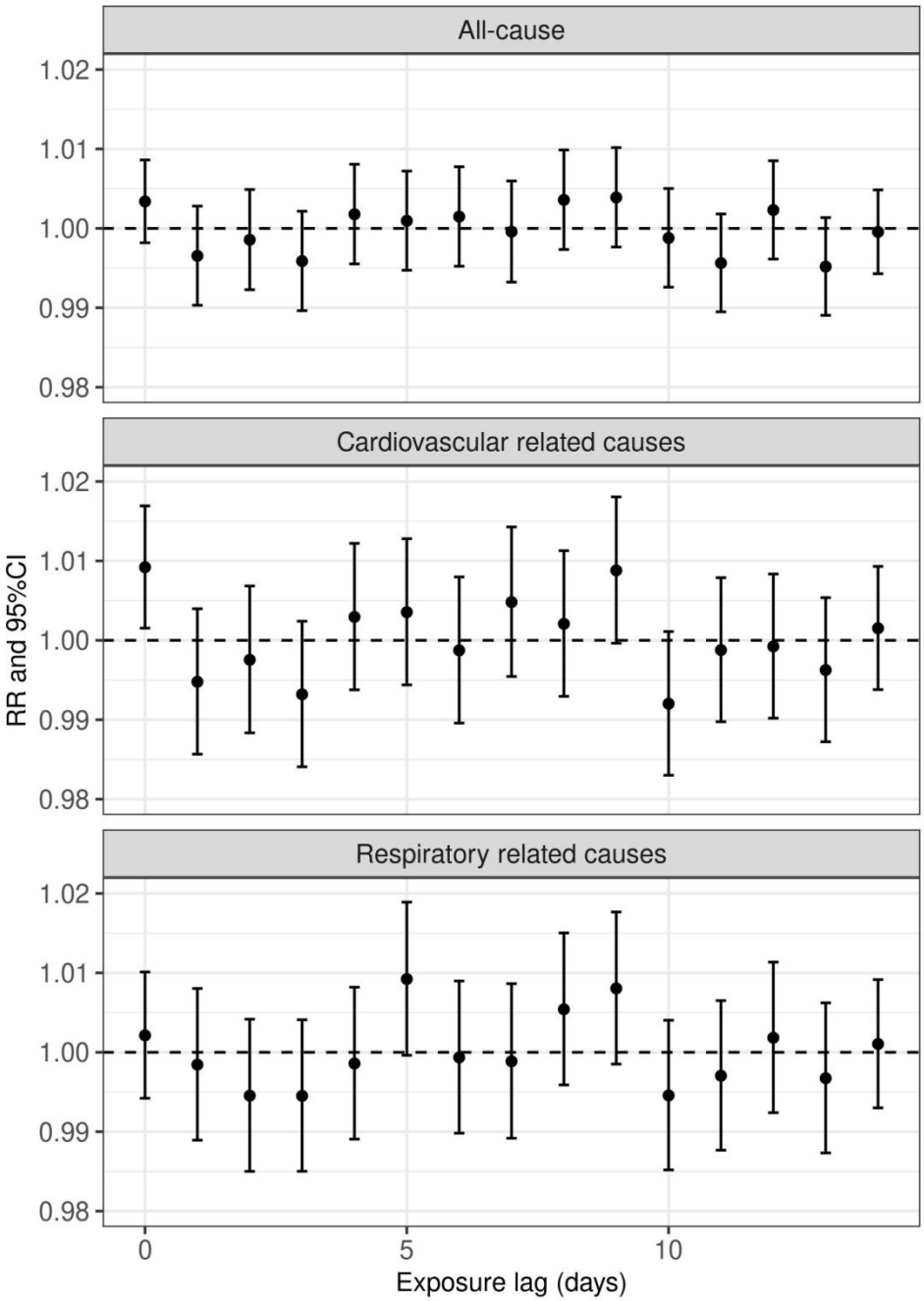


Figure S2. Relative risk (RR ± 95%CI) for daily county admission rates for all-cause hospitalization associated with a 10 μg/m^3 increase in $PM_{2.5}$ for exposure lags 0-14 days using an unconstrained distributed lag model (Table S1).

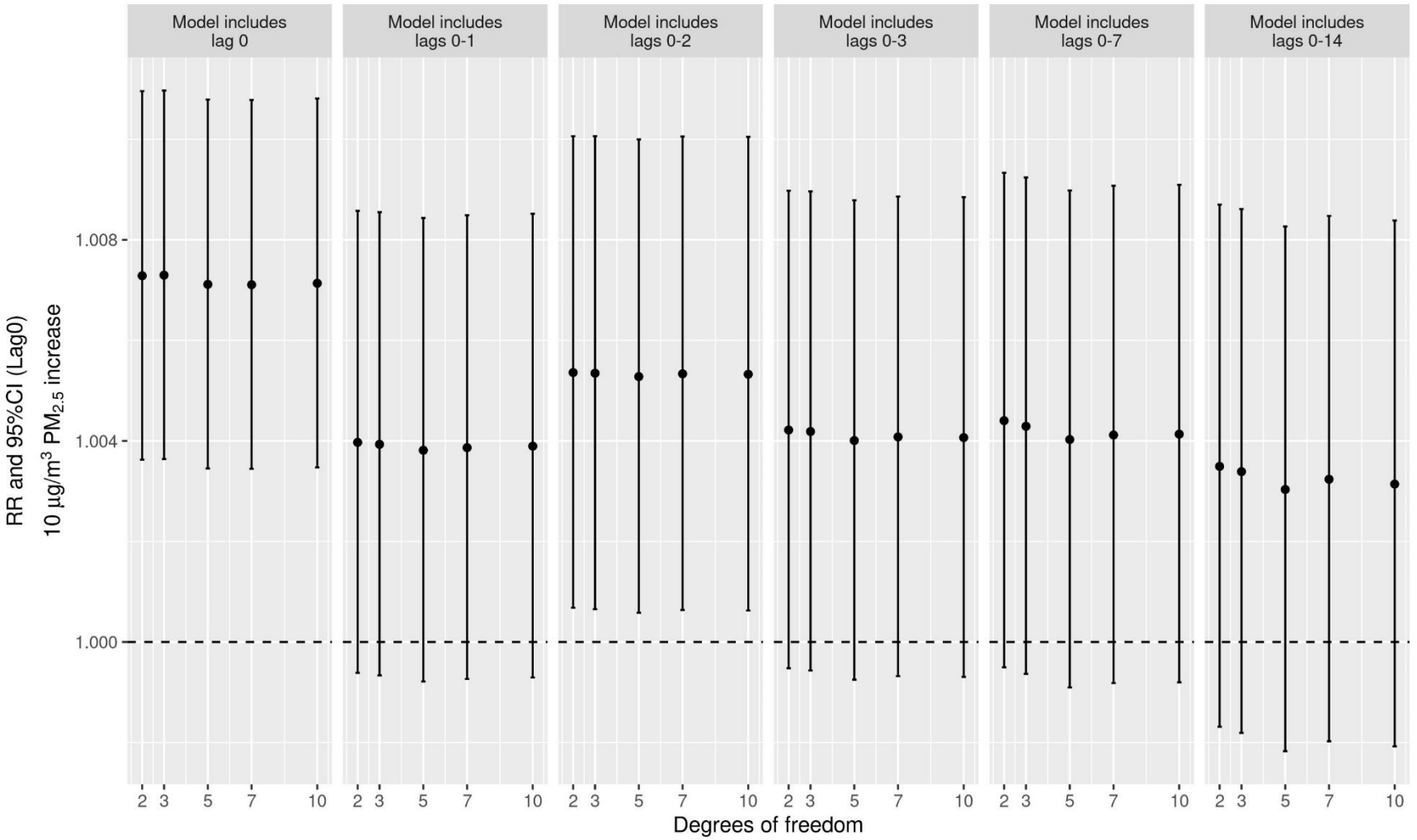


Figure S3. Sensitivity analysis for all-cause admissions models showing the impact on the lag 0 estimate from changing the number of lags considered (grouped figures), and the number of degrees of freedom (x-axis) for the temperature and relative humidity variables. Relative risk (RR ± 95%CI) of all-cause daily county admission rates associated with a 10 µg/m^3 increase in $PM_{2.5}$ on lag 0.

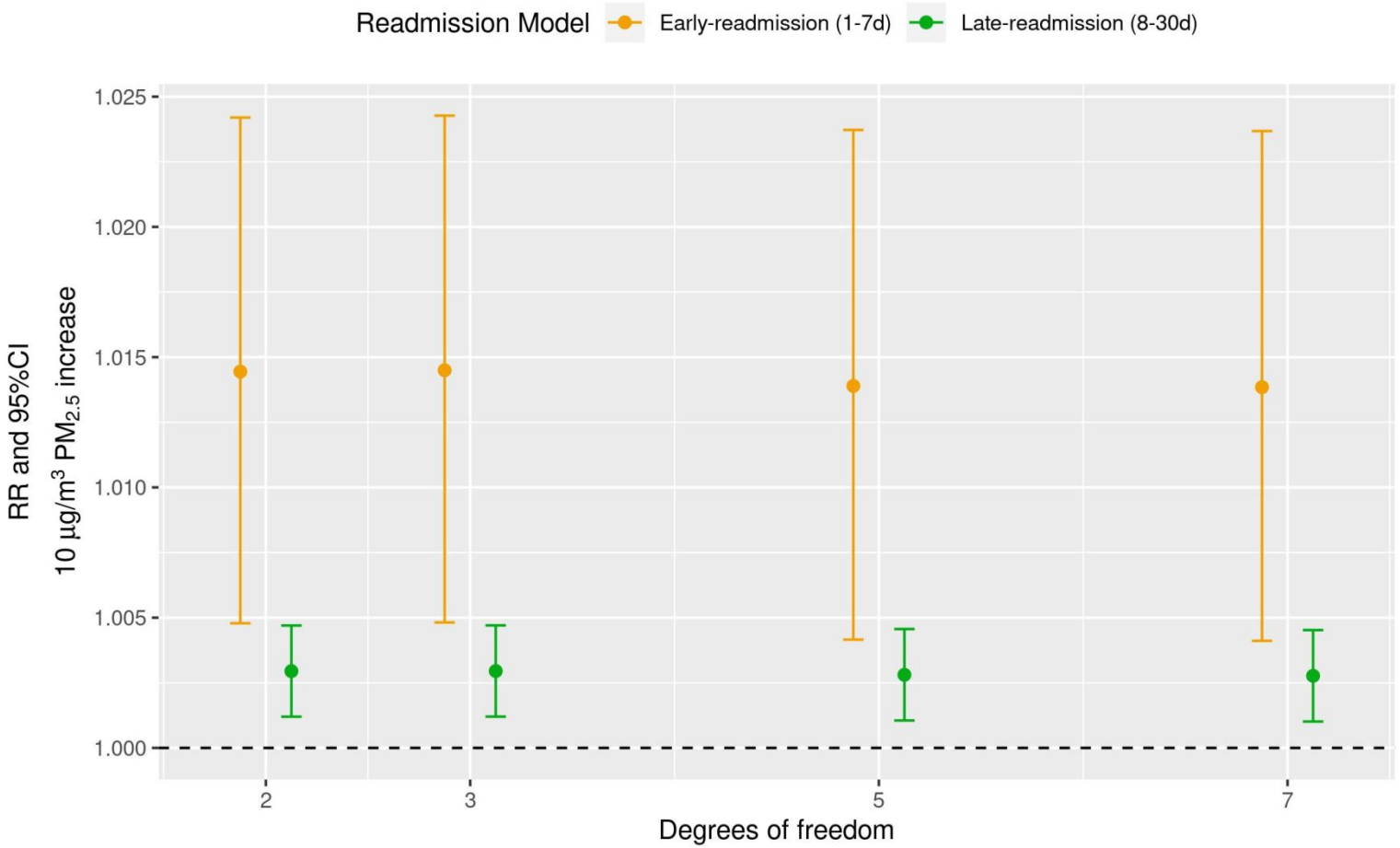


Figure S4. Sensitivity analysis for all-cause readmission models showing the impact on the lag 0 estimate from changing the number of degrees of freedom (x-axis) for the temperature and relative humidity variables. Relative risk (RR ± 95%CI) of all-cause daily county admission rates associated with a 10 µg/m^3 increase in $PM_{2.5}$ on lag 0.

Supplemental Materials for

Association of short-term ambient PM2.5 with hospital admissions and 30-day readmissions in end-stage renal disease patients: population based retrospective cohort study

Table S1. Summary statistics of $PM_{2.5}$ and meteorological variables across 530 counties.

Variable	Mean ± SD	Minimum	Maximum
$PM_{2.5}$ (μg/m^3)	9.29 ± 5.39	0.05	155.16
Temperature (°F)	56.37 ± 18.50	-37.30	104.74
Relative humidity (%)	65.24 ± 16.24	0	100

Table S2. Relative risk (RR ± 95% CI) of all-cause and cause-specific daily county admission rates associated with a 10 μg/m^3 increase in $PM_{2.5}$ for exposure lags 0-14 days

Endpoint	Lag	RR (95% CI)
All-cause	0	1.003 (0.998, 1.009)
All-cause	1	0.997 (0.990, 1.003)
All-cause	2	0.999 (0.992, 1.005)
All-cause	3	0.996 (0.990, 1.002)
All-cause	4	1.002 (0.996, 1.008)
All-cause	5	1.001 (0.995, 1.007)
All-cause	6	1.001 (0.995, 1.008)
All-cause	7	1.000 (0.993, 1.006)
All-cause	8	1.004 (0.997, 1.010)
All-cause	9	1.004 (0.998, 1.010)
All-cause	10	0.999 (0.993, 1.005)
All-cause	11	0.996 (0.989, 1.002)

All-cause	12	1.002 (0.996, 1.009)
All-cause	13	0.995 (0.989, 1.001)
All-cause	14	1.000 (0.994, 1.005)
CVD broad definition	0	1.009 (1.002, 1.017)
CVD broad definition	1	0.995 (0.986, 1.004)
CVD broad definition	2	0.998 (0.988, 1.007)
CVD broad definition	3	0.993 (0.984, 1.002)
CVD broad definition	4	1.003 (0.994, 1.012)
CVD broad definition	5	1.004 (0.994, 1.013)
CVD broad definition	6	0.999 (0.990, 1.008)
CVD broad definition	7	1.005 (0.995, 1.014)
CVD broad definition	8	1.002 (0.993, 1.011)
CVD broad definition	9	1.009 (1.000, 1.018)
CVD broad definition	10	0.992 (0.983, 1.001)
CVD broad definition	11	0.999 (0.990, 1.008)
CVD broad definition	12	0.999 (0.990, 1.008)
CVD broad definition	13	0.996 (0.987, 1.005)
CVD broad definition	14	1.002 (0.994, 1.009)
Respiratory broad definition	0	1.002 (0.994, 1.010)
Respiratory broad definition	1	0.998 (0.989, 1.008)
Respiratory broad definition	2	0.995 (0.985, 1.004)
Respiratory broad definition	3	0.995 (0.985, 1.004)
Respiratory broad definition	4	0.999 (0.989, 1.008)
Respiratory broad definition	5	1.009 (1.000, 1.019)
Respiratory broad definition	6	0.999 (0.990, 1.009)

Respiratory broad definition	7	0.999 (0.989, 1.009)
Respiratory broad definition	8	1.005 (0.996, 1.015)
Respiratory broad definition	9	1.008 (0.999, 1.018)
Respiratory broad definition	10	0.995 (0.985, 1.004)
Respiratory broad definition	11	0.997 (0.988, 1.007)
Respiratory broad definition	12	1.002 (0.992, 1.011)
Respiratory broad definition	13	0.997 (0.987, 1.006)
Respiratory broad definition	14	1.001 (0.993, 1.009)

Table S3. Relative risk (RR ± 95% CI) for early and late-readmissions following all-cause and cause-specific discharges. RR is associated with a 10 μg/m^3 increase in $PM_{2.5}$.

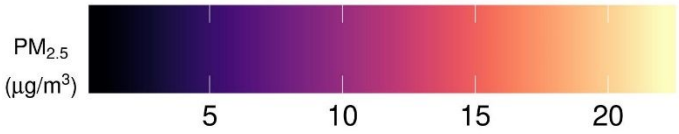
Discharge Cause	Model	RR (95% CI)
All-cause	Early-readmission (1-7d)	1.014 (1.005, 1.024)
All-cause	Late-readmission (8-30d)	1.003 (1.001, 1.005)
CVD broad definition	Early-readmission (1-7d)	1.017 (1.004, 1.031)
CVD broad definition	Late-readmission (8-30d)	1.003 (1.001, 1.006)
Respiratory broad definition	Early-readmission (1-7d)	1.016 (1.002, 1.031)
Respiratory broad definition	Late-readmission (8-30d)	1.002 (0.999, 1.005)

Table S4. Relative risk (RR ± 95% CI) for early and late all-cause and cause specific readmissions following all-cause, cardiovascular, and respiratory discharges. RR is associated with a 10 μg/m^3 increase in $PM_{2.5}$.

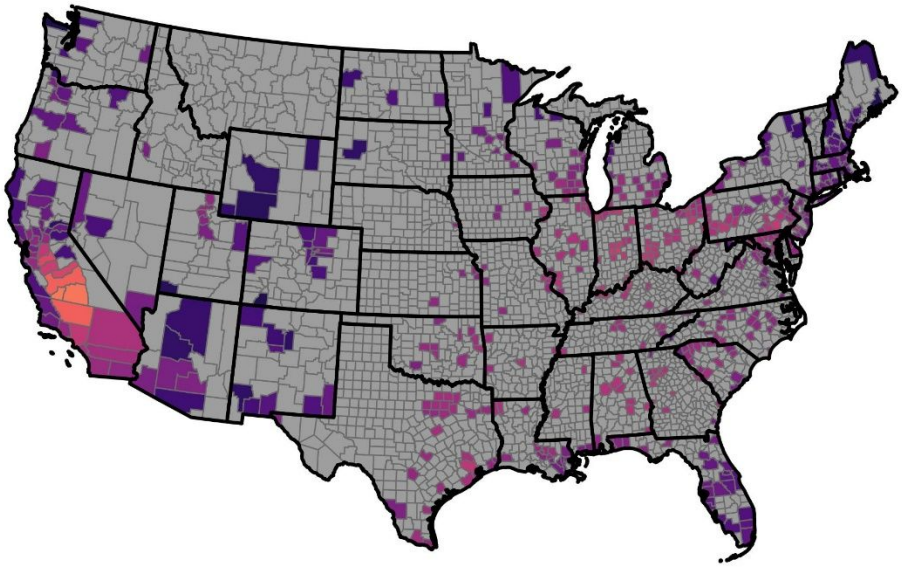
Discharge Cause	Readmission cause	Model	RR (95% CI)
All-cause	All-cause	Early-readmission (1-7d)	1.014 (1.005, 1.024)
All-cause	All-cause	Late-readmission (8-30d)	1.003 (1.001, 1.005)
All-cause	CVD broad definition	Early-readmission (1-7d)	1.009 (0.995, 1.023)
All-cause	CVD broad definition	Late-readmission (8-30d)	1.014 (1.008, 1.020)
All-cause	Dysrhythmia and conduction disorder	Early-readmission (1-7d)	1.046 (1.021, 1.071)
All-cause	Dysrhythmia and conduction disorder	Late-readmission (8-30d)	1.025 (1.015, 1.036)
All-cause	Heart failure	Early-readmission (1-7d)	1.036 (1.013, 1.059)
All-cause	Heart failure	Late-readmission (8-30d)	1.037 (1.027, 1.047)
All-cause	Hypertension	Early-readmission (1-7d)	1.007 (0.990, 1.024)
All-cause	Hypertension	Late-readmission (8-30d)	1.006 (0.999, 1.014)
All-cause	Ischemic heart disease	Early-readmission (1-7d)	0.974 (0.934, 1.016)
All-cause	Ischemic heart disease	Late-readmission (8-30d)	1.016 (0.998, 1.035)
All-cause	Myocardial infarction	Early-readmission (1-7d)	0.962 (0.913, 1.014)
All-cause	Myocardial infarction	Late-readmission (8-30d)	0.999 (0.976, 1.022)
All-cause	Peripheral arterial disease	Early-readmission (1-7d)	0.902 (0.752, 1.083)
All-cause	Peripheral arterial disease	Late-readmission (8-30d)	0.975 (0.903, 1.054)
All-cause	Pulmonary embolism	Early-readmission (1-7d)	1.047 (0.932, 1.177)
All-cause	Pulmonary embolism	Late-readmission (8-30d)	1.032 (0.973, 1.094)
All-cause	Asthma	Early-readmission (1-7d)	1.098 (0.988, 1.222)
All-cause	Asthma	Late-readmission (8-30d)	1.013 (0.971, 1.058)
All-cause	COPD	Early-readmission (1-7d)	1.037 (0.998, 1.077)
All-cause	COPD	Late-readmission (8-30d)	1.022 (1.004, 1.039)
All-cause	Other non-cardiac chest pain or resp syndrome	Early-readmission (1-7d)	1.027 (1.011, 1.042)
All-cause	Other non-cardiac chest pain or resp syndrome	Late-readmission (8-30d)	1.035 (1.029, 1.041)
All-cause	Pneumonia	Early-readmission (1-7d)	1.061 (1.032, 1.092)
All-cause	Pneumonia	Late-readmission (8-30d)	1.046 (1.033, 1.058)

All-cause	Respiratory broad definition	Early-readmission (1-7d)	1.025 (1.011, 1.039)
All-cause	Respiratory broad definition	Late-readmission (8-30d)	1.034 (1.028, 1.040)
CVD broad definition	All-cause	Early-readmission (1-7d)	1.017 (1.004, 1.031)
CVD broad definition	All-cause	Late-readmission (8-30d)	1.003 (1.001, 1.006)
CVD broad definition	CVD broad definition	Early-readmission (1-7d)	1.006 (0.989, 1.024)
CVD broad definition	CVD broad definition	Late-readmission (8-30d)	1.013 (1.005, 1.020)
CVD broad definition	Dysrhythmia and conduction disorder	Early-readmission (1-7d)	1.042 (1.010, 1.074)
CVD broad definition	Dysrhythmia and conduction disorder	Late-readmission (8-30d)	1.027 (1.013, 1.041)
CVD broad definition	Heart failure	Early-readmission (1-7d)	1.027 (1.000, 1.056)
CVD broad definition	Heart failure	Late-readmission (8-30d)	1.031 (1.019, 1.043)
CVD broad definition	Hypertension	Early-readmission (1-7d)	1.006 (0.985, 1.028)
CVD broad definition	Hypertension	Late-readmission (8-30d)	1.002 (0.993, 1.011)
CVD broad definition	Ischemic heart disease	Early-readmission (1-7d)	1.015 (0.964, 1.070)
CVD broad definition	Ischemic heart disease	Late-readmission (8-30d)	1.017 (0.993, 1.041)
CVD broad definition	Myocardial infarction	Early-readmission (1-7d)	0.991 (0.927, 1.058)
CVD broad definition	Myocardial infarction	Late-readmission (8-30d)	1.002 (0.972, 1.032)
CVD broad definition	Peripheral arterial disease	Early-readmission (1-7d)	0.914 (0.688, 1.215)
CVD broad definition	Peripheral arterial disease	Late-readmission (8-30d)	1.029 (0.922, 1.148)
CVD broad definition	Pulmonary embolism	Early-readmission (1-7d)	1.129 (0.984, 1.296)
CVD broad definition	Pulmonary embolism	Late-readmission (8-30d)	1.004 (0.928, 1.085)
CVD broad definition	Asthma	Early-readmission (1-7d)	1.085 (0.947, 1.242)
CVD broad definition	Asthma	Late-readmission (8-30d)	1.006 (0.949, 1.066)
CVD broad definition	COPD	Early-readmission (1-7d)	1.032 (0.982, 1.085)
CVD broad definition	COPD	Late-readmission (8-30d)	1.026 (1.003, 1.049)
CVD broad definition	Other non-cardiac chest pain or resp syndrome	Early-readmission (1-7d)	1.025 (1.005, 1.045)
CVD broad definition	Other non-cardiac chest pain or resp syndrome	Late-readmission (8-30d)	1.036 (1.027, 1.044)
CVD broad definition	Pneumonia	Early-readmission (1-7d)	1.076 (1.036, 1.117)
CVD broad definition	Pneumonia	Late-readmission (8-30d)	1.041 (1.024, 1.058)
CVD broad definition	Respiratory broad definition	Early-readmission (1-7d)	1.026 (1.007, 1.045)
CVD broad definition	Respiratory broad definition	Late-readmission (8-30d)	1.034 (1.026, 1.042)
Respiratory broad definition	All-cause	Early-readmission (1-7d)	1.016 (1.002, 1.031)

Respiratory broad definition	All-cause	Late-readmission (8-30d)	1.002 (1.000, 1.005)
Respiratory broad definition	CVD broad definition	Early-readmission (1-7d)	1.007 (0.988, 1.026)
Respiratory broad definition	CVD broad definition	Late-readmission (8-30d)	1.013 (1.005, 1.021)
Respiratory broad definition	Dysrhythmia and conduction disorder	Early-readmission (1-7d)	1.042 (1.008, 1.077)
Respiratory broad definition	Dysrhythmia and conduction disorder	Late-readmission (8-30d)	1.018 (1.004, 1.033)
Respiratory broad definition	Heart failure	Early-readmission (1-7d)	1.016 (0.987, 1.045)
Respiratory broad definition	Heart failure	Late-readmission (8-30d)	1.028 (1.015, 1.041)
Respiratory broad definition	Hypertension	Early-readmission (1-7d)	1.014 (0.991, 1.039)
Respiratory broad definition	Hypertension	Late-readmission (8-30d)	1.007 (0.997, 1.017)
Respiratory broad definition	Ischemic heart disease	Early-readmission (1-7d)	0.971 (0.918, 1.028)
Respiratory broad definition	Ischemic heart disease	Late-readmission (8-30d)	0.998 (0.973, 1.023)
Respiratory broad definition	Myocardial infarction	Early-readmission (1-7d)	0.940 (0.874, 1.011)
Respiratory broad definition	Myocardial infarction	Late-readmission (8-30d)	0.979 (0.948, 1.011)
Respiratory broad definition	Peripheral arterial disease	Early-readmission (1-7d)	0.844 (0.596, 1.197)
Respiratory broad definition	Peripheral arterial disease	Late-readmission (8-30d)	1.050 (0.935, 1.179)
Respiratory broad definition	Pulmonary embolism	Early-readmission (1-7d)	1.071 (0.910, 1.260)
Respiratory broad definition	Pulmonary embolism	Late-readmission (8-30d)	1.027 (0.941, 1.120)
Respiratory broad definition	Asthma	Early-readmission (1-7d)	1.068 (0.932, 1.224)
Respiratory broad definition	Asthma	Late-readmission (8-30d)	0.973 (0.918, 1.031)
Respiratory broad definition	COPD	Early-readmission (1-7d)	1.039 (0.991, 1.090)
Respiratory broad definition	COPD	Late-readmission (8-30d)	1.015 (0.994, 1.037)
Respiratory broad definition	Other non-cardiac chest pain or resp syndrome	Early-readmission (1-7d)	1.028 (1.008, 1.048)
Respiratory broad definition	Other non-cardiac chest pain or resp syndrome	Late-readmission (8-30d)	1.022 (1.014, 1.030)
Respiratory broad definition	Pneumonia	Early-readmission (1-7d)	1.044 (1.006, 1.084)
Respiratory broad definition	Pneumonia	Late-readmission (8-30d)	1.046 (1.029, 1.063)
Respiratory broad definition	Respiratory broad definition	Early-readmission (1-7d)	1.025 (1.006, 1.044)
Respiratory broad definition	Respiratory broad definition	Late-readmission (8-30d)	1.022 (1.014, 1.030)



A) Long-term county $PM_{2.5}$ (7yr average)



B) 20% of county days are above $PM_{2.5}$ (80th percentile)

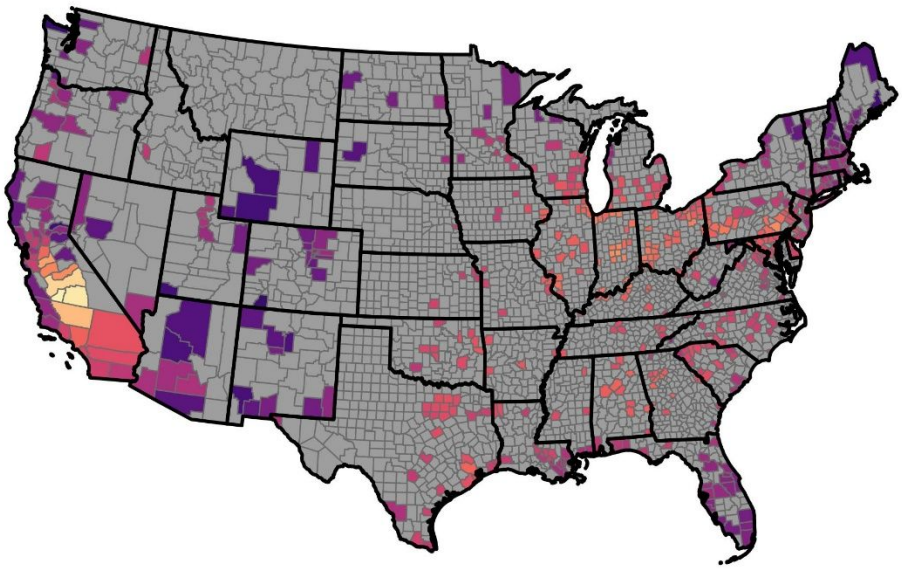


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Figure S1. County $PM_{2.5}$ levels for the 530 counties included in the study. $PM_{2.5}$ levels shown include the A) long-term average and B) 80th percentile (indicating that 20% of county days are at or above this $PM_{2.5}$ level) for the years 2008-2014.

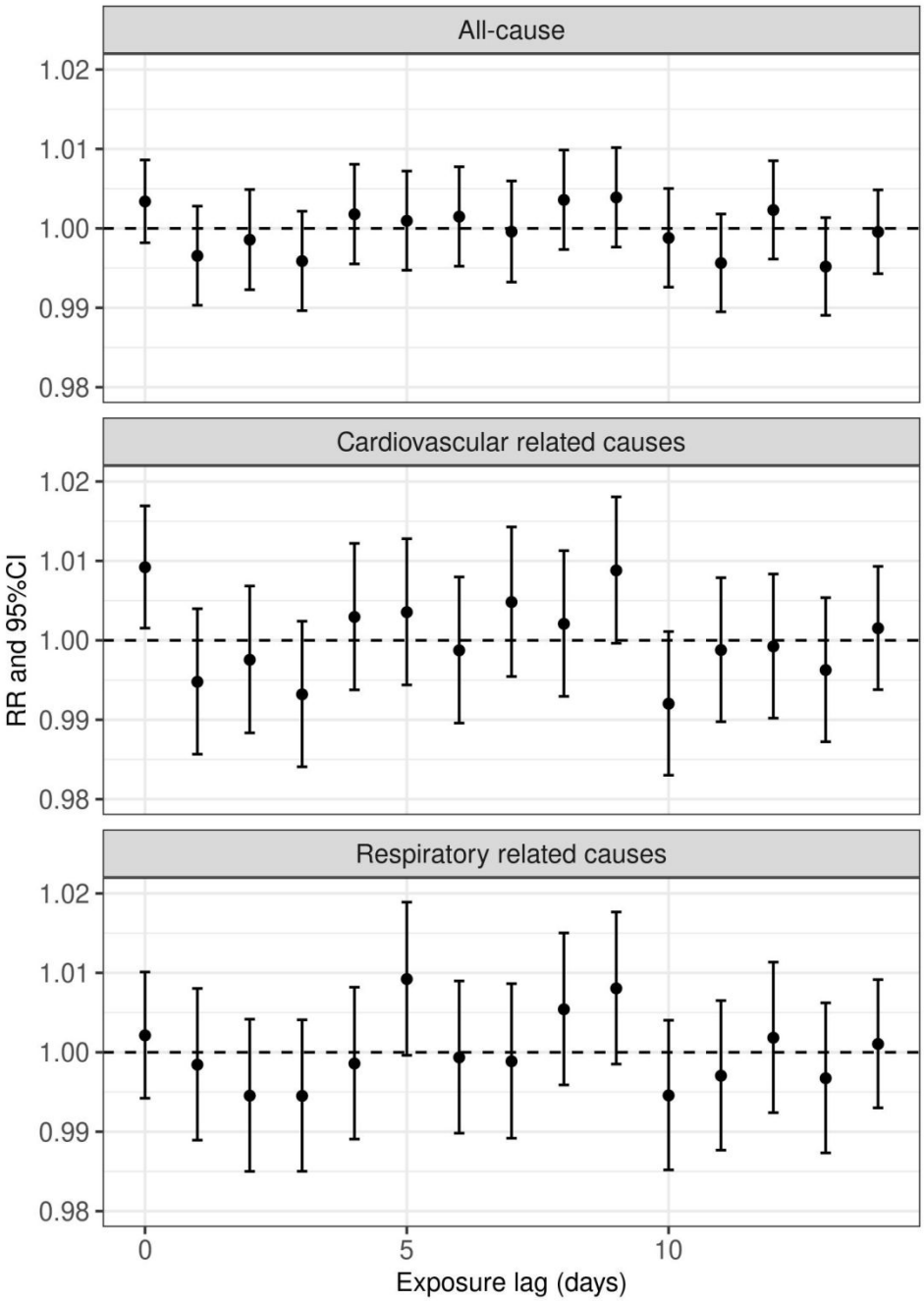

Figure S2. Relative risk (RR ± 95%CI) for daily county admission rates for all-cause hospitalization associated with a 10 μg/m^3 increase in $PM_{2.5}$ for exposure lags 0-14 days using an unconstrained distributed lag model (Table S1).

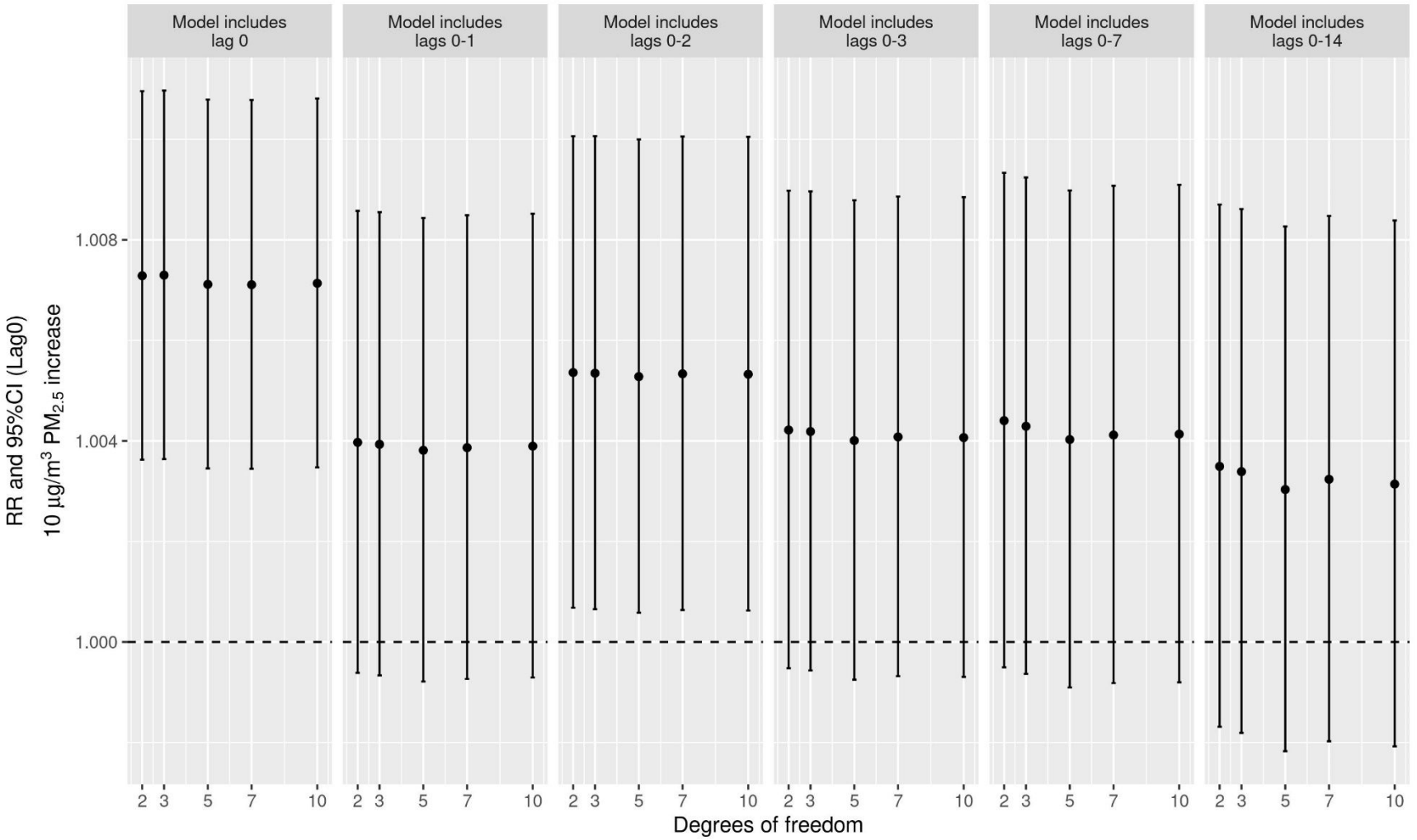

Figure S3. Sensitivity analysis for all-cause admissions models showing the impact on the lag 0 estimate from changing the number of lags considered (grouped figures), and the number of degrees of freedom (x-axis) for the temperature and relative humidity variables. Relative risk (RR ± 95%CI) of all-cause daily county admission rates associated with a 10 µg/m^3 increase in $PM_{2.5}$ on lag 0.

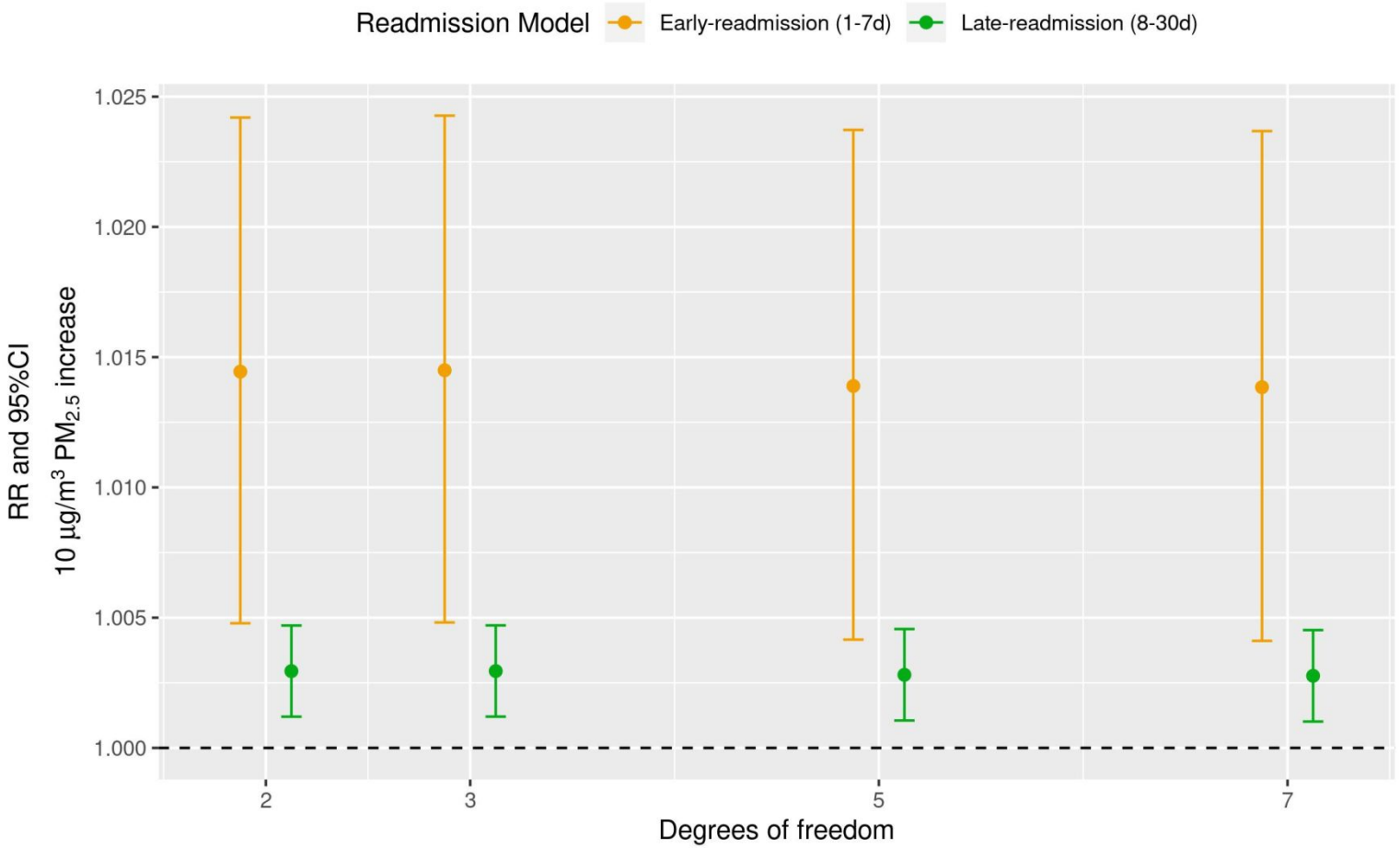

Figure S4. Sensitivity analysis for all-cause readmission models showing the impact on the lag 0 estimate from changing the number of degrees of freedom (x-axis) for the temperature and relative humidity variables. Relative risk (RR ± 95%CI) of all-cause daily county admission rates associated with a 10 µg/m^3 increase in $PM_{2.5}$ on lag 0.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association of short-term exposure to ambient PM2.5 with hospital admissions and 30-day readmissions in end-stage renal disease patients: population based retrospective cohort study

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Title

Association of short-term exposure to ambient $PM_{2.5}$ with hospital admissions and 30-day readmissions in end-stage renal disease patients: population based retrospective cohort study

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Abstract

Objectives: To examine the effect of short-term exposure to ambient fine particulate matter ($PM_{2.5}$) on all-cause, cardiovascular, and respiratory related hospital admissions and readmissions among patients receiving outpatient hemodialysis.

Design: Retrospective cohort study.

Setting: Inpatient hospitalization claims identified from the United States Renal Data System in 530 US counties.

Participants: All patients receiving in-center hemodialysis between 2008 and 2014.

Primary and secondary outcome measures: Risk of all-cause, cardiovascular, and respiratory related hospital admissions and 30-day all-cause and cause-specific readmission following an all-cause, cardiovascular, and respiratory related discharges. Readmission risk was

evaluated for early (1-7 days post-discharge) and late (8-30 days post-discharge) readmission time-periods. Relative risk is expressed per 10 μg/m^3 of $PM_{2.5}$.

Results: Same day ambient $PM_{2.5}$ was associated with increased hospital admission risk for cardiovascular causes (0.9%, 95%CI: [0.2, 1.7]). Greater $PM_{2.5}$-related associations were observed with 30-day readmission risk. Early-readmission risk was increased by 1.6-1.8% following all-cause (1.6%, [0.6, 2.6]), cardiovascular (1.8%, [0.4, 3.2]), and respiratory (1.8%, [0.4, 3.2]) discharges; while late-readmission risk increased by 1.2-1.3% following all-cause and cardiovascular discharges. $PM_{2.5}$-related associations with readmission risk were greatest for certain cause-specific readmissions ranging 4.0-6.5% for dysrhythmia and conduction disorder, heart failure, COPD, other non-cardiac chest pain or respiratory syndrome, and pneumonia. Following all-cause discharges, the cause-specific early-readmission risk was increased by 6.5% (3.5, 9.6) for pneumonia, 4.8% (2.3, 7.4) for dysrhythmia and conduction disorder, 3.7% (1.4, 6.0) for heart failure, and 2.7% (1.2, 4.2) for other non-cardiac chest pain or respiratory syndrome related causes.

Conclusions: Daily ambient $PM_{2.5}$ was associated with an increased risk of cardiovascular admissions and 30-day readmissions following cardiopulmonary-related discharges in a vulnerable ESRD population. In the first week following discharge, greater $PM_{2.5}$-related risk of rehospitalization was identified for some diagnoses.

Strengths and limitations of this study

- Nearly complete representation of hospitalization records (> 1.8 million inpatient admissions), identified using the US Renal Data System, of patients undergoing in-center hemodialysis between 2008 and 2014.
- Location of last dialysis visit was linked with daily population-weighted air pollution.
- Admission risk estimated using time and county stratified design to control for county-level time trends.

- Cox proportional hazard model with time-varying exposure was used to estimate readmission risk associated with daily fluctuations in ambient $PM_{2.5}$ controlled for time-varying confounders.
- Potential diagnosis misclassification from using diagnosis codes to classify cause-specific hospitalizations and exposure misclassification related to $PM_{2.5}$ exposure not captured by ambient air quality near dialysis centers.

Introduction

Ambient fine particulate matter ($PM_{2.5}$) is a leading risk factor for all-cause mortality [1-4], accounting for millions of premature deaths each year [5]. Daily variation in ambient $PM_{2.5}$ is also associated with increased rates of unplanned hospital admissions, urgent care visits, and medication usage [6 7]. Greater health impacts have been observed consistently in sensitive populations, including the elderly and individuals with chronic health conditions such as chronic kidney disease (CKD) [3 8-11]. Additionally, $PM_{2.5}$ exposure during wildfire periods has been shown to increase the risk of mortality among patients managing their end stage renal disease with hemodialysis [12]. However, the role of short-term $PM_{2.5}$ exposure at ambient levels on progression of disease and cause-specific morbidities has not been characterized.

CKD is a progressive condition that affects 8 to 16% of the population worldwide [13-15], and in the final stage, end-stage renal disease (ESRD), many patients are transitioned to hemodialysis to prolong life. Patients receiving dialysis represent a particularly vulnerable population because of high rates of co-morbidities, including diabetes and cardiovascular disease, which may contribute to the greater likelihood of hospital admission and readmission following PM exposure. In the US, patients on hemodialysis average 1.7 inpatient admissions annually with a 30-day readmission rate twice that of other Medicare beneficiaries [16], contributing to a substantial economic impact [17]. In 2016, $35.4 billion in Medicare fee-for-service costs were attributed to ESRD [16], motivating health promotion and cost-containment efforts to slow the progression of CKD and reduce hospitalizations and readmissions [18]. While many current strategies to reduce hospitalizations focus on care processes and patient-level factors [19-22], there is a knowledge gap on the role of modifiable environmental risk factors - specifically ambient $PM_{2.5}$ [2 23-25].

In this study, we examined the risk of daily hospitalization and subsequent 30-day readmission in relation to daily ambient $PM_{2.5}$ using data from the US Renal Data System (USRDS) over a 7-year period. We focused on all-cause, cardiovascular, and respiratory hospitalizations and estimated changes in risk for early (1 to 7 days post-discharge) and late (8 to 30 days post-discharge) readmission accounting for the influence of different causal factors (i.e. acute and chronic illness burden) that may influence early versus late-readmissions [26 27].

Methods

Setting and study population

Using patient level data from the USRDS, we constructed an open cohort of individuals receiving in-center hemodialysis between 2008 and 2014. USRDS is a national data registry for dialysis services and includes records of patient demographic characteristics, hospitalizations, and provider information on all patients receiving hemodialysis. Baseline demographic characteristics (sex, birth date, race, and smoking status) recorded at the initiation of dialysis were extracted from the Medical Evidence Form CMS-2728 for each patient. For every inpatient hospital visit, we extracted the admission date, discharge date, discharge diagnoses codes, and discharge status.

For the analysis of 30-day readmission risk, we considered only admissions where patients were discharged alive. Each readmission was counted once as a readmission relative to the prior index admissions and was then considered as a new index admission. Thus, each admission could serve as both an index admission and readmission, consistent with previous studies [28]. An admission that occurred on the same day as a discharge was combined with the previous admission. These readmissions are likely to represent facility transfers for which we were not able to obtain information. Discharges occurring within 30 days of the end of the study period were excluded, as 30 days of follow-up data were not available. For both admissions and

readmissions, patients could be represented more than once if they were admitted multiple times during the study period.

Health outcomes

The primary outcomes included daily counts of all-cause, respiratory, and cardiovascular-related admissions and the time to readmission following the cause-specific discharges. All-cause and cause-specific readmissions were examined separately. Readmissions were classified further as early-readmissions, occurring within 1 to 7 days of an index hospitalization discharge, and late-readmissions, occurring 8 to 30 days post-discharge.

International Classification of Diseases, 9th Revision (ICD-9) codes were used to identify cause-specific hospitalizations. Cardiovascular-related diagnoses included hypertension (ICD-9 codes 401-405), myocardial infarction (410), ischemic heart disease (410-411, 413), pulmonary embolism (415), dysrhythmia and conduction disorder (426-427), heart failure (428), and peripheral arterial disease (444). Respiratory-related diagnoses included asthma (493), chronic obstructive pulmonary disease (491-492, 496), pneumonia (480-486), and other non-cardiac chest pain or respiratory syndrome (786).

Environmental data

Daily concentrations of fine particulate matter ($PM_{2.5}$) were estimated using a previously described exposure prediction model [29 30]. Briefly, this model estimates daily $PM_{2.5}$ on a 1 km grid for the entire continental US by incorporating satellite aerosol optical depth measurements, chemical transport model simulations, meteorology, land-use, and other variables. Gridded $PM_{2.5}$ estimates were subsequently converted to population-weighted county-level estimates using 2010 Census tract population values. To enable adjustment for potential confounding by weather conditions, temperature and relative humidity data were obtained from the National

Centers for Environmental Information's Global Historical Climatology Network (Global Surface Summary of the Day) [31] and using the Community Multiscale Air Quality model, respectively. The study area was restricted to all counties containing at least one land surface station from the Global Historical Climatology Network (n = 530).

Daily $PM_{2.5}$ was linked to patient hospitalizations based on the county of their last dialysis visit. Previous work has shown that patients in the USRDS cohort that receive in-center dialysis three times a week have a median travel distance of 5.7 miles to their initial dialysis center [32 33].

Study design and statistical analysis

Daily county hospital admissions. The relative risks of hospital admissions associated with daily $PM_{2.5}$ were estimated using a case-crossover design with conditional Poisson models for each of the three health outcomes separately (all-cause, cardiovascular, respiratory). Aggregated counts of daily admissions were time stratified by county-day, where each county served as its own control. For each county-day strata, $PM_{2.5}$ on the day of admission was compared with $PM_{2.5}$ concentrations on control days. Control days were defined as occurring on the same day of the week in the same month and year. This, by design, enabled us to control for differences in county characteristics, such as population size and risk characteristics, and the influence of day of the week, seasonal, and long-term time trends [34].

The relative risk of hospital admissions related to daily $PM_{2.5}$ for each health outcome was estimated using daily counts with respect to county-time strata, adjusted for meteorological conditions (temperature and humidity). Temperature and humidity effects were averaged over lag days 0, 1, and 2 and modeled using natural splines (df = 3) to allow for non-linear effects [35].

We evaluated immediate (same day) and delayed $PM_{2.5}$ effects on all-cause and cause-specific hospital admissions. Unconstrained distributed lag models were used to assess the delayed effects of short-term exposures to $PM_{2.5}$. Delayed exposure up to 14 days and models stratified on county socioeconomic status were considered. To assess the impact of county socioeconomic level, we used the percent of individuals below poverty from the 2010 US Census. Associations were assessed for counties both above and below the median poverty level (12.5%).

Early and late readmissions occurring within 30 days of discharge. Cox proportional hazards models were used to assess the relative risk of early (1 to 7 days post-discharge) and late (8 to 30 days post-discharge) readmission associated with daily $PM_{2.5}$ following all-cause and cause-specific index hospitalizations. Early-readmission models were censored at 7 days and late-readmission models at 30 days.

Models for readmissions incorporated both time-dependent and time-independent risk factors. Time-dependent variables included daily $PM_{2.5}$, daily temperature, daily relative humidity, and day-of-the-week. Time-independent factors included patient-specific, hospitalization event-specific, and county socioeconomic variables. Patient-specific variables included indicator of sex, race, baseline smoking status, whether the patient had three or more previous hospital visits in the year prior, and age at discharge. Event-specific variables included whether the discharge occurred on a holiday and length of stay. To adjust for county socioeconomic level, the percent of individuals below poverty was included as a covariate. Models were also adjusted for patient-specific clusters to account for repeated measures by individual. Lastly, models were adjusted for the competing cause of death by including death as an additional censoring criteria. The presented models represent the cause-specific readmission hazard. Non-linear $PM_{2.5}$ associations were also explored.

Daily county admission and readmission risks were expressed as the rate ratio (RR) per 10-$\mu g/m^3$ increase in $PM_{2.5}$. The proportion hospital admissions and readmissions associated with $PM_{2.5}$ is reported as the attributable fraction (AF), where AF = (RR-1) / RR [36]. All statistical analyses were performed with R software (version 3.6.0) [37].

Results

Characterization of clinical cohort and daily $PM_{2.5}$

Among 361,568 patients who were hospitalized during the study period, 10,274 were excluded due to missing baseline demographic values, with 351,294 patients remaining. Demographic descriptions are in Table 1. Patients had on average 2.97 hospital visits in the year prior to an admission and more than 70% of patients had at least one hospital admission related to cardiovascular and respiratory causes (Table 2). The average daily county-level $PM_{2.5}$ concentration was 9.3 $\mu g/m^3$ (range: 0.05 to 155.16 $\mu g/m^3$) (Table S1). The highest daily county-level $PM_{2.5}$ was observed in California (Figure S1, Supplementary file).

Description of clinical events, hospital admissions, and readmissions

In total, there were 1,801,966 hospital admissions, of which 1,493,795 recorded the patient as alive at discharge. Of admissions that were discharged alive, 11.8% were readmitted within 7 days and 21.3% were readmitted 8 to 30 days post-discharge. The mean length of stay for all-cause, cardiovascular, and respiratory admissions was 7.0, 7.0, and 7.1 days, respectively (Table 2).

Associations between $PM_{2.5}$ and readmission

Early-readmission. Daily $PM_{2.5}$ was positively associated with increased risk for early-readmission following all-cause, cardiovascular, and respiratory related discharges. Same day (lag 0) $PM_{2.5}$ was associated with a 1.6% (95%CI: 0.6, 2.6), 1.8% (95%CI: 0.4, 3.2), and 1.8%

(95%CI: 0.4, 3.2) increased risk of an early-readmission for any cause following all-cause, cardiovascular, and respiratory related discharges, respectively (Figure 1, Table S2).

$PM_{2.5}$ associated early-readmission risk was greater for certain cause-specific outcomes. Following all-cause discharges, same day (lag 0) $PM_{2.5}$ was associated with increased early-readmission risk for dysrhythmia and conduction disorder (4.8% [2.3, 7.4]), heart failure (3.7% [1.4, 6.0]), pneumonia 6.5% [3.5, 9.6]), and other non-cardiac chest pain or respiratory syndrome (2.7% [1.2, 4.2]) causes. $PM_{2.5}$ associated early-readmission risk was greatest for pneumonia related readmissions following cardiovascular related discharges (7.5% [3.5, 11.7]). Other cause-specific early-readmission risks following cardiovascular and respiratory related discharges were similar to estimates observed following discharge for any cause (Figure 2, Table S2).

An average AF at 10 $\mu g/m^3$ of $PM_{2.5}$ at lag 0 was 1.5% (95%CI: 0.6, 2.5), 1.7% (95%CI: 0.4, 3.1), and 1.7% (95%CI: 0.3, 3.2) for an early-readmission for any cause following all-cause, cardiovascular, and respiratory discharges, respectively (Figure 3). County AF ranged 0.5-2.5%, 0.6-2.8%, and 0.6-2.8% for an early-readmission following all-cause, cardiovascular, and respiratory related discharges, respectively (Figure 4).

Late-readmission. Daily $PM_{2.5}$ was also associated with increased risk of late-readmission following all-cause, cardiovascular, and respiratory related discharges and the magnitude of risk related to all-cause readmissions was similar to that observed with early-readmission. Same day $PM_{2.5}$ was associated with a 1.3% (95%CI: 0.6, 2.0), 1.2% (95%CI: 0.3, 2.2), and 1.0% (95%CI: 0.01, 2.0) increased risk of a late all-cause readmission following all-cause, cardiovascular, and respiratory related discharges, respectively (Figure 1, Table S2).

Similar to observations made for early-readmissions, $PM_{2.5}$ associated late-readmission risk was greater for certain cause-specific outcomes. Following all-cause discharges, a 10 μg/m^3 increase in same day (lag 0) $PM_{2.5}$ was associated with increased late-readmission risk for dysrhythmia and conduction disorder (3.1% [1.3, 5.0]), heart failure (4.1% [2.5, 5.8]), COPD (4.6% [1.7, 7.6]), pneumonia (5.9% [3.7, 8.2]), and other non-cardiac chest pain or respiratory syndrome (3.0% [1.9, 4.1]) (Figure 2, Table S2).

The average AF at 10 μg/m^3 was 0.1% (95%CI: 0.5, 1.8) and 1.0% (95%CI: 0.1, 2.0) for a late-readmission following all-cause and cardiovascular discharges, respectively (Figure 3). County AF ranged 0.3-1.9% for a late-readmission following any cause (data not shown).

Associations between $PM_{2.5}$ and daily admissions

Same day $PM_{2.5}$ was associated with an increase in rate ratio of 0.3% (95%CI: -0.2, 0.9) for all-cause admissions and 0.9% (95%CI: 0.2, 1.7) for cardiovascular admissions (Figure S2, Table S3, Supplementary file). We estimated 0.9% (95%CI: 0.1, 1.7) of cardiovascular admissions could be attributed to 10 μg/m^3 ambient $PM_{2.5}$ (Figure 3). Across counties, exposures accounted for 0.3% to 1.5% of cardiovascular admissions when evaluated at the average daily $PM_{2.5}$ for each county (data not shown).

No change in risk of all-cause and cardiovascular admissions was observed related to prior exposure (lags 1-14). Similarly, no change in risk for respiratory admissions was observed with same day exposure (lag 0) or prior exposure (lags 1-14) (Figure S2, Table S3, Supplementary file). The model with a dose-specific association for $PM_{2.5}$ (non-linear dose-response function) did not improve model fit. Models stratified on median percent below poverty were similar (Figure S2, Table S3, Supplementary file). In a sensitivity analysis, changing the number of

degrees of freedom considered for temperature and relative humidity had a negligible effect (Figure S3, Figure S4, Supplementary file).

Discussion

In a nationwide cohort study of 351,294 patients with ESRD managed with hemodialysis, we evaluated the association between 1.8 million inpatient admissions and nearly 0.5 million corresponding 30-day readmissions and the variation in daily ambient $PM_{2.5}$ in the US over 7 years, 2008-2014. Daily variation in $PM_{2.5}$ was associated with increased risk of hospital admission and even greater risk of rehospitalization. Following all-cause, cardiovascular, and respiratory related discharges, the early-readmission risk for any cause was increased by 1.6, 1.8, 1.8%, respectively per 10 μg/m^3 increase in daily $PM_{2.5}$. Importantly, readmissions related to some cardiorespiratory diagnoses had the greatest $PM_{2.5}$ attributed readmission risk that was observed to be elevated for both early and late-readmissions. The early-readmission risk following all-cause discharges, was increased by 6.5, 4.8, 3.7, and 2.7% for pneumonia, dysrhythmia and conduction disorder, heart failure, and other non-cardiac chest pain or respiratory syndrome related readmissions, respectively. Overall, these results suggest that at 10 μg/m^3, 1.5-1.7% of early-readmissions for any cause were attributable to short-term exposure. In the context of the daily $PM_{2.5}$ National Ambient Air Quality Standard (35 μg/m^3), this attributable fraction would be 5.3-6.0%.

Our findings are consistent with previous studies that observed increased admission risks in elderly populations [6 9 38-42] and patients with cardiovascular health complications [7 43], and increased readmission risk following cardiovascular related admissions [7 43 44]. Studies in the Medicare population similarly observed a 1-2% increase in cardiovascular hospital admissions associated with same-day $PM_{2.5}$ concentrations [6 9 38 40]. Risk appears to vary by diagnosis, as the increased risk was slightly less (0.13%) for ST-elevation myocardial infarction related

admissions in a Chinese population [7] and greater (29%) for incident heart failure admissions in an Australian population [43]. Increases in respiratory admissions (1-2%) have been noted in the Medicare population [6 9 38-40], but were not observed in this study. Prior studies provide evidence that air pollution exposure is associated with adverse health outcomes including increased infection rates, acute lung edema, and elevated concentrations of systematic inflammation markers [45-47]. Despite known associations between PM exposure and adverse cardiovascular and respiratory health outcomes, previous studies have not evaluated the impacts on hospital readmissions among individuals with ESRD.

Few studies have examined $PM_{2.5}$-related effects on readmissions, and those that have report on the long-term (>1yr) risk following cardiovascular related admissions. Following cardiovascular hospitalization, greater $PM_{2.5}$-related rehospitalization risk was observed for some cardiac and respiratory readmissions (dysrhythmia, pneumonia) compared to our observations of all-cause readmissions (4.3-7.5% vs 1.6%).

Studies in other populations, have noted similar same-day cardiovascular related readmission risks of 5.5-7.7% and 2.6% associated with $PM_{2.5}$ [7] and PM_{10} [44], respectively. Additionally, one study in an Australian population with very low ambient air pollution concentrations (mean $PM_{2.5}$ = 2.9 μg/m^3) found no relationship between $PM_{2.5}$ and all-cause readmissions after an incident heart failure hospitalization [43]. In some instances, short-term readmission risks were greater in comparison to the long-term readmission risks, suggesting the week following a discharge to be a window of heightened vulnerability. Prior work indicates that factors related to index hospitalizations and acute illness burden are predictive of an early-readmission [26 27]. This may indicate that hospital readmissions related to certain acute illness burdens may be more susceptible to $PM_{2.5}$ exposure.

Our study contributes to the currently limited literature on the association between air pollution and health impacts among hemodialysis patients and shines a light on the vulnerability in this clinical population related to ambient airborne particulate matter. The 30-day rehospitalization rate is 33% in this population, which is twice that of older Medicare beneficiaries without a kidney disease diagnosis [16]. As many as 70% of readmissions are thought to be unnecessary [48], prompting efforts to improve outcomes. Economic healthcare costs associated with short-term increases in $PM_{2.5}$ are considerable; annual inpatient and post-acute care costs related to a 10 $\mu g/m^3$ in daily $PM_{2.5}$ ranges $30-70 million for cardiovascular and respiratory related diseases [49]. $PM_{2.5}$ is a modifiable risk factor and reductions in short-term exposures could contribute to reduced healthcare costs. Our findings suggest that short-term increases in $PM_{2.5}$ contribute to healthcare usage through unplanned admissions and readmissions.

Additionally, the findings of the study may have a broader public health implication. In the conceptual framework for public health action, ambient airborne particulate matter fits well into the base of a 5-tiered pyramid as a socioeconomic or social determinant of health [50]. Interventions that address the base of the pyramid may provide the greatest potential impact given the widespread population exposure of such a determinant of health like ambient airborne particulate matter. Mitigation strategies would need to include policy initiatives to curb the expulsion of airborne pollutants, as well as education of persons, patients, hospital staff, and others. Areas with the higher concentrations of ambient airborne particulate matter may see the greatest benefit from mitigation strategies.

Strengths and Limitations

This study included a nearly complete cohort of US patients undergoing in-center hemodialysis. To our knowledge this is the largest analysis of short-term exposure to air pollution in the US in this highly vulnerable population. The USRDS registry provides a complete registry of all

hospitalizations and contains detailed information regarding demographics, dialysis, hospitalization, rehospitalization, and co-morbid conditions. Secondly, ambient $PM_{2.5}$ was estimated using a prediction model with highly resolved spatial and temporal resolution with proven accuracy [29 30]. Thirdly, the time-stratified design allowed for county matching that reduced the potential confounding by factors that very slowly with time and those that are time-invariant. Fourthly, the use of time-dependent risk factors in the Cox proportional hazard model allowed for readmission risk estimates to reflect the risk associated with daily fluctuations in ambient $PM_{2.5}$ and time-varying confounders.

This study also had some limitations. Firstly, there was the potential for exposure misclassification as the location of the last dialysis visit was used to estimate individual level exposures. $PM_{2.5}$ around dialysis centers could differ from concentrations around hospitals and patient residences. However, given that patients generally reside less than 6 miles from their initial dialysis center, differences in temporal variation of exposure should be small and not likely to contribute a systematic bias favoring an association between ambient $PM_{2.5}$ and clinical events [32 33]. Secondly, diagnosis misclassification was possible but was not likely to confound the relationship because it is not likely to vary on the same temporal scale as $PM_{2.5}$. Thirdly, there is the possibility that some unmeasured time variant factors may have confounded our estimates (smoking status, medication usage, behaviors, lipid levels, C-reactive protein levels, etc.). Data availability restricted the consideration of some patient level confounders, such as smoking status, to values recorded at baseline. We used a time stratified design to control for time-varying confounding for time scales larger than a month, such as the number of patients enrolled in the USRDS. At scales smaller than a month, the control of person time was not possible. Lastly, generalization of the results is limited to the Medicare population with ESRD managed with hemodialysis treatment. Future studies are needed to understand $PM_{2.5}$-related

impacts on specific health conditions, and if health impacts vary based on race, socioeconomic indicators, or other individual and population factors.

Conclusion

In conclusion, this United States wide cohort study identified increased risk in patients receiving in-center hemodialysis associated with short-term increases in ambient air particle pollution. Elevated $PM_{2.5}$ concentrations were found to be associated with increased inpatient hospital admissions related to cardiovascular causes, and an increased likelihood of hospital readmission following cardiovascular and respiratory related hospitalizations. Medicare spending for beneficiaries with ESRD is high. Traditional efforts to reduce the burden of disease focus on patient factors; however, these data suggest that air particle pollution is a factor that contributes to increased risks for hospital admission and subsequent readmission. To reduce $PM_{2.5}$-related morbidities, we echo the recommendations made in the Million Hearts initiative, that healthcare systems, insurers, physicians, and health care professionals should incorporate health risks related to ambient PM into patient care.

Disclaimer

The research described in this article has been reviewed by the Center for Public Health and the Environment, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency, nor does the mention of trade names of commercial products constitute endorsement or recommendation for use.

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Contributors

LHW, AGR conceived and designed the study. TJW, WEC, and AVK provided subject expert input into the study design and interpretation of evidence. AVK, QD, and CWC provided access to the data for the study; LHW managed and analyzed the data and AGR oversaw the analysis. LHW and AGR wrote the first draft of the manuscript. LHW, YX, AVK, CWC, TJW, WEC, and AGR critically contributed to the manuscript and approved the final draft. LHW and AGR are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This study was reviewed by the institutional review board at the University of North Carolina at Chapel Hill and determined to be exempt based on the study design involving secondary data analysis (IRB Number: 20-0984).

Data sharing

Data access to USRDS data sets is through an internal data use agreement with the University of North Carolina at Chapel Hill's Cecil G. Sheps Center. $PM_{2.5}$ data was obtained through collaboration with Drs. Joel Schwartz (Harvard TH Chan School of Public Health) and Qian Di (Tsinghua University). For general data sharing inquiries, contact rappold.ana@epa.gov or wyatt.lauren@epa.gov.

Transparency

The lead and corresponding authors (LHW and AGR) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient and Public Involvement

This study utilized a deidentified database, thus contact with patients was not possible.

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Figure 1. The relative risk (RR, 95%CI) for an all-cause early and late-readmission following all-cause and cause-specific discharges. Discharges are color coded: all-cause discharges are indicated in black, cardiovascular causes in orange, and respiratory causes in blue. Early-readmissions are indicated with filled in circles, late-readmissions with open circles. RR is expressed per 10 μg/m^3 increase in $PM_{2.5}$.

Figure 2. The relative risk (RR, 95%CI) of cause-specific early and late-readmission following all-cause discharge. Readmission causes are color coded: all-cause readmissions are indicated in black, cardiovascular causes in orange, and respiratory causes in blue. RR is expressed per 10 μg/m^3 increase in $PM_{2.5}$.

Figure 3. Mean proportion (95%CI) of all-cause and cause-specific hospital admissions, early readmissions (1-7d), and late readmissions (8-30d) with respect to $PM_{2.5}$ (μg/m^3). Hash marks above the x-axis represent the density of daily county PM2.5. The 95% CI under 15.9 μg/m^3 is shaded darker to indicate where 90 percent of the data falls.

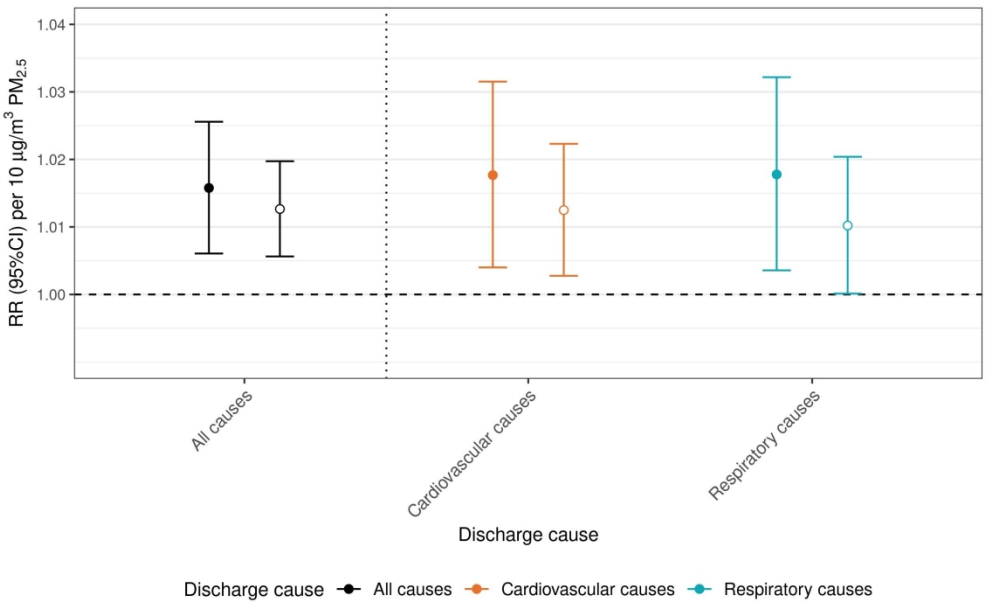
Figure 4. Average daily county $PM_{2.5}$ (μg/m^3) between 2008 and 2014 (A) and the attributable fraction for early-readmission following an all-cause discharge based on the average $PM_{2.5}$ (B) for the 530 counties included in the study.

Table 1. Baseline Demographic Characteristics of the Study Population Between 2008 and 2014 by Hospital Admission Category.

Characteristic	No. (%)		
	All-cause	Cardiovascular	Respiratory
	N = 351,294	n = 262,385	n = 247,829
Age (yr), mean (SD)	64·69 (14.70)	65·58 (14.53)	65·61 (14.48)
Male sex (%)	190,716 (54.3)	140,206 (53.4)	132,288 (53.4)
Race			
White	209,921 (59.8)	155,405 (59.2)	147,204 (59.4)
Black	122,943 (35.0)	93,325 (35.6)	87,831 (35.4)
Other	18,430 (5.2)	13,655 (5.2)	12,794 (5.2)
Smoking status at initiation (no)	330,837 (94.2)	246,634 (94.0)	232,396 (93.8)

Table 2. Hospital Admission Characteristics Among the Study Population Between 2008 and 2014.

Outcome	Number of Events (Number of Unique Patients)		
	All-cause	Cardiovascular	Respiratory
Admissions	1,801,966 (351,294)	832,255 (262,385)	766,447 (247,829)
Discharged alive	1,493,795 (312,521)	685,680 (229,780)	637,250 (217,221)
Early-readmission (1-7d)	176,822 (91,508)	83,193 (52,374)	78,392 (49,343)
Late-readmission (8-30d)	317,948 (130, 454)	150,080 (80,851)	141,656 (76,444)
Length of stay, d			
Mean (SD)	6.98 (10.68)	7.05 (10.34)	7.07 (10.38)
Median (IQR)	4 (2-7)	4 (2-8)	4 (2-8)
Hospital visits in prior year			
3+ visits	637,503 (123,949)	307,891 (93,399)	292,803 (89,905)
Mean (SD)	2.97 (3.80)	3.14 (3.95)	3.21 (3.89)
Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)



The relative risk (RR, 95%CI) for an all-cause early and late-readmission following all-cause and cause-specific discharges. Discharges are color coded: all-cause discharges are indicated in black, cardiovascular causes in orange, and respiratory causes in blue. Early-readmissions are indicated with filled in circles, late-readmissions with open circles. RR is expressed per 10 µg/m3 increase in PM2.5.

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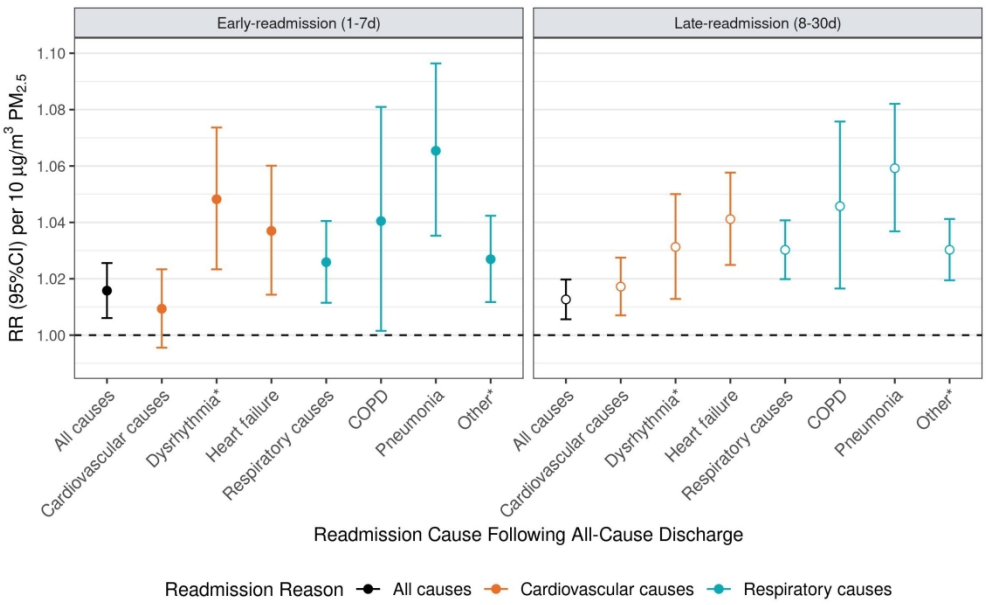

The relative risk (RR, 95%CI) of cause-specific early and late-readmission following all-cause discharge. Readmission causes are color coded: all-cause readmissions are indicated in black, cardiovascular causes in orange, and respiratory causes in blue. RR is expressed per 10 µg/m3 increase in PM2.5.

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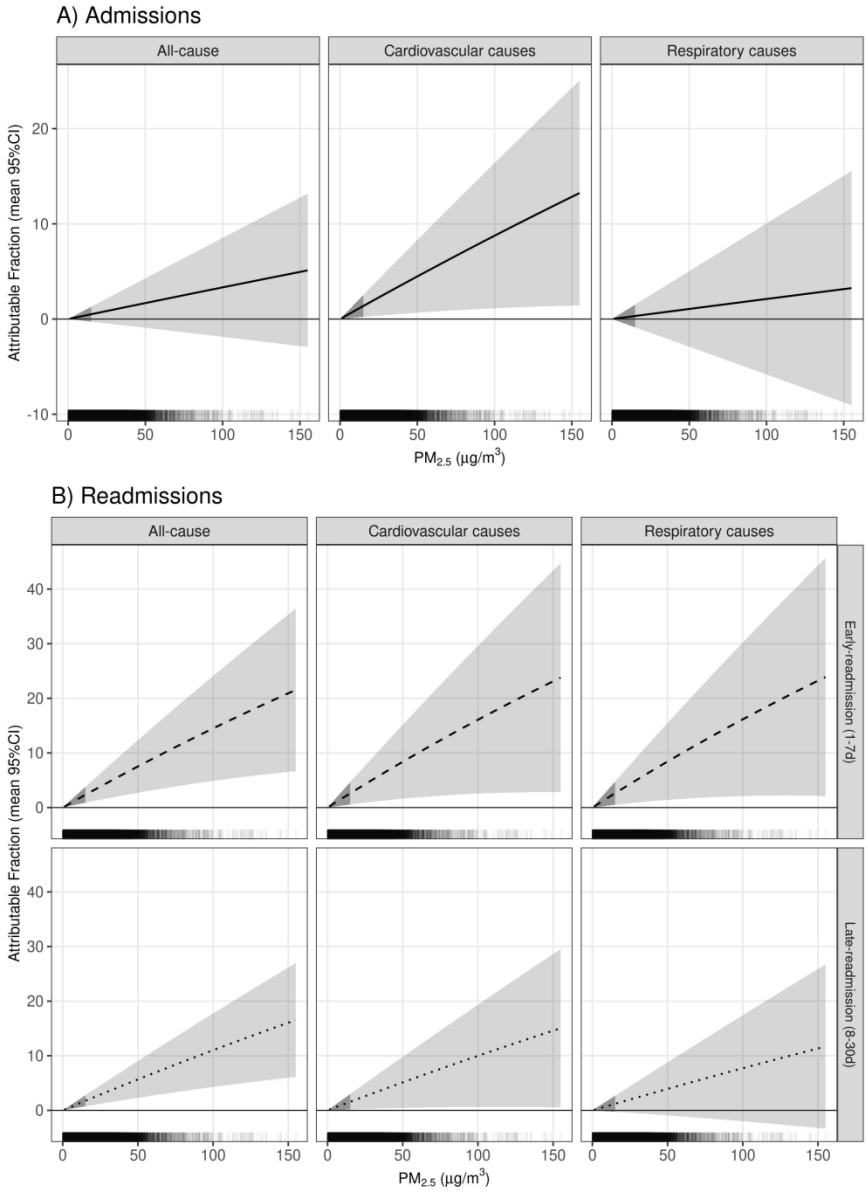

Mean proportion (95%CI) of all-cause and cause-specific hospital admissions, early readmissions (1-7d), and late readmissions (8-30d) with respect to PM2.5 (µg/m3). Hash marks above the x-axis represent the density of daily county PM2.5. The 95% CI under 15.9 µg/m3 is shaded darker to indicate where 90 percent of the data falls.

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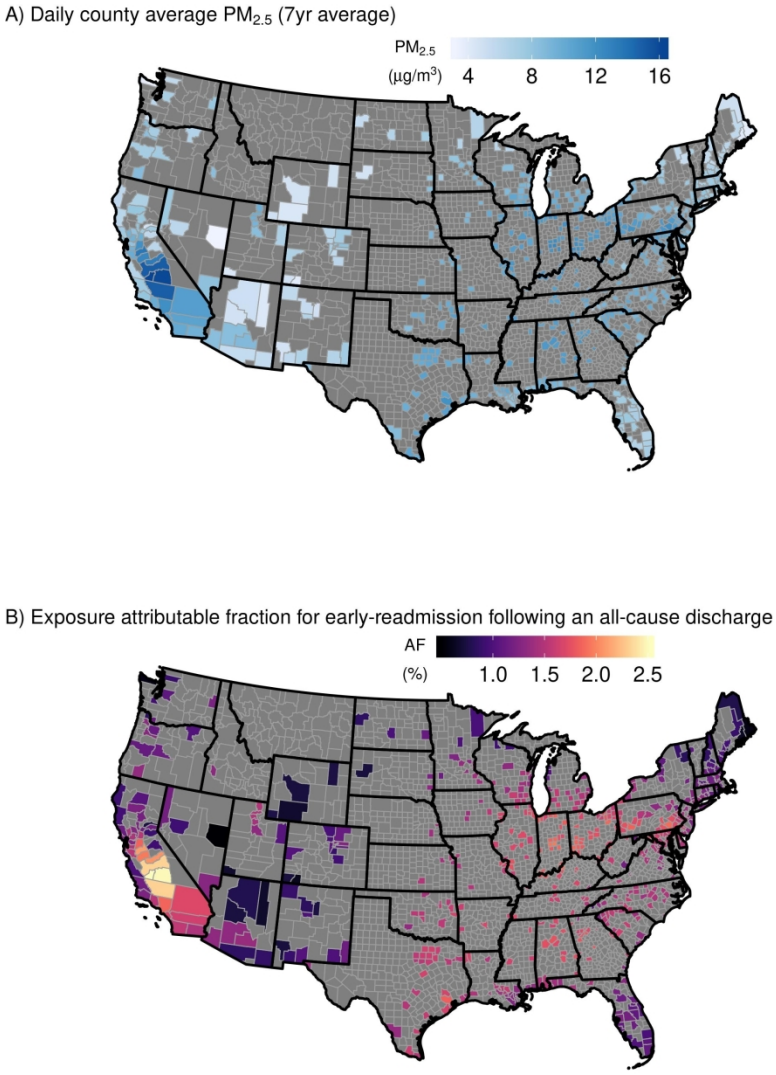

Average daily county PM2.5 (µg/m3) between 2008 and 2014 (A) and the attributable fraction for early-readmission following an all-cause discharge based on the average PM2.5 (B) for the 530 counties included in the study.

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Supplemental Materials

Table S1. Summary statistics of $PM_{2.5}$ and meteorological variables across 530 counties.

Variable	Mean ± SD	Minimum	Maximum
$PM_{2.5}$ ($\mu g/m^3$)	9.29 ± 5.39	0.05	155.16
Temperature (°F)	56.37 ± 18.50	-37.30	104.74
Relative humidity (%)	65.24 ± 16.24	0	100

Table S2. The relative risk (RR, 95%CI) for an all-cause, cardiovascular, and respiratory related early and late-readmission following all-cause and cause-specific discharges. RR is expressed per 10 μg/m^3 increase in $PM_{2.5}$. Models presented include the main model presented in the paper (model 1) where $PM_{2.5}$ is considered as a linear variable and a model that considers $PM_{2.5}$ as a non-linear variable (model 2).

			Model 1 PM linear	Model 2 PM non-linear
Readmission model	Discharge cause	Readmission cause	RR (95%CI)	RR (95%CI)
Early-readmission (1-7d)	All Causes	All Causes	1.016 (1.006, 1.026)	1.089 (1.016, 1.168)
Early-readmission (1-7d)	All Causes	All Cardiovascular	1.009 (0.996, 1.023)	0.984 (0.892, 1.085)
Early-readmission (1-7d)	All Causes	Dysrhythmia*	1.048 (1.023, 1.074)	0.898 (0.754, 1.070)
Early-readmission (1-7d)	All Causes	Heart failure	1.037 (1.014, 1.060)	1.065 (0.906, 1.252)
Early-readmission (1-7d)	All Causes	Hypertension	1.007 (0.990, 1.025)	1.011 (0.895, 1.141)
Early-readmission (1-7d)	All Causes	Ischemic heart disease	0.970 (0.929, 1.012)	0.910 (0.678, 1.222)
Early-readmission (1-7d)	All Causes	Myocardial infarction	0.955 (0.906, 1.007)	0.940 (0.651, 1.358)
Early-readmission (1-7d)	All Causes	Peripheral arterial disease	0.900 (0.748, 1.083)	0.389 (0.121, 1.254)
Early-readmission (1-7d)	All Causes	All Respiratory	1.026 (1.011, 1.040)	1.082 (0.977, 1.199)
Early-readmission (1-7d)	All Causes	Asthma	1.102 (0.992, 1.226)	0.464 (0.240, 0.900)
Early-readmission (1-7d)	All Causes	COPD	1.040 (1.002, 1.081)	1.021 (0.763, 1.366)
Early-readmission (1-7d)	All Causes	Other*	1.027 (1.012, 1.042)	1.093 (0.981, 1.218)
Early-readmission (1-7d)	All Causes	Pneumonia	1.065 (1.035, 1.096)	1.263 (1.012, 1.576)
Early-readmission (1-7d)	All Causes	Pulmonary embolism	1.047 (0.930, 1.179)	0.911 (0.371, 2.233)
Early-readmission (1-7d)	All Cardiovascular	All Causes	1.018 (1.004, 1.032)	1.034 (0.933, 1.145)
Early-readmission (1-7d)	All Cardiovascular	All Cardiovascular	1.006 (0.989, 1.024)	0.938 (0.823, 1.070)
Early-readmission (1-7d)	All Cardiovascular	Dysrhythmia*	1.043 (1.012, 1.076)	1.006 (0.793, 1.278)
Early-readmission (1-7d)	All Cardiovascular	Heart failure	1.027 (0.999, 1.056)	0.994 (0.810, 1.221)
Early-readmission (1-7d)	All Cardiovascular	Hypertension	1.006 (0.985, 1.028)	0.911 (0.776, 1.069)
Early-readmission (1-7d)	All Cardiovascular	Ischemic heart disease	1.014 (0.963, 1.069)	0.888 (0.603, 1.309)
Early-readmission (1-7d)	All Cardiovascular	Myocardial infarction	0.987 (0.924, 1.054)	0.901 (0.557, 1.459)
Early-readmission (1-7d)	All Cardiovascular	Peripheral arterial disease	0.924 (0.693, 1.230)	0.195 (0.044, 0.875)

Early-readmission (1-7d)	All Cardiovascular	All Respiratory	1.025 (1.006, 1.045)	1.015 (0.882, 1.169)
Early-readmission (1-7d)	All Cardiovascular	Asthma	1.086 (0.948, 1.243)	0.335 (0.144, 0.781)
Early-readmission (1-7d)	All Cardiovascular	COPD	1.035 (0.985, 1.087)	0.877 (0.604, 1.275)
Early-readmission (1-7d)	All Cardiovascular	Other*	1.025 (1.005, 1.045)	1.067 (0.919, 1.238)
Early-readmission (1-7d)	All Cardiovascular	Pneumonia	1.075 (1.035, 1.117)	1.124 (0.831, 1.521)
Early-readmission (1-7d)	All Cardiovascular	Pulmonary embolism	1.134 (0.986, 1.303)	1.879 (0.544, 6.491)
Early-readmission (1-7d)	All Respiratory	All Causes	1.018 (1.004, 1.032)	1.041 (0.939, 1.154)
Early-readmission (1-7d)	All Respiratory	All Cardiovascular	1.007 (0.988, 1.026)	1.011 (0.880, 1.161)
Early-readmission (1-7d)	All Respiratory	Dysrhythmia*	1.045 (1.011, 1.080)	0.936 (0.731, 1.198)
Early-readmission (1-7d)	All Respiratory	Heart failure	1.017 (0.988, 1.047)	0.989 (0.802, 1.220)
Early-readmission (1-7d)	All Respiratory	Hypertension	1.014 (0.990, 1.038)	1.056 (0.885, 1.260)
Early-readmission (1-7d)	All Respiratory	Ischemic heart disease	0.971 (0.918, 1.028)	0.783 (0.534, 1.149)
Early-readmission (1-7d)	All Respiratory	Myocardial infarction	0.938 (0.872, 1.009)	0.682 (0.422, 1.102)
Early-readmission (1-7d)	All Respiratory	Peripheral arterial disease	0.857 (0.603, 1.219)	0.189 (0.035, 1.004)
Early-readmission (1-7d)	All Respiratory	All Respiratory	1.025 (1.006, 1.044)	1.087 (0.947, 1.248)
Early-readmission (1-7d)	All Respiratory	Asthma	1.074 (0.938, 1.230)	0.407 (0.180, 0.920)
Early-readmission (1-7d)	All Respiratory	COPD	1.041 (0.993, 1.092)	0.856 (0.600, 1.223)
Early-readmission (1-7d)	All Respiratory	Other*	1.028 (1.008, 1.048)	1.114 (0.963, 1.289)
Early-readmission (1-7d)	All Respiratory	Pneumonia	1.049 (1.011, 1.089)	1.185 (0.890, 1.578)
Early-readmission (1-7d)	All Respiratory	Pulmonary embolism	1.075 (0.913, 1.265)	0.921 (0.265, 3.202)
Late-readmission (8-30d)	All Causes	All Causes	1.013 (1.006, 1.020)	1.024 (0.974, 1.077)
Late-readmission (8-30d)	All Causes	All Cardiovascular	1.017 (1.007, 1.027)	1.071 (0.995, 1.153)
Late-readmission (8-30d)	All Causes	Dysrhythmia*	1.031 (1.013, 1.050)	1.103 (0.961, 1.266)
Late-readmission (8-30d)	All Causes	Heart failure	1.041 (1.025, 1.058)	1.027 (0.915, 1.154)
Late-readmission (8-30d)	All Causes	Hypertension	1.010 (0.998, 1.023)	1.036 (0.947, 1.135)
Late-readmission (8-30d)	All Causes	Ischemic heart disease	1.008 (0.975, 1.042)	0.858 (0.676, 1.089)
Late-readmission (8-30d)	All Causes	Myocardial infarction	0.974 (0.933, 1.017)	0.722 (0.538, 0.968)
Late-readmission (8-30d)	All Causes	Peripheral arterial disease	1.003 (0.873, 1.153)	1.367 (0.511, 3.653)
Late-readmission (8-30d)	All Causes	All Respiratory	1.030 (1.020, 1.041)	1.083 (1.004, 1.169)
Late-readmission (8-30d)	All Causes	Asthma	1.071 (0.998, 1.150)	1.327 (0.739, 2.382)
Late-readmission (8-30d)	All Causes	COPD	1.046 (1.017, 1.076)	1.001 (0.813, 1.232)
Late-readmission (8-30d)	All Causes	Other*	1.030 (1.019, 1.041)	1.113 (1.028, 1.206)

Late-readmission (8-30d)	All Causes	Pneumonia	1.059 (1.037, 1.082)	1.104 (0.940, 1.297)
Late-readmission (8-30d)	All Causes	Pulmonary embolism	1.063 (0.959, 1.178)	1.774 (0.742, 4.240)
Late-readmission (8-30d)	All Cardiovascular	All Causes	1.012 (1.003, 1.022)	1.030 (0.956, 1.109)
Late-readmission (8-30d)	All Cardiovascular	All Cardiovascular	1.016 (1.003, 1.029)	1.048 (0.950, 1.157)
Late-readmission (8-30d)	All Cardiovascular	Dysrhythmia*	1.035 (1.012, 1.058)	1.058 (0.884, 1.266)
Late-readmission (8-30d)	All Cardiovascular	Heart failure	1.035 (1.015, 1.055)	1.055 (0.907, 1.227)
Late-readmission (8-30d)	All Cardiovascular	Hypertension	1.007 (0.991, 1.023)	1.002 (0.889, 1.129)
Late-readmission (8-30d)	All Cardiovascular	Ischemic heart disease	0.977 (0.936, 1.020)	0.740 (0.542, 1.010)
Late-readmission (8-30d)	All Cardiovascular	Myocardial infarction	0.946 (0.894, 1.002)	0.593 (0.405, 0.868)
Late-readmission (8-30d)	All Cardiovascular	Peripheral arterial disease	1.013 (0.815, 1.258)	1.084 (0.257, 4.566)
Late-readmission (8-30d)	All Cardiovascular	All Respiratory	1.028 (1.015, 1.042)	1.086 (0.978, 1.206)
Late-readmission (8-30d)	All Cardiovascular	Asthma	1.057 (0.963, 1.160)	1.424 (0.654, 3.097)
Late-readmission (8-30d)	All Cardiovascular	COPD	1.047 (1.011, 1.084)	0.840 (0.645, 1.094)
Late-readmission (8-30d)	All Cardiovascular	Other*	1.028 (1.014, 1.042)	1.130 (1.012, 1.262)
Late-readmission (8-30d)	All Cardiovascular	Pneumonia	1.052 (1.023, 1.082)	1.203 (0.963, 1.504)
Late-readmission (8-30d)	All Cardiovascular	Pulmonary embolism	1.036 (0.909, 1.181)	1.251 (0.389, 4.020)
Late-readmission (8-30d)	All Respiratory	All Causes	1.010 (1.000, 1.020)	1.039 (0.963, 1.120)
Late-readmission (8-30d)	All Respiratory	All Cardiovascular	1.020 (1.006, 1.034)	1.076 (0.970, 1.194)
Late-readmission (8-30d)	All Respiratory	Dysrhythmia*	1.037 (1.012, 1.062)	1.053 (0.869, 1.277)
Late-readmission (8-30d)	All Respiratory	Heart failure	1.034 (1.013, 1.055)	1.130 (0.968, 1.319)
Late-readmission (8-30d)	All Respiratory	Hypertension	1.013 (0.996, 1.030)	1.040 (0.914, 1.184)
Late-readmission (8-30d)	All Respiratory	Ischemic heart disease	0.975 (0.932, 1.002)	0.759 (0.553, 1.040)
Late-readmission (8-30d)	All Respiratory	Myocardial infarction	0.948 (0.893, 1.006)	0.710 (0.472, 1.069)
Late-readmission (8-30d)	All Respiratory	Peripheral arterial disease	1.102 (0.894, 1.359)	1.895 (0.351, 10.226)
Late-readmission (8-30d)	All Respiratory	All Respiratory	1.019 (1.005, 1.032)	1.078 (0.974, 1.193)
Late-readmission (8-30d)	All Respiratory	Asthma	0.996 (0.905, 1.095)	1.200 (0.579, 2.489)
Late-readmission (8-30d)	All Respiratory	COPD	1.026 (0.991, 1.063)	0.887 (0.691, 1.138)
Late-readmission (8-30d)	All Respiratory	Other*	1.019 (1.005, 1.033)	1.119 (1.005, 1.246)
Late-readmission (8-30d)	All Respiratory	Pneumonia	1.062 (1.033, 1.092)	1.178 (0.947, 1.465)
Late-readmission (8-30d)	All Respiratory	Pulmonary embolism	1.070 (0.915, 1.252)	1.848 (0.599, 5.701)

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Table S3. Relative risk (RR ± 95% CI) of all-cause and cause-specific daily county admission rates associated with a 10 μg/m^3 increase in $PM_{2.5}$ for exposure lags 0-14 days. Models presented include the main model presented in the paper (model 1) where $PM_{2.5}$ is considered as a linear variable and a model that considers $PM_{2.5}$ as a non-linear variable (model 2). Additionally, the main model was stratified on the median of percent of individuals below poverty with respect to county (12.5% below poverty), with model 3 representing the model with counties with high % below poverty and model 4 representing counties with low % below poverty.

		Model 1, PM linear	Model 2, PM non-linear	Model 3, PM linear high % poverty	Model 4, PM linear low % poverty
Endpoint	Lag	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
All-cause	0	1.003 (0.998, 1.009)	0.998 (1.009, 0.996)	1.009 (0.996, 0.978)	0.996 (0.978, 1.015)
All-cause	1	0.997 (0.99, 1.003)	0.99 (1.003, 0.988)	1.003 (0.988, 0.968)	0.988 (0.968, 1.008)
All-cause	2	0.999 (0.992, 1.005)	0.992 (1.005, 0.998)	1.005 (0.998, 0.978)	0.998 (0.978, 1.018)
All-cause	3	0.996 (0.99, 1.002)	0.99 (1.002, 1.011)	1.002 (1.011, 0.991)	1.011 (0.991, 1.032)
All-cause	4	1.002 (0.996, 1.008)	0.996 (1.008, 1.006)	1.008 (1.006, 0.986)	1.006 (0.986, 1.027)
All-cause	5	1.001 (0.995, 1.007)	0.995 (1.007, 0.977)	1.007 (0.977, 0.957)	0.977 (0.957, 0.997)
All-cause	6	1.001 (0.995, 1.008)	0.995 (1.008, 0.988)	1.008 (0.988, 0.968)	0.988 (0.968, 1.009)
All-cause	7	1 (0.993, 1.006)	0.993 (1.006, 0.982)	1.006 (0.982, 0.961)	0.982 (0.961, 1.003)
All-cause	8	1.004 (0.997, 1.01)	0.997 (1.01, 1.001)	1.01 (1.001, 0.981)	1.001 (0.981, 1.022)
All-cause	9	1.004 (0.998, 1.01)	0.998 (1.01, 0.985)	1.01 (0.985, 0.965)	0.985 (0.965, 1.006)
All-cause	10	0.999 (0.993, 1.005)	0.993 (1.005, 1.02)	1.005 (1.02, 1)	1.02 (1, 1.042)
All-cause	11	0.996 (0.989, 1.002)	0.989 (1.002, 0.998)	1.002 (0.998, 0.978)	0.998 (0.978, 1.019)
All-cause	12	1.002 (0.996, 1.009)	0.996 (1.009, 1.006)	1.009 (1.006, 0.986)	1.006 (0.986, 1.028)
All-cause	13	0.995 (0.989, 1.001)	0.989 (1.001, 0.979)	1.001 (0.979, 0.959)	0.979 (0.959, 0.999)
All-cause	14	1 (0.994, 1.005)	0.994 (1.005, 0.987)	1.005 (0.987, 0.968)	0.987 (0.968, 1.006)
Cardiovascular related causes	0	1.009 (1.002, 1.017)	1.002 (1.017, 0.994)	1.017 (0.994, 0.967)	0.994 (0.967, 1.022)
Cardiovascular related causes	1	0.995 (0.986, 1.004)	0.986 (1.004, 0.978)	1.004 (0.978, 0.949)	0.978 (0.949, 1.007)

Cardiovascular related causes	2	0.998 (0.988, 1.007)	0.988 (1.007, 0.997)	1.007 (0.997, 0.968)	0.997 (0.968, 1.028)
Cardiovascular related causes	3	0.993 (0.984, 1.002)	0.984 (1.002, 1)	1.002 (1, 0.97)	1 (0.97, 1.03)
Cardiovascular related causes	4	1.003 (0.994, 1.012)	0.994 (1.012, 1.029)	1.012 (1.029, 0.999)	1.029 (0.999, 1.06)
Cardiovascular related causes	5	1.004 (0.994, 1.013)	0.994 (1.013, 0.976)	1.013 (0.976, 0.947)	0.976 (0.947, 1.006)
Cardiovascular related causes	6	0.999 (0.99, 1.008)	0.99 (1.008, 0.991)	1.008 (0.991, 0.962)	0.991 (0.962, 1.022)
Cardiovascular related causes	7	1.005 (0.995, 1.014)	0.995 (1.014, 0.979)	1.014 (0.979, 0.949)	0.979 (0.949, 1.01)
Cardiovascular related causes	8	1.002 (0.993, 1.011)	0.993 (1.011, 0.999)	1.011 (0.999, 0.969)	0.999 (0.969, 1.03)
Cardiovascular related causes	9	1.009 (1, 1.018)	1 (1.018, 0.992)	1.018 (0.992, 0.963)	0.992 (0.963, 1.023)
Cardiovascular related causes	10	0.992 (0.983, 1.001)	0.983 (1.001, 0.996)	1.001 (0.996, 0.966)	0.996 (0.966, 1.026)
Cardiovascular related causes	11	0.999 (0.99, 1.008)	0.99 (1.008, 1.017)	1.008 (1.017, 0.987)	1.017 (0.987, 1.048)
Cardiovascular related causes	12	0.999 (0.99, 1.008)	0.99 (1.008, 1.004)	1.008 (1.004, 0.974)	1.004 (0.974, 1.035)
Cardiovascular related causes	13	0.996 (0.987, 1.005)	0.987 (1.005, 0.969)	1.005 (0.969, 0.94)	0.969 (0.94, 0.999)
Cardiovascular related causes	14	1.002 (0.994, 1.009)	0.994 (1.009, 1.007)	1.009 (1.007, 0.978)	1.007 (0.978, 1.036)
Respiratory related causes	0	1.002 (0.994, 1.01)	0.994 (1.01, 0.998)	1.01 (0.998, 0.97)	0.998 (0.97, 1.027)
Respiratory related causes	1	0.998 (0.989, 1.008)	0.989 (1.008, 0.977)	1.008 (0.977, 0.948)	0.977 (0.948, 1.008)
Respiratory related causes	2	0.995 (0.985, 1.004)	0.985 (1.004, 1.007)	1.004 (1.007, 0.976)	1.007 (0.976, 1.039)
Respiratory related causes	3	0.995 (0.985, 1.004)	0.985 (1.004, 1.006)	1.004 (1.006, 0.975)	1.006 (0.975, 1.038)
Respiratory related causes	4	0.999 (0.989, 1.008)	0.989 (1.008, 0.997)	1.008 (0.997, 0.967)	0.997 (0.967, 1.029)

Respiratory related causes	5	1.009 (1, 1.019)	1 (1.019, 0.993)	1.019 (0.993, 0.962)	0.993 (0.962, 1.024)
Respiratory related causes	6	0.999 (0.99, 1.009)	0.99 (1.009, 0.974)	1.009 (0.974, 0.944)	0.974 (0.944, 1.005)
Respiratory related causes	7	0.999 (0.989, 1.009)	0.989 (1.009, 0.984)	1.009 (0.984, 0.952)	0.984 (0.952, 1.017)
Respiratory related causes	8	1.005 (0.996, 1.015)	0.996 (1.015, 1.011)	1.015 (1.011, 0.98)	1.011 (0.98, 1.043)
Respiratory related causes	9	1.008 (0.999, 1.018)	0.999 (1.018, 0.979)	1.018 (0.979, 0.948)	0.979 (0.948, 1.01)
Respiratory related causes	10	0.995 (0.985, 1.004)	0.985 (1.004, 0.994)	1.004 (0.994, 0.963)	0.994 (0.963, 1.026)
Respiratory related causes	11	0.997 (0.988, 1.007)	0.988 (1.007, 1.013)	1.007 (1.013, 0.981)	1.013 (0.981, 1.046)
Respiratory related causes	12	1.002 (0.992, 1.011)	0.992 (1.011, 0.998)	1.011 (0.998, 0.967)	0.998 (0.967, 1.03)
Respiratory related causes	13	0.997 (0.987, 1.006)	0.987 (1.006, 0.979)	1.006 (0.979, 0.948)	0.979 (0.948, 1.011)
Respiratory related causes	14	1.001 (0.993, 1.009)	0.993 (1.009, 0.995)	1.009 (0.995, 0.966)	0.995 (0.966, 1.025)

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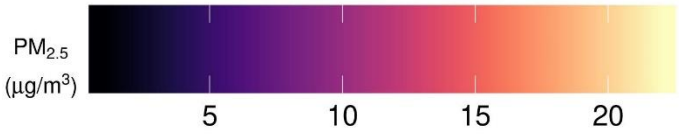
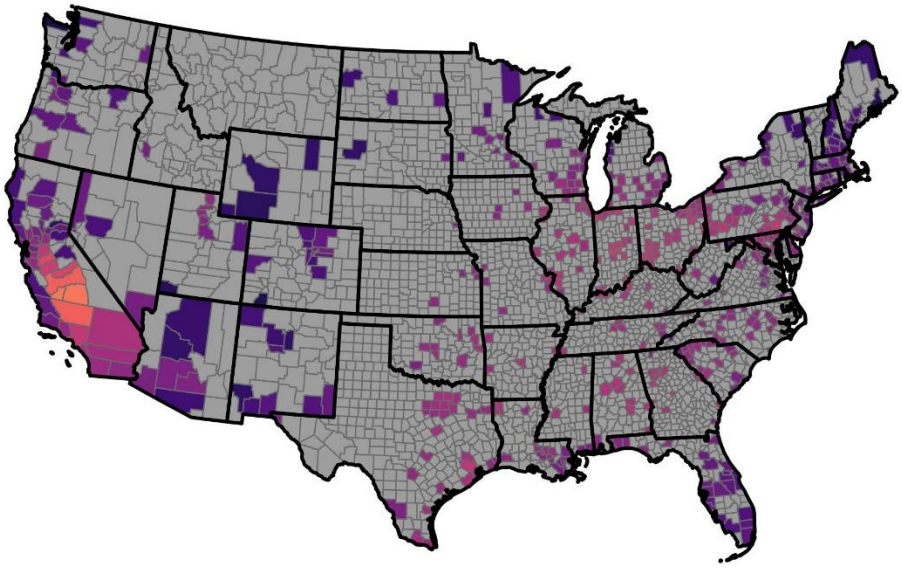


A) Long-term county $PM_{2.5}$ (7yr average)



B) 20% of county days are above $PM_{2.5}$ (80th percentile)

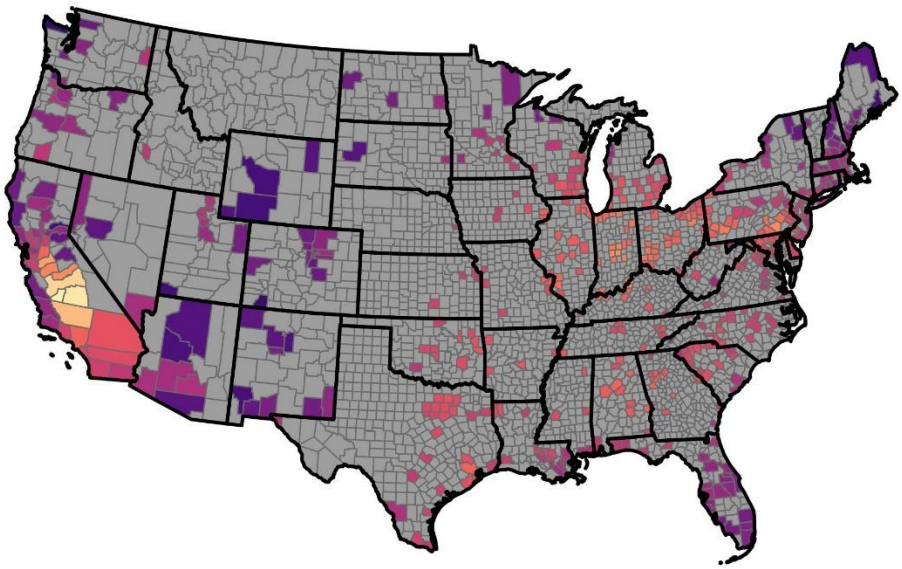


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Figure S1. County $PM_{2.5}$ levels for the 530 counties included in the study. $PM_{2.5}$ levels shown include the A) long-term average and B) 80th percentile (indicating that 20% of county days are at or above this $PM_{2.5}$ level) for the years 2008-2014.

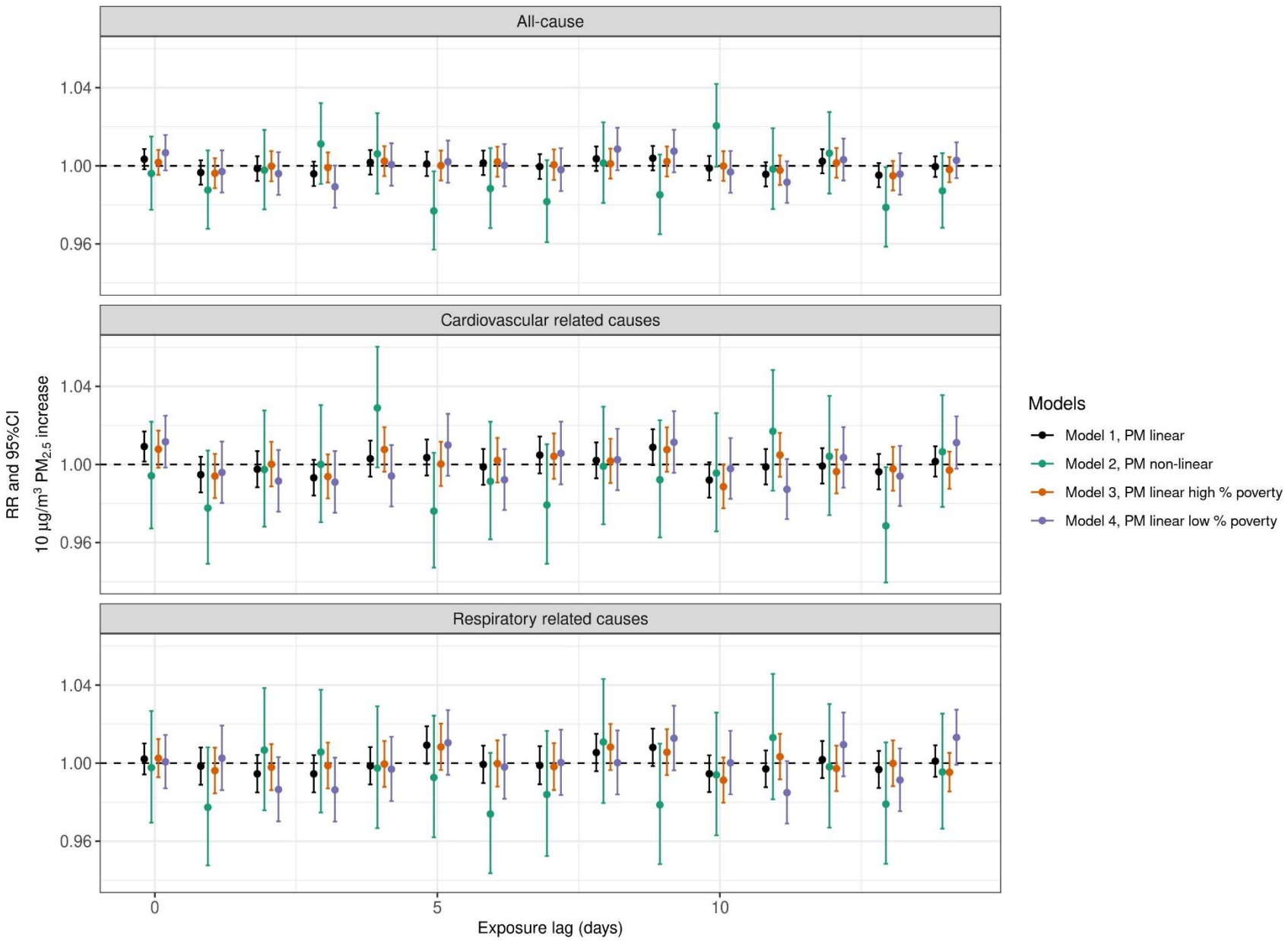
All-cause
Cardiovascular related causes
Respiratory related causes
1.04
1.00
0.96
RR and 95%CI
10 µg/m³ PM2.5 increase
0
5
10
Exposure lag (days)
Models
Model 1, PM linear
Model 2, PM non-linear
Model 3, PM linear high % poverty
Model 4, PM linear low % poverty

Figure S2. Relative risk (RR ± 95%CI) for daily county admission rates for all-cause hospitalization associated with a 10 μg/m^3 increase in $PM_{2.5}$ for exposure lags 0-14 days using an unconstrained distributed lag model. Models presented include the main model presented in the paper (model 1) where $PM_{2.5}$ is considered as a linear variable in black and a model that considers $PM_{2.5}$ as a non-linear variable (model 2) in green. Additionally, the main model was stratified on the median of percent of individuals below poverty with respect to county (12.5% below poverty), with model 3 representing the model with counties with high % below poverty in orange and model 4 representing counties with low % below poverty in purple (Table S2).

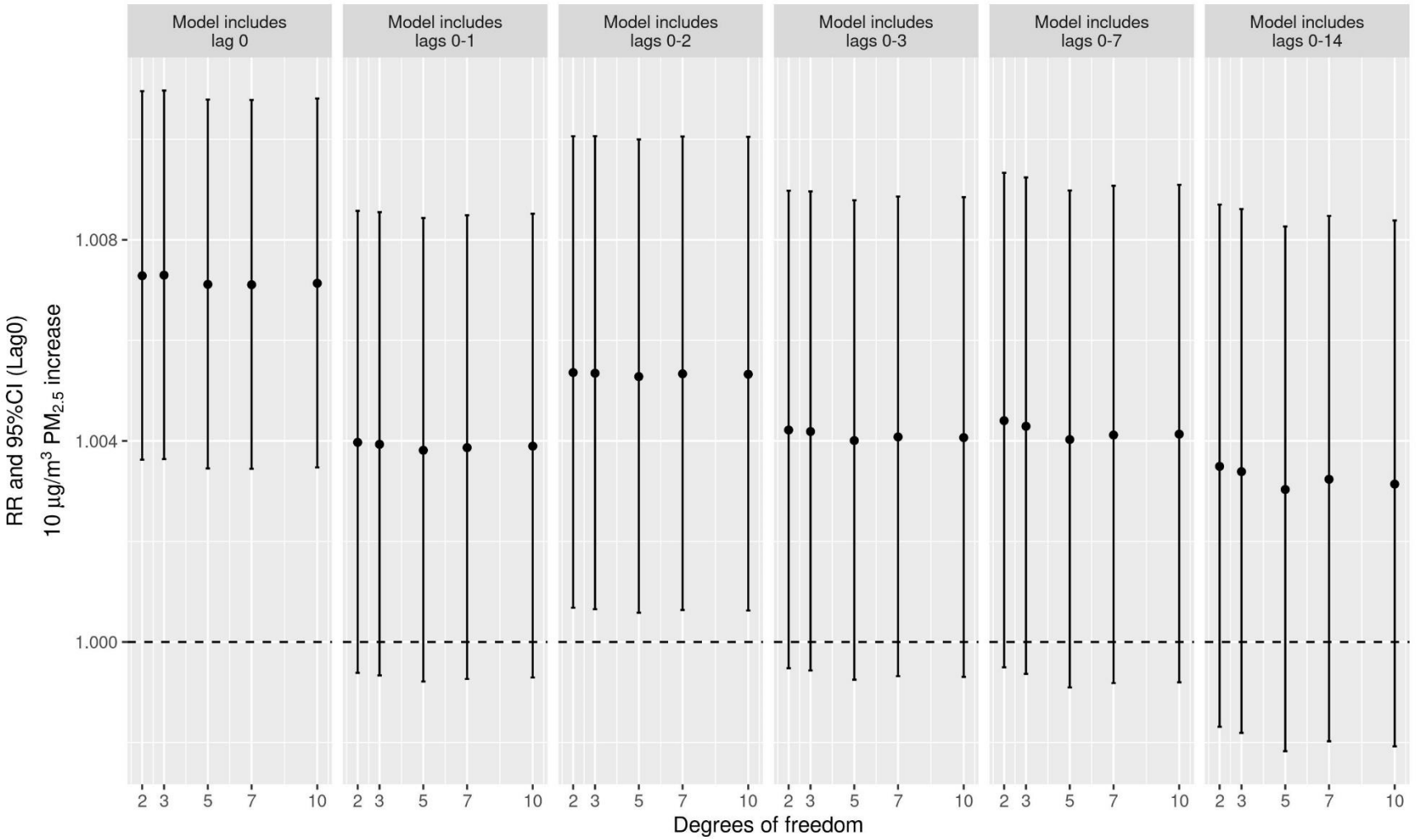

Figure S3. Sensitivity analysis for all-cause admissions models showing the impact on the lag 0 estimate from changing the number of lags considered (grouped figures), and the number of degrees of freedom (x-axis) for the temperature and relative humidity variables. Relative risk (RR ± 95%CI) of all-cause daily county admission rates associated with a 10 µg/m^3 increase in $PM_{2.5}$ on lag 0.

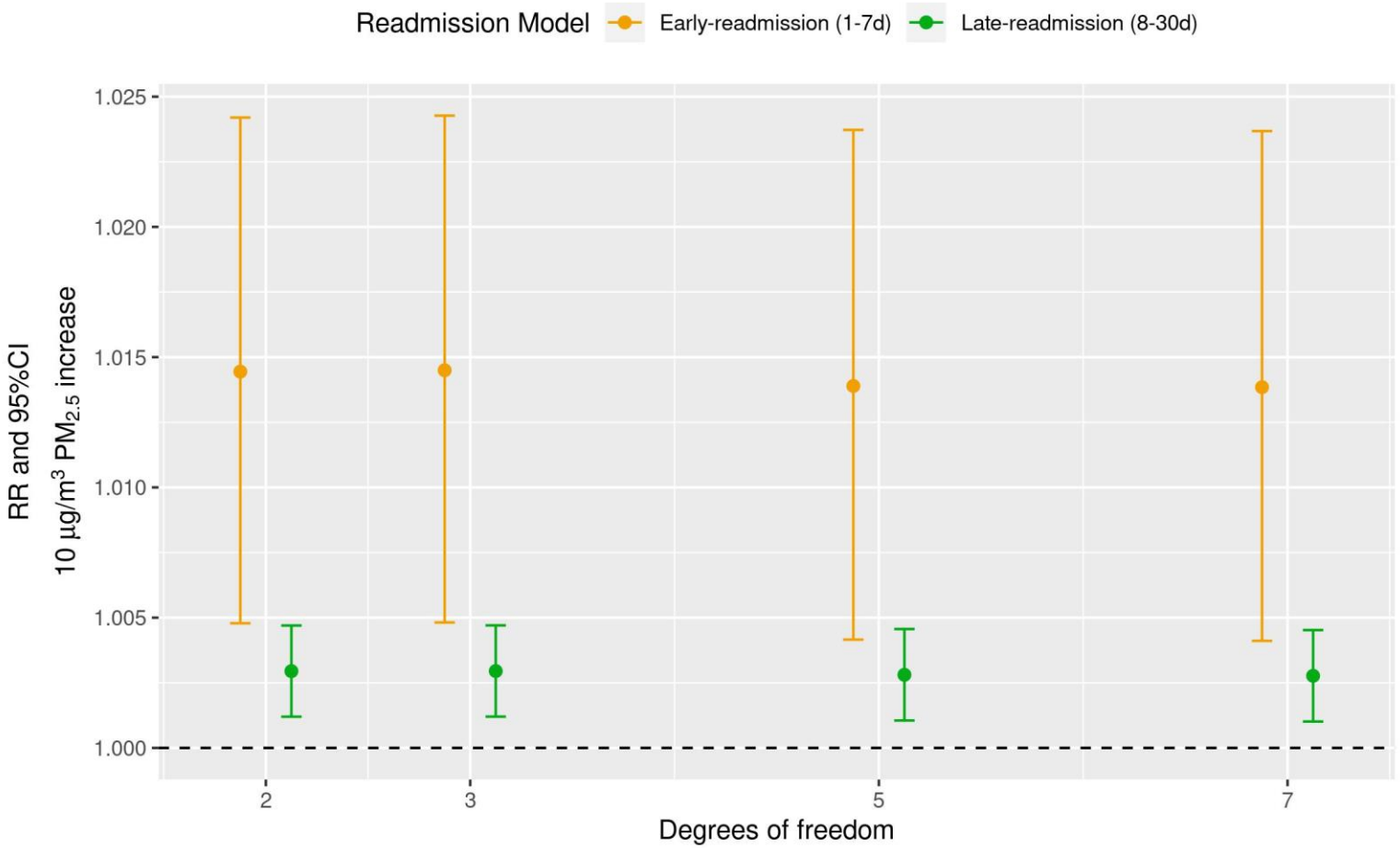

Figure S4. Sensitivity analysis for all-cause readmission models showing the impact on the lag 0 estimate from changing the number of degrees of freedom (x-axis) for the temperature and relative humidity variables. Relative risk (RR ± 95%CI) of all-cause daily county admission rates associated with a 10 µg/m^3 increase in $PM_{2.5}$ on lag 0.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.