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Relationship between exposure to ozone and exacerbation requiring hospital admission among patients with asthma: a case-control study in central Taiwan

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ABSTRACT

Objective The convergence of asthma and air pollutants in ageing populations is currently a growing health issue worldwide, and hence there is an essential need to investigate the association between exposure to air pollution, particularly ozone (O_3), and exacerbation requiring admission in patients with asthma.

Setting A case-control study at a tertiary referral hospital in central Taiwan.

Participants We used an asthma cohort, which included 11 400 patients with asthma, for the period 2006–2018 at Taichung Veterans General Hospital.

Primary and secondary outcome measures We identified patients who had admitted for exacerbation as cases and selected patients with asthma without exacerbation, matching (1:4) the cases for age, gender and season of exacerbation, as controls. Data on hourly level of air pollutants were obtained from the Taiwan Environmental Protection Administration. We used conditional logistic regression and calculated adjusted ORs (adjORs) with 95% CIs.

Results We enrolled 11 400 participants with asthma, and 4.4% (501) of them had been admitted for exacerbation. Participants with asthma with exacerbation requiring hospitalisation were exposed to a higher level of O_3 8-hour daily maximum (adjOR 1.009, 95% CI 1.001 to 1.016) and were more likely to have high Charlson Comorbidity Index (CCI ≥3; adjOR 2.198, 95% CI 1.729 to 2.794) and asthma-chronic obstructive pulmonary disease overlap (adjOR 4.542, 95% CI 3.376 to 6.611) compared with those without exacerbation. The aforementioned associations between exacerbation of asthma requiring hospitalisation and exposure to O_3 were similar when defined by either O_3 1-hour daily maximum or O_3 24-hour average. Moreover, the O_3 relevant exacerbation of asthma mainly existed in those aged older than 65 years and patients with medical comorbidities, including gastrointestinal diseases, cardiovascular diseases, neurological diseases, diabetes and renal disease.

Conclusions Our findings highlight the need for vigilance of exposure to O_3 among elderly with asthma, particularly those with medical comorbidities. Further studies are warranted to investigate the underlying mechanisms.

Strengths and limitations of this study

- ► This study linked a hospital-based asthma cohort with a dataset of air pollutants across Taiwan.
- ► We included a relatively large sample size of people with asthma aged older than 65 years.
- ► We employed a case-control study design to determine whether exposure to air pollutant was associated with exacerbation of asthma.
- ► This was a single-centre study; hence, external validation is needed.

BACKGROUND

Asthma affects nearly 339 million people worldwide in 2016, with a rise in prevalence of 3.5% compared with that in 2006.[1] Exacerbation is critical in patients with asthma, and it is estimated that approximately 12.5% in the USA and 8.4% of persons with asthma in the UK had one or more asthma exacerbations between 2009 and 2011.[2] Growing pieces of evidence have shown that environmental triggers, including airborne allergens and air pollutants, may lead to aggravation of allergic diseases including asthma,[3] and exacerbation of asthma has increasingly been found to be associated with exposure to air pollutants, mainly particulate matter (PM) and ozone (O_3).[4 5]

O_3, a solar intensity-dependent air pollutant, is currently an increasing health hazard worldwide, partly due to the warming climate.[6–8] Exposure to O_3 is estimated to be responsible for 470 000 respiratory deaths per year worldwide and may increase up to 70% by 2050 in the UK.[6] Di *et al*, investigating the US Medicare population with approximately 60 million people 65 years of age or older between 2000 and 2013, reported that an increase of 10 ppb in O_3 was associated with an increase in all-cause mortality of 1.1% (95% CI 1.0 to 1.2).[7]

Accumulating pieces of evidence have shown that exposure to O_3 correlated with exacerbation of asthma.[8–10] Goodman *et al* investigated the effects of O_3 on asthma exacerbation in Texas and found a positive association between increased O_3 exposure and hospital admission due to asthma in patients aged 5–14 years.[9] Sacks *et al*, using a time-stratified case-crossover study in North Carolina, also reported a positive association between O_3 and asthma-associated emergency department visits in children (5–17 years of age).[10] However, in most studies investigating the impact of O_3 on asthma exacerbation, the target population is children with asthma.[11–14] The effect of O_3 on asthma in adulthood remains unclear.

Given the distinct pathogenesis of asthma in the elderly,[15] there is a crucial need to address the impact of air pollutant on exacerbation of asthma in the elderly. In the present study, we linked the database of asthma cohort at Taichung Veterans General Hospital (TCVGH) and data on hourly levels of air pollutants across Taiwan obtained from Taiwan's Environmental Protection Administration (EPA). We conducted a case-control study using data obtained from the two aforementioned datasets between 2006 and 2018 to determine the associations between exposure to air pollutants and asthma exacerbation requiring admission.

METHODS

Study population

This retrospective study was conducted at TCVGH, a tertiary-care referral hospital with approximately 1500 beds in central Taiwan. Data regarding demographic information, Charlson Comorbidity Index (CCI), ambulatory/inpatient diagnoses and medications were obtained from the TCVGH clinical data warehouse.[16] We enrolled patients with asthma, defined by having at least three ambulatory visits or one hospital admission with a diagnosis of asthma, at TCVGH between 2006 and 2018. Patients with asthma and had at least three ambulatory visits with a diagnosis of chronic obstructive pulmonary disease (COPD) was classified as asthma-COPD overlap (ACO).[17]

Measurement of exposure to air pollutants

EPA has established approximately 60 air quality monitoring stations across Taiwan, and we used the hourly levels of air pollutants 1 day prior to the index date of the nearest air quality monitoring station for analyses.[18] The air pollutants analysed in this study included particulate matter <2.5 µm in size (PM2.5), particulate matter <10 µm in size (PM10), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and carbon monoxide (CO). Notably, unlike the gradual decline of O_3 in countries such as the USA and France,[19 20] increased level of O_3 remains a major concern in Taiwan and countries located in the tropical and subtropical areas.[21] Previous studies including our previous study have shown that the completeness of the Taiwan's air quality data appears to be high, with the exception of eastern Taiwan, which had some missing data; therefore, the data on air pollutants in this study should be considered complete given that we used data for central Taiwan.[22 23]

Study design

This study employed matched case-control design, and we used a strict definition of asthma-specific hospitalisation, that is, the primary admission diagnosis was asthma and systemic corticosteroid was administered on admission, to define exacerbation in patients with asthma.[24] We matched the index season to mitigate the potential season-relevant confounding effect in the present study. Among the asthma cohort, we randomly selected those without exacerbation matching (1:4) by sex, age (±3 years) and the index season.

Statistical analysis

The numbers of patients were expressed as percentages for categorical variables, and mean±SD was used for continuous variables. Categorical variables were compared using the χ^2 test or the Fisher's exact test, and continuous variables were compared using the t-test. Variables were considered as candidates for inclusion in the multivariable model if the associated univariable p value was lower than 0.20.[25] The association between the risk for exacerbation of asthma and exposure to air pollutants was examined using a multivariable conditional logistic regression analysis after adjusting for age, gender and index season. Adjusted OR (adjOR) and the corresponding 95% CI for each variable were presented. In the present study, we used three distinct indicators to address the impact of O_3, namely, 1-hour daily maximum concentrations, 8-hour daily maximum concentrations and 24-hour average concentrations.[26] All data were analysed using the Statistical Analysis Software program, V.9.3 (SAS Institute). A p value <0.05 was considered statistically significant.

RESULTS

Demographic data of enrolled participants

A total of 11 400 patients with asthma were eligible for analyses, and 4.4% (501) of them had been admitted for exacerbation of asthma during the study period. We selected comparable controls by matching (1:4) for age (±3 years), gender and index season. In total, 1988 matched controls were selected. Four (0.8%, 4/501) patients with asthma with exacerbation were excluded due to the lack of matched control subjects (figure 1). We found that patients with asthma with exacerbation requiring hospitalisation had a higher CCI (3.72±2.99 vs 2.68±2.56, p<0.01), exposure to PM (PM2.5, 28.92±17.73 vs 27.45±16.49 mg/m^3, p=0.09; PM10, 51.26±31.49 vs 48.87±26.05 mg/m^3, p=0.16), were more likely to have ACO (28.4% vs 9.5%, p<0.01), and exposure to a higher level of O_3 (O_3 1-hour daily maximum, 57.24±20.25 vs 55.24±20.94 ppb, p=0.05; O_3 8-hour daily maximum,

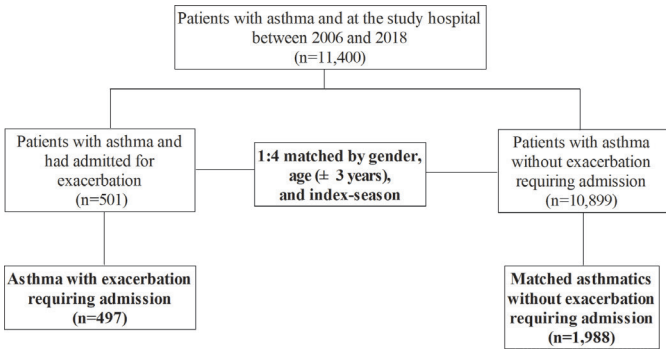

Figure 1 Flowchart of subject enrolment.

46.42±16.91 vs 44.54±17.28 ppb, p=0.03; O_3 24-hour average, 28.66±10.26 vs 27.53±10.74, p=0.03) (table 1).

Association between variables and incident asthma exacerbation requiring admission

Among the three indicators of O_3 exposure, O_3 8-hour daily maximum is currently the representative indicator for the impact of exposure to O_3 on exacerbation of asthma; therefore, we used O_3 8-hour daily maximum in the following multivariable logistical regression.[26] Intriguingly, in contrast to the positive association between the level of O_3 and hot summers, we found the level of O_3 was lower in the summer compared with levels seen in the other seasons (online supplemental figure 1). Similar findings with regard to a low O_3 level in summer have been reported in previous Taiwanese studies, and meteorological conditions and frequent typhoons might explain the low levels of O_3 in summer in central Taiwan.[27 28] Therefore, we further matched the index season in this study. A conditional logistic regression model, adjusted for age, sex and index season, showed that patients with asthma with exacerbation requiring hospitalisation had a higher O_3 8-hour daily maximum (adjOR 1.009, 95% CI 1.001 to 1.016) and were more likely to have ACO (adjOR 4.542, 95% CI 3.376 to 6.611) as well as high CCI score (CCI ≥3; adjOR 2.198, 95% CI 1.729 to 2.794) compared with patients with asthma without exacerbation (table 2).

Table 1 Characteristics and exposures to air pollutants of enrolled subjects with asthma

	All N=2485	Asthma with exacerbation n=497	Asthma without exacerbation n=1988	P value
Demographic data				
Age (years)	64.03±15.91	64.6±16.29	63.89±15.81	0.38
Age group				0.99
20–49	436 (17.55%)	86 (17.30%)	350 (17.61%)	
50–64	666 (26.8%)	135 (27.16%)	531 (26.71%)	
>=65	1383 (55.65%)	276 (55.53%)	1107 (55.68%)	
Sex (female)	1740 (70.02%)	348 (70.02%)	1392 (70.02%)	1.00
Index season				
Spring	735 (29.58%)	147 (29.58%)	588 (29.58%)	1.00
Summer	510 (20.52%)	102 (20.52%)	408 (20.52%)	
Autumn	535 (21.53%)	107 (21.53%)	428 (21.53%)	
Winter	705 (28.37%)	141 (28.37%)	564 (28.37%)	
Air pollutants 1 day prior to exacerbation				
PM2.5 (g/m^3)	27.74±16.75	28.92±17.73	27.45±16.49	0.09
PM10 (g/m^3)	49.3±27.24	51.26±31.49	48.87±26.05	0.16
O_3				
O_3 (1-hour maximum, ppb)	55.64±20.81	57.24±20.25	55.24±20.94	0.05
O_3 (8-hour maximum, ppb)	44.92±17.22	46.42±16.91	44.54±17.28	0.03
O_3 (24 hours average, ppb)	27.75±10.65	28.66±10.26	27.53±10.74	0.03
SO_2 (ppb)	2.83±1.34	2.85±1.35	2.82±1.34	0.67
CO (ppm)	0.41±0.19	0.41±0.19	0.40±0.19	0.39
NO_2 (ppb)	14.07±6.97	14.14±7.05	14.05±6.95	0.81
Temperature (°C)	22.32±5.35	22.57±5.29	22.25±5.37	0.24
Relative humidity (%)	72.76±8.39	72.44±8.11	72.84±8.46	0.33
Comorbidities				
ACO	329 (13.2%)	141 (28.4%)	188 (9.5%)	<0.01
CCI	2.89±2.68	3.72±2.99	2.68±2.56	<0.01
CCI ≥3	861 (34.65%)	245 (49.3%)	616 (30.99%)	<0.01

Data are presented as mean±SD and N (%).
CCI, Charlson Comorbidity Index; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM10, particulate matter <10 µm; PM2.5, particulate matter <2.5 µm; SO2, sulfur dioxide.

Table 2 Crude and adjusted ORs for the association between incident hospitalised exacerbation of asthma and variables

	Univariable analysis		Multivariable conditional regression	
Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	1.003 (0.997 to 1.009)	0.37	–	–
Sex	1.000 (0.807 to 1.239)	1.00	–	–
Season	1.000 (0.784 to 1.276)	1.00	–	–
ACO	5.121 (3.830 to 6.846)	<0.001	4.542 (3.376 to 6.11)	<0.001
CCI ≥3	2.565 (2.042 to 3.222)	<0.001	2.198 (1.729 to 2.794)	<0.001
PM2.5	1.006 (1.000 to 1.012)	0.057	0.999 (0.991 to 1.006)	0.754
O_3 (8-hour maximum)	1.007 (1.001 to 1.013)	0.020	1.009 (1.001 to 1.016)	0.025

ACO, asthma COPD (chronic obstructive pulmonary disease) overlap; CCI, Charlson Comorbidity Index; O_3, ozone; PM2.5, particulate matter <2.5 µm.

Additionally, we determined the association among distinct indicators for exposure to O_3 and found that O_3 8-hour daily maximum was highly correlated with O_3 1-hour daily maximum (r=0.96, p<0.01) and was less likely to be correlated with O_3 24-hour average (r=0.84, p<0.01) (table 3). Furthermore, we also used the O_3 1-hour daily maximum and the O_3 24-hour average as indicators for exposure to O_3, and the results were consistent with the aforementioned results using O_3 8-hour daily maximum (online supplemental tables 1 and 2). Collectively, we used distinct indicators for O_3 exposure and found that exposure to O_3 as well as a high CCI was associated with an increased risk for asthma exacerbation requiring hospitalisation.

Impacts of age and underlying comorbidities on the risk of O_3-associated exacerbation of asthma

We next determined the impacts of age and distinct comorbidities on the O_3-associated exacerbation of asthma requiring admission. We found that the O_3 relevant exacerbation of asthma mainly existed in those aged older than 65 years, and similar trends also existed in the other two age groups, 50–64 years and 20–49 years, with the relatively small case number in the present study (figure 2). With regard to the impacts of distinct underlying comorbidities on the risk of O_3-related exacerbation of asthma, we found that O_3-associated exacerbation of asthma was significantly associated with a number of comorbidities, including gastrointestinal diseases (peptic ulcer and liver disease), cardiovascular diseases (congestive heart failure, myocardial infarction, peripheral vascular disease, neurological diseases (cerebrovascular disease, dementia and hemiplegia/paraplegia), diabetes and renal disease (figure 3). These findings demonstrated the impacts of distinct comorbidities on O_3-associated exacerbation in adult patients with asthma.

DISCUSSION

In the present case-control study, we used Taiwan's EPA database and the asthma cohort at TCVGH to explore the effects of exposure to air pollutants on exacerbation requiring hospitalisation in patients with asthma. We found that exposure to O_3 and coexistent medical comorbidities were independently associated with asthma exacerbation requiring hospitalisation, particularly in those older than 65 years. These findings highlight the need for vigilance regarding exacerbation of asthma in the elderly after exposure to a high O_3 environment, particularly for those with medical comorbidities.

O_3 is a substantial and growing health concern worldwide.[8 29] Madrigano *et al*, using Bayesian hierarchical model to estimate the mortality risk that can be attributed to O_3 in 91 cities across the USA, found that a 10 ppb increase in O_3 was associated with a 0.45% increase in mortality (95% PI 0.08–0.83) in urban counties and a 0.73% increase (95% CI 0.19 to 1.26) in non-urban counties.[30] Notably, unlike the gradual decline of O_3 in countries including the USA and France,[19 20] increased level of O_3 remains a concern in the tropical and subtropical countries, including Taiwan.[21] In contrast with the gradually decreased levels of PM2.5 from 36.60 mg/m^3 in 2006 and 20.70 mg/m^3 in 2018, we found persistently elevated levels of O_3 during the study period (49.17 ppb in 2006 and 47.81 ppb in 2018) in central Taiwan (online supplemental figure 1). In line with the trend of O_3 in Taiwan, Gao *et al*, investigating the long-term trend of O_3 in

Table 3 Pearson's correlation coefficients (r^2) among the three indicators for O_3

	O_3 (1-hour maximum)	O_3 (8-hour maximum)	O_3 (24-hour average)
O_3(1-hour maximum)	1.00	0.96	0.74
O_3(8-hour maximum)	<0.01	1.00	0.84
O_3(24-hour average)	<0.01	<0.01	1.00

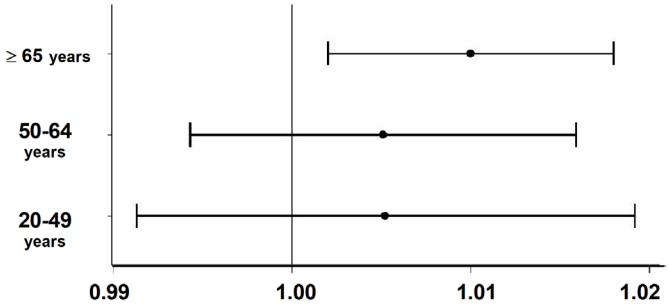

Figure 2 Association between O_3 8-hour daily maximum and risk for asthma exacerbation categorised by age group.

Shanghai, found that O_3 increased by 67%, whereas NOx decreased by 38% from 2006 to 2015.[31] Taken together, these pieces of evidence highlight the crucial need to clarify the impact of O_3 on health worldwide, particularly in tropical and subtropical areas with a soaring level of O_3 in recent decades.

Asthma in the elderly is currently a critical public health issue, especially as there has been a disproportionate increase in individuals aged older than 65 years. Indeed, asthma is increasingly being found to be an important cause of morbidity and mortality in the elderly.[15] Asthma in the elderly is a complex disease and is frequently attributed to intrinsic rather than allergic asthma. Unlike the predominant Th2 adaptive immunity in allergic asthma, environmental activation of innate immunity appears to play a crucial role in intrinsic asthma.[15] Sohn *et al* recently used Bayesian network analysis to explore risk factors for exacerbations in three adult asthma cohorts (n=1086) and found that an increase in eosinophil count was less likely to be associated with asthma exacerbation in the elderly than those in non-elderly.[32] Furthermore, Kim *et al* conducted a sputum transcriptomic analysis in 55 elderly patients with asthma and 10 elderly controls and found an increased expression of oxidative phosphorylation, unfolded protein response, myogenesis and epithelial–mesenchymal transition gene sets in the

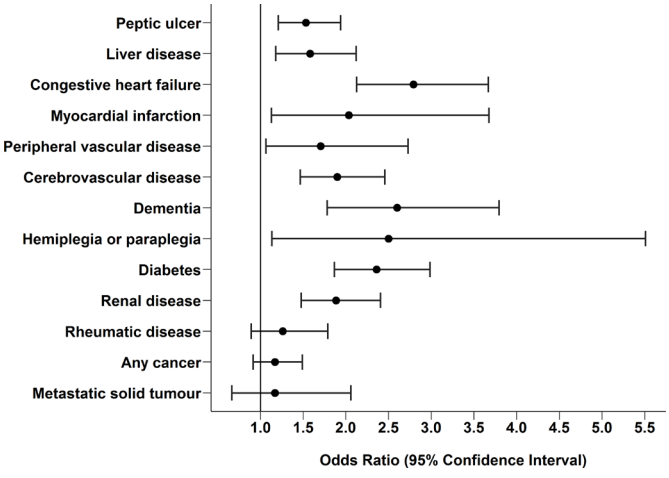

Figure 3 Association between O_3 8-hour daily maximum and risk for asthma exacerbation categorised by comorbidities.

elderly with asthma.[33] Ilmarinen *et al*, using the data of 170 adults with asthma with 12-year follow-up data, reported that elevation of serum interleukin-6 as well as C-reactive protein and multi-morbidities were associated with a negative outcome in adults with asthma.[34] Therefore, the underlying non-allergic pathway might possibly reflect coexisting comorbidities in the elderly with asthma as we have shown in the present study. Furthermore, the association between exposure to O_3 and exacerbation of asthma in the elderly as we have shown in the present study might possibly be attributed to the potential O_3-mediated augmentation of non-allergic signalling pathways, including innate lymphoid cell-2, airway mucus cell metaplasia and interleukin-33 in the airway.[35 36] Collectively, there are distinct non-allergic mechanisms underlying asthma in the elderly, and our data provide epidemiological evidence of an association between O_3 and asthma in the elderly, particularly those with coexistent comorbidities.

One recently published global study conducted in 20 countries reported crucial differences in the O_3-mortality association across countries[8]; however, few studies have been conducted in Taiwan to explore the association between O_3 and exacerbation of asthma, particularly in adult persons with asthma.[37 38] Lin *et al* explored the association between cumulative 6-day outpatient visits for asthma and three O_3 metrics, including daily 1-hour maximum, 8-hour average maximum and 24-hour average, in Taipei between 2000 and 2009.[37] The author reported that 24-hour average O_3 appeared to be the optimal O_3 metric to be associated with the outpatient visits for asthma (relative risk 1.18; 95% CI 1.00 to 1.39). The results are largely in line with the finding of the present study that showed 24-hour average O_3 was a predictor for exacerbation of asthma. Pan *et al*, using the Taiwanese National Health Insurance Research Database to investigate the effect of air pollutants on the utilisation of healthcare services among patients with asthma between 2000 and 2009 at a seasonal level, found no significant association between O_3 and asthma-associated inpatient/outpatient visits.[38] Given that the authors focused on the association between seasonal average air pollutant exposure and seasonal frequency of healthcare service, the short-term impact of O_3 on exacerbation might not be fully explored. Additionally, the study hospital is located in central Taiwan, which has a distinct air pollutant profile due to the mountainous area located to the east of the city, urbanised areas with heavy traffic, as well as a massive power station and industrial region in the western area. This unique and diverse environment warrants further investigation to determine the impact of O_3 in persons with asthma.[27]

Most previous studies, including our recently published studies, on the health impact of air pollutants have used levels of air pollutant in residential areas as a surrogate of exposure to air pollution, although this approach might not precisely reflect the exposure to air pollution among individual patients.[23 39] Some

wearable devices have been proposed to measure the precise exposure of air pollution in individual patients; however, the accuracy of measurements of O_3 obtained by wearable devices appears to be lower compared with the standardised measurement of levels of air pollutants conducted by Taiwan's EPA.[40]

There were limitations in this study. First, this was a single-centre study conducted in Taiwan, and our findings may therefore not be generalisable to other populations. Second, owing to the observational nature of this study, we were unable to make causal inferences with respect to exposure to air pollutants and the exacerbation of asthma. Third, the accuracy of asthma diagnosis is a potential concern; however, the study hospital is one of the original hospitals in the Taiwanese pay-for-performance asthma programme.[41] The diagnosis and management of patients with asthma has been continuously scrutinised. Furthermore, 89.3% (10 180/11 400) of patients with asthma had received inhaled corticosteroid, a fundamental medication in the management of asthma, and the accuracy of asthma diagnosis in this study was probably high. The prevalence of ACO and increased risk of exacerbation in patients with ACO were also consistent with previous studies including one Taiwanese population-based study.[17 42] Fourth, we focused on hospitalised exacerbation of asthma, a fundamental indicator for control of asthma, in the present study, and the severity of asthma prior to exacerbation was not assessed. Furthermore, there are some unmeasured confounding factors, such as smoking, occupation exposure and socioeconomic status; nonetheless, these factors likely did not lead to a differential error in this case-control study. Moreover, the stringent definition of asthma exacerbation requiring hospital admission may have led to an underestimation, rather than an overestimation, of the association between exposure to ozone and exacerbation of asthma.

CONCLUSIONS

The convergence of asthma and air pollutants in ageing populations is an increasing global health threat, particularly the steadily growing threat of O_3 in Asian countries, including Taiwan. In the present case-control study, we correlated data from an asthma cohort at TCVGH with data from Taiwan's EPA database to explore the effects of exposure to air pollutants on asthma exacerbation requiring hospital admission. We found that exposure to O_3 and medical comorbidities were associated with risk for exacerbation requiring hospitalisation among patients with asthma, particularly elderly individuals with asthma. The evidence presented herein suggests the need for vigilance regarding exposure to O_3 among elderly individuals with asthma, particularly those with medical comorbidities. Further studies are warranted to explore strategies aimed at reducing exposure to O_3 in high-risk individuals with asthma.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All of the data and materials are provided in the manuscript and the supplemental data.

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