Title Page

Title of the article:

Short-term effects of air pollution on daily asthma-related emergency department visits in an Industrial City

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Key Words: Air pollution, Asthma, Emergency, Time-series, Saudi Arabia

Word count (3197), excluding title page, abstract, references, figures and tables**.**

Abstract:

Background: Epidemiological studies from Europe and North America have provided evidence that exposure to air pollution can aggravate symptoms in asthmatic patients.

Objective: This study was designed to investigate the statistical association between exposure to air pollution and Asthma-related Emergency Department visits (AEDv) in a city in the Middle East.

Methods: Daily number of AEDv, air pollution levels (PM_{10}, $PM_{2.5}$, SO_2, NO_2 and CO) and meteorological variables were obtained from Jubail Industrial City, Saudi Arabia, for the period (2007-2011). Data were analyzed using a time-series approach. Relative risks (RRs) were estimated using Poisson regression.

Results: The associations between AEDv and PM_{10}, $PM_{2.5}$, SO_2 and NO_2 remained positive and statistically significantly after mutual adjustment in the multi-pollutants model. The RR of AEDv increased by 5.4%, 4.4%, 3.4% and 2.2% per an inter-quartile range increase in SO_2 (2.0*ppb*), $PM_{2.5}$ (36$\mu g/m^3$), NO_2 (7.6*ppb*) and PM_{10} (140$\mu g/m^3$) respectively. No significant associations between AEDv and CO were found.

Conclusions: Current levels of ambient air pollution are associated with AEDv in this industrial setting in the Middle East. Greater awareness of environmental health protection and the implementation of effective measures to improve the quality of air in such settings would be beneficial to public health.

Main Text

BACKGROUND

Air pollution is a known risk factor for adverse cardio-respiratory health effects [1]. Time-series analyses have been used to estimate the influence of daily variations in air pollutant levels on daily counts of asthma-related admissions within a geographically defined population [2,3]. Several studies have identified an increase in asthma-related admissions associated with increases in Particulate Matter with diameter of 10 micrometers or less (PM_{10}) [4-16]. These studies have reported a significant positive association between PM_{10} levels and asthma-related hospital visits, with an increase of 10-90*μg/m*^{3} of PM_{10} associated with an estimated increase of 0.1%-14% of asthma-related admissions.

Some studies reported on the relationship between exposure to Particulate Matter with diameter of 2.5 micrometers or less ($PM_{2.5}$) and hospital visits for asthma patients [4,10,11,17-22]. These studies indicate that an increase in $PM_{2.5}$ level by 7-20*μg/m*^{3} was associated with increased asthma-related admissions of 3%-9%.

Other studies have considered the relationship between Nitrogen Dioxide (NO_2) levels and asthma-related admissions [4,6,8-11,13,16,17,20,23-26]. Most of these studies have reported a significant positive association between NO_2 levels and asthma-related hospital visits, with an increase in NO_2 levels by 9-27*μg/m*^{3} associated with an estimated 0.2%-9.0% increase in asthma-related admissions. In contrast, some studies found limited evidence for an association between the level of NO_2 and hospital admissions in single and multi-pollutants model [6,8,9,16]. These inconsistent results may be due to a high correlation between NO_2 and other pollutants, such as Particulate Matter (PM), Carbon Monoxide (CO) and Sulphur Dioxide (SO_2) reported in previous studies [6,8,9,16].

Several studies have reported on the association between exposure to SO_2 and hospital visits for asthma patients [4,6,9-11,13,16,20,23-27]. Most of these studies have reported a positive association with an increase in SO_2 levels by 10-50*μg/m*^{3} associated with an estimated increase of 1.1%-7.8% in asthma-related hospital admissions [4,6,11,20,23-25,27]. However, some studies found limited evidence for an association between the level of SO_2 and hospital admissions in single and multi-pollutants model [9,10,13,16,26].

Little research on this topic has been carried out in the Middle East. Studies in Asian [28] and Latin American countries [29] with rapid urbanization and industrialization, where levels of air pollution and meteorological conditions are different from North America and Western Europe have also been carried out [30]. This study fills important gaps in our understanding of the influence of air pollutants levels on Asthma-related Emergency Department visits (AEDv) in an industrial city in Saudi Arabia.

METHODS

Study Location

This study was set in Al Jubail Industrial City, which is located in the Eastern Province. The Eastern province is the largest province in Saudi Arabia. The Kingdom's main oil and gas fields, onshore and offshore, are mostly located in the Eastern Province. In 1975, Jubail Industrial City was designated as a site for a new industrial city by the Saudi government, and has seen a rapid expansion and industrialization since. The industrial city hosts a global hub for chemical industries and the largest industrial city in the Middle East. It also holds the Middle East's largest and the world's fourth largest petrochemical company. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3863874/) (https://www.rcjy.gov.sa/en-US/Jubail/AboutCity/Pages/default.aspx)

Air pollution and meteorological data

Hourly fixed-site air quality monitoring data for the period 1st January 2007 to 31st December 2011 were collected from the residential fixed-site monitoring station (site 8, coordinates of 27° 7'54.03"N 49°31'57.02"E) located within the community area in Jubail Industrial City, Saudi Arabia (See Supplemental Material; selection of fixed-site monitoring station, Table S1, Table S2 and Figure S1). The monitored pollutants include: PM_{10}, $PM_{2.5}$, SO_2, NO_2 and carbon monoxide (CO). The fixed-site monitoring station also measured hourly meteorological conditions including temperature (T), relative humidity (RH), wind speed (WS) and wind direction (WD). The daily missing value from the residential fixed-site station (number 8) was replaced with the mean level of the remaining stations multiplied by a correction factor, which was the ratio of the seasonal mean (three months) for the missing station to the corresponding seasonal mean for the remaining stations on that particular day [32].

Data on asthma-related emergency department visits

The health data were obtained from the Royal Commission Health Service Program in Jubail Industrial City, which is responsible for the Royal Commission Hospital. Relevant records were identified based on a discharge diagnosis of asthma using the International Classification for Diseases, 9th revision (ICD-9 code 493). The data on AEDv were obtained for the period 1st January 2007 to 31st December 2011, for all ages.

Statistical analysis

The time-series analysis was conducted using Generalized Linear Models (GLM) with Poisson regression. The steps used to apply the GLM with Poisson regression were adopted from the method described by Tadano, et al. [5]. Relative risks (RRs) were estimated using Poisson regression, while controlling for meteorological variables, day of the week and public holidays, for lag times of 0 - 7 days. The results were expressed as percent increase in AEDv (with 95% confidence intervals (95% CI)) per interquartile range (IQR; 75-25th percentile) increase of each pollutant. The original results used 7 degrees of freedom (*df*) per year for the natural cubic spline of temporal trend (See Supplemental Material; Time-series analysis: Akaike Information Criterion, Table S4).

Single and multiple pollutant models

After adjusting the GLM with Poisson regression, including all the time trends and explanatory variables, and choosing *df* that best fits the data, the fitted model was tested using the pseudo (R^2) and the chi-squared (X^2) statistic to ensure the best fit model was applied to create the single-pollutant model [5,31] (See Supplemental Material; Time-series analysis: Partial autocorrelation functions, Figures S2-S6 and Single-pollutant model, Tables S5-S6).

Multi-pollutant models were used to study the impact on AEDv of PM_{10}, $PM_{2.5}$, SO_2 and NO_2, adjusting for the other pollutants, as well as relative humidity, temperature and indicator variables for day of the week and holidays. Multi-pollutant models used the same basic steps as the single-pollutant model, with the inclusion of two or more pollutant variable terms [32]. Pollutants that were significant in the single-pollutant analysis and the lag that had the strongest univariate effect were tested, using GLM with Poisson regression applied in R software.

RESULTS

Descriptive analysis

A total of 8434 AEDv occurred during the study period (Table 1). The time-series plots of daily AEDv revealed a prominent seasonal cycle as shown in Figure 1. The day-to-day variations in air pollutants levels of PM_{10}, $PM_{2.5}$ and NO_2 also showed clear seasonal patterns. SO_2 levels increased steadily over years 2-4, but decreased over the last year of the study period. CO did not show any seasonally or yearly trend, but variability in CO appears to decrease over the study period.

Comparisons of recorded air quality with Jubail Air Quality Standard (AQS) and WHO Air Quality Guidelines (AQG) are shown in Table 1. SO_2, $PM_{2.5}$ and PM_{10} exceeded the daily Jubail AQS and WHO AQG limits, while $PM_{2.5}$ and PM_{10} also exceeded annual Jubail AQS and WHO AQG limits for each of the five years.

AEDv were negatively correlated with PM_{10} and $PM_{2.5}$, and positively correlated with NO_2 (See Supplemental Material; selection of fixed-site monitoring station, Table S3). A strong positive correlation was observed between PM_{10} and $PM_{2.5}$ ($r=0.816$, $p<0.01$). While, a weak but significant positive correlation was observed for NO_2 with CO and SO_2 ($r=0.258$ and $r=0.217$ respectively).

Comparisons of recorded air quality with and WHO Air Quality Guidelines (AQG) are shown in (Table 1). $PM_{2.5}$ and PM_{10} exceeded the daily and annual WHO AQG limits, and SO_2, exceeded only daily WHO AQG limits. However, NO_2, and CO did not exceeded the limit values.

Single and multi-pollutant models

All pollutants studied in the single and multi-pollutant model, except CO, were associated with an increase in daily AEDv as shown in Table 2. The lags associated with the most statistically significant increase in AEDv for PM_{10}, $PM_{2.5}$ on the same day (lag 0), SO_2 after two days (lag 2) and NO_2 after three days (lag 3) from the single-pollutant model were subsequently considered in a multi-pollutant model. The relative risks (together with 95% confidence intervals) for AEDv per IQR increase in pollutant concentration, after mutual adjustment for the remaining pollutants, are shown in Table 3. Owing to the multi-collinearity of PM_{10} and $PM_{2.5}$ (See Supplemental Material; selection of fixed-site monitoring station, Table S3), these pollutants were separately included in the multi-pollutant model. For SO_2 and NO_2, the result similar with either PM_{10} or $PM_{2.5}$, and only the set of results with $PM_{2.5}$ included in the multi-pollutant model is presented in Table 3 (it gave the highest RR for AEDv when compared with PM_{10}). The effects of these four pollutants appeared to be independent, as the associations remained significant after adjustment for the remaining pollutants which were simultaneously introduced (See Supplemental Material; the exposure-response association Figures S7).

DISCUSSION

Main finding of this study

The main results yielded by this study suggest that the risk of AEDv increased positively and with statistical significance with increasing ambient levels of $PM_{2.5}$, PM_{10}, SO_2 and NO_2 in the setting of the industrial city of Jubail, Saudi Arabia. The effects of these four pollutants were independent, as the associations remained significant after mutual adjustment.

PM_{10}

The most statistically significant increase in AEDv was a 2.2% increase (95% CI: 1.3, 3.2) associated with an IQR change in PM_{10} levels (140$\mu g/m^3$) on the same day in the multi-pollutant model in the present study. This positive association is in line with findings of many of the previous studies of PM_{10} and AEDv or asthma hospitalization for all ages at different lags from other areas of the world [4,5,9,10,12,13]. The systematic review and meta-analysis by Zheng et al. published in 2015 reported a significant positive association between PM_{10} and asthma-related emergency visits/hospitalization for all ages. This review, which included 51 studies for PM_{10} in their meta-analysis, suggested that the RR increased 1.0% with a 10$\mu g/m^3$ increase in PM_{10} levels on lag day 1 in the single-pollutant model [4]. Similarly, a statistically significant relationship was detected in single-pollutant model for asthma-related emergency visits/hospitalization for all ages in Sao Paulo, Brazil (a 5.0% increase in hospital visits per 90$\mu g/m^3$ increase in PM_{10} levels on lag day 3 [5]); in Taipei, Taiwan (a 4.5% increase in hospitalizations per 28$\mu g/m^3$ increase in PM_{10} levels on lag day 3 [9]); in Madrid, Spain (a 3.9% increase in hospitalizations per 10$\mu g/m^3$ increase in PM_{10} levels on lag day 3 [13]); in Atlanta, USA (a 3.9% increase in hospitalizations per 10$\mu g/m^3$ increase in PM_{10} levels on lag day 3 [12]); in Hong Kong, China (a 1.9% increase in hospitalizations per 10$\mu g/m^3$ increase in PM_{10} levels on lag day 0-5 [10]). These previous studies have only generated the results from the single-pollutant model which are likely confounded, at least in part, by correlated pollutants [12]. Possible explanations for differences in the RR results in these previous studies are the study designs, timeframe and city, as different regions may have divergent pollutant mixtures [9,33].

However, the results presented in this study did not show a correlation between PM_{10} and CO, SO_2 and NO_2, and the estimated effect remained significant after further adjustment for SO_2 and NO_2 in the multi-pollutant model. This indicates that PM_{10} is not acting as a proxy for other pollutants, but rather points to an independent association.

$PM_{2.5}$

In the current study, the most significant increase in AEDv was 4.4% (95% CI: 2.4, 6.6) per IQR change of $PM_{2.5}$ level (36$\mu g/m^3$) on the current day. This finding is consistent with those of other studies, which reported a positive association between $PM_{2.5}$ levels and asthma-related emergency visits/hospitalization for all ages at different lags [4,9,10,17-19,22]. A statistically significant increase in AEDv (1.5% per 10$\mu g/m^3$ increase in $PM_{2.5}$ levels on lag day 1) was detected in a meta-analysis from 2016 which included 16 studies from developed countries, with 13 studies from the USA and the other three from Canada, Finland and Taiwan [19]. Similarly, a systematic review and meta-analysis conducted in 2015 observed a significant positive association between $PM_{2.5}$ and asthma-related emergency visits/hospitalization for all ages, which included 37 studies for $PM_{2.5}$ in their meta-analysis, RR increased 2.3% with a 10$\mu g/m^3$ increase in $PM_{2.5}$ levels on lag day 1 in the single-pollutant model [4]. Also, a statistically significant relationship was reported in single-pollutant model for asthma-related emergency visits/hospitalization for all ages in Beijing, China (0.51% per 10$\mu g/m^3$ increase in $PM_{2.5}$ levels on lag day 1 [18]); in Erie County, NY/USA (6.8% per IQR change (6.20$\mu g/m^3$) on lag day 2 [17]); in Tacoma, Washington/USA (4% per IQR change (7$\mu g/m^3$) on lag day 2 [22]); and in Hong Kong, China (2.1% per 10$\mu g/m^3$ increase in PM_{10} levels on lag (0-5) days [10]). In contrast, a study conducted in Taipei, Taiwan, did not observe an association between AEDv for asthma and $PM_{2.5}$ (IQR = 20.2$\mu g/m^3$) in the single-pollutant model [9]. However, these previous studies did not report results from multi-pollutant models which are necessary if we are to determine which pollutants contribute to the association [34]. The reported RR results of $PM_{2.5}$ and asthma-related emergency visits/hospitalization from the previous studies may be inconsistent due to differing exposure sources, climate factors, seasonal patterns and related pathways which affect emissions, composition and kinetics of pollutants [9,33-35].

SO_2

The most significant increase in AEDv was 10.3% (95% CI: 4.6, 16.3) for all ages associated with a 10$\mu g/m^3$ increase in SO_2 on lag day 2 in the multi-pollutant model in the present study. This positive association supports previous research, which reported a positive association between SO_2 levels and asthma-related emergency visits/hospitalization for all ages at different lags [4,24].[4,10,13,24,25]. A systematic review and meta-analysis of 65 studies conducted in 2015 observed 1.1% increase in RR in asthma-related emergency visits/hospitalization for all ages per 10$\mu g/m^3$ increase in SO_2 levels on lag day 0 in the single-pollutant model [4]. Similarly, a statistically significant relationship was detected in single and multi-pollutants model for asthma-related emergency visits/hospitalization for all ages in a study conducted in Cartagena, Spain, which found a 5.2% (95% CI: 1.4, 11.0) increase in asthma visits for all ages per 10$\mu g/m^3$ increase in SO_2 levels at lag day 4 [24].

Other studies have reported no significant effect of SO_2 on asthma visits [9,10,13,15,25-27]. Most of these studies have reported an interaction between SO_2 levels and other pollutants such as PM, CO and NO_2 due to collinearity among pollutants generated by the same sources [9,10,13,20,27]. This can result in removal of statistical significance of SO_2 in the multi-pollutant model. The estimated effect in the current study remained significant after adjustment for $PM_{2.5}$ and NO_2 in the multi-pollutant model, which suggests that SO_2 may not simply act as a proxy for other pollutants, but has an independent effect. In addition, the results of most controlled-chamber experiments with asthmatics have consistently shown that they are more sensitive to SO_2 than non-asthmatics [26,36], lending plausibility to there being an independent effect of SO_2 on asthma/asthma exacerbation.

NO_2

The most significant increase in AEDv was at lag day 3 (2.4% (95% CI: 0.5, 4.2) per a 10$\mu g/m^3$ increase in NO_2 levels in the current study. This positive association agrees with other studies that observed similar associations for all ages on different lag days [4,13,17,24]. A systematic review and meta-analysis of 66 studies conducted in 2015 observed a significant positive association between NO_2 and asthma-related emergency visits/hospitalization for all ages (RR increased 1.8% per 10$\mu g/m^3$ increase in NO_2 levels on lag day 0 in the single-pollutant model [4]). Another recent study conducted in Erie

County, NY/USA, also showed a similar positive effect (a 7.8% increase in asthma visits at lag day 1 per IQR change in NO_2 (17.7$\mu g/m^3$) [17]). Furthermore, a study conducted in Cartagena, Spain, detected a positive association in single and multi-pollutants model (2.6% (95% CI: 1.4, 11.0) increase in asthma visits for all ages per 10$\mu g/m^3$ increase in NO_2 levels at lag day 4 [24]). Similarly, another study conducted in Madrid, Spain, reported a 3.3% increase in asthma visits at lag day 3 for all ages per 10$\mu g/m^3$ increase in NO_2 level in single-pollutant model [13].

Conversely, a study in Taipei, Taiwan, found no statistically significant association for asthma visits for all ages with NO_2 [9]. Likewise, studies of asthmatic children visits and NO_2 levels in Athens, Greece, [6], Milan-Italy [8] and Seattle, USA, [16] found no significant associations. These inconsistent results may be due to a high correlation between NO_2 and other pollutants, such as PM, CO and SO_2 reported in previous studies [6,8,9,16]. Hence, NO_2 could be a marker of other pollutants generated by traffic-related sources, such as PM [14,25]. However, the estimated risk shown in this study in Jubail remained unaltered on inclusion of the other pollutants in the multi-pollutant model, suggesting that NO_2 may be independently associated with AEDv. Asthmatics are the most responsive group to nitrogen dioxide studied to date, although controlled studies on the effects of short-term exposure on the symptoms and severity of asthma have not led to clear-cut findings [36]. Panel studies among asthmatic subjects show acute health effects when exposure to NO_2 at levels higher than 500$\mu g/m^3$, and one meta-analysis has indicated effects at levels exceeding 200$\mu g/m^3$ [36]. This suggests that the observed association with ambient NO_2 levels in the general population may be plausible [25,36].

CO

Our study did not find a statistically significant association between daily CO levels and AEDv. The lack of association observed in this study supports previous works conducted in Erie County, NY/USA [17], Taipei, Taiwan [9] and Milan, Italy [8]. However, a significant positive effect of CO on asthma visits was found in two previous studies conducted in two cities within the USA; Tacoma [22] and Seattle [16]. These studies reported that an IQR increase in CO levels of 0.6*ppm* in Tacoma and 0.7*ppm* in Seattle resulted in 10% (95% CI: 2.0, 19.0) and 3.0% increase (95% CI: 0.1, 6.0) in AEDv, respectively. These previous studies have only generated the results from the single-pollutant model which are likely confounded, at least in part, by high correlations between CO and particulates which range between 0.74 in Tacoma and 0.82 in Seattle. CO has no biological plausible mechanism for exacerbation of asthma, so this effect is interpreted as being related to traffic air pollution, and not to CO itself [16,22].

Limitations of this study

Similar to other ecological time-series studies, this study was limited by the fact that precise individual level of exposure to a specific pollutant could not be assessed.

Although many important confounding variables have been controlled in the analysis, further adjustment of other confounders such as pollens and aeroallergens which may be alter the associations between AEDv and air pollution, would be desirable. Some studies have observed that pollen and aeroallergens could precipitate the exacerbation of asthma [24,37], whereas other studies have not [13,38]. It was not possible to include pollen in the present study, but we would encourage this to be the focus of further works [21].

There is experience around the world, especially from developed countries, that can be drawn on regarding effective industrial, environmental and health policy. Until air quality issues are resolved, the levels of air pollutants should be incorporated into weather forecasts and alerts, as is practiced elsewhere [39,40], so as to inform populations at risk, which may enable individuals to reduce their risks from outdoor air pollution.

What is already known on this topic?

There is a growing literature on time-series studies of air pollution and asthma-related admissions for populations in North America and Western Europe, little research on this topic has been carried out in the Middle East. Importance of this study is that to the best of our knowledge, this study is the first to investigate the association between air pollution and Asthma-related Emergency Department visits (AEDv) in an industrial city in Saudi Arabia.

What this study adds?

- Levels of $PM_{2.5}$, PM_{10}, SO_2 and NO_2, were associated with an increase in daily AEDv.
- No significant associations between AEDv and CO were found.
- $PM_{2.5}$ and PM_{10} exceeded daily and annual WHO air quality guidelines limits.

Conclusions

The present study in the setting of an industrial city in Saudi Arabia has revealed that risks of AEDv increased with increasing ambient levels of PM_{10}, $PM_{2.5}$, SO_2 and NO_2. The effects of these four pollutants appeared independent, effect sizes were in line with those reported from other areas of the world. The current air quality standards in Jubail Industrial City might not be sufficient to protect public health in this setting. This calls for greater awareness of environmental protection and the implementation of effective measures to improve the quality of air.

Funding:

This work was supported by Saudi Ministry of Education.

Acknowledgements:

We would like to convey special thanks to the Royal Commission of Jubail and Yanbue for providing us with the health data on asthma emergency department visits, and the environmental data on air pollution levels and weather variables in Jubail Industrial City.

References

1. WHO. *Ambient air pollution: A global assessment of exposure and burden of disease*. Geneva, Switzerland: World Health Organization, 2016.
2. Tobías A, Campbell MJ, Sáez M. Modelling asthma epidemics on the relationship between air pollution and asthma emergency visits in Barcelona, Spain. *European Journal of Epidemiology* 1999;15(9):799-803.
3. Wilkinson P. *Environmental Epidemiology*. Understanding Public Health. 1 ed. England: Open University Press, 2006.
4. Zheng X-y, Ding H, Jiang L-n, Chen S-w, Zheng J-p, Qiu M, Zhou Y-x, Chen Q, Guan W-j. Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis. *PLoS ONE* 2015;10(9):e0138146.
5. Tadano YdS, Ugaya CML, Franco AT. Methodology to Assess Air Pollution Impact on Human Health Using the Generalized Linear Model with Poisson Regression, Air Pollution - Monitoring, Modelling and Health. In: Khare DM, ed. Croatia: InTech, 2012;281-304.
6. Samoli E, Nastos PT, Paliatsos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: Evidence of association and effect modification. *Environmental Research* 2011.
7. Nastos PT, Paliatsos AG, Anthracopoulos MB, Roma ES, Priftis KN. Outdoor particulate matter and childhood asthma admissions in Athens, Greece: A time-series study. *Environmental Health* 2010;9(1):45.

8. Giovannini M, Sala M, Riva E, Radaelli G. Hospital admissions for respiratory conditions in children and outdoor air pollution in Southwest Milan, Italy. *Acta Paediatrica* 2010;99(8):1180-1185.

9. Bell ML, Levy JK, Lin Z. The effect of sandstorms and air pollution on cause-specific hospital admissions in Taipei, Taiwan. *Occup Environ Med* 2008;65(2):104-11.

10. Ko FW, Tam W, Wong TW, Lai CK, Wong GW, Leung TF, Ng SS, Hui DS. Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. *Clin Exp Allergy* 2007;37(9):1312-9.

11. Lee SL, Wong WHS, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2006;36(9):1138-46.

12. Peel JL, Tolbert PE, Klein M, Metzger KB, Flanders WD, Todd K, Mulholland JA, Ryan PB, Frumkin H. Ambient Air Pollution and Respiratory Emergency Department Visits. *Epidemiology* 2005;16(2):164-174.

13. Galan I, Tobias A, Banegas JR, Aranguez E. Short-term effects of air pollution on daily asthma emergency room admissions. *European Respiratory Journal* 2003;22(5):802-808.

14. Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. Acute effects of particulate air pollution on respiratory admissions: results from APHEA

2 project. Air Pollution and Health: a European Approach. *Am J Respir Crit Care Med* 2001;164(10 Pt 1):1860-6.

15. Wong TW, Lau TS, Yu TS, Neller A, Wong SL, Tam W, Pang SW. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med* 1999;56(10):679-83.

16. Norris G, YoungPong SN, Koenig JQ, Larson TV, Sheppard L, Stout JW. An Association between Fine Particles and Asthma Emergency Department Visits for Children in Seattle. *Environmental Health Perspectives* 1999;107(6):489-493.

17. Castner J, Guo L, Yin Y. Ambient air pollution and emergency department visits for asthma in Erie County, New York 2007–2012. *International Archives of Occupational and Environmental Health* 2018;91(2):205-214.

18. Tian Y, Xiang X, Juan J, Sun K, Song J, Cao Y, Hu Y. Fine particulate air pollution and hospital visits for asthma in Beijing, China. *Environmental Pollution* 2017;230:227-233.

19. Fan J, Li S, Fan C, Bai Z, Yang K. The impact of PM2.5 on asthma emergency department visits: a systematic review and meta-analysis. *Environmental Science and Pollution Research* 2016;23(1):843-850.

20. Li S, Batterman S, Wasilevich E, Wahl R, Wirth J, Su F-C, Mukherjee B. Association of daily asthma emergency department visits and hospital admissions with ambient air pollutants among the pediatric Medicaid population in Detroit: time-series and time-stratified case-crossover analyses with threshold effects. *Environmental research* 2011;111(8):1137-47.

21. Silverman RA, Ito K. Age-related association of fine particles and ozone with severe acute asthma in New York City. *J Allergy Clin Immunol* 2010;125(2):367-373 e5.

22. Mar TF, Koenig JQ, Primomo J. Associations between asthma emergency visits and particulate matter sources, including diesel emissions from stationary generators in Tacoma, Washington. *Inhal Toxicol* 2010;22(6):445-8.

23. Cai J, Zhao A, Zhao J, Chen R, Wang W, Ha S, Xu X, Kan H. Acute effects of air pollution on asthma hospitalization in Shanghai, China. *Environmental Pollution* 2014;191:139-144.

24. Cirera L, Garcia-Marcos L, Gimenez J, Moreno-Grau S, Tobias A, Perez-Fernandez V, Elvira-Rendeles B, Guillen JJ, Navarro C. Daily effects of air pollutants and pollen types on asthma and COPD hospital emergency visits in the industrial and Mediterranean Spanish city of Cartagena. *Allergol Immunopathol (Madr)* 2012;40(4):231-7.

25. Sunyer J, Spix C, Quenel P, Ponce-de-Leon A, Ponka A, Barumandzadeh T, Touloumi G, Bacharova L, Wojtyniak B, Vonk J, Bisanti L, Schwartz J, Katsouyanni K. Urban air pollution and emergency admissions for asthma in four European cities: the APHEA Project. *Thorax* 1997;52(9):760-5.

26. Castellsague J, Sunyer J, Saez M, Anto JM. Short-term association between air pollution and emergency room visits for asthma in Barcelona. *Thorax* 1995;50(10):1051-1056.

27. Sunyer J, Atkinson R, Ballester F, Le Tertre A, Ayres JG, Forastiere F, Forsberg B, Vonk JM, Bisanti L, Anderson RH, Schwartz J, Katsouyanni K, study A.

Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. *Occup Environ Med* 2003;60(8):e2.

28. Wong CM, Vichit-Vadakan N, Kan H, Qian Z. Public Health and Air Pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality. *Environ Health Perspect* 2008;116(9):1195-202.

29. Romieu I, Gouveia N, Cifuentes LA, de Leon AP, Junger W, Vera J, Strappa V, Hurtado-Diaz M, Miranda-Soberanis V, Rojas-Bracho L, Carbajal-Arroyo L, Tzintzun-Cervantes G. Multicity study of air pollution and mortality in Latin America (the ESCALA study). *Res Rep Health Eff Inst* 2012(171):5-86.

30. Gouveia N, Fletcher T. Time series analysis of air pollution and mortality: effects by cause, age and socioeconomic status. *Journal of Epidemiology and Community Health* 2000;54(10):750-755.

31. Peng RD, Dominici F, Louis TA. Model choice in time series studies of air pollution and mortality. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2006;169(2):179-203.

32. Katsouyanni K, Schwartz J, Spix C, Touloumi G, Zmirou D, Zanobetti A, Wojtyniak B, Vonk JM, Tobias A, Ponka A, Medina S, Bacharova L, Anderson HR. Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. *Journal of Epidemiology & Community Health* 1996;50(Suppl 1):S12-S18.

33. Chimonas MA, Gessner BD. Airborne particulate matter from primarily geologic, non-industrial sources at levels below National Ambient Air Quality Standards is associated with outpatient visits for asthma and quick-relief medication

prescriptions among children less than 20 years old enrolled in Medicaid in Anchorage, Alaska. *Environ Res* 2007;103(3):397-404.

34. PITARD A, VIEL JF. Some methods to address collinearity among pollutants in epidemiological time series. *Statistics in Medicine* 1997;16(5):527-544.

35. Tecer LH, Alagha O, Karaca F, Tuncel G, Eldes N. Particulate matter (PM2.5, PM10-2.5, and PM 10) and children's hospital admissions for asthma and respiratory diseases: A bidirectional case-crossover study. *Journal of Toxicology and Environmental Health - Part A: Current Issues* 2008;71(8):512-520.

36. WHO. *Air quality guidelines. Global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide*. Copenhagen, Denmark: World Health Organization, Regional Office for Europe, 2006.

37. Gleason JA, Bielory L, Fagliano JA. Associations between ozone, PM2.5, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey: a case-crossover study. *Environmental research* 2014;132:421-9.

38. Anderson HR, de Leon AP, Bland JM, Bower JS, Emberlin J, Strachan DP. Air pollution, pollens, and daily admissions for asthma in London 1987-92. *Thorax* 1998;53(10):842-848.

39. UK-AIR. Air Information Resource (Pollution forecast provided by the Met Office). https://uk-air.defra.gov.uk/ Accessed 01/06/2017.

40. USEPA. AirNow - Air Quality Forecast. https://www.airnow.gov/ Accessed 01/06/2017.

Table titles:

Table 1: Descriptive Statistics for Daily Asthma-related Emergency Department visits, Air Pollution and Meteorological Variables in Jubail Industrial City, Saudi Arabia, for the period 2007-2011

Table 2: Relative Risks (95% Confidence Interval for AEDv Per IQR Change in Pollutants Concentration for 0-7 Lag Days in The Single-Pollutant Model in Jubail Industrial City, Saudi Arabia, for the Period 2007-2011

Table 3: Relative Risks (95% Confidence Interval for AEDv Per Increase in Pollutants Concentration for 0-7 Lag Days in the Multi-Pollutant Model in Jubail Industrial City, Saudi Arabia, for the Period 2007-2011

Figure legends:

Figure 1: Time-series plots of daily AEDv and air pollutants for the period 2007-2011

Table 1: Descriptive Statistics for Daily Asthma-related Emergency Department visits, Air Pollution and Meteorological Variables in Jubail Industrial City, Saudi Arabia, for the period 2007-2011

		AEDv	PM_{10} (*μg/m³*)	$PM_{2.5}$ (*μg/m³*)	SO_2 (*ppb*)	NO_2 (*ppb*)	CO (*ppm*)	Temp (ºC)	RH (%)
Total number of days		1826	1764	1786	1788	1793	1794	1793	1793
Missing days*		0	62	40	38	33	32	33	33
Mean		4.60	220.16	64.61	3.06	15.48	0.46	26.39	49.69
Median		4	129.56	45.63	2.74	14.39	0.43	27.53	49.69
Standard Deviation		3.30	308.49	64.52	1.80	6.37	0.19	8.02	15.18
Minimum		0	2.00	9.96	0.01	0.07	0.02	6.33	12.94
Maximum		28	3599.26	643.70	14.11	45.95	1.49	39.13	95.30
Quartiles	25%	2	81.60	32.13	1.96	11.04	0.32	19.21	37.69
	50%	4	129.56	45.63	2.74	14.39	0.43	27.53	49.69
	75%	6	222.35	68.41	3.95	18.63	0.57	33.97	61.26
IQR		4	140.75	36.28	1.99	7.59	0.25	14.76	23.57
Air Quality Exceedance (WHO, AQQ)	Daily		1618 (88.6%) days exceeded limit value (50μg/m³)	1623 (88.9%) days exceeded limit value (25μg/m³)	43 (2.3%) days exceeded limit value (7.7ppb)	Did not exceeded	Did not exceeded	Did not exceeded	Did not exceeded
	Annual		All five years exceeded limit value (20μg/m³)	All five years exceeded limit value (10μg/m³)	Did not exceeded	Did not exceeded	Did not exceeded	Did not exceeded	Did not exceeded

*Days excluded due to missing data (≥75% of the hourly values per day)

**N.A = Not applicable

List abbreviations: AEDv=Asthma-related Emergency Department visits, PM10= Particulate Matter with diameter of 10 micrometers or less, PM2.5= Particulate Matter with diameter of 2.5 micrometers or less, SO2=Sulphur Dioxide, NO2=Nitrogen Dioxide, Co=Carbon Monoxide, Temp=Temperature, RH=Relative Humidity, IQR=Inter-Quartiles Range, *μg/m3*=micrograms per cubic meter, *ppb*=parts per billion, *ppm*=parts per million, ºC= degrees Celsius, %=percentage, WHO,AQQ= World Health Organization, Air Quality Guidelines

Table 2: Relative Risks (95% Confidence Interval for AEDv Per IQR Change in Pollutants Concentration for 0-7 Lag Days in The Single-Pollutant Model in Jubail Industrial City, Saudi Arabia, for the Period 2007-2011

Pollutant	Lag days	Relative Risk (95% CI)	*T* value
PM_{10} IQR *(140μg/m³)*	0#	1.023 (1.014, 1.033)	4.71*
	1	1.011 (1.001,1.022)	2.19*
	2	1.003 (0.992, 1.014)	0.51
	3	0.996 (0.985, 1.007)	-0.68
	4	0.997 (0.985, 1.008)	-0.60
	5	1.004 (0.993, 1.016)	0.73
	6	1.003 (0.992, 1.014)	0.54
	7	0.984 (0.973, 0.996)	-2.65
$PM_{2.5}$ IQR *(36μg/m³)*	0#	1.037 (1.026, 1.049)	6.31*
	1	1.019 (1.007, 1.031)	3.09*
	2	0.997 (0.985, 1.010)	-0.42
	3	0.989 (0.976, 1.002)	-1.62
	4	0.995 (0.982, 1.009)	-0.70
	5	1.006 (0.993, 1.020)	0.92
	6	0.995 (0.982, 1.009)	-0.70
	7	0.975 (0.962, 0.989)	-3.47
SO_2 IQR *(2.0ppb)*	0	1.040 (1.010, 1.071)	2.61*
	1	1.052 (1.022, 1.083)	3.44*
	2#	1.058 (1.028, 1.089)	3.84*
	3	1.039 (1.009, 1.070)	2.54*
	4	1.004 (0.997, 1.011)	2.12
	5	1.003 (0.996, 1.010)	2.38
	6	1.002 (0.995, 1.009)	3.20
	7	1.003 (0.996, 1.010)	2.09
NO_2 IQR *(7.6ppb)*	0	1.001 (0.975, 1.029)	0.10
	1	1.031 (1.005, 1.058)	2.38*
	2	1.015 (0.990, 1.042)	1.18
	3#	1.036 (1.010, 1.062)	2.71*
	4	1.002 (0.998, 1.005)	1.07
	5	1.012 (0.986, 1.038)	0.87
	6	1.008 (0.982, 1.034)	0.62
	7	1.010 (0.984, 1.037)	0.78
CO IQR *(0.25ppm)*	0	0.963 (0.933, 0.993)	-2.38
	1	0.962 (0.932, 0.993)	-2.42
	2	0.982 (0.952, 1.014)	-1.12
	3	1.007 (0.975, 1.039)	0.41
	4	0.983 (0.952, 1.014)	-1.09
	5	0.999 (0.968, 1.031)	-0.05
	6	0.990 (0.960, 1.022)	-0.62
	7	0.987 (0.960, 1.014)	-0.95

*Statistically Significant (P <0.001).

#The better model after control for seasonality, temperature, humidity, day of the week and holidays.

List abbreviations: AEDv=Asthma-related Emergency Department visits, PM10= Particulate Matter with diameter of 10 micrometers or less, PM2.5= Particulate Matter with diameter of 2.5 micrometers or less, SO2=Sulphur Dioxide, NO2=Nitrogen Dioxide, Co=Carbon Monoxide, IQR=Inter-Quartiles Range, *μg/m3*=micrograms per cubic meter, *ppb*=parts per billion, *ppm*=parts per million, CI=Confidence Interval, %=percentage

Table 3: Relative Risks (95% Confidence Interval for AEDv Per Increase in Pollutants Concentration for 0-7 Lag Days in the Multi-Pollutant Model in Jubail Industrial City, Saudi Arabia, for the Period 2007-2011

Multi-pollutant model#	Lag days	Relative Risk (95% CI)		*T* value
		Per IQR	Per 10*µg/m*^{3}	
PM_{10} Adjusted for SO_2 and NO_2	0	1.022 (1.013, 1.032)	1.002 (1.001, 1.003)	4.50*
$PM_{2.5}$ Adjusted for SO_2 and NO_2	0	1.044 (1.024, 1.066)	1.012 (1.007, 1.018)	4.24*
SO_2 Adjusted for $PM_{2.5}$ and NO_2	2	1.054 (1.024, 1.085)	1.103 (1.046, 1.163)	3.60*
NO_2 Adjusted for $PM_{2.5}$ and SO_2	3	1.034 (1.008, 1.061)	1.024 (1.005, 1.042)	2.54*

*Statistically Significant (*P* <0.001).

#Owing to the multi-collinearity of PM10 and PM2.5, they were separately put into the multi-pollutant model. For SO2 and NO2, the result is similar when putting either PM10 or PM2.5, and only the set of results when PM2.5 was included in the multi-pollutant model is presented.

List abbreviations: AEDv=Asthma-related Emergency Department visits, PM10= Particulate Matter with diameter of 10 micrometers or less, PM2.5= Particulate Matter with diameter of 2.5 micrometers or less, SO2=Sulphur Dioxide, NO2=Nitrogen Dioxide, Co=Carbon Monoxide, *µg/m3*=micrograms per cubic meter, *ppb*=parts per billion, *ppm*=parts per million, CI=Confidence Interval, %=percentage, IQR – Inter-Quartile Range; PM10 IQR *(140µg/m3),* PM2.5 IQR *(36µg/m3),* SO2 IQR *(2.0ppb) and* NO2 IQR *(7.6ppb).*