Short-term exposure to ambient air pollution and readmissions for heart failure among 3660 post-discharge patients with hypertension in older Chinese adults

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ABSTRACT

Background Despite ambient air pollution being associated with various adverse cardiovascular outcomes, the acute effects of ambient air pollution on hospital readmissions for heart failure (HF) among post-discharge patients with hypertension remain less understood.
Methods We conducted a time-stratified case-crossover study among 3660 subjects 60 years or older who were admitted to hospital for HF after discharge for hypertension in Guangzhou, China during 2016–2019. For each subject, individualised residential exposures to ambient particulate matter with an aerodynamic diameter ≤1 µm (PM_1), ≤2.5 µm ($PM_{2.5}$), ≤10 µm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone were extracted from our validated grid dataset.
Results An IQR increase of lag 04-day exposure to PM_1 (IQR: 11.6 µg/m^3), $PM_{2.5}$ (IQR 21.9 µg/m^3), PM_{10} (IQR 35.0 µg/m^3), SO_2 (IQR 4.4 µg/m^3), NO_2 (IQR 23.3 µg/m^3) and CO (IQR 0.25 mg/m^3) was significantly associated with a 9.77% (95% CI 2.21% to 17.89%), 8.74% (95% CI 1.05% to 17.00%), 13.93% (95% CI 5.36% to 23.20%), 10.81% (95% CI 1.82% to 20.60%), 14.97% (95% CI 8.05% to 22.34%) and 7.37% (95% CI 0.98% to 14.16%) increase in odds of HF readmissions, respectively. With adjustment for other pollutants, the association for NO_2 exposure remained stable, while the associations for PM_1, $PM_{2.5}$, PM_{10}, SO_2 and CO exposures became insignificant. Overall, an estimated 19.86% of HF readmissions were attributable to NO_2 exposure, while reducing NO_2 exposure to the WHO and China air quality standards would avoid 12.87% and 0.54% of readmissions, respectively. No susceptible populations were observed by sex, age or season.
Conclusion Short-term exposure to ambient NO_2 was significantly associated with an increased odds of HF readmissions among post-discharge patients with hypertension in older Chinese adults.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Post-discharge patients with hypertension are at a high risk of heart failure (HF). As a major public health issue globally, ambient air pollution was demonstrated to trigger various adverse cardiovascular outcomes; however, the health effects of ambient air pollution on risk of hospital readmissions for HF among post-discharge patients with hypertension remain less understood.

WHAT THIS STUDY ADDS

⇒ Short-term exposure to ambient nitrogen dioxide was significantly associated with an increased odds of readmissions for HF among older post-discharge patients with hypertension, which may result in considerable excess hospital readmissions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that exposure to ambient air pollution, especially nitrogen dioxide, substantially contributes to the occurrence of HF among post-discharge patients with hypertension, which provides useful clues for clinical practitioners to help prevent readmissions for HF by taking into consideration the adverse effects of air pollution during the post-discharge health management for patients with hypertension.

INTRODUCTION

As a leading chronic non-communicable disease, hypertension affects up to 1.28 billion adults worldwide in 2019 and this number was doubled since 1999.[1] Over the past few years, accumulating evidence has proven that patients with hypertension especially post-discharge patients with hypertension are at an increased risk of heart failure (HF) which was well known as a condition with poor prognosis.[2 3] In the USA, HF is reported as one of the most common cardiovascular causes of readmissions after discharge for hypertension.[4] Likewise, in China, approximately 55% of patients hospitalised for HF were accompanied by hypertension,[5] which has raised much attention because the prevalence of hypertension among the general Chinese population was up to 45%.[6] Given the alarmingly unoptimistic outcomes of hypertension and HF after discharge, it is of great interest and importance to prevent HF readmissions for post-discharge patients with hypertension.

To date, several sociodemographic factors (including age, sex, race, insurance status, income,

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smoking, alcohol use) and comorbidity conditions have been associated with a higher risk of HF in post-discharge patients with hypertension.[7] Unlike these personal risk factors, ambient air pollution was ubiquitous and its potential adverse effects on human health have gained mounting public attentions.[8] In 2013, a systematic review and meta-analysis concluded that short-term exposure to ambient particulate matter with an aerodynamic diameter ≤2.5 µm ($PM_{2.5}$), ≤10 µm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), but not ozone (O_3), was significantly associated with an increased risk of HF hospitalisation or death[9]; however, for post-discharge patients with hypertension with higher risk of HF, only one study specifically investigated the association of PM_{10} exposure with readmissions for HF among post-discharge patients with hypertension and the results were limited.[10] In addition, the acute effects of other criteria air pollutants including particulate matter with an aerodynamic diameter ≤1 µm (PM_1), $PM_{2.5}$, SO_2, NO_2, CO and O_3 are far from being elucidated. The inconclusive evidence hindered policymakers to formulate target protective policies or interventions to prevent HF readmissions for post-discharge patients with hypertension.

Here, we conducted a population-based case-crossover study to investigate the association of short-term exposure to ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 with HF readmissions among post-discharge patients with hypertension, and estimate the corresponding excess hospital readmissions in Guangzhou, China during 2016–2019.

METHODS

Study area

This study was conducted in Guangzhou, which is the capital city of Guangdong province in southern China. According to the Seventh Population Census in 2021, Guangzhou covers an area of 7434 km^2 with a total population of 18.7 million in 2020. As an important city in Pearl River Delta, Guangzhou has experienced considerable air pollution issues alongside its rapid economic development.

Study population

Hospital admission data in Guangzhou, China from 2016 to 2019 were obtained from the Guangzhou Health Technology Identification and Human Resources Assessment Center, which included all hospitals that provided inpatient care services in Guangzhou. The total number of included hospitals increased from 345 in 2016 to 372 by the end of 2019. Patients with an admission for hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) who had HF readmission records after their first hypertension admission were identified.[11] After excluding subjects with incomplete or missing residential address information (n=2) or those living outside Guangdong province (n=31), we finally included 3660 patients 60 years or older who were admitted for HF after discharge for hypertension with 6258 hospital admission records in the analyses. Demographic information including date of birth, sex, race and date of readmission was extracted for each readmission.

Outcomes

The study outcome was readmission for HF after hospital discharge for hypertension. According to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), we used I50 to define readmission for HF.

Study design

We estimated the association of ambient air pollution with hospital readmissions for HF with a time-stratified case-crossover design. This design was first described by Maclure in 1992 and has been broadly used to investigate transient effects of air pollution on the risk of acute events.[12–14] In this design, each subject serves as his or her own control by assessing referent exposures before and/or after the day of event within a given time stratum (eg, a month). For each readmission, we defined a case day as the date of readmission, and defined its corresponding control days as dates with the same day of week in the same month and year as the case day.[15] For example, if a subject was admitted on 10 October 2019 (Thursday), the case day was defined as 10 October 2019 and all other Thursdays in October 2019 (ie, 3, 17, 24, 31 October) were chosen as the corresponding control days. According to this approach, we eventually matched 21 336 control days for 6258 case days in the analyses. As each subject serves as his or her own reference, the case-crossover design provides unique opportunities to control for the effects of stable individual-specific covariates.[16]

Exposure assessment

Daily grid data at a spatial resolution of 10×10 km on ambient air pollution concentrations in Guangdong province during 2016–2019 were retrieved from our ChinaHighAirPollutants (CHAP) dataset. Generated using our proposed artificial intelligence models combining with big data including ground measurements, satellite remote sensing products, model simulations, and atmospheric reanalysis,[17–21] this dataset has high cross-validated coefficient of determination (R^2) for daily ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 of 0.83, 0.91, 0.88, 0.84, 0.84, 0.80 and 0.87, respectively. For each readmission, daily ambient air pollution exposures during the case and control days were assessed by extracting the daily 24-hour average PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and maximum 8-hour moving average O_3 concentrations from the CHAP dataset based on each subject's geocoded residential address. We chose different lag structures (including single day from lag 0-day to lag 6-day and moving average day from lag 01-day to lag 06-day) exposures to examine the short-term associations of air pollution exposure with readmissions and used the lag day showing the strongest association

Table 1 Characteristic of study subjects in Guangzhou, China during 2016–2019

Characteristic	N (%)
Heart failure readmission patients	3660
Case days	6258
Control days	21 336
Age, year, mean±SD	81.24±8.11
≤80	2512 (40.1)
>80	3746 (59.9)
Sex	
Male	2437 (38.9)
Female	3821 (61.1)
Race	
Han	6228 (99.5)
Other	7 (0.1)
Unknown	23 (0.4)
Season at readmission	
Warm (May–October)	3092 (49.4)
Cool (November–April)	3166 (50.6)

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Table 2 Distribution of ambient air pollutants and meteorological conditions on the date of readmissions for heart failure among older patients with hypertension

	Mean (SD)	Min	P_5	P_{25}	P_{50}	P_{75}	P_{95}	Max	IQR
Air pollutant									
PM_1, µg/m^3	19.5 (10.8)	2.2	7.3	12.4	17.1	24.0	40.3	94.9	11.6
$PM_{2.5}$, µg/m^3	33.6 (18.5)	5.6	12.5	20.5	29.5	42.4	68.1	189.2	21.9
PM_{10}, µg/m^3	57.1 (28.5)	10.7	23.8	36.4	49.7	71.4	112.8	256.3	35.0
SO_2, µg/m^3	9.8 (3.5)	2.7	5.8	7.2	9.1	11.6	16.5	33.5	4.4
NO_2, µg/m^3	49.5 (22.1)	10.0	23.0	34.9	44.9	58.2	90.1	247.9	23.3
CO, mg/m^3	0.90 (0.23)	0.36	0.62	0.75	0.85	1.00	1.37	2.64	0.25
O_3, µg/m^3	100.2 (53.6)	3.8	21.0	61.1	93.8	135.7	201.5	284.0	74.6
Meteorological condition									
Temperature, °C	23.6 (5.6)	4.7	13.8	19.4	24.3	28.6	30.8	33.4	9.2
Relative humidity, %	75.6 (13.4)	26.0	48.1	68.4	79.8	85.7	90.6	96.4	17.3

CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM_1, particulate matter with an aerodynamic diameter ≤1 µm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 µm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 µm; SO_2, sulfur dioxide.

in the main analysis for each air pollutant.[14] For example, lag 0-day exposure refers to the exposure on the day of readmission; lag 1-day (2-day, 3-day, 4-day, 5-day, 6-day) exposure refers to the exposure on 1 day (2, 3, 4, 5, 6 days) before the day of readmission, while lag 01-day (02-day, 03-day, 04-day, 05-day, 06-day) exposure refers to the mean of exposure on the same day of readmission and 1 day (2, 3, 4, 5, 6 days) prior.

Covariates

Using meteorological grid data from the China Meteorological Administration Land Data Assimilation System (CLDAS, V.2.0; spatial resolution: 0.0625°×0.0625°), we obtained daily average temperature (°C) and daily average relative humidity (%) in Guangdong province during the study period and assessed residential exposure to these two meteorological conditions by extracting daily 24-hour average values during the case days and corresponding control days for each readmission.[22 23] As most individual-level covariates (eg, demographic information, socioeconomic status) were unlikely to vary substantially during the case and corresponding control days (ie, within a month), we did not consider them as potential confounders in the analyses.[24]

Statistical analysis

The correlations between air pollutant exposure levels on case days were evaluated by Spearman's correlation analyses because the distributions of air pollution were not normally distributed. We fitted conditional logistic regression models to quantitatively assess the associations of short-term exposure to ambient

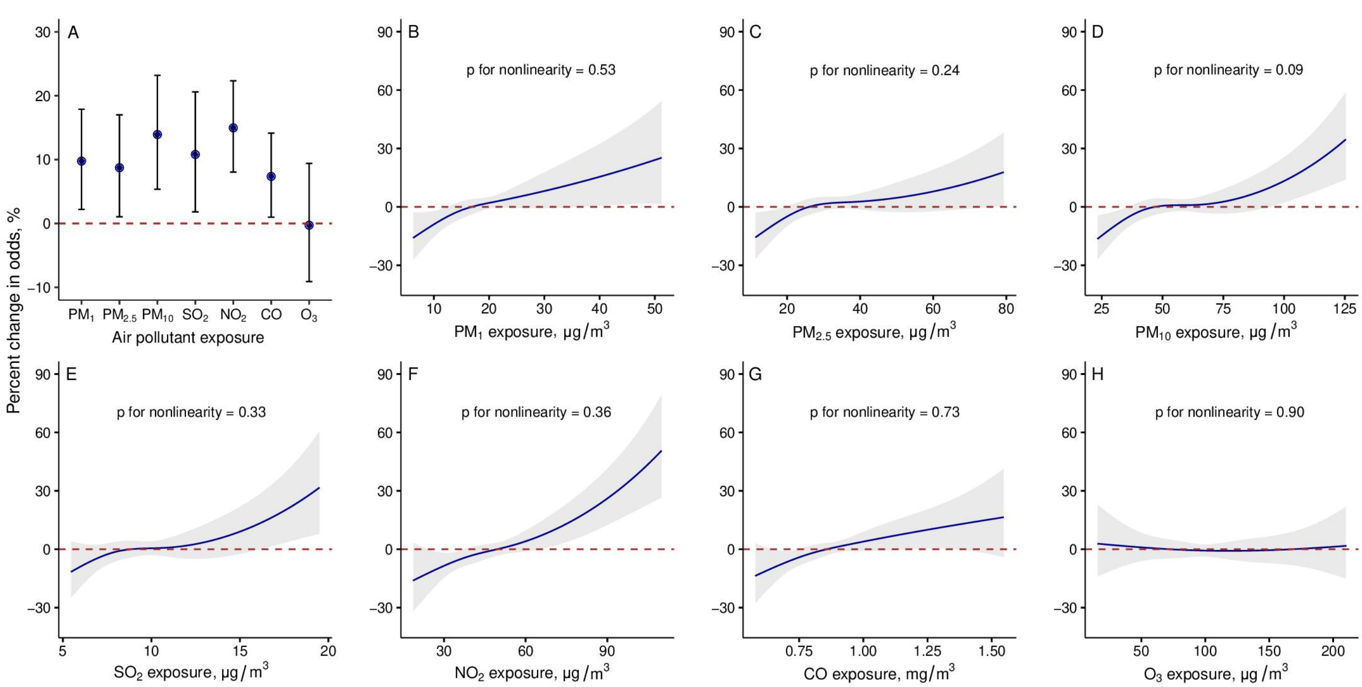

Figure 1 Associations of lag 04-day exposure to ambient air pollutants with readmissions for heart failure after hospital discharge among older patients with hypertension. (A) The percent change in odds (95% CI) of readmissions for each increase by an IQR in ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3. (B–H) The exposure–response curve of readmissions associated with lag 04-day exposure to ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3, respectively. CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM_1, particulate matter with an aerodynamic diameter ≤1 µm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 µm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 µm; SO_2, sulfur dioxide.

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Table 3 Percent change (95% CI) in odds of readmissions for heart failure after hospital discharge among older patients with hypertension associated with each increase by an IQR of lag 04-day exposure to ambient air pollutants in single-pollutant and two-pollutant models

Model	PM_1	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3
Single-pollutant	9.77 (2.21 to 17.89)	8.74 (1.05 to 17.00)	13.93 (5.36 to 23.20)	10.81 (1.82 to 20.60)	14.97 (8.05 to 22.34)	7.37 (0.98 to 14.16)	−0.27 (−9.10 to 9.41)
Adjusted for PM_1	–	–	–	5.69 (−5.14 to 17.75)	16.28 (7.09 to 26.25)	4.17 (−2.98 to 11.86)	−5.78 (−14.82 to 4.23)*
Adjusted for $PM_{2.5}$	–	–	–	7.09 (−4.88 to 20.56)	20.61 (10.10 to 32.11)	4.70 (−2.88 to 12.87)	−5.75 (−14.96 to 4.45)*
Adjusted for PM_{10}	–	–	–	0.07 (−11.51 to 13.18)*	16.84 (5.37 to 29.57)	1.52 (−5.97 to 9.62)*	−7.65 (−16.60 to 2.25)*
Adjusted for SO_2	6.64 (−2.63 to 16.80)	4.32 (−5.85 to 15.59)	13.88 (1.65 to 27.57)	–	17.22 (7.89 to 27.36)	4.83 (−2.13 to 12.28)	−4.51 (−13.49 to 5.40)*
Adjusted for NO_2	−1.96 (−10.81 to 7.77)*	−7.41 (−16.85 to 3.10)*	−2.50 (−14.37 to 11.01)*	−3.90 (−14.16 to 7.58)*	–	−1.36 (−8.54 to 6.39)*	−7.69 (−16.36 to 1.87)*
Adjusted for CO	7.14 (−1.38 to 16.40)	5.34 (−3.71 to 15.23)	12.62 (2.12 to 24.20)	7.60 (−2.13 to 18.30)	15.91 (7.36 to 25.14)	–	−1.38 (−10.16 to 8.26)*
Adjusted for O_3	11.75 (3.42 to 20.76)	10.94 (2.30 to 20.31)	17.11 (7.49 to 27.58)	12.41 (2.74 to 22.98)	17.03 (9.58 to 24.99)	7.47 (1.04 to 14.30)	–

*p<0.05 estimated using the likelihood ratio test.
CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM_1, particulate matter with an aerodynamic diameter ≤1 µm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 µm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 µm; SO_2, sulfur dioxide.

air pollution with readmissions for HF after hospital discharge among older patients with hypertension. In main models, we included each air pollution exposure as the main effect and adjusted for two meteorological conditions at lag 03-day as natural cubic splines (including temperature with 6 *df* and relative humidity with 3 *df*) to control their possible confounding effects. The risk estimate was expressed as percent change in odds of readmissions and its 95% CI for each IQR increase of ambient air pollution exposures. The percent change in odds was calculated as (OR−1)×100%. In addition, we included ambient air pollution exposures in the model as a natural cubic spline with 3 *df* and visualised the exposure–response relationships. The likelihood ratio test was performed to test the nonlinearity of associations. For each air pollutant, we further included each of the other air pollutants in the same model to fit two-pollutant models and compared them using the likelihood ratio test.

Based on the established associations in two-pollutant models, we further estimated the excess hospital readmissions attributable to ambient air pollution exposures by calculating the excess fraction and number of excess hospital readmissions for each air pollution which was significantly associated with an increased odds of readmissions for HF with the following formula:

$$\text{Excess fraction} = \frac{\sum_{i=1}^{N} 1-\frac{1}{e^{\beta\times(C_i-C_0)}}}{N}\times 100\%$$

where β indicates the point estimate in conditional logistic regression models; N indicates the number of readmission cases; C_i indicates the ambient air pollution exposure on case days with pollutant concentration levels exceeding C_0; C_0 indicates the minimum exposure level of each air pollutant; or the reference levels of each air pollutant according to the 2021 WHO air quality guidelines (AQGs) and the ambient air quality standards in China.[25] The corresponding number of excess hospital readmissions was calculated as excess fraction×N.

We performed subgroup analyses to investigate possible susceptible populations by sex, age (≤80 years, >80 years) and season (cool season, warm season). Cool season was from May to October, while warm season was from November to April. For each subgroup, we separately implemented conditional logistic regression models to evaluate the association of ambient air pollution with readmissions. The associations across stratification variables were compared by two-sample z tests, based on the stratification-specific point estimate (β) and SE[26]:

$$z=\frac{\beta_1-\beta_2}{\sqrt{SE^2_{\beta_1}+SE^2_{\beta_2}}}$$

The robustness of our results was tested by several sensitivity analyses. First, we restricted the analyses to the first HF readmission record after the index hypertension admission for each patient in any medical institution during 2016–2019 (including 3660 patients with 3660 readmission records for HF). Second, we only included patients living in Guangzhou city in the analyses. Third, we restricted the analyses to Han race cases only. We performed all statistical analyses in R software (V.4.1.2), and two-sided p values less than 0.05 were considered statistically significant.

RESULTS

From 2016 to 2019, we identified 3660 subjects (6258 case days) who were admitted to hospital for HF after discharge for hypertension in Guangzhou, China. Of these, most of them were Han race, 59.9% were aged >80 years, 61.1% were female and 50.6% were admitted in cool season (table 1). The readmission rates of 30 days, 90 days, 1 year, and 3 years were

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Table 4 Excess fraction and number of excess readmissions for heart failure after hospital discharge among older patients with hypertension attributable to lag 04-day exposure to NO_2 in single-pollutant and two-pollutant models

Variable	Above minimal exposure level*		Above 2021 WHO air quality guidelines†		Above China air quality standards‡	
	Excess fraction, % (95% CI)	Number of excess readmissions, N (95% CI)	Excess fraction, % (95% CI)	Number of excess readmissions, N (95% CI)	Excess fraction, % (95% CI)	Number of excess readmissions, N (95% CI)
NO_2	19.86 (11.69 to 27.13)	1243 (731 to 1698)	12.87 (7.48 to 17.77)	805 (468 to 1112)	0.54 (0.31 to 0.75)	34 (20 to 47)
NO_2+PM_1	21.25 (10.43 to 30.50)	1330 (653 to 1909)	13.79 (6.67 to 20.09)	863 (417 to 1257)	0.58 (0.28 to 0.85)	36 (17 to 53)
$NO_2+PM_{2.5}$	25.53 (14.27 to 35.03)	1598 (893 to 2192)	16.68 (9.17 to 23.26)	1044 (574 to 1455)	0.70 (0.38 to 0.98)	44 (24 to 61)
NO_2+PM_{10}	21.83 (8.09 to 33.14)	1366 (506 to 2074)	14.19 (5.15 to 21.93)	888 (323 to 1372)	0.59 (0.21 to 0.93)	37 (13 to 58)
NO_2+SO_2	22.22 (11.49 to 31.40)	1391 (719 to 1965)	14.45 (7.35 to 20.72)	904 (460 to 1296)	0.61 (0.31 to 0.87)	38 (19 to 55)
NO_2+CO	20.86 (10.79 to 29.57)	1305 (675 to 1850)	13.53 (6.90 to 19.45)	847 (432 to 1217)	0.57 (0.29 to 0.82)	36 (18 to 51)
NO_2+O_3	22.02 (13.62 to 29.44)	1378 (852 to 1843)	14.31 (8.75 to 19.36)	896 (547 to 1212)	0.60 (0.37 to 0.82)	8 (23 to 51)

*Using the minimum exposure level as the reference level. The minimum exposure level of NO_2 was 10.0 μg/m^3.
†Using the 2021 WHO air quality guideline values as the reference level. The guideline value of 24-hour average NO_2 concentration was 25 μg/m^3.
‡Using the ambient air quality standards in China as the reference level. The grade II standard of 24-hour average NO_2 concentration was 80 μg/m^3.
CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM_1, particulate matter with an aerodynamic diameter ≤1 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; SO_2, sulfur dioxide.

6.9% (readmission cases: 253), 17.6% (645), 47.8% (1748), and 92.8% (3397), respectively. Online supplemental figure S1 shows the spatial distribution of subjects' residential addresses in Guangdong province.

Table 2 shows that mean daily average concentrations of ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 were 19.5 μg/m^3, 33.6 μg/m^3, 57.1 μg/m^3, 9.8 μg/m^3, 49.5 μg/m^3, 0.90 mg/m^3 and 100.2 μg/m^3, respectively, while the mean exposure to temperature and relative humidity was 23.6℃ and 75.6%, respectively. Seasonal distribution of ambient air pollutants and meteorological conditions on the date of readmissions was presented in online supplemental table S1. Exposure levels of ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO were higher in cool season, while exposure levels of O_3, temperature and relative humidity were higher in warm season. Exposure to all air pollutants was positively correlated, except that O_3 exposure was negatively correlated with CO exposure (all pairwise $p<0.05$; online supplemental figure S2).

In single-pollutant models, we observed significantly positive associations between short-term exposure to ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO with an increased risk of readmissions (figure 1A; online supplemental figure S3). For each air pollutant, the lag 04-day exposure produced the strongest associations. Each increase by an IQR of ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO exposure was significantly associated with a 9.77% (95% CI 2.21% to 17.89%; IQR 11.6 μg/m^3), 8.74% (95% CI 1.05% to 17.00%; IQR 21.9 μg/m^3), 13.93% (95% CI 5.36% to 23.20%; IQR 35.0 μg/m^3), 10.81% (95% CI 1.82% to 20.60%; IQR 4.4 μg/m^3), 14.97% (95% CI 8.05% to 22.34%; IQR 23.3 μg/m^3), and 7.37% (95% CI 0.98% to 14.16%; IQR 0.25 mg/m^3) increase in odds of readmissions, respectively (figure 1A). The exposure–response curves for associations showed that the odds of readmissions for HF increased monotonically with increasing air pollution exposure levels, suggesting that all these exposure–response associations were linear with no indication of thresholds at low exposure levels (figure 1B–H, all p for nonlinearity<0.05). No significant associations were observed between O_3 exposure and HF readmissions ($p>0.05$; figure 1A, online supplemental figure S3).

In two-pollutant models, the association for ambient NO_2 exposure remained stable with further adjustment for each of the other pollutants, while the associations for ambient PM_1, $PM_{2.5}$, PM_{10}, SO_2 and CO exposures became insignificant especially when adjusted for NO_2 (table 3, online supplemental figure S4). The association of NO_2 exposure increased with adjustment for $PM_{2.5}$, SO_2, CO and O_3 simultaneously in the same model (percent change in odds: 21.27%; 95% CI 9.75% to 34.01%; online supplemental table S2).

Table 4 presents the estimates of excess fraction and number of excess readmissions due to lag 04-day exposure to NO_2 in Guangzhou, China in 2016–2019. Using the minimum air pollution exposure level as the reference, we estimated that 19.86% (95% CI 11.69% to 27.13%) of the readmissions were attributable to ambient NO_2 exposure, while the excess fractions were 21.25% (95% CI 10.43% to 30.50%), 25.53% (95% CI 14.27% to 35.03%), 21.83% (95% CI 8.09% to 33.14%), 22.22% (95% CI 11.49% to 31.40%), 20.86% (95% CI 10.79% to 29.57%) and 22.02% (95% CI 13.62% to 29.44%) for readmissions with adjustment for PM_1, $PM_{2.5}$, PM_{10}, SO_2, CO and O_3, respectively. According to the WHO AQGs values, an estimated 12.87% (95% CI 7.48% to 17.77%) of readmissions were attributable to NO_2 exposure, while an estimated 0.54% (95% CI 0.31% to 0.75%) of readmissions were associated with NO_2 exposure based on the ambient air quality standards in China.

In subgroup analyses, no potential susceptible populations were observed across age, sex or season (all p for difference>0.05; online supplemental table S3). Restricting the analyses to the first readmission record for each patient during the study period, patients living in Guangzhou city and Han race cases showed similar results (online supplemental figures S5–S7).

DISCUSSION

In this 4-year Chinese case-crossover study, we quantitatively investigated the associations of short-term exposure to ambient air pollution with readmissions for HF after hospital discharge among older patients with hypertension. We found consistent evidence that short-term exposure to ambient NO_2 may increase the odds of readmissions and cause considerable excess hospital readmissions. In addition, reducing NO_2 exposure to the 2021 WHO AQGs and the China air quality standards would avoid 12.87% and 0.54% of readmissions, respectively. No susceptible populations by age, sex or season were observed.

The acute adverse effects of ambient air pollution on HF readmissions among post-discharge patients with hypertension have been rarely investigated. To date, only one case-crossover study carried out in Italy reported that each 10 μg/m^3 increase of PM_{10} exposure on lag 0-day was significantly associated with a 2.08%

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increase in odds of HF readmissions, which was slightly higher than our estimates (1.71%).[10] It should be noted that the association disappeared with adjustment for NO_2 exposure in our study, suggesting that the association between PM_{10} exposure and HF readmissions was dependent on the NO_2 exposure. This is the first study to identify a consistent association between NO_2 exposure and HF readmissions after discharge among patients with hypertension. Two previous studies in China and the USA reported positive associations of NO_2 exposure with increased risks of hospitalisation for HF in population comorbid with hypertension.[27 28] However, it has been proposed that patients with a history of hypertensive hospitalisation usually suffered from marked elevated blood pressure, chronic or acute end-organ damages and complex cardiovascular comorbidities, and may be more likely to be readmitted for cardiovascular disease than patients with hypertension without any hypertension admissions.[2 29] Therefore, the results of these two studies may not be directly comparable with our estimates.

As a proxy of traffic-related ambient air pollution, NO_2 is one of the essential contributors to the air pollution in most urban areas. Although the ambient NO_2 concentration has decreased under regulation in many countries, emerging evidence suggests that ambient NO_2 exposure can trigger numerous cardiovascular events.[30] Similarly, our study adds to the pivotal evidence that ambient NO_2 exposure is an independent risk factor for HF readmissions among post-discharge patients with hypertension. Additionally, unlike other risk factors, ambient NO_2 exposure was ubiquitous and unavoidable. Given that direct control over ambient NO_2 exposure is often beyond an individual's ability, our findings highlight a potential approach that individuals, clinicians and policymakers could corporately take effective interventions (eg, controlling traffic-related air pollution emissions and exposures, staying indoors) to reduce ambient NO_2 exposures to prevent HF readmissions for post-discharge patients with hypertension.

As in previous studies, we found that short-term exposure to air pollution was significantly associated with an increased odds of readmissions for HF on early lag days (eg, lag 0-day, 1-day) but decreased odds on the following lag days (eg, lag 5-day, 6-day), suggesting the presence of certain harvesting effects.[31 32] This phenomenon refers to that air pollution can principally advance hospital admissions by a number of days or weeks among subjects with already poor health conditions, but result in less adverse effects on healthy subjects. Therefore, the initial increase in odds of hospital admissions is followed by a period with a lower risk of hospital admissions. Further studies are warranted to illustrate the potential mechanisms.

Consistent with findings in previous studies, our study suggests that women seem to be more susceptible to air pollution than men, although the differences did not reach statistical significance.[33 34] These known differences in biology (eg, airway size, particulate deposition and inflammatory response) and behaviour (eg, smoking) may help explain the higher admission risks in women observed in this study.[35] Specifically, prior studies have proposed that women have smaller airway size as well as greater airway reactivity, which may induce more particulate matter deposition and higher immune-inflammatory reactivity than men.[36 37] In addition, it has been reported that the effects of air pollution may be stronger in non-smokers than that in smokers, because oxidative stress and inflammation caused by smoking may weaken additional effects of co-exposure to air pollutants in men.[38] Nonetheless, the exact mechanisms of these sex-specific associations remain unclear and need to be further investigated.

The biological mechanisms of readmissions for HF after discharge among patients with hypertension attributable to ambient NO_2 exposure are yet to be completely elucidated. One hypothesis is that inhaled NO_2 might induce pulmonary inflammation, traverse the alveolar space and enter the circulation system, which can trigger systemic inflammation.[39] In addition to inflammation, ambient air pollution (including NO_2) exposure has been reported to induce acute arterial vasoconstriction, elevate blood pressure, increase plasma viscosity, and trigger atherosclerosis and thrombus formation; these effects of air pollution will significantly increase the demands on failing hearts and thereby lead to acute compensatory decompensation, especially for patients with hypertension.[9 40 41]

Our study has several strengths. The relatively large-scale populations provide the unique opportunity for us to conduct exposure–response analyses with a sufficient statistical power. In addition, by employing the time-stratified case-crossover design, we performed air pollutant exposure assessment for each subject in an individual level by using data from a validated high-quality ground-level air pollutant grid dataset in China. Benefiting from the relatively high spatial resolution, the personal exposure assessment in our study was more accurate than previous studies which used the mean daily air pollutant concentrations at one or more fixed monitoring stations in a city to replace individual-level exposures.[42 43]

Despite these strengths, several potential limitations in our study should be mentioned. First, limited by data, we were unable to adjust for personal activity data (eg, staying indoors, personal protective measures) in the analyses, which could introduce some exposure misclassifications; however, these possible misclassifications in individual-level exposure assessment have been proposed to be nondifferential and may not induce inaccurate estimations.[44] Second, although we took the advantage of case-crossover design to control for the individual-level stable confounding factors and adjusted for two time-variant meteorological conditions (temperature and relative humidity) in the model, unmeasured individual-level factors (eg, pre-existing vascular risk factors, medication use, lifestyle) which may change within the time stratum (ie, a month) still possibly existed, and might confound the associations between air pollution and hospital readmissions for HF. Finally, since we conducted this study among older adults who were admitted in a single megacity in China, it should be cautious when generalising our results to other populations or regions (eg, other cities, rural areas).

In conclusion, our study provides novel evidence that exposure to ambient NO_2 is significantly associated with an increased odds of hospital readmissions for HF among post-discharge patients with hypertension, which may lead to substantial excess hospital readmissions in older Chinese adults. These findings highlight a potential approach to prevent HF readmissions for post-discharge patients with hypertension by reducing exposure to ambient NO_2. Future investigations are needed to confirm our results and explore potential susceptible populations.

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Contributors RX searched the literature, conducted the data analysis, interpreted the data and drafted the manuscript. QT acquired the data and drafted the manuscript. JW acquired the data and conducted the data analysis. CS acquired the data. YL designed the study, acquired the data, directed the study's implementation, designed the analytical strategy and obtained the funding. All authors critically revised the manuscript. YL and WX share joint correspondence in this work and are responsible for the overall content as guarantors.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Ethical Committee of School of Public Health, Sun Yat-sen University, and has conformed to the principles embodied in the Declaration of Helsinki. Because the clinical data used in this study were historically collected, and the identity information on the study subjects was confidential to all research investigators, the informed consent was waived.

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Data availability statement Data are available in a public, open access repository. The air pollution data are available at: https://weijing-rs.github.io/product.html. The clinical and meteorological data are not publicly available.

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