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ORIGINAL RESEARCH

Long-Term Exposure to Particulate Air Pollution Is Associated With 30-Day Readmissions and Hospital Visits Among Patients With Heart Failure

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BACKGROUND: Long-term air pollution exposure is a significant risk factor for inpatient hospital admissions in the general population. However, we lack information on whether long-term air pollution exposure is a risk factor for hospital readmissions, particularly in individuals with elevated readmission rates.

METHODS AND RESULTS: We determined the number of readmissions and total hospital visits (outpatient visits+emergency room visits+inpatient admissions) for 20 920 individuals with heart failure. We used quasi-Poisson regression models to associate annual average fine particulate matter at the date of heart failure diagnosis with the number of hospital visits and 30-day readmissions. We used inverse probability weights to balance the distribution of confounders and adjust for the competing risk of death. Models were adjusted for age, race, sex, smoking status, urbanicity, year of diagnosis, short-term fine particulate matter exposure, comorbid disease, and socioeconomic status. A 1-µg/m^3 increase in fine particulate matter was associated with a 9.31% increase (95% CI, 7.85%–10.8%) in total hospital visits, a 4.35% increase (95% CI, 1.12%–7.68%) in inpatient admissions, and a 14.2% increase (95% CI, 8.41%–20.2%) in 30-day readmissions. Associations were robust to different modeling approaches.

CONCLUSIONS: These results highlight the potential for air pollution to play a role in hospital use, particularly hospital visits and readmissions. Given the elevated frequency of hospitalizations and readmissions among patients with heart failure, these results also represent an important insight into modifiable environmental risk factors that may improve outcomes and reduce hospital use among patients with heart failure.

Key Words: 30-day readmissions ■ air pollution ■ electronic health records ■ heart failure ■ hospital use ■ $PM_{2.5}$

Heart failure (HF) represents one of the most severe forms of cardiovascular diseases. As a clinical syndrome, it is marked by a progression through 4 stages, where in the final stage symptoms such as shortness of breath, fatigue, and swelling, all of which result from myocardium disorders, are present with minimal activity or even at rest.[1] In the United States, the prevalence of HF is increasing, and by 2030, an estimated 8 million individuals will have HF, a 46% increase from 2012.[1,2] This rise in HF prevalence will bring along a substantial rise in HF burden on the healthcare system both in terms of hospital use and total costs. In 2012, the total cost of HF in the United States was estimated at $30.7 billion, with approximately 68% of those costs coming from direct healthcare costs such as hospital visits and inpatient stays.[1,3] By 2030, the cost of HF is estimated to grow to $69.8 billion, a 127% increase.[2]

Much of the costs and patient burden of HF is tied to increased healthcare use, particularly hospital

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CLINICAL PERSPECTIVE

What Is New?

- Elevated long-term air pollution has been associated with inpatient hospital admissions but has not been evaluated for readmission risk or outpatient visits.

What Are the Clinical Implications?

- Elevated air pollution exposure among patients with heart failure increases 30-day readmissions, outpatient visits, and inpatient admissions, pointing to an overall increase in morbidity with increasing exposure.
- Air quality may be an important risk factor for readmissions as well as increased hospital use and may impact readmission rates for hospitals serving areas with poor air quality.

Nonstandard Abbreviations and Acronyms

$PM_{2.5}$	Particulate matter <2.5 μm in diameter

visits. One study estimated that 83% of patients with HF would be hospitalized at least once after diagnosis, and 43% would be hospitalized 4 or more times.[4] Although overall hospitalization rates appear to be declining (29.5% decline from 1998 to 2007), this decline was heterogeneous across race, sex, and state of primary residence.[5] Hospital readmissions are also high among patients with HF, particularly 30-day readmissions, which are used to evaluate quality of care. In 2012, 30-day readmissions among individuals with HF was 19%, only a slight decrease from the 30-day readmission rates of 20% seen in 2009.[6] This rate is also nearly twice the 30-day readmission rate of 11.6% seen for the general US population.[7] Elevated 30-day readmission rates can be particularly important for hospital systems given the substantial penalties imposed under the Hospital Readmission Reduction Program in the Affordable Care Act. In this program, up to 3% of Centers for Medicare and Medicaid Services fee-for-service payments can be withheld for elevated 30-day readmissions for HF and 5 other conditions, which is estimated to result in hundreds of millions of dollars in penalties in the 2020 fiscal year. Thus, there is a substantial need for patients, hospital systems, and public health officials alike to understand the risk factors for hospitalizations and readmissions among patients with HF.

Long-term exposure to air pollution has been understudied as a risk factor for hospitalizations and readmissions, relative to short-term exposures.[8,9] In a recent study, elevated long-term exposure to particulate matter <2.5 μm in diameter ($PM_{2.5}$) was associated with an increased likelihood of an inpatient admission among the Medicare population, even in areas with $PM_{2.5}$ concentrations below the current annual National Ambient Air Quality Standard of 12 μg/m^3.[10] However, there has not yet been a study of the increased number of 30-day readmissions and total hospital visits (outpatient visits+emergency room visits+inpatient admissions) associated with poor air quality, which may be of particular importance for vulnerable individuals with preexisting cardiovascular disease. Thus, we sought to evaluate the association between annual average $PM_{2.5}$ exposure and the number of 30-day readmissions and hospital visits after a diagnosis of HF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and approval of the appropriate institutional review board.

Study Population

The population for this study came from the Environmental Protection Agency Clinical and Archived Records Research for Environmental Studies (EPA CARES) research resource, a resource of electronic health records merged with environmental exposure data to facilitate environmental health studies of patient populations.[11] All electronic health records came from the University of North Carolina Healthcare System. This study was approved by the institutional review board of the University of North Carolina–Chapel Hill (IRB 17-0150), and informed consent was waived for this analysis of existing health records. We required primary addresses to be geocoded at the street level, and excluded all individuals who reported being homeless or who reported a prison or hospital as their primary address. We determined the date of initial HF diagnosis on the basis of the individual's electronic health records. We required individuals to have at least one hospital visit before their HF diagnosis, we removed people who were diagnosed at other hospital systems but entered the University of North Carolina Healthcare System later, and we retained all individuals with an initial HF diagnosis between July 1, 2004 and December 31, 2016, the time period of our study.

Exposures

For this study we used daily $PM_{2.5}$ predictions from an ensemble machine-learning model that has been well validated, with an R^2 of 0.89 for the mid-Atlantic region, which includes North Carolina,[12] and was used in a previous study of the Environmental Protection Agency Clinical and Archived Records Research for Environmental Studies resource.[11] Briefly, the model incorporates multiple machine-learning algorithms to integrate land-use variables, meteorology, chemical transport models, ground-based monitoring, and aerosol optical depth measurements from satellites to estimate $PM_{2.5}$ concentrations at a 1-km^2 resolution for the continental United States. We linked each individual to a 1-×1-km grid cell on the basis of their primary address location. After matching each participant to the appropriate grid cell, daily air pollution values were averaged into an annual average (mean of prior 365 days) based on their date of HF diagnosis.

Statistical Analysis

For our study, we defined a hospital visit as an inpatient admission, emergency room visit, or outpatient visit to the hospital. Emergency room visits that resulted in an inpatient admission were grouped with inpatient admissions to prevent double counting. Multiple visits on the same calendar day were collapsed into a single visit to prevent overcounting because of transfers between hospital departments. A N-day readmission is defined as any inpatient admission whose admission date was within N days of the discharge date for a preceding inpatient admission. To limit overcounting because of transfers between departments, hospitalizations where the discharge date was the same as the admission date for the subsequent hospitalization were merged into a single hospitalization. Our primary outcomes were the number of 30-day readmissions and the number of total hospital visits observed from the initial diagnosis of HF until the end of the study observation time (December 31, 2016). We also examined associations with the number of inpatient admissions and emergency room visits, as well as the number of 7-, 60-, and 90-day readmissions experienced by each individual from initial HF diagnosis until the end of the observation time.

We used quasi-Poisson models that adjusted for age, race, sex, year of HF diagnosis, smoking status (current, former, never, or unknown), neighborhood socioeconomic status, percent urbanicity of the 2010 census block group in which the individual resided, preexisting chronic disease, and short-term air pollution exposure. Log-transformed follow-up time in years was included as an offset. We refer to this model as the Primary model to distinguish it from subsequent models and sensitivity analyses. Beause 36% of individuals had an unknown smoking status, we undertook a sensitivity analysis where we used multiple-imputation chained equations as implemented in the mice package in R[13] to impute the missing smoking status based on the rest of the available data. We imputed 5 data sets and then compared original associations with associations obtained using each imputation of smoking status as well as pooled estimates from all 5 imputations. The neighborhood socioeconomic status variables were all assessed at the block group level using the 2010 census block groups and were median household income, median home value, percent of block group on public assistance, and percent of block group residents below the federal poverty line. All neighborhood socioeconomic status variables were included as separate variables in the models. To adjust for short-term air pollution exposure, we included the mean of the 5-day average $PM_{2.5}$ concentration. The 5-day average $PM_{2.5}$ was calculated as the mean of the $PM_{2.5}$ concentration on the day of each hospital visit and the 4 days before each hospital visit. To adjust for potential confounding by preexisting chronic disease, we adjusted for a diagnosis of chronic kidney disease, peripheral arterial disease, type 2 diabetes mellitus, chronic obstructive pulmonary disease, ischemic heart disease, dyslipidemia, and hypertension in all models, which may make our estimates conservative, because some chronic conditions are also associated with long term $PM_{2.5}$ exposure. Preexisting conditions were defined by *International Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision (ICD-10)* codes, which are detailed in Data S1.

Because electronic health records and census data only partially captured the socioeconomic and behavioral characteristics used, we added an Extended model, which included all terms from the Primary model, including adjustment for preexisting conditions, as well as an additional 20 county-level variables from the 2015 County Health Rankings from the University of Wisconsin Population Health Institute and the Robert Wood Johnson Foundation[14] to the Primary model described above. We chose the 2015 data because they contained the county-level variables that best supplemented the electronic health record data, and county data were sampled in 2006 to 2014, which overlapped well with our observation period. The variables chosen captured access to health care, healthcare costs, crime, physical activity, employment, access to healthy foods, income inequality, and public water system violations. The full list of the county-level measures included in the additional adjustment along with their distribution in the study cohort is given in Table S1.

Given that there is a high mortality rate among individuals with HF, we used stabilized inverse probability weights to account for the competing risk of death, as done in a similar study of inpatient admissions.[10] The stabilized inverse probability weights also included weights for the distribution of confounders that would act to better balance the distribution of confounders across the exposure distribution, which can also allow for causal interpretations subject to certain assumptions. We estimated the standardized difference in the inverse probability weights to determine the degree of imbalance between the upper and lower quartiles of the $PM_{2.5}$ distribution. We classified the imbalance as very weak (0–0.2), weak (0.2–0.4), moderate (0.4–0.6), or strong (>0.6), which follows published guidelines.[15] Moderate or even strong categories of the standardized difference do not invalidate models but do indicate that causal interpretations require further investigation, because the assumption of positivity, required for causal interpretations of associations from observational studies, is likely violated. The other 2 assumptions needed for causal interpretations are no unmeasured confounding and the stable unit treatment value assumption. The stable unit treatment value assumption captures the principle of no interference, which states that the potential outcome for any individual does not depend on the treatment (here the annual average $PM_{2.5}$ exposure) received by other individuals, and the principle of consistency, which is the assumption that all treatments can be considered equivalent. The stable unit treatment value assumption and no unmeasured confounding can often not be tested for directly, and the reasonableness of these assumptions is typically evaluated on the basis of the treatment, outcome, and study design.

We stratified associations on age at HF diagnosis (<65 years versus ≥65 years), race, sex, the median income of each census block groups (<$49 318 versus ≥$49 318), and the percent urbanicity of each census block group. For stratification on income, we examined individuals residing in US census block groups with below median income (<$49 318, low income) versus those residing in census block groups with above median income (≥$49 318, high income). For stratifications on urbanicity, we classified individuals living in the bottom third of the block group urbanicity distribution (<38% urban) as rural, and compared associations with all other individuals (nonrural). Urbanicity was defined according to the 2010 US Census (https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/2010-urban-rural.html), which classified areas as urban if the area encompassed at least 2500 individuals. We also examined stratifications by $PM_{2.5}$ concentration by restricting to those individuals with $PM_{2.5}$ concentrations <12 μg/m^3.

To guard against late-age HF diagnoses or potential birthday entry errors, we performed a sensitivity analysis restricting to those <100 years old at the end of observation. As previously mentioned, we also performed sensitivity analyses using multiple imputation by chained equations to impute missing smoking status and compare associations across imputations and in the pooled imputations.

For the readmissions outcomes, we also added a sensitivity analysis that removed readmissions following an inpatient admission lasting 0 days or zero-length readmissions, which we defined as a readmission where the individual was admitted and discharged on the same day. Given that only 20.9% of inpatient admissions resulted in a 30-day readmission, similar to readmission rates seen in other studies of patients with HF,[6] we also implemented a zero-inflated Poisson model using the pscl package[16] in R. We used an intercept-only model to model the excess number of zeros in the distribution and assumed the true counts came from a model with the confounder adjustments as previously described. As with the Primary model, log-transformed follow-up time in years was included as an offset. The output of the zero-inflated Poisson model has the same interpretation as the quasi-Poisson model used in the Primary model. We used R version 3.5.1[17] for all analyses. Results are presented as the percent change per 1 μg/m^3 increase in annual average $PM_{2.5}$ and the associated 95% CI. Percent change was calculated as $(e^{\beta}-1)*100$, where β is the regression coefficient from the quasi-Poisson or zero-inflated Poisson model and *e* is the base of the natural logarithm.

RESULTS

The final study population was 20 920 individuals. We observed 442 244 hospital visits over an average follow-up of 2.79 year (7.6 visits per person-year). The total number of visits included emergency room visits (7.3%, 69% of which resulted in an inpatient admission), inpatient admissions (7.1%), and outpatient visits (91%). As mentioned in the Methods, emergency room visits resulting in an inpatient admission were considered inpatient admissions to avoid double counting. There were 12 474 individuals with a valid inpatient admission and who could thus qualify to have a readmission. Among these individuals, we observed 1739 seven-day readmissions; 7114 thirty-day readmissions; 10 612 sixty-day readmissions, and 12 624 ninety-day readmissions. Descriptions of the overall cohort and those with an inpatient admission are given in Table 1. We examined the distribution of readmissions, and to combat outliers, we removed all individuals with 10 or more readmissions for each readmission window, which removed 0.07% of 7-day readmissions, 0.49% of 30-day readmissions, 0.96% of 60-day readmissions, and 1.27% of 90-day readmissions. For the total number of visits, we removed outliers by removing individuals whose number of visits was more than the third quartile plus 1.5*interquartile range (55.5 visits, 9.4% observations removed). No individuals fell below the first quartile minus 1.5*interquartile range in the distribution of

Table 1. Study Cohort

	Study Cohort, N=20 920		Inpatient Admission Cohort, N=12 474	
	Mean	SD	Mean	SD
Age, y	68.8	14.8	69.0	15.1
Urbanicity, %	63.6	41.9	64.9	41.5
Median home value, $	182 744	107 940	193 088	111 825
Households below federal poverty line, %	17.0	14.0	16.6	14.0
Public assistance, %	1.98	2.97	1.96	2.95
Total visits, n	14.2	14.3	16.4	15.5
Outpatient visits, n	12.4	13.1	13.6	14.3
Inpatient admissions, n	1.34	1.77	2.29	1.79
Emergency visits, n	1.16	1.82	1.90	2.05
7-d readmissions, n	0.12	0.48	0.12	0.48
30-d readmissions, n	0.49	1.10	0.49	1.10
60-d readmissions, n	0.70	1.36	0.70	1.36
90-d readmissions, n	0.81	1.50	0.81	1.50
Follow-up time, n	2.79	3.05	3.02	3.21
$PM_{2.5}$, μg/m^3	9.87	1.75	10.2	1.84
	N	%	N	%
Women	10 998	52.6	6657	53.4
Men	9922	47.4	5817	46.6
Race, White	13 875	66.3	8345	66.9
Race, Black	5564	26.6	3423	27.4
Race, other	1481	7.08	706	5.66
Never smoker	6176	29.5	3244	26.0
Former smoker	6515	31.1	3607	28.9
Current smoker	2029	9.70	1222	9.80
Unknown smoking status	6200	29.6	4401	35.3
Chronic kidney disease	13 183	63.0	8505	68.2
Ischemic heart disease	13 438	64.2	8650	69.3
Hypertension	16 602	79.4	10 275	82.4
Chronic obstructive pulmonary disorder	9025	43.1	5930	47.5
Type 2 diabetes mellitus	7627	36.5	4947	39.7
Dyslipidemia	17 042	81.5	10 490	84.1
Peripheral arterial disease	9229	44.1	5969	47.9

The overall study cohort is described, as well as those with at least one inpatient admission, who thus formed the basis for the study of readmissions. "Race, other" refers to individuals who did not self-identify as Black or White race.

outpatient visits; hence, only upper outliers were removed. Violin plots showing the distribution of total visits and 30-day readmissions by year are given in Figure S1.

Associations With Total Visits

A 1-μg/m^3 increase in annual average $PM_{2.5}$ was associated with a 9.31% (95% CI, 7.85%–10.8%; Figure 1, Table 2, Figure S2) increase in the number of hospital visits. There was minimal difference in the associations with inclusion of an additional 20 county-level variables to adjust for healthcare access, behavioral, and socioeconomic features not well captured in electronic health records (Table 2). Associations were virtually unchanged in 5 imputations of the missing smoking information (Figure S3). Associations with total visits were observed across stratifications by age, income, race, sex, and urbanicity, and were strongest among Black participants and those diagnosed with HF before the age of 65 years (Figure 1, Table S2). The mean number

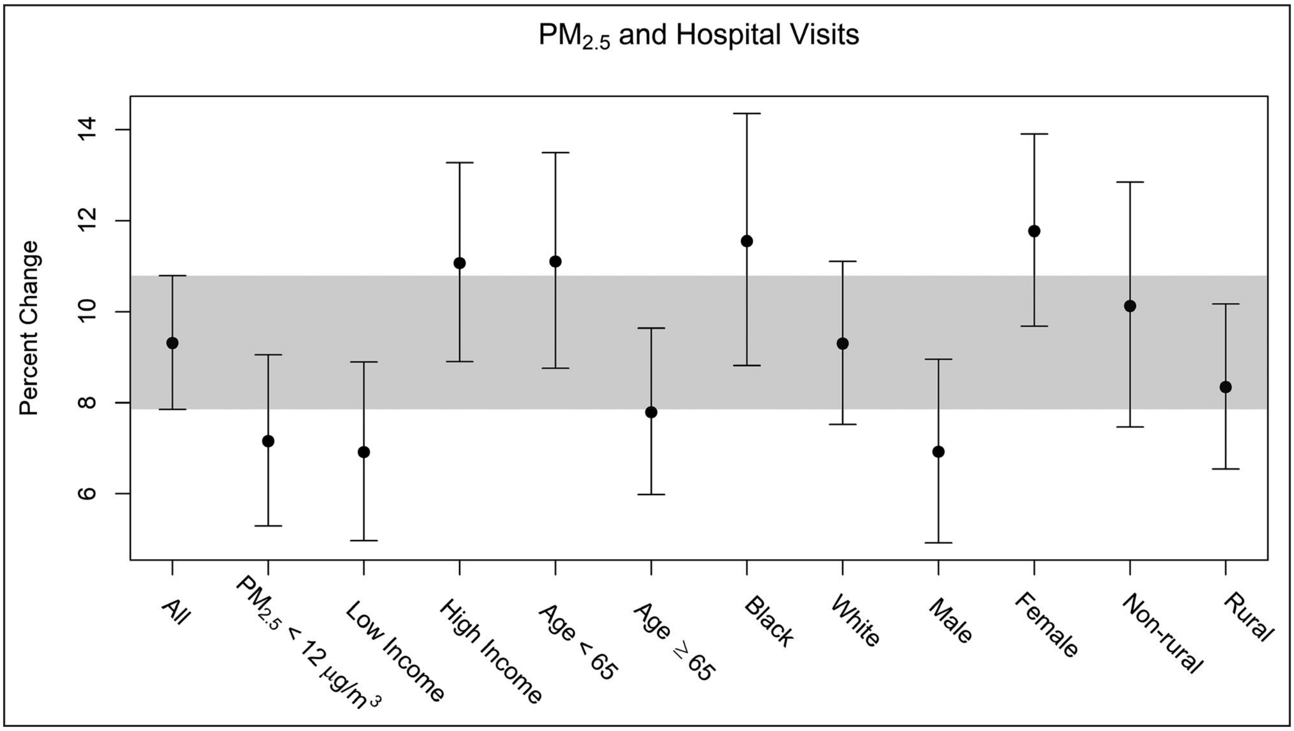

Figure 1. Associations between annual average particulate matter <2.5 μm in diameter ($PM_{2.5}$) and hospital visits.
The percent change in hospital visits is given per 1-μg/m^3 increase in annual average $PM_{2.5}$. The gray shaded area represents the range of values for the 95% CI for associations in the overall cohort (All). Low Income refers to participants living in census block groups where the median income of that census block group is less than the median of all census block groups represented by participants within the study. High Income refers to participants living in census block groups where the median income is higher than the median of all census block groups represented by participants within the study. Rural refers to participants living in census block groups in the bottom third of the urbanicity (% of census block group that is urban) distribution, and Non-rural refers to all other participants (upper two thirds or urbanicity distribution). Age refers to the age at heart failure diagnosis. Models were adjusted using the Primary model adjustment as described in the Methods.

of total visits by each stratification did not differ substantially (Table S3). Associations remained present even for individuals with exposures below the current $PM_{2.5}$ national standard (7.16% increase; 95% CI, 5.29%–9.06%), and sensitivity analyses did not reveal substantial differences in associations (Table 2).

When broken down by visit type, we observed associations for outpatient visits (9.87% increase; 95% CI, 8.41%–11.4%), inpatient admissions (4.35% increase; 95% CI, 1.12%–7.68%), and emergency department visits (10.0% increase; 95% CI, 6.40%–13.8%). To provide a more complete picture of associations with emergency department use, we regrouped visits, creating a category of all emergency department visits whether they resulted in an inpatient admission or not, and still observed associations (4.18% increase; 95% CI, 0.56%–7.93%).

Table 2. Sensitivity Analyses for Total Visits

Sensitivity Analysis	Percent Change	LCI	UCI
Participants with age <100 y at end of observation	9.20	7.74	10.7
Extended model	11.4	9.88	13.0

Associations remained in sensitivity analyses restricting based on age as well as in the Extended model. The Primary model adjusted for age, race, sex, year of heart failure diagnosis, smoking status, median home value for the census block group, median household income for the census block group, percent of households on public assistance in the census block group, percent of households below the federal poverty line for the census block group, preexisting conditions, and short-term $PM_{2.5}$ exposure. The Extended model adjusted the Primary model for an additional 20 county-level behavioral, socioeconomic, and healthcare access variables (Table S1). LCI, indicates lower 95% CI; and UCI, upper 95% CI.

Associations With Readmissions

A 1-μg/m^3 increase in annual average $PM_{2.5}$ exposure was associated with a 14.2% increase in 30-day readmissions (95% CI, 8.4%–20.2%; Figure 2, Table 3, Figure S4). As with total visits, associations between annual average $PM_{2.5}$ exposure and 30-day readmissions were strongest among Black participants and those diagnosed with HF before the age of 65 years (Figure 2, Table S4). The mean and standard deviation for 30-day readmissions were highly similar across each subgroup for the stratified analyses (Table S3). Imputation of the missing smoking information slightly attenuated associations; however, there was stronger overlap of the 95% CIs for the Primary model and

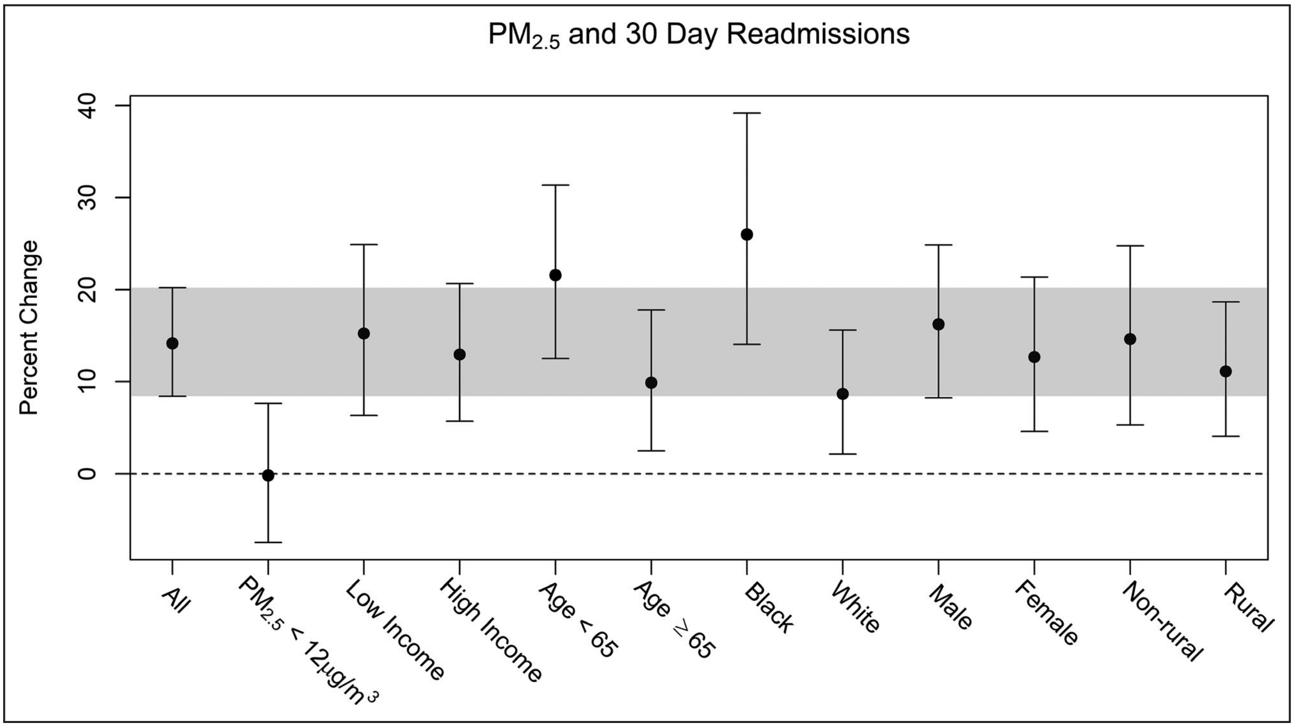

Figure 2. Associations between annual average particulate matter <2.5 μm in diameter (PM2.5) and 30-day readmissions. The percent change in hospital visits is given per 1-μg/m^3 increase in annual average $PM_{2.5}$. The gray shaded area represents the range of values for the 95% CI for associations in the overall cohort (All). Low Income refers to participants living in census block groups where the median income of that census block group is less than the median of all census block groups represented by participants within the study. High Income refers to participants living in census block groups where the median income is higher than the median of all census block groups represented by participants within the study. Rural refers to participants living in census block groups in the bottom third of the urbanicity (% of census block group that is urban) distribution, and Non-rural refers to all other participants (upper two thirds or urbanicity distribution). Age refers to the age at heart failure diagnosis. All models used the Primary model adjustment as described in the Methods.

models with imputed data, indicating high agreement across all models (Figure S5). Associations remained in the sensitivity analyses, and were somewhat stronger in the Extended model, which included an additional 20 county-level behavioral and socioeconomic indicators (Table 3). We did not observe associations with 30-day readmissions when restricting to $PM_{2.5}$ exposures <12 μg/m^3 (Figure 2; Table S4).

We also observed associations between annual average $PM_{2.5}$ exposure and the number of 7- (28.3%; 95% CI, 17.5%–40.1%), 60- (12.3%; 95% CI, 7.49%–17.3%), and 90-day (13.0%; 95% CI, 8.55%–17.7%) readmissions. As with 30-day readmissions, associations for the other readmission windows were not observed for exposure below the current 12-μg/m^3 $PM_{2.5}$ national standard (Figure 3). Associations with 7-, 60-, and 90-day readmissions remained when removing admissions with same-day discharges as well in zero-inflated Poisson models (Table S5).

DISCUSSION

We observed that long-term exposure to particulate matter air pollution substantially increases hospital visits (both outpatient visits and inpatient admissions) as well as readmissions among patients with HF. These associations give a key insight into the morbidity

Table 3. Sensitivity Analyses for 30-Day Readmissions

Sensitivity Analysis	Percent Change	LCI	UCI
Zero-length readmissions removed	10.5	4.50	16.8
Participants with age <100 y at end of observation	13.6	7.92	19.7
Extended model	17.6	11.6	23.9
Zero-inflated Poisson	8.43	5.48	11.5

Associations were attenuated when restricting to individuals who reported only a single address, and thus are assumed to have never moved; however, this might have been driven by the reduced sample size, which is highlighted by the increased width of the 95% CI. The zero-length readmissions removed sensitivity analysis refers to removing all hospital admissions where the individual was admitted and discharged on the same day and then recalculating the number of 30-day readmissions. The Primary model adjusted for age, race, sex, year of heart failure diagnosis, smoking status, median home value for the census block group, median household income for the census block group, percent of households on public assistance in the census block group, percent of households below the federal poverty line for the census block group, preexisting conditions, and short-term $PM_{2.5}$ exposure. The Extended model adjusted the Primary model for an additional 20 county-level behavioral, socioeconomic, and healthcare access variables (Table S1). LCI, indicates lower 95% CI; and UCI, upper 95% CI.

effects of long-term exposure to air pollution for individuals with HF. The biological mechanisms that likely underlie these associations have been well established and include systemic inflammation, increased activation of the autonomic nervous system, and oxidative stress induced by penetration of $PM_{2.5}$ particles into the respiratory tract.[18–20]

Total Visits

A 1-μg/m^3 increase in annual average $PM_{2.5}$ was associated with a 9.50% increase in total hospital visits. Because the majority of hospital visits were outpatient visits, this association was driven by outpatient visits where we saw a similar association. This is one of the first studies to examine long-term air pollution exposures in relation to total hospital visits and outpatient visits, as opposed to just inpatient admissions. Outpatient hospital visits are often scheduled visits and would include routine visits as well as visits because of an illness, but not one threatening enough to warrant a visit to the emergency room. Thus, associations with outpatient visits possibly indicate associations with general increases in morbidity and illnesses causing greater use of hospital services. We also saw associations

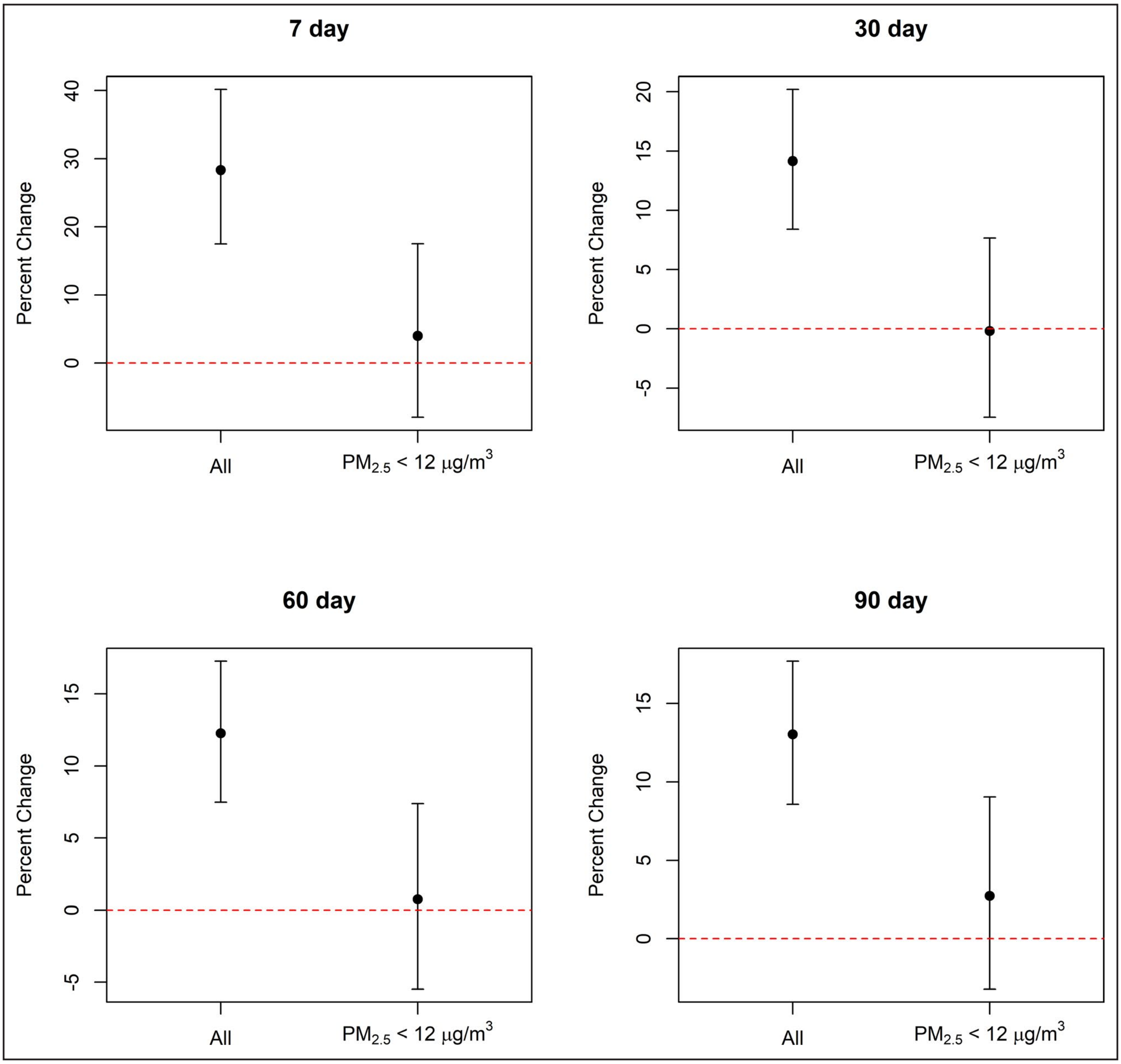

Figure 3. Associations between annual average particulate matter <2.5 μm in diameter ($PM_{2.5}$) and hospital readmissions. Associations are shown for each readmission window and for the entire study cohort (All) as well as for those with annual average $PM_{2.5}$ exposure less than current national standards ($PM_{2.5}$<12 μg/m^3).

with emergency room visits indicating that multiple forms of hospital use are elevated by long-term $PM_{2.5}$ exposure. A study of HF hospitalization rates from 1998 to 2008 found that although rates declined by nearly 30%, Black men experienced the smallest decline.[5] We also observed that Black patients with HF had the highest associations between total hospital visits and long-term air pollution exposure (Figure 1), and the association was 40% higher in Black patients with HF as opposed to White patients with HF. The racial disparity was even larger for 30-day readmissions (Figure 2, Table S3). Given that minorities are often exposed to higher levels of air pollution than nonminority populations, it is possible that some of the racial health disparities seen in patients with HF are in part driven by environmental factors like air pollution. We observed substantial sex differences with female patients with HF having stronger associations with total visits than male patients with HF. This has not been previously reported, and further work is warranted to understand if these differences are driven by differential exposures, possibly because of different time-activity patterns, or other factors. We also observed differences by age at HF diagnosis with individuals <65 years old having larger associations than older individuals. Early onset cardiovascular disease is associated with a strong genetic component,[21] and gene-by-air pollution interactions have been shown for many cardiovascular outcomes.[22] Thus, differences by age at HF diagnosis may reflect genetic components to the underlying HF, which confer more environmental sensitivity. Healthcare access has a large role in determining rates of outpatient visits and total hospital visits. However, associations remained when adjusting for the average annual healthcare cost, number of primary physicians per 100 000 people, number of non–primary care physicians per 100 000 people, and the number of mental health providers per 100 000 people in the Extended model (Table 2). We also did not observe consistent, substantial differences in the number of visits and 30-day readmissions across the stratified analyses, which otherwise could have been an explanation for differences seen in the stratified analyses (Table S3).

Inpatient Admissions and Readmissions

There are few existing studies that have examined associations between long-term air pollution exposure and inpatient hospital admissions. In a study of Medicare recipients in the Southeast region of the United States, a 1-μg/m^3 increase in annual average $PM_{2.5}$ was associated with a 5.3% increased risk of an inpatient hospital admission for HF.[10] This is similar to the 4.35% increase (95% CI, 1.12%–7.68%) observed for inpatient admissions in this study. This similarity increases our confidence that our results may generalize to other HF populations.

In addition to hospital admissions, we also examined readmissions that have not been commonly examined in relation to environmental exposures. Thirty-day hospital readmissions are a closely watched measure that is used to evaluate the quality of hospital operations, and there have been recent national campaigns to lower readmission rates by 20%.[23] In our study, annual average $PM_{2.5}$ exposure was associated with a 14.1% increase in the number of 30-day readmissions, suggesting that a portion of 30-day readmissions may be influenced by long-term air pollution exposure. Annual average $PM_{2.5}$ exposure was also associated with the number of 7-, 60-, and 90-day readmissions. These associations represent some of the first insights into long-term air pollution exposures and readmission risks. Understanding the association between readmissions and potentially modifiable risk factors like air pollution is particularly important for patients with HF, because they have high 30-day readmission rates.[6] A nationwide study found a minor decline in 30-day all-cause readmission rates between 2009 and 2012, and only 1.4% of hospitals examined achieved the 20% decline in relative 30-day readmission rates targeted by quality-improvement campaigns. No hospital achieved a 20% decline in 60-day readmission rates.[6] Although the study did find that hospitals that referred patients to HF disease management programs had lower readmission rates, they did not evaluate if environmental conditions might have contributed to readmission rates.

Strengths and Limitations

One of the primary strengths of this study is the large sample size and use of electronic health records to estimate the number of outpatient hospital visits, inpatient admissions, and 30-day readmissions within patients with HF. Patients with HF have previously been shown to have elevated environmental health risks,[11] and they have high hospital use and readmission rates, making them an ideal population to study for environmental determinants of hospital visits. One drawback of electronic health records is that not all confounders typically captured in an epidemiological study are represented within them. We used a combination of medical records data, census data, and county-level health data to perform a broad adjustment for potential confounders. We did not observe substantial differences in the association when adding additional potential confounders beyond our Primary model, indicating a robustness to confounding that has been demonstrated in previous similar studies.[10] Because we used only a single hospital system located in North Carolina, these results may not generalize to HF populations in other states. However, we found good agreement when comparing associations with inpatient admissions in our study and a comparable analysis of inpatient admissions for over 11 million Medicare recipients in the southeastern United States. Other limitations of electronic health record analyses include the use of *ICD-9* and *ICD-10* codes for disease definitions and potential changes in the underlying software/technology that captures and stores the medical information. Although limited, *ICD-9* and *ICD-10* codes present the single broadest possible capture of disease history in the electronic medical record. We also eliminated codes listed as billing or diagnostic to refine determinations of HF and preexisting disease. Our models included an adjustment for time that can capture changes in technology over time. We also examined restricting to records before 2014 and adjusting for this time period because the University of North Carolina Healthcare System underwent a change in health-record management software around that time. There were no substantial differences in visits or readmissions for patients diagnosed before versus after 2014 (Figure S1), and neither restriction nor adjustment for this potential change altered results, so we proceeded with the analysis as described. However, because our study observation time ended on December 31, 2016, it is possible that gathering more data might reveal some differences as compared with earlier records, which should be carefully considered and accounted for in future analyses. Because the primary reason for most visits was recorded as HF, we did not do a breakdown by reason for visit. Future advancements in medical record capture may allow for this important aspect of these associations to be explored. Although we did not observe differences in hospital visits or 30-day readmission rates across the stratified analyses (Table S3), associations may not generalize to populations with limited access to health care, and stratified analyses should be interpreted carefully. North Carolina had air quality generally just below the current $PM_{2.5}$ national standard, allowing us to examine associations below the standard, providing useful information on association in low-exposure scenarios. A strength of the study is the stabilized inverse probability weights used to allow for causal interpretations of results. Although there was a moderate violation of the positivity assumption for the 30-day readmissions in the Primary model, as shown by the moderate differences in weights (Table S3), this was not observed in the Extended model, and there were little to no violations seen for total visits in either model (Table S2). In addition to positivity, causal interpretations of associations from observational studies require the additional assumptions of no unmeasured confounding and stable unit treatment value assumption, that is, that exposure to one individual does not alter associations for others, and all exposures can be treated equally. Although the treatment of all ambient $PM_{2.5}$ concentrations is the same, and the assumption that one individual's exposure does not alter responses of an independent individual are considered reasonable in these studies, the assumption of no unmeasured confounding requires careful consideration. Although we did adjust for a broad array of confounders in the Primary model, and did not observe differences when adding 20 additional confounders in the Extended model, it is always impossible to conclude with certainty that associations are not impacted by unmeasured confounding. However, these unmeasured confounders would need to be largely independent of all 37 confounders considered in the Extended model to alter associations and causal interpretations.

In conclusion, we observed that long-term exposure to particulate air pollution is associated with substantial increases in total hospital visits, outpatient visits, inpatient admissions, as well as 7-, 30-, 60-, and 90-day readmissions in individuals with HF. These associations expand our knowledge of the relationship between air quality and hospital use and highlight the potential for long-term environmental exposure to play a role in readmission rates.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Data S1
Tables S1–S5
Figures S1–S5

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Co-morbid disease ICD-9 and ICD-10 codes:

International Classification of Disease (ICD)-9 and ICD-10 codes used to determine existing co-morbidities are given below. A * is used as a wildcard character which was used to capture all subcodes for relevant disease definitions.

Type 2 diabetes: 250, 250.0, 250.00, 250.02, 250.1, 250.10, 250.12, 250.2, 250.20, 250.22, 250.3, 250.30, 250.32, 250.4, 250.40, 250.42, 250.5, 250.50, 250.52, 250.6, 250.60, 250.62, 250.7, 250.70, 250.72, 250.8, 250.80, 250.82, 250.9, 250.90, 250.92, E11.*

Hypertension: 401*, I10*

Dyslipidemia: 272*, E78*

Peripheral Arterial Disease: 443*, I73*

Chronic Obstructive Pulmonary Disorder (bronchitis): 491*, J44*

Emphysema: 492*, J43*

Ischemic Heart Disease: 414*, I20, I21, I22, I23, I24, I25

Table S1. County-level indicators included in expanded adjustment model along with their mean and standard deviation (SD) in study cohort.

Variable	Mean in Study sample	SD in study sample
Average annual health care cost ($)	8859.47	920.23
Food Environment Index	6.87	0.77
Mortality rate for drug poisoning deaths	10.17	3.33
Number of Dentists per 100,000 people	60.92	48.90
Number of mental health providers per 100,000 people	201.92	160.84
Number of non-primary care physicians per 100,000 people	81.12	47.32
Number of Primary Care Physicians per 100,000 people	79.28	44.78
Number of social associations (organizations) per 10,000 people	11.07	1.82
Number of violent crimes per 100,000 people	297.77	150.78
Percent Adult Smokers	18.56	5.51
Percent Adults Physically Inactive	23.36	5.17
Percent Adults with Obesity (body mass index > 30)	28.58	4.73
Percent of Single Parent Households	34.00	7.57
Percent Population Unemployed	18.47	2.76
Percent Residents with Access to Exercise Opportunities	76.48	15.46
Percentage of households with at least 1 of 4 housing problems: overcrowding, high housing costs, or lack of	16.25	2.22
Percentage of population unemployed	7.30	1.72
Percentage of population with limited access to healthy foods	6.10	3.56
Proportion of population with public water service that is affected by a water violation	5.04	10.44
Ratio of Income in the upper quintile to income in the lower quintile	4.76	0.66

Table S2. Associations between annual average $PM_{2.5}$ exposure and total visits.

Model	Stratification	Percent Change	LCI	UCI	Standardized Difference
Primary	None	9.31	7.85	10.8	Very Weak
Extended	None	11.4	9.88	13.0	Very Weak
Primary	$PM_{2.5}$ < 12 μg/m^3	7.16	5.29	9.06	Very Weak
Extended	$PM_{2.5}$ < 12 μg/m^3	8.15	6.11	10.2	Very Weak
Primary	Age $\geq$ 65	7.79	5.98	9.64	Very Weak
Extended	Age $\geq$ 65	10.9	8.83	12.9	Very Weak
Primary	Age < 65	11.1	8.76	13.5	Weak
Extended	Age < 65	10.9	8.46	13.4	Weak
Primary	Black	11.6	8.82	14.4	Very Weak
Extended	Black	9.52	6.73	12.4	Very Weak
Primary	White	9.30	7.53	11.1	Weak
Extended	White	13.0	11.1	15.0	Very Weak
Primary	Female	11.8	9.68	13.9	Very Weak
Extended	Female	11.9	9.65	14.2	Very Weak
Primary	Male	6.92	4.92	8.95	Very Weak
Extended	Male	11.0	8.83	13.3	Very Weak
Primary	Low Income	6.91	4.97	8.89	Very Weak
Extended	Low Income	8.37	6.28	10.5	Very Weak
Primary	High Income	11.1	8.90	13.3	Weak
Extended	High Income	13.6	11.3	16.0	Weak
Primary	Non-rural	8.34	6.54	10.2	Very Weak
Extended	Non-rural	11.9	9.93	14.0	Very Weak
Primary	Rural	10.1	7.47	12.8	Very Weak
Extended	Rural	10.5	7.73	13.4	Very Weak

The Primary model adjusted for age, race, sex, year of HF diagnosis, smoking status, median household income, median home value, percent of block group on public assistance, percent of block group residents below the federal poverty line, percent urbanicity of the 2010 census block group in which the individual resided, and short-term air pollution exposure. Associations are given as the percent change per 1 μg/m^3 increase in annual average $PM_{2.5}$. The Extended model adjusted for all the terms in the Primary model plus all of the county-level indicators appearing in **Table S1**. Stratifications were defined as given in the manuscript text. Standardized Difference refers to the standardized difference of the propensity scores as was categorized as very weak (0-0.2), weak (0.2-0.4), moderate (0.4-0.6), or strong (> 0.6). Moderate or even strong categories of the standardized difference do not invalidate models but do suggest that causal interpretations require further investigation as the assumption of positivity, required for causal interpretations, may be violated. LCI = lower 95% confidence interval; UCI = upper 95% confidence interval.

Table S3. Mean and standard deviation (SD) for the total visits and 30-day readmissions for each stratified analysis performed.

Dataset	Total Visits Mean (SD)	30-day Readmissions Mean (SD)
All	12.7 (12.7)	0.49 (0.49)
$PM_{2.5}$ < 12 μg/m^3	12.1 (12.2)	0.43 (0.43)
Low Income	11.7 (12.2)	0.47 (0.47)
High Income	13.7 (13.2)	0.5 (0.5)
Age < 65	13.2 (13.1)	0.56 (0.56)
Age $\geq$ 65	12.4 (12.5)	0.44 (0.44)
Black	13.1 (13.2)	0.55 (0.55)
White	12.8 (12.7)	0.46 (0.46)
Male	12.7 (12.7)	0.49 (0.49)
Female	12.6 (12.7)	0.48 (0.48)
Non-rural	12.7 (12.8)	0.49 (0.49)
Rural	12.5 (12.6)	0.47 (0.47)

Table S4. Associations between annual average $PM_{2.5}$ exposure and 30-day readmissions.

Model	Stratification	Percent Change	LCI	UCI	Standardized Difference
Primary	None	14.2	8.41	20.2	Moderate
Extended	None	17.6	11.6	23.9	Weak
Primary	$PM_{2.5}$ < 12 μg/m^3	-0.19	-7.47	7.66	Very Weak
Extended	$PM_{2.5}$ < 12 μg/m^3	1.02	-6.98	9.70	Very Weak
Primary	Age ≥ 65	9.88	2.48	17.8	Moderate
Extended	Age > 65	12.0	3.73	21.0	Weak
Primary	Age < 65	21.6	12.5	31.4	Moderate
Extended	Age < 65	24.6	15.5	34.5	Weak
Primary	Black	26.0	14.0	39.2	Moderate
Extended	Black	22.7	11.3	35.3	Weak
Primary	White	8.66	2.13	15.6	Moderate
Extended	White	15.4	8.24	23.0	Weak
Primary	Female	12.7	4.59	21.4	Moderate
Extended	Female	20.1	11.5	29.4	Weak
Primary	Male	16.2	8.23	24.8	Moderate
Extended	Male	19.0	10.4	28.2	Weak
Primary	Low Income	15.2	6.32	24.9	Weak
Extended	Low Income	21.6	12.1	32.0	Weak
Primary	High Income	12.9	5.72	20.7	Moderate
Extended	High Income	15.9	8.13	24.2	Moderate
Primary	Non-rural	11.1	4.06	18.7	Moderate
Extended	Non-rural	19.5	11.5	28.2	Weak
Primary	Rural	14.6	5.31	24.8	Moderate
Extended	Rural	17.8	7.92	28.5	Moderate

Associations are given as the percent change per 1 μg/m^3 increase in annual average $PM_{2.5}$. The Primary model adjusted for age, race, sex, year of HF diagnosis, smoking status, median household income, median home value, percent of block group on public assistance, percent of block group residents below the federal poverty line, percent urbanicity of the 2010 census block group in which the individual resided, and short-term air pollution exposure. The Extended model adjusted for all the terms in the Primary model plus all of the county-level indicators appearing in **Table S1**. Stratifications were defined as given in the manuscript text. Standardized Difference refers to the standardized difference of the propensity scores as was categorized as very weak (0-0.2), weak (0.2-0.4), moderate (0.4-0.6), or strong (> 0.6). Moderate or even strong categories of the standardized difference do not invalidate models but do suggest that causal interpretations require further investigation as the assumption of positivity, required for causal interpretations, may be violated. LCI = lower 95% confidence interval; UCI = upper 95% confidence interval.

Table S5. Sensitivity analyses for 7, 60, and 90-day readmissions.

Sensitivity Analysis	Outcome	Percent Change	LCI	UCI
Zero-inflated Poisson	7-day readmissions	18.3	11.7	25.2
Zero-inflated Poisson	60-day readmissions	5.86	3.53	8.24
Zero-inflated Poisson	90-day readmissions	6.66	4.49	8.88
Zero length admissions removed	7-day readmissions	14.4	7.09	22.3
Zero length admissions removed	60-day readmissions	7.73	5.29	10.2
Zero length admissions removed	90-day readmissions	8.69	6.43	11.0

Associations were adjusted for age, race, sex, year of HF diagnosis, smoking status, median household income, median home value, percent of block group on public assistance, percent of block group residents below the federal poverty line, percent urbanicity of the 2010 census block group in which the individual resided, and short-term air pollution exposure. Associations are given as the percent change per 1 $\mu g/m^3$ increase in annual average $PM_{2.5}$. The Zero-inflated Poisson sensitivity analysis used a zero-inflated Poisson model which modeled the excess 0's in the data as using an intercept only model and the "true" counts using the aforementioned adjustment. The zero length admissions removed sensitivity analysis removed all inpatient admission where the individual was admitted and discharged on the same day prior to calculating the number of 7, 60, and 90-day readmissions and also used a zero-inflated Poisson model. LCI = lower 95% confidence interval; UCI = upper 95% confidence interval.

Figure S1. Total visits and total readmissions by year of heart failure diagnosis.

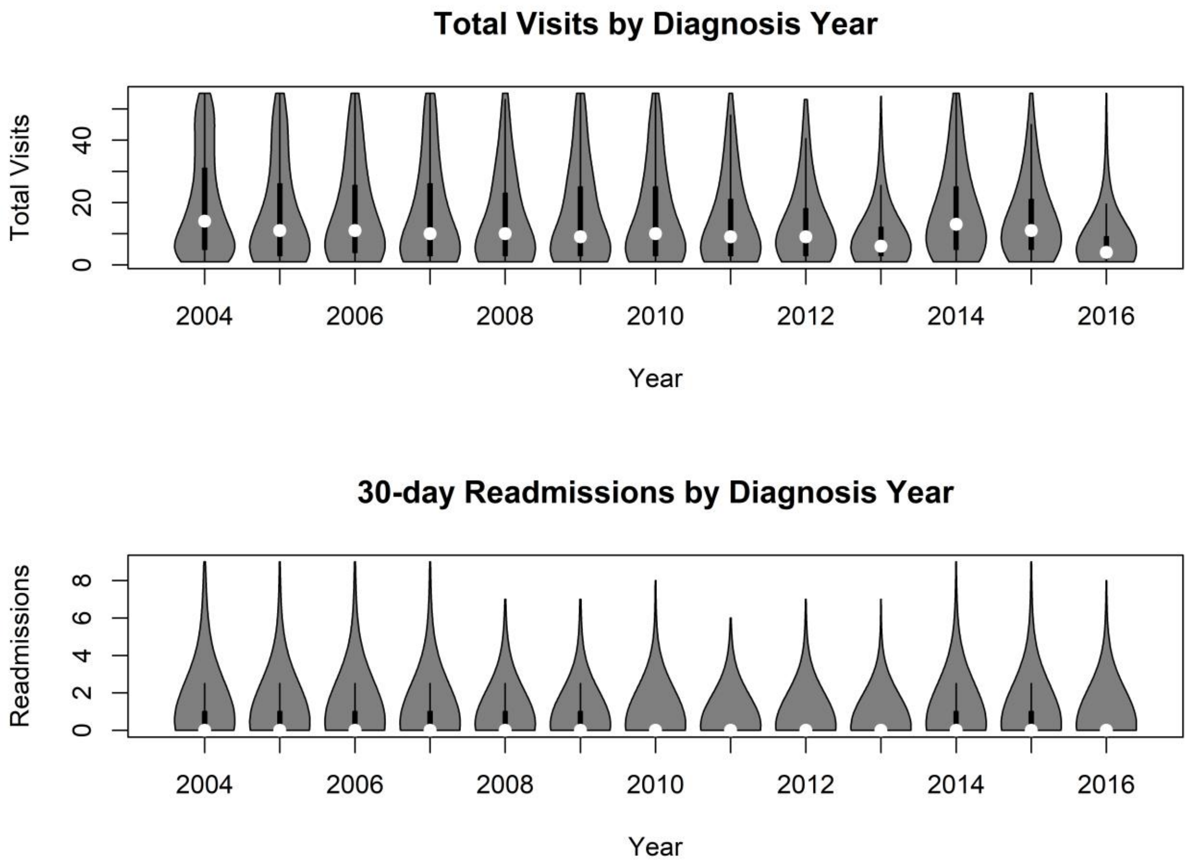
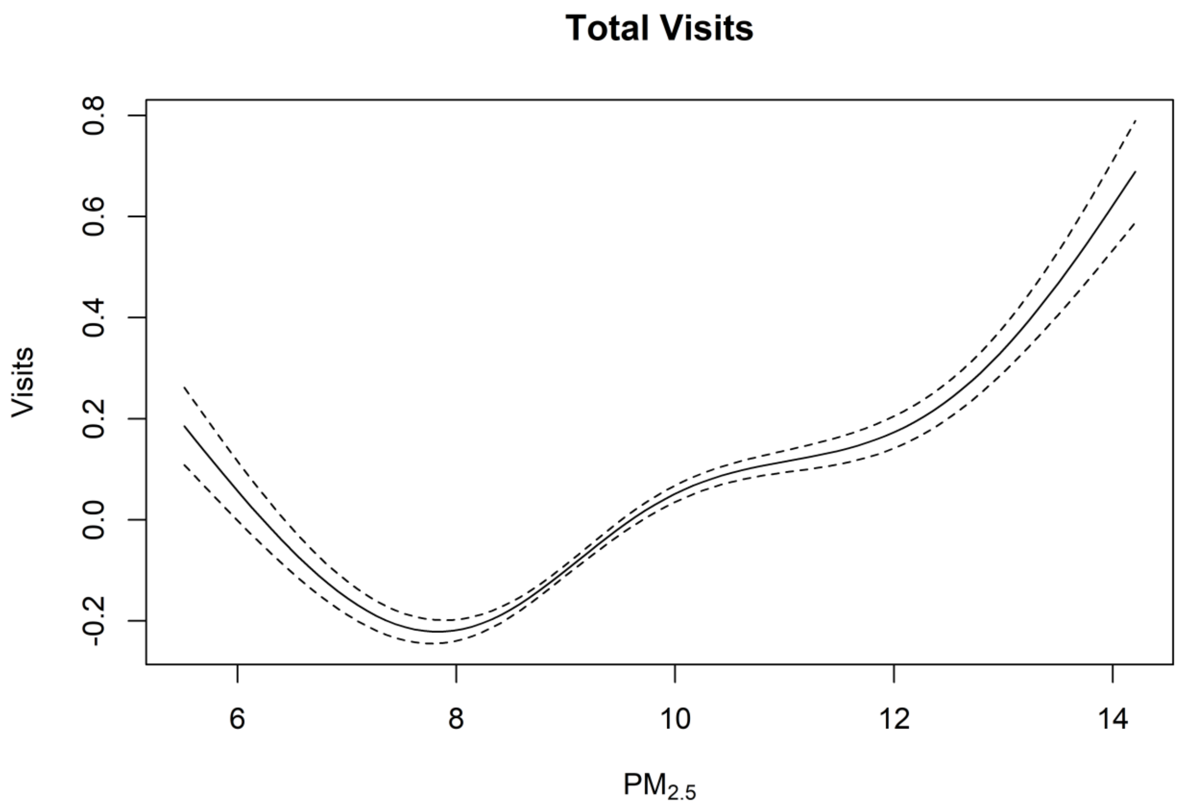


Figure S2. Concentration-response curve for total visits.



The upper and lower 0.5% of the annual average $PM_{2.5}$ values (202 observations out of 20,282) have been trimmed from the plot for improved visualization and because estimates at the extremes are supported by relatively few observations.

Figure S3.Association between total visits and annual average $PM_{2.5}$ in the original model "Original" as well as five imputations of missing smoking information (Impute 1 – 5) and in the pooled results of all five imputation (Pooled Impute).

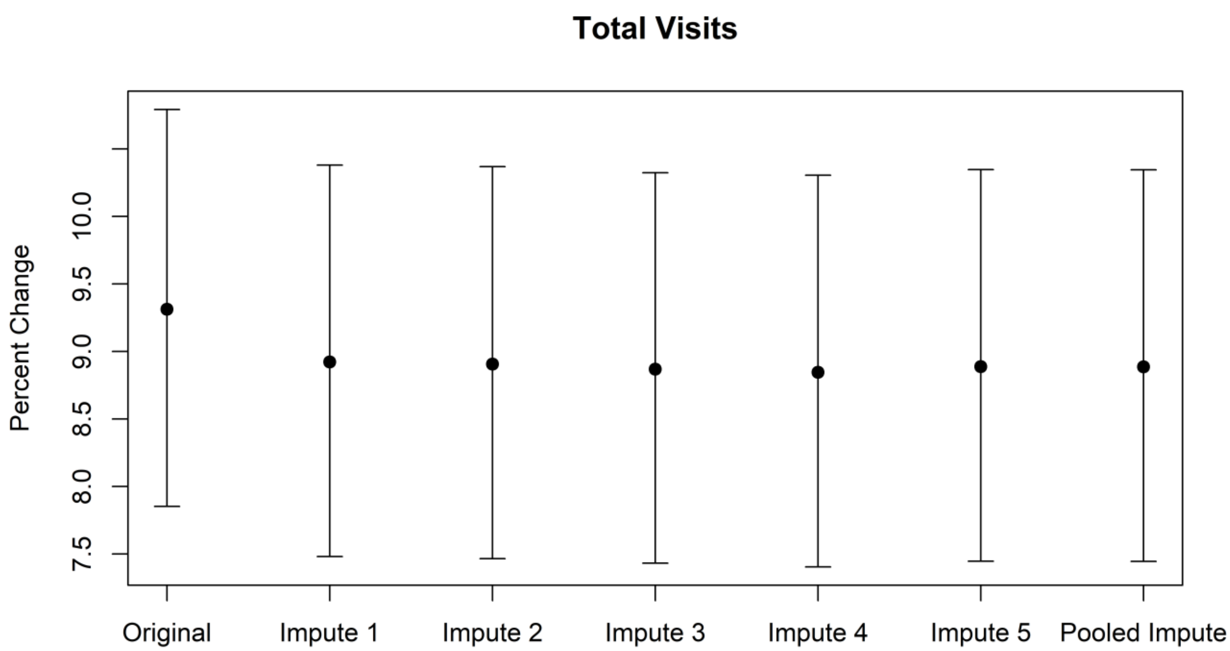
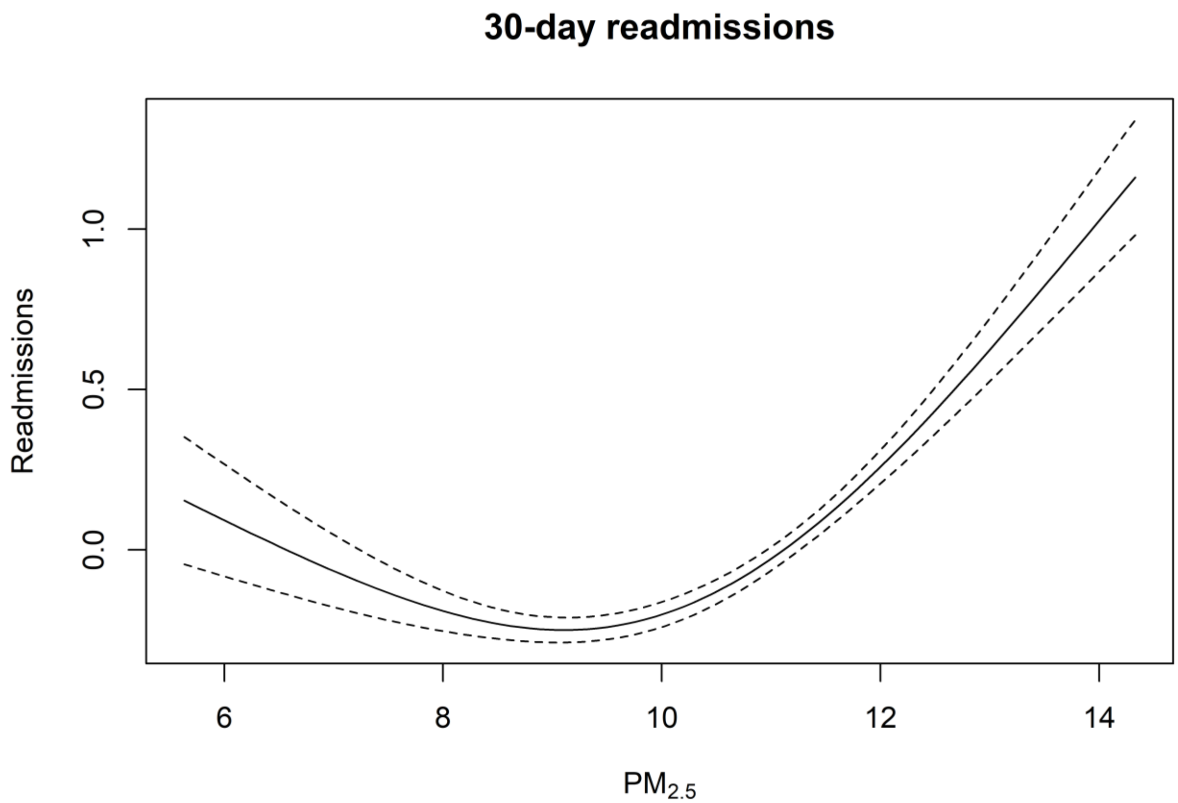


Figure S4. Concentration-response curve for 30-day readmissions.



The upper and lower 0.5% of the annual average $PM_{2.5}$ values (105 total observations out of 10,510) have been trimmed from the plot for improved visualization and because estimates at the extremes are supported by relatively few observations.

Figure S5. Association between 30-day readmissions and annual average $PM_{2.5}$ in the original model "Original" as well as five imputations of missing smoking information (Impute 1 – 5) and in the pooled results of all five imputation (Pooled Impute).