How air pollution altered the association of meteorological exposures and the incidence of dengue fever

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Abstract

Meteorological exposures are well-documented factors underlying the dengue pandemics, and air pollution was reported to have the potential to change the behaviors and health conditions of mosquitoes. However, it remains unclear whether air pollution could modify the association of meteorological exposures and the incidence of dengue fever. We matched the dengue surveillance data with the meteorological and air pollution data collected from monitoring sites from 2015 through 2019 in Guangzhou area. We developed generalized additive models with Poisson distribution to regress the daily counts of dengue against four meteorological exposures, while controlling for pollution and normalized difference vegetation index to evaluate the risk ratio (RR) of dengue for each unit increase in different exposures. The interaction terms of meteorological exposures and air pollution were then included to assess the modification effect of different pollution on the associations. Daily dengue cases were nonlinearly associated with one-week cumulative temperature and precipitation, while not associated with humidity and wind speed. RRs were 1.07 (1.04, 1.11) and 0.95 (0.88, 1.03) for temperature below and above 27.1 °C, 0.97 (0.96, 0.98) and 1.05 (1.01, 1.08) for precipitation below and above 20.3 mm, respectively. For the modification effect, the RRs of low-temperature, wind speed on higher SO\(_2\) days and low-precipitation on both higher PM\(_{2.5}\) and SO\(_2\) days were greater compared to the low-pollution days with \(P_{interaction}\) being 0.037, 0.030, 0.022 and 0.018. But the RRs of both high-temperature on higher SO\(_2\) days and high-precipitation on higher PM\(_{2.5}\) d were smaller with \(P_{interaction}\) being 0.001 and 0.043. Air pollution could alter the meteorology-dengue associations. The impact of low-temperature, low-precipitation and wind speed on dengue occurrence tended to increase on days with high SO\(_2\) levels while the impact of high-temperature decreased. The impact of low-precipitation increased on high-PM\(_{2.5}\) d while the impact of high-precipitation decreased.
1. Introduction

Dengue fever is one of the leading vector-borne communicable diseases which was included in the top ten list of global health threats by the World Health Organization in 2019 [1]. It is estimated that about 2.5 billion people are living in dengue epidemic areas of the world, with 50–100 million infected annually [2]. However, since dengue infections could be asymptomatic and lead to severe issues of misdiagnosis and under-reporting [3, 4], the reported number of infections could be much smaller than the true number estimated [5]. Guangdong, China locates in the east of Asia, the most affected area with 70% global burden of dengue being estimated in this area [3]. Furthermore, Guangdong as the socioeconomic center of South China suffers from dengue cases imported from surrounding countries such as Myanmar, Laos, Philippines and Thailand [6, 7], with 57,515 cases reported during 2004 and 2018, which accounted for more than 80% of the nationwide estimate (www.phsciencedata.cn/Share/index.jsp). Messina and colleagues suggested that the eastern coastal areas of China, including Guangdong, would be one of the most suitable regions for dengue transmission due to climate change, particularly the increase in temperature [8]. Therefore, dengue pandemics may be more frequent in this area and a better understanding of the dominant risk factors will be particularly important for developing targeted prevention strategies.

A large number of studies have reported the close relationship between dengue and meteorological factors such as temperature, precipitation, humidity, and wind speed [9–11]. For example, a meta-analysis on top of 25 studies from East and Southeast Asia, and South America suggested a 12% increase in dengue incidence for each 1 °C increase in temperature [12]. A higher temperature may promote the growing of dengue virus in the vectors. For example, the extrinsic incubation period plays a crucial role in the occurrence of dengue cases, which generally ranged between 2 and 33 d [13]. When the temperature went up from 25 to 30 °C, it averagely decreased by 9.5 d [13], which could lead to a higher transmission rate of dengue [14]. Similarly, the potential impact of other meteorological factors was also biologically plausible. For example, water accumulation in containers after precipitation provided oviposition sites for mosquitoes [15] while an optimum relative humidity condition could stimulate the egg hatching [16]. Wind speed was considered to affect the horizontal dispersal behavior and stability of mosquitoes in flight, and indirectly associated with dengue spread [17]. Previous studies have suggested the potential associations between these meteorological factors and dengue pandemic [11, 12, 18].

Although the association between meteorological exposures and the incidence of dengue has been well-documented, it remains unclear whether the association could be modified by air pollution, another type of atmospheric factors that commonly explored in environmental health studies. Currently, no evidence was available on such modification effect. However, it may be biologically plausible as air pollution may change the behaviors and health conditions of mosquitoes which are the dominant vector of dengue virus. For example, Wan-Norafikah et al observed in an experiment that the ozone-producing air purifier could repel 68.59% Ae. aegypti and 77.14% Ae. albopictus away from bait [19]. Another experiment observed that the blood-feeding rate of mosquitoes at the PM$_{2.5}$ level of 50–100 µg m$^{-3}$ was 41.0% lower than that in non-exposure situations while the vacuolated degeneration of ovaries of the female Ae. aegypti significantly increased at higher concentration of PM$_{2.5}$ [20]. Therefore, the impact of pollution exposures may alter the possibility of dengue infection among the residents in response to environmental exposures such as weather conditions. By incorporating this information, further studies may include air pollution into the dengue predictive models and early-warning systems, investigate the impact of meteorological factors in different air pollution scenarios, and derive a more precise prediction. However, evidence on such combined effect of air pollution and meteorological exposures is limited in existing literature.

Therefore, this study was aimed to evaluate the association between meteorological exposures and dengue incidence as well as how the association varied across different levels of air pollution in Guangzhou, China. This study offers important implications for reducing dengue in Guangzhou, as well as in other regions with similar natural environment and pollution conditions. Our new insight about dengue also provides new ideas for future related studies.

2. Methods

2.1. Study area and dengue data

This study was carried out in Guangzhou, the capital city of Guangdong Province. It is the most affected city over the country in recent years, with 41,941 cases reported during 2004–2018, accounting for 73% burden in Guangdong and approximate 60% burden in China (www.phsciencedata.cn/Share/index.jsp). Detailed information on each dengue case including the date of disease onset, case category (clinical diagnosis or laboratory confirmation) and basic demographics is compulsively reported to the China National Notifiable Disease Surveillance System within the first 24 h after clinical diagnosis or laboratory confirmation by hospitals. We collected case data for the period between January 2015 and
December 2019 from the Guangzhou Center for Disease Control and Prevention, and computed the daily number of cases as the primary outcome of the current study.

2.2. Atmospheric data
Meteorological exposures including daily average temperature (°C), cumulative precipitation (mm), average relative humidity (%), and average wind speed (m s\(^{-1}\)) were obtained from the China Meteorological Administration (http://data.cma.cn) for the period from 1/1/2014 through 31/12/2019. We also collected the data of daily concentration (\(\mu g m^{-3}\)) of five main air pollutions from the China National Environmental Monitoring Centre (https://air.cnemc.cn:18007), including PM\(_{10}\), PM\(_{2.5}\), SO\(_2\), NO\(_2\), and O\(_3\) for the same period. The daily observations were averaged across the monitoring sites in the study area as described in figure S1.

2.3. Other covariates
Mosquitoes favor dense vegetation (e.g. trees and bushes) to rest and breed since the vegetation could provide microclimate with less evaporation, higher humidity and lower wind speed [21–24]. Therefore, normalized difference vegetation index (NDVI), an established indicator of vegetation, was the most commonly used to represent the coverage of mosquito-favored habitats [25, 26]. The NDVI ranges from 0 to 1, with a greater value representing a higher vegetation coverage while a smaller value representing a higher water coverage. Usually, a value of 0.4–0.6 represents a median vegetation coverage [27]. We downloaded the Terra Moderate Resolution Imaging Spectroradiometer vegetation index—NDVI data (MOD13Q1, version 6, generated every 16 d at 250 m spatial resolution) from the Land Processing Distributed Active Archive Center (https://lpdaac.usgs.gov) for the same period as the atmospheric data. The average of the values across the cells covered by Guangzhou was calculated as the regional mean by using raster package in R software. The annual population of Guangzhou was collected from the Guangzhou Statistical Yearbook (http://tjj.gz.gov.cn) to adjust for the potential impact of background population changes.

2.4. Statistical analysis
Descriptive analysis was used for the grouped description of dengue cases, meteorological exposures, air pollution and NDVI. Besides the non-case days, we also defined low-incidence days (\(\leq 4\) cases) and high-incidence days (>4 cases) where 4 was the median number of cases on days with case reported. Means and standard errors for the whole study period and each group were acquired, ANOVA or Kruskal–Wallis H test were selected for the intergroup difference test according to the assumptions of normality and homogeneity of variance.

Generalized additive models (GAMs) with Poisson distribution were used to evaluate the meteorology-dengue association. The Poisson rather than quasi-Poisson distribution was used since we did not detect an over-dispersion issue with our data using the performance package in R software. We regressed daily counts of dengue against meteorological exposures while adjusting for main air pollution and NDVI. The long-term trend and seasonality were also fitted using a natural cubic spline (ns) of time with seven degrees of freedom (df) per year as commonly used in previous studies [28–30]. All the four meteorological factors were included in models. Besides, we also used the diurnal temperature range (DTR), maximum and minimum temperature instead of the average temperature to capture a more comprehensive picture of the impact of temperature. However, we only included three main air pollutions (i.e. PM\(_{2.5}\), SO\(_2\), O\(_3\)) without strong correlations with each other (Pearson’s rho \(< 0.8\), figure S2) to avoid collinearity. The logarithm of the annual population was included as an offset. The model was specified as follows:

\[
Y_t \sim \text{Poisson}(\mu_t)
\]

\[
\log(\mu_t) = \alpha + s(\text{TEMP}) + s(\text{PRE}) + s(\text{HUMD}) + s(\text{WIND}) + \beta_1 \text{PM}_{2.5} + \beta_2 \text{SO}_2 + \beta_3 \text{O}_3 + \beta_4 \text{NDVI} + \text{ns (time, df = 7 × 5)} + \text{offset(\log(\text{POP})})
\]

where \(\mu_t\) refers to the expected daily counts of dengue cases on day \(t\); \(\alpha\) is the intercept; \(s(\cdot)\) is the smoothing function for meteorological exposures. We used the cubic spline with three df as was commonly used in literature [31–33]; \(\beta\) indicates the coefficient of the corresponding term.

Since existing evidence mainly focused on the adverse effect of air pollution on the behaviors of adult mosquitoes, we selected 28 d as the maximum lag days to focus on the stage after the infection of mosquitoes, covering the extrinsic incubation period (~15 d), the possible transmission period (0–7 d), and the intrinsic incubation period (~6 d) of dengue virus [13, 34–36]. Specifically, we considered five scenarios of the cumulative effect: lag 0, lag 0–7, lag 0–14, lag 0–21 and lag 0–28. In each scenario, we computed the corresponding moving average of meteorological exposures, the concentration of air pollution, and NDVI for modeling. The scenario which minimized the Akaike information criterion was used to assess the relationships and for further analyses. If the relationship between a meteorological variable and dengue incidence showed a nonlinear trend, we
performed a piecewise linear fitting according to the inflection point (the values of meteorological variables at which the effect reached a maximum or minimum). We reported the risk ratio (RR) (i.e. RR = \exp(\beta_i)) for each unit increase in an exposure.

To evaluate whether the associations of meteorological exposures with dengue incidence were modified by air pollution, we included an interaction term of each meteorological exposure and dichotomous air pollution stratum indicators (high level: concentration higher than the median concentration over the entire study period; low level: concentration lower than the median) into models. The following medians were used for strata definition: \(\text{PM}_{2.5}\): 33.10 \(\mu\)g m\(^{-3}\); \(\text{SO}_2\): 10.42 \(\mu\)g m\(^{-3}\); \(\text{O}_3\): 89.92 \(\mu\)g m\(^{-3}\). Furthermore, we integrated the three dichotomous air pollution variables into an eight-level categorical indicator (table S1) to evaluate the combined effect of these factors as well as its interaction with the meteorological exposures. \(P\) for interaction was also computed.

To confirm that our results were robust, we performed sensitivity analyses by (a) changing the degrees of freedom for the spline functions from 3 to 4 and 5 respectively; (b) including each of the three pollution variables in the primary models separately rather than simultaneously. We further applied a meta-regression to compare the results between sensitivity models and the primary models. All statistical analyses were conducted using R software (version 4.0.5).

3. Results

3.1. Descriptive statistics

Table 1 presents the characteristics of dengue cases and atmospheric factors between 2015 and 2019 (1826 d). A total of 3712 dengue cases were reported in Guangzhou during this period. The time series displays a long-term trend and seasonality with more cases reported in warmer months and less cases in other months (figure S3). The averages for meteorological exposures over the previous week were 22.37 °C (average temperature), 6.30 mm (cumulative precipitation), 81.29% (average relative humidity), and 2.08 m s\(^{-1}\) (average wind speed), respectively. The average temperature over the previous week was 33.21 and 6.77 mm, and \(P\) < 0.001). As for NDVI, the average during our study period was 0.49, days with cases reported had a greater average of NDVI compared with non-case days (\(P\) < 0.001).

3.2. Association between meteorological exposures and dengue

We chose the best cumulative scenario of 0–7 lag days for our models (table S2). Figure 1 illustrates the exposure-response relationship between meteorological exposures and daily dengue cases. The effects of average temperature (figure 1(A), \(P\) < 0.001) and cumulative precipitation (figure 1(B), \(P\) < 0.001) on dengue were non-linear (approximate logarithm-shaped and approximate U-shaped shaped) with cutoffs of 27.1 °C and 20.3 mm, respectively. However, the effects of both average relative humidity (figure 1(C), \(P\) = 0.908) and average wind speed (figure 1(D), \(P\) = 0.770) was not significant. Besides, the effects of minimum and maximum temperature had a similar pattern with the effect of average temperature (figures S4(A) and (B)), but the effect of DTR was statistically insignificant (figure S4(C)). According to figure 1, the effects of average temperature and cumulative precipitation could then be divided into two sets of linear associations.

As shown in table 2, each degree increase in average temperature was associated with a 7.3% (95% CI: 3.5%–11.2%) increase in the daily number of dengue cases when the temperature was below 27.1 °C. Additionally, the effect of higher temperature (above 27.1 °C) showed a negative trend, but was not significant (\(P\) = 0.232). As for cumulative precipitation, each 1 mm increase in precipitation was related to a 2.7% (95% CI: 1.7%–3.8%) decrease of cases when the precipitation was below the threshold (20.3 mm). On the contrary, when the precipitation was above the threshold, each millimeter rise in precipitation was positively related to dengue, that is a 4.7% (95% CI: 1.2%–8.3%) increase in cases.

3.3. Effect modification by air pollution on the associations

As depicted in figure 2, effect modification by \(\text{PM}_{2.5}\) and \(\text{SO}_2\) on the associations of meteorological exposures with dengue was observed, but the effect modification by \(\text{O}_3\) was not significant. We found that each degree increase in the average temperature below 27.1 °C was associated with a greater RR of 1.11 (95%CI: 1.06–1.17) in high \(\text{SO}_2\) conditions compared to low \(\text{SO}_2\) conditions (figure 2(A)). However, when the average temperature was above 27.1 °C, we observed an inverse effect modification by \(\text{SO}_2\), that is 1 °C rise in temperature was associated with a smaller RR of 0.78 (95%CI: 0.90–1.15) in high \(\text{SO}_2\) conditions.
Table 1. Descriptive statistics of dengue cases and environmental variables over the previous week (i.e. lag 0–7 d) in Guangzhou, 2015–2019.

|                          | Overall (1826 d) | Daily dengue counts = 0 (1255 d) | Daily dengue counts ≤ 4 (298 d) | Daily dengue counts > 4 (273 d) | P value |
|--------------------------|------------------|----------------------------------|----------------------------------|----------------------------------|---------|
| **Daily dengue cases**   |                  |                                  |                                  |                                  |         |
| **Meteorological variables** |                  |                                  |                                  |                                  |         |
| Average temperature (°C) | 22.37 ± 5.50     | 20.90 ± 5.64                     | 25.60 ± 3.83                     | 25.57 ± 2.92                     | <0.001  |
| Cumulative precipitation (mm) | 6.30 ± 8.25     | 6.77 ± 8.72                      | 6.19 ± 7.87                      | 4.24 ± 5.74                      | <0.001  |
| Average relative humidity (%) | 81.29 ± 7.06   | 81.03 ± 7.43                     | 82.58 ± 5.59                     | 81.09 ± 6.55                     | 0.011   |
| Average wind speed (m s⁻¹) | 2.08 ± 0.50     | 2.13 ± 0.50                      | 2.01 ± 0.46                      | 1.94 ± 0.52                      | <0.001  |
| **Main air pollution**    |                  |                                  |                                  |                                  |         |
| PM2.5 (µg m⁻³)           | 33.21 ± 14.00    | 34.73 ± 14.90                    | 29.59 ± 11.94                    | 30.18 ± 10.09                    | <0.001  |
| PM10 (µg m⁻³)            | 52.79 ± 18.96    | 54.33 ± 19.80                    | 48.98 ± 17.23                    | 49.84 ± 15.65                    | <0.001  |
| NO₂ (µg m⁻³)             | 41.30 ± 13.19    | 43.21 ± 14.33                    | 37.05 ± 9.93                     | 37.17 ± 7.76                     | <0.001  |
| SO₂ (µg m⁻³)             | 10.23 ± 3.34     | 10.61 ± 3.50                     | 9.95 ± 3.08                      | 8.75 ± 2.27                      | <0.001  |
| O₃ (µg m⁻³)              | 90.84 ± 36.21    | 80.46 ± 31.35                    | 103.39 ± 32.60                   | 124.86 ± 35.69                   | <0.001  |
| NDVI                     | 0.49 ± 0.11      | 0.46 ± 0.12                      | 0.55 ± 0.06                      | 0.59 ± 0.02                      | <0.001  |

* 4 was the median daily dengue counts on days with case reported.

![Figure 1](image-url) Partial effect of each one-week cumulative meteorological exposure on daily dengue cases from 2015 to 2019. Note: The x axis refers to the mean level of each meteorological exposure. The y axis refers to the smoother to the fitted values. P value refers to the significant level of the smooth term. Black lines indicate the estimated mean value, blue bands indicate the 95% CI. Horizontal red dash lines indicate 0 reference lines. Vertical red dash lines indicate the values of exposures at which the effects reach a maximum or minimum. (A): the effect of average temperature; (B): the effect of cumulative precipitation; (C): the effect of average relative humidity; (D): the effect of average wind speed.

(figure 2(B)). The effect modification by PM₂.₅ on precipitation-dengue association was similar to that by SO₂ on temperature-dengue association. Each millimeter rise in the cumulative precipitation below 20.3 mm was related to a greater RR of 1.00 (95%CI: 0.97–1.02) in high PM₂.₅ conditions (figure 2(C)), but 1 mm increase in precipitation above 20.3 mm was related to a smaller RR of 0.93 (95%CI: 0.83–1.05) in
Table 2. Linear association between one-week cumulative meteorological exposures and daily dengue cases.

| Meteorological variable                  | RR (95%CI)   | P     |
|------------------------------------------|--------------|-------|
| Average temperature (non-linear)         |              |       |
| Below 27.1 °C                           | 1.07 (1.04,1.11) | <0.001|
| Above 27.1 °C                           | 0.95 (0.88,1.03) | 0.232 |
| Cumulative precipitation (non-linear)    |              |       |
| Below 20.3 mm                            | 0.97 (0.96,0.98) | <0.001|
| Above 20.3 mm                            | 1.05 (1.01,1.08) | 0.008 |
| Average relative humidity (linear)       | 1.00 (0.99,1.02) | 0.908 |
| Average wind speed (linear)              | 1.02 (0.90,1.15) | 0.769 |

Figure 2. Linear associations between one-week cumulative meteorological exposures and the risk of dengue by binary air pollution.

Note: Asterisks indicate the interaction term of meteorological exposures and air pollution was significant (*: P for interaction <0.05; **: P for interaction <0.01). AT: average temperature; CP: cumulative precipitation; ARH: average relative humidity; AWS: average wind speed.

As shown in figure 3, we observed similar effect modification by the multi-pollution indicator with that by single-pollution indicators in general. Compared with good air quality days (low PM$_{2.5}$ & low SO$_2$ & low O$_3$), the associations between temperature and dengue (positive effect of low-level temperature & negative effect of high-level temperature) were strengthened on some bad air quality days; whereas, the associations between precipitation and dengue (negative effect of low-level precipitation & positive effect of high-level precipitation) were offset in some bad air quality scenarios. As for humidity and wind speed, although some of the interaction terms were significant, the risk effects of these exposures were still not significant.

3.4. Sensitivity analyses

Figure S6 is a summary of the results of sensitivity analyses. The associations of meteorological exposures with dengue incidence were almost robust after a series of adjustments for the primary model. Cutoffs derived based on GAM results in different models were similar with a maximum difference of 0.7 °C and 1.1 mm, respectively (table S3). Although the effect
Figure 3. Linear associations between one-week cumulative meteorological exposures and the risk of dengue by the eight-level air pollution indicator. 

Note: asterisks indicate the interaction term of meteorological exposures and air pollution indicator was significant (*: P for interaction < 0.05; **: P for interaction < 0.01). AT: average temperature; CP: cumulative precipitation; ARH: average relative humidity; AWS: average wind speed. ‘+’ refers to high-pollution level; ‘−’ refers to low-pollution level; ‘PM$_{2.5}$ (+) & SO$_2$ (−) & O$_3$ (−)’ refers to the stratum with high PM$_{2.5}$, low SO$_2$ and low O$_3$. The effect estimates of CP (>20.3 mm) in high PM$_{2.5}$ & low SO$_2$ & low O$_3$ stratum was not acquired because the values of CP on these days were all smaller than 20.3 mm.

4. Discussion

In this study, we investigated the association between meteorological exposures and the risk of dengue fever, and more importantly, assessed the modification effect of multiple major air pollution. Our results suggested that temperature and precipitation were significantly associated with dengue cases in approximately a logarithm-shaped and a U-shaped trend whereas no significant associations were identified for humidity and wind speed. We also revealed diverse patterns of the effect modification by air pollution on these relationships, including the facilitation effects of some pollution conditions on the health impact of increased temperature (both low- and high temperature conditions) and increased wind speed, and the prohibition effects of some other pollution conditions on the impact of increased precipitation (both low- and high-precipitation conditions). We speculate that higher air pollution level may affect both human behaviors and the activities of mosquito, as a potential mechanism. To our knowledge, this is one of the few studies that investigated how air pollution modify the association between meteorological exposures and dengue incidence.

4.1. Dengue and meteorological exposures

We found an approximately logarithm relationship between average temperature and dengue, which peaked at 27.1 ºC. We also found that increased cumulative precipitation below 20.3 mm was negatively associated with dengue. These findings are in accordance with existing epidemiological and biological evidence [11, 37–40].

As for the cumulative precipitation above 20.3 mm, it was positively associated with dengue incidence. However, this result has not previously
been described. On the one hand, although mosquitoes can fly on rainy days, persistent heavy rainfall threatens the survival of mosquitoes in the open air [41, 42]. On the other hand, high rainfall can reduce people’s outdoor activities [43, 44]. Therefore, humans and mosquitoes tend to get into houses on days with high rainfall thus leading to a possible increase in the density of vectors (some may have been infected already by dengue virus) in a limit space, which facilitates biting activities of these vectors and hence the transmission of dengue virus.

In contrast to earlier findings, we found another inconsistency about relative humidity-dengue association. Relative humidity is recognized as a key factor affecting vectors’ oviposition and egg hatching [16, 45]. An appropriate relative humidity can increase the population density of vectors, facilitating the transmission of dengue [11, 31]. However, no significant association between relative humidity and dengue was detected in our study. This discrepancy could be attributed to the difference settings of lag days in different studies. A potential interpretation for that is atmospheric factors tend to affect the entire chain of dengue transmission, including the development (egg, larva, pupa, adult), survival and behavior of mosquitoes, as well as the extrinsic and intrinsic incubation period of dengue virus. Xiao et al reported an approximate logarithm relationship between relative humidity and dengue incidence at a lag of 4 months [31]. Whereas, we found that the relationship between cumulative exposures and dengue was best fitted with a 0–7 d lag in our study, it most likely only covered the adult stage of vectors and the intrinsic incubation period of dengue virus, which were less affected by relative humidity.

### 4.2. Effect modification by air pollution

Regarding the interactive analysis, we found PM$_{2.5}$ and SO$_2$ could modify the effects of meteorological exposures in different patterns. Firstly, in high temperature condition (above 27.1 °C), we observed a significant negative association between temperature and dengue when SO$_2$ concentration was high. Synergistic effect of high temperature and high SO$_2$ concentration may lead to this variation compared to low SO$_2$ concentration situation. It may shorten the lifespan of vectors and reduce their population density. A meta-analysis on experiment data revealed that high temperature (above 25 °C) could significantly shorten the lifespan of adult mosquitoes [38]. Although no direct evidence confirmed the adverse effect of SO$_2$ on mosquitoes, Tan et al conducted an experiment and thought acidic SO$_2$ might cause tissue damage in the larvae of another kind of insect—butterfly [46]. Moreover, several studies suggested that other air pollution were harmful to mosquitoes, such as the repellency effect of O$_3$ and the adherence effect of fine particles [19, 20, 47], which may also be a potential possibility underlying our findings.

However, the risk effect of temperature under the threshold was strengthened when SO$_2$ concentration was high. Similarly, in low-precipitation conditions, the negative effect of increased precipitation was not significant anymore when SO$_2$ or PM$_{2.5}$ concentration was high. The reasons may also relate to human and mosquito behaviors. Chen et al and An et al suggested that a terrible air quality may reduce outdoor leisure activities [48, 49]. In addition, Wilder-Smith and colleagues thought mosquitoes may be driven indoors because of the adverse effect of pollution [50]. These two reasons could result in prolonged stay indoors of humans and create more chances of exposure to infected mosquitoes. According to above information, we can update current dengue-control strategies, that is, people may strengthen environment management and individual protection to reduce contact with mosquitoes on days with bad air quality.

We also found that wind speed was positively associated with dengue in higher SO$_2$ condition. A possible explanation for this result may be the dilution effect of pollution by wind [51], which alleviates the adverse effect of pollution on mosquitoes. However, the effect of wind on regional air pollution concentration is complex. Several key factors, including the locations of pollutant emission source, wind direction and speed, play vital roles in this process [52–54], which may be the possible reason why only the effect modification by SO$_2$ was detected in the study.

Besides above findings, we also observed that in high-precipitation condition, the positive association between precipitation-increase and dengue was not significant anymore when the concentration of air pollution was high (all three pollutions, but only the interaction term of PM$_{2.5}$ was significant). However, the modification effect by O$_3$ was not detected on any meteorological exposures. As for the modification by multi-pollution indicator, we found a similar trend as single-pollution indicator in general, except for the modification on the effect of wind speed. Analyses of these effect modification can help us identify the environmental conditions in which dengue transmission is more easily, and can help us establish more specific early warning systems.

### 4.3. Limitations

The limitation of this study should be acknowledged. Firstly, we only included data from Guangzhou, which may result in an increased difficulty of conclusion extrapolation. However, Guangzhou is the largest city in South China with a population of 19 million. More importantly, it reported with the majority of dengue cases in the country in recent years. It is of great public health significance to investigate the modification effect of air pollution on meteorology-dengue associations in this area. Second, similar to other ecological studies, our study may suffer from the ecological fallacy and could not...
confirm the causal relationship. However, our study still provides a new insight on the potential impact of atmospheric factors underlying the dengue pandemic, which may offer ideas for future experimental researches.

5. Conclusion

In conclusion, the meteorological exposures may significantly affect the incidence of dengue fever, the impact of which were observed to be modified by the concentration of multiple air pollution. Compared with low-pollution level: The effects of temperature (positive effect of low-level temperature & negative effect of high-level temperature) and wind speed (positive effect on dengue) were enhanced on high-level SO2 days. The effects of precipitation (negative effect of low-level precipitation & positive effect of high-level precipitation) were alleviated on both SO2 and PM2.5 d. This information is an important complement of the existing dengue-related knowledge, which could help us establish more specific and accurate early-warning systems as well as preventive strategies.

Data availability statement

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

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