Association between emergency admission for peptic ulcer bleeding and air pollution: a case-crossover analysis in Hong Kong's elderly population

Linwei Tian, Hong Qiu, Shengzhi Sun, Hilda Tsang, King-Pan Chan, Wai K Leung

Summary

Background Air pollution increases intestinal permeability, alters the gut microbiome, and promotes inflammation, which might contribute towards gastrointestinal bleeding. In the present study, we aim to examine whether short-term elevations in air pollution are associated with increased numbers of emergency hospital admissions for peptic ulcer bleeding in Hong Kong.

Methods Daily air pollution (particulate matter with aerodynamic diameter less than 2·5 μm [$PM_{2·5}$], nitric oxide [NO_2], sulpher dioxide [SO_2], and ozone [O_3]) data during 2005–10 were collected from the Environmental Protection Department and emergency admission data for peptic ulcer bleeding in elderly people (aged 65 years or older) from the Hospital Authority of Hong Kong. A time stratified case-crossover analysis with conditional logistic regression was used to estimate the excess risk of peptic ulcer bleeding associated with each air pollutant, in single-pollutant and multi-pollutant models. Cardiorespiratory diseases were used as positive controls.

Findings 8566 emergency admissions for peptic ulcer bleeding were recorded among Hong Kong's elderly population during 2005–10; the daily number of admissions ranged from 0 to 13. An IQR increment of 5-day moving average (lag_{04}) of NO_2 concentration (25·8 μg/m³) was associated with a 7·6% (95% CI 2·2–13·2) increase in emergency admissions for peptic ulcer bleeding. Multi-pollutant models confirmed the robustness of the risk estimates for NO_2. Other pollutants ($PM_{2·5}$, SO_2, and O_3) were not associated with peptic ulcer bleeding admissions.

Interpretation Short-term elevation in ambient NO_2 might trigger peptic ulcer bleeding events and increase the risk of emergency admissions for peptic ulcer bleeding in Hong Kong's elderly population. These findings strengthen the hypothesis that air pollution affects not just cardiopulmonary diseases, but also certain diseases of the digestive system.

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Introduction

Air pollution has been labelled by WHO to be the single environmental health risk that leads to 7 million premature deaths annually.[1] Although there is compelling evidence for the association between air pollution and cardiovascular and respiratory diseases, there have been few studies to examine the potential association between air pollution and gastrointestinal diseases. Previous epidemiological studies often used intestinal diseases as a negative control when examining the health effects of air pollution.[2,3] Indeed, earlier studies that examined the association between emergency room visits for gastroenteritis and gaseous pollutants or particulate matter indices did not show any positive findings.[4,5] However, ecological studies have revealed positive associations between short-term air pollution exposure and several gastrointestinal diseases including acute appendicitis,[6,7] inflammatory bowel diseases,[8,9] non-specific abdominal pain in young adults,[10] and gastroenteric disorders in infants.[11] Additionally, our cohort study[12] has reported a positive association between long-term exposure to ambient fine particulate matter (with aerodynamic diameter less than 2·5 microns; $PM_{2·5}$) air pollution and hospital admission for peptic ulcer disease in Hong Kong's elderly population (aged 65 years and older). Long-term exposure to $PM_{2·5}$ was found to be associated with an increase in risk of hospital admission for peptic ulcer disease over a 10-year follow-up period (adjusted hazard ratio per 10 μg/m³ of $PM_{2·5}$ 1·18, 95% CI 1·02–1·36).

Peptic ulcer is a break in superficial epithelial cells of the gastroduodenal mucosa that lead to pain, bleeding, or even perforation. Bleeding from peptic ulcer is a common complication of peptic ulcer that requires immediate medical attention and admission to hospital. In this regard, peptic ulcer bleeding is a common cause of emergency admission to hospital in Hong Kong where about 40% of all emergency hospital admissions for peptic ulcer were due to bleeding in 2010. Although the prevalence and incidence of peptic ulcer disease is declining in recent years, peptic ulcer bleeding remains a serious medical condition with considerable morbidity and mortality, high health-care burden, and decreased quality of life.[13,14] The major risk factors for peptic ulcer bleeding include *Helicobacter pylori* infection,

Research in context

Evidence before this study

We searched PubMed with the MeSH terms "air pollution" and ("digestive diseases" or "gastrointestinal") for all reports published before Dec 31, 2016. With the assumption of cardiopulmonary disease as the only health outcomes associated with air pollution, gastroenteritis was used to serve as a negative control in previous studies. But there has been some emerging evidence that short-term air pollution exposure might also increase the risk of certain gastrointestinal diseases, including acute perforated appendicitis, inflammatory bowel diseases, non-specific abdominal pain in young adults, and gastroenteric disorders in infants. Air pollution might increase intestinal permeability, alter the gut microbiome, and promote inflammation.

Added value of this study

We examined for the first time, the association of air pollution with upper gastrointestinal bleeding, one of the most important complications of peptic ulcer. We used a time stratified case-crossover analysis with conditional logistic regression to estimate the excess risk of peptic ulcer bleeding associated with air pollution, while using cardiorespiratory diseases to assess the specificity of the findings. We found that short-term elevations in ambient nitric oxide levels were associated with an increased risk of emergency admissions for peptic ulcer bleeding in Hong Kong's elderly population (aged 65 years or older). Multi-pollutant models confirmed the robustness of the risk estimates for NO_2.

Implications of all the available evidence

This novel observation suggests that ambient NO_2 pollution might trigger peptic ulcer bleeding in elderly people. This study, along with earlier work, helps to refine the hypothesis that air pollution affects not just cardiopulmonary diseases, but also certain digestive disease outcomes. Future patient-level and mechanistic studies are warranted to substantiate these findings based only on aggregated population level data.

non-steroidal anti-inflammatory drugs (NSAIDs), and low-dose aspirin use.[15,16] However, there is evidence to suggest that an increasing proportion of peptic ulcer bleeding could not be explained by these conventional risk factors.[17,18] To further support the possibility of environmental involvement in peptic ulcer bleeding, a previous study also suggested seasonal variation in gastrointestinal bleeding with more bleeding occuring during winter months.[19] The reason behind these seasonal variations remains elusive.

Several animal studies suggest that air pollution exposure might alter intestinal immunity, increase gut permeability, and influence intestinal microbial composition,[10,20–22] which might contribute to the development of peptic ulcer and even bleeding. Although we have shown a positive association between long-term exposure to $PM_{2.5}$ and hospital admission for peptic ulcer diseases in Hong Kong,[12] the role of short-term exposure to $PM_{2.5}$ and other gaseous pollutants such as nitric dioxide (NO_2), sulphur dioxide (SO_2) and ozone (O_3) have not been characterised. Moreover, the effect of air pollution on bleeding, one of the most important complications of peptic ulcer, has not been determined.

In this study, we postulate that short-term elevations of air pollution increase the risk of peptic ulcer bleeding. We applied a case-crossover design to examine the association between short-term air pollution exposure and emergency hospital admissions for peptic ulcer bleeding in Hong Kong's elderly population.

Methods

Study design

We did a time-stratified case-crossover study to estimate the association between air pollution and emergency hospital admission for peptic ulcer bleeding.[7,23] The case-crossover design (introduced by Malcolm Maclure in 1991) is an adaptation of the case-control study in which cases serve as their own controls.[24] This design is commonly used to investigate the transient effect of an exposure on the risk of acute events. Besides time-series study, the case-crossover design has been used as an alternative approach to examine the acute effects of air pollution on health.[25] For each patient admitted to hospital on a specified date (case day), the patient is matched with themselves on nearby time periods where they did not have the event (control days). Each risk set consists of one case on the case day and no event on several control days (a stratum). We then compared the patient's air pollution exposure on case day and control days to estimate the association between pollution exposure and the onset of disease. Air pollution has the short-term serial correlation, so we used a time-stratified approach to select the control days which are in the same calendar month with the same day of week, to ensure the relative independence of air pollution on all control days.[26] The simulation study and a systematic review have shown that the time-stratified approach ensures unbiased conditional logistic regression estimates, avoids bias resulting from time trend in the exposure series, and can be tailored to match with specific time-varying confounders.[27,28] As the case and control days in each risk set are in the same calendar year, month, and day of the week, the case-crossover design controls for seasonal variation, time trends, and chronic and slowly varying potential confounders by matching.

Data collection

We obtained records of emergency hospital admissions for peptic ulcer bleeding (International Classification of Diseases [ICD]-9 codes: 53X.0, 53X.2, 53X.4, and 53X.6,

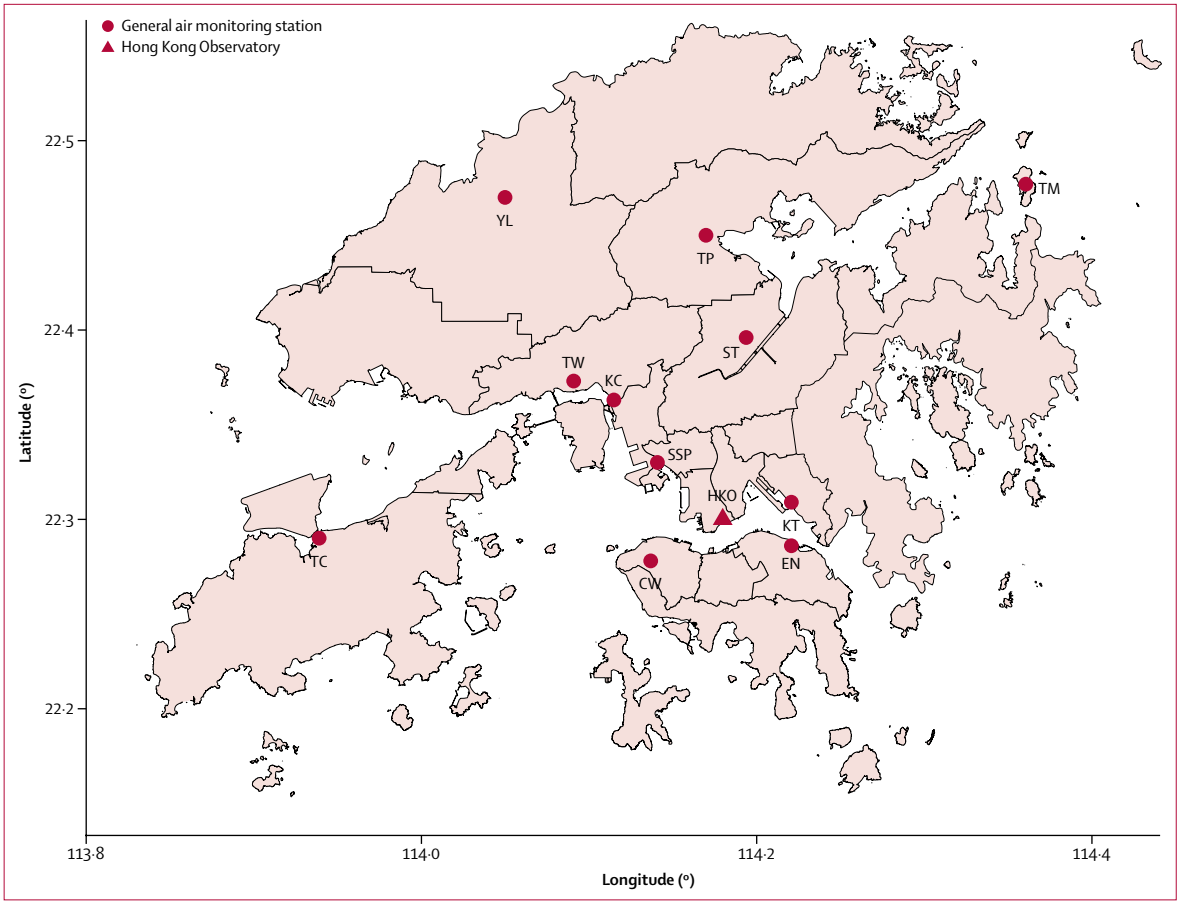

Figure 1: **Map of Hong Kong showing the location of the general or background air pollution monitoring stations and Hong Kong Observatory**
NO_2, SO_2, and O_3 concentrations were averaged from ten stations except TM, whereas $PM_{2·5}$ concentrations were computed from three stations (TW, YL, and TC) during the study period of 2005–10. $PM_{2·5}$=particulate matter with aerodynamic diameter less than 2·5 μm. NO_2=nitrogen dioxide. SO_2=sulfur dioxide. O_2=ozone.

	Mean	SD	Minimum	P_{25}	Median	P_{75}	Maximum
Peptic ulcer bleeding	3·9	2·1	0·0	2·0	4·0	5·0	13·0
In warm season (May to October)	3·4	2·0	0·0	2·0	3·0	4·0	13·0
In cool season (November to April)	4·4	2·2	0·0	3·0	4·0	6·0	12·0
All respiratory diseases	156·1	34·1	85·0	131·0	150·0	177·0	300·0
All circulatory diseases	130·9	25·6	64·0	112·0	128·0	145·0	251·0
Pollution concentration (μg/m³)							
$PM_{2·5}$	37·3	22·5	7·5	18·9	32·1	50·4	174·5
NO_2	55·7	19·7	14·1	41·2	52·7	67·0	146·7
SO_2	19·0	12·2	3·6	10.7	16.0	23.6	115·9
O_3	46·0	28·8	5·2	22.9	39·1	63·7	194·3
Weather conditions							
Mean temperature (°C)	23·4	5·1	8·8	19·3	24·6	27·8	31·8
Relative humidity (%)	78·4	10·7	31·0	74.0	80·0	86·0	98·0
Air pressure (hPa)	1012·7	6·3	992·5	1008·0	1012·5	1017·6	1030·7

P_{25}=25th percentile. P_{75}=75th percentile. $PM_{2·5}$=particulate matter with aerodynamic diameter less than 2·5 μm. NO_2=nitrogen dioxide. SO_2=sulfur dioxide. O_3=ozone.

Table 1: **Descriptive statistics for daily emergency hospital admissions (counts per day) for peptic ulcer bleeding, respiratory and circulatory diseases, air pollution concentrations, and weather conditions in Hong Kong, 2005–10 (n=2191 days)**

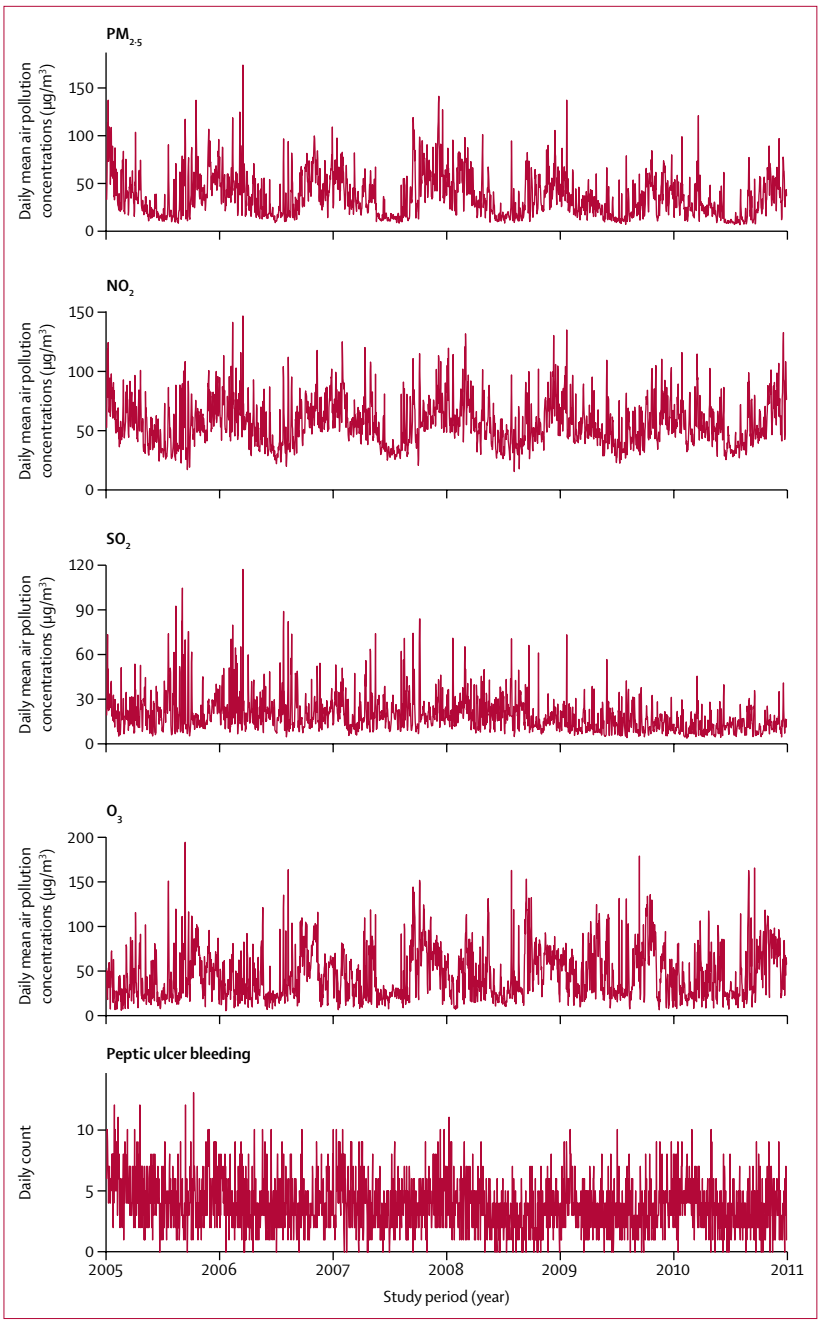

Figure 2: **Time series plot of the daily mean air pollution concentrations and emergency hospital admissions for peptic ulcer bleeding in the elderly population in Hong Kong, 2005–10**
$PM_{2·5}$=particulate matter with aerodynamic diameter less than 2·5 μm. NO_2=nitrogen dioxide. SO_2=sulfur dioxide. O_3=ozone.

where X=1–3) as principal diagnosis between 2005 and 2010 from the Hong Kong Hospital Authority Corporate Data Warehouse. The Hospital Authority is the statutory body responsible for the operations of all public hospitals in Hong Kong, which covered 90% of hospital beds in the territory. The records of hospital admission were collected from all publicly funded hospitals providing 24 h emergency services. Due to data availability, we focused on the elderly population (aged 65 years and older) in this study. Elderly patients often have more comorbidities and more complicated peptic ulcer bleeding, so they are likely to be more vulnerable to air pollution exposure.[29] The use of the ICD-9 codes for peptic ulcer disease has been verified in our previous study that investigated gastrointestinal bleeding.[30] Emergency hospital admissions for all respiratory (ICD-9: 460–519) and circulatory diseases (ICD-9: 390–459) during the same time period were also extracted for comparison to test the specificity of the associations.

We obtained air pollution data from 14 fixed-site air quality monitoring stations of the Hong Kong Environmental Protection Department between Jan 1, 2005, and Dec 31, 2010. One background station in the remote area (TM) and three roadside stations for data aggregation were excluded. The remaining ten background monitoring stations were used to calculate the daily mean concentrations of NO_2, SO_2, and O_3. The monitoring data for $PM_{2·5}$, which were available at three general stations only (TW, YL, and TC), were used to estimate the $PM_{2·5}$ daily mean concentrations during the study period (figure 1). For this study, we calculated the 24 h mean concentrations of $PM_{2·5}$, NO_2, and SO_2, and 8 h daytime (1000 h to 1800 h) mean concentrations of O_3 across stations to represent the general population's exposure to air pollution. Meteorological data on daily average temperature and relative humidity were obtained from the Hong Kong Observatory (figure 1).

Statistical analyses

The daily time-series dataset was expanded by matching each case day with 3–4 control days in the same calendar month with the same day of the week. Daily count of emergency hospital admissions was treated as the frequency and weight of each risk set.[31] We used conditional logistic regression to estimate the association between air pollution concentrations and the onset of peptic ulcer bleeding, while adjusting for weather conditions and public holidays.[25] We controlled for temperature effect by including the same-day mean temperature to present the immediate effect and the moving average of the previous 3 days (lags 1–3) to represent the delayed effects. Although the risk might vary non-linearly with temperature, we used natural cubic spline with three degrees of freedom (df) for both the same day and the moving average of the previous 3 days, and included them simultaneously in the model.[11] We also included a natural cubic spline with three dfs to control for relative humidity and air pressure, because a previous study[19] has shown the association between these weather factors and incidence of upper gastrointestinal bleeding. Public holidays were adjusted as binary factors.[32]

We estimated the linear effect of air pollutant on the same day (lag_0) and up to the previous 4 days (from lag_1 to lag_4) to show the single-day effect, and the moving

average concentrations from the same day to the previous 4 days (lag_{04} in short) to show the cumulative effects over 5 days.[6] Hospital admissions due to all respiratory diseases and circulatory diseases were used for comparison to test the specificity of the association between air pollution and emergency peptic ulcer bleeding hospital admissions. The linearity of the exposure-response relationship was graphically examined by using nature cubic spline with three dfs for pollutants in the model.[33] The pairwise Pearson correlations among air pollutants and weather factors are considered moderate or strong when the absolute values of the coefficients are in the range of 0·3–0·7 and 0·7–1·0, respectively. We also assessed potential confounding from other co-pollutants by using multi-pollutant models. Considering the wide seasonal variations of hospital admissions for peptic ulcer bleeding, stratified analysis by season was done in the warm season (May–October) and the cool season (November–April), respectively.

The risk estimate was the odds ratio (OR) from conditional logistic regression. We expressed it in terms of the percent excess risk (ER%; ER%=[OR–1] multiplied by 100%) in emergency hospital admissions per IQR increase of pollution concentration, and their respective 95% CIs. All analyses were done in the statistical environment R3.1.3 (R Development Core Team, 2015), with its survival package to fit the conditional logistic regression and Hmisc package to plot the exposure-response relationship curves.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We included 8566 emergency hospital admissions for peptic ulcer bleeding among Hong Kong's elderly population during the 6-year study period. On average, there were 3·9 emergency hospital admissions for peptic ulcer bleeding per day, with 55 (2·5%) days of zero admissions and a maximum of 13 admissions in a single day during the study period. There were seasonal variations in the daily peptic ulcer bleeding hospital admission counts, which were slightly higher during the cool season than during warm season (p<0·0001; table 1).

During the study period, the daily mean ambient temperature was 23·4°C and the relative humidity was 78·4%. The daily 24 h mean concentration was 37·3 μg/m³ for $PM_{2·5}$, 55·7 μg/m³ for NO_2, and 19·0 μg/m³ for SO_2, and the daytime 8 h mean concentration for O_3 was 46·0 μg/m³ (table 1). The time-series plots of daily variation of air pollution concentrations and emergency peptic ulcer bleeding hospital admission counts show a seasonal pattern as well as a long-term trend of both air pollution and peptic ulcer bleeding (figure 2).

We further studied the potential correlation between different pollutants and weather conditions during the study period (table 2). There was a strong correlation

	NO_2	$PM_{2·5}$	SO_2	O_3	Temperature	Relative humidity
NO_2	1·000		..	..	..	..
$PM_{2·5}$	0·759	1·000	..	..	..	..
SO_2	0·526	0·475	1·000		..	..
O_3	0·436	0·536	0·158	1·000	..	..
Temperature	–0·403	–0·374	0·075	0·031	1·000	
Relative humidity	–0·339	–0·415	–0·228	–0·542	0·245	1·000
Air pressure	0·405	0·440	–0·090	0·127	–0·834	–0·425

$PM_{2·5}$=particulate matter with aerodynamic diameter less than 2·5 μm. NO_2=nitrogen dioxide. SO_2=sulfur dioxide. O_3=ozone.

Table 2: **Pearson correlation coefficients between air pollution concentrations and weather conditions in Hong Kong, 2005–10 (n=2191 days)**

	$PM_{2·5}$	NO_2	SO_2	O_3
Peptic ulcer bleeding				
lag_0 (same day as admission)	2·6 (–2·0 to 7·3)	3·1 (–1·4 to 7·8)	1·3 (–1·7 to 4·4)	–3·3 (–8·2 to 2·0)
lag_1 (1 day previous)	–0·7 (–4·9 to 3·7)	3·0 (–1·2 to 7·4)	0·3 (–2·6 to 3·3)	3·3 (–1·3 to 8·1)
lag_2 (2 day previous)	0·8 (–3·4 to 5·2)	4·0 (0·0 to 8·2)†	1·5 (–1·4 to 4·5)	3·5 (–0·9 to 8·1)
lag_3 (3 day previous)	2·7 (–1·6 to 7·1)	5·2 (1·2 to 9·4)†	1·9 (–0·9 to 4·8)	5·9 (1·6 to 10·4)†
lag_4 (4 day previous)	0·9 (–3·2 to 5·2)	3·9 (0·0 to 8·0)†	0·1 (–2·6 to 2·9)	3·4 (–0·8 to 7·8)
lag_{04} (5-day moving average of lag_0–lag_4)	2·2 (–3·1 to 7·8)	7·6 (2·2 to 13·2)†	2·4 (–1·7 to 6·6)	5·8 (0·0 to 12·0)
Cardiorespiratory diseases for comparison (pollutants at lag_{04})				
All respiratory diseases	5·5 (4·6 to 6·4)†	5·6 (4·7 to 6·5)†	2·3 (1·6 to 2·9)†	7·5 (6·5 to 8·4)†
All circulatory diseases	1·8 (0·9 to 2·8)†	3·5 (2·6 to 4·5)†	1·9 (1·2 to 2·7)†	2·2 (1·2 to 3·2)†

Data are percent excess risk (ER%; 95% CI). $PM_{2·5}$=particulate matter with aerodynamic diameter less than 2·5 μm. NO_2=nitrogen dioxide. SO_2=sulfur dioxide. O_3=ozone. *Case-crossover approach estimated the associations using conditional logistic regression model. Each risk set (stratum) consisted of a case day and control days from the same calendar month with the same day of week. Other time-varying confounders including temperature, relative humidity, air pressure, and public holiday were adjusted as well. †Statistically significant effect estimates.

Table 3: **The association between air pollution and emergency hospital admissions for peptic ulcer bleeding (percent excess risk per IQR increase of pollutant)***

	Whole period	Warm season (May to October)	Cool season (November to April)
NO_2	18·5 (5·4 to 33·2)†	19·8 (–3·4 to 48·4)	18·7 (2·7 to 37·3)†
$PM_{2·5}$	–9·4 (–17·8 to –0·1)	–16·4(–32·1 to 2·9)	–9·9 (–19·9 to 1·4)
SO_2	–3·3 (–10·3 to 4·2)	–3·9 (–13·4 to 6·7)	–0·3 (–11·9 to 12·9)
O_3	3·9 (–5·2 to 13·8)	10·8 (–4·9 to 29·1)	1·1 (–11·3 to 15·3)

Data are percent excess risk (ER%; 95% CI). $PM_{2·5}$=particulate matter with aerodynamic diameter less than 2·5 μm. NO_2=nitrogen dioxide. SO_2=sulfur dioxide. O_3=ozone. *The associations were estimated in the multi-pollutant model with a case-crossover approach using conditional logistic regression model, adjusting for the other time-varying confounders including temperature, relative humidity, air pressure, and public holiday. †Statistically significant effect estimates.

Table 4: **Percent excess risk of emergency hospital admissions for peptic ulcer bleeding per IQR increase in 5-day moving average (lag_{04}) of NO_2 and co-pollutants in multi-pollutant model and stratified analysis by season***

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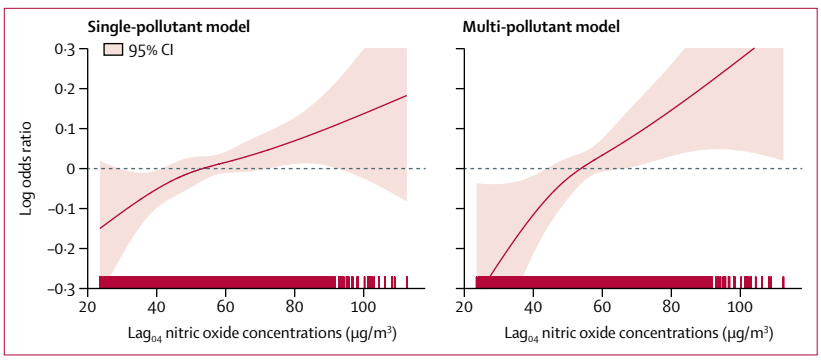

Figure 3: **Exposure-response relationship curves for the association between emergency hospital admissions for peptic ulcer bleeding and 5-day moving average (lag_{04}) of NO_2 concentrations in single-pollutant and multi-pollutant models, respectively**

between NO_2 and $PM_{2·5}$ (Pearson correlation coefficient (r) 0·759), but the correlation between other pairs of pollutants were weak (0·158 between SO_2 and O_3) to moderate (0·526 between NO_2 and SO_2).

All four pollutants were associated with overall respiratory and circulatory diseases, showing the general validity of the model specifications in the present study (table 3). We also observed significant associations between emergency hospital admission for peptic ulcer bleeding and NO_2, but not for other pollutants including $PM_{2·5}$ (table 3). There was a 7·6% (95% CI 2·2–13·2) increase in emergency hospital admissions for peptic ulcer bleeding that was associated with an IQR increment of NO_2 (25·8 μg/m³), measured as lag_{04}, which is the 5-day moving average concentration from current day to previous 4 days to show the cumulative effect of NO_2 over 5 days.

Although a significant association between peptic ulcer bleeding and O_3 exposure on lag_3 was observed in single-pollutant model, the effect estimate lost statistical significance after adjustment for NO_2 (data not shown). The multi-pollutant model confirmed the robustness of the effect estimates for NO_2, which became larger with the inclusion of $PM_{2·5}$, SO_2, and O_3 (18·5%, 5·4–33·2; table 4). Further stratified analysis by season did not show much difference of the effect estimates for NO_2 between the warm and cool season, and only the NO_2 effect during the cool season was significant. The exposure-response relationship curves showed essentially linear associations between hospital admissions for emergency peptic ulcer bleeding and lag_{04} NO_2 concentrations in both single-pollutant and multi-pollutant models (figure 3).

Discussion

In this study, we observed a significant association between NO_2 air pollution levels and emergency hospital admission for peptic ulcer bleeding in elderly patients (aged 65 years or older) in Hong Kong. This novel observation suggests that NO_2 present in air pollution might have worsened peptic ulcer bleeding in elderly people.

Among the various air pollutants examined in this study, the risk estimate for NO_2 was the most robust in both single-pollutant and multi-pollutant models. The risk estimates for O_3 lost statistical significance after adjustment for NO_2. The concentrations of $PM_{2·5}$ and NO_2, both traffic-related pollutants, were highly correlated in this study, hence it is difficult to distinguish the individual effects between these two pollutants. Pollutants with smaller measurement error, such as NO_2, tend to maintain statistical significance in the multi-pollutant model.[34] The risk estimates for NO_2 found in this study were consistent with earlier findings that residential exposures to SO_2 and NO_2 increased the risk of early-onset ulcerative colitis and Crohn's disease.[8] However, some researchers have proposed that gaseous pollutants might be surrogates of $PM_{2·5}$ exposure,[34,35] and the potential acute effect of $PM_{2·5}$ on hospital admissions for emergency peptic ulcer bleeding should be studied further.

Only a few epidemiological studies have revealed the association between pollution exposure and gastrointestinal diseases. In contrast to our findings, a study from Canada[36] suggested that the incidence of upper gastrointestinal bleeding secondary to peptic ulcer disease is not associated with air pollution. We included 8566 cases of peptic ulcer bleeding over a period of 6 years in the whole elderly population in Hong Kong, whereas Quan and colleagues' study[36] only identified 2523 cases in adult residents (aged 18 years or older) in Calgary and Edmonton, Canada. The small sample size might have resulted in low statistical power to detect an association. The difference might also relate to the different study population characteristics and the higher air pollution exposure levels in Hong Kong than those in North America. Another study reported the correlations between higher mortality rate of peptic ulcer disease and elevated ambient pollution levels in England,[37] where only correlation coefficients were presented, but not the regression estimates.

The biological mechanisms underlying the association between air pollution and the exacerbation of peptic ulcer bleeding remain elusive. However, exposure of the gastrointestinal tract to air pollutants occurs via mucociliary clearance of particulate matter from the lungs as well as ingestion of pollutants through contaminated food and water. Gaseous pollutants might also affect the digestive tract through swallowed air (aerophagia). A person with chronic upper gastrointestinal disorder including peptic ulcer disease might intentionally or unintentionally develop a habit of belching to relieve discomfort.[38] Swallowed NO_2 through belching might cause nitration of different compounds including nitrate and nitrite in the stomach, which could induce the redox interplay and moderate the signal pathway in the digestive system.[39,40] Other mechanisms mediating the effects of air pollutants on the gastrointestinal tract could also include direct effects on epithelial cells, systemic inflammation and

immune activation, and modulation of the intestinal microbiota.[41] Air pollutants increase intestinal permeability, which might contribute towards gastric and duodenal bleeding.[20–22,42] Exposure to air pollution, either through inhalation or ingestion, might incite oxidative damage and inflammatory pathways that have been postulated to be central in the pathogenesis of peptic ulcer bleeding.[43]

Some limitations of our study should be noted. First, we used the date of emergency hospital admission for peptic ulcer bleeding as the index date for analysis, which might be affected by the difference of the symptom onset and the delays of presentation to hospital. However, these errors are probably non-differential, which would lead to bias towards the null hypothesis. Second, the case-crossover design controls time-independent covariates (eg, infection with *H pylori* or genetic predisposition to peptic ulcer) because the patients serve as their own control. However, the design is still subject to confounding by time-dependent covariates, such as the use of NSAIDs or aspirin, because this information was unavailable. Because the control days were the same weekdays in the same month and same year as the case day, we could assume that the use of NSAIDs did not change in such a short time period within a month. Finally, all ecological air pollution studies are subject to multiple comparison errors because associations between air pollution and health outcomes (eg, peptic ulcer bleeding) were explored with several pollutants and several lagged exposures. Thus, the probability of observing significant findings by chance is increased and the replication of this work in other study populations is necessary to confirm our findings.

In conclusion, short-term elevation in ambient NO_2 levels might trigger peptic ulcer bleeding events and increase the risk of emergency admissions for peptic ulcer bleeding in the elderly population of Hong Kong. These findings strengthen the hypothesis that air pollution affects not just cardiopulmonary diseases, but also certain diseases of the digestive system. Future patient-level and mechanistic studies should be done to substantiate the findings.

Contributors

LT and HQ defined the research theme and wrote the manuscript. HQ and SS analysed the data and interpreted the results. HT and K-PC co-worked on the method and interpretation of the results. WKL guided the coding of the diseases and provided comments from clinical perspectives. LT and WKL reviewed and revised the manuscript and approved the submission.

Declaration of interests

We declare no competing interests.

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