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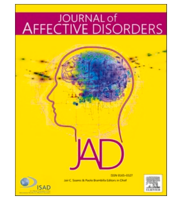

Research paper

Association of short-term exposure to ambient fine particulate matter and ozone with outpatient visits for anxiety disorders: A hospital-based case-crossover study in South China

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A R T I C L E   I N F O

Keywords:
Anxiety disorders
Fine particulate matter
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Case-crossover study

A B S T R A C T

Background: The short-term adverse effects of ambient fine particulate matter ($PM_{2.5}$) and ozone (O_3) on anxiety disorders (ADs) remained inconclusive.
Methods: We applied an individual-level time-stratified case-crossover study, which including 126,112 outpatient visits for ADs during 2019–2021 in Guangdong province, China, to investigate the association of short-term exposure to $PM_{2.5}$ and O_3 with outpatient visits for ADs, and estimate excess outpatient visits in South China. Daily residential air pollutant exposure assessments were performed by extracting grid data (spatial resolution: 1 km × 1 km) from validated datasets. We employed the conditional logistic regression model to quantify the associations and excess outpatient visits.
Results: The results of the single-pollutant models showed that each 10 μg/m^3 increase of $PM_{2.5}$ and O_3 exposures was significantly associated with a 3.14 % (95 % confidence interval: 2.47 %, 3.81 %) and 0.88 % (0.49 %, 1.26 %) increase in odds of outpatient visits for ADs, respectively. These associations remained robust in 2-pollutant models. The proportion of outpatient visits attributable to $PM_{2.5}$ and O_3 exposures was up to 7.20 % and 8.93 %, respectively. Older adults appeared to be more susceptible to $PM_{2.5}$ exposure, especially in cool season, and subjects with recurrent outpatient visits were more susceptible to O_3 exposure.
Limitation: As our study subjects were from one single hospital in China, it should be cautious when generalizing our findings to other regions.
Conclusion: Short-term exposure to ambient $PM_{2.5}$ and O_3 was significantly associated with a higher odds of outpatient visits for ADs, which can contribute to considerable excess outpatient visits.

1. Introduction

Anxiety disorders (ADs) constitute one of the most prevalent mental health afflictions, which have posed a considerable disease burden worldwide. Globally, ADs were responsible for nearly 28.7 million disability-adjusted life-years (DALYs), ranking the second leading cause of DALYs among all mental health disorders in 2019 (GBD 2019 Mental Disorders Collaborators, 2022). During the same year in China, ADs became a rising health concern and led to >4.6 million DALYs. As psychiatric disorders characterized by excessive nervousness, fear, and

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worry, ADs are receiving more and more attention due to their high prevalence and strong functional impacts (e.g., fitness, work productivity, interpersonal relations, and quality of life) (Javaid et al., 2023). Given ADs are widespread across the world and the corresponding disease burden is surging, it has been a prominent public health priority to uncover the possibly modifiable risk factors and adopt target intervention policies for ADs.

The risk factors for ADs are complex, including genetics, stressful or traumatic events, social support, socioeconomic status (SES), and environmental exposures (Anuk et al., 2019; Blanco et al., 2014; Isaacs et al., 2018; Xue et al., 2019). As a focal environmental issue, ambient air pollutants, particularly fine particulate matter ($PM_{2.5}$) and ozone (O_3), have become a remarkable public health challenge globally due to their harmful health impacts and high levels in many parts of the world (Liu et al., 2019b; Xu et al., 2022a, 2022b). Although multiple epidemiological studies have linked $PM_{2.5}$ and O_3 exposures with mental disorder morbidity (Braithwaite et al., 2019; Xue et al., 2019; Zhao et al., 2018; Zundel et al., 2022), the association of acute exposure to $PM_{2.5}$ and O_3 with ADs is scant and inconclusive. To date, two case-crossover studies in China have been performed on associations of acute exposure to ambient $PM_{2.5}$ and/or O_3 with outpatient visits for ADs (Li et al., 2022; Lu et al., 2020). While these studies consistently reported positive associations for $PM_{2.5}$ exposure, only one of them evaluated the association for O_3 exposure and reported null association (Lu et al., 2020). Note that these studies performed exposure assessment using air pollutant data derived from limited city-level fixed monitoring stations or coarse-resolution grid pollutant datasets, which would have inevitably contributed to misclassification in exposure assessment and led to an inaccuracy of the effect estimates. Therefore, investigations at an individual-level based on high-resolution pollutant datasets are warranted to clarify the association of $PM_{2.5}$ and O_3 exposures with outpatient visits for ADs and thereby help to formulate targeted intervention policies.

Based on clinical data from the largest Grade-A tertiary psychiatric hospital in South China, we conducted an individual-level case-crossover study, soughing to comprehensively examine the association of $PM_{2.5}$ and O_3 exposures with outpatient visits for ADs, and estimate corresponding excess outpatient visits. Stratified analysis based on sex, age, season, SES, and type of outpatient visit were assessed to discern possibly vulnerable populations.

2. Methods

2.1. Study population

By extracting electronic administrative data from the Affiliated Brain Hospital of Guangzhou Medical University, we included 12,500 patients who were from Guangdong province, China, and sought outpatient visits for ADs during 2019–2021. As an oldest Chinese psychiatric hospital established in 1898, this hospital has now become the largest Grade-A tertiary psychiatric hospital in South China. For each outpatient visit, we gathered individual information on sex, age, date of outpatient visit, type of outpatient visit, and residential address. In addition, we extracted the county-level gross domestic product (GDP) per capita data at each subject's residential address from the authoritative Guangdong Statistical Yearbook from 2020 to 2022. This study has gained approval from the Ethics Committee of the School of Public Health, Sun Yat-sen University with an exemption from informed consent.

2.2. Outcome definition

The outcome of our study was outpatient visits for ADs (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes: F40-F41) as a clinical diagnosis, which includes phobic anxiety disorders (F40) and other anxiety disorders (F41).

2.3. Study design

We employed a time-stratified case-crossover design to explore the association of short-term exposure to ambient $PM_{2.5}$ and O_3 with outpatient visits for ADs, which has been prevalently used in assessing the acute effects of environmental exposure on human health (Di et al., 2017; Liu et al., 2021; Liu et al., 2019b; Xu et al., 2022c, 2023). This design allows each case to be his or her self-control by comparing environmental exposure on the date of outpatient visits with those on control periods when outpatient visits had not occurred during the same time stratum of outpatient visits (i.e., month). In respect to each outpatient visit, the date of outpatient visit was regarded as the case day, and 3 or 4 days that occurred on the same day of week with the date of outpatient visit within the time stratum were matched as the control days. For instance, if a subject took an outpatient visit on June 15, 2020 (Monday), June 15, 2020 was designated to be the case day, while all other Mondays in June 2020 (i.e., June 1, 8, 22 and 29) were defined as the control days. Accordingly, there were 126,112 case days and 429,622 control days in our study. By this design, seasonality and mid- and long-term time variations can be controlled automatically (Bateson and Schwartz, 1999; Carracedo-Martínez et al., 2010).

2.4. Exposure assessment

Data on daily concentrations of $PM_{2.5}$, O_3, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) were derived from the ChinaHighAirPollutants datasets, which have a complete spatiotemporal coverage of Chinese mainland since 2000 and a high-resolution of 1 km × 1 km. These pollutant datasets showed good predictive performance in China, with the cross-validated coefficient of determination (R^2) of 0.92, 0.89, 0.93, 0.84, and 0.80 for $PM_{2.5}$, O_3, NO_2, SO_2, and CO (Wei et al., 2022a; Wei et al., 2021, 2023). Daily 24-h average $PM_{2.5}$, NO_2, SO_2, CO, and daily maximum 8-h average O_3 concentrations were extracted at each subject's residential address during the case and control days. In line with previous researches, the exposure period of O_3 was limited to the warm season (July to September) (Di et al., 2017; Wei et al., 2022b). Individual-level exposure from the date of outpatient visit to 3 days before, including single-day lag (lag 0-day to lag 3-day) and moving average day (lag 01-day to lag 03-day) exposures, was used as the exposure metric for each outpatient visit.

2.5. Covariates

The daily 24-h average air temperature (°C) and relative humidity (%) data at each residential address were estimated based on meteorological data provided by the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0, spatial resolution: 0.0625° × 0.0625°) (Han et al., 2020; Liu et al., 2019c; Tie et al., 2022). We gathered data on public holidays during the study period from holiday arrangements issued by the General Office of the State Council of China. To consider the potential confounding effects of COVID-19 pandemic, the year of outpatient visits was regarded as a potential covariate in our study. Individual-level time-invariant confounders (i.e., sex, age, chronic diseases) tended to remain stable during a short term (e.g., the month of outpatient visits), thereby, they were not incorporated as covariates in further analysis (Janes et al., 2005).

2.6. Statistical analysis

We employed the conditional logistic regression model to explore the association of short-term ambient $PM_{2.5}$ and O_3 exposures with outpatient visits for ADs. In the main model, we included exposure to each pollutant as a continuous variable and adjusted for covariates, including air temperature (lag 03-day; a natural cubic spline with 6 degrees of freedom [*df*]), relative humidity (lag 03-day; $df = 3$), and year of outpatient visits (a categorical variable) (Liu et al., 2019a). The association for each pollutant was estimated by percent change in odds of outpatient visits ([OR − 1] × 100%) and the 95 % confidence interval (CI). Furthermore, we incorporated each pollutant as a natural cubic spline ($df = 3$) to fit nonlinear models and visualize exposure-response curves, aiming at exploring possible nonlinear associations with the combination of likelihood ratio tests.

Based on the above association estimates, we then quantified the corresponding excess outpatient visits (i.e., excess fraction and number) attributable to exposure to $PM_{2.5}$ and O_3. Both of them were calculated according to the minimum air pollutant exposure levels, the 2021 World Health Organization (WHO) air quality guidelines (AQG 2021), and the China ambient air quality standards (GB 3095-2012), separately. The calculation method has been described detailedly in our previous published studies (Liu et al., 2022; Xu et al., 2022a, 2022b, 2023).

Stratified analyses were carried out to determine the possibly vulnerable populations by sex (male and female), age (based on the mean value of age; ≤50 years and >50 years), season at outpatient visit (warm [July to September] and cool [December to February]), SES (low: ≤the median GDP per capita and high: >the median GDP per capita), and type of outpatient visit (first outpatient visit and recurrent outpatient visit). Two-sample z test was applied to compare stratum-specific estimates of associations (Altman and Bland, 2003).

Several sensitivity analyses were conducted to test the robustness of our results as follows. First, based on the main model for each pollutant (e.g., single-pollutant model: O_3), we separately included other pollutants with a Spearman's correlation coefficient lower than 0.6 (e.g., $PM_{2.5}$, SO_2, NO_2, CO) by a natural cubic spline function with 3 df in the main model to construct its corresponding 2-pollutant models (e.g., O_3 + $PM_{2.5}$, O_3 + SO_2, O_3 + NO_2, O_3 + CO) (Liu et al., 2021). Second, we adjusted the df of air temperature to 3 in the models. Third, we specifically focused on outpatient visits in 2019 and 2021, when the COVID-19 pandemic did not occur or remained stable, in order to eliminate the possible impacts of COVID-19 pandemic. Fourth, we only included subjects who lived in Guangzhou city in the analysis. Fifth, we further adjusted for public holiday as a binary variable to consider its underlying impact. Statistical analyses were implemented in R 4.3.1. A 2-sided p-value <0.05 was deemed statistically significant.

3. Results

There were 126,112 outpatient visits for ADs (case days; 12,500 patients) with 429,622 control days in this study, of whom 75,093 were female, 66,644 aged >50 years, 112,789 visited in cool season, and 95,501 lived in Guangzhou city. The mean (standard deviation [SD]) age of study population at outpatient visits was 50.1 (18.1) years (Table 1; Fig. 1B). Summary statistics of daily ambient air pollutants and meteorological conditions on the case day show median $PM_{2.5}$, O_3, air temperature, and relative humidity levels of 22.5 μg/m^3, 114.5 μg/m^3, 25.4 °C and 75.7 %, respectively (Table S1). Fig. 1C–D presents the spatial distribution of ambient $PM_{2.5}$ and O_3 concentrations in Guangdong province, China during 2019–2021. Ambient air pollutants and weather conditions were moderately correlated (Table S1; all p <0.05). Specifically, for $PM_{2.5}$ exposure, positive correlation was found with O_3, but negative correlation was found with weather conditions; for O_3 exposure, positive correlation was found with air temperature, while negative correlation was found with relative humidity.

Table 1
Characteristic of study population.

Characteristic	N (%)
No. of AD patients	12,500
No. of case days	126,112
No. of control days	429,622
Sex	
Male	51,019 (40.5)
Female	75,093 (59.5)
Age, year	
Mean (SD)	50.1 (18.1)
Median (IQR)	51.4 (30.1)
≤50	59,468 (47.2)
>50	66,644 (52.8)
Socioeconomic status	
Low	13,323 (10.6)
High	112,789 (89.4)
Type of outpatient visit	
First outpatient visit	12,500 (9.9)
Recurrent outpatient visit	113,612 (90.1)

ADs, anxiety disorders; IQR, interquartile range; SD, standard deviation.

Fig. 2 and Table S2 show the association of short-term exposure to ambient $PM_{2.5}$ and O_3 with outpatient visits for ADs. In single-pollutant models, $PM_{2.5}$ and O_3 exposures were significantly associated with an increased odds of outpatient visits for ADs. The association appeared strongest at lag 01-day and lag 02-day for $PM_{2.5}$ and O_3, respectively. Each increase of 10 μg/m^3 in $PM_{2.5}$ exposure at lag 01-day and O_3 exposure at lag 02-day was significantly associated with a 3.14 % (95 % CI: 2.47 %, 3.81 %) and 0.88 % (0.49 %, 1.26 %) increase in odds of outpatient visits. These associations were slightly diminished but still significant in 2-pollutant models (Fig. 2). The exposure-response curves showed that the associations between air pollution exposure and odds of outpatient visits were almost linear, though significant differences between linear and nonlinear models for $PM_{2.5}$ exposure were detected by the likelihood ratio test (p <0.001; Fig. 3).

Excess outpatient visits attributable to acute $PM_{2.5}$ and O_3 exposures are displayed in Table 2. A total of 7.20 % (95 % CI: 5.74 %, 8.62 %) and 8.93 % (5.14 %, 12.55 %) of outpatient visits, corresponding to 9076 (7244, 10,870) and 3789 (2181, 5323) outpatient visits were attributed to short-term $PM_{2.5}$ and O_3 exposures, respectively. When employing the 2021 WHO AGQs as reference, an estimated 3.47 % (95 % CI: 2.76 %, 4.16 %) and 2.62 % (1.49 %, 3.71 %) of outpatient visits were due to $PM_{2.5}$ and O_3 exposures, respectively. When applying the China ambient air quality standard values to calculate the excess outpatient visits, only 0.04 % (95 % CI: 0.03 %, 0.05 %) and 0.57 % (0.32 %, 0.81 %) of visits was attributable to $PM_{2.5}$ and O_3 exposures, respectively. All of these estimated excess outpatient visits decreased slightly when estimated using the effect estimates derived from the 2-pollutant models.

Stratified analyses show that the associations of exposure to $PM_{2.5}$ with odds of outpatient visits for ADs were stronger among adults aged >50 years old, especially in cool season, and slightly higher associations for O_3 exposure were observed among subjects with recurrent outpatient visits (p for difference <0.05; Table 3). No statistically significant difference of effect estimates was observed across sex or SES. Sensitivity analyses achieved by changing the df of the air temperature to 3 in the models, restricting analysis to outpatient visits in 2019 and 2021, restricting analysis to subjects lived in Guangzhou city, and adjusting for public holidays in the models all gave similar results (Figs. S1–S4 and Tables S3–S6). The results of 2-pollutant models in Table S7 and Fig. S5 showed that the associations for O_3 remained after adjusting for NO_2 and SO_2 and become slightly weaker or insignificant when adjusting for CO.

4. Discussion

This hospital-based case-crossover study in South China revealed that short-term exposure to ambient $PM_{2.5}$ and O_3 was significantly associated with an increased odds of outpatient visits for ADs. Each increase of 10 μg/m^3 in $PM_{2.5}$ and O_3 exposures was associated with a 3.14 % and 0.88 % increase in odds of outpatient visits. We estimated that up to 7.20 % and 8.93 % of outpatient visits was attributable to exposure to $PM_{2.5}$ and O_3, respectively, whereas improving air quality to the WHO or China standards would reduce up to 3.47 % and 2.62 % of outpatient visits for $PM_{2.5}$ and O_3, respectively. People aged >50 years old had higher susceptibility to $PM_{2.5}$ exposure, especially in cool season, and people with recurrent outpatient visits were more susceptible to

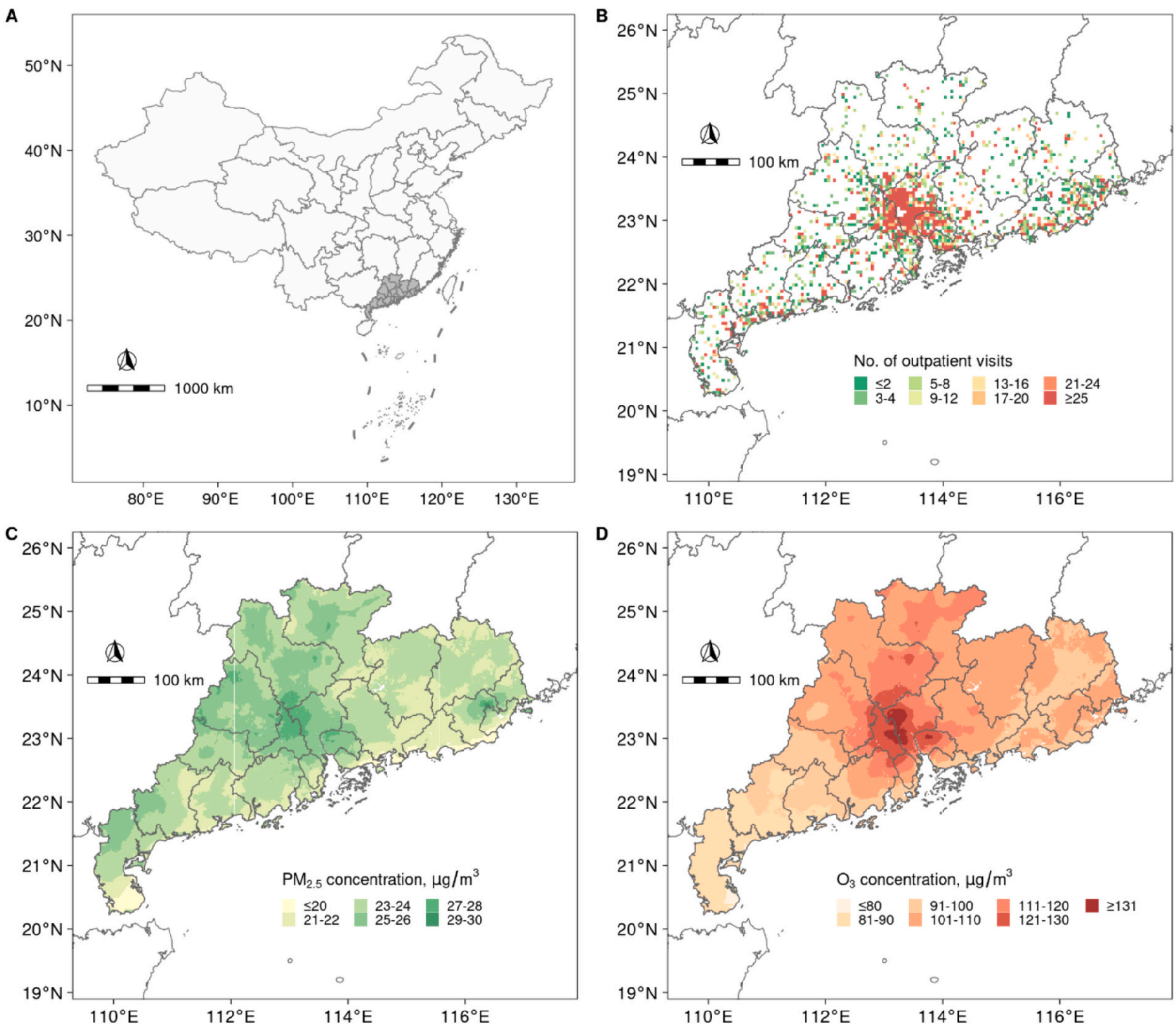

Fig. 1. Spatial distribution of study population, ambient $PM_{2.5}$, and O_3 in Guangdong province, China, during 2019–2021.
O_3, ozone; $PM_{2.5}$, fine particulate matter.

O_3 exposure.

To date, two studies have evaluated the association of acute $PM_{2.5}$ and O_3 exposures with outpatient visits for ADs and the findings were inconsistent (Li et al., 2022; Lu et al., 2020). Both of these two case-crossover studies in multi-cities in China found significant associations between $PM_{2.5}$ exposure and an increased odds of outpatient visits for ADs, which were both smaller than ours (percent change in odds for each 10 μg/m^3 increase in $PM_{2.5}$ exposure: 0.972 % and 1.51 %) (Li et al., 2022; Lu et al., 2020). For O_3 exposure, only one of these two case-crossover studies evaluated its association with outpatient visits for ADs, and failed to show any association (Lu et al., 2020). Notably, we observed significantly robust associations of short-term O_3 exposure with outpatient visits for ADs in our study. The inconsistency of findings among previous researches and ours can be attributed to the difference in population features, exposure assessment, analytical strategy, and statistical power.

Ambient O_3 is a major gaseous air pollutant in summer season, and its concentration continues to increase in the context of global warming recently (Zhang et al., 2018). Exploring the mental health effects of O_3 exposure is necessary and has important implications for public health. However, the association of short-term exposure to ambient O_3 with outpatient visits for ADs remained largely unclear. Our study is the first to provide more accurate individual-level support for the negative effect of short-term O_3 exposure on outpatient visits for ADs, suggesting that acute exposure to O_3 is likely to be a modifiable risk factor for ADs. Additionally, exposure to O_3 may contribute to substantial outpatient visits (up to 8.93 %); however, reducing the O_3 exposure level to the WHO and China standards could only avoid up to 3.47 % and 2.62 % of visits, respectively. These findings indicate that current WHO and China air quality guidelines may be insufficient to protect people from ADs, which may need a more comprehensive re-evaluation.

Stratified analysis revealed stronger associations in short-term exposure to $PM_{2.5}$ with outpatient visits for ADs among adults aged >50 years old and in cool season, which has not been identified in previous studies. It is possible that older adults tended to be exposed to $PM_{2.5}$ even on highly polluted days, and were more likely to experience the death of spouses or work pressures that can lead to long-term adverse consequences for people's mental health (Boyle et al., 2011; Lu et al., 2020). Furthermore, the higher prevalence of co-existing comorbidities may be another reason for the observed stronger associations in older adults under ambient air pollution exposure (Shumake et al., 2013). The seasonal patterns where positive associations for $PM_{2.5}$ found in cool season is probably because the common usage of heating facilities (e.g., coal, oil, diesel, or wood burn), well-known to produce much particulate matter, may cause higher $PM_{2.5}$ concentrations in winter than that in summer. Besides, $PM_{2.5}$ is a mixed air pollutant and its toxicity varies by its components. As the $PM_{2.5}$ composition may change seasonally, the $PM_{2.5}$-related mental health effects may differ

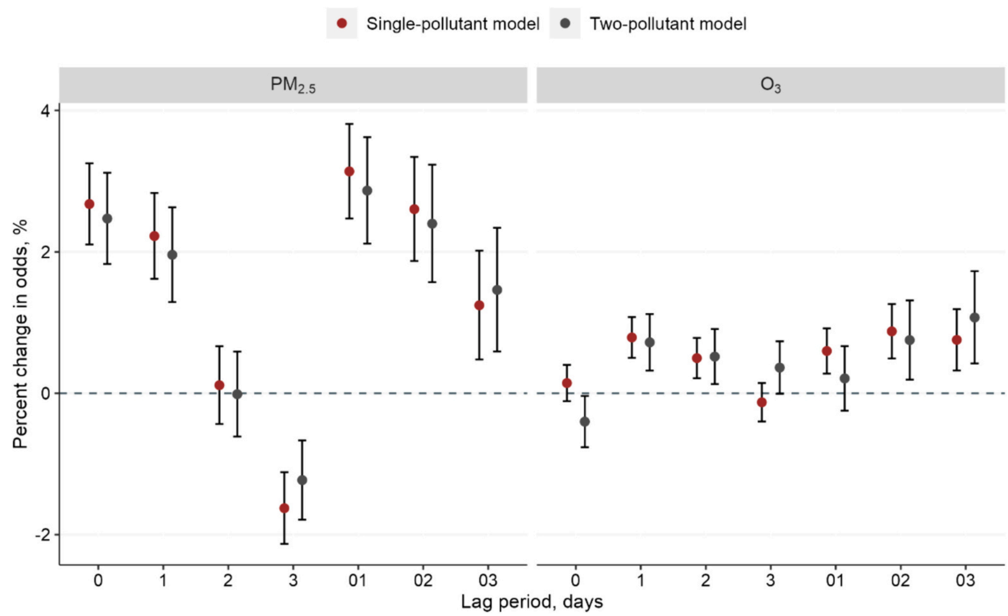

Fig. 2. Association of exposure to ambient $PM_{2.5}$ and O_3 with outpatient visits for ADs at different lag days.
ADs, anxiety disorders; O_3, ozone; $PM_{2.5}$, fine particulate matter.

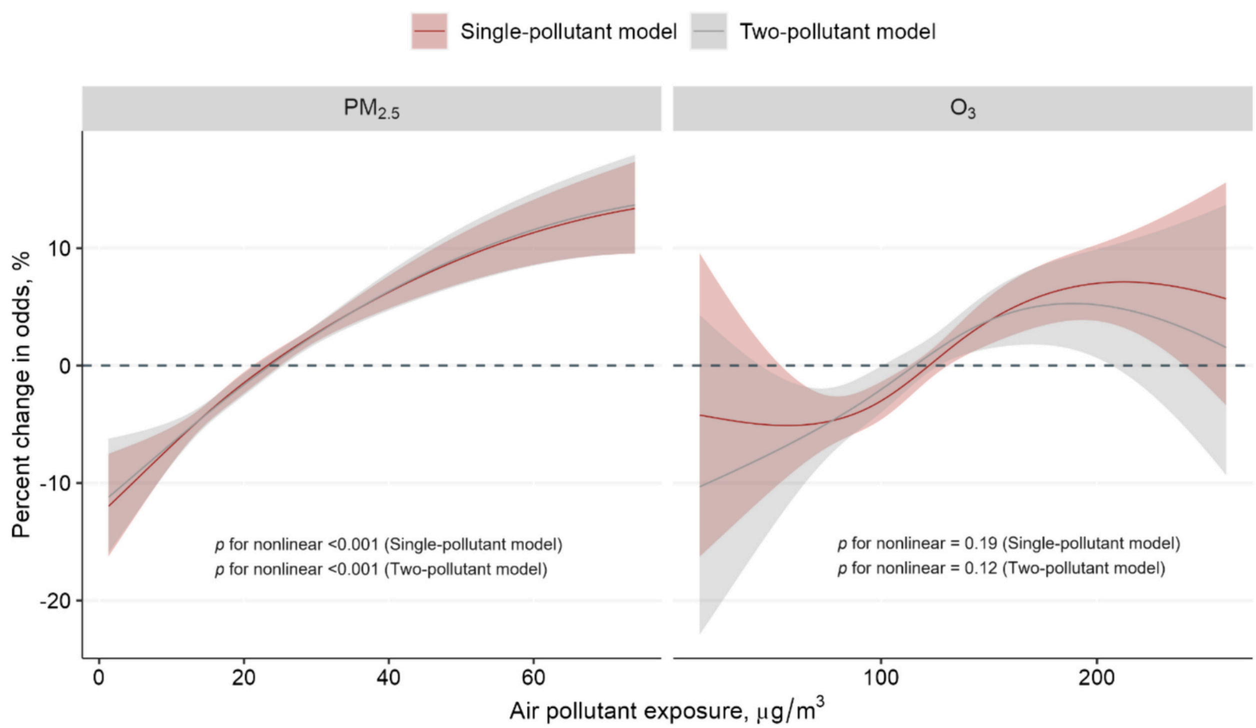

Fig. 3. Exposure-response curve of the association of exposure to ambient $PM_{2.5}$ and O_3 with outpatient visits for ADs.
ADs, anxiety disorders; O_3, ozone; $PM_{2.5}$, fine particulate matter.

across seasons (Peng et al., 2009). Additionally, the observed higher associations among subjects with recurrent outpatient visits can possibly be explained by the difference in the clinical profile of first-onset and recurrent psychiatric episodes (McIntyre et al., 2016). Patients with recurrent anxiety generally display an overall increased severity and poorer clinical outcomes, which can increase their susceptibility when exposed to O_3 pollution. Nonetheless, more investigations are warranted to assist in explaining the difference in associations across different subgroups.

Although the exact biological mechanism underlying the associations of ambient $PM_{2.5}$ and O_3 exposures with ADs is yet to be elucidated, several postulated mechanisms may help explain the observed associations in our study. Previous toxicological studies revealed that exposure to particulate matter may cause inflammation and oxidative stress, and these pathophysiologic changes can further conduce to the incidence and severity of anxiety in animals (de Oliveira et al., 2007; Hou and Baldwin, 2012; Patki et al., 2013; Salim et al., 2012). This evidence was consistent with findings of epidemiological studies that

Table 2
Excess fraction and number of excess outpatient visits for ADs attributable to exposure to ambient $PM_{2.5}$ and O_3 in single- and two-pollutant models.

Excess outpatient visits	Overall[a]	WHO[b]	China[c]
Excess fraction, %			
$PM_{2.5}$	7.20 (5.74, 8.62)	3.47 (2.76, 4.16)	0.04 (0.03, 0.05)
$PM_{2.5}$ + O_3	6.61 (4.96, 8.23)	3.18 (2.38, 3.97)	0.04 (0.03, 0.05)
O_3	8.93 (5.14, 12.55)	2.62 (1.49, 3.71)	0.57 (0.32, 0.81)
O_3 + $PM_{2.5}$	7.73 (2.06, 13.03)	2.26 (0.60, 3.86)	0.49 (0.13, 0.84)
Number of excess outpatient visits, n			
$PM_{2.5}$	9076 (7244, 10,870)	4376 (3486, 5250)	54 (43, 64)
$PM_{2.5}$ + O_3	8336 (6252, 10,373)	4016 (3006, 5008)	49 (37, 61)
O_3	3789 (2181, 5323)	1111 (634, 1575)	241 (137, 344)
O_3 + $PM_{2.5}$	3281 (876, 5525)	959 (252, 1637)	208 (54, 358)

ADs, anxiety disorders; O_3, ozone; $PM_{2.5}$, fine particulate matter; WHO, World Health Organization.

[a] Estimated by using the minimum exposure level as the reference level. The reference level of $PM_{2.5}$ and O_3 was 1.3 μg/m^3 and 16.0 μg/m^3, respectively.

[b] Estimated by using the 2021 WHO air quality guideline values as the reference level. The reference level of $PM_{2.5}$ and O_3 was 15 μg/m^3 and 100 μg/m^3, respectively.

[c] Estimated by using the ambient air quality standards in China as the reference level. The reference level of $PM_{2.5}$ and O_3 was 75 μg/m^3 and 160 μg/m^3, respectively.

Table 3
Association of exposure to ambient $PM_{2.5}$ and O_3 with outpatient visits for ADs, stratified by sex, age, season at outpatient visit, socioeconomic status, and type of outpatient visit.

Stratification variable	Percent change in odds, % (95 % CI)	
	$PM_{2.5}$	O_3
Sex		
Male	3.57 (2.51, 4.64)	0.55 (-0.05, 1.16)
Female	2.86 (2.00, 3.72)	1.09 (0.59, 1.59)
p value[a]	0.31	0.18
Age		
≤50 year	2.32 (1.32, 3.33)	0.74 (0.17, 1.32)
>50 year	3.73 (2.84, 4.63)	0.97 (0.46, 1.49)
p value[a]	0.04	0.56
Season at outpatient visit		
Warm (July to September)	3.33 (1.76, 4.93)	0.88 (0.49, 1.26)
Cool (December to February)	5.99 (5.01, 6.97)	–
p value[a]	0.01	–
Socioeconomic status		
Low	3.67 (0.74, 6.70)	-0.42 (-2.15, 1.34)
High	3.09 (2.41, 3.78)	0.98 (0.58, 1.38)
p value[a]	0.71	0.13
Type of outpatient visit		
First outpatient visit	3.30 (1.17, 5.47)	-0.69 (-1.65, 0.27)
Recurrent outpatient visit	3.01 (2.31, 3.72)	1.18 (0.76, 1.60)
p value[a]	0.80	0.001

ADs, anxiety disorders; CI, confidence interval; O_3, ozone; $PM_{2.5}$, fine particulate matter.

[a] *p* value was estimated by the 2-sample *z* test.

linked markers of oxidative stress and inflammation to symptoms of anxiety in people (Liukkonen et al., 2011; Pitsavos et al., 2006; Sørensen et al., 2003). Additionally, O_3 has been reported to significantly impact emotional regulation functions of human brain (Thomson, 2019). Inhaled O_3 could result in oxidative damage to the central nervous system by inducing lipid peroxidation and dopaminergic neurons death, triggering the synthesis of inflammatory factors, and subsequently increasing neurotoxicity by prompting abnormal circulating factors to enter the human brain (Martínez-Lazcano et al., 2013). Besides, after inhalation, O_3 can activate the hypothalamic-pituitary-adrenal (HPA) axis and promote the release of glucocorticoids and stress hormones, which have been recognized to act as an essential role in the mental disorder pathological process (Henriquez et al., 2019).

Our study had some strengths. The major strength is the application of high-resolution grid air pollutant datasets. In this study, we carried out air pollutant exposure assessment at the individual-level by extracting pollutant data from high-resolution validated grid datasets at each subject's residential address (1 km × 1 km). Unlike three related studies that performing exposure assessment by using pollutant data from city-level monitor stations or grid pollutant datasets with coarse resolution (15 km × 15 km), the application of our high-resolution grid pollutant datasets enhanced the accuracy of our exposure assessments and helped mitigate the exposure misclassification. Second, this is the largest study on short-term ambient air pollution exposure and outpatient visits for ADs, of which the clinical data were from the largest Grade-A tertiary psychiatric hospital in South China and were collected under strict quality control. The large sample size of the high-quality clinical data provided adequate statistical power for us to accurately estimate the adverse effects not only in the whole population but also in stratified analyses. Third, the time-stratified case-crossover design facilitates the causal inference by controlling for possible effects of time-trend bias, day of week, seasonality, and time-invariant factors at the individual-level.

Our study also has certain limitations. First, owing to the absence of personal behavior patterns information (e.g., the application of air conditioning, air purifiers, or wearing a mask outdoors), exposure misclassification still existed, even though our individual-level air pollution exposure assessment was performed based on a high-resolution grid dataset. However, it has been reported that this misclassification tends to be nondifferential and would not substantially bias our results (Whitcomb and Naimi, 2020). Second, though time-invariant confounders can be autonomically controlled by the study design, the existence of confounders that may change transiently within the time stratum (e.g., medicine usage and stressful or traumatic events) cannot be thoroughly avoided and may lead to certain residual bias. Third, we tried our best to control for the possible influences of the COVID-19 pandemic in the statistical analyses by adjusting for the year in outpatient visits and restricting analysis to subjects visited in 2019 and 2021; nonetheless, the uncontrolled influence of COVID-19 pandemic on outpatient visit behaviors made it challenging for us to accurately quantify the associations. Forth, due to lack of data on regular visits, we were unable to control its potential effects on our estimates. Finally, the study subjects from one single hospital in Guangzhou limited the generalizability of our findings.

In this hospital-based case-crossover study in South China, we found that short-term exposure to ambient $PM_{2.5}$ and O_3 was associated with a higher odds of outpatient visits for ADs, which was attributable to considerable excess outpatient visits. These findings add to the important evidence that air pollution is a modifiable and preventable risk factor for ADs, and highlight the urgent need to prevent ADs by reducing $PM_{2.5}$ and O_3 exposures.

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CRediT authorship contribution statement

Ruijun Xu: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Lu Luo:** Writing – review & editing, Writing – original draft, Formal analysis. **Ting Yuan:** Writing – review & editing. **Wangni Chen:** Writing – review & editing. **Jing Wei:** Data curation. **Chunxiang Shi:** Data curation. **Sirong Wang:** Writing – review & editing. **Sihan Liang:** Writing – review & editing. **Yingxin Li:** Writing – review & editing. **Zihua Zhong:** Writing – review & editing. **Likun Liu:** Writing – review & editing. **Yi Zheng:** Writing – review & editing. **Xinyi Deng:** Writing – review & editing. **Tingting Liu:** Writing – review & editing. **Zhaoyu Fan:** Writing – review & editing. **Yuewei Liu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization. **Jie Zhang:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.06.007.

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