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Abstract

The established evidence associating air pollution with health is limited to populations from specific regions. Further large-scale studies in several regions worldwide are needed to support the literature to date and encourage national governments to act. Brazil is an example of these regions where little research has been performed on a large scale. To address this gap, we conducted a study looking at the relationship between daily $PM_{2.5}$, NO_2, and O_3, and hospital admissions for circulatory and respiratory diseases across Brazil between 2008 and 2018. A time-series analytic approach was applied with a distributed lag modeling framework. We used a generalized conditional quasi-Poisson regression model to estimate relative risks (RRs) of the association of each air pollutant with the hospitalization for circulatory and respiratory diseases by sex, age group, and Brazilian regions. Our study population includes 23,791,093 hospital admissions for cardiorespiratory diseases in Brazil between 2008 and 2018. Among those, 53.1% are respiratory diseases, and 46.9% are circulatory diseases. Our findings suggest significant associations of ambient air pollution ($PM_{2.5}$, NO_2, and O_3) with respiratory and circulatory hospital admissions in Brazil. The national meta-analysis for the whole population showed that for every increase of $PM_{2.5}$ by 10µg/m^3, there is a 3.28% (95%CI: 2.61; 3.94) increase in the risk of hospital admission for respiratory diseases. For O_3, we found positive associations only for some sub-group analyses by age and sex. For NO_2, our findings suggest that a 10ppb increase in this pollutant, there was a 35.26% (95%CI: 24.07; 46.44) increase in the risk of hospital admission for respiratory diseases. This study may better support policymakers to improve the air quality and public health in Brazil.

Keywords: Air pollution, Hospital admissions, Respiratory diseases, Circulatory diseases, Brazil.

1. INTRODUCTION

Air pollution is a major environmental risk to global health (Cohen et al., 2017). It is well established that exposure to ambient air pollution is associated with increased hospital admissions (Carugno et al., 2016; Danesh Yazdi et al., 2021; Phung et al., 2016) and mortality (Burnett et al., 2018; Schwartz et al., 2021b; Shi et al., 2021). Meta-analysis studies have reported consistent positive associations worldwide between air pollutants and several causes of hospitalization, including hospital admissions for respiratory and circulatory diseases (Moore et al., 2016; Requia et al., 2017). According to the World Health Organization (WHO), about 4.2 million deaths worldwide all-cause and all-age occur every year due to exposure to ambient air pollution (WHO, 2022). Particles with a mass aerodynamic diameter below 2.5 µm ($PM_{2.5}$), itself contributes to approximately two million premature deaths per year, ranking it as the 13th leading cause of worldwide mortality (Lozano et al., 2012). The WHO estimates that 80% of outdoor air pollution-related premature deaths are associated with ischemic heart disease and strokes; and 14% with chronic obstructive pulmonary disease and acute lower respiratory infections (WHO, 2022). More recently, numerous investigations have indicated consistency in the link between health outcomes and other air pollutants, including gaseous pollutants such as nitrogen dioxide (NO_2) and tropospheric ozone (O_3) (Danesh Yazdi et al., 2021; Schwartz et al., 2021b, 2021a; Shi et al., 2021; Wei et al., 2021; Yazdi et al., 2021).

Overall, this established evidence associating air pollution with health is limited to populations from specific regions. A systematic review by (Requia et al., 2017) found that most of the evidence is based on populations in the United States, some countries in Europe, and China. Further large-scale studies in several other populated countries are needed to support the literature to date. Numerous regions worldwide face critical challenges related to poor air quality and public health, and governments are reluctant to embark on expensive controls based on studies from other nations. Epidemiological studies are essential in these regions, which could provide evidence for policymakers with the objective of improving the air quality and public health.

Brazil is an example of these regions with critical challenges and where little research has been performed at a large scale (national-level spatial resolution). We searched in PubMed and Web of Science using the following keywords: “air pollution”, “health effects”, “human exposure”, and “Brazil”. We found only 3 studies at national level in Brazil looking only at the effects from $PM_{2.5}$, in which one investigation focused on the association between $PM_{2.5}$ and cancer hospitalizations (Yu et al., 2021), another one focused on the link between $PM_{2.5}$ and cancer mortality (Yu et al., 2022), and the third one looked at the association between hospital admissions and wildfire-related $PM_{2.5}$ (Ye et al., 2021).

Among the critical challenges in Brazil related to air quality and public health, we highlight i) about 25% of the Brazilian schools are located within a distance ≤ 250m of a major roadway, have ≥ 2km of roadway within a buffer of 1km, and have ≥ 7 wildfires records within a buffer of 10km (Requia et al., 2021); ii) Brazil is a very fire-prone region where, according to the National Institute of Spatial Research - INPE (http://queimadas.dgi.inpe.br/queimadas/), between January/2020 and August/2020 there were about 120,000 km^2 of burned area. Wildfires emit substantial amounts of air pollutants that can travel over large distances, affecting air quality and human health far from the originating fires (Youssouf et al., 2014). On an equal-mass basis, wildfire-related $PM_{2.5}$ may be more toxic than ambient $PM_{2.5}$ in the same region during non-fire periods, due to the formation of secondary pollutants as a result of the atmospheric photochemistry. Fine particulate matter ($PM_{2.5}$) is the major pollutant emitted by wildfires. About 12-16% of global wildfire-related particulate emissions occur across Brazil (Reddington et al., 2015); iii) Third, Brazil has a lack of control and monitoring policies leading to increased air pollution (Barcellos et al., 2009; Huneeus et al., 2020; Renata et al., 2015); and iv) Brazil also has a considerable difference in the quality of health/environment and healthcare across different populations (influencing health/environment equity in negative ways), which is a critical determinant of the health impacts of air pollution (Rappold et al. 2012).

Therefore, more research is needed to explore the nationwide effect of air pollution on health in Brazil, and to investigate the health outcomes associated with multiple air pollutants in a region with challenges related to air pollution sources, environmental characteristics, and public health conditions. To address this gap, we have conducted a study looking at the relationship between daily $PM_{2.5}$, NO_2, and O_3, and hospital admissions for circulatory and respiratory outcomes across Brazil between 2008 and 2018.

2. METHODS

2.1. Study population and outcome assessment

The hospital admission data were provided by the Ministry of Health in Brazil. The data encompass individual hospital admissions records in Brazil between 1st January 2008 and 31st

December 2018. During the study period, there were a total of 129,978,694 records of hospital admissions (all cases) in Brazil.

Hospital admission information included event date, home municipality, age, sex, and principal diagnosis according to the International Classification of Diseases, version 10 (ICD-10) codes. In this study, we selected only the hospitalizations for respiratory (ICD-10 codes J00-J99) and cardiovascular (ICD-10 codes I00-I99) diseases. This filter resulted in 12,621,970 (9.71%) records of hospital admissions for respiratory outcomes and 11,169,123 (8.59%) hospital admissions for circulatory diseases.

We grouped the data by summing the number of hospital admissions for every municipality and date in the study period. The hospital admission counts were also divided by sex, age group (15-25, 26-35, 36-45, 46-55, 56-65, >65 years old), health outcome (respiratory, circulatory, and cardiorespiratory), and region. Each group representing the counts of hospital admissions is composed by a complete time series of equality-spaced observations taken in each municipality and each day in the period 2018-2018. We observed some inconsistencies in the data (missing values for several municipalities) for the age group <15 years old. Therefore, this age group was not included in the analyses. There are 5,572 municipalities in Brazil, representing the smallest areas considered by the Brazilian political system. The municipalities are grouped into five regions: North, Northeast, Midwest, Southeast, and South. In Supplementary Materials (Figure S1), we show the spatial distribution of all municipalities and regions in Brazil.

2.2. Exposure assessment

Air pollution data were obtained from ensemble models that used various satellite observations. We studied daily $PM_{2.5}$ ($\mu g\ m^{-3}$), NO_2 (ppb), and O_3 (ppb) concentrations from 2008 to 2018. The data was accessed from the European Centre for Medium-Range Weather Forecasts (ECMWF). The ECMWF operates services related to meteorology and air pollution covariates and implements the Copernicus Atmosphere Monitoring Service (CAMS) on behalf of the European Union, including CAMS-Reanalysis and CAMS Near Real Time (CAMS-NRT) forecasts. The CAMS service runs ensemble models using several satellite observations and emission inventories, amongst other predictors. We obtained the data at a spatial resolution of 0.125 degrees (approximately 12.5 km) and a temporal resolution of 6 hours, including daily estimates for 00, 06, 12, and 18 UTC (Universal Time Coordinated). In our analyses, we used CAMS-Reanalysis for the period between 2008- 2017 and CAMS-NRT for the year 2018. We calculated the daily mean temporal resolution for each pollutant. Finally, we aggregated the air pollution data by the municipality, considering the geographical location of the headquarters of each municipality in Brazil.

2.3. Confounders

Meteorological data were treated as potential confounders. The data was retrieved from reanalysis data that used satellite remote sensing and was accessed from the ECMWF. Weather data included surface temperature (°C), humidity (%), and precipitation (mm/day). Temperature and humidity were derived from Era-Interim reanalysis, with a spatial resolution of 0.125 degrees and temporal resolution of 6 hours. This reanalysis was performed by the ECMWF. Precipitation data was accessed from the Climate Prediction Center (CPC) and the National Ocean and Atmospheric Administration (NOAA). This data has an original spatial resolution of 0.50 degrees (approximately 50 km), with interpolation to 12.5 km, and a temporal resolution of 6 hours. As for the air pollution data, we calculated the daily mean temporal resolution for each weather variable, and then we aggregated the data by the municipality.

2.4. Statistical analysis

A time-series analytic approach was applied to look at the relationship between short-term exposure to $PM_{2.5}$, NO_2, O_3, and admissions with cardiovascular and respiratory outcomes. Our statistical approach was divided into three stages, as described below.

First, we used a distributed lag modeling framework to create two cross-basis functions, including one for the exposure (air pollution) and the other one for temperature – a potential confounder, as suggested by the literature (Di et al., 2018; Shi et al., 2021; Weinberger et al., 2021). For the effect of the air pollutant, we defined the cross-basis function with a linear term for the air pollution-hospitalization relationship, known as the distributed lag linear model (DLM). We accounted for the lagged effect of each air pollutant up to 15 days of lag (0-15 days) with a 4th-degree polynomial function.

For the temperature effect, we used a distributed lag non-linear model – DLMN (Gasparrini et al., 2010) to define a cross-bases function with a natural cubic spline with 5 degrees of freedom for the temperature exposure-response and then 2 lagged terms (lag strata), including lag 0 and lag

1-15. We considered the effects as constant within each stratum. The internal knots were placed by natural cubic spline equally spaced quantiles, while the boundary knots were located at the temperature range. Note that although we are using non-linear term to represent the distributed lag function for the confounder (temperature), the modeling framework of our study can be defined as a DLM, given that the effect of the exposure (air pollution) was included in the cross-basis function with a linear term.

In the second stage, we included the two cross-basis functions in a generalized conditional quasi-Poisson regression model. We fit only single-air pollutant models. The analyses were stratified by sex, age group (15-25, 26-35, 36-45, 46-55, 56-65, >65 years old), health outcome (respiratory, circulatory, and cardiorespiratory), and Brazilian regions (North, Northeast, Midwest, Southeast, and South).

Relative risks (RRs) and 95% confidence interval (CI) were derived to represent the association of every 10 units increases each air pollutant with the hospitalization for circulatory and respiratory diseases. We used (RR-1) x 100% to report the percentage increase in the health outcome.

To control for temporal trends within each municipality in the Poisson model, we used a time-stratified sampling to define strata based on the day of the week, month, calendar year, and the municipality of the time series. This allows the comparison of the exposure on the day of a health event on Monday in January 2008, for example, with exposures on all other Mondays in January 2008. Note that in this study design, each case period has 3 or 4 control periods. Also given the matching periods were close in time, the approach reduces the effects of confounding related to the seasonal trend by controlling for time-dependent risk factors, including the day of the week, season, and long-term trends by matching. Note that although we included the municipalities in the strata, we obtained the impact (RR) by region, not by municipality.

Finally, in the third stage, we applied meta-analysis to estimate a national RR. Specifically, we accounted for intra- and inter-region variability by applying regression meta-analysis with random effects. This approach assumes that the average effect size in the Brazilian population varies randomly from region to region (Viechbauer, 2010). Heterogeneity was examined using the I-squared (I^2) statistic. A p-value >0.05 and/or I^2 <50% was considered homogeneous.

All computations of this study were run on the Google Cloud Platform. R software, version 4.0.2, was used for all analyses. We used the R package “dlnm” (Distributed Lag Non-Linear

Models) for the distributed lag modeling framework and the R package “gnm” (Generalized Nonlinear Models) for the generalized conditional quasi-Poisson regression model.

2.5. Sensitivity analysis

We tested the robustness of our results by changing several modeling assumptions. First, we added in the primary Poisson model the adjustment for humidity, resulting in a model with the exposure (air pollution) represented by the cross-basis function (first stage), one confounder represented by the cross-basis function for the temperature (first stage), and humidity as the second confounder (without cross-basis function). Subsequently, we tested a model with one more confounder, precipitation (humidity + precipitation, both without cross-basis functions). We also analyzed the sensitivity of our primary model by removing the adjustment for the cross-basis function for temperature. Note that this was a simple unadjusted model, with only the exposure. Finally, we checked the robustness of our primary results by changing the cross-basis function for the air pollution-hospitalization relationship. Specifically, we defined a model with a non-linear term represented by a B-spline with 5 degrees of freedom for the lag structure.

3. RESULTS

3.1. Hospital admission characteristics

Table 1 provides the descriptive characteristics of these health events in Brazil during our study period. Our study population includes 23,791,093 hospital admissions for cardiorespiratory diseases in Brazil between 2008 and 2018. Among those, 53.1% are respiratory diseases, and 46.9% are circulatory diseases. The number of male admissions was slightly higher for both respiratory and circulatory diseases, representing 52.7% and 50.2% of the total admissions, respectively. For the age groups, the largest proportion was for patients aged >65 years, with 25.85% hospitalized due to respiratory diseases and 45.11% due to circulatory diseases. Figure 1 shows Brazil's spatial distribution of respiratory and circulatory hospital admissions in the study period.

Table 1 – Descriptive characteristics of hospital admission events in Brazil, 2008-2018.

Health outcome	Age	Number of hospital admissions (%)[1]		
		Men	Women	All sex
Respiratory hospital admissions	15-25	382,347 (3.03)	394,697 (3.13)	777,044 (6.16)
	26-35	322,265 (2.55)	319,398 (2.53)	641,663 (5.08)
	36-45	324,760 (2.57)	309,308 (2.45)	634,068 (5.02)
	46-55	423,052 (3.35)	403,144 (3.19)	826,196 (6.55)
	56-65	565,438 (4.48)	507,324 (4.02)	1,072,762 (8.50)
	>65	1,630,513 (12.92)	1,632,364 (12.93)	3,262,877 (25.85)
	All ages[2]	6,646,890 (52.66)	5,975,080 (47.34)	12,621,970 (100)
Circulatory hospital admissions	15-25	125,708 (1.13)	140,488 (1.26)	266,196 (2.38)
	26-35	219,681 (1.97)	313,996 (2.81)	533,677 (4.78)
	36-45	445,269 (3.99)	572,156 (5.12)	1,017,425 (9.11)
	46-55	949,565 (8.5)	917,064 (8.21)	1,866,629 (16.71)
	56-65	1,412,606 (12.65)	1,135,610 (10.17)	2,548,216 (22.81)
	>65	2,516,053 (22.53)	2,522,032 (22.58)	5,038,085 (45.11)
	All ages[2]	5,611,256 (50.24)	5,557,867 (49.76)	11,169,123 (100)

Notes: [1] the percentages were based on the total number of hospital admissions in Brazil between 2008 and 2018, which for respiratory hospital admissions were 12,621,970 cases, and for circulatory admissions were 11,169,123 cases. [2] this includes people under 15 years old.

3.2. Characteristics of the exposure and covariate variables

Table 2 shows the summary statistics for air pollution and weather variables. Figure 1 illustrates the nationwide concentrations of air pollutants in Brazil. The mean concentrations (with the standard deviations) of $PM_{2.5}$, NO_2, and O_3 over the study period in Brazil were 10.01 (8.28) μg/m³, 1.51 (1.48) ppb, and 20.07 (7.01) ppb, respectively. The mean $PM_{2.5}$ exceed the 2021 Air Quality Guidelines (2021 AQG) from the World Health Organization - WHO (5μg/m³ annual mean). To compare the concentrations of NO_2 and O_3 with the 2021 AQG, we converted the original unit of these pollutants (ppb) to the unit used in the 2021 AQG (μg/m³). The WHO recommends the following conversion factors: for NO_2, 1 ppb = 1.88 μg/m³; for O_3, 1ppb = 1.96 μg/m³. After applying the conversion factors, the estimated mean of NO_2 and O_3 concentrations were 2.83 μg/m³ and 39.33 μg/m³, respectively, which did not exceed the 2021 AQG (10 μg/m³ annual mean for NO_2 and 60 μg/m³ peak season for O_3). For the weather variables, we estimated a mean (with the standard deviation) of 23.59 (3.79)°C for temperature, 77.76 (13.64)% for relative humidity, and 3.39 (8.16) mm/day for precipitation.

Table 2 – Summary statistics for air pollution and weather data in Brazil, 2008-2018.

Variable	**Min**	**Q1**	**Mean**	**SD**	**Q3**	**Max**
$PM_{2.5}$ (μg/m³)	3.03	5.05	10.01	8.28	11.85	61.35
NO_2 (ppb)	0.10	0.60	1.51	1.48	1.88	10.05
O_3 (ppb)	3.36	15.22	20.07	7.01	24.77	39.15
Temperature (°C)	1.25	21.60	23.59	3.79	26.23	34.92
Relative humidity (%)	20.00	69.75	77.76	13.64	88.50	100
Preciptation (mm/day)	0	0	3.39	8.16	3.00	486.00

Note: Minimum (Min), first quartile (Q1), standard deviation (SD), third quartile (Q3), and maximum (Max).

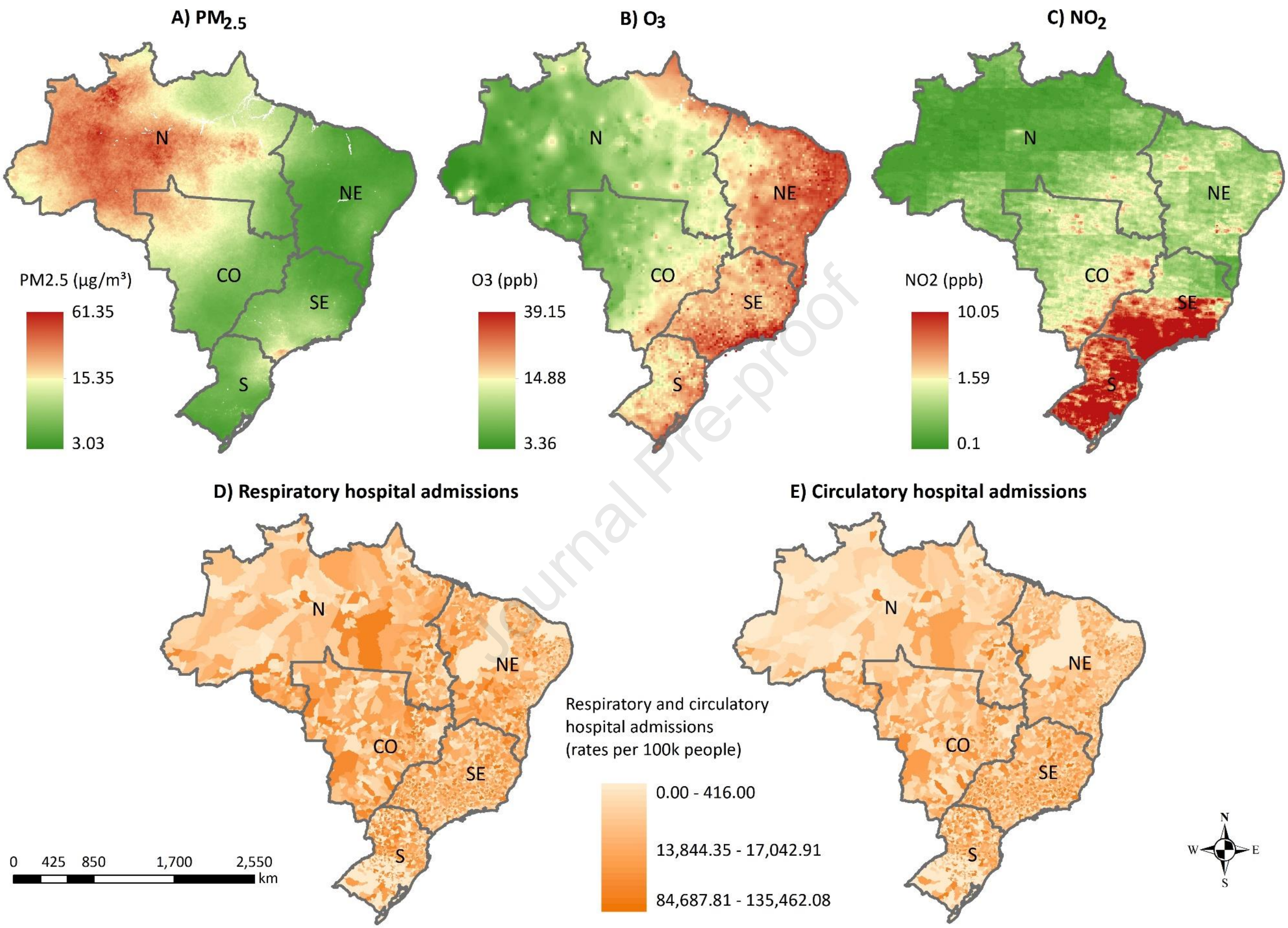

Figure 1 – Spatial variation of respiratory and circulatory hospital admissions (sum between 2008-2018) and air pollution concentrations (average between 2008-2018) in Brazil. Note: the polygons in gray represent the Brazilian regions, including North (N), Northeast (NE), Midwest (CO), Southeast (SE), and South (S).

3.3. Association between air pollution and hospital admissions

Figures 2-4 show the national average RR of hospital admissions associated with $PM_{2.5}$, O_3, and NO_2, respectively. This is the overall cumulative effect of a 10-unit increase in each ambient air pollutant over 15 days of lag (summing all the contributions up to the maximum lag). We present in the Supplementary Materials a table with all the national average RR (from the primary analysis, for all sub-group analyses, pollutants, and health outcomes) along with the estimated heterogeneity test from the meta-analysis (Table S1).

The national meta-analysis for the whole dataset (without stratification by sex and age) showed that for every increase of $PM_{2.5}$ by 10 $\mu g/m^3$, there is a 3.28% (95%CI: 2.61; 3.94) increase in the risk of hospital admission for respiratory diseases and a 1.86% (95%CI: 0.83; 2.89) increase in the risk of hospital admission for cardiorespiratory diseases. The associations were highly uncertain for circulatory hospital admissions (Figure 2). The subgroup analysis for sex and age indicated a positive association with respiratory diseases for almost all groups. Uncertain associations were found only for men 15-25 years old, men 46-55 years old, and women 15-25 years old. For circulatory admissions, we observed positive associations only for men/women 36-45 years old and women 36-45 years old (Figure 2).

The national meta-analysis for O_3 (Figure 3) indicated a positive association with respiratory hospital admissions for eight sub-group analyses, mostly for people aged >45 years old, including men/women 46-55, men/women 56-65, men/women >65, men >65, women 36-45, women 46-55, women 56-65, and women >65. For circulatory diseases, the results were similar, with some difference that indicated positive associations for youngest population, including people aged 15-25 and 26-35 years old (Figure 3).

At the national level, the highest percentage increase in the risk of hospital admissions for respiratory diseases occurred when we used NO_2 as the exposure (Figure 4). The national meta-analysis for the whole dataset showed that a 10ppb increase in NO_2, there is a 35.26% (95%CI: 24.07; 46.44) and 16.90% (95%CI: 11.17; 22.64) increase in the risk of hospital admission for respiratory and cardiorespiratory diseases, respectively. For respiratory hospital admissions, this positive association persisted for several sub-group analyses, including the group with the oldest people, men >65 and women >65. There were no positive associations for the relationship between NO_2 and hospital admissions for circulatory diseases (Figure 4).

Similar to the figures 2-4 presented here, we show in the Supplementary Materials the charts of the RR (from the primary analysis) stratified by Brazilian regions (Figures S2-S10). Overall, when we looked at the $PM_{2.5}$ exposure, the North was the region with the greatest number of positive and consistent associations among the sub-group analyses for the three health outcomes, respiratory, circulatory, and cardiorespiratory hospital admissions (Figures S2-S4). Specifically, when we examined cardiorespiratory hospital admissions, our findings suggested a positive association with $PM_{2.5}$ in all sub-group analyses, except for three groups, including man/women, 46-55; men, 15-25; and men, 46-55 (Figure S4). For NO_2, when we examined the whole dataset (without stratification by sex and age), we found positive associations with respiratory admissions and cardiorespiratory admissions in all Brazilian regions (Figures S5-S7). This positive association persisted across the regions when we stratified the analyses by men of all ages and women of all ages (Figures S5 and S7). In contrast, only the Midwest and Southeast regions presented a few positive associations when looking at the relationship between NO_2 and circulatory diseases (Figure S6). For O_3, Midwest, Southeast, and South were the regions most impacted when we examined respiratory and cardiorespiratory hospital admissions (Figures S8 and S10). Table S2 in Supplementary Materials shows all the RR values from the primary and sensitivity analysis for all sub-groups, pollutants, health outcomes, and regions.

Lag-response curves for a 10-unit increase in ambient air pollution in each region are shown in Figure 5. Lag-response curves of incremental cumulative effects are shown in Figure 6. For both lag-response curves (Figures 5 and 6), we show only the results for the respiratory hospital admissions, the most critical health outcome, according to the above results. Our results indicate that the lag-response curves are very heterogeneous among the regions and air pollutants (Figure 5). For example, in the Southeast, for every increase of $PM_{2.5}$ by $10\mu g/m^3$, there is approximately 0.3% increase in the risk of hospital admission due to respiratory diseases on the same day as the exposure, lag 0 (Figure 5). The exposure from about 7-10 days ago has an uncertain association (95% CI includes the value 1) with respiratory admissions. In contrast, in the Midwest region, $PM_{2.5}$ presented a positive association with respiratory admissions over 15 days of lag (Figure 5).

Regarding the cumulative relative risk (Figure 6), we can also observe heterogeneous lag-response curves among the regions and air pollutants. Overall, there is a consistent increased cumulative risk over 15 days of lag in all regions, except for O_3 in the North, Northeast, and South regions (Figure 6).

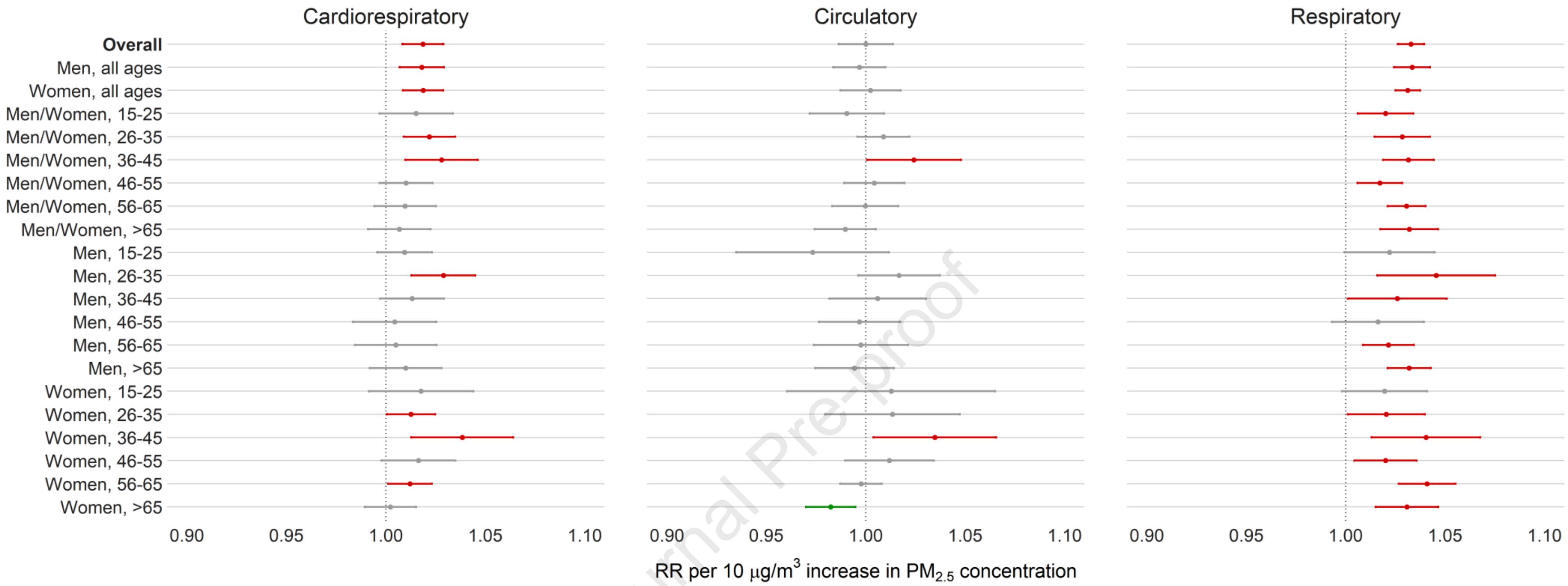

Figure 2 – Risk ratio (95%CI) per 10 μg/m^3 increase in **PM$_{2.5}$ concentration** in Brazil (results from meta-analysis) stratified by health outcome, sex, and age group. This is the overall cumulative effect of a 10-unit increase in each ambient air pollutant over 15 days of lag (summing all the contributions up to the maximum lag).

Note: gray color represents the insignificant coefficients (which the RR includes the value 1), red color represents the significant positive associations, and green color represents the significant negative associations.

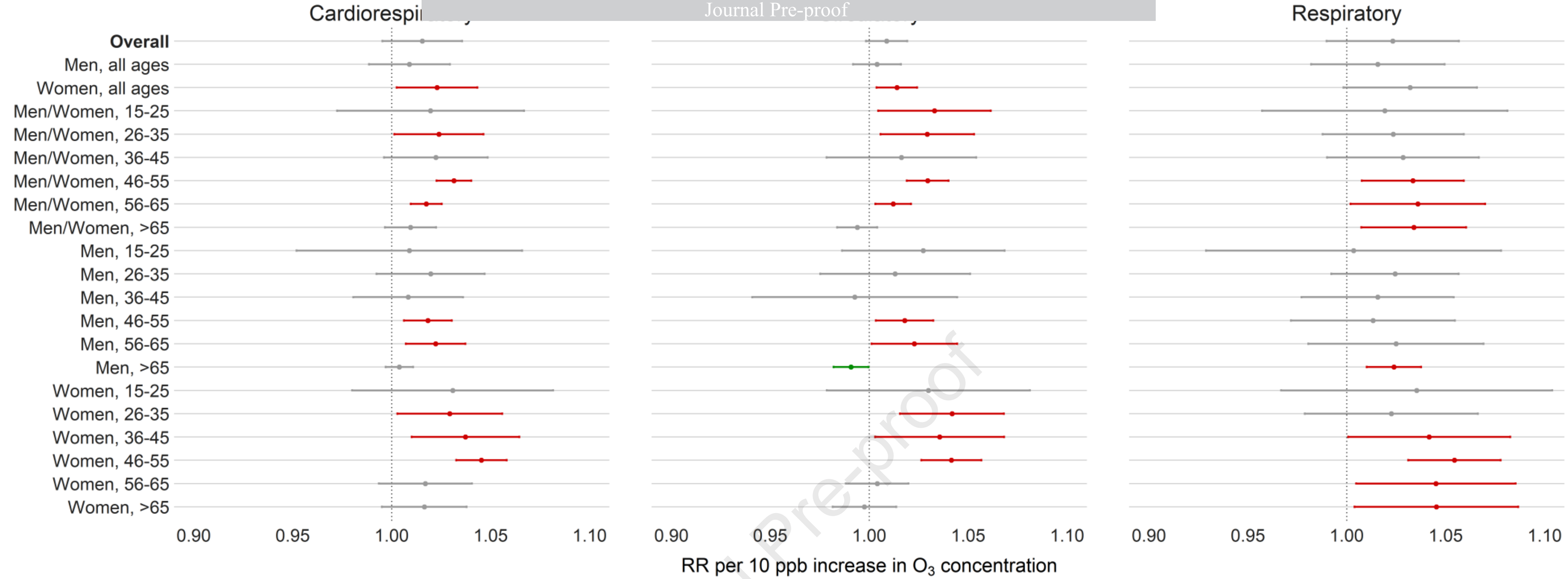

Figure 3 – Risk ratio (95%CI) per 10 ppb increase in **O_3 concentration** in Brazil (results from meta-analysis) stratified by health outcome, sex, and age group. This is the overall cumulative effect of a 10-unit increase in each ambient air pollutant over 15 days of lag (summing all the contributions up to the maximum lag).

Note: gray color represents the insignificant coefficients (which the RR includes the value 1), red color represents the significant positive associations, and green color represents the significant negative associations.

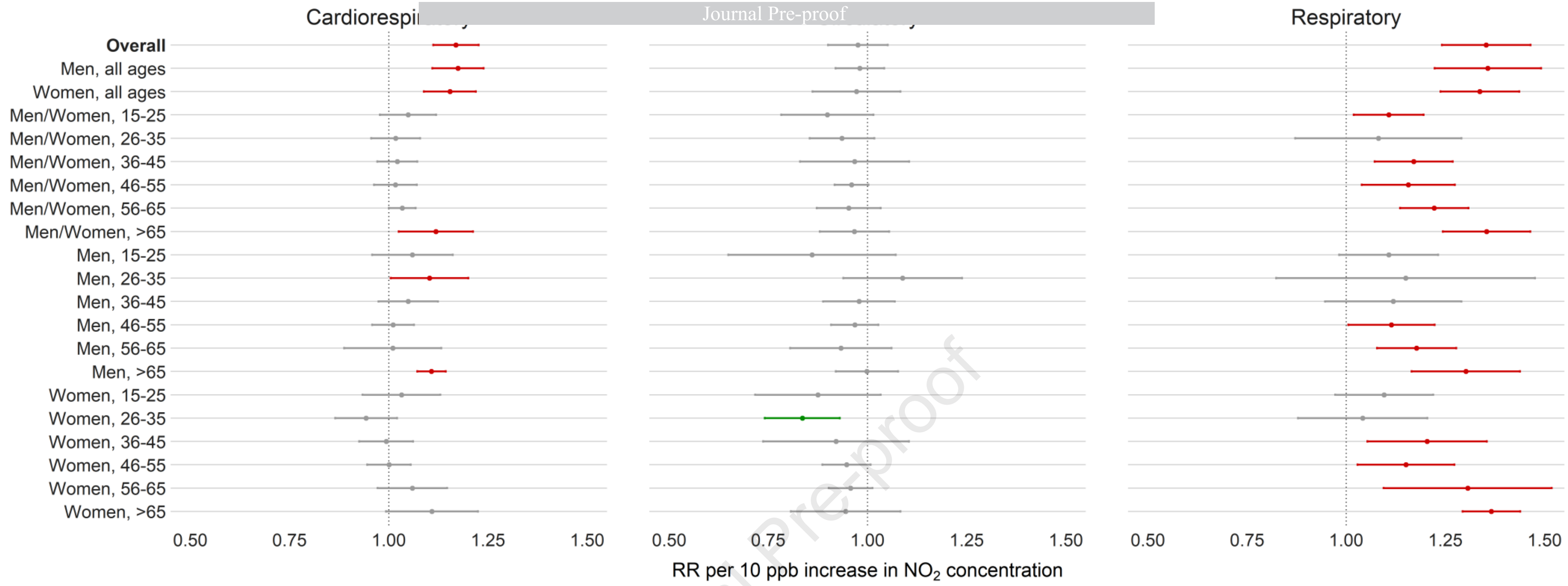

Figure 4 – Risk ratio (95%CI) per 10 ppb increase in **NO_2 concentration** in Brazil (results from meta-analysis) stratified by health outcome, sex, and age group. This is the overall cumulative effect of a 10-unit increase in each ambient air pollutant over 15 days of lag (summing all the contributions up to the maximum lag).

Note: gray color represents the insignificant coefficients (which the RR includes the value 1), red color represents the significant positive associations, and green color represents the significant negative associations.

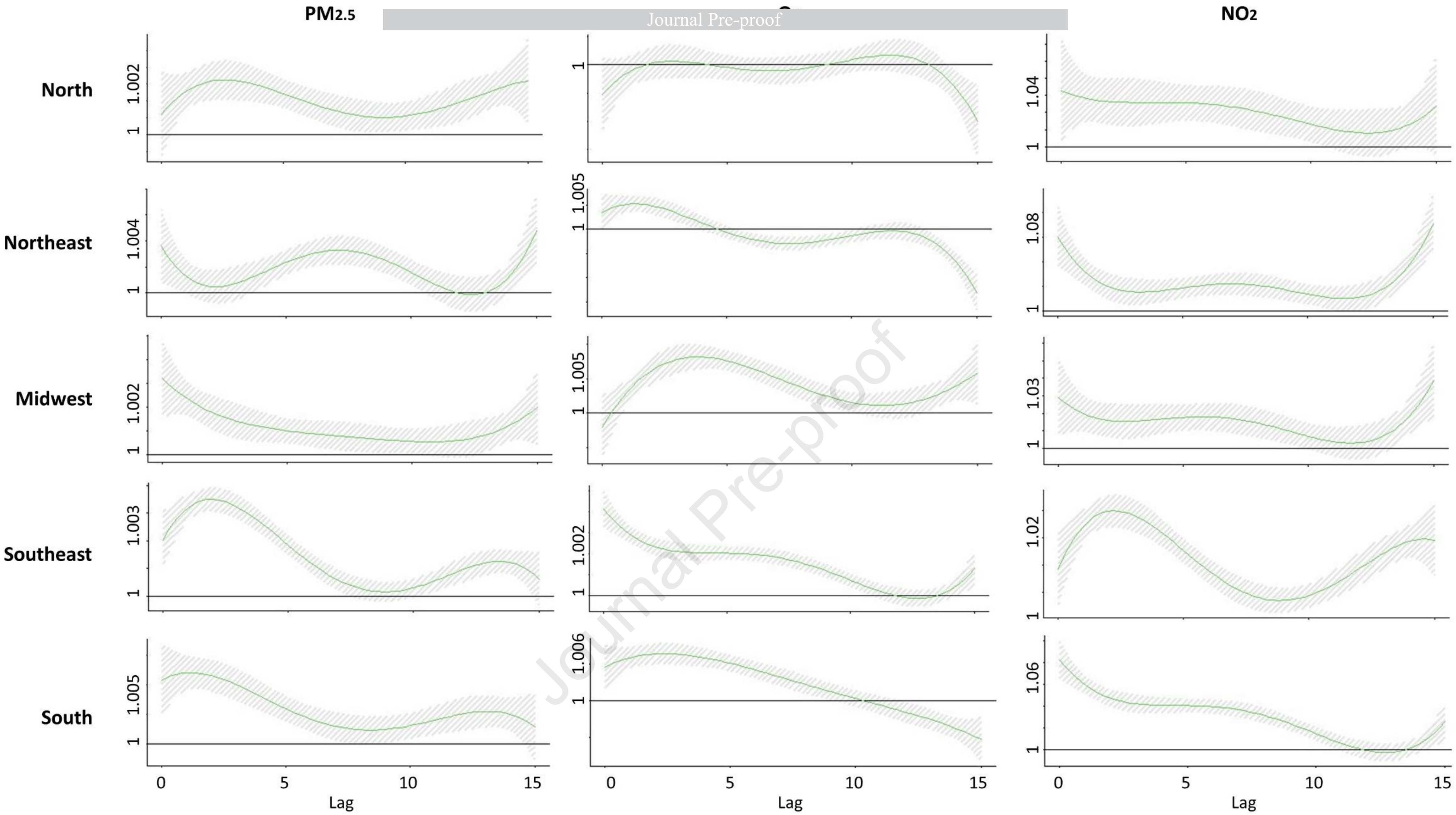

Figure 5 – Risk ratio (95%CI) per 10-unit increases in air pollution by lag for respiratory hospital admissions for the overall population. Charts are stratified by air pollutants and regions.

Note: the y-axis represents the risk ratio (RR).

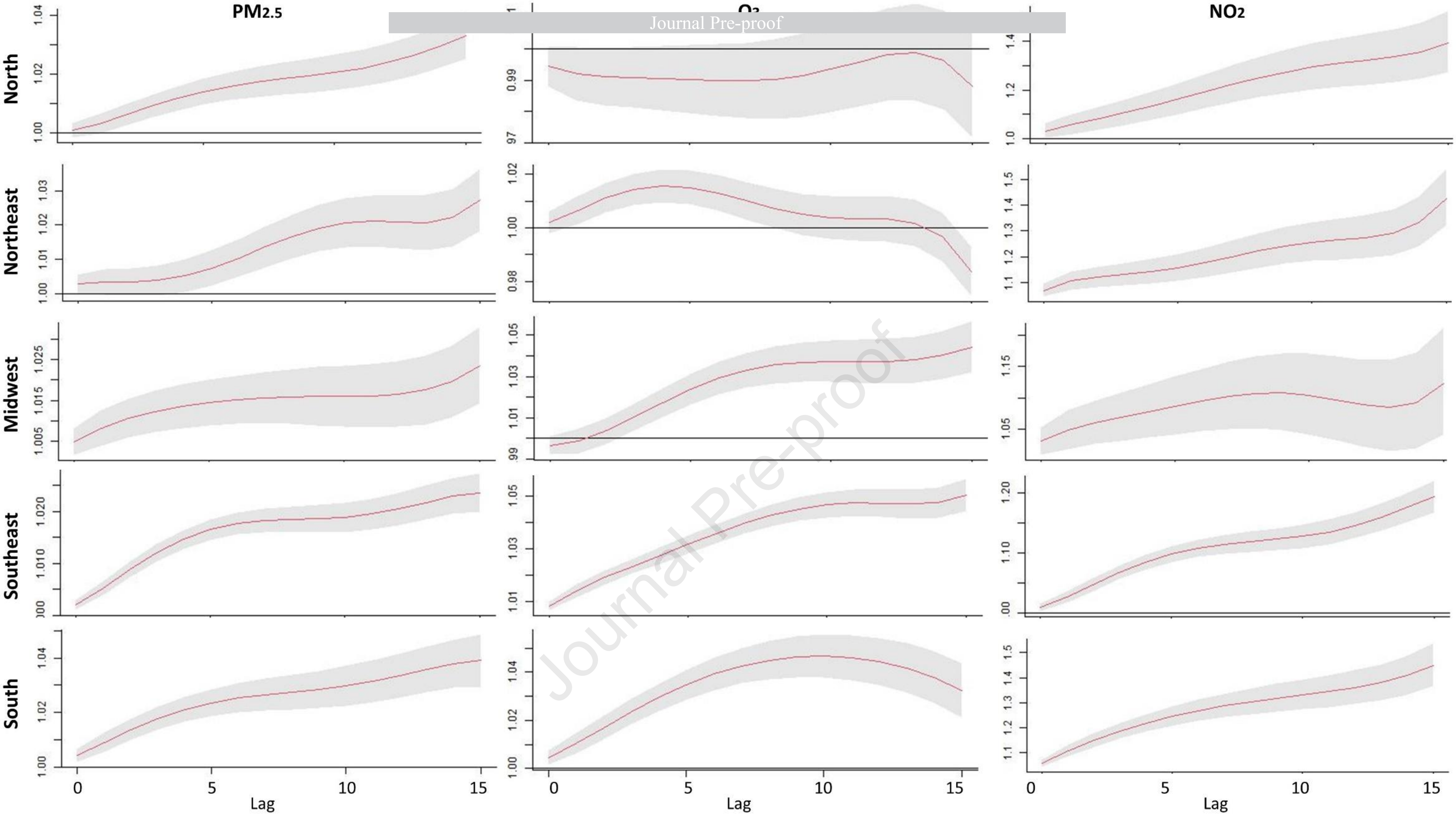

Figure 6 – Cumulative risk ratio (95%CI) per 10-unit increases in air pollution for respiratory hospital admissions for the overall population. Charts are stratified by air pollutants and regions.

Note: the y-axis represents the risk ratio (RR).

4. DISCUSSION

To our knowledge, this is the largest and most comprehensive study to quantify the relationship between short-term exposures to ambient air pollution and hospital admissions in Brazil. We explored the effects of the three most impactful ambient air pollutants, $PM_{2.5}$, O_3, and NO_2 (previous studies in Brazil have only accounted for $PM_{2.5}$). We included approximately 23 million hospital admissions from all Brazilian municipalities, 5,572 municipalities (previous studies in Brazil have considered less than 2,000 municipalities). Our findings suggest a significant association of ambient air pollution ($PM_{2.5}$, NO_2, and O_3) with respiratory and circulatory hospital admissions in Brazil. The statistical significance, the direction, and the effect size of this association varied substantially depending on the type of air pollutant, region, sex, and age group. This is consistent with results from previous Brazilian investigations (a limited number of studies, as presented in the introduction) at the national level and local Brazilian studies. We highlight that the comparison of our results with previous studies performed in Brazil that we present below should be done with caution due to the differences in the study design, model, and data among our study and the Brazilian literature. This comparison should be done based on the public health overview, particularly, looking at the evidence about the health effects risk associated with air pollution exposure.

A recent study at the national level in Brazil focused on the association between $PM_{2.5}$ (only this pollutant) and cancer hospitalizations (Yu et al., 2021), and found that with each 1μg/m^3 increase in two-year-average concentrations of $PM_{2.5}$, the RR of hospitalization was 1.04 (95%CI: 1.02; 1.07) for all-site cancers from 2002 to 2015 without sex and age differences. In our study, we estimated that for each 10μg/m^3 increase in $PM_{2.5}$ over 15 days of lag, the RR of respiratory and circulatory hospitalization were 1.032 (95%CI: 1.026; 1.039) without sex and age differences. We did not find significant associations for circulatory hospital admissions. Another Brazilian study at the national level looked at the association between hospital admissions and wildfire-related $PM_{2.5}$ and reported that a 10μg/m^3 increase in wildfire-related $PM_{2.5}$ was associated with a 5.09% (95%CI: 4.73; 5.44) increase in respiratory hospital admissions and a 1.10% (95%CI: 0.78; 1.42) increase in circulatory hospital admissions, over 0–1 day after the exposure (Ye et al. 2021). In our study, for every increase of $PM_{2.5}$ by 10 μg/m^3, we estimated a 3.28% (95%CI: 2.61; 3.94) increase in the risk of hospital admission for respiratory diseases over 0-15 days after de exposure. In addition, Ye et al. (2021) found the highest attributable rate in the North, South, and Midwest regions, with the consistent results for respiratory diseases across regions and inconsistent for circulatory diseases. Our results were similar, in which circulatory hospital admissions presented the highest number of mixed results (statistical significance, direction of the association, and the effect size) among the regions.

In terms of health outcomes, our results may be more comparable with local studies in Brazil. (Gouveia et al., 2017) used Poisson models to estimate the association between air pollution and hospitalizations for cardiorespiratory diseases in the Metropolitan region of São Paulo, Brazil. The authors found that the RR of respiratory admissions for an increase of 10 µg/m^3 in the levels of PM$_{10}$ ranged from 1.011 (95%CI: 1.009; 1.013) to 1.032 (95%CI: 1.024;1.040) in their study area. Inconsistent results were found for circulatory diseases (Gouveia et al., 2017). In our study, we estimated an RR of 1.023 (95%CI: 1.019; 1.027) associated with respiratory admissions for every increase of PM$_{2.5}$ by 10 µg/m^3 over 15 days of lag in the Southeast region, where São Paulo is located. In contrast, another local study was performed in a city in the state of Rio de Janeiro (also located in the Southeast region), in which the investigators estimated an increase of 3.84% (95%CI: 0.40; 7.40) in hospital admissions from circulatory diseases for people aged 65 or more associated with each increment of 10 µg/m^3 in PM$_{10}$ (Oliveira et al., 2017). The authors did not find significant associations when they used O$_3$ as their exposure. In our study, for the overall cumulative effect over 15 days of lag (summing all the contributions up to the maximum lag), we found positive associations with circulatory hospital admissions when we subtracted the analysis for people aged 65 or more in the Southeast region only for NO$_2$ as exposure, with an estimated increase of 5.31% (95%CI: 1.94; 8.79) in hospital admissions from circulatory diseases. We did not find studies in the Brazilian literature looking at the association between NO$_2$ and hospital admissions.

Regarding the regional heterogeneity of the impact of ambient air pollution exposure indicated by our results, we suggest that part of this variability can be explained by Brazil's cultural, social, behavioral, and environmental/geographical conditions. These conditions may determine the use of health services by affected people during episodes with poor air quality, including i) the perception and decision of each person to seek medical care after getting symptoms of cardiorespiratory diseases during wildfire events and ii) the spatial distribution of health care facilities - e.g., hospitals, clinics, outpatient care centers. In Brazil, the distribution of health facilities varies drastically by region. For example, there are many more health facilities per capita in the South than in the Amazon region, including the North. In Brazil, equity in health services is still poorly distributed among the regions. This important condition needs further exploration in studies exploring health impacts from ambient air pollution. In addition, the modeled exposure accuracy may vary across regions of Brazil.

Our findings suggest positive associations (only from $PM_{2.5}$ and NO_2) with circulatory hospital admissions when we subtracted the analysis for women before menopause (aged 26-45 years old). While this effect is not expected, given that postmenopausal women may be at higher risk (Miller et al., 2007), increased hospitalization due to circulatory events in women aged 26-45 years old may be due to pre-existing condition diseases, including women with congestive heart failure (Mann et al., 2002), chronic lung disease (Goldberg et al., 2001), frequent arrhythmias (Mann et al., 2002), and diabetes (Hart et al., 2015).

Our study has some strengths. First, our sample size includes more than 23 million hospital admissions nationwide over a period of 11 years. To our knowledge, this study has the largest sample size and the most extensive study period in Brazil. As we mentioned above, a limited number of previous studies in Brazil have only conducted regional analyses (only in the Southeast region). Second, we used a modeling approach that flexibly describe associations showing potentially non-linear and delayed effects in time series data. Environmental stressors, such as air pollution, frequently show effects that are delayed in time, requiring specific models that account for the time dimension of the exposure-response relationship. Third, we accounted for spatiotemporal trends in our model by using a time-stratified sampling to define strata based on the day of the week, month, calendar year, and the municipality of the time series. This approach reduces the effects of confounding related to the spatiotemporal trend (a common effect with some environmental stressors as well, such as air pollution exposure) by controlling for time-dependent risk factors within the municipalities, including the day of the week, season, and long-term trends by matching.

Our results, however, should be interpreted considering some limitations. First, given the presence of the individual perceptions and decisions to seek medical care after symptoms of cardiorespiratory diseases, there will be people who went to the hospital on the first day of the exposure, people who wait until symptoms become too severe and went to the hospital five days after the exposure, people who got acute symptoms but did not go to the hospitals etc. Therefore, given that we used a time-series framework, this issue may have affected our results. Second, there is a possibility of some residual confounding bias, even after adjusting for spatiotemporal factors, meteorological conditions, and stratifying the analysis by sex and age. Third, the predicted concentration of ambient air pollution may have resulted in some exposure measurement error. Fourth, our study design does not capture the cause-effect between exposure to ambient air pollution and cardiorespiratory diseases. We only estimated associations between exposure to air pollution and hospital admissions due to cardiorespiratory diseases.

5. CONCLUSIONS

We have found significant associations between exposure to $PM_{2.5}$, NO_2, and O_3 and cardiorespiratory hospital admissions. Most of these associations were not consistent in the subgroup analysis by sex and age. Given the lack of air pollution studies on the national scale in Brazil, further investigations are essential to consolidate a body of local literature that may provide better support for policymakers with the objective of improving air quality and public health.

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- This is the largest and most comprehensive study to quantify the relationship between air pollution and hospitalizations in Brazil.

- Our study population includes 23,791,093 hospital admissions for cardiorespiratory diseases.

- Our findings suggest a significant association of ambient air pollution with cardiorespiratory admissions in Brazil.

- The statistical significance, the direction, and the effect size of the associations varied substantially depending on the type of air pollutant, region, sex, and age group.

- This study is essential in Brazil, a region with a lack of control and monitoring policies leading to increased air pollution.

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.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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