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The burden of acute conjunctivitis attributable to ambient particulate matter pollution in Singapore and its exacerbation during South-East Asian haze episodes

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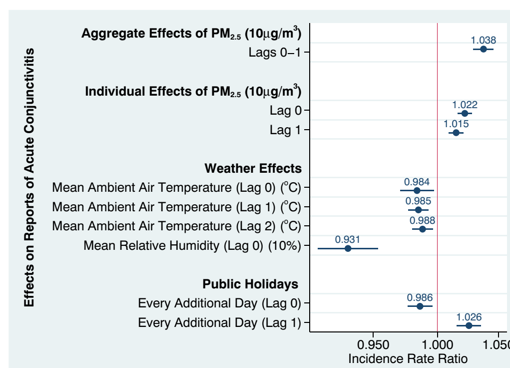
HIGHLIGHTS

- $PM_{2.5}$ and PM_{10} were positively associated with acute conjunctivitis (AC) reports.
- Majority of PM-related AC reports were attributable to $PM_{2.5}$.
- AC reports were disproportionately higher during South-East Asian haze episodes.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Urban air quality in South-East Asia is influenced by local and transboundary sources of air pollutants. Research studies have well characterized the short-term effects of air pollution on cardiovascular and respiratory health but less so on ocular health. We investigated the relationship between air pollution and acute conjunctivitis in Singapore, a tropical city-state located in South-East Asia.
Methods: Assuming a negative-binomial distribution, we examined the short-term associations between all-cause acute conjunctivitis reports from 2009 to 2018 and contemporaneous ambient air pollutant concentrations using a time-series analysis. In separate pollutant models for $PM_{2.5}$ and PM_{10}, we fitted fractional polynomials to investigate the linearity between air pollutant exposures and conjunctivitis, adjusting for long-term trend, seasonality, climate variability, public holidays, immediate and lagged exposure effects, and autocorrelation.
Results: There were 261,959 acute conjunctivitis reports over the study period. Every 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 3.8% (Incidence Rate Ratio (IRR): 1.038, 95% Confidence Interval (CI): 1.029–1.046, $p < 0.001$) cumulative increase in risk of conjunctivitis over the present and subsequent week. Every 10 μg/m^3 increase in PM_{10} was associated with a 2.9% (Incidence Rate Ratio (IRR): 1.029, 95% Confidence Interval (CI): 1.022–1.036, $p < 0.001$) cumulative increase in risk of conjunctivitis over the present and subsequent week. Acute conjunctivitis reports exhibited an inverse dependence on ambient air temperature and relative humidity

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variability. Approximately 3% of all acute conjunctivitis reports were attributable to $PM_{2.5}$. Particulate matter attributed acute conjunctivitis was disproportionately higher during transboundary haze episodes.
Conclusion: Our study strengthens the evidence linking particulate matter exposure to an increased risk of conjunctival disease, with a disproportionately higher disease burden during South-East Asia transboundary haze episodes. Our findings underscore the importance of reducing the health impact of indigenous and transboundary sources of ambient particulate matter pollution.

1. Introduction

The conjunctiva is a thin clear membrane that covers the anterior of the sclera (the white portion of the eye) and the interior surface of the eyelids. Conjunctivitis refers to the infection or inflammation of the conjunctiva, often causing the eye to appear pinkish or reddish. Common causes of conjunctivitis include those of viral, bacterial, allergenic, fungal, parasitic, chemical and physical origins (Rapp, 2015). Interactions between air pollutants and allergens may also initiate or exacerbate conjunctivitis (Leonardi and Lanier, 2008). The economic burden of conjunctivitis is substantial. In the United States, annual emergency department visits for ocular health amounted to appropriately USD$2 billion, with conjunctivitis accounting for 28% of all visits (Channa et al., 2016).

Air pollution is the presence of any substance of anthropogenic or natural origin that is emitted into the atmosphere and can cause adverse effects. According to the World Health Organization, populations in the Middle East, Africa and Asia live in environments with much higher levels of air pollutants than those in other parts of the world (World Health Organization, 2016). Important anthropogenic sources of air pollution include power generation, industrial activity, biomass burning, on-road transportation, and household heating and cooking (Unger et al., 2010). Although industrial and on-road traffic are common sources of urban air pollution in South-East Asia, haze from biomass burning is increasingly a concern for governments seeking to improve urban air quality. Biomass burning has been reported to be a major contributor to increased air pollutant concentrations in urban cities in South-East Asia (Vadrevu et al., 2014; Lee et al., 2017). In addition to atmospheric and terrestrial environments, biomass burning and haze episodes can also be detrimental to marine ecosystems (Jaafar and Loh, 2014).

The principal agricultural slash-and-burn technique employed by many farmers to clear land in South-East Asia has resulted in extensive land fires (Tacconi, 2016). The air quality impact of these land fires extended well beyond the immediate geographical boundaries of their sources. Weather conditions have been reported to exacerbate the transport and the geographical range of air pollutants (Oozeer et al., 2016). In the last 10 years, countries in South-East Asia experienced several episodes of haze from land fires, with the air quality in 2013 and 2015 reaching record unsafe levels (Sharma and Balasubramanian, 2018; Velasco and Rastan, 2015).

Systematic reviews have well documented the effects of air pollution on cardiovascular and respiratory health in humans (Hamra et al., 2014; Orellano et al., 2017; Teng et al., 2014; Atkinson et al., 2014; Li et al., 2016a; Shah et al., 2013, 2015). However, less well studied are its effects on ocular health. Several studies have examined the effects of air pollution on conjunctivitis in Taiwan (Chang et al., 2012; Chiang et al., 2012; Chang et al., 2013), China (Li et al., 2016b; Fu et al., 2017a; Lu et al., 2019), Daegu, Republic of Korea (Lee et al., 2018), Ontario, Canada (Szyszkowicz et al., 2016) and Milan, Italy (Nucci et al., 2017). To the best of our knowledge, none have examined this relationship in South-East Asia where urban air quality is strongly influenced by local and transboundary sources of pollution.

In this ecological time-series analysis, we aimed to examine the impact of ambient air pollutant concentrations on acute conjunctivitis reports in Singapore, a city-state located in South-East Asia.

2. Methods

2.1. Study population and area

Singapore is one of the most densely populated cities in the world, with an estimated population of 5.7 million over a land area of 725 km^2. Approximately 80% of the resident population live in public residential estates built by the government (Housing Development Board (Singapore), 2018) while the minority live in residences built by private developers. Located within public residential estates are polyclinics built and operated by the Singapore government (see Fig. 1). These polyclinics provide primary healthcare services for acute medical conditions, chronic illnesses and dental care. Their typical operating hours are from Mondays to Fridays (full days) and Saturdays (half days), and do not operate on Sundays and public holidays. Collectively, these polyclinics account for approximately 20% of all primary healthcare services in Singapore (Wee et al., 2016). According to a national cross-sectional study, approximately half of government polyclinic primary care users were male and 40% of all users were between 40 and 64 years of age. The majority (95%) lived in public housing estates (Health Information Division, M.o.H.S, 2014).

2.2. Ethics statement

The Environmental Health Institute of the National Environment Agency, Singapore approved this study (TS248). The study did not involve human participants.

2.3. Outcome measure: acute conjunctivitis

We obtained reports of all-cause acute conjunctivitis from the Weekly Infectious Disease Bulletin published by the Ministry of Health (Singapore) from 2009 to 2018 (Ministry of Health (Singapore), 2018). These reports represented patients who were diagnosed with acute conjunctivitis based on their clinical presentation at government polyclinics. Onset dates were not available so we used notification dates in our analysis. An epidemiological week begins on a Sunday and ends on a Saturday. The bulletin published disease reports as epidemiological weekly aggregates prior to 2012 and as daily averages over a week after that. We aggregated the weekly average of daily reports by epidemiological week for the period 2012 to 2018 in order to analyse the outcome measure on a weekly timescale over the entire study duration.

2.3.1. Exposure measures: ambient air quality data

In Singapore, the NEA monitors ambient air quality continuously with the use of 22 remote sensors deployed across the city-state. The NEA reviews collected air quality data before committing them as permanent records. We obtained from the NEA daily measures of ambient concentrations averaged over a week for the following air pollutants: Sulphur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter of aerodynamic diameter of <2.5 μm ($PM_{2.5}$), particulate matter of aerodynamic diameter of <10 μm (PM_{10}), ozone (O_3) and carbon monoxide (CO). We used the average values of data collected from 2009 to 2018 to represent the historical ambient air quality conditions in Singapore.

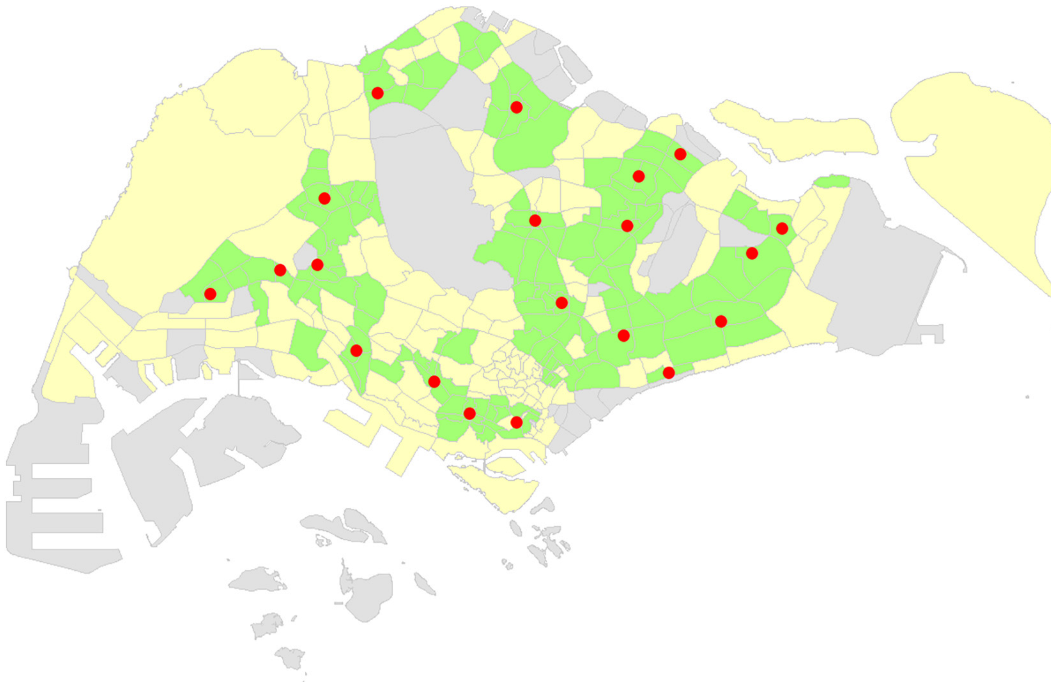

Fig. 1. Locations of public residential estates and government polyclinics in Singapore, 2018. The solid red circles represent the locations of the 20 government polyclinics. The areas in green represent the public residential estates built by the government while the areas in beige contain non-public residential estates built by private developers. The areas in grey represent non-residential land uses.

2.3.2. Climate data

We obtained contemporaneous local climate data from 11 mainland weather stations located across the study area from the Meteorological Services Singapore (MSS). The MSS reviews collected climate data before committing them as permanent records. We used the arithmetic mean of climate data across all stations to derive daily mean measures of air temperature, relative humidity and cumulative rainfall. We then computed the measures of temperature, humidity and cumulative rainfall for each week before incorporating them into our analysis.

2.4. Statistical analysis

2.4.1. Acute conjunctivitis associations with air pollutants

Our main study question was "Are present and subsequent reports of acute conjunctivitis associated with variations in ambient air quality in the present week?". We accounted for overdispersion in the outcome measure by assuming a negative binomial distribution. We analysed the short-term associations between reports of acute conjunctivitis and metrics of ambient air pollutant exposure using a time-series analytical study design. We adjusted for long-term trend and seasonal fluctuations in acute conjunctivitis reports using smoothing spline functions with 8 degrees of freedom (*df*) per year.

We constructed a core time-series regression model that included only the outcome measure and the smoothing spline terms for long-term trend and seasonality. Using this core model, we first simultaneously assessed the immediate and all lagged effects of each of the six air pollutants (SO_2, NO_2, $PM_{2.5}$, PM_{10}, O_3 and CO) and each of the three climatic factors (ambient air temperature, relative humidity and cumulative rainfall) in nine separate basic models. Previous studies reported statistically significant maximum lagged pollutant effects not exceeding 2 weeks (Fu et al., 2017a; Szyszkowicz et al., 2016). In our study, we analysed lagged exposure effects up to 3 weeks. We investigated the presence of any non-linear associations between ambient air quality and acute conjunctivitis using multivariable fractional polynomial modelling. We also accounted for the immediate and delayed effects of statutory public holidays. We created two separate penultimate models for $PM_{2.5}$ and PM_{10} because the former is a subset of the latter. These two penultimate models comprised the core regression model, immediate and lagged measures of $PM_{2.5}$ or PM_{10} and all other statistically significant air pollutant and climatic variables at the 10% level from the initial basic models.

We examined the Autocorrelation Function Plots (ACF) and Partial Autocorrelation Function plots (PACF) of the deviance residuals from the penultimate regression models to determine the degree of unaccounted autocorrelation. We then added lagged deviance residuals that corresponded to the degree of observed autocorrelation to obtain the final regression models (Brumback et al., 2000).

Finally, we used backward elimination to obtain the most parsimonious final multivariable models. We then assessed whether haze episodes modified the relationship between particulate matter and acute conjunctivitis in the same week. The measure of effect for each independent linear term was the incidence rate ratio (IRR); that is the change in the weekly proportion of acute conjunctivitis reports (referencing the mean), associated with each unit change in the corresponding independent exposure. Where more than a single term for a specific air pollutant remained in the final model, we estimated the cumulative effect of that exposure effect on the outcome by combining the beta-coefficients of those terms. In sensitivity analyses, we evaluated how varying the degree of control for long term trend and seasonality influenced out pollutant effect estimates. The final $PM_{2.5}$ and PM_{10} multivariable regression models are described in Eqs. (1) and (2) respectively:

$$\begin{aligned}\log \mathrm{E}(\mathrm{Y_t}) = {} & \beta_0 + \mathrm{S}\,(\mathrm{ts}, \mathrm{df} = 8/\mathrm{year}) + \beta_1 \mathrm{PM}_{2.5,\mathrm{i}=0} + \beta_2 \mathrm{PM}_{2.5,\mathrm{i}=1} \\ & + \beta_3 \mathrm{holidays}_{\mathrm{i}=0} + \beta_4 \mathrm{holidays}_{\mathrm{i}=1} + \beta_5 \mathrm{temp}_{\mathrm{i}=0} + \beta_6 \mathrm{temp}_{\mathrm{i}=1} \\ & + \beta_7 \mathrm{temp}_{\mathrm{i}=2} + \beta_8 \mathrm{humidity}_{\mathrm{i}=0} + \sum_{\mathrm{i}=1}^{20} \beta_{\mathrm{ri}} \mathrm{deviance}_{\mathrm{i}=\mathrm{x}}\end{aligned} \tag{1}$$

$$\begin{aligned}\log \mathrm{E}(\mathrm{Y_t}) = {} & \beta_0 + \mathrm{S}\,(\mathrm{ts}, \mathrm{df} = 8/\mathrm{year}) + \beta_1 \mathrm{PM}_{10,\mathrm{i}=0} + \beta_2 \mathrm{PM}_{10,\mathrm{i}=1} \\ & + \beta_3 \mathrm{holidays}_{\mathrm{i}=0} + \beta_4 \mathrm{holidays}_{\mathrm{i}=1} + \beta_5 \mathrm{temp}_{\mathrm{i}=0} + \beta_6 \mathrm{temp}_{\mathrm{i}=1} \\ & + \beta_7 \mathrm{temp}_{\mathrm{i}=2} + \beta_8 \mathrm{humidity}_{\mathrm{i}=0} + \sum_{\mathrm{i}=1}^{20} \beta_{\mathrm{ri}} \mathrm{deviance}_{\mathrm{i}=\mathrm{x}}\end{aligned} \tag{2}$$

where $E(Y)$ is the expected number of reports of acute conjunctivitis at week t, β_0 is the model intercept, S refers to the cubic spline functions for long term trend and season with the corresponding df used, $PM_{2.5}$ and PM_{10} refer to the ambient air concentrations of particulate matter of aerodynamic diameter of <2.5 μm and 10 μm respectively, *holidays* refer to the number of statutory public holidays in a given week, *temp* refers to the ambient air temperature, *humidity* refers to relative humidity, *deviance* refers to the deviance residuals derived from penultimate regression models, i corresponds to the lag week of the indicated numeral, β_1 to β_8 and β_{ri} are the coefficients for the respective independent variables described.

2.4.2. Burden of acute conjunctivitis attributable to air pollutants

Using Eqs. (3) and (4), we first estimated the attributable fraction (AF) and absolute number (AN) for each air pollutant and any of its lags associated with acute conjunctivitis reports:

$$\mathrm{AF_w} = \frac{\mathrm{IRR_w} - 1}{\mathrm{IRR_w}} \tag{3}$$

$$\mathrm{AN_w} = \mathrm{AF_w} \times \mathrm{N_w} \tag{4}$$

where AF_w refers to the attributable fraction for a single pollutant, N_w refers to the number of acute conjunctivitis reports in week w and IRR_w refers to the cumulative risk corresponding to the rise in pollutant level referencing World Health Organization (WHO) air quality guideline (AQG) values. In sensitivity analysis, we compared our estimated burden referencing the lowest observed air pollutant concentrations in our study. To obtain the air pollutant-specific total attributable fraction for the study, we took the sum of its immediate and lagged contributions from all weeks of the study and divided it by the total number of acute conjunctivitis reports. We also calculated the sum of the immediate and lagged pollutant-specific fraction for all South-East Asia haze episodes that occurred in the epidemiological weeks of 17–23 October 2010 (Salinas et al., 2013), 16–22 June 2013 (Velasco and Rastan, 2015) and 6 September to 24 October 2015 (Urbančok et al., 2017) which affected Singapore. Similar to other studies (Chen et al., 2017; Qiu et al., 2018a, 2018b), we used the 95% CIs for the IRRs to calculate the CIs for the AFs.

We evaluated statistical significance at the 5% level and presented Wald p-values, IRRs and the corresponding 95% CIs for the effects of independent linear and categorical terms. We used a range of diagnostic tools to determine goodness-of-fit for our final multivariable models. We used Akaike's Information Criterion (AIC) (Akaike, 1974) to compare model fit. We produced Fig. 1 using R version 3.3 and performed all other analyses using STATA 12.1 software (StataCorp, USA).

3. Results

3.1. Descriptive analysis

From 2009 to 2018, there were 261,959 reports of acute conjunctivitis corresponding to an average of about 503 per week (Table 1). Mean air pollutant concentration levels for $PM_{2.5}$ and PM_{10} over 521 epidemiological weeks exceeded annual WHO AQG reference values (Krzyzanowski and Cohen, 2008), with the top one percentile of values observed in June 2013, September 2015 and October 2015. $PM_{2.5}$ and PM_{10} concentrations were highly correlated over the study period ($r = 0.987$, $p < 0.001$). Ambient air temperatures did not vary considerably from the weekly mean of 27.9 °C, while the mean relative humidity of 80.8% was high and expected of a tropical setting.

3.1.1. Effects of $PM_{2.5}$

After adjusting for long-term trend, seasonality, public holidays, the immediate and lagged effects of climate variations and autocorrelation, we found strong evidence of an association between ambient air $PM_{2.5}$ concentrations and reports of acute conjunctivitis (univariate results reported in Appendix A). Every 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 2.2% increase (IRR: 1.022, 95% CI: 1.016 to 1.028, $p < 0.001$) in reports in the same week and a 1.5% increase (IRR: 1.015, 95% CI: 1.009 to 1.021, $p < 0.001$) in reports one week later (Fig. 2). Varying the degree of control for long term trend and seasonality in sensitivity analysis did not alter these effect estimates to an important degree (see Appendix C). Haze episodes did not modify the relationship between $PM_{2.5}$ and conjunctivitis ($p = 0.465$). Increases in ambient air temperature were independently associated with an immediate and delayed reduction in acute conjunctivitis reports of up to 2 weeks while an increase in relative humidity was associated with a reduction in reports in the same week (Table 2). We did not observe any non-linear effects for $PM_{2.5}$, temperature or relative humidity (see multivariable fractional polynomial modelling estimates in Appendix B). Public holidays were associated with a decrease in acute conjunctivitis reports. The AIC value for the model unadjusted for autocorrelation was 10.5. After adjustment, we obtained an improved model fit with an AIC value of 9.2 (see Appendix D for ACF and PACF plots and Appendix E for the results of regression diagnostics).

3.1.2. Effects of PM_{10}

In our fully adjusted model, we found strong evidence of an association between ambient air PM_{10} concentrations and reports of acute conjunctivitis. Every 10 μg/m^3 increase in PM_{10} was associated with a 1.7% increase (IRR: 1.017, 95% CI: 1.013 to 1.022, $p < 0.001$) in acute conjunctivitis reports in the same week and a 1.2% increase (IRR: 1.012, 95% CI: 1.007 to 1.017, $p < 0.001$) in reports one week later (Fig. 3). Varying the degree of control for long term trend and seasonality in sensitivity analysis did not alter these effect estimates to an important degree (see

Table 1
Weekly measures of acute conjunctivitis, ambient air pollutant concentrations and climate conditions in Singapore, 2009 to 2018.

Variable	N	Mean (SD)	Median	IQR	Minimum	Maximum
Number of acute conjunctivitis reports	261,959	502.8 (79.5)	495	446–552	341	924
Air pollutant concentrations						
$PM_{2.5}$ (μg/m^3)	521	18.4 (11.1)	15.9	13.6–19.8	9.1	167.0
PM_{10} (μg/m^3)	521	30.0 (13.5)	27.3	24.0–32.0	16.7	213.9
SO_2 (μg/m^3)	521	10.8 (5.0)	11.1	6.3–14.0	2.2	30.2
NO_2 (μg/m^3)	521	23.9 (5.7)	23.8	19.8–27.8	10.3	44.3
O_3 (μg/m^3)	521	24.3 (8.0)	23.1	18.3–28.7	10.0	57.3
CO (mg/m^3)	521	0.5 (0.1)	0.5	0.5–0.6	0.3	2.2
Climate conditions						
Ambient air temperature (°C)	521	27.8 (0.9)	27.9	27.2–28.4	25.0	30.1
Mean relative humidity (%)	521	79.4 (3.9)	79.3	76.6–82.2	63.5	91.4
Cumulative rainfall (mm)	521	41.7 (46.2)	29.4	8.6–58.0	0	380.6

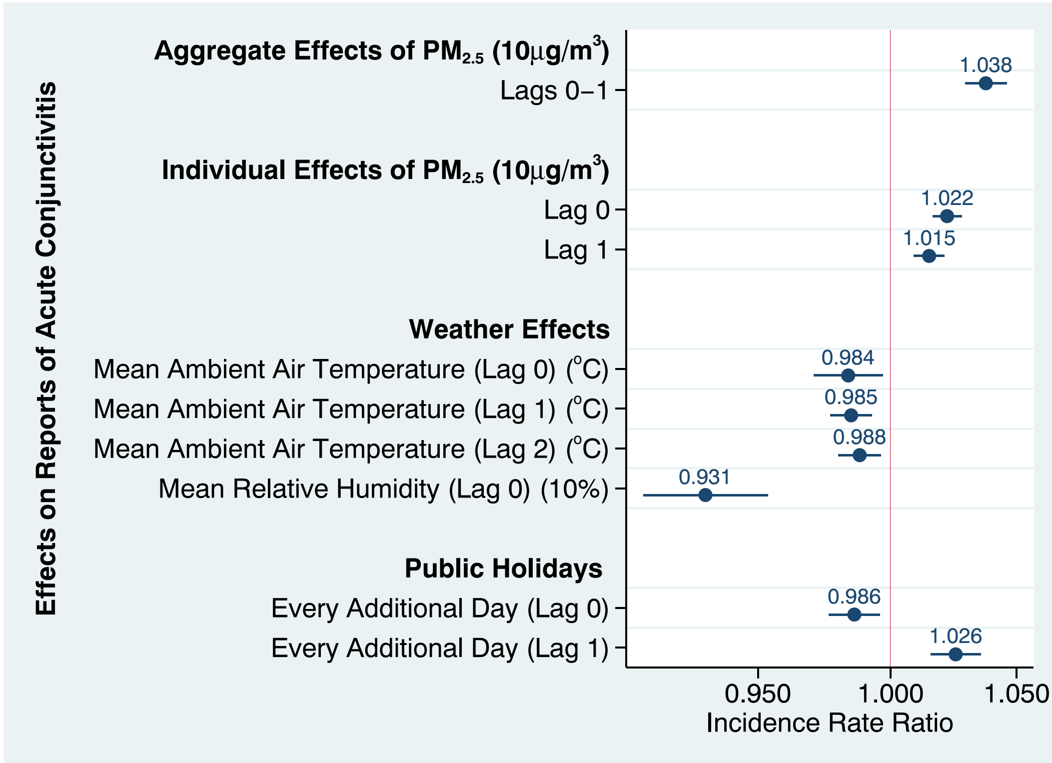

Fig. 2. Results from the fully adjusted model examining the independent effects of $PM_{2.5}$ on reports of acute conjunctivitis. The solid vertical red line indicates the null effect. The solid navy circles represent the point estimates of the independent exposure effects while the solid horizontal navy lines represent the corresponding 95% confidence intervals.

Appendix C). Haze episodes did not modify the relationship between PM_{10} and conjunctivitis ($p = 0.759$). Increases in ambient air temperature in the present week were associated with reductions in acute conjunctivitis reports in the immediate and the following two weeks (Table 3). We did not observe any non-linear effects for PM_{10}, temperature or relative humidity (Appendix B). Public holidays were associated with a reduction in acute conjunctivitis reports. Adjustment for autocorrelation improved the model AIC value from 10.5 to 9.2 (see Appendix F for ACF and PACF plots and Appendix E for the results of regression diagnostics).

3.2. Attributable fraction and attributable number

The mean concentrations of $PM_{2.5}$ and PM_{10} during the haze episodes were 82.9 μg/m^3 and 107.3 μg/m^3 respectively. Based on WHO AQG reference values, we estimated that 3.02% (95% CI: 2.08% to 3.95%) and 2.82% (95% CI, 1.92% to 3.71%) of all acute conjunctivitis reports were attributable to $PM_{2.5}$ and PM_{10} respectively. Of these, 1046 (13.2%) of $PM_{2.5}$-related and 1052 (14.2%) of PM_{10}-related acute conjunctivitis reports occurred during the 2010, 2013 and 2015 South-East Asia haze episodes (1.7% of the entire study period). In sensitivity analysis using the minimum observed values of particulate matter in our study, we observed marginal differences in our estimates with largely overlapping confidence intervals for both approaches (Tables 4 and 5).

Table 2
Adjusted associations between $PM_{2.5}$ concentrations and acute conjunctivitis reports.

Variable	β	p-Value (Wald test)	95% CI		AIC value 9.2
$PM_{2.5}$ (10 μg/m^3)					
Lag 0	0.022	<0.001	0.016	0.028	
Lag 1	0.015	<0.001	0.009	0.021	
Ambient air temperature (°C)					
Lag 0	−0.016	0.017	−0.030	−0.003	
Lag 1	−0.015	<0.001	−0.023	−0.007	
Lag 2	−0.012	0.005	−0.020	−0.004	
Mean relative humidity (10%)					
Lag 0	−0.072	<0.001	−0.096	−0.047	
Public holidays					
Lag 0	−0.014	0.006	−0.024	−0.004	
Lag 1	0.025	<0.001	0.016	0.035	

4. Discussion

In the present study, we examined the associations between air quality and the risk of acute conjunctivitis in Singapore. We found positive associations between ambient air $PM_{2.5}$ and PM_{10} concentrations with reports of acute conjunctivitis, with a disproportionately higher number of particulate matter-attributable reports occurring during the 2010, 2013 and 2015 South-East Asia haze episodes. To the best of our knowledge, no other international or domestic study has quantified the effects and health burden of independent air pollutants on acute conjunctivitis in South-East Asia at the national level. Our findings strengthen the evidence base for the implementation of measures aimed at reducing the burden of air pollution-related health outcomes not just in Singapore but in similar metropolitan cities around the globe.

4.1. Effects of particulate matter exposure

We observed a similar range of immediate and delayed effects of $PM_{2.5}$ and PM_{10} on acute conjunctivitis, though the strength of association for $PM_{2.5}$ was slightly greater than that for PM_{10}. Our study findings on the effects of particulate matter associated acute conjunctivitis were consistent with a number of studies which reported positive associations between ambient air particulate matter levels and conjunctivitis (Chang et al., 2012; Lu et al., 2019; Lee et al., 2018; Szyszkowicz et al.,

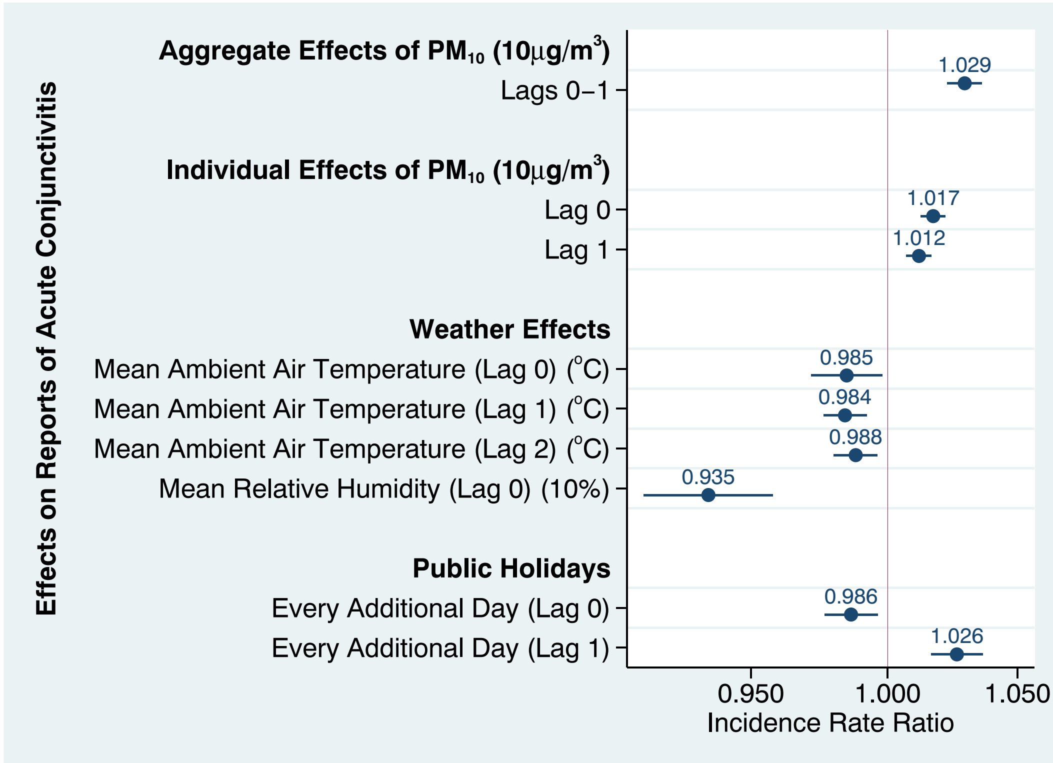

Fig. 3. Results from the fully adjusted model examining the independent effects of PM_{10} on reports of acute conjunctivitis. The solid vertical red line indicates the null effect. The solid navy circles represent the point estimates of the independent exposure effects while the solid horizontal navy lines represent the corresponding 95% confidence intervals.

2016). In general, our effect estimates were higher than those reported in those studies. However, differences in the ambient absolute air pollutant concentrations levels, composition of particulate matter, demographics and health surveillance systems across study settings may have contributed to the differential estimates across studies. The minimum concentration values observed over the study duration were similar to WHO AQG values. This suggests that the WHO AQG values may be appropriate targets for mitigation measures aimed at reducing the burden of conjunctivitis in similar settings.

Several plausible underlying mechanisms may explain our main study findings. These relate to how particulate matter exposure increases ocular surface susceptibility to cellular breakdown and pathogens, thus increasing the risk of conjunctivitis. Firstly, particulate matter deposition on the ocular surface may mechanically increase friction during ocular and eyelid movements, thus increasing the probability of abrasion and consequently inflammation in the eye. Secondly, particulate matter is known to contain infectious agents that could cause conjunctival infections to occur. A previous study reported the positive relationship between ambient particulate matter and pathogenic bacteria (Liu et al., 2018). Thirdly, the highly oxidising components of particulate matter may lower the pH of the lacrimal fluid, leading to the acidification of tears and thus cellular damage on the ocular surface. Fourthly, increased ocular exposure to atmospheric particulate matter has been reported to reduce tear-film breakup time (a measure of tear film stability) (Torricelli et al., 2013). Shorter tear-film breakup durations that are not compensated by an increased frequency of blinking will result in the occurrence of dry areas on the ocular surface, rendering them more susceptible to epithelial cell damage and infection. A previous study reported the positive association between $PM_{2.5}$ exposure and cell damage of human epithelial corneal cells (Fu et al., 2017b). Higher concentrations of $PM_{2.5}$ exposure to mice eyes were associated with ocular surface damage, ulceration, epithelial defects, decreased tear volume and decreased tear film break-up time (Tan et al., 2018). It is plausible that human ocular exposure to

Table 3
Adjusted associations between PM_{10} concentrations and acute conjunctivitis reports.

Variable	β	p-Value (Wald test)	95% CI		AIC value 9.2
PM_{10} (10 μg/m^3)					
Lag 0	0.017	<0.001	0.013	0.022	
Lag 1	0.012	<0.001	0.007	0.017	
Ambient air temperature (°C)					
Lag 0	−0.015	0.025	−0.029	−0.002	
Lag 1	−0.016	<0.001	−0.024	−0.008	
Lag 2	−0.012	0.005	−0.020	−0.004	
Mean relative humidity (10%)					
Lag 0	−0.067	<0.001	−0.092	−0.043	
Public holidays					
Lag 0	−0.014	0.007	−0.024	−0.004	
Lag 1	0.026	<0.001	0.016	0.036	

Table 4
Attributable fractions of acute conjunctivitis reports due to $PM_{2.5}$ and PM_{10}.

Pollutant	Reference levels	Acute conjunctivitis reports		Attributable fraction (%, 95% CI)
		Attributable number (95% CI)	Observed total number	
WHO 24-h AQG				
$PM_{2.5}$	10 μg/m^3	7911 (5458–9940)	261,959	3.02 (2.08–3.95)
PM_{10}	20 μg/m^3	7385 (5027–9715)	261,959	2.82 (1.92–3.71)
Study minimum				
$PM_{2.5}$	9.1 μg/m^3	8779 (5603–11,030)	261,959	3.35 (2.31–4.38)
PM_{10}	16.7 μg/m^3	9689 (6715–12,986)	261,959	3.70 (2.56–4.96)

Table 5
Attributable fractions of acute conjunctivitis reports due to $PM_{2.5}$ and PM_{10} during the 2010, 2013 and 2015 South-East Asia haze episodes.

Pollutant	Reference levels	Acute conjunctivitis reports				Attributable fraction (%, 95% CI)
		Attributable number (95% CI)			Total (95% CI)	
		2010	2013	2015		
WHO 24-h AQG						
$PM_{2.5}$	10 μg/m^3	84 (56–111)	246 (171–314)	716 (483–941)	1046 (710–1366)	13.2 (9.0–17.3)
PM_{10}	20 μg/m^3	83 (57–108)	252 (180–318)	717 (494–932)	1052 (731–1358)	14.2 (9.9–18.4)
Study minimum						
$PM_{2.5}$	9.1 μg/m^3	89 (62–116)	260 (188–326)	779 (545–1004)	1128 (795–1446)	12.8 (9.1–16.5)
PM_{10}	16.7 μg/m^3	87 (60–114)	256 (183–323)	746 (515–969)	1089 (757–1406)	11.2 (7.8–14.5)

particulate matter may also contribute to reduced viability, reduced proliferation and increased degradation of epithelial cells, resulting in an increased risk of ocular disease.

We estimated that the fraction of observed acute conjunctivitis independently attributable to $PM_{2.5}$ and PM_{10} were largely similar at 3% each. As $PM_{2.5}$ is a subset of PM_{10}, our findings suggest that most of the PM_{10}-attributed acute conjunctivitis reports were in fact due to $PM_{2.5}$. This is not surprising given that $PM_{2.5}$ is much smaller than PM_{10} and thus has greater penetrating potential into the conjunctiva and consequently a greater likelihood of inducing inflammation and infection. This finding reinforces the importance of considering intervention measures specifically targeting the reduction of finer fractions of particulate matter.

The combined duration of the South-East Asia haze episodes in 2010, 2013 and 2015 occurred over an extremely small fraction of our entire study duration (<2%). However, the combination of these episodes was associated with a disproportionately higher number of particulate matter-driven conjunctivitis. Short-term increases in particulate matter concentrations especially during haze episodes may thus be used as signals to anticipate rises in the demand for primary healthcare resources. However, the practicality of achieving adequate preparedness within a short span of time is healthcare system-dependent. In settings where healthcare resources are limited, the complementary use of satellite imagery for the detection of regional fires could provide a longer lead-time for anticipatory preparedness before the peak influence of regional haze episodes.

4.2. Effects of public holidays

The reduction in conjunctivitis in the same week where statutory public holidays occur is likely due to the closure of all government polyclinics on public holidays. A number of private primary healthcare services continue during such holidays, therefore the observed reduction may represent a shift in healthcare service providers, rather than an actual reduction in conjunctival disease. The subsequent delayed rise in conjunctivitis may have been contributed partially by delayed healthcare seeking behaviour resulting from polyclinic closures during public holidays.

4.3. Effects of weather exposures

In our study, we found that an increase in ambient relative humidity was protective against acute conjunctivitis. Elevated evaporation rate of the tear film in the eye has been reported to be associated with tear film instability (Peng et al., 2014). Higher moisture levels in the atmosphere may reduce the evaporation rate in the tear film, thus retaining the eye's ability to moisten the conjunctival epithelial cells and consequently its effectiveness in eliminating foreign bodies through blinking. Previous studies have reported a positive association between ambient air temperature and conjunctivitis (Chiang et al., 2012; Kern et al., 2016). Our findings on the protective effect of temperature were inconsistent with them. We hypothesize that temperature may have indirect effects on the occurrence of conjunctivitis, given that ambient temperature has been reported to influence the activity patterns of people (Horanont et al., 2013). A study of households in Singapore found that higher ambient temperatures were associated with increased water demand among lower income households and increased electricity consumption among higher income households, suggesting different socioeconomic approaches to heat relief (Salvo, 2018). It may be plausible that an increased frequency of baths contributed to the removal of physical and microbiological agents from the ocular surface that could cause inflammation. The use of air-conditioners during warmer periods together with a reduction on outdoor activities may also reduce ocular exposure to outdoor air contaminants and consequently reduce conjunctivitis risk. Further studies are required to elucidate the mechanisms through which ambient temperature influences conjunctivitis.

4.4. Effects of other air pollutant exposures

Studies examining the impact of air quality on conjunctivitis have also investigated the independent effects of SO_2, NO_2, O_3 and CO, though not all individual studies examined this entire range of air pollutants. Several studies have reported associations between ambient SO_2, NO_2 and O_3 concentrations (Chang et al., 2012; Chiang et al., 2012; Lu et al., 2019; Szyszkowicz et al., 2016) with acute conjunctivitis while one study reported an additional association between ambient CO concentration and acute conjunctivitis but not for O_3 (Fu et al., 2017a). SO_2, NO_2, O_3 and CO were not significantly included in our final multivariable regression models.

The lack of observable effects of SO_2, NO_2, O_3 and CO on acute conjunctivitis in our study does not imply that these air pollutants play no role in increasing the risk of this ocular health outcome. In fact, sulphur dioxide and nitrogen oxides are important precursors to secondary particulate matter formation (Guo et al., 2014), with ozone also playing a mediating role in the formation sulphates, a major chemical component of particulate matter (Xue et al., 2016). A previous study characterizing the chemical components of on-road traffic related particulate matter pollution in Singapore reported that sulphates and nitrates in combination represented 3% of the mass of $PM_{2.5}$ collected from the roadside and 6.5% of the mass of $PM_{2.5}$ collected in an urban area (Zhang et al., 2017). Sulphates and nitrates were among the major species of ions identified in $PM_{2.5}$ collected in Singapore during both clear and hazy days (See et al., 2006). Mitigation measures that target reductions in sulphur dioxide, nitrogen oxides and ozone in the ambient environment continue to remain relevant in addressing their corresponding health effects. In addition, those measures may contribute to reductions in particulate matter and thus particulate matter-driven outcomes including ocular health.

4.5. Strengths and limitations

We included all acute conjunctivitis reports from government polyclinics and our results are therefore generalizable to individuals that rely on public primary healthcare services. We have no reason to believe that the effects of particulate matter would differ for individuals who sought primary care through private healthcare service providers. Therefore, our estimates likely underrepresent the true burden of particulate matter driven conjunctivitis events. The generalization of mean air pollutant concentrations across Singapore may have resulted in some exposure misclassification and attenuated our effect estimates. Individual-level daily living conditions such as the use of air-conditioning or air purifiers that may have altered pollutant exposures were not taken into consideration in this ecological study. We analysed data on a weekly timescale and could not provide conjunctivitis burden estimates over the entire duration of haze episodes. However, we referenced the epidemiological weeks in which the haze episodes were most severe, therefore our burden estimates are likely to be slightly conservative. We obtained similar estimates on the burden of acute conjunctivitis despite using different reference levels. We did not analyse the effects of air quality on cause-specific conjunctivitis nor did we conduct age- and gender-specific analysis as this data was not available. Our estimates therefore reflect the aggregated dependency of acute conjunctivitis on air quality and are not generalizable beyond the range of pollutant concentrations included in our study. Though we were unable to consider the diverse aetiology of acute conjunctivitis in our study, the health resource implications for rises in particulate matter pollution remain the same.

5. Conclusions

We presented a national-level analysis attributing a fraction of acute conjunctivitis to short-term changes in ambient air particulate matter exposure. We showed that this disease fraction was disproportionately higher during South-East Asia transboundary haze episodes. Short-term increases in particulate matter concentrations especially at the onset of haze episodes may be used to anticipate a rise in demand for primary healthcare resources related to conjunctivitis. Our findings underscore the importance of reducing the health impact of indigenous and transboundary sources of ambient particulate matter pollution.

CRediT authorship contribution statement

Joel Aik: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Rae Chua:** Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing. **Natasha Jamali:** Writing - review & editing. **Elaine Chee:** Conceptualization, 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.

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Declaration on conflict of interest

All authors declare that they have no conflict of interests.

Appendix A. Supplementary data

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