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Do temporal trends of associations between short-term exposure to fine particulate matter ($PM_{2.5}$) and risk of hospitalizations differ by sub-populations and urbanicity—a study of 968 U.S. counties and the Medicare population

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Abstract

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

While associations between short-term exposure to fine particulate matter ($PM_{2.5}$) and risk of hospitalization are well documented and evidence suggests that such associations change over time, it is unclear whether these temporal changes exist in understudied less-urban areas or differ by sub-population. We analysed daily time-series data of 968 continental U.S. counties for 2000-2016, with cause-specific hospitalization from Medicare claims and population-weighted $PM_{2.5}$ concentrations originally estimated at 1km×1km from a hybrid model. Circulatory and respiratory hospitalizations were categorized based on primary diagnosis codes at discharge. Using modified Bayesian hierarchical modelling, we evaluated the temporal trend in association between $PM_{2.5}$ and hospitalizations and whether disparities in this trend exist across individual-level characteristics (e.g., sex, age, race, and Medicaid eligibility as a proxy for socio-economic status) and urbanicity. Urbanicity was categorized into three levels by county-specific percentage of urban population based on urban rural delineation from the U.S. Census. In this cohort with understudied less-urban areas without regulatory monitors, we still found positive association between circulatory and respiratory hospitalization and short-term exposure to $PM_{2.5}$, with higher effect estimates towards the end of study period. Consistent with current literature, we identified significant disparity in associations by race, socioeconomic status and urbanicity. We found that the percentage change in circulatory hospitalization rate per 10 $\mu g/m^3$ increase in $PM_{2.5}$ was higher in the 2008-2016 time period compared to the 2000-2007 period by 0.33% (95% posterior credible interval 0.22, 0.44%), 0.52% (0.33, 0.69%), and 0.67% (0.53, 0.83%) for low, medium and high tertiles of urban areas, respectively. We also observed significant differences in temporal trends of associations across socioeconomic status, sex, and age, indicating a possible widening in disparity of $PM_{2.5}$-related health burden. This study raises the importance of considering environmental justice issues in $PM_{2.5}$-related health impacts with respect to how associations may change over time.

Keywords

fine particulate matter; hospitalization; vulnerable sub-population; urbanicity; temporal trend

INTRODUCTION

Deleterious associations between short-term exposure to fine particulate matter ($PM_{2.5}$) and risk of hospitalizations were identified in many national studies (Dominici et al., 2006; Tian et al., 2019; Wei et al., 2019; Zhao et al., 2020). Changes to the complex mixture of varying chemicals that comprise particles due to variation in emissions sources as well as changes in population characteristics that relate to susceptibility to $PM_{2.5}$ could affect $PM_{2.5}$-related health impact (Atkinson et al., 2015; Bell et al., 2014; Krall et al., 2013). Many factors that affect the source and composition of $PM_{2.5}$ change over time, such as promulgation of air pollution control policy, technology improvement in vehicle engines, trends in fuel sources, and climate change, potentially leading to temporal changes in association between $PM_{2.5}$ and risk of hospitalizations. While suggestive evidence on temporal changes in this association has been observed in various regions and time periods, evidence of temporal changes in U.S. rural areas and on their effect modifiers is lacking (Breitner et al., 2009; Carugno et al., 2017; Chen et al., 2021; Choi et al., 2018; Dominici et al., 2007; Kim et al., 2015).

Understanding the health impact of $PM_{2.5}$ and its temporal trend in both urban and rural areas is particularly important as the sources of $PM_{2.5}$ changed over time in the U.S. and such scientific evidence could lead to better understanding of the relative harm of different emissions. Analyses on U.S. industrial contribution to air pollution from 2008 to 2014 identified a consistent high contribution from agricultural emissions, which became the largest contributors to air pollution damages from $PM_{2.5}$-related emissions when contributions from other industries like electricity generation and transportation steadily decreased (Tschofen et al., 2019). Agricultural emissions mostly impacted areas with lower urban population, and the pattern described above highlights the need for better understanding of $PM_{2.5}$-health association in these areas. Further, assuming a constant $PM_{2.5}$-related health impact over time, or even assuming that such a trend exists but is the same across populations, levels of urbanicity, etc., might lead to incorrect estimation of health burden of $PM_{2.5}$. Estimates of the public health impacts of air pollution and associated air quality regulations and policies routinely incorporate evidence from the scientific literature based on timeframes in the past, such as studies based on air pollution from decades ago. The degree to which these prior studies apply to current and future conditions could be impacted by temporal changes in these associations and how they differ across region or population.

Further, most national level epidemiological studies of $PM_{2.5}$-related health impact, including the limited studies of the temporal changes, focused on urbanized areas due to data limitations. Most studies utilized measured exposure data from monitors established for regulatory purposes, such as those from U.S. Environmental Protection Agency Air Quality System (US EPA, 2013). These monitoring sites are largely located in densely populated areas with higher urban population, socioeconomic status, and education level (Bell and Ebisu, 2012; Bravo et al., 2012). $PM_{2.5}$-health associations in less populated and less urbanized areas are understudied, although some research suggests different impacts from $PM_{2.5}$ on health by urbanicity (Bravo et al., 2017). Recent studies attempted to fill this gap by using modelled $PM_{2.5}$ concentrations (Bravo et al., 2017; Di et al., 2017; Kloog et al., 2014; Wei et al., 2019), but to the best of our knowledge none have explored the temporal trend of the association between $PM_{2.5}$ and risk of hospitalizations.

Previous studies found evidence on effect modification of $PM_{2.5}$-related health impact by community-level characteristics and individual-level characteristics, with higher risk found in more urbanized areas, women, older populations, racial/ethnic minorities, and populations with lower socioeconomic status, although evidence was inconsistent across studies (Bell et al., 2015, 2013; Bravo et al., 2017; Deguen and Zmirou-Navier, 2010; Di et al., 2017). We hypothesize that the temporal trend could also vary by sub-population. The association between $PM_{2.5}$ and risk of hospitalization and its temporal changes could vary across community-level and individual-level characteristics due to difference in composition of $PM_{2.5}$ exposed (Bell and Ebisu, 2012; Krall et al., 2013), different baseline health status (e.g., greater barriers to health care access in rural areas or among those financially deprived), and differential measurement error (e.g., variation in time spent outdoors during high $PM_{2.5}$ episodes). Exploration of disparities across community-level and individual-level characteristics could highlight disparities in the health burden of $PM_{2.5}$ over time and

thereby facilitates better understanding of environmental justice in the U.S. and supports evidence-based mitigation policy design.

In this study, we explored whether the association between $PM_{2.5}$ and risk of hospitalization changed over time, using analysis that included understudied, less densely populated areas. We also evaluated whether disparity in associations and temporal trends of associations existed across levels of urbanicity and individual-level characteristics related to environmental justice concerns.

METHODS

Study population

We studied Medicare beneficiaries residing in 968 U.S. counties from 2000 to 2016. Under consideration of statistical power, we selected counties with a population larger or equal to 50,000 in U.S. Census Bureau 2010 Decennial Census. To categorize these counties into different levels of urbanicity, we utilized the county-level percentage of urban population from the U.S. Census Bureau 2010 Census (US Census Bureau, n.d.). The U.S. Census first categorizes tracts and blocks as urban or rural based on a combination of characteristics including population density, land use, and other measures of dense development, and then calculates county-specific percentages, ranging between 0 to 100%, of urban population as the proportion of total population residing in urban census tracts and blocks within the county (Ratcliffe et al., 2016). To alleviate the concern over different statistical power across categories, we divided counties into three urbanicity categories by setting cut points for percentage of urban population to achieve similar size of population in each category: high (97.9% to 100% urban population), medium (87.7% to 97.5% urban population), and low urbanicity (9.9% to 87.7% urban population). Although we did not include counties that are completely rural (0% urban population), we included many counties that are mostly rural (less than 50% urban population) based on U.S. Census Bureau definition (Ratcliffe et al., 2016). This study was approved by Yale and Harvard Universities' Institutional Review Boards. Health data were previously collected administrative data, thus informed consent requirements did not apply.

Health outcomes

We analyzed county-level daily counts of circulatory and respiratory hospitalization aggregated from Medicare fee-for-service patient claims (age ≥ 65 years) from January 1, 2000 to December 31, 2016. We categorized hospitalization counts into different causes based on primary diagnosis at discharge and the International Classification of Diseases, Ninth Revision, Clinical Modification through September 30, 2015 and the International Classification of Diseases, Tenth Revision, Clinical Modification for the remaining years (Appendix A). We also obtained county-level number of persons at risk. These aggregated data were stratified by individual-level characteristics including sex (men and women), race (White, Black, and other), age groups (65 to 74 years and ≥ 75 years), and eligibility for Medicaid (eligible and non-eligible). The "other" race category included individuals with self-reported racial group other than White or Black or with unknown race. Individuals' eligibility for Medicaid could be interpreted as a surrogate for lower socioeconomic status.

Air pollution exposure and meteorological data

We utilized estimated daily $PM_{2.5}$ concentration from a hybrid model using convolutional neural network technique to incorporate data from sources such as monitor measurements from U.S. Environmental Protection Agency Air Quality System, satellite-based measurements, simulation outputs from a chemical transport model, land-use terms, meteorological data, etc. (Di et al., 2016). This modelled daily $PM_{2.5}$ dataset was extensively validated with a R^2 value of 0.84 between fitted and measured values among left out monitors in 10-fold cross-validation (Di et al., 2016), and was utilized in previous epidemiological studies (Di et al., 2017; Wei et al., 2019). This dataset allows estimation of exposure in locations without regulatory monitors. We spatially allocated $PM_{2.5}$ concentrations estimated at 1 × 1 km grid across the continental U.S. to county-level averages by population weighting. For daily average temperature and dew point temperature, we obtained daily estimates from Parameter-elevation Relationships on Independent Slopes Model AN81D dataset and processed them with population weighing to achieve county-level averages (Daly et al., 2008). Details of county-level exposure and meteorological data calculation are in Appendix B.

Statistical approach

We utilized a modified two-stage Bayesian hierarchical model to evaluate whether the temporal trend in association between short-term exposure to $PM_{2.5}$ and risk of hospitalizations varies across individual- and community-level characteristics. The base model was previously applied in studies evaluating the association between adverse health outcomes and short-term exposure to air pollutants, which consists of a quasi-Poisson model to estimate county-specific association between $PM_{2.5}$ and risk of hospitalizations, and a Bayesian hierarchical model to pool normal-approximated county-level estimates to generate a national average estimate that accounts for variabilities within and across counties (Bell et al., 2004a; Dominici et al., 2006; Samet et al., 2000). Details of the epidemiological modelling structure are described in Appendix C.

There are several features in our analysis that build and extend upon previous methods. We chose $PM_{2.5}$ concentration for the moving average of the same day and previous two days (L02) *a priori* as the main exposure of interest because previous studies reported positive associations between exposure to $PM_{2.5}$ and hospitalization in this lag interval (Dominici et al., 2006; Qiu et al., 2020; Shah et al., 2013, 2015), and L02 $PM_{2.5}$ will likely capture the health impact of $PM_{2.5}$ more fully than single-day lag model while remaining parsimonious. Similar approach was utilized in previous studies (Di et al., 2017; Zanobetti and Schwartz, 2009). Similar to a previous study, we evaluated the temporal trend in the $PM_{2.5}$-hospitalization association separately for each county in two ways with increasing flexibility: 1) time-stratification model calculating associations separately for two time periods of similar length (2000-2007 and 2008-2016), and comparing associations between periods; and 2) nonlinear temporal model by replacing the term for $PM_{2.5}$ with both a $PM_{2.5}$ term and an interaction term between daily $PM_{2.5}$ and natural cubic spline function of year with 4 internal knots at quantiles (Chen et al., 2021). The nonlinear method accounts for the possibility that the stratification model may not fully capture the temporal trend. In the quasi-Poisson model, we included variables to account for factors that could confound

the relationship between $PM_{2.5}$ and risk of hospitalization, such as changing meteorological conditions and long-term trends in risk of hospitalizations (Equation C.1 in Appendix C). In this way, we disentangled the temporal trends in health effect estimates for $PM_{2.5}$ from other factors that influence risk of the hospitalization over time.

We evaluated whether $PM_{2.5}$-hospitalization associations vary by individual- and community-level characteristics with different methods. For individual-level characteristics (sex, race, age group, and eligibility for Medicaid), we added interaction terms with the indicator variable of the characteristic in the first stage (county-specific model as shown in Equation C.2 in Appendix C). This interaction method investigates whether persons who are from the same county but in different sub-populations could be affected differently by $PM_{2.5}$ as well as other model covariates (e.g., temperature). For community-level characteristics (e.g., urbanicity), we conducted first-stage modelling without consideration of effect modification and assessed the effect modification of the characteristics using its spatial disparity across counties, making no assumption about other covariates in the first-stage model. Using urbanicity as an example, we combined county-specific estimates by categories of urbanicity separately in the second-stage model to evaluate effect modification by urbanicity (subset method).

Analyses were performed with R3.5.1 software with “zoo”, “splines”, “tsModel” and “tlnise” packages (Everson and Morris, 2000; R Core Team, 2018; Roger D. Peng and with contributions from Aidan McDermott, 2013; RStudio Team, 2018; Zeileis and Grothendieck, 2005).

Sensitivity analysis

Since previous studies provided evidence that $PM_{2.5}$ did not advance adverse health outcomes by only a few days (Bell et al., 2004b; Qiu et al., 2020), we conducted sensitivity analysis with different lag structures for the base model to evaluate whether the exposure metric chosen fully captured the health impacts of $PM_{2.5}$, using moving averages of same day and previous day (L01), and single day lags of same day (L0), previous day (L1), and 2 days previous (L2).

To explore whether the categorization of urbanicity affects the results, we also categorized counties into five levels by setting cut points for percentage of urban population at 90%, 80%, 60% and 40%, and conducted similar analyses as the three-level categorization in the main analysis. This five-level categorization prioritized similar range for percentage of urban population in each level over balance in population size across levels and was used in previous study of health disparity by urbanicity (Bravo et al., 2017). Further, we included percentage of urban population as a covariate in the second stage model for the base model (covariate method), which avoided categorization of urbanicity as in the subset method and was applied in previous studies of effect modification (Bell and Dominici, 2008). This also tested whether a linear relationship exists between county-level percentage of urban population and $PM_{2.5}$-hospitalization association.

RESULTS

This study included an average of 23.1 million Medicare beneficiaries residing in 968 U.S. counties with 32.9 million circulatory and 9.8 million respiratory hospitalizations for 2000-2016 (Figure D.1). The number of beneficiaries were balanced across most individual-level characteristics except for race and Medicaid eligibility, with more Whites (85.1%) and persons non-eligible for Medicaid (87.3%) (Table 1). Hospitalization rates were higher in men, those ≥ 75 years, Blacks, and persons eligible for Medicaid than corresponding comparison groups, and decreased over the study period for all sub-populations (Table 1). Medians of county-level daily hospitalization rates and average $PM_{2.5}$ concentrations were highest in the low urban category in comparison to the medium and high urban categories and decreased over time for all levels of urbanicity (Table 2).

Entire study population

In the base model of the entire study population, a 10 $\mu g/m^3$ increase in L02 $PM_{2.5}$ was associated with a 0.56% (95% posterior credible intervals (PI): 0.45, 0.68%) change in risk of circulatory hospitalization and a 0.17% (95% PI: −0.03, 0.37%) increase in respiratory hospitalization (Table 3). Central estimates for associations between $PM_{2.5}$ and circulatory hospitalization were positive in all lags tested and were most significant and highest for L0 exposure (Table D.1). Central estimates for associations with respiratory hospitalization were positive in all lags tested and most significant and highest for L1 exposure (Table D.1).

Results from the time-stratified model, with separate results for 2000-2007 and 2008-2016, indicate changes over time in $PM_{2.5}$ risk. We observed a 0.49% (95% PI: 0.40, 0.58%) increase in association (expressed as percentage change in hospitalization per L02 $PM_{2.5}$ 10 $\mu g/m^3$ increase) for circulatory hospitalization and 0.67% (95% PI: 0.53, 0.82%) decrease for respiratory hospitalization comparing association in the first period (2000-2007) to second period (2008-2016) (Table 4). The nonlinear model also demonstrated changes in the $PM_{2.5}$ risk over time. Results from nonlinear model indicate a fluctuating but overall increasing trend in $PM_{2.5}$ risk for circulatory hospitalization consistent with the stratification model, whereas results for respiratory hospitalization showed a hook shape with risk that was lowest around 2010 and increased to its highest level in 2016 (Figure 1). The decrease in association between $PM_{2.5}$ and respiratory hospitalizations over time in the stratification model was likely driven by the dip around 2010 although the association increased to its highest level in the last years of study. The association between $PM_{2.5}$ and circulatory hospitalization increased 2.59% (95% PI: 2.03, 3.17%) from the lowest estimate in 2007 to the highest estimate in 2016, whereas the association for respiratory hospitalization increased 3.13% (95% PI: 2.12, 4.14%) from the lowest estimate in 2010 to the highest estimate in 2016.

Effect modification by urbanicity

Across levels of urbanicity, associations were lowest in low urban (lowest third of urban population) counties. High urban (highest third) counties demonstrated a 0.80% (95% PI: 0.54, 1.05%) increase in risk of circulatory hospitalization per 10 $\mu g/m^3$ L02 $PM_{2.5}$ increase, which was significantly higher than the 0.43% (95% PI: 0.27, 0.59%) increase in

low urban counties, and 0.60% (95% PI: 0.37, 0.82%) increase in medium urban (middle third) counties (Table 3). Medium urban counties demonstrated the highest association for respiratory hospitalization while associations were not statistically significant in the other two urban categories (Table 3). Results from the covariate model also indicated increase in $PM_{2.5}$-hospitalization association with increase in percentage of urban population, but these trends were not statistically significant and suggested the lack of a linear relationship (Figure D.2).

Using the stratification model, we observed similar temporal patterns in three levels of urbanicity as in the entire study population: increase in associations for circulatory hospitalization and decrease in associations for respiratory hospitalizations. The temporal change in associations (expressed as percentage change in hospitalization per L02 $PM_{2.5}$ 10 $\mu g/m^3$ in 2008-2016 minus the value in 2000-2007) for circulatory hospitalizations was 0.35% (95% PI: 0.29, 0.43%) lower in low urban counties than high urban counties (Table 4). The nonlinear temporal model revealed that the association for circulatory hospitalizations in medium and high urban counties steadily increased over time, while the association in low urban counties dipped around 2009 then increased in later years (Figure 2). For temporal changes of respiratory hospitalizations, we observed a similar dip in 2010 across all levels of urbanicity but the increase in recent years were more prominent in high and medium urban counties (Figure 2).

When using the five-level categorization of urbanicity that ensures similar range for percentage of urban population in each level, we obtained five urbanicity categories accounting for 62.8%, 13.8%, 15.3%, 5.6% and 2.5% of the total study population. The above 90% level strata included almost all counties in the high and medium urban levels in the main analysis of three-level categorization. We found similar patterns as the three-level categorization, where the above 90% level demonstrated the highest association and most increase in association over time (Table D.2 and Table D.3). Additionally, two levels with the lowest urban population, below 40% and 40% to 60%, showed higher $PM_{2.5}$-hospitalization association for circulatory conditions than the two levels in the middle, with 60% to 90% urban population (Table D.2). The 40% to 60% level also demonstrated large increase in the association for both circulatory and respiratory hospitalizations during recent years (Figure D.3).

Effect modification by individual-level characteristics

Among sub-populations, associations between $PM_{2.5}$ and hospitalization (percentage change in hospitalization per 10 $\mu g/m^3$ L02 $PM_{2.5}$ increase) were 0.26% (95% PI: 0.00, 0.53%) and 0.54% (95% PI: 0.12, 0.95%) higher among persons eligible for Medicaid compared to those not eligible, for circulatory and respiratory hospitalizations, respectively (Table 3). Whites had lower associations than the other racial groups (Blacks, other), but the difference was only statistically significant when compared to Blacks for respiratory hospitalization (Table 3). Due to imbalance in population size by racial groups, not all counties had sufficient sample size for quasi-Poison model in base and stratification models, thus this analysis excluded ~79% of counties from pooling at second stage. Therefore, this finding was more based on urban areas. We also observed slightly higher associations between $PM_{2.5}$

and circulatory and respiratory hospitalizations in women compared to men, and in those age 65-74 years compared to those ≥ 75 years, although differences were not statistically significant (Table 3).

When incorporating temporal trend in the stratification model, we observed similar temporal patterns in most sub-populations as in the entire study population with some exceptions: Black and "other" race groups and persons eligible for Medicaid demonstrated increases in $PM_{2.5}$-respiratory hospitalization risk, while all other sub-populations demonstrated decreases in this association over time (Table 4). Results from the stratification model indicate significant disparities across some sub-populations in the temporal change in associations (percentage change in hospitalization per L01 $PM_{2.5}$ 10 $\mu g/m^3$ increase in 2008-2016 minus the value in 2000-2007): 1) the temporal change was 0.25% (95% PI: 0.01, 0.51%) and 0.41% (95% PI: 0.09, 0.73%) higher for men than women for circulatory hospitalizations and respiratory hospitalizations, respectively; 2) the temporal change was 0.21% (95% PI: 0.07, 0.36%) higher for those ≥ 75 years than those 65-74 years for circulatory hospitalizations; and 3) the temporal change was 0.29% (95% PI: 0.03, 0.50%) and 1.00% (95% PI: 0.67, 1.32%) higher for persons eligible for Medicaid than those who were not eligible for circulatory hospitalizations and respiratory hospitalizations, respectively (Table 4). Results from the non-linear model for most sub-populations demonstrated similar trends, with the largest differences in risk among groups in recent years (Figure 3, Figure 4 and Figure D.4). Most sub-populations also showed a dip around 2010 in $PM_{2.5}$ associations for respiratory hospitalizations and increases for later years in associations for both hospitalizations, except for persons eligible for Medicaid, who only experienced sharp increases in $PM_{2.5}$ associations for both hospitalizations towards the end of study period (Figure 3). We did not conduct non-linear temporal trend analysis for race subpopulations given sample size restriction.

DISCUSSION

In this study, we created a daily time-series dataset of >23 million Medicare beneficiaries in 968 U.S. counties, including understudied less-urban areas without regulatory monitors, and observed: 1) positive associations between L02 $PM_{2.5}$ and risk of circulatory and respiratory hospitalizations; 2) temporal changes in these associations with higher risk towards the end of study period; 3) significant effect modification on associations by levels of urbanicity, socioeconomic status and race; and 4) significant effect modification on the temporal trends of associations by levels of urbanicity, socioeconomic status, sex and age.

Specifically, we found that: 1) high urban counties had higher risk of respiratory and circulatory hospitalization associated with $PM_{2.5}$ compared to the low urban counties, while the highest $PM_{2.5}$-respiratory hospitalization association was in the middle counties for urbanicity; 2) Medicare participants who are eligible for Medicaid, as a proxy for lower socioeconomic status, had higher associations of $PM_{2.5}$ with respiratory and circulatory hospitalizations than those not eligible for Medicaid; and 3) Blacks had higher $PM_{2.5}$ risk of respiratory hospitalization than Whites. These results were consistent with previous studies for the direction of modification (Bell et al., 2013; Bravo et al., 2017; Di et al., 2017). With respect to temporal trends in $PM_{2.5}$-hospitalization associations, we found that: 1) both

circulatory and respiratory hospitalizations associated with $PM_{2.5}$ increased faster in recent years for the high urban counties compared to the low urban counties; 2) $PM_{2.5}$ risk for both circulatory and respiratory hospitalizations increased faster in recent years for persons eligible for Medicaid compared to those not eligible; and 3) $PM_{2.5}$ risk of both circulatory and respiratory hospitalizations increased faster in recent years for men than women. These results suggest growing disparities over time in the health response to $PM_{2.5}$.

To our knowledge, this study is the largest multi-city time-series study on temporal trends of association between $PM_{2.5}$ and hospitalization and the first study to explore disparity in temporal trends of $PM_{2.5}$-health impacts. Our overall $PM_{2.5}$-hospitalization estimates were consistent with previous studies on U.S. urban counties using measured exposure data from regulatory monitors (Bell et al., 2008; Dominici et al., 2006). Temporal changes in $PM_{2.5}$-hospitalization associations estimated by this study were more significant than those observed in a previous study with exposure data from monitors, especially the increases in recent years, which may relate to the larger sample size in this study; the current study considers a much larger study area, notably the understudied less-urban areas, with a focus on disparity by urbanicity and sub-population (Chen et al., 2021). This study accounted for confounding from seasonal and long-term trends in risk of hospitalization and $PM_{2.5}$ due to concavity when estimating the temporal changes of $PM_{2.5}$-hospitalization association.

A likely contributor to differences in the health impacts of $PM_{2.5}$ over time is the change in the chemical composition of particles as sources and emissions vary over time. Earlier studies on $PM_{2.5}$ indicate that the associated health burden differs by chemical component, chemical structure, and emission sources (Atkinson et al., 2015; Bell et al., 2014; Krall et al., 2013; Levy et al., 2012). This likely explains why the health impacts of $PM_{2.5}$ total mass vary by spatially and regionally (Bell et al., 2008; Hsu et al., 2017). Further potential explanations and issues needing future research for the observed overall temporal trend, specifically the hook shape around 2010, the increase in recent years and the disparity between cardiovascular and respiratory hospitalizations were discussed elsewhere (Chen et al., 2021). For example, the economic recession from December 2007 to June 2009 could be a driver behind the hook shape around 2010, since both behavior-related exposure patterns and composition of $PM_{2.5}$ changed with economic activities (Davis et al., 2010; National Bureau of Economic, n.d.; Russell et al., 2012).

As more evidence emerges supporting temporal variation in the association between $PM_{2.5}$ and health, likely due to combined effect of multiple time-variant factors, characterization of these temporal changes and further research on these issues is necessary to understand the associated health burden. The increase in $PM_{2.5}$-hospitalization association in recent years suggests that the $PM_{2.5}$-related health burden in the U.S. might persist even when the absolute level of $PM_{2.5}$ decreased in recent years. Future studies might consider temporal variation in their analysis of $PM_{2.5}$-related health impact to provide more insights from different populations and time periods if data are available. Temporal trend could also be considered in meta-analysis of previously conducted studies. Also, efforts are needed to disentangle the various potential contributors of temporal trends in the association, which involve complex, interconnected systems that may be operating at different time scales or even directions. This includes economic drivers, shifts in demographics, changes

in exposure patterns such as indoor/outdoor activity patterns, occupational exposures, technology, emissions sources, shifts in fuel sources, and more.

Evidence of disparity across categories of urbanicity and identification of vulnerable subpopulations raise the importance of considering environmental justice issues in $PM_{2.5}$-related health impact, including how associations may change over time. Further, the overall risk from $PM_{2.5}$ is a function not only of the health response (i.e., effect estimate), but also the level of exposure and baseline health status, among other factors. Although $PM_{2.5}$-hospitalization risks were lowest in the least urbanized areas (9.9% to 87.7% urban population), average $PM_{2.5}$ concentrations were highest in these areas, contributing to the overall health impact from $PM_{2.5}$. Areas with the highest association were in the medium urbanization category (87.7% to 97.5% urban population) for respiratory hospitalization and high urbanization category (97.8% to 100% urban population) for circulatory hospitalization, both of which also exhibited increases in associations during recent years, suggesting that focused interventions for areas with different urbanicity could be particularly effective. As shown in Figure D.1, most medium urban counties belong to metropolitan areas centered around high urban counties. The higher association for respiratory hospitalization among medium urbanized than high urbanized counties is likely the result of many combined factors, potentially a more toxic composition of $PM_{2.5}$ and a population that overall is more susceptible to $PM_{2.5}$. Besides, in sensitivity analysis with finer categorization of urbanicity among counties with smaller urban population, we found counties with 40% to 60% urban population experienced an increase in associations during recent years, similar to the increase for counties with above 90% urban population, emphasizing the importance of further studying $PM_{2.5}$-related health impacts in rural areas. Further study on urbanicity is warranted as there exists no single metric for urbanicity, which relates to population density, but also proximity to cities, access to services such as health care, etc. More studies are needed to fully understand mechanisms behind these disparities.

Since vulnerable sub-populations, such as those who are financially deprived or racial minority populations, were exposed to higher $PM_{2.5}$ exposure (Bell and Ebisu, 2012; Hajat et al., 2015), the observed higher $PM_{2.5}$-hospitalization associations among these sub-populations suggest an even higher health burden, through the combined impacts of disparities in exposure and in health response to a given level of exposure. The increase in the $PM_{2.5}$-hospitalization during recent years among vulnerable sub-populations also suggests a possible widening in disparity of $PM_{2.5}$-related health burdens. According to the Gini index, the U.S. experienced increasing disparity in income (Bureau, n.d.), suggesting a growing difference between those who are and are not financially deprived over time, which likely contributed to the widening disparity in $PM_{2.5}$-associated hospitalizations observed here. Targeted interventions to reduce $PM_{2.5}$ levels among these high-risk communities, and the various social, cultural, and economic systems that contribute to income disparities, would effectively contribute to lowering the health burden.

This study has several limitations. First, we utilized modelled $PM_{2.5}$ concentrations instead of monitor measurements, which allows investigation of understudied areas, but also has higher uncertainty. Modelled daily $PM_{2.5}$ estimates performed well compared with measured

concentrations (Di et al., 2016), and application of such modeled data in health analysis is growing (Di et al., 2017; Wei et al., 2019). Still, these values are estimates, not measurements, and such estimates in rural areas undergo less validation than those in urban areas as there are fewer monitors for comparison (Bravo et al., 2012), hence the need for such approaches. Although the high R^2 values between modelled and measured $PM_{2.5}$ among monitors left out of the modelling in cross-validation alleviated our concern over differential measurement error between areas with and without monitors (Di et al., 2016), measurement error might still attenuate or exaggerate the difference in temporal trends of $PM_{2.5}$-related health estimates across areas with varying levels of urbanicity depending on the type of error introduced (Goldman et al., 2011). Besides, current modelling of $PM_{2.5}$ does not support estimation of $PM_{2.5}$ chemical components and hinders our exploration of $PM_{2.5}$ chemical components as effect modifiers for the temporal trends observed. Expansion of monitor networks and advance in exposure modelling methods could further mitigate these concerns in the future. Second, counties with population ≤ 50,000 were not included (~13% of U.S. population). We excluded these counties for statistical power considerations. Thus, additional work on the most rural areas is warranted, as the population characteristics, pollution mixture, and other factors may differ. Third, categorization of urbanicity and age groups were based on the balance of beneficiaries, which might not fully capture potential disparity across these sub-populations and future studies could explore aspects of urbanicity and race/ethnicity more thoroughly, such as with more detailed categorization of race/ethnicity. Last, we selected L02 for exposure, which might underestimate the true health impact from $PM_{2.5}$. As shown in Table D.1, we observed highest effect estimates of $PM_{2.5}$ in the same day circulatory hospitalization and the next day respiratory hospitalization, while estimates for the moving average of the same day and previous two days were slightly lower. We kept L02 as our main result for parsimony, although an alternative is the distributed lag model, where exposures over a lag interval (up to a week or longer) are modelled simultaneously with or without constrain on the shape of the exposure-response curve (Gasparrini et al., 2010; Peng et al., 2009). We did not incorporate the distributed lag model under the consideration of bias-variance trade-off, where the cost of incurring greater variability does not balance with the benefit of considering longer lag intervals with more flexibility.

Despite these limitations, this study provides evidence that the risk of hospitalization from $PM_{2.5}$ is changing over time, and that these temporal changes in risk vary across subpopulation. The results further indicate a widening of disparities in $PM_{2.5}$-related health burden, with important implications for environmental justice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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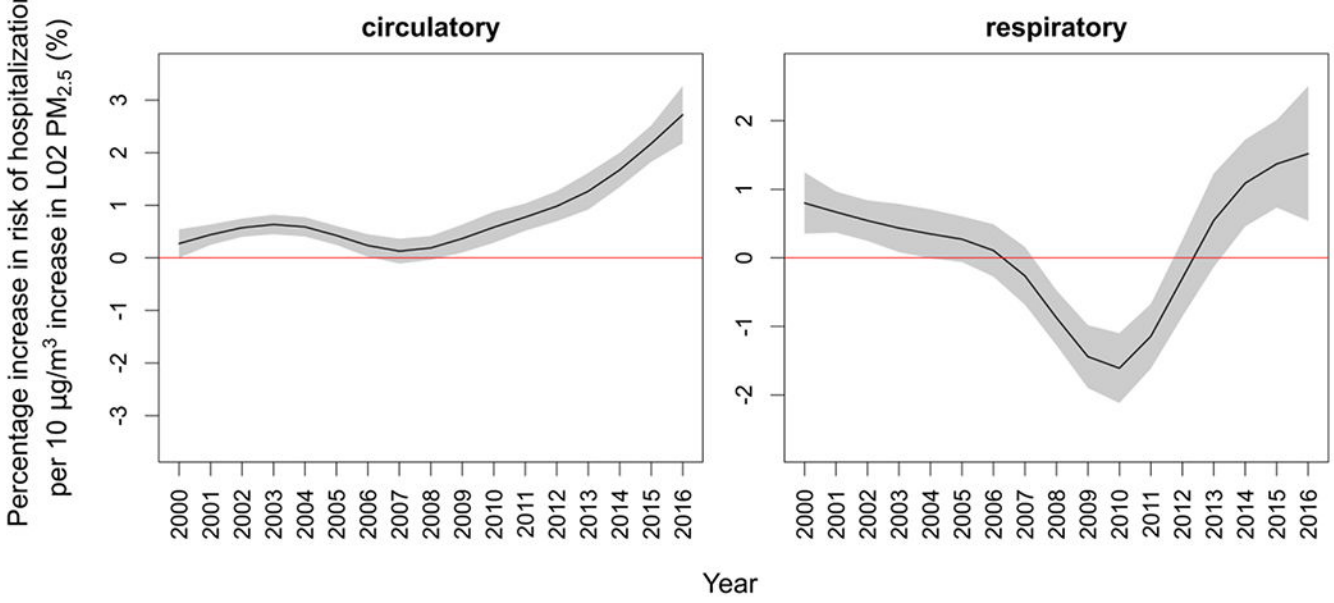

Figure 1.

Temporal trend of the association between $PM_{2.5}$ and hospitalizations. Percentage change in risk of hospitalization per 10 μg/m^3 increase in L02 $PM_{2.5}$ based on non-linear model.

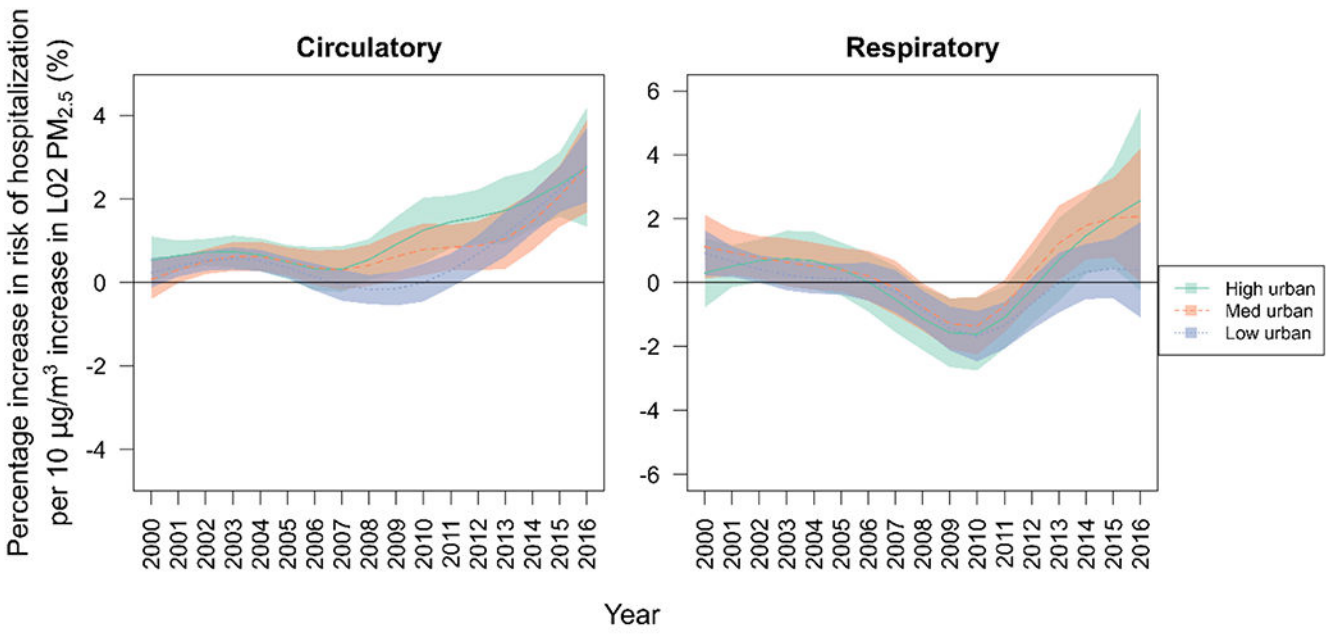

Figure 2.

Temporal trend of the association between $PM_{2.5}$ and hospital admissions by levels of urbanicity. Percentage change in risk of hospitalization per 10 μg/m^3 increase in L02 $PM_{2.5}$ based on non-linear model.

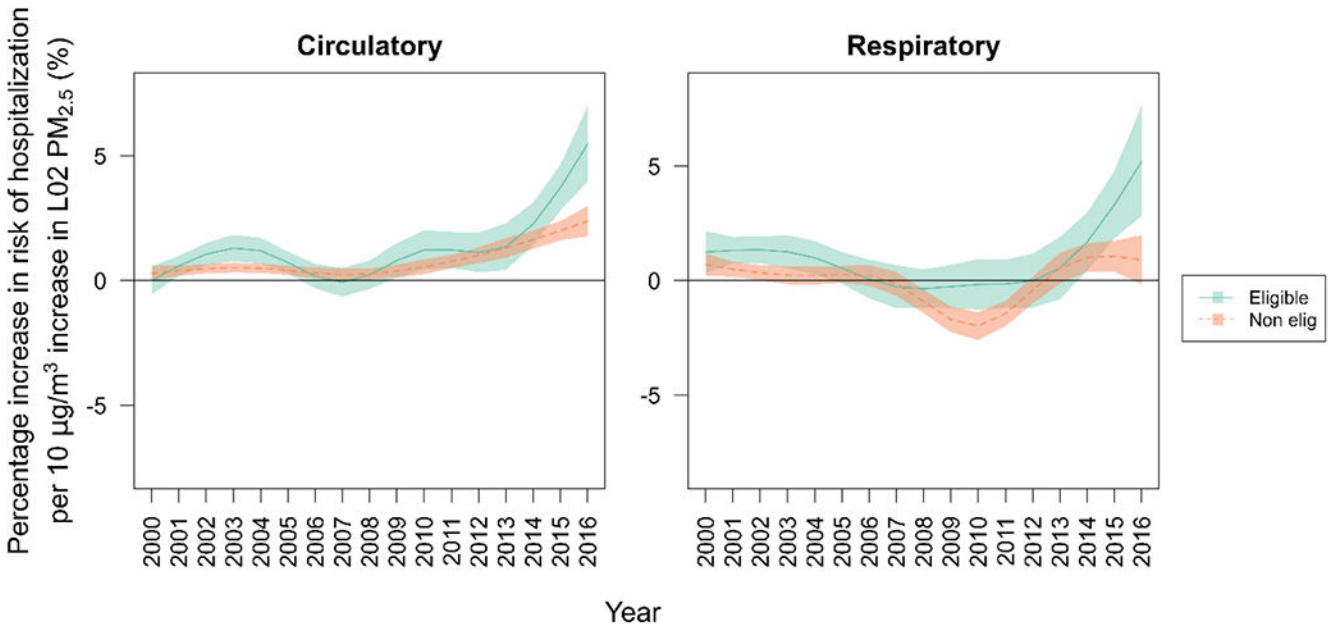

Figure 3.

Temporal trend of the association between $PM_{2.5}$ and hospital admissions by eligibility for Medicaid. Percentage change in risk of hospitalization per 10 $\mu g/m^3$ increase in L02 $PM_{2.5}$ based on non-linear model.

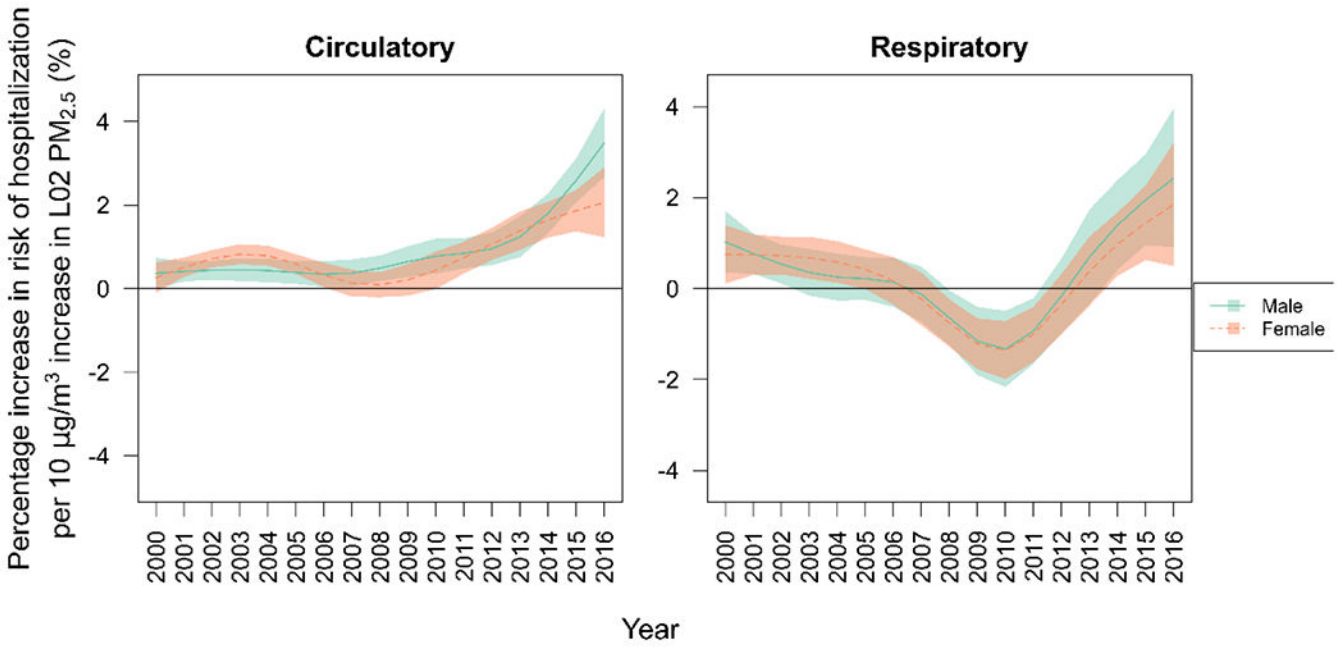

Figure 4.

Temporal trend of the association between $PM_{2.5}$ and cause-specific hospital admissions by sex. Percentage change in risk of hospitalization per 10 μg/m^3 increase in L02 $PM_{2.5}$ based on non-linear model.

Table 1.

Summary of study population by individual-level characteristics.

Individual-level characteristics	No. of beneficiaries* (% of total)	Circulatory hospitalization rate (admissions per 100,000 person-day)			Respiratory hospitalization rate (admissions per 100,000 person-day)		
		Entire study period (2000-2016)	Start year (2000)	Final year (2016)	Entire study period (2000-2016)	Start year (2000)	Final year (2016)
Total population	23,071,914	23.0	29.4	15.6	6.8	8.6	4.5
Sex							
Men	9,873,477 (42.8)	25.1	32.7	17.1	6.9	9.1	4.4
Women	13,198,437 (57.2)	21.4	27.1	14.4	6.7	8.1	4.6
Age							
65 to 74 y	12,279,029 (53.2)	15.8	22.1	10.5	4.5	5.8	3.1
≥ 75 y	10,792,886 (46.8)	31.1	37.0	22.9	9.5	11.4	6.6
Race							
White	19,643,757 (85.1)	23.0	29.4	15.7	7.0	8.6	4.6
Black	1,926,719 (8.4)	28.4	33.9	20.6	6.8	8.7	5.1
Others	1,501,438 (6.5)	15.3	21.3	10.2	4.7	6.8	2.9
Medicaid eligibility							
Eligible	2,935,891 (12.7)	31.7	38.6	23.4	13.0	16.2	9.3
Non-eligible	20,136,023 (87.3)	21.7	28.0	14.6	5.9	7.4	3.9

*The number of beneficiaries changed over time and this value was calculated as the sum of the county specific average number of beneficiaries.

Table 2.

Summary of county-level average exposure and outcomes by levels of urbanicity.

	Total population	Urbanicity		
		High	Medium	Low
No. of counties (% of total)	968 (100)	78 (8.0)	177 (18.3)	713 (73.7)
Median % of urban population (min, max)	74.6 (9.9, 100)	99.4 (97.8, 100)	93.2 (87.7, 97.5)	66.3 (9.9, 87.7)
Median No. of beneficiaries * (1st quartile, 3rd quartile)	12, 464 (8,295, 24,420)	64,105 (32,574, 97,774)	31,631 (20,318, 53,465)	10,120 (7,372, 14,764)
Median study period average $PM_{2.5}$ concentration ($\mu g/m^3$) (Q1, Q3)				
Entire study period (2000-2016)	10.6 (9.1, 11.8)	10.0 (9.7, 12.1)	10.4 (8.7, 11.7)	10.7 (9.0, 11.8)
Start year (2000)	14.0 (10.6, 15.1)	13.8 (11.7, 15.7)	12.4 (10.4, 14.9)	13.1 (10.6, 15.1)
Final year (2016)	7.6 (6.4, 8.2)	7.8 (7.1, 8.3)	7.5 (6.5, 8.2)	7.6 (6.3. 8.2)
Median circulatory hospitalization rate (admissions per 100,000 person-day) (Q1, Q3)				
Entire study period (2000-2016)	23.5 (20.1, 26.6)	22.4 (18.7, 25.0)	22.0 (19.5, 25.2)	24.0 (20.7, 27.1)
Start year (2000)	30.0 (26.1, 34.3)	27.8 (24.0, 31.3)	27.8 (24.6, 31.4)	30.8 (26.5, 35.2)
Final year (2016)	16.4 (13.7, 18.5)	15.5 (12.6, 17.2)	15.8 (12.6, 17.4)	16.7 (14.2, 19.0)
Median respiratory hospitalization rate (admissions per 100,000 person-day) (Q1, Q3)				
Entire study period (2000-2016)	7.2 (6.0, 7.4)	6.0 (4.9, 7.1)	6.6 (5.4, 7.6)	7.6 (6.3, 9.2)
Start year (2000)	9.0 (7.5, 10.8)	7.7 (6.6, 9.1)	8.1 (6.8, 9.3)	9.4 (7.8, 11.5)
Final year **(2016)**	4.7 (3.5, 5.9)	4.0 (3.2, 4.9)	4.3 (3.2, 5.3)	4.9 (3.7, 6.2)

* The number of beneficiaries changed over time and this column was the summary of county specific average number of beneficiaries over the study period.

Table 3.

Association between risk of hospitalization and $PM_{2.5}$ for the entire study period (2000 to 2016) and differences across levels of individual-level and community-level characteristics based on base model, among 968 Counties.*

	Association for the entire study period (2000-2016) (%)		Difference in association across characteristics (%)	
	Estimate	95% Posterior Confidence Interval	Estimate	95% Posterior Confidence Interval
Circulatory hospitalizations				
Entire study population	0.56	0.45, 0.68	NA	NA
Sex +				
Men	0.56	0.39, 0.71	Reference	Reference
Women	0.58	0.44, 0.73	0.03	−0.17, 0.23
Age +				
65 to 74 y	0.56	0.38, 0.74	Reference	Reference
≥ 75 y	0.58	0.44, 0.71	0.02	−0.19, 0.22
Race +				
White	0.67	0.49, 0.85	Reference	Reference
Black	1.02	0.61, 1.43	0.34	−0.09, 0.77
Other	0.76	0.14, 1.38	0.09	−0.53, 0.71
Medicaid eligibility +				
Eligible	0.80	0.55, 1.05	Reference	Reference
Non-eligible	0.53	0.41, 0.66	−0.26	−0.53, 0.00
Urbanicity				
High	0.80	0.54, 1.05	Reference	Reference
Medium	0.60	0.37, 0.82	−0.20	−0.25, −0.12
Low	0.43	0.27, 0.59	−0.37	−0.47, −0.27
Respiratory hospitalizations				
Entire study population	0.17	−0.03, 0.37	NA	NA
Sex				
Men	0.16	−0.12, 0.44	Reference	Reference
Women	0.21	−0.05, 0.47	0.05	−0.31, 0.41
Age +				
65 to 74 y	0.15	−0.16, 0.46	Reference	Reference
≥ 75 y	0.21	−0.03, 0.45	0.06	−0.31, 0.44
Race +				
White	0.25	−0.06, 0.56	Reference	Reference
Black	1.27	0.47, 2.1	1.02	0.15, 1.89
Other	1.25	0.14, 2.38	1.00	−0.09, 2.09

	Association for the entire study period (2000-2016) (%)		Difference in association across characteristics (%)	
	Estimate	**95% Posterior Confidence Interval**	**Estimate**	**95% Posterior Confidence Interval**
Medicaid eligibility [+]				
Eligible	0.59	0.22, 0.96	Reference	Reference
Non-eligible	0.05	−0.18, 0.28	−0.54	−0.95, −0.12
Urbanicity				
High	0.24	−0.16, 0.62	Reference	Reference
Medium	0.41	0.02, 0.79	0.17	0.10, 0.25
Low	−0.02	−0.31, 0.28	−0.26	−0.34, −0.12

[*] Associations are expressed as the percent change in risk of cause-specific hospitalizations per 10 $\mu g/m^3$ increase in L02 $PM_{2.5}$. Differences in associations are expressed as the difference of those associations in two categories (e.g., women compared to men).

[+] The number of counties included in calculation of sub-population estimates were 966 for sex, 967 for age group, 206 for race, 938 for Medicaid eligibility.

Table 4.

Temporal change in association between risk of hospitalization and $PM_{2.5}$ across two time periods (2008-2016 vs. 2000-2007), and difference across levels of individual-level and community-level characteristics based on time-stratified model, among 968 counties.*

	Temporal change (2008-2016 minus 2000-2007) (%)		Difference in change across characteristics (%)	
	Estimate	95% Posterior Confidence Interval	Estimate	95% Posterior Confidence Interval
Circulatory hospitalizations				
Entire study population	0.49	0.40, 0.58	NA	NA
Sex +				
Men	0.63	0.44, 0.82	Reference	Reference
Women	0.38	0.19, 0.55	−0.25	−0.51, −0.01
Age +				
65 to 74 y	0.38	0.23, 0.51	Reference	Reference
≥ 75 y	0.59	0.48, 0.68	0.21	0.07, 0.36
Race +				
White	0.65	0.41, 0.89	Reference	Reference
Black	0.67	−0.05, 1.53	0.02	−0.66, 0.90
Other	1.38	−0.22, 2.98	0.73	−0.88, 2.34
Medicaid eligibility +				
Eligible	0.75	0.50, 0.95	Reference	Reference
Non-eligible	0.46	0.36, 0.55	−0.29	−0.50, −0.03
Urbanicity				
High	0.67	0.53, 0.83	Reference	Reference
Medium	0.52	0.33, 0.69	−0.15	−0.27, 0.01
Low	0.33	0.22, 0.44	−0.35	−0.43, −0.29
Respiratory hospitalizations				
Entire study population	−0.67	−0.82, −0.53	NA	NA
Sex				
Men	−0.41	−0.67, −0.17	Reference	Reference
Women	−0.82	−1.04, −0.6	−0.41	−0.73, −0.09
Age +				
65 to 74 y	−0.68	−0.9, −0.47	Reference	Reference
≥ 75 y	−0.6	−0.81, −0.41	0.08	−0.22, 0.37
Race +				
White	−0.62	−0.85, −0.4	Reference	Reference
Black	0.25	−1.31, 1.69	0.86	−0.70, 2.37
Other	0.82	−1.50, 2.96	1.43	−0.82, 3.56

	Temporal change (2008-2016 minus 2000-2007) (%)		Difference in change across characteristics (%)	
	Estimate	**95% Posterior Confidence Interval**	**Estimate**	**95% Posterior Confidence Interval**
Medicaid eligibility [+]				
Eligible	0.12	−0.19, 0.41	Reference	Reference
Non-eligible	−0.88	−1.04, −0.73	−1.00	−1.32, −0.67
Urbanicity				
High	−0.40	−0.83, −0.08	Reference	Reference
Medium	−0.53	−0.75, −0.33	−0.13	−0.37, 0.17
Low	−0.90	−1.08, −0.73	−0.50	−0.72, −0.20

[*] Temporal change is expressed as the change in associations in the second time period (2008-2016) minus the first time period (2000-2007). Difference in temporal change is expressed as the difference of those temporal changes in two categories.

[+] The number of counties included in calculation of sub-population estimates were 966 for sex, 967 for age group, 206 for race, 938 for Medicaid eligibility.