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**Key Points:**

- Short-term exposure to high concentration of $PM_{2.5}$ and $NO_2$ significantly raise upper gastrointestinal bleeding (UGIB) emergency visits
- The impact of air pollution on the occurrence of UGIB emergencies is exacerbated by cold weather and among the elderly population
- The results of our study underscore the necessity for policy interventions aimed at enhancing air quality and promoting health safety

**Supporting Information:**

Supporting Information may be found in the online version of this article.

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# Association Between Short-Term Exposure to Air Pollutants and Emergency Attendance for Upper Gastrointestinal Bleeding in Hong Kong: A Time-Series Study

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**Abstract** The relationship between exposure to ambient air pollutants and emergency attendance for upper gastrointestinal bleeding (UGIB) remains inconclusive. This study examines the association between short-term exposure to various ambient pollutants and the risk of UGIB emergency attendance. Data on daily UGIB emergency attendance, ambient pollutants, and meteorological conditions in Hong Kong were collected from 2017 to 2022. A time-series study using a distributed lag non-linear model to analyze the data, considering lag days. Stratified analysis was performed based on sex, seasons, and the COVID-19 pandemic period. The burden was quantified using attributable fraction (AF) and number (AN). The study included 31,577 UGIB emergency records. Exposure to high levels of $PM_{2.5}$ significantly increased the risk of UGIB emergency attendance from lag day 3 (RR: 1.012) to day 6 (RR: 1.008). High $NO_2$ exposure also posed a significant risk from lag day 0 (RR: 1.026) to day 2 (RR: 1.014), and from lag day 5 (RR: 1.013) to day 7 (RR: 1.024). However, there was no association between UGIB and high $O_3$ levels. The attributable burden of high-concentration $NO_2$ exposure was higher compared to those of $PM_{2.5}$. Males and elderly individuals (≥65 years) faced a higher risk of UGIB emergencies, particularly during cold seasons. Our study suggests that both $PM_{2.5}$ and $NO_2$ exposure are associated with an increased risk of emergency attendance for UGIB. Ambient pollutant exposure has a stronger effect on UGIB in males and the elderly, particularly during cold seasons.

**Plain Language Summary** Our research in Hong Kong from 2017 to 2022 investigated the impact of brief exposure to air pollution on emergency visits for upper gastrointestinal bleeding (UGIB). We examined various types of air pollutants, including fine particulate matter (PM) and ozone, with a specific focus on identifying the most harmful pollutants and their temporal patterns. Our findings demonstrate that even a slight increase in levels of fine PM and nitrogen dioxide can significantly contribute to an upsurge in emergency cases of UGIB. Notably, these effects are more pronounced during colder months and in the elderly. The burden was more severe before the COVID-19 pandemic. This study underscores the direct influence of air pollution on public health and emphasizes the imperative need to enhance air quality, particularly in densely populated urban areas. Our finding could help to inform public health policies and to promote measures aiming at reducing individuals' exposure to pollutants.

## 1. Introduction

Upper gastrointestinal bleeding (UGIB), which typically refers to bleeding from the esophagus, stomach, or duodenum, remains a major clinical burden (Gralnek et al., 2015; Nahon et al., 2008; Sung et al., 2021). Furthermore, approximately 10% of UGIB patients died during their hospitalization for UGIB, which escalated to nearly 30% among patients who were hospitalized for other reasons (Hay et al., 1996). Peptic ulcer remains the most important cause of UGIB (Quan et al., 2014), which is increasingly linked to the use of drugs such as non-steroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants and selective serotonin reuptake inhibitors (W. C. Chen et al., 2017; Guo et al., 2019; Lin et al., 2013). The overall incidence of UGIB has progressively decreased in recent years as a result of both the declining prevalence of Helicobacter pylori infection and the use of potent acid-suppressive therapy (Guo et al., 2021; Laine et al., 2021).

Emerging pieces of evidence have suggested an association between exposure to air pollution and pathological conditions such as inflammatory bowel disease (IBD), rheumatoid arthritis, or Sjogren's syndrome (Y. Chen

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et al., 2022; Ding et al., 2022; Wu et al., 2021). The gastrointestinal tract can also be exposed to ambient air pollutants through the inhalation of gaseous pollutants, mucociliary clearance of particulate matter (PM) from the lungs, and contamination of food and water sources. The impact of ambient air pollutants on gastrointestinal disease remains uncertain and controversial (Gu et al., 2020; Pritchett et al., 2022). Short-term exposure to high concentrations of inhaled pollutants is believed to impact gut permeability and sensitivity to immune response. Individual ambient air pollutants such as carbon monoxide (CO), nitrogen dioxide ($NO_2$), and fine particulate matter ($PM_{2.5}$) have demonstrated a close association with IBD (Ding et al., 2022). In our cross-sectional study conducted between 2005 and 2010 in Hong Kong, it was observed that ambient air pollutants have the potential to trigger peptic ulcer bleeding and increase the risk of emergency admissions among the elderly population. However, these findings were confined to the older age group, without fully considering other factors such as the patient's sex and meteorological conditions. Further, the attributable burden of the UGIB emergency to diverse pollutants was not conducted (Tian et al., 2017). Moreover, during the recent Coronavirus disease 2019(COVID-19) pandemic, the lockdown measures have resulted in improved air quality as substantiated by the World Meteorological Organization (Organization, 2021). The impacts of these factors on UGIB emergency attendance have not been thoroughly investigated.

Given the limited existing research on the aforementioned topics, our study will utilize extensive population-based databases as a foundation. We will employ a distributed lag non-linear model (DLNM) to capture the lag effect between exposure to pollutants and the risk of UGIB. Additionally, we will investigate the impact of sex, age, seasons, and notably, the factor of the COVID-19 pandemic on emergency visits for UGIB through stratified analysis. This would help to provide valuable insights for other regions, particularly those characterized by subtropical climates and urbanization.

## 2. Materials and Methods

### 2.1. Study Area

Hong Kong is a metropolitan city situated in Southern China at 22°08′∼35′N and 113°49′–114°31′E, covering a total area (combined area and water) of 2,755 $km^2$. As of mid-2022, the population stands at 7.33 million. Hong Kong has a typical oceanic subtropical monsoon climate and a temperate monsoon climate in the highlands (Observatory, 2023).

### 2.2. UGIB Emergency Attendance Data

Daily data (including patient's birth date, attending date, and sex) on emergency attendance to all public hospitals for UGIB in Hong Kong between 1 January 2017, and 31 December 2022, were retrieved from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hong Kong Hospital Authority is the only local public health care provider with universal access for the whole population. The CDARS captures patient's demographical information, diagnoses, drug prescription and dispensing records, and laboratory results in all local public hospitals and clinics. The coding system of principal diagnosis in CDARS follows the International Classification of Diseases, ninth Revision (ICD-9). The database segregates information pertaining to outpatients, inpatients, and Accident and Emergency (A&E) attendances. Detailed documentation of the database has been described in previous studies (Leung et al., 2018). The reliability of the coding for UGIB in the CDARS has been validated in our previous study and detailed information has been listed in Table S1 in Supporting Information S1 (Chan et al., 2015). This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster. Since data were anonymized in the database, informed consent from patients was not required by the Institutional Review Board.

### 2.3. Ambient Air Pollutants and Meteorological Data

The primary ambient air pollutants, including the 24-hr average concentrations of $NO_2$, $SO_2$, CO, $PM_{10}$, $PM_{2.5}$, and the 8-hr average $O_3$ levels were obtained from Hong Kong's Environmental Protection Department (Department, 2023). The department operates a network of 18 air quality monitoring stations consisting of 15 general stations and three roadside stations (Figure 1). The daily data was obtained as an average of the values recorded at these stations. The overall monthly data acquisition rate exceeded 96% for all stations. Meteorological data, including mean temperature (°C), relative humidity (%), and wind speed (m/s), were collected from the Hong Kong Observatory (Observatory, 2023).

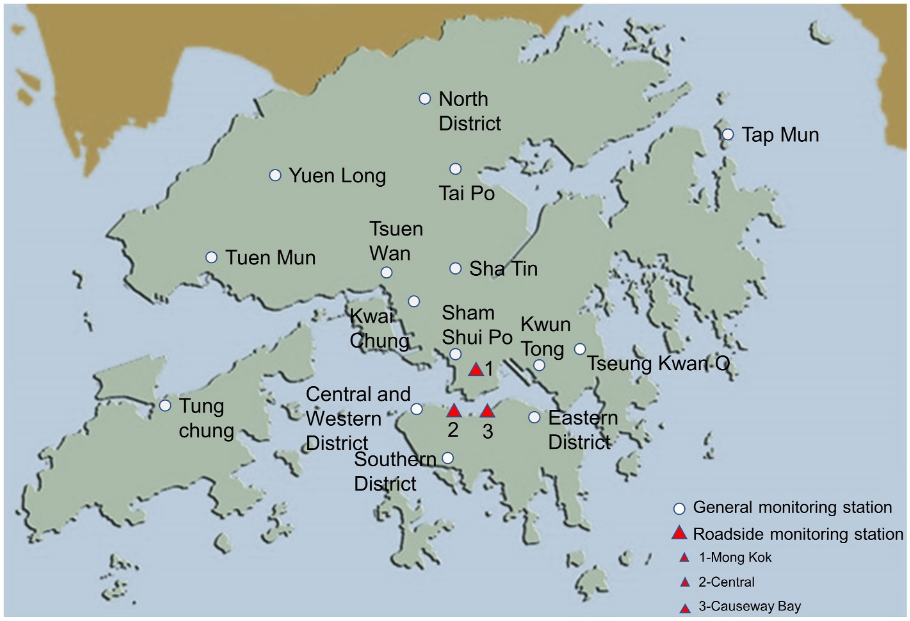


**Figure 1.** Geographical distribution of air quality monitoring stations in Hong Kong.

### 2.4. Statistical Analysis

To investigate the association between emergency attendance of UGIB and ambient air pollutants, we adopted a DLNM developed by Gasparrini (Gasparrini et al., 2010). The DLNM model is widely recognized as the preferred approach for addressing the conventional exposure-response question and capturing the significant lag-response correlation, as it enables simultaneous characterization of non-linear and lagged relationships. The emergency attendance of UGIB daily is considered to be an event with low probability. To address issues related to multicollinearity, Spearman's correlation coefficients of less than 0.7 were utilized for the selection of covariates (Dormann et al., 2013; Schober et al., 2018). Based on the retrieved data, $PM_{10}$ ($r = 0.703$), CO ($r = 0.709$), and $SO_2$ ($r = 0.717$) were eliminated from the final regression model due to potential collinearity with $PM_{2.5}$ (Figure S1 in Supporting Information S1). The synthesized model is demonstrated below:

$$Y_t \sim \text{quasiPoisson}(\mu_t)$$

$$\text{Log}(\mu_t) = a + cb(x_{t,l}, df = 3) + ns(\text{Temperature}, df = 3) + ns(\text{Humidity}, df = 3) + ns(\text{Wind speed}, df = 3) + ns(\text{Time}, 6 * df = 8) + \beta\text{Holiday} + \gamma\text{DOW}$$

The variable $\mu_t$ represents the number of attendances for UGIB in the Accident and Emergency department on day $t$. The coefficient α denotes the intercept in this model. The term cb denoted the cross-basis function of ambient pollutants and lag time. The variable $x_t$ represents the selected air pollutants, while $l$ indicates their lag. Finally, ns stands for the natural cubic spline function. The mean temperature, wind speed, and relative humidity were adjusted using a natural cubic spline with 3 degrees of freedom (*df*). Additionally, a natural cubic spline ($df = 8$ per year) was employed to account for long-term trends and seasonal factors based on previous research findings (Y. Chen et al., 2022; Wang et al., 2022; Wu et al., 2021). γDOW refers to the dummy variable of the day of the week. $\beta$Holiday was adopted to control the effect of holidays based on the public holidays of Hong Kong. The quasi-Poisson Akaike Information Criterion (Q-AIC) served as the foundation for assessing model fits and selecting final model parameters. A lag of 7 days was chosen to quantify the relationship between exposure to air pollutants and emergency visits for UGIB, based on the lowest Q-AIC value. We considered both single-day lags (ranging from lag 0 day to lag 7 days) and cumulative lags (ranging from lag 1 day to lag 7 days) (H. Chen et al., 2021; Wei et al., 2020) (Table S1 in Supporting Information S1). The relationship between daily UGIB emergency risk and pollutant concentrations and meteorological factors was examined by generating dose-response curves using a smoothing function ($df = 3$, lag 7 days). The relative risk (RR) with a 95%

confidence interval (CI) was used to describe the association between high levels of ambient air pollutants (90th percentile) and the minimum risk of UGIB emergency attendance, both for single-day and multi-day estimates.

A generalized additive model was employed to investigate the interaction effects among air pollutants on daily emergency visits for UGIB. The attributable burden of UGIB emergency attendance to ambient air pollutants was also estimated through the use of attributable fractions (AF) and attributable numbers (AN) from a backward perspective, which summarizes the current burden resulting from past exposure events (Gasparrini & Leone, 2014). The 95% empirical CI (2.5th and 97.5th percentiles of distributions) was obtained using the Monte Carlo simulation method (Greenland, 2004; Zhou & Zhao, 2012). The detailed formula of the estimation was shown in Figure S2 in Supporting Information S1. We used the two-sample Z-test to examine the potential difference of AF between different stratified factors including age (≥65 years, <65 years), sex (male, female), seasons (cold, warm), and period (before/during Covid-19 pandemic) (Altman & Bland, 2003).

Predetermined stratified factors, including age, sex, seasons (cold seasons are defined as October to March, and warm seasons are predefined as April to September) (Thach et al., 2015), and before/during COVID-19 pandemic (with 4 January 2020 as the cut-off date in which the local Government announced the "Preparedness and Response Plan for Emerging Infectious Diseases of Public Health Importance" and implemented the highest level of response) were considered for subgroup analysis. The robustness of our results was further validated through sensitivity analysis, where we altered the dfs for ambient air pollutants (4/5 dfs), meteorological factors (4/5 dfs), and calendar time (7/9 dfs). The stable model was confirmed as there were no significant changes observed in the RR estimate results (Gasparrini et al., 2010).

Statistical analyses and visualization were mainly conducted by the R software (version 3.6.1 with the "dlnm," "mcgv," and "splines" packages developed by Gasparrini et al. (Gasparrini, 2011). Two-sided P value < 0.05 was considered statistically significant in this study.

## 3. Results

### 3.1. Baseline Information

The number of total UGIB emergency attendance within the six study years was 31,577, with 17,837 (56.5%) male and 18,523 (58.7%) aged 65 or above. The daily emergency attendance of UGIB ranged from 1 to 46. The details of the demographic characteristics of UGIB patients are presented in Table 1.

The average levels of $PM_{2.5}$, $NO_2$, and $O_3$ were 18.31 ± 10.41 μg/m$^3$ (range: 2.7–79.8 μg/m$^3$), 43.24 ± 14.80 μg/m$^3$ (range: 4.4–136.9 μg/m$^3$), and 31.28 ± 17.76 μg/m$^3$ (range: 6.3–158.9 μg/m$^3$), respectively (Table 1). Temporal trends for the alteration of the daily number of UGIB emergency attendance, ambient air pollutants, and meteorological factors in Hong Kong between 2017 and 2022 are shown in Figure 2.

### 3.2. Association Between Ambient Air Pollutants Exposure and UGIB Emergency Attendance

$PM_{2.5}$ concentrations of 16.4 μg/m$^3$, $NO_2$ concentrations of 46.4 μg/m$^3$, and $O_3$ concentrations of 6.3 μg/m$^3$ were associated with the lowest risk of UGIB and were set as the reference for further analysis. The RR of UGIB emergency attendance exhibited a significant negative association with temperature with a protective effect demonstrated when temperatures exceeded 20°C. However, no such association was observed concerning wind speed and humidity (Figure S3a in Supporting Information S1). The GAMs were constructed to demonstrate the interactive effects of air pollutants on UGIB emergency attendance, as depicted in Figure S3b in Supporting Information S1. It suggested that there was no significant mutual modulation effect between these pollutants and the risk of UGIB emergency visits.

The overall exposure-response association between three ambient air pollutants and the risk of UGIB emergency attendance across different lag days are shown in Figure 3. The findings demonstrated a positive association between exposure to high levels of $PM_{2.5}$ or $NO_2$ and an increased risk of UGIB emergency attendance. Conversely, there was no significant association observed between $O_3$ exposure and UGIB. The lag-specific and cumulative risk of UGIB emergency attendance compared to high concentrations (90th percentile) of pollutants (37.8 μg/m$^3$ for $PM_{2.5}$, 69.9 μg/m$^3$ for $NO_2$, and 110 μg/m$^3$ for $O_3$) was shown in Figure 4 and Tables S2–S4 in Supporting Information S1.

**Table 1**
*Summary Statistics of Ambient Air Pollutants, Meteorological Factors, and Emergency Attendance for Upper Gastrointestinal Bleeding*

| Variables | No. | Mean (SD) | MIN | MAX | P25 | P50 | P75 | IQR |
|---|---|---|---|---|---|---|---|---|
| Air pollutants or meteorological factor | | | | | | | | |
| $PM_{2.5}$ (μg/m$^3$) | – | 18.31 (10.41) | 2.7 | 79.8 | 10.4 | 16.7 | 24.1 | 13.7 |
| $PM_{10}$ (μg/m$^3$) | – | 30.37 (15.92) | 2.6 | 116.3 | 17.4 | 27.9 | 40.1 | 22.7 |
| $SO_2$ (μg/m$^3$) | – | 5.53 (2.08) | 2.6 | 21.9 | 4.2 | 5.0 | 6.3 | 3 |
| CO (mg/m$^3$) | – | 64.09 (15.93) | 33.9 | 149.6 | 52.4 | 61.9 | 73.8 | 21.4 |
| $O_3$ (μg/m$^3$) | – | 31.28 (17.76) | 6.3 | 158.9 | 27.6 | 45.3 | 68.8 | 41.2 |
| $NO_2$ (μg/m$^3$) | – | 43.24 (14.80) | 4.4 | 136.9 | 33.1 | 40.8 | 51.5 | 18.4 |
| Temperature (°C) | – | 24.2 (5.21) | 9.8 | 36.6 | 22.9 | 27.8 | 31.4 | 8.5 |
| Humidity (%) | – | 77.18 (10.06) | 30 | 96 | 73 | 78 | 84 | 11 |
| Wind speed (m/s) | – | 10.52 (4.54) | 1.6 | 38.0 | 7.0 | 9.7 | 13.5 | 6.5 |
| Demographic factors | | | | | | | | |
| Total UGIB emergency attendance | 31577 | 14.41 (6.89) | 1 | 46 | 10 | 13 | 18 | 8 |
| Young (<65 years) | 13054 | 5.96 (3.51) | 0 | 26 | 3.5 | 5 | 8 | 4.5 |
| Elderly (≥65 years) | 18523 | 8.45 (4.68) | 0 | 36 | 5 | 8 | 11 | 6 |
| Male | 17837 | 8.14 (4.40) | 0 | 34 | 5 | 7 | 10 | 5 |
| Female | 13740 | 6.27 (3.74) | 0 | 30 | 4 | 6 | 8 | 4 |
| Warm season[a] | 17540 | 13.70 (6.19) | 1 | 44 | 10 | 12 | 17 | 7 |
| Cold season[a] | 14037 | 15.41 (7.67) | 1 | 46 | 10 | 14 | 19 | 9 |
| Before COVID-19 pandemic[b] | 17703 | 16.69 (8.41) | 1 | 46 | 10 | 15 | 22 | 12 |
| During COVID-19 pandemic[b] | 13874 | 12.28 (4.05) | 1 | 31 | 9 | 12 | 15 | 6 |

*Note.* UGIB: Upper gastrointestinal bleeding; SD: Standard Deviation; $PM_{2.5/10}$: particulate matter with aerodynamic diameter < 2.5/10 μm; $NO_2$: nitrogen dioxide; $SO_2$: sulfur dioxide; CO: carbon monoxide; $O_3$: ozone; SD: standard error; COVID-19: Coronavirus disease 2019; IQR: interquartile range; P25/50/75: 25/50/75th percentile. [a]Cold seasons are defined as October to March, and warm seasons are predefined as April to September. [b]Before or during COVID-19 pandemic set 4 January 2020 as the cut-off date which the Hong Kong Special Administrative Region Government announced the "Preparedness and Response Plan for Emerging Infectious Diseases of Public Health Importance" and implemented the highest level of response.

For $PM_{2.5}$, the single-day RR appears to be significant on lag day 3 (RR:1.012, 95%CI:1.003–1.020) to 6 (RR:1.008, 95%CI:1.000–1.016). The cumulative risk was significant from lag days 0–6 to 0–7, ranging from 1.043 (95%CI: 1.003–1.084) to 1.046 (95%CI: 1.002–1.092). As for the $NO_2$ exposure, the single-day lag association shows a significance from lag day 0 (RR:1.026, 95%CI:1.004–1.049) to 2 (RR:1.014, 95%CI:1.004–1.025) and from lag day 5 (RR:1.013, 95%CI:1.003–1.023) to 7 (RR:1.024, 95%CI:1.004–1.044). The multi-day lag association appears to be statistically significant from lag 0-0 to 0–7 days, with the highest risk occurring at lag 0–7 days (Cumulative RR:1.143, 95%CI: 1.074–1.216). Regarding the $O_3$ model, exposure to high concentrations of the pollutant did not show a significant association with UGIB emergency attendance risk, either on a single-day or multi-day lag basis.

### 3.3. Stratified Analysis

Stratified analysis based on the patient's age, sex, and season were shown in Figures S4–S6 in Supporting Information S1 and Tables S5–S7 in Supporting Information S1. Males exhibit a higher propensity for increased RR in response to elevated levels of $PM_{2.5}$ concentration. A statistically significant elevation in the risk of single-day UGIB emergency attendance among males was observed from lag day 2 (RR: 1.008, 95%CI: 1.000–1.016) to lag day 5 (RR: 1.010, 95%CI: 1.002–1.017) following exposure to high concentrations of $PM_{2.5}$; conversely, no statistically significant association was found between $PM_{2.5}$ exposure and UGIB emergency attendance among females for both single and multi-lag days effects. Regarding $NO_2$ exposure, a significant association was

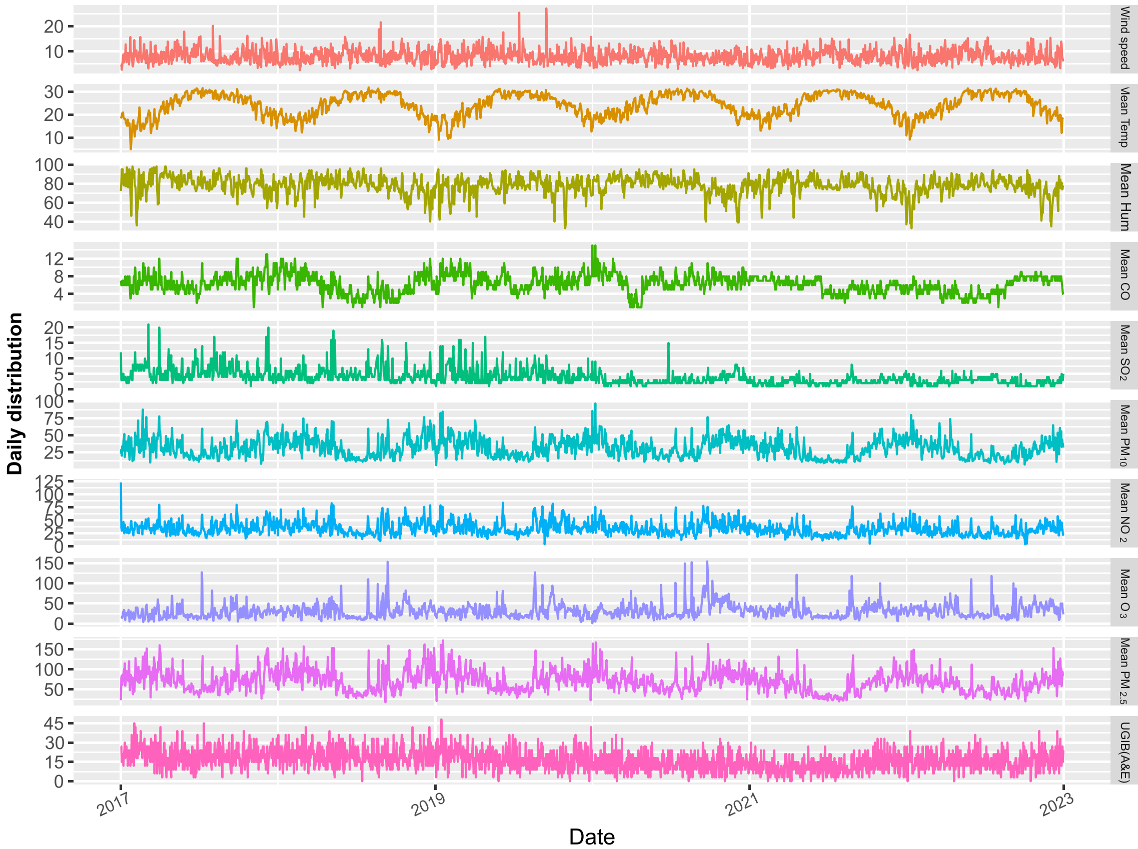


**Figure 2.** Daily distribution ambient air pollutants concentration, meteorological factors, and UGIB emergency visits in Hong Kong from 2017 to 2022. Abbreviation: UGIB: Upper gastrointestinal bleeding.

observed among males from lag day 0 (RR: 1.035, 95%CI: 1.011–1.061) to lag day 2 (RR: 1.011, 95%CI: 1.000–1.023) for single-lag days effect and from the lag day 0 (RR: 1.035, 95% CI: 1.011–1.611) to lag day7 (RR: 1.118, 95%CI: 1.044–1.196) for multi-lag days effect; however, only multi-lag days showed statistical significance for females with generally lower relative risks compared to males.

For high concentration of $PM_{2.5}$ exposure, the elderly (≥65 years) demonstrated a significantly higher risk of UGIB emergency attendance from lag day 3 (RR:1.011, 95%CI: 1.002–1.020) to day 5 (RR: 1.011, 95%CI: 1.002–1.017). Elderly individuals also had a significantly higher risk of UGIB emergency attendance for high $NO_2$ exposure from lag day 0 (RR:1.026, 95%CI:1.003–1.050) to day 2 (RR:1.014, 95%CI:1.003–1.025), and from day 5 (RR:1.011, 95%CI:1.001–1.022) to day 7 (RR:1.020, 95%CI:1.000–1.041).

The impact of exposure to high concentrations of $PM_{2.5}$ and $NO_2$ on UGIB emergencies was found to be more pronounced during cold seasons. For high concentrations of $PM_{2.5}$ exposure, there was a significantly single lag-day risk from day 2 (RR:1.013, 95%CI: 1.000–1.026) to day 4 (RR:1.016, 95%CI:1.001–1.031). For high-level $NO_2$ exposure, significantly higher risk occurred from lag day 1 (RR: 1.019, 95%CI:1.004–1.035) to day 6 (RR:1.015, 95%CI:1.001–1.029).

When considering the impact of the COVID-19 pandemic, it was observed that high-concentration $NO_2$ exposure had a more significant effect before the pandemic compared to the period during the pandemic (single day effect lag0: RR: 1.030, 95%CI: 1.008–1.053 to lag 7: RR: 1.020, 95%CI: 1.000–1.040). However, no significant differences in association were found for $PM_{2.5}$ and $O_3$ exposure.

### 3.4. Sensitivity Analysis

The association between exposure to high concentrations of ambient air pollutants and UGIB emergency remains relatively stable after adjusting dfs for meteorological factors (4/5 dfs), and time factor (7/9 dfs per year), which

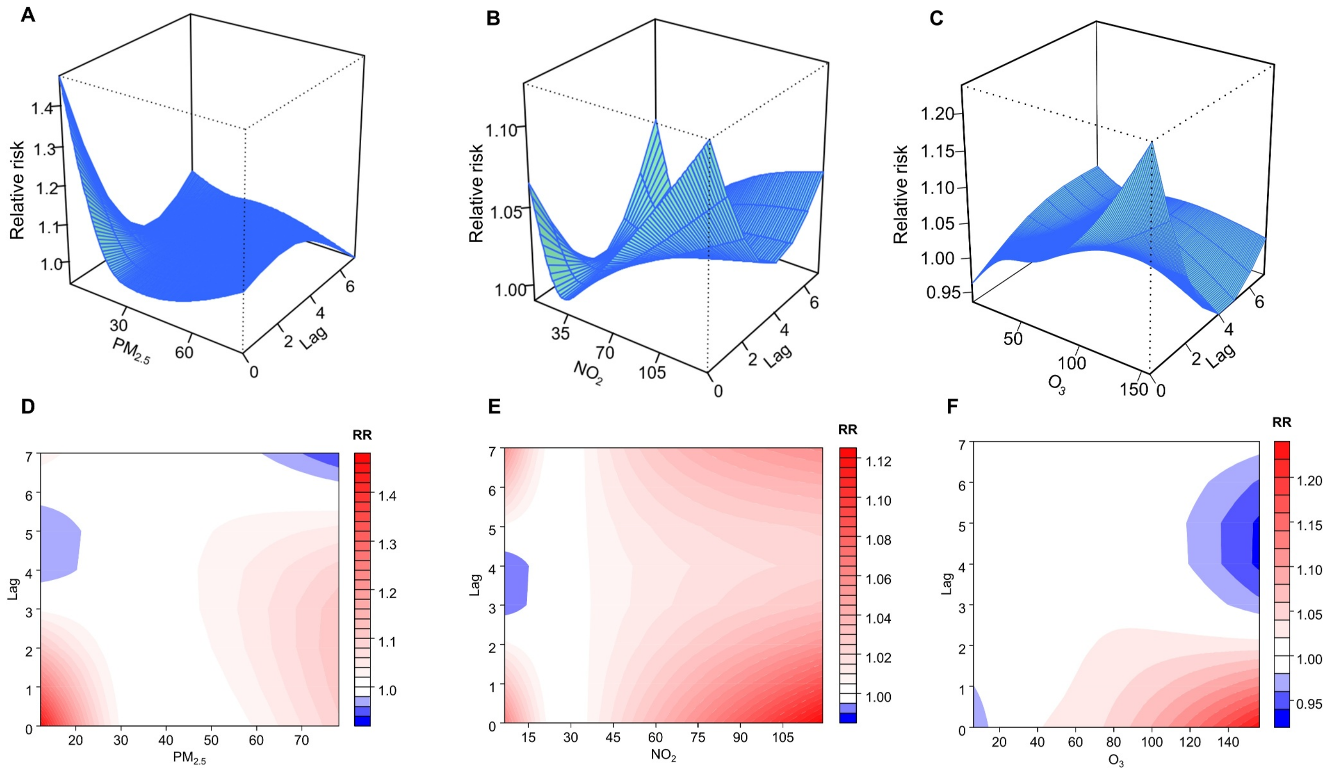


**Figure 3.** Relative Risk of UGIB emergency attendance along $PM_{2.5}$, $NO_2$ and $O_3$ at lag periods. Abbreviation: UGIB: Upper gastrointestinal bleeding; $PM_{2.5}$: particulate matter with aerodynamic diameter < 2.5 μm; $NO_2$: nitrogen dioxide; $O_3$: ozone.

exemplified the impeccably fitted model and reliable outcomes obtained (Figures S7–S9 in Supporting Information S1).

### 3.5. Number of UGIB Emergency Attendance Attributable to Ambient Air Pollutants

Table 2 demonstrates the associations between the number of UGIB emergency attendance and AF or AN of various ambient air pollutants exposure. In comparison, the total AN (3453, 95%CI: 1903 to 4907) and AF (1.25%, 95%CI: 0.69%–1.78%) associated with $NO_2$ exposure were consistently higher than those associated with $PM_{2.5}$ (AN: 1216, 95%CI:55 to 2327; AF: 0.44%, 95%CI: 0.02 to 0.84%) and $O_3$ exposure (AN: 304, 95%CI: −2468 to 7298; AF: 0.11%, 95%CI: −0.89% to 2.64%) (both $p$ for difference<0.05). The burden of UGIB emergency visits attributable to $PM_{2.5}$ and $NO_2$ exposure was significantly higher among males and the elderly compared to female and young individuals (both $p$ for difference<0.05). When stratified by different periods, the attributable burden was generally higher before the COVID-19 pandemic and during the cold seasons, as opposed to the warm seasons and the period during the pandemic. However, only exposure to $NO_2$ showed statistical significance (p for difference = 0.029). The AF did not vary significantly across stratified factors for $O_3$ exposure (all P for difference >0.05).

## 4. Discussion

In this study, we employed the DLNM to observe a heightened risk of UGIB emergency attendance when individuals were exposed to elevated concentrations of $PM_{2.5}$ and $NO_2$, but not with $O_3$. The incidence of UGIB emergencies was found to be higher in male and elderly individuals. Furthermore, a positive association was observed between high levels of air pollutants and an increased risk of UGIB emergencies during cold seasons and before the COVID-19 pandemic. The burden attributable to exposure to high concentrations of $NO_2$ was higher than those of $PM_{2.5}$ and $O_3$.

In a nationwide study in China, Gu et al. (2020) found a higher risk of GIB when exposed to air pollution, especially $PM_{2.5}$. Tian et al. investigated the association between peptic ulcer bleeding and ambient air pollutants

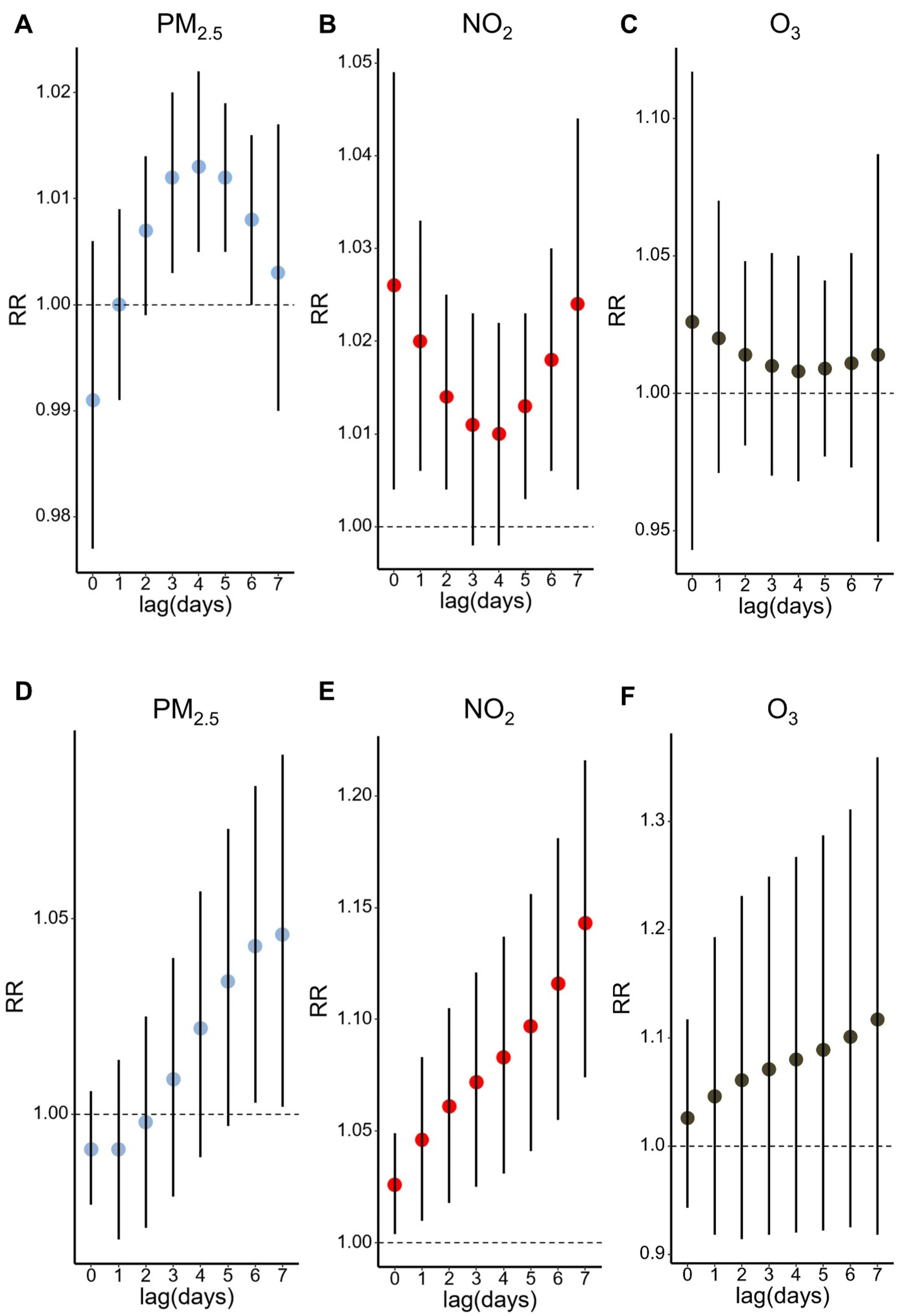


**Figure 4.** Single (a–c) and the multi-day (d–f) lag-specific association between high concentration (90th percentile) of ambient air pollutants exposure and UGIB emergency attendance along $PM_{2.5}$, $NO_2$, and $O_3$ at lag periods. Abbreviation: UGIB: Upper gastrointestinal bleeding; $PM_{2.5}$: particulate matter with aerodynamic diameter < 2.5 μm; $NO_2$: nitrogen dioxide; $O_3$: ozone.

among elderly individuals in Hong Kong, finding that $NO_2$ significantly increased the risk, which was consistent with our results (Tian et al., 2017). Also, in a time-stratified case-crossover study by Tsai et al., peptic ulcer hospitalizations in Taipei increased significantly with air pollutant concentration (Tsai et al., 2019). Wong et al. found a close association between PUD hospitalization and long-term (more than 10 years follow-up) exposure to $PM_{2.5}$ in a large cohort of Hong Kong elderly (Wong et al., 2016). However, Quan et al. found an insignificant relationship between air pollution and PUD exacerbation among adults in Calgary (Quan et al., 2014). The

**Table 2**
*Attributable Number and Fractions of Ambient Air Pollutants for Upper Gastrointestinal Bleeding Emergency Attendance by Diverse Subgroups*

| Groups | No. of patients | $PM_{2.5}$[b] | | $NO_2$[b] | | $O_3$[b] | |
|---|---|---|---|---|---|---|---|
| | | AN | AF | AN | AF | AN | AF |
| Total | 31577 | 1216 (55,2327)* | 0.44 (0.02,0.84)* | 3453 (1903, 4907)* | 1.25 (0.69, 1.78)* | 304 (−2468, 7298) | 0.11 (−0.89, 2.64) |
| Male | 17837 | 663 (52,1240)* | 0.50 (0.04, 0.94)* | 2059 (1194, 2865)* | 1.42 (0.83, 1.98)* | 1153 (−2359, 3867) | 0.88 (−1.79, 2.94) |
| Female | 13740 | 556 (−102,1194) | 0.38 (−0.07, 0.83) | 1389 (555, 2157)* | 1.06 (0.42, 1.64)* | 1831 (−2512, 5071) | 1.27 (−1.74, 3.51) |
| Elderly (≥65 years) | 18523 | 1105 (72,2113)* | 0.46 (0.03, 0.88)* | 2831 (1430, 4170)* | 1.77 (0.92, 2.54)* | −467 (−7743, 5173) | −0.19 (−3.21, 2.14) |
| Young (<65 years) | 13054 | 112 (−127,339) | 0.32 (−0.36, 0.97) | 620 (322, 891)* | 1.17 (0.59, 1.73)* | 590 (−105, 1516) | 2.35 (−0.30, 4.32) |
| Warm season[a] | 17540 | −862 (−1282, −111)* | −0.56 (−1.05, −0.09)* | −743 (−1666, 402) | −0.48 (−1.36, 0.33) | 77 (−4337, 3293) | 0.05 (−3.55, 2.70) |
| Cold season[a] | 14037 | 526 (−542,1773) | 0.43 (−0.35, 1.15) | 1575 (913, 2982)* | 1.29 (0.59, 1.94)* | 2309 (−3428, 7106) | 1.89 (−2.22, 4.61) |
| Before COVID-19 pandemic[b] | 17703 | 756 (−112, 1674) | 0.82 (−0.16, 1.78) | 3023 (1563, 4314)* | 1.82 (0.90, 2.74)* | 1466 (−108, 1862) | 1.02 (−0.03, 1.16) |
| During COVID-19 pandemic[b] | 13874 | 593 (−246, 1346) | 0.60 (−0.34, 1.86) | 477 (−629, 1425) | 0.66 (−0.87, 1.97) | 304 (−832, 1288) | 0.42 (−1.15, 1.78) |

*Note.* UGIB: Upper gastrointestinal bleeding; $PM_{2.5/10}$: particulate matter with aerodynamic diameter < 2.5/10 μm; $NO_2$: nitrogen dioxide; $O_3$: ozone; COVID-19: Coronavirus disease 2019; AN: attributable number; AF: attributable fractions. *: $P < 0.05$. [a]Cold seasons are defined as October to March, and warm seasons are predefined as April to September; b: Reference value (50th percentile): $PM_{2.5}$: 16.7 μg/m$^3$; $NO_2$: 40.8 μg/m$^3$; $O_3$: 45.3 μg/m$^3$. [b]Before or during COVID-19 pandemic set 4 January 2020 as the cut-off date which the Hong Kong Special Administrative Region Government announced the "Preparedness and Response Plan for Emerging Infectious Diseases of Public Health Importance" and implemented the highest level of response.

possible reasons for the disparity might originate from the different models, inclusion criteria, or regional factors such as the baseline levels of various pollutants.

Researchers have long been elucidating the potential mechanisms by which air pollutants contribute to diseases. Some researchers have discovered an association between air pollutants and T-cell imbalance (Kasdagli et al., 2022; Zhao et al., 2019), which helped to explain the close association between autoimmune disease and ambient air pollutants. In particular, $PM_{2.5}$ could penetrate the alveolar space or bloodstream leading to systemic diseases in the central nervous and cardiovascular systems (Du et al., 2016; Lawal, 2017). However, the mechanism by which air pollutant exposure might cause gastrointestinal bleeding remains uncertain. Several possibilities have been proposed including disruption of gut microbiota after ingesting air pollutant particles (Kish et al., 2013) as well as increased intestinal permeability and inflammatory response related to ambient pollutant exposure (Mutlu et al., 2018). In our study, we observed more significant impacts of $PM_{2.5}$ and $NO_2$ on UGIB, while the influence of ozone was not found to be statistically significant. The underlying mechanism behind this disparity is thought-provoking. Due to its minute size, $PM_{2.5}$ particles can penetrate the lungs and bloodstream, potentially exacerbating existing intestinal diseases or causing new complications (Fongsodsri et al., 2021). $NO_2$ can induce oxidative stress, inflammation, vascular endothelial dysfunction, and impair the integrity of the intestinal mucosal barrier function, ultimately leading to bleeding episodes (Mohammadi et al., 2024). However, the oxidative stress response of ozone is more limited to the respiratory system, so it may not trigger a significant systemic inflammatory response. Also, ozone exists in a gaseous state with high reactivity but has a short half-life within the body; therefore, it tends to react locally in areas such as the respiratory tract rather than spreading extensively to distant sites like the GI tract (Knowlton et al., 2004). Further investigations at a fundamental level are warranted to elucidate these observed discrepancies between different pollutants.

The subgroup analysis in this study demonstrated the susceptibility to air pollutants associated with UGIB among males and the elderly. Compared to females, the relatively higher vulnerability of male individuals to ambient air pollutants has been demonstrated through several studies, which may be attributed to their lack of vascular protection from estrogen (C. Chen et al., 2019; Hess & Cooke, 2018; Wu et al., 2021). The higher risk for the elderly to suffer from UGIB or other gastrointestinal diseases after short-term ambient air pollutant exposure might partially be due to the presence of comorbidities such as diabetes, chronic obstructive pulmonary disease, and asthma, as well as the concurrent use of anti-platelets and anti-coagulants in preventing thromboembolic diseases (Chunxi et al., 2020; Cortopassi et al., 2017; Raftery et al., 2020). These diseases may make the respiratory mucosa more vulnerable to air pollutants and incur a high concentration of $PM_{2.5}$ or $NO_2$ in the blood. In Hong Kong, it was estimated that over 20% of the total population was over 65 years old in the 2022 Census, which will grow to 38.4% after five decades (Kong et al., 2023). The public health burden of UGIB in the elderly population should not be overlooked.

The impacts of social distancing measures implemented during the COVID-19 pandemic exhibited significant changes in emissions across different pollutants. Based on a previous report, $NO_2$ emissions displayed distinct emission characteristics compared to other pollutants, demonstrating an overall reduction of 42.5% after implementing various control measures. Conversely, $SO_2$, CO, $PM_{2.5}$, and $PM_{10}$ witnessed a relatively modest decrease ranging from 7.9% to 12.1% (Kong et al., 2023). In our study, the disparity in risk of UGIB emergency attendance before and after COVID-19 was most prominently observed regarding to $NO_2$ exposure compared to $PM_{2.5}$ and $O_3$, providing further evidence of this association.

To our knowledge, it is the most updated study to discern the association between UGIB emergency attendance and ambient air pollution exposure, especially combining meteorological factors and the latest impact of COVID-19 social distancing measures. We have demonstrated the attributable burden of ambient pollutants to UGIB was more pronounced during the cold season and before COVID-19. While the seasonal pattern of UGIB was well reported in our population (Guo et al., 2021), our findings could provide another explanation for this observation. Moreover, the identification of the vulnerable population could help to inform targeted prevention measures for UGIB when levels of air pollutants are abnormally high.

Some limitations of this study should be considered. First, we have integrated three primary air pollutants and included several meteorological factors in the model to adjust for the results. However, it is crucial to acknowledge that due to restricted access to some of the patient's baseline clinical data, there might exist other variables linked to ambient air pollutant levels that are not considered. Second, the findings of this study were derived exclusively from data collected in Hong Kong with its distinctive subtropical climate and predominantly metropolitan area. The major source and background pollutant levels may also differ from other regions. Third, while our study utilized data from Hong Kong's comprehensive air quality monitoring network, consisting of distributed fixed monitoring stations across urban, suburban, and roadside areas, we acknowledge the inherent limitations of relying solely on these stationary sites. The spatial heterogeneity of air pollution exposure in a densely populated and high-rise city like Hong Kong may not be fully captured by these stations alone. Although these certified and internationally standardized stations are designed to meet rigorous requirements, they might not account for micro-environmental variations in pollutant concentrations, particularly in densely populated or heavy-traffic regions. Hence, validating the results in future studies from other regions is imperative.

## 5. Conclusions

Exposure to high concentrations of $PM_{2.5}$ and $NO_2$ is associated with an elevated risk of emergency attendance for UGIB, with exposure to $NO_2$ posing a greater burden. It is crucial to develop preventive measures that mitigate exposure to adverse ambient air pollutants to reduce the risk of UGIB emergency, particularly among males and elderly individuals. Additionally, heightened vigilance should be exercised during the cold seasons.

## Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

## Data Availability Statement

The daily air pollutants concentration and meteorological factors level data used for this study were accessed from Hong Kong's Environmental Protection Department (Department, 2024) and Hong Kong Observatory (Observatory, 2024), respectively. Data be accessed via the following url: https://cd.epic.epd.gov.hk/EPICDI/air/station/?lang=en; https://www.hko.gov.hk/en/abouthko/opendata_intro.htm. The open-source software used for data analyses to generate the quantitative statistical findings was “R” (R-3.6.1 for Windows (2019) and they can be found at the following respective urls: https://cran-archive.r-project.org/bin/windows/base/old/3.6.1/?C=D;

O=D, associated packages are openly available for download on GitHub and the comprehensive R archive network (Gasparrini, 2011). Population-based UGIB emergency cases data, and data contained in all Figures, R code, and all Supporting Information have been deposited in the following Zenodo repository: https://doi.org/10.5281/zenodo.13836153 (Li, 2024).

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