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Acute effects of air pollution on cardiovascular hospital admissions in the port district of Klang, Malaysia: A time-series analysis

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HIGHLIGHTS

- The relationship between air pollution and cardiovascular hospitalisations in a port district was studied.
- Nitrogen dioxide was associated with cardiovascular hospitalisations, with less pronounced associations with other pollutants.
- Younger males (below 65 years old) are highly susceptible to the effects of NO_2.
- A collaborative approach with input from health, environment, and shipping experts is recommended.

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ABSTRACT

Cardiovascular diseases are recognised as a significant burden on healthcare systems globally. In this study, the acute impacts of air pollution, especially from shipping emissions, on cardiovascular hospital admissions in Klang, Malaysia, a notable port district, are explored. Time-series analysis and Quasi-Poisson regressions, combined with distributed lag non-linear models, were employed to examine the relationships between daily levels of pollutants and hospital admissions for cardiovascular issues. Focus was placed on the pollutants NO_2 (nitrogen dioxide), SO_2 (sulphur dioxide), O_3 (ozone), particulate matters with diameters $\leq$10 μm (PM_{10}), particulate matters with diameters $\leq$2.5 μm ($PM_{2.5}$), and CO (carbon monoxide), with consideration of lag effects up to 7 days. An increment of 10 μg/m^3 in NO_2 concentrations was associated with a 7.32% increase in cardiovascular admissions on the exposure day, with statistically significant elevations in relative risks at lag 0 were observed for admissions among patients with ischaemic heart disease, those aged less than 65 years, and male patients. At lag 4, an association was identified between O_3 levels and an increase in relative risk of 1.0513 for hypertensive diseases. Two-pollutant models further highlighted significant interactions between NO_2 and PM_{10}, which influenced overall cardiovascular admissions, admissions due to ischaemic heart disease, and particularly affected patients below 65 years old and males, especially at earlier lags. Additionally, interactions involving NO_2 and O_3 were noted, impacting overall cardiovascular admissions, as well as admissions among patients aged less than 65 years and male patients. The findings underscore the severe health risks posed by air pollution in port areas, highlighting the urgent need for targeted interventions to mitigate these effects. Stricter air quality regulations in port cities are supported by the results to protect public health.

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1. Introduction

Cardiovascular diseases remain a significant health concern in Malaysia, exerting a substantial burden on the national healthcare

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system. In 2021, it was recorded that circulatory system disorders accounted for 7.93% of total hospitalisations across both government and private medical facilities. This elevated incidence placed cardiovascular diseases as the third leading reason for hospital admissions in the country (Health Informatics Centre, 2021). Furthermore, data from the Department of Statistics Malaysia in 2022 identified ischaemic heart diseases, cerebrovascular diseases, and hypertensive diseases as substantial contributors to mortality rates, ranking them as the second, fourth, and eighth main causes of death respectively (Department of Statistics Malaysia, 2022b). The health significance of these disorders becomes particularly pronounced when noting that mortality from ischaemic heart diseases were surpassed only by those from the globally impactful COVID-19 pandemic.

With the rise of global trade and the pivotal role of maritime transport, a critical examination of the environmental and health impacts of shipping emissions becomes necessary. The shipping industry, responsible for transporting 80% of global goods or an equivalent of 10 billion tonnes annually, has inadvertently become a considerable contributor to global pollution (Mueller et al., 2022). The release of 13% of global nitrogen oxides and 12% of sulphur oxides can be attributed to this sector. A study conducted in Hamburg, Germany reported that shipping contributes with 14% to nitrogen dioxide (NO_2) and 3% to particles with aerodynamic diameter <2.5 μm ($PM_{2.5}$) population weighted exposure (Ramacher et al., 2020). Additionally, other hazardous pollutants, including particulate matter, black carbon, and methane, are consistently emitted, with potential adverse effects on both the environment and human health. A recent study examining the impact of ports on local air pollution and public health across a global dataset found that port regions emit higher levels of greenhouse gases (GHGs) compared to non-port areas (Ducruet et al., 2024). The study highlighted that extended berthing times are associated with increased air pollution, whereas emission control areas and higher wind speeds contribute to reduced emissions. Concentrations of GHGs were notably higher in densely populated port regions. Furthermore, industrial port areas were identified as particularly significant in terms of their impact on health and pollution levels.

Klang, being a significant maritime nexus in Malaysia, experiences first-hand the potential environmental repercussions of such an industrious maritime network. Emissions from the shipping industry, especially those occurring close to the shore and within port vicinities, can greatly influence local air quality. Two studies spanning different time periods, which analysed air pollutant data across districts in the Klang Valley, identified Klang as the district experiencing the highest temperatures and most severe pollution from PM_{10} within the region (Mohd Shafie et al., 2022; Rahman et al., 2015). Additionally, one of these studies characterised Klang as a high-risk area for chronic bronchitis among adults, attributing this to prolonged exposure to pollutants. The estimated prevalence of affected individuals ranged from 600,001 to 900,000 during the period from 2002 to 2009. High population growth, driven by rapid economic development and the subsequent increase in job opportunities and infrastructure, has been identified as another major source of air pollution in Klang (Abdullah et al., 2012).

Studies from other global regions, such as Shanghai, have already illustrated the detrimental effects of these emissions. Elevated $PM_{2.5}$ levels in Shanghai's coastal areas were predominantly ascribed to shipping emissions (Liu et al., 2017). This phenomenon is not exclusive to Shanghai. Studies examining major waterways like the Yangtze River have reported similar trends. In a more direct health association, a 2015 study from the Pearl River Delta established a link between the rise in $PM_{2.5}$ and O_3 concentrations (both attributed to shipping emissions) and an increase in premature mortalities (Chen et al., 2019).

Such evidence underscores the need for an in-depth understanding of the health and environmental impacts of shipping emissions, especially in maritime hubs like Klang. While global studies offer insights, regional differences in shipping activity, meteorological conditions, population density, and health infrastructure suggest the need for location-specific research. Southeast Asia, despite its integral role in global maritime transport, remains underrepresented in scientific literature addressing these concerns. As the maritime industry continues to grow in the region, this knowledge gap becomes increasingly critical.

To this end, this study endeavours to fill this void by focusing on the port district of Klang, Malaysia. By examining the nexus between resultant air quality fluctuations and cardiovascular hospital admissions, this research aims to provide a clearer picture of the health ramifications of maritime activities in the region. Such insights are crucial not only for public health initiatives but also for environmental policymaking, ensuring that as the maritime industry grows, it does so sustainably and without compromising the well-being of the population. By investigating these concerns within the specific context of Klang, this study aims to provide valuable insights, potentially guiding policy decisions to balance economic growth with public health and environmental preservation.

2. Materials and methods

2.1. Study setting

Klang, located on Peninsular Malaysia's western coast, is a key coastal town in Selangor with 1.07 million residents in a 623 km^2 district, making it the third most populous district in the state of Selangor (Fig. 1(a)) (Department of Statistics Malaysia, 2020). Historically significant, it is now renowned for Port Klang – Southeast Asia's primary shipping gateway and an essential the Association of Southeast Asian Nations (ASEAN) trade route. The primary port of Malaysia, which comprises the South, North, and West Port terminals, holds the 12th position in global traffic rankings. Its geographical location is depicted in Fig. 1(b). In 2020, it handled over 13.24 million TEUs (Twenty-foot Equivalent Unit containers), with West Port's volume increasing 3% in early 2021. Klang also features the Port Klang Cruise Centre for naval and cruise vessels. The shipping sector emits pollutants like sulphur oxides, nitrogen oxides, and $PM_{2.5}$, which are environmental and health concerns (Andersson et al., 2009; Richter et al., 2004). Notably, those near ports experience heightened air pollution levels (Saxe and Larsen, 2004).

2.2. Data collection

2.2.1. Cardiovascular hospital admission data

Data on daily hospital admissions for cardiovascular diseases was collected for the period spanning from 1st January 2011 to 31st December 2019 from a public hospital in Klang. This institution, is the sole public hospital in the district, boasting 1258 inpatient beds (Hospital Tengku Ampuan Rahimah Klang, 2021). While there are several private hospitals within the district, the public sector shoulders the bulk of patient care – accounting for 64% of outpatient visits and 75% of inpatient bed days (Ministry of Health Malaysia, 2022).

For this study, data was extracted from the Malaysian Health Data Warehouse (MyHDW), a comprehensive electronic database for all public hospitals in Malaysia. The dataset encompassed details like the admission date, age, sex, and diagnosis – categorised under the International Classification of Diseases 10th revision (ICD-10) diagnosis code. Specifically, the cardiovascular diseases considered in this study fall under ICD-10 codes I00–I99. For subgroup analysis, the study stratified the data according to categories of cardiovascular diseases, focusing on the three subgroups with the highest frequencies among all ICD codes for diseases of the circulatory system. These included hypertensive diseases (ICD-10 codes I10–I15), ischemic heart diseases (ICD-10 codes I20–I25), and cerebrovascular diseases (ICD-10 codes I60–I69). Owing to stringent data privacy and confidentiality standards, patient addresses were inaccessible to the authors.

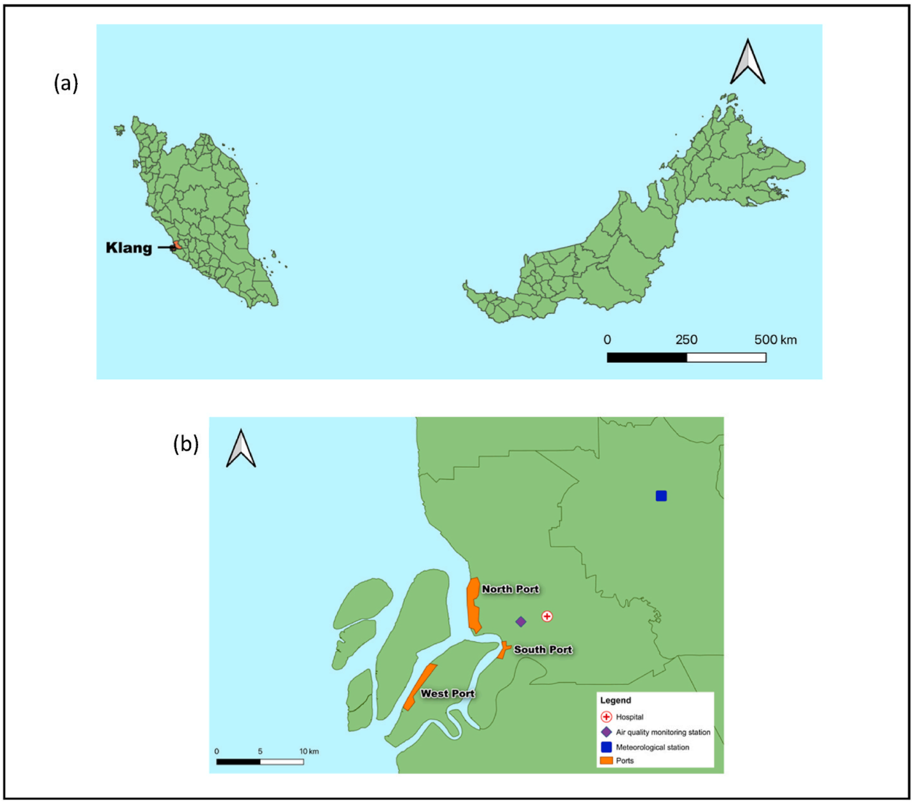

Fig. 1. (a) Location of Klang, Malaysia, (b) Study area.

2.2.2. *Air quality and meteorological data*

Daily ambient air pollution and meteorological data were sourced from the Malaysia Department of Environment (DOE)'s Continuous Air Quality Monitoring Station (CAQMS) between 1st January 2011 and 31st December 2019. Klang's sole monitoring station is centrally located, with ports within a 20 km radius. This study considered six pollutants: particulate matter with diameters ≤10 μm (PM_{10}), particulate matter with diameters ≤2.5 μm ($PM_{2.5}$), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO). Additionally, two meteorological parameters, temperature and relative humidity, were included. Due to an absence of $PM_{2.5}$ data before July 2017, significant data gaps were identified for this parameter, leading to its exclusion from that period. Another data void spanning three months was observed across all parameters, attributed to a transition in the concession holder in 2017.

The daily 24-h time series for PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, temperature, and relative humidity were deduced by averaging hourly concentrations. However, O_3 was calculated using the highest 8-h rolling average concentration. Of the total observations across the 3281-day study duration, 11.9% were categorised as 'missing', distributed as follows: PM_{10} (3%), NO_2 (8%), CO (6%), SO_2 (4%), O_3 (7%), relative humidity (31%), temperature (0%), and $PM_{2.5}$ (0% for the period between July 2017 to December 2019). To address these gaps, the Multivariate Imputation by Chained Equations (MICE) algorithm in R Studio's MICE package was employed. This choice was influenced by the algorithm's widespread success in multiple air pollution epidemiological studies, where it outperformed alternative imputation methods (Ibrahim et al., 2022; Javadi et al., 2021; Mohammed et al., 2021; Nordeide Kuiper et al., 2021; Strak et al., 2021).

3. Statistical analysis

Descriptive analysis presented quantitative data as follows: hospital admissions were reported using frequency, percentages, median, and interquartile ranges, while air quality levels and meteorological parameters were conveyed using means and standard deviations. Time series plots were generated for air pollutants and meteorological parameters to discern potential trends over the study duration. To evaluate the relationships between the six air pollutants and the two meteorological parameters, Spearman's correlation test was employed.

A quasi-Poisson generalised linear model (GLM) integrated with a distributed lag non-linear model (DLNM) was utilised to assess the association between air pollution levels and hospital admissions for cardiovascular diseases. The influence of daily air pollution levels on short-term cardiovascular hospitalisations was examined. Recognising the influence of seasonal variations and long-term trends on the dependent variable, the regression model was refined based on the adjustments proposed by Bhaskaran et al. (2013).

To mitigate the impact of long-term seasonality and potential confounding elements, the model integrated a natural spline function of time, characterised by 6 degrees of freedom annually. Additionally, time-varying covariates were incorporated. Temperature and humidity effects were controlled for through a spline boasting 3 degrees of freedom (*df*). The model also incorporated day-of-the-week (DOW) and public holidays to address potential confounding variables.

To account for the possible lagged effects of air pollution on health, time-lagged versions of the exposure variables were included, permitting the exploration of relationships between previous exposure days and current-day health consequences.

All pollutants were encapsulated using cross-basis matrices within a core DLNM. This facilitated a simultaneous assessment of effects across exposure and lag dimensions. The core model is articulated as:

$$\log(E(Yt)) = \alpha + cb(xt) + ns\left(\frac{6}{years}\right) + ns(Temp, df = 3) + ns(RH, df = 3) + DOW + Holiday$$

In this equation, *(E(Yt))* represents the cardiovascular or respiratory hospitalisations on day *t*; α is the intercept; *cb* denotes the cross-basis function; *(xt)* represents the daily average concentration of each air pollutant; *ns* indicates the natural spline function; *df* represents the degree of freedom; *Temp* denotes the average daily temperature; *RH* represents the daily relative humidity. The day of the week is represented by *DOW*, while *Holiday* is a binary variable that accounts for the effect of national and state public holidays.

Each pollutant was analysed using a single pollutant model that considered its effects from the current day, exposures over the previous seven days, and the cumulative impact of these exposures. Cumulative lag effects involves summing the effects of a pollutant over a specified range of lag days to observe the total impact on health outcomes across those days. It accounts for both the immediate and delayed impacts of exposures to pollutants, offering a comprehensive view of how exposure over several days influences health, not just on a single day but over a period. The optimal model was selected based on the smallest Akaike Information Criterion (AIC) value.

Stratified analyses were employed to determine the possible modifications in effects based on different cause-specific cardiovascular diseases and demographics, which encompassed admissions due to hypertensive conditions (ICD-10 I10–I15), ischaemic heart diseases (ICD-10 I20–I25), cerebrovascular diseases (ICD-10 I60–I69), sex, and age brackets (both below and above 65 years). Sensitivity tests, based on initial degrees of freedom concerning time, temperature, and relative humidity were also performed on the selected analysis for the entire population.

Furthermore, the model was modified to concurrently include two pollutants, selected based on their significance in the analysis of cardiovascular hospital admissions, to elucidate potential confounding or synergistic effects of multiple pollutants. In this study, two-pollutant models employing a combined cross-basis function were used to assess the joint impacts of pollutants such as NO_2 and PM on health outcomes across various lag times. This approach is particularly advantageous for evaluating synergistic effects, where the combined influence of pollutants exceeds the sum of their individual effects. By modelling these interactions, the models capture the temporal dynamics of pollutant exposure, identifying periods of heightened risk. The use of a combined cross-basis function simplifies the interpretation of complex pollutant effects by consolidating interactions into a single model component. Additionally, the two-pollutant models strike a balance between model complexity and interpretability, managing the computational burden effectively while controlling for the influence of one pollutant over another. This method reduces potential collinearity issues and preserves statistical power, facilitating a clearer understanding of the pollutants' impacts on health. However, $PM_{2.5}$ and PM_{10} were exceptions, owing to their high collinearity (Spearman rank correlations of 0.90; see Table 2). Notably, $PM_{2.5}$ is encompassed within PM_{10}, so their mutual effects were not explored.

Outcomes are presented in terms of relative risks (RR) and the associated 95% confidence intervals (CI) for daily cardiovascular hospital admissions, related to increments of 10 μg/m^3 for pollutants like PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and 1 mg/m$_3$ for CO, spanning both single lag effects (from lag 0 to lag 7) and cumulative lag effects from lag 00 to 07. Statistical analyses were executed utilising R software (version 4.2.2), incorporating the 'dlnm' and 'splines' packages.

4. Results

4.1. Descriptive analysis

Throughout the study period, there were a total of 59,681 hospital admissions due to cardiovascular diseases. On average, there were 18.22 admissions daily for this category, fluctuating within a range defined by a minimum of 1 and a maximum of 44 cases. Ischaemic heart diseases followed, with a total count of 26,438 and a daily average of 8.11 cases. The incidence for hypertensive and cerebrovascular conditions was lower, standing at 9266 and 10,740 cases, respectively.

The younger demographic (<65 years) recorded a higher number of admissions, totalling 42,983, compared to the older age group (≥65 years) with 16,583 cases. Sex-wise, males experienced a higher incidence with 36,296 cases, while females had 23,381 cases. Fig. 2(a)

Table 1
Summary statistics of daily cardiovascular hospital admissions by subtypes, age group, and sex, air pollutants, and meteorological parameters in Klang, Malaysia, January 2011–December 2019.

Variable	Total	Mean	SD	Min	P_{25}	Median	P_{75}	Max
Hospitalisations								
Cardiovascular diseases	59681	18.22	5.69	1	14	18	22	44
Hypertensive diseases	9266	3.16	1.95	1	2	3	4	15
Ischaemic heart diseases	26438	8.11	3.41	1	6	8	10	21
Cerebrovascular diseases	10740	3.45	1.80	1	2	3	5	10
Age group								
<65	42983	13.14	4.60	1	10	13	16	34
≥65	16583	5.12	2.41	1	3	5	7	16
Sex								
Male	36296	11.10	3.99	1	8	11	14	30
Female	23381	7.16	3.11	1	5	7	9	21
Air pollutants								
SO_2 (μg/m^3)		13.82	9.84	1.57	7.86	11.27	15.72	94.32
NO_2 (μg/m^3)		70.18	23.03	5.64	54.52	67.68	82.72	240.64
O_3 (μg/m^3)[a]		89.28	35.39	1.96	62.92	84.28	111.13	239.12
CO (μg/m^3)		1.91	0.85	0.21	1.35	1.76	2.29	9.73
PM_{10} (μg/m^3)		76.07	43.62	23.25	54.00	66.00	83.56	595.00
$PM_{2.5}$ (μg/m^3)		61.59	40.64	18.58	41.04	51.81	66.98	475.61
Meteorological parameters								
Temperature (°C)		28.14	1.14	24.80	27.30	28.10	29.00	31.50
Relative humidity (%)		81.83	4.08	75.10	78.58	81.40	84.73	96.30

Abbreviations: CO = carbon monoxide; Max = maximum; Min = minimum; NO_2 = nitrogen dioxide; O_3 = ozone; P_{25} = 25th percentile; P_{75} = 75th percentile; PM_{10}, particles with aerodynamic diameter <10 μm; $PM_{2.5}$ = particles with aerodynamic diameter <2.5 μm; SD = standard deviation; SO_2 = sulphur dioxide.

[a] Maximum 8 h moving average.

Table 2
Spearman's correlation coefficients (*r*) among air pollutants and meteorological variables in Klang, Malaysia.

	SO_2	NO_2	O_3	CO	PM_{10}	$PM_{2.5}$	Temp	RH
SO_2	1.00							
NO_2	**0.06**	1.00						
O_3	−0.02	**0.38**	1.00					
CO	−0.03	**0.33**	**0.07**	1.00				
PM_{10}	0.03	**0.24**	**0.23**	**0.43**	1.00			
$PM_{2.5}$	**−0.13**	**0.21**	**0.19**	**0.38**	**0.90**	1.00		
Temp	**0.09**	**−0.19**	**0.14**	**−0.11**	**0.19**	**0.18**	1.00	
RH	**−0.06**	**0.21**	**−0.12**	**0.13**	**−0.17**	**−0.10**	**−0.73**	1.00

Abbreviations as in Table 1. RH = relative humidity; Temp = Temperature. **Bold** indicates significant at $p < 0.05$.

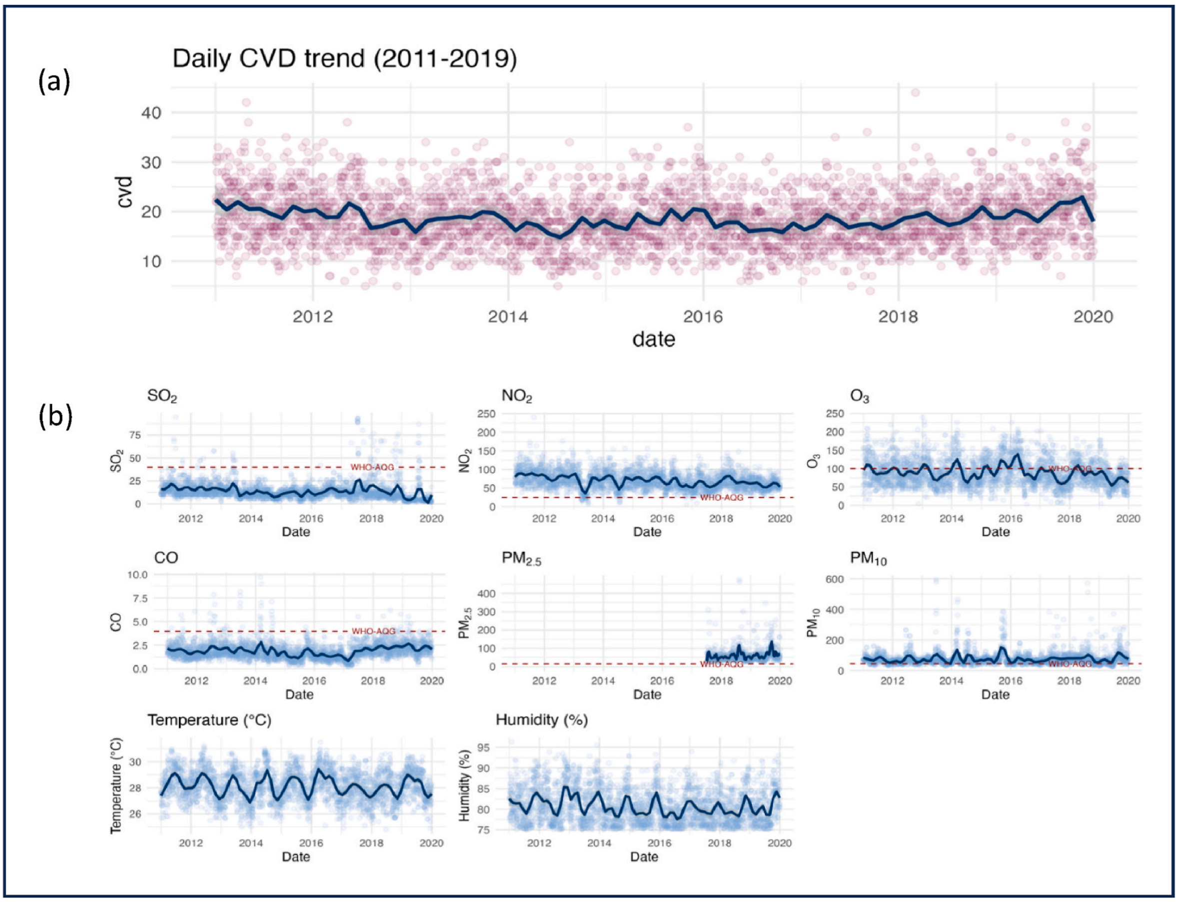

Fig. 2. Daily (a) cardiovascular hospital admission and (b) air pollutants level, temperature and relative humidity with smoothed trend in Klang, Malaysia from January 2010 to December 2019. Note: The red dashed line represents the World Health Organization's Air Quality Guideline (WHO-AQG) 2021 level.

depicts the daily cardiovascular hospital admissions, which have remained relatively consistent over the years.

The concentration of SO_2 was determined to average at 13.82 μg/m^3. Notably, NO_2 and O_3 displayed elevated mean concentrations, registering at 70.18 μg/m^3 and 89.28 μg/m^3, respectively. PM_{10} and $PM_{2.5}$ were found to have mean concentrations of 76.07 μg/m^3 and 61.59 μg/m^3, respectively. In contrast, CO manifested a lower mean concentration, averaging at 1.91 mg/m^3. Fig. 2(b) depicts the temporal variation of air pollutants and meteorological parameters over the duration of the study. When juxtaposed with the World Health Organization's Air Quality Guidelines (WHO-AQG) 2021, it was evident that the concentrations of PM_{10}, $PM_{2.5}$, and NO_2 exceeded the designated 24-h limits of 45 μg/m^3, 15 μg/m^3, and 25 μg/m^3, respectively. Conversely, the levels of SO_2 and CO were below the set guidelines, while O_3 concentrations closely aligned with the recommended threshold.

Regarding weather patterns, the data showed an average temperature of 28.14 °C, with relative humidity averaging at 81.83%. Temperature values mainly varied between 24.80 °C and 31.50 °C, while humidity ranged from 75.10% to 96.30%.

4.2. *Correlation between air pollutants and meteorological variables*

In Table 2, Spearman's correlation coefficients were utilised to examine the relationships between various air pollutants and meteorological factors. Significant correlations were observed in most of these relationships. However, significant associations between SO_2 and O_3, CO, and PM_{10} were not detected. A notable correlation between PM_{10} and $PM_{2.5}$ was identified, characterised by an *r* value of 0.90. A slight yet significant relationship between NO_2 and SO_2 was found, represented by an *r* value of 0.06. A moderate correlation between NO_2 and O_3 was also observed, with an *r* value of 0.38. Among the meteorological parameters, a strong inverse relationship between temperature and relative humidity was determined, evidenced by an *r* value of −0.73.

4.3. Association between air pollutants and cardiovascular hospital admissions

4.3.1. Single-pollutant models for total, subtype-, age- and sex-specific hospital admissions for cardiovascular diseases

Figs. 3 and 4 present the findings derived from single-pollutant models, focusing on single and cumulative lag effects influencing cardiovascular-related hospital admissions. These admissions are further segmented into categories: total, subtype, age, and sex. Among these, NO_2 was prominently associated with a surge in total cardiovascular hospital admissions. Specifically, at lag 0, a 10 μg/m^3 increment in NO_2 concentrations resulted in a 7.32% escalation in such admissions. Following this, at lag 1, both PM_{10} and $PM_{2.5}$ demonstrated discernible positive effects, although the magnitude was somewhat subdued compared to NO_2. Analysing the cumulative lag effects for total cardiovascular hospital admissions revealed consistent positive associations for NO_2 across various lags.

Delving deeper into disease-specific admissions, a marked positive association was evident at lag 4 for O_3 concerning hospitalisations attributed to hypertensive diseases, showcasing an RR of 1.0513 (95% CI: 1.013–1.091), with negative correlations observed at lag 1 for hypertensive diseases, and overall cardiovascular diseases and the male population within the cumulative lag effects. For ischaemic heart disease-related admissions, NO_2 presented a conspicuous association at lag 0, with an RR of 1.090 (95% CI: 1.037–1.146). Examining age-related trends, patients under 65 showed significant positive associations with NO_2 across multiple lags. In contrast, the senior demographic indicated heightened cardiovascular hospitalisations at lags 1 and 2, influenced predominantly by increased levels of CO and PM_{10}. Sex-based trends highlighted that male patients encountered a 9.36% rise

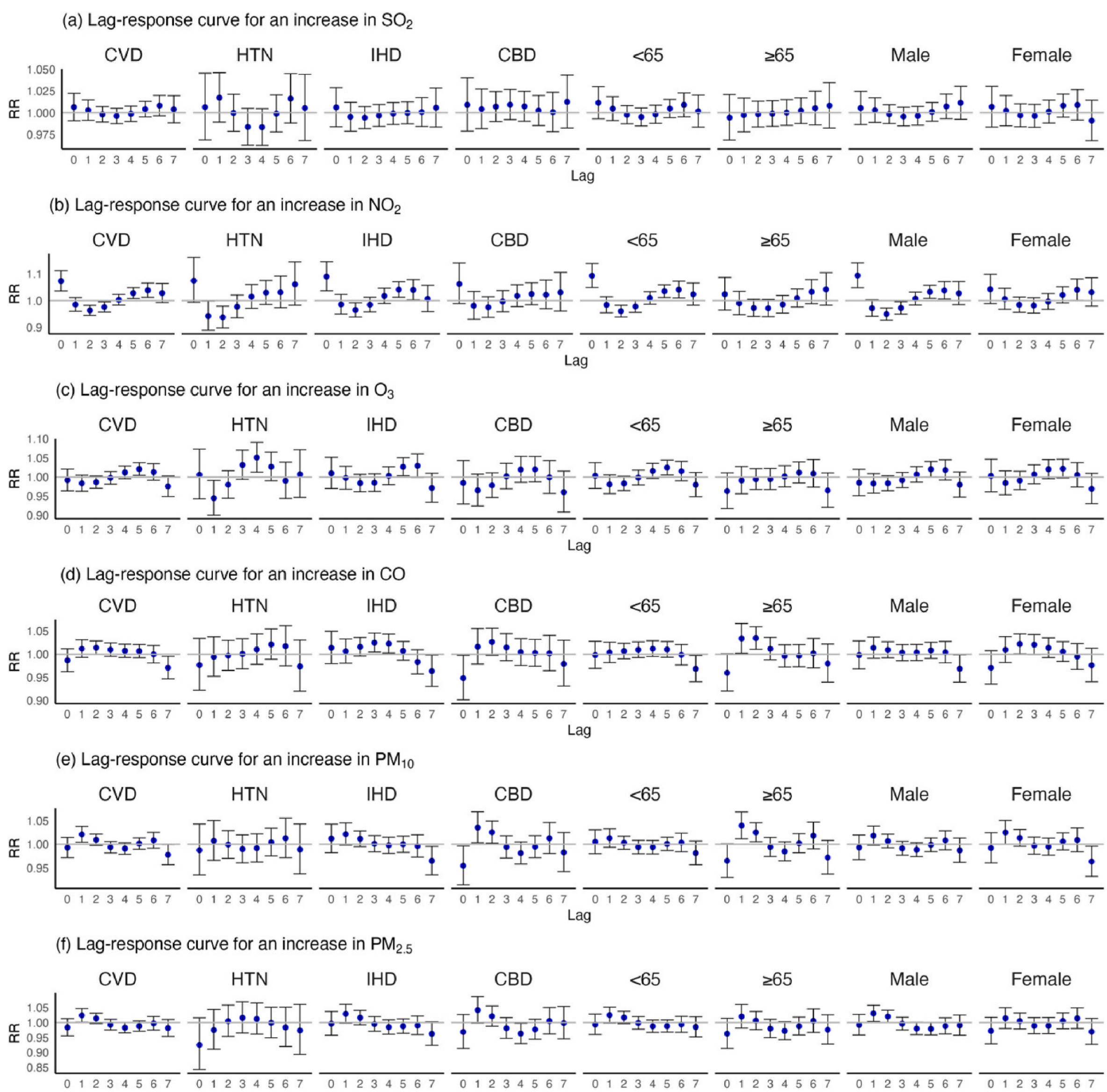

Fig. 3. Single lag effects of cardiovascular hospitalisations associated with a 10 μg/m^3 increase in (a) SO_2, (b) NO_2, (c) O_3, (e) PM_{10}, and (f) $PM_{2.5}$ and a 1 mg/m^3 increase in (d) CO in the distributed lag non-linear model.
Abbreviations: CVD = cardiovascular disease; HTN = hypertensive disease; IHD = ischaemic heart disease; CBD = cerebrovascular disease; <65 = patients below 65 years of age; ≥ = patients at or above 65 years of age. For age and sex subgroups, analysis was done for overall cardiovascular disease.

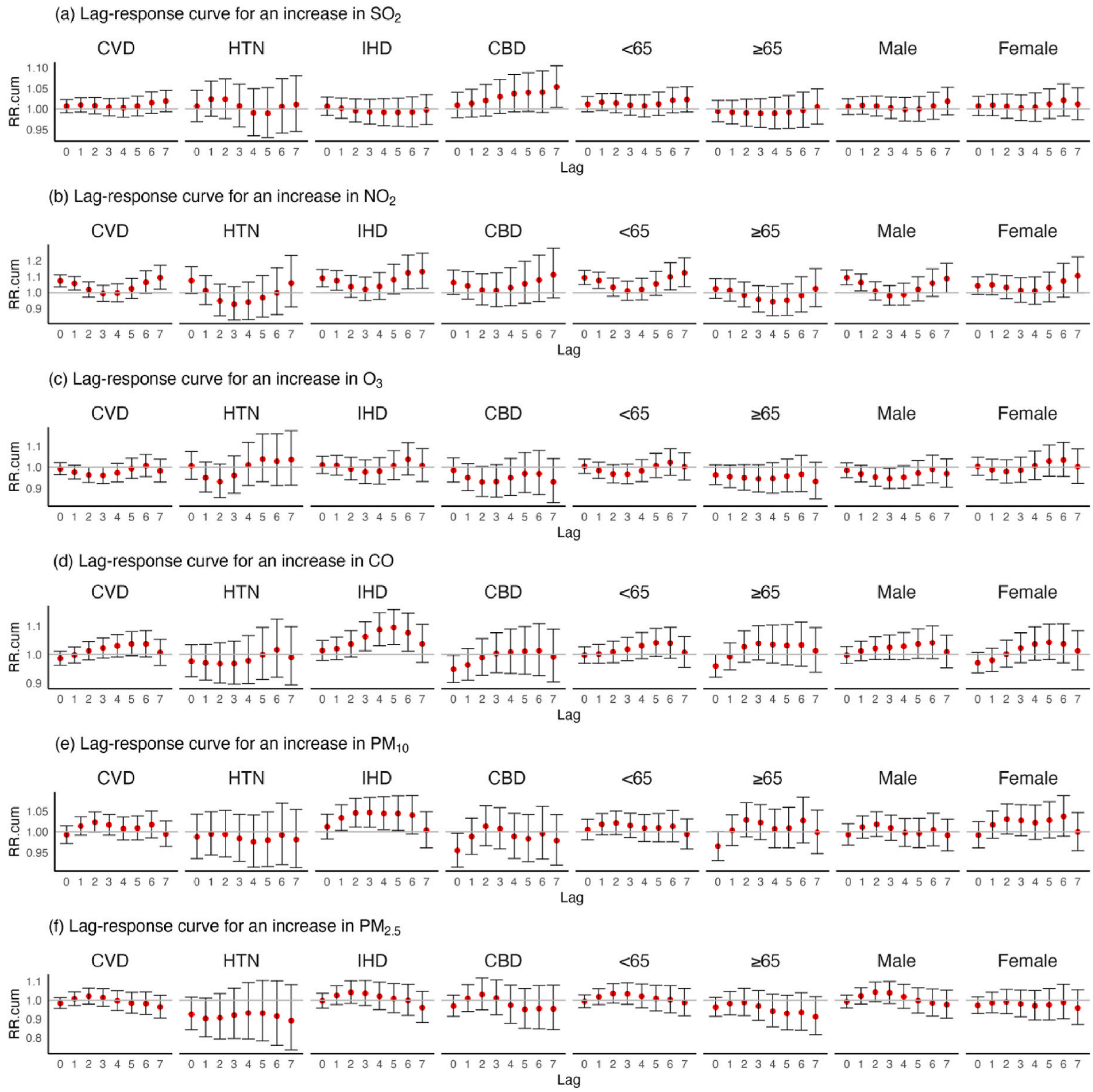

Fig. 4. Cumulative lag effects of cardiovascular hospitalisations associated with a 10 μg/m^3 increase in (a) SO_2, (b) NO_2, (c) O_3, (e) PM_{10}, and (f) $PM_{2.5}$ and a 1 mg/m^3 increase in (d) CO in the distributed lag non-linear model.
Abbreviations as in Fig. 3.

in hospitalisations at lag 0 for every 10 μg/m^3 increment in NO_2 concentrations, reflected by an RR of 1.094 (95% CI: 1.045–1.141). Interestingly, no such pronounced associations were observed for female patients.

In assessing cumulative lag effects, for SO_2, the peak RR was observed at lag 07 for cerebrovascular disease hospitalisations, registering an RR of 1.053 (95% CI: 1.004–1.105). For PM_{10}, the highest RR was found at lag 03, with a value of 1.047 (95% CI: 1.011–1.083). Notably, an increase of 10 μg/m^3 in O_3 at lag03 was associated with a 5.5% decrease in male patient hospitalisations, producing an RR of 0.945 (95% CI: 0.899–0.994). The association of NO_2 with hospital admissions for ischaemic heart diseases was particularly evident, presenting a 13.1% increase in hospitalisations for each 10 μg/m$_3$ rise in NO_2 concentration at lag07. This resulted in an RR of 1.131 (95% CI: 1.026–1.247). The strongest association for CO was identified at lag 05, with an RR of 1.095 (95% CI: 1.035–1.158). Fig. 5 presents an exposure-response curve that illustrates the association between primary air pollutants and the relative risks of cardiovascular hospital admissions, considering cumulative effects over a 7-day lag period.

4.3.2. Two-pollutant models for total, age- and sex-specific hospital admissions for cardiovascular diseases

Fig. 6 illustrates the relationship between cardiovascular disease-related hospital admissions and air pollution, as analysed through single-lag effects in two-pollutant models. SO_2 was excluded from these models due to the lack of significant correlations with total cardiovascular hospital admissions. Given the marked collinearity between PM_{10} and $PM_{2.5}$, and the more pronounced effects of PM_{10}, this pollutant was prioritised for subsequent analyses despite the evident associations that both pollutants displayed with cardiovascular hospital admissions in single-pollutant models. Consequently, composite two-pollutant models incorporating NO_2, O_3, CO, and PM_{10} were developed, following the methodologies outlined in the previous section for both total and categorical cardiovascular hospital admissions.

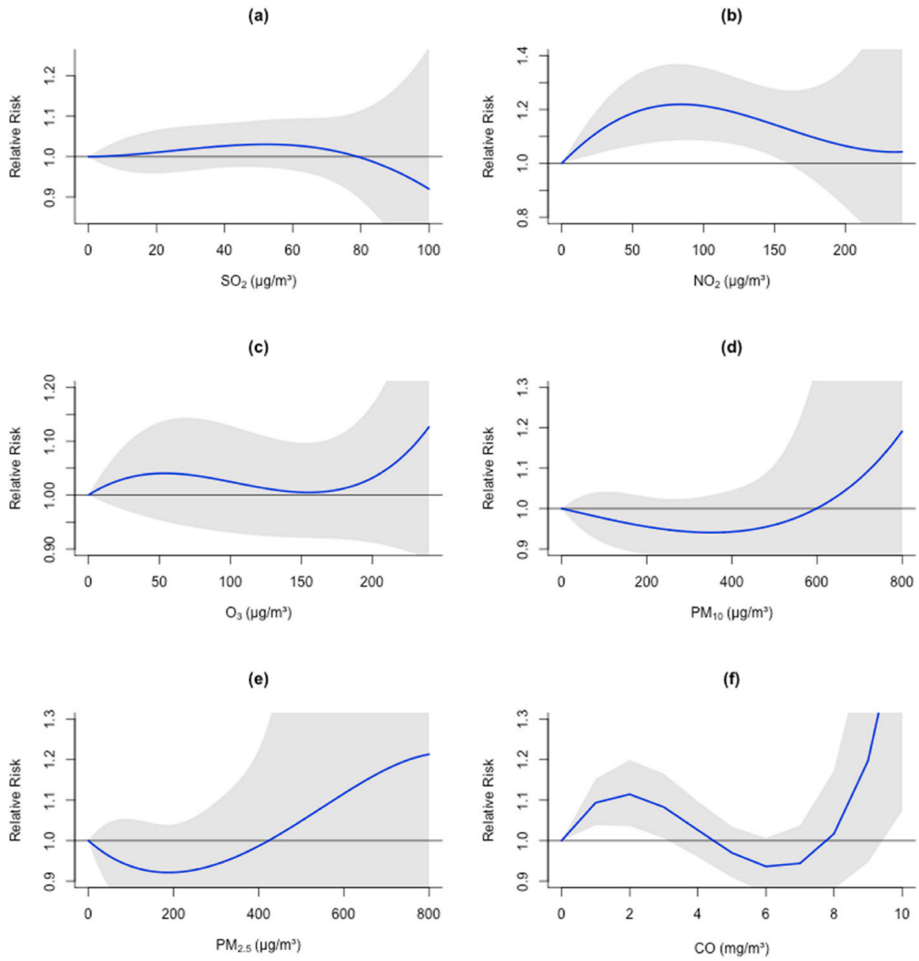

Fig. 5. Cumulative 7-day lagged association between (a) SO_2, (b) NO_2, (c) O_3, (d) PM_{10}, (e) $PM_{2.5}$, and (f) CO and cardiovascular hospital admissions. The shaded areas represent 95% confidence intervals (95%CI).

Significant increases in risk are predominantly seen at earlier lags for PM_{10}/NO_2 and NO_2/O_3 combinations, indicating an immediate health impact following exposure. Notably, at lag 0, NO_2 and PM_{10} are associated with an increased risk for overall CVD and IHD admissions, among individuals under 65 and males, with relative risks between 1.0392 and 1.0444. In contrast, for NO_2 and O_3 combinations, there is a reduction in hospital admissions at lag 2 for total CVD, in younger individuals and males, with relative risks from 0.9727 to 0.9792. Other pollutant combinations did not show significant associations at any lag days for the groups analysed. Furthermore, no significant risk changes were observed in CBD admissions, the elderly population, or females, implying that the immediate effects of these pollutants are either less pronounced or not detectable in these demographics.

4.3.3. Sensitivity analysis

Based on the findings from the sensitivity analysis, the application of varied degrees of freedom for long-term time trends, temperature, and humidity appeared not to notably alter the associations between air pollutant concentrations and cardiovascular disease-related hospital admissions (Appendix B). Consequently, the preliminary selection of 6 *df* for the time trend, and 3 *df* for both temperature and relative humidity, was retained for the final analytical models.

5. Discussion

This study, spanning January 2011 to December 2019, explored the associations between six pollutants (SO_2, NO_2, O_3, CO, PM_{10}, and $PM_{2.5}$) and various categories of cardiovascular admissions in Klang, Malaysia, focusing on both overall and specific conditions like hypertensive, ischaemic, and cerebrovascular diseases. Age and sex subgroups highlighted differences in vulnerability to these pollutants, underscoring the study's relevance due to the industrial nature of the port district and its elevated pollution levels.

Ischaemic heart diseases emerged as the predominant condition leading to hospital admissions, particularly among individuals under 65, reflecting the younger demographic structure in Malaysia where only 7.3% are aged 65 or older (Department of Statistics Malaysia, 2022a). Notably, males exhibited a higher rate of hospital admissions than females, possibly due to the progressive nature of atherosclerosis which is influenced by age, hypertension, and cholesterol levels (Bots et al., 2017).

Of particular concern were the heightened concentrations of NO_2, PM_{10}, and $PM_{2.5}$, which recurrently exceeded the prescribed guidelines. In Klang, the rise in NO_2 levels can be attributed to a notable increase in vehicular numbers and various combustion processes. An assessment of the NO_2 emission load revealed that power plants contributed 66%, motor vehicles 25%, industries 7%, and other sources accounted for 2% (Department of Environment Malaysia, 2020).

Annually, $PM_{2.5}$ and PM_{10} concentrations consistently register at elevated levels. In port regions such as Klang, these heightened pollution concentrations can be ascribed to a multitude of factors. Predominant sources encompass vehicular emissions, diverse industrial activities, and

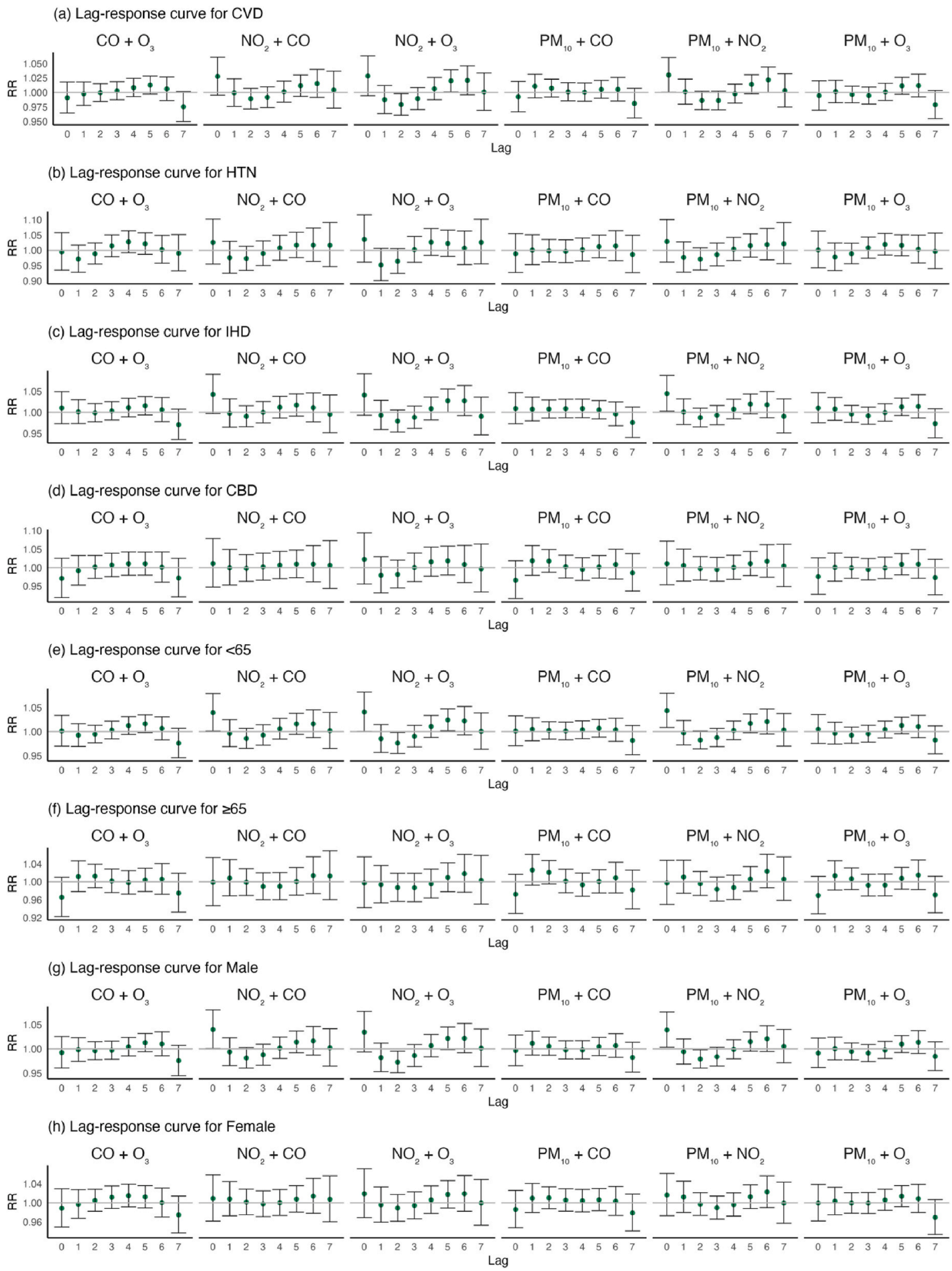

Fig. 6. Two-pollutant models of cardiovascular hospitalisations associated with a 10 μg/m^3 increase in NO_2, O_3, PM_{10}, and a 1 mg/m^3 increase in CO in the distributed lag non-linear model. Abbreviations as in Fig. 3.

extensive maritime operations. Moreover, the recurring Southeast Asian haze phenomenon further augments these particulate matter levels. This haze is largely a consequence of deforestation, notably in regions like Sumatra and Kalimantan (Yusof et al., 2017). Factors that exacerbate this haze encompass climatic anomalies, such as the El Niño event, which predisposes regions to drier conditions, thereby elevating their vulnerability (Ewing and McRae, 2012).

The most pronounced impact of air pollutants on cardiovascular hospital admissions and its subcategories was evident in NO_2 exposure. For overall hospital admissions and its three subcategories, significant relative risks were discernible at lag 0 (the same day as elevated pollutant concentrations). This association experienced a marked decrease, resulting in an inverse relationship between lags 1 and 4. Thereafter, the risks exhibited an upward trend, although they were not statistically significant. Specifically, at lag 0, an elevation of 10 $\mu g/m^3$ in NO_2 concentrations correlated with a 7.32% augmentation in overall cardiovascular hospital admissions (RR = 1.073, 95% CI = 1.036–1.111). The findings of this research concur with several other studies that highlight the association between NO_2 concentrations and cardiovascular complications. Specifically, our findings align with studies conducted both in Iran, which identified a direct correlation between increasing NO_2 levels and a rise in cardiovascular hospital admissions (Dastoorpoor et al., 2019), and in Kuala Lumpur (Sofwan et al., 2021). NO_2 can adversely impact the cardiovascular system in diverse manners. For instance, one study demonstrated that NO_2 exposure impairs cardiac mitochondrial function. When combined with coronary endothelial dysfunction, this impairment can lead to cardiac anomalies, signifying NO_2 as a plausible risk factor for ischaemic heart diseases (Karoui et al., 2020). Land-use regression modelling undertaken in Kuala Lumpur indicated a significant relationship between NO_2 concentrations and the city's proliferating road network. This finding further cements NO_2's designation as a traffic-related pollutant (Halim et al., 2020).

Interestingly, while a discernible positive association was observed between cardiovascular diseases and NO_2 exposure on the same day (lag 0), a negative correlation emerged at lag 2. This pattern persisted across hypertensive diseases, ischaemic heart diseases, individuals under 65 years of age, and the male group. This pattern, suggests a direct impact of NO_2 on cardiovascular function through mechanisms such as increased oxidative stress or inflammation initially. However, the negative correlation at lag 2 may reflect delayed physiological adaptations or desensitisation to NO_2 exposure, possibly due to regulatory feedback mechanisms within the cardiovascular system that enhance resilience to pollution, or behavioural changes following high exposure days (Guo et al., 2022; Huang et al., 2023; Lederer et al., 2021). Additionally, confounding factors like variations in medication use following higher pollution days could also influence these correlations (Lee et al., 2023; Tornevi et al., 2023).

For CO, a statistically significant reduction in hospital admissions due to cerebrovascular diseases was observed at lag 0. Notably, total cardiovascular and other subcategories of hospital admissions did not demonstrate any significant risks across the evaluated lag days. This observation contrasts with a recent systematic review which found no significant associations between elevated CO concentrations and stroke incidence and mortality (Niu et al., 2021). Conversely, another study identified a correlation between CO exposure and haemorrhagic stroke at lag 01 (Li et al., 2023). Supporting this, research employing animal models revealed that CO influences vasodilation, neurotransmission, inhibition of platelet aggregation, and anti-smooth muscle proliferation (Kamat et al., 2019). These mechanisms suggest potential pathways through which CO might induce vascular damage, culminating in haemorrhagic stroke.

The negative association at lag 1 for O_3 in hypertensive diseases, overall cardiovascular diseases and male populations within the cumulative lag effects could potentially be explained by the negative correlation might reflect a short-term displacement effect, where vulnerable individuals who are most susceptible to the effects of O_3 might experience health events sooner, leading to a temporary reduction in event rates following the initial exposure day. This phenomenon, often referred to as the harvesting effect, might explain the apparent protective effect in subsequent days (Adebayo-Ojo et al., 2022; Zhu et al., 2023).

In the present study, elevations in PM_{10} and $PM_{2.5}$ concentrations were not associated with an increase in total cardiovascular hospital admissions or its subtypes across various lags. However, a statistically significant inverse association was observed between these particulate concentrations and cerebrovascular disease admissions at lag 0. This finding contrasts with existing literature, where robust evidence has established a link between PM exposure and cerebrovascular disease outcomes (de Bont et al., 2022; Kowalska and Kocot, 2016; Tian et al., 2022). There were no discernible associations observed between the remaining air pollutants SO_2 and O_3 and total cardiovascular hospital admissions and its subcategories.

In the stratified age analysis, the following observations were made: For individuals aged below 65, there was an associated increase in hospital admissions on the same day (lag 0) with a relative risk (RR) of 1.093 (95% CI = 1.049–1.139). In contrast, among individuals aged 65 and above, inverse associations were detected for cardiovascular hospital admissions in relation to CO and PM_{10} concentrations at lag 0, exhibiting relative risks of 0.960 (95% CI = 0.920–1.001) and 0.965 (95% CI = 0.930–1.001), respectively. Subsequent lags (1 and 2) revealed positive associations for these pollutants in the same age category.

In the sex-stratified analysis, there was a statistically significant association between an increase in NO_2 at lag 0 and a 9.26% increase in cardiovascular hospital admission rates (95% CI: 1.049–1.139). The associations between other pollutants and cardiovascular hospital admissions across various time lags were not as pronounced. This is in line with a broader scientific understanding that suggests differential responses to air pollution-related cardiovascular disease between males and females. Underlying causes for this disparity are multifaceted, encompassing hormonal, genetic, and lifestyle factors (Kittnar, 2020; Liao et al., 2023).

Further analysis, focusing on a cumulative 7-day lagged association, has revealed distinct patterns in how different pollutants impact cardiovascular health. NO_2, O_3, and CO are particularly noteworthy due to their pronounced influence on cardiovascular admissions at relatively low concentrations. The significant increase in relative risks associated with these pollutants suggests that even modest elevations in their levels can exacerbate cardiovascular conditions. This might be attributed to their direct effects on cardiovascular and respiratory systems, such as NO_2's role in inducing oxidative stress and inflammatory responses, O_3's impact on lung function and systemic inflammatory processes, and CO's interference with oxygen transport in the bloodstream. An intriguing pattern was observed with PM_{10} and $PM_{2.5}$. At lower levels, an inverse relationship was noted between particulate concentrations and cardiovascular admissions, a phenomenon that did not hold once concentrations of PM_{10} and $PM_{2.5}$ reached 600 $\mu g/m^3$ and 400 $\mu g/m^3$, respectively. At these higher thresholds, there was a notable uptick in the relative risks of cardiovascular hospital admissions. This could suggest a threshold effect, where particulate matter impacts cardiovascular health significantly only beyond certain concentration levels. The initial inverse relationship might be influenced by the body's ability to cope with or adapt to lower levels of particulates without overt health consequences, or it could reflect variances in exposure assessment or reporting in areas with generally lower pollution levels.

The observed synergistic effects of NO_2 and PM_{10} in the two-pollutant model can be attributed to several factors. Epidemiological evidence consistently indicates that the associations with NO_2 may not solely represent the direct adverse effects of NO_2 itself but rather reflect the health impacts of other air pollutants, primarily PM or other components typically associated with traffic-related air pollution (Mills et al., 2016). This interpretation is largely due to the strong correlations identified between NO_2 and other combustion-derived pollutants, particularly PM. Numerous studies have demonstrated a positive correlation between NO_2 and PM (Cesaroni et al., 2013; Dominici et al., 2010; Siddika et al., 2020; Szyszkowicz, 2015). In certain analyses, NO_2 has been used as a surrogate for PM, while others have emphasised the confounding effects of PM (Brook et al., 2007; Pan et al., 2018; Samoli et al., 2006; Seaton and Dennekamp, 2003). According to a seven-year air pollutant study in Iran analysed using the AirQ + model, Naghan et al. reported that the short-term health impacts of $PM_{2.5}$ were more pronounced than those of NO_2, although the long-term effects of NO_2 exceeded those of $PM_{2.5}$ (Naghan et al., 2022).

In this study, significant concerns for public health and environmental safety in a port district were highlighted. High levels of NO_2 were found to be linked to an increase in hospital admissions for cardiovascular issues, with older males being particularly affected. Given these insights, we recommend the implementation of stricter air quality monitoring and control measures in port cities. Policies focusing on reducing NO_2 emissions from shipping and other industrial sources could significantly mitigate the health risks associated with air pollution. Additionally, public health initiatives should aim to educate residents about the risks of high pollution days and promote behaviours that could reduce exposure.

Future research should focus on longitudinal studies that can further elucidate the chronic effects of repeated short-term NO_2 exposure on cardiovascular health. Moreover, exploring the effectiveness of specific intervention strategies in real-world settings would provide valuable data to guide policy decisions and public health recommendations.

Several limitations of this study should be considered and their potential effects acknowledged. This study's reliance on data from a single public hospital introduces limitations that might affect the generalisability of the findings. There is a concern regarding the potential under-representation of wealthier segments of the population who may prefer private hospitals, as opposed to the less affluent who predominantly use public services. A significant income gradient exists in the utilisation of public sector services, with 93% of patients from the lowest income quintile using public services compared to only 42% from the highest income quintile (Ministry of Health Malaysia, 2016). The combined analysis of elective and emergency cases could introduce noise into the data, potentially masking the true association between air pollution and cardiovascular admissions. These factors are crucial in understanding health impacts of air pollution within varying demographic and health infrastructure contexts. The approach of selecting pollutants based solely on their statistical significance in exploratory models is recognised as a limitation of this study, as it does not facilitate robust causal inferences. Future research would benefit from employing causal inference frameworks and methodologies capable of handling multi-pollutant interactions more comprehensively. Lastly, the potential information bias arising from the use of fixed monitoring stations could lead to misclassification of exposure levels, possibly diluting the observed associations or generating spurious findings.

6. Conclusion

In this time-series analysis, an association was observed between same day exposure to NO_2 and daily cardiovascular disease-related hospital admissions in populations residing near shipping ports, with less pronounced associations in other pollutants. The association between ambient air pollution and cardiovascular hospital admissions appeared more pronounced in elderly individuals and males. These results contribute to the existing evidence, enhancing the foundation upon which environmental regulations are designed to ensure optimal public health protection. In regions where the maritime sector is a significant economic driver, additional studies focusing on ambient air pollution and cardiovascular diseases are warranted.

Ethical approval

This research received approval from the Medical Research and Ethics Committee of the Malaysia Ministry of Health (NMRR-21-593-58554 (IIR)). Given the absence of direct patient involvement and the anonymity of all data, written consent was deemed unnecessary.

CRediT authorship contribution statement

N.N. Abd Rahim: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **R. Ahmad Zaki:** Conceptualization, Methodology, Supervision, Writing – review & editing. **A. Yahya:** Supervision, Writing – review & editing. **W.R. Wan Mahiyuddin:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

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

Data availability

Data will be made available on request.

Acknowledgments

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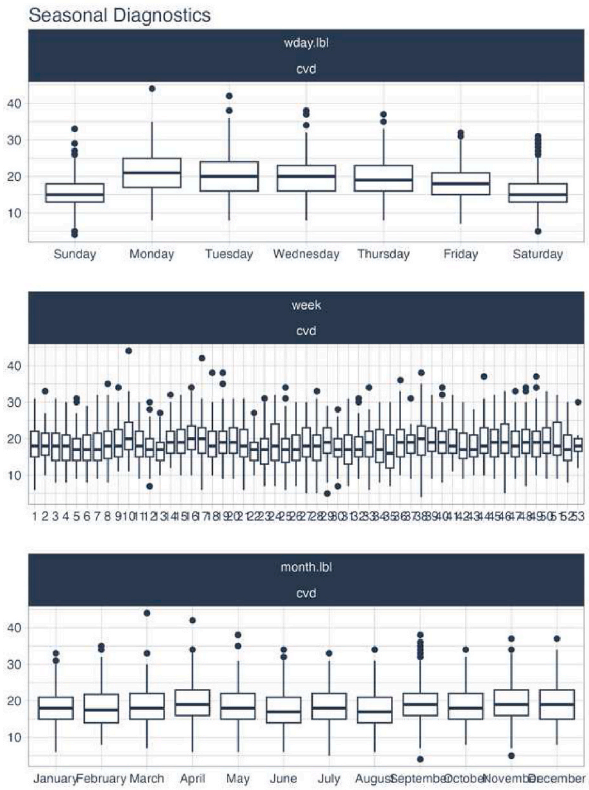
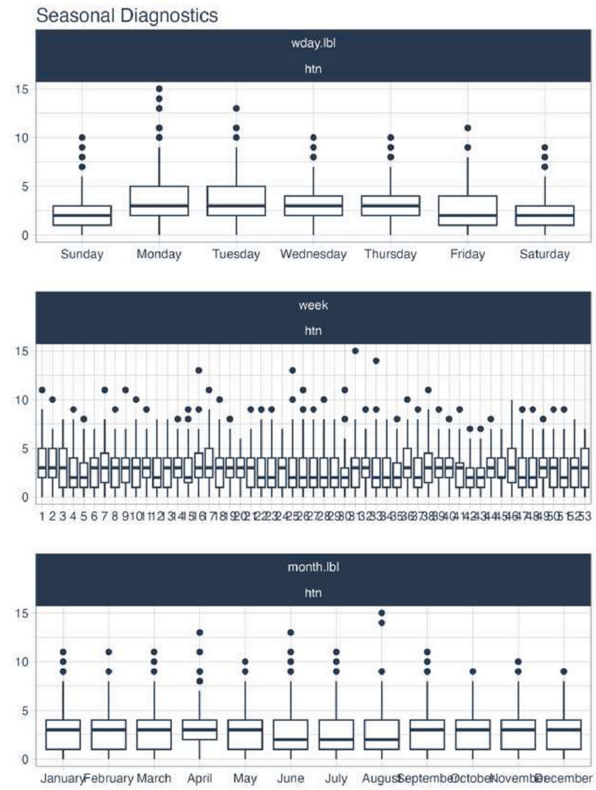
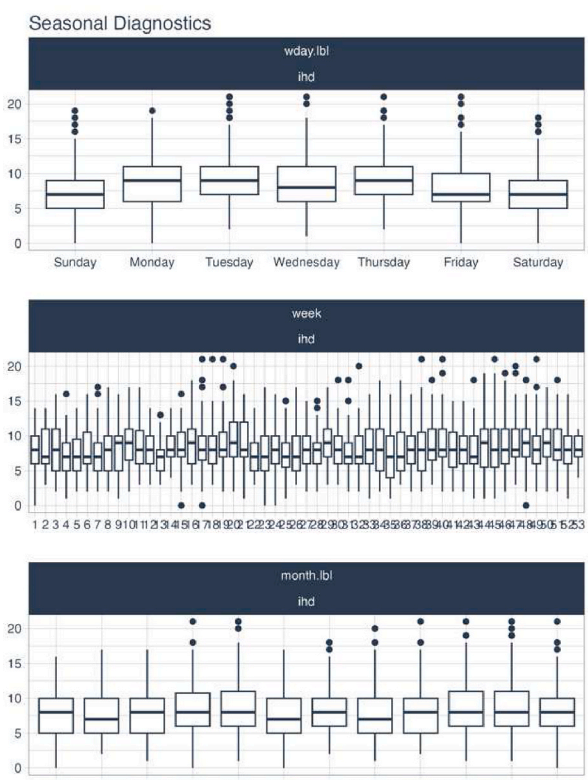
Appendix C. Supplementary data

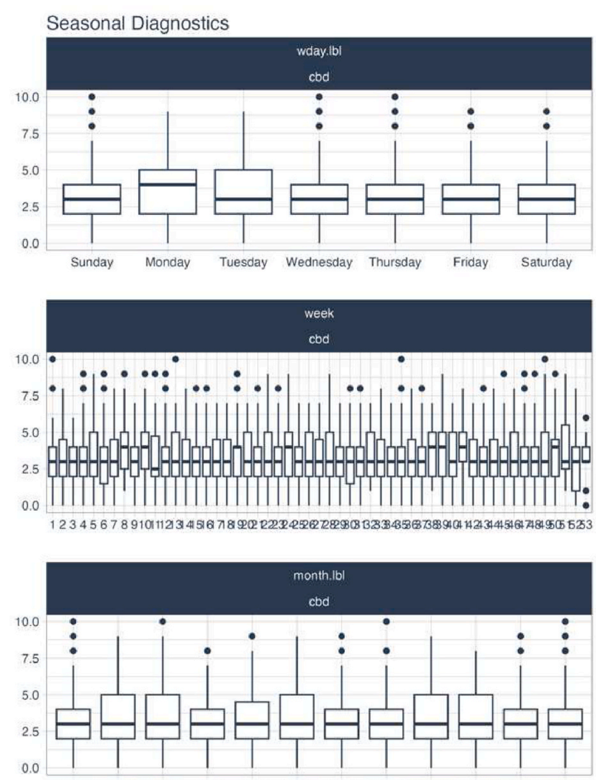
Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2024.120629.

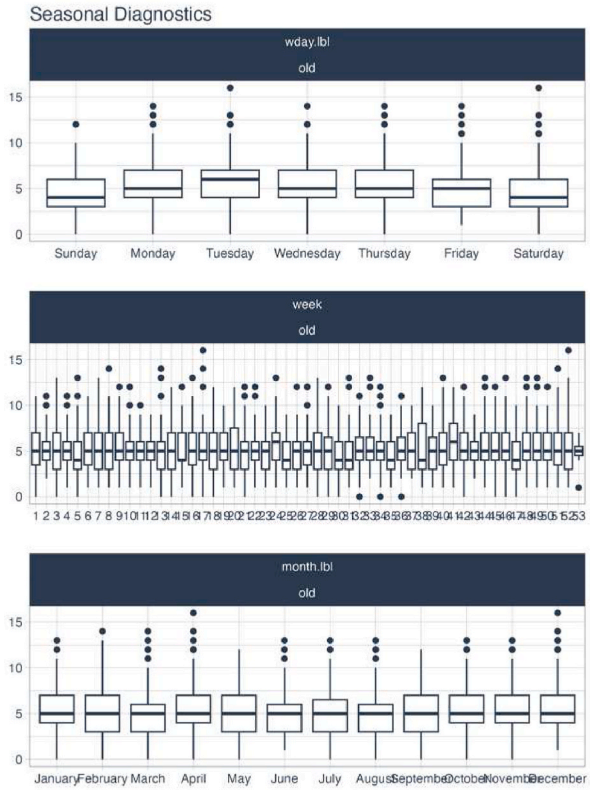
APPENDIX A. Analysis of Seasonal Patterns in Cardiovascular Hospital Admissions










Seasonal Diagnostics
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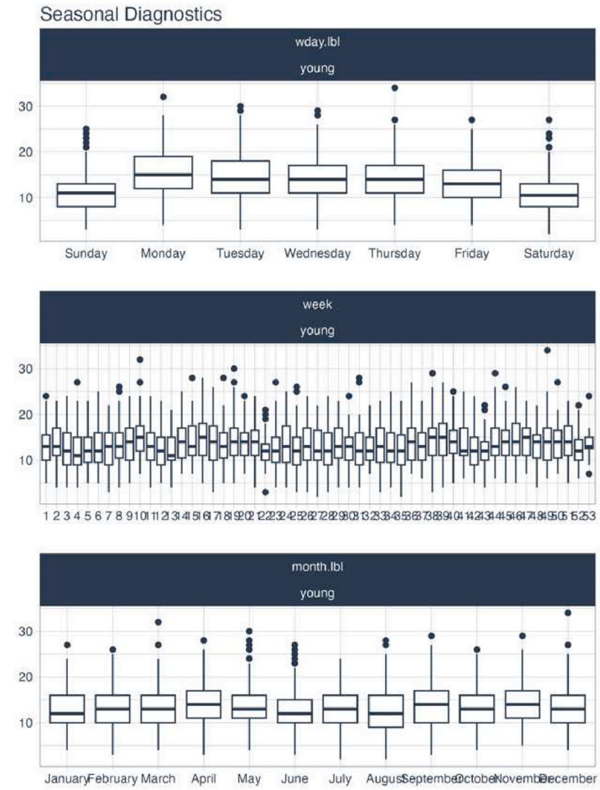
old
Sunday Monday Tuesday Wednesday Thursday Friday Saturday
week
old
month.lbl
old
January February March April May June July August September October November December
0
5
10
15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wday.lbl
young
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week
young
month.lbl
young
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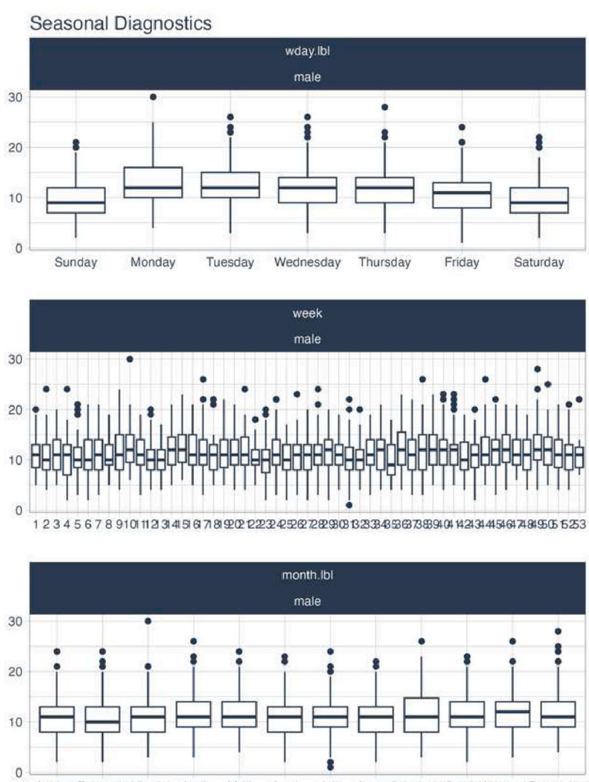
10
20
30


Seasonal Diagnostics
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male
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male
month.lbl
male
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0
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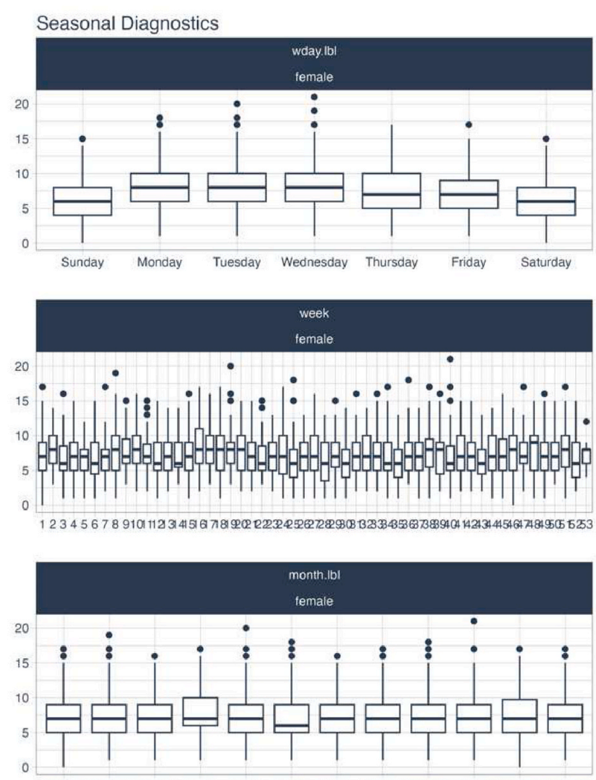
30


Seasonal Diagnostics
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week
female
month.lbl
female
January February March April May June July August September October November December
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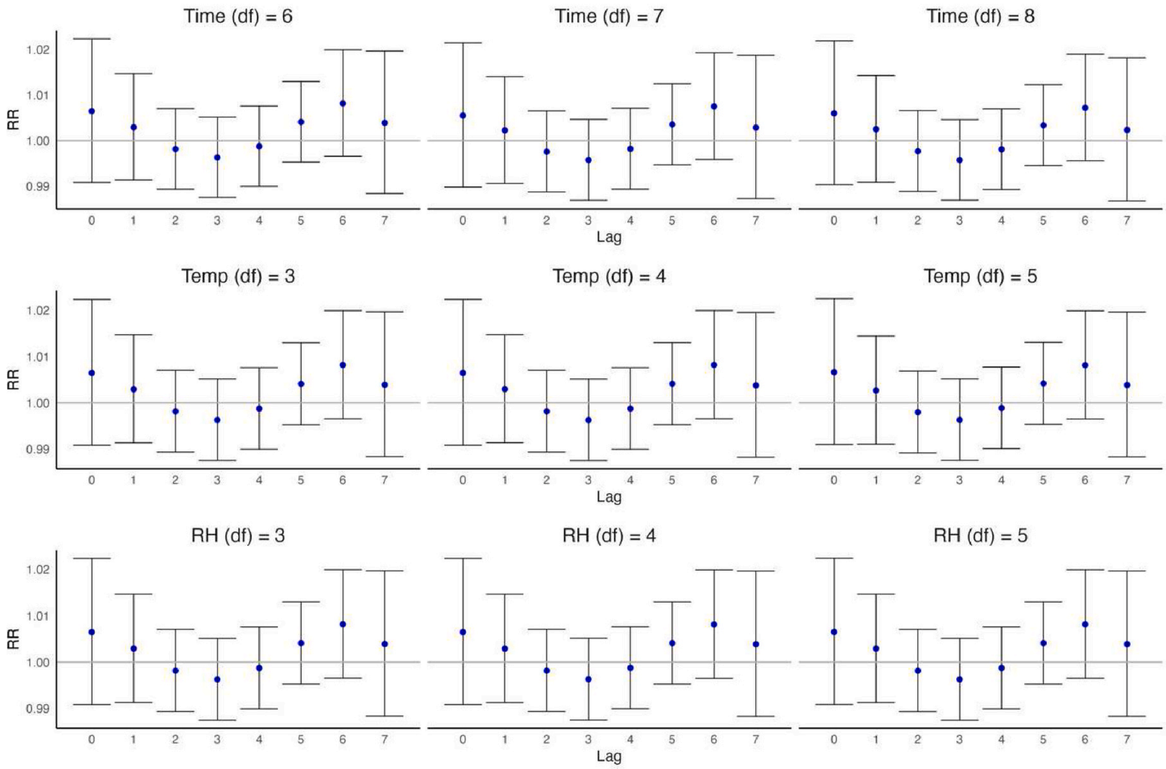
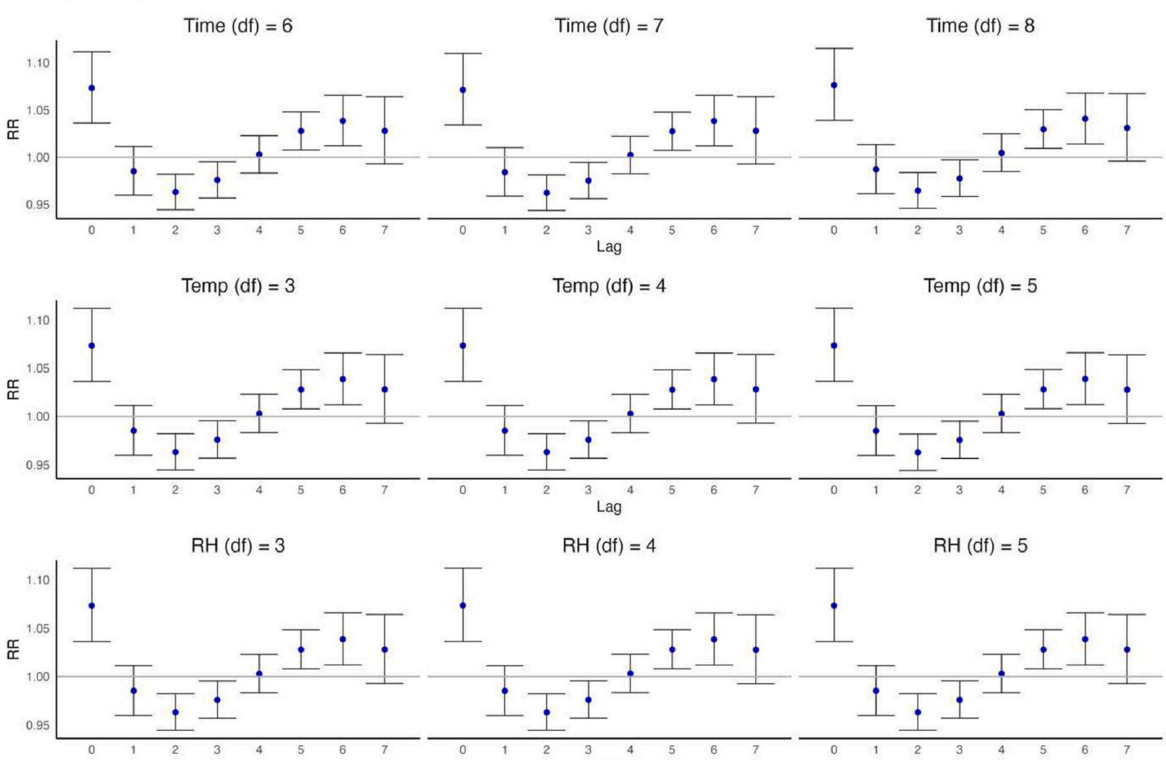
APPENDIX B. Sensitivity Analysis for Degrees of Freedom in Time Trend, Temperature, and Humidity Variables

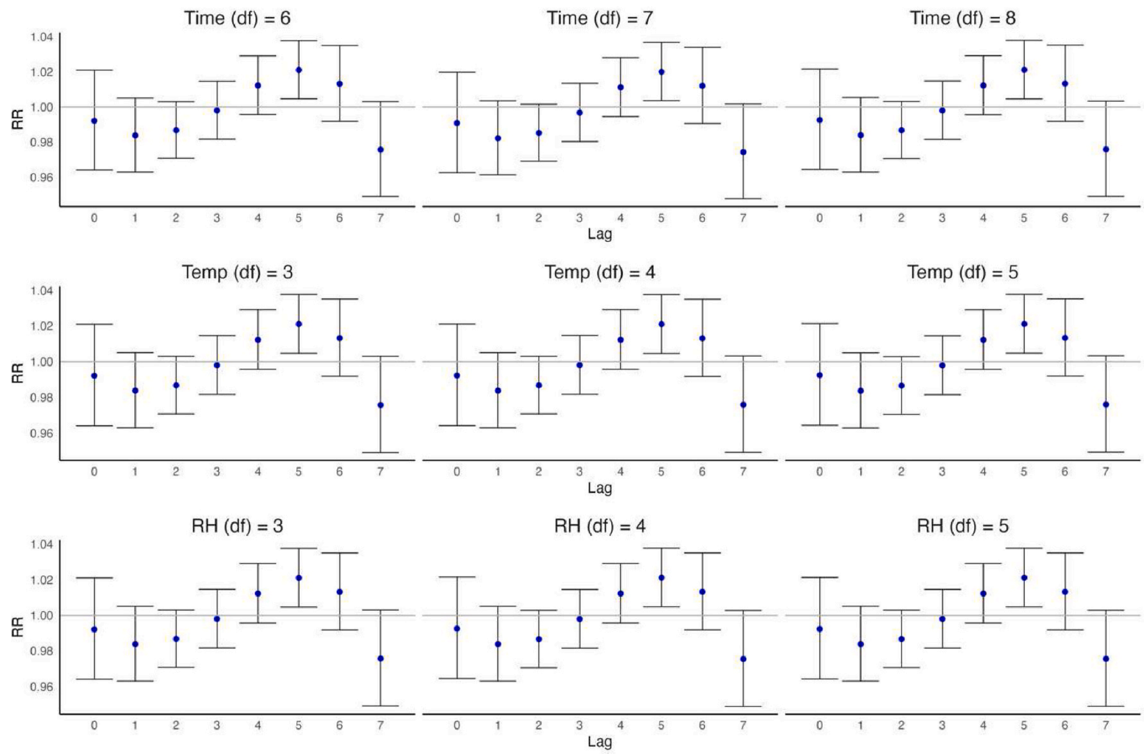
a) SO_2



b) NO_2



c) O_3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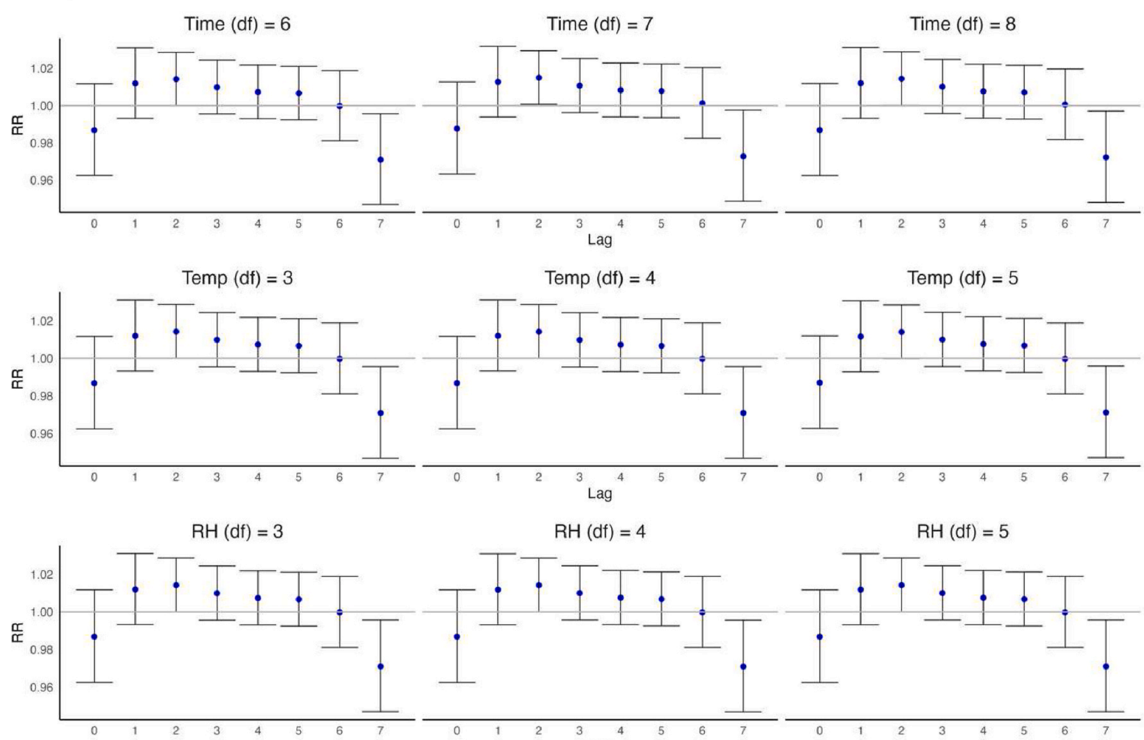
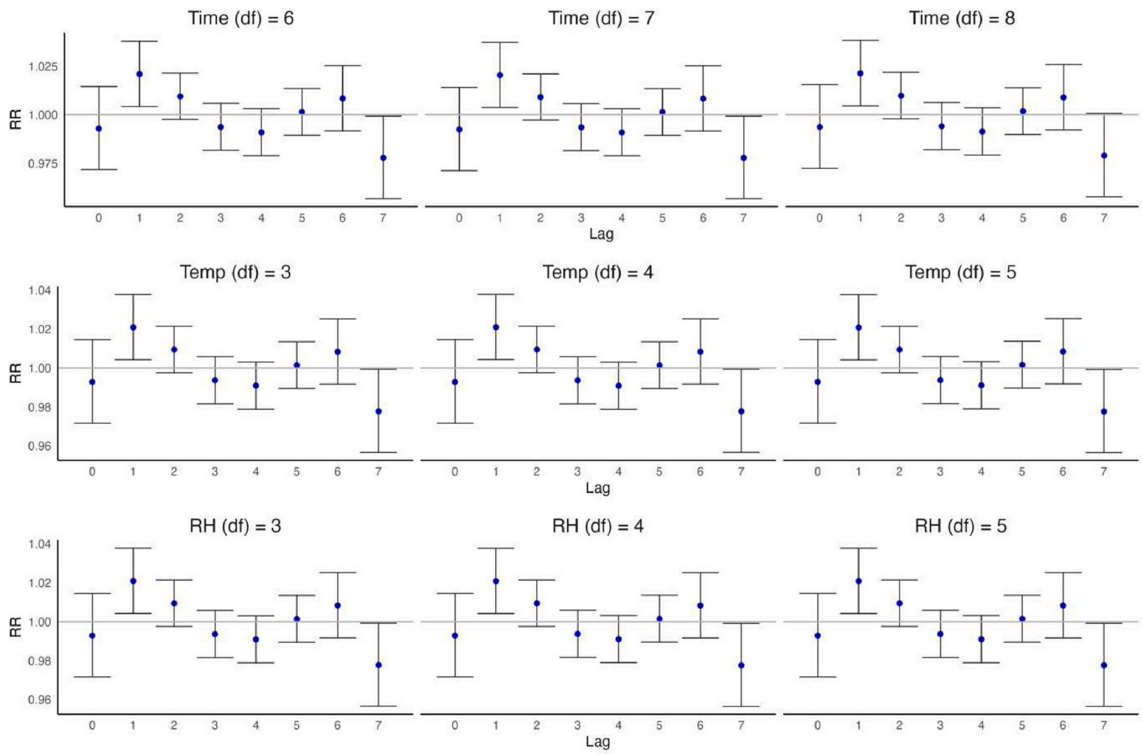
Time (df) = 7
Time (df) = 8
Temp (df) = 3
Temp (df) = 4
Temp (df) = 5
RH (df) = 3
RH (df) = 4
RH (df) = 5
RR
Lag
0.96
0.98
1.00
1.02
1.04
0
1
2
3
4
5
6
7

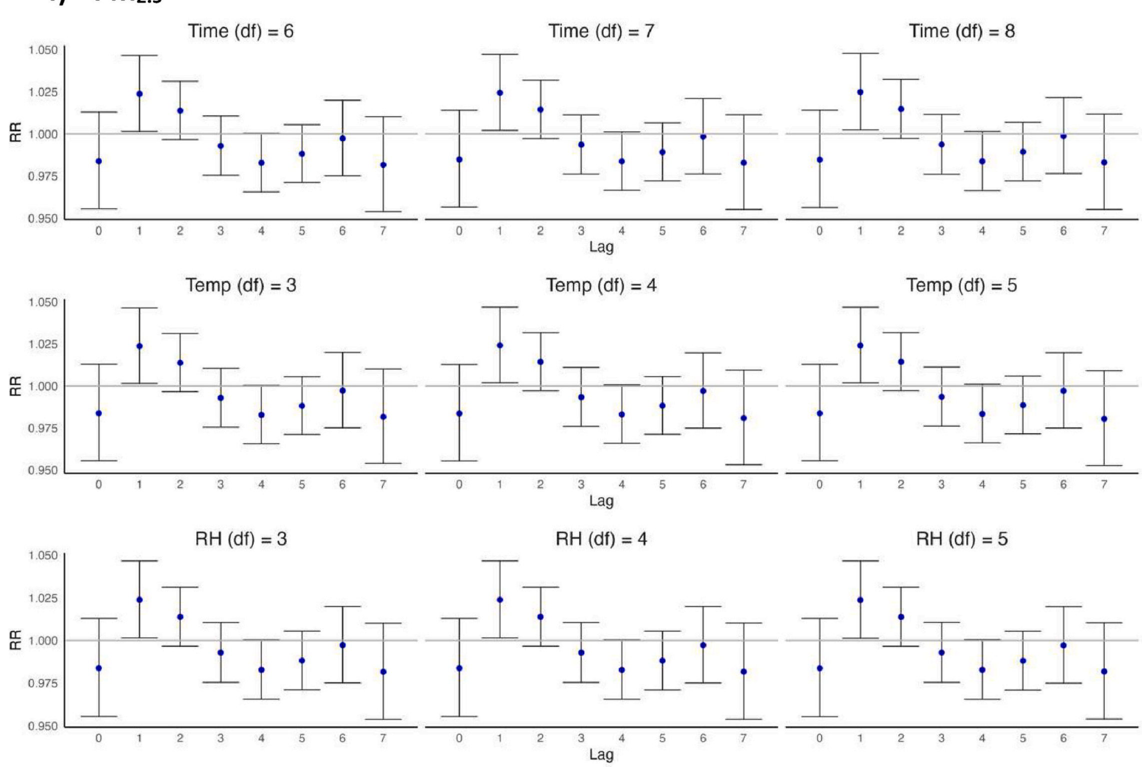
d) CO


Time (df) = 6
Time (df) = 7
Time (df) = 8
Temp (df) = 3
Temp (df) = 4
Temp (df) = 5
RH (df) = 3
RH (df) = 4
RH (df) = 5
RR
Lag
0.96
0.98
1.00
1.02
0
1
2
3
4
5
6
7

e) PM_{10}


Time (df) = 6
Time (df) = 7
Time (df) = 8
Temp (df) = 3
Temp (df) = 4
Temp (df) = 5
RH (df) = 3
RH (df) = 4
RH (df) = 5
RR
Lag
0 1 2 3 4 5 6 7
1.025
1.000
0.975
1.04
1.02
1.00
0.98
0.96

f) $PM_{2.5}$


Time (df) = 6
Time (df) = 7
Time (df) = 8
Temp (df) = 3
Temp (df) = 4
Temp (df) = 5
RH (df) = 3
RH (df) = 4
RH (df) = 5
RR
Lag
0 1 2 3 4 5 6 7
1.050
1.025
1.000
0.975
0.950

References

Abdullah, A., Samah, M., Tham, Y., 2012. An overview of the air pollution trend in Klang Valley, Malaysia. Open Environ. Sci. 6, 13–19.

Adebayo-Ojo, T.C., Wichmann, J., Arowosegbe, O.O., Probst-Hensch, N., Schindler, C., Künzli, N., 2022. Short-term effects of PM10, NO2, SO2 and O3 on cardio-respiratory mortality in Cape Town, South Africa, 2006–2015. Int. J. Environ. Res. Publ. Health 19 (13), 8078.

Andersson, C., Bergström, R., Johansson, C., 2009. Population exposure and mortality due to regional background PM in Europe–Long-term simulations of source region and shipping contributions. Atmos. Environ. 43 (22–23), 3614–3620.

Bhaskaran, K., Gasparrini, A., Hajat, S., Smeeth, L., Armstrong, B., 2013. Time series regression studies in environmental epidemiology. Int. J. Epidemiol. 42 (4), 1187–1195. https://doi.org/10.1093/ije/dyt092.

Bots, S.H., Peters, S.A.E., Woodward, M., 2017. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. BMJ Glob. Health 2 (2), e000298. https://doi.org/10.1136/bmjgh-2017-000298.

Brook, J.R., Burnett, R.T., Dann, T.F., Cakmak, S., Goldberg, M.S., Fan, X., Wheeler, A.J., 2007. Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. J. Expo. Sci. Environ. Epidemiol. 17 (2), S36–S44.

Cesaroni, G., Badaloni, C., Gariazzo, C., Stafoggia, M., Sozzi, R., Davoli, M., Forastiere, F., 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ. Health Perspect. 121 (3), 324–331.

Chen, C., Saikawa, E., Comer, B., Mao, X., Rutherford, D., 2019. Ship emission impacts on air quality and human health in the Pearl River Delta (PRD) region, China, in 2015, with projections to 2030. Geohealth 3 (9), 284–306. https://doi.org/10.1029/2019gh000183.

Dastoorpoor, M., Sekhavatpour, Z., Masoumi, K., Mohammadi, M.J., Aghababaeian, H., Khanjani, N., Hashemzadeh, B., Vahedian, M., 2019. Air pollution and hospital admissions for cardiovascular diseases in Ahvaz, Iran. Sci. Total Environ. 652, 1318–1330. https://doi.org/10.1016/j.scitotenv.2018.10.285.

de Bont, J., Jaganathan, S., Dahlquist, M., Persson, Å., Stafoggia, M., Ljungman, P., 2022. Ambient air pollution and cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. J. Intern. Med. 291 (6), 779–800. https://doi.org/10.1111/joim.13467.

Department of Environment Malaysia, D, 2020. Environmental Quality Report (ISSN 2636-9834).

Department of Statistics Malaysia, D, 2020. Census 2020. https://www.mycensus.gov.my/index.php/media-2/newsletter-infographics/125-newsletter-infographics/343-infografik#infographic-by-state.

Department of Statistics Malaysia, D, 2022a. Key Findings Population and Housing Census of Malaysia 2020.

Department of Statistics Malaysia, D, 2022b. Statistics on causes of death, Malaysia, 2022. Retrieved 30 December 2022 from. https://www.dosm.gov.my/v1/index.php?r=column/cthemeByCat&cat=401&bul_id=QkxLckg3WjlzcEZyVzRIajllnBIQT09&menu_id=L0pheU43NWJwRWVSZklWdzQ4TlhUUT09.

Dominici, F., Peng, R.D., Barr, C.D., Bell, M.L., 2010. Protecting human health from air pollution: shifting from a single-pollutant to a multipollutant approach. Epidemiology 21 (2), 187–194.

Ducruet, C., Polo Martin, B., Sene, M.A., Lo Prete, M., Sun, L., Itoh, H., Pigné, Y., 2024. Ports and their influence on local air pollution and public health: a global analysis. Sci. Total Environ. 915, 170099 https://doi.org/10.1016/j.scitotenv.2024.170099.

Ewing, J.J., McRae, E., 2012. Transboundary Haze in Southeast Asia: Challenges and Pathways Forward. NTS Alert.

Guo, E., Zhong, H., Li, J., Gao, Y., Li, J., Wang, Z., 2022. The influence of air pollution on residents' outdoor exercise participation behaviour: evidence from China Family Panel Studies. PLoS One 17 (8), e0270994.

Halim, N.D.A., Latif, M.T., Mohamed, A.F., Maulud, K.N.A., Idrus, S., Azhari, A., Othman, M., Sofwan, N.M., 2020. Spatial assessment of land use impact on air quality in mega urban regions, Malaysia. Sustain. Cities Soc. 63, 102436 https://doi.org/10.1016/j.scs.2020.102436.

Health Informatics Centre, P.D., 2021. Health Facts 2021: Reference Data for Year 2020.

Hospital Tengku Ampuan Rahimah Klang, H., 2021. *Summary Statistics*. JKN Selangor. https://jknselangor.moh.gov.my/htar/statistik/624-statistik-summary-in-htar.

Huang, G., Jiang, Y., Zhou, W., Pickett, S.T.A., Fisher, B., 2023. The impact of air pollution on behavior changes and outdoor recreation in Chinese cities. Landsc. Urban Plann. 234, 104727 https://doi.org/10.1016/j.landurbplan.2023.104727.

Ibrahim, M.F., Hod, R., Ahmad Tajudin, M.A.B., Wan Mahiyuddin, W.R., Mohammed Nawi, A., Sahani, M., 2022. Children's exposure to air pollution in a natural gas industrial area and their risk of hospital admission for respiratory diseases. Environ. Res. 210, 112966 https://doi.org/10.1016/j.envres.2022.112966.

Javadi, S., Bahrampour, A., Saber, M.M., Garrusi, B., Baneshi, M.R., 2021. Evaluation of four multiple imputation methods for handling missing binary outcome data in the presence of an interaction between a dummy and a continuous variable. J. Probabil. Statist. 2021, 6668822 https://doi.org/10.1155/2021/6668822.

Kamat, P.K., Ahmad, A.S., Doré, S., 2019. Carbon monoxide attenuates vasospasm and improves neurobehavioral function after subarachnoid hemorrhage. Arch. Biochem. Biophys. 676, 108117 https://doi.org/10.1016/j.abb.2019.108117.

Karoui, A., Crochemore, C., Harouki, N., Corbière, C., Preterre, D., Vendeville, C., Richard, V., Fardel, O., Lecureur, V., Vaugeois, J.-M., Sichel, F., Mulder, P., Monteil, C., 2020. Nitrogen dioxide inhalation exposures induce cardiac mitochondrial reactive oxygen species production, impair mitochondrial function and promote coronary endothelial dysfunction. Int. J. Environ. Res. Publ. Health 17 (15), 5526. https://www.mdpi.com/1660-4601/17/15/5526.

Kittnar, O., 2020. Selected sex related differences in pathophysiology of cardiovascular system. Physiol. Res. 69 (1), 21–31. https://doi.org/10.33549/physiolres.934068.

Kowalska, M., Kocot, K., 2016. Short-term exposure to ambient fine particulate matter (PM2,5 and PM10) and the risk of heart rhythm abnormalities and stroke. Postepy Hig. Med. Dosw. 70 (0), 1017–1025. https://doi.org/10.5604/17322693.1220389.

Lederer, A.M., Fredriksen, P.M., Nkeh-Chungag, B.N., Everson, F., Strijdom, H., De Boever, P., Goswami, N., 2021. Cardiovascular effects of air pollution: current evidence from animal and human studies. Am. J. Physiol. Heart Circ. Physiol. 320 (4), H1417–H1439. https://doi.org/10.1152/ajpheart.00706.2020.

Lee, H., Kim, S.H., Lee, S.-K., Choi, H., Chung, S.J., Park, D.W., Park, T.S., Moon, J.-Y., Kim, T.-H., Kim, S.-H., 2023. Impact of air pollution on healthcare utilization in patients with bronchiectasis. Front. Med. 10, 1233516.

Li, M., Edgell, R.C., Wei, J., Li, H., Qian, Z., Feng, J., Tian, F., Wang, X., Xin, Q., Cai, M., Lin, H., 2023. Air pollution and stroke hospitalization in the Beibu Gulf Region of China: a case-crossover analysis. Ecotoxicol. Environ. Saf. 255, 114814 https://doi.org/10.1016/j.ecoenv.2023.114814.

Liao, M., Braunstein, Z., Rao, X., 2023. Sex differences in particulate air pollution-related cardiovascular diseases: a review of human and animal evidence. Sci. Total Environ. 884, 163803 https://doi.org/10.1016/j.scitotenv.2023.163803.

Liu, Z., Lu, X., Feng, J., Fan, Q., Zhang, Y., Yang, X., 2017. Influence of ship emissions on urban air quality: a comprehensive study using highly time-resolved online measurements and numerical simulation in Shanghai. Environ. Sci. Technol. 51 (1), 202–211. https://doi.org/10.1021/acs.est.6b03834.

Mills, I., Atkinson, R., Anderson, H., Maynard, R., Strachan, D., 2016. Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis. BMJ Open 6 (7), e010751.

Ministry of Health Malaysia, M, 2016. Malaysia health systems research: volume 1, contextual analysis of the Malaysian health system. Retrieved from. https://www.moh.gov.my/moh/resources/Vol_1_MHSR_Contextual_Analysis_2016.pdf.

Ministry of Health Malaysia, M, 2022. Health indicators 2021 (MOH/S/RAN/203.21 (AR)). Putrajaya Retrieved from. https://www.moh.gov.my/moh/resources/Penerbitan/Penerbitan/20Utama/HEALTH/20INDICATOR/Petunjuk_Kesihatan_2021.pdf.

Mohammed, M.B., Zulkafli, H.S., Adam, M.B., Ali, N., Baba, I.A., 2021. Comparison of five imputation methods in handling missing data in a continuous frequency table. AIP Conf. Proc. 2355 (1), 040006 https://doi.org/10.1063/5.0053286.

Mohd Shafie, S.H., Mahmud, M., Mohamad, S., Rameli, N.L.F., Abdullah, R., Mohamed, A.F., 2022. Influence of urban air pollution on the population in the Klang Valley, Malaysia: a spatial approach. Ecological Processes 11 (1), 3. https://doi.org/10.1186/s13717-021-00342-0.

Mueller, N., Westerby, M., Nieuwenhuijsen, M., 2022. Health impact assessments of shipping and port-sourced air pollution on a global scale: a scoping literature review. Environ. Res., 114460

Naghan, D.J., Neisi, A., Goudarzi, G., Dastoorpoor, M., Fadaei, A., Angali, K.A., 2022. Estimation of the effects PM2. 5, NO2, O3 pollutants on the health of Shahrekord residents based on AirQ+ software during (2012–2018). Toxicol Rep 9, 842–847.

Niu, Z., Liu, F., Yu, H., Wu, S., Xiang, H., 2021. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants. Environ. Health Prev. Med. 26 (1), 15. https://doi.org/10.1186/s12199-021-00937-1.

Nordeide Kuiper, I., Svanes, C., Markevych, I., Accordini, S., Bertelsen, R.J., Bråbäck, L., Heile Christensen, J., Forsberg, B., Halvorsen, T., Heinrich, J., Hertel, O., Hoek, G., Holm, M., de Hoogh, K., Janson, C., Malinovschi, A., Marcon, A., Miodini Nilsen, R., Sigsgaard, T., Johannessen, A., 2021. Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood. Environ. Int. 146, 106219 https://doi.org/10.1016/j.envint.2020.106219.

Pan, A., Sarnat, S.E., Chang, H.H., 2018. Time-series analysis of air pollution and health accounting for covariate-dependent overdispersion. Am. J. Epidemiol. 187 (12), 2698–2704. https://doi.org/10.1093/aje/kwy170.

Rahman, S.R.A., Ismail, S.N.S., Raml, M.F., Latif, M.T., Abidin, E.Z., Praveena, S.M., 2015. The assessment of ambient air pollution trend in Klang Valley, Malaysia. World Environ. 5 (1), 1–11.

Ramacher, M.O.P., Matthias, V., Aulinger, A., Quante, M., Bieser, J., Karl, M., 2020. Contributions of traffic and shipping emissions to city-scale NOx and PM2.5 exposure in Hamburg. Atmos. Environ. 237, 117674 https://doi.org/10.1016/j.atmosenv.2020.117674.

Richter, A., Eyring, V., Burrows, J.P., Bovensmann, H., Lauer, A., Sierk, B., Crutzen, P.J., 2004. Satellite measurements of NO2 from international shipping emissions. Geophys. Res. Lett. 31 (23).

Samoli, E., Aga, E., Touloumi, G., Nisiotis, K., Forsberg, B., Lefranc, A., Pekkanen, J., Wojtyniak, B., Schindler, C., Niciu, E., 2006. Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. Eur. Respir. J. 27 (6), 1129–1138.

Saxe, H., Larsen, T., 2004. Air pollution from ships in three Danish ports. Atmos. Environ. 38 (24), 4057–4067.

Seaton, A., Dennekamp, M., 2003. In: Hypothesis: Ill Health Associated with Low Concentrations of Nitrogen Dioxide—An Effect of Ultrafine Particles?, vol. 58. BMJ Publishing Group Ltd, pp. 1012–1015.

Siddika, N., Rantala, A.K., Antikainen, H., Balogun, H., Amegah, A.K., Ryti, N.R., Kukkonen, J., Sofiev, M., Jaakkola, M.S., Jaakkola, J.J., 2020. Short-term prenatal exposure to ambient air pollution and risk of preterm birth-A population-based cohort study in Finland. Environ. Res. 184, 109290.

Sofwan, N.M., Mahiyuddin, W.R.W., Latif, M.T., Ayub, N.A., Yatim, A.N.M., Mohtar, A.A.A., Othman, M., Aizuddin, A.N., Sahani, M., 2021. Risks of exposure to ambient air pollutants on the admission of respiratory and cardiovascular diseases in Kuala

Lumpur. Sustain. Cities Soc. 75, 103390 https://doi.org/10.1016/j.scs.2021.103390.

Strak, M., Weinmayr, G., Rodopoulou, S., Chen, J., de Hoogh, K., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bekkevold, T., Bellander, T., Boutron-Ruault, M.-C., Brandt, J., Cesaroni, G., Concin, H., Fecht, D., Forastiere, F., Gulliver, J., Hertel, O., Hoffmann, B., Samoli, E., 2021. Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. Br. Med. J. 374, n1904. https://doi.org/10.1136/bmj.n1904.

Szyszkowicz, M., 2015. An approach to represent a combined exposure to air pollution. Int. J. Occup. Med. Environ. Health 28 (5), 823–830.

Tian, F., Cai, M., Li, H., Qian, Z.M., Chen, L., Zou, H., Zhang, Z., Wang, C., Xian, H., McMillin, S.E., Lin, H., 2022. Air pollution associated with incident stroke, poststroke cardiovascular events, and death: a trajectory analysis of a prospective cohort. Neurology 99 (22), e2474–e2484. https://doi.org/10.1212/wnl.0000000000201316.

Tornevi, A., Olstrup, H., Forsberg, B., 2023. Increase in daily asthma medication sales in association with air pollution levels in Greater Stockholm. Environ. Epidemiol. 7 (4), e256. https://doi.org/10.1097/ee9.0000000000000256.

Yusof, K.M.K.K., Azid, A., Samsudin, M.S., Jamalani, M.A., 2017. An overview of transboundary haze studies: the underlying causes and regional disputes on Southeast Asia region. Malaysian J. Fundament. Appli. Sci. 13 (4), 747–753.

Zhu, F., Yu, H., Fan, X., Ding, Z., Wang, Q., Zhou, J., 2023. Particulate air pollution and cardiovascular disease mortality in Jiangsu Province, China: a time-series analysis between 2015 and 2021. Front. Public Health 11, 1218479.