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Ambient air pollution, temperature and kawasaki disease in Shanghai, China

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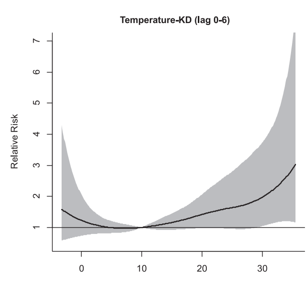
HIGHLIGHTS

- Air pollutants were not significantly associated with Kawasaki disease (KD).
- The results suggested that high temperature might increase KD incidence.
- The curve for the association between daily temperature and KD was "J-shaped".
- The effects of temperature increased from lag 0 d–6 d, and then decreased.
- The daily temperature with minimum risk of KD was about 10.0 °C.

GRAPHICAL ABSTRACT



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ABSTRACT

Kawasaki disease (KD) is a kind of pediatric vasculitis of unknown etiology which mainly affects the development of coronary artery aneurysms. Few studies have explored the potential environmental risk factors on KD incidence. We performed a time-series analysis to investigate the associations between air pollution and temperature and KD in Shanghai, China. We collected daily-hospitalized KD patients that were admitted in major pediatric specialty hospitals located in the urban areas of Shanghai from 2001 to 2010. The over-dispersed generalized additive model was used to estimate the effects of air pollutants on KD incidence on each day. Then, this model was combined with a distributed lag non-linear model to estimate the cumulative effects of temperature over a week. There were positive but statistically insignificant associations between three major air pollutants and KD incidence. The association between daily mean temperature and KD was generally J-shaped with higher risks on hot days. The cumulative relative risk of KD at extreme hot temperature (99th percentile, 32.4 °C) over a week was 1.91 [95%

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Kawasaki disease
Risk factor

confidence interval (CI): 1.13, 3.23], compared with the referent temperature (10.0 °C). This study suggested that a short-term exposure to high temperature may significantly increase the incidence of KD, and the evidence linking air pollution and KD incidence was limited.

1. Introduction

Kawasaki disease (KD) has become the most common acquired pediatric heart disease in developed countries, and is increasingly recognized in developing countries. KD is initially characterized by high fever, multisystem inflammation, and cervical lymphadenopathy. It then strikingly targets the coronary arteries and may result in myocardial infarction, sudden death or ischemic heart disease in childhood or early adulthood (Dodds et al., 2011; Newburger et al., 2004). About 20% of the patients will develop coronary artery aneurysms if they are not treated with intravenous immunoglobulin in the acute phase of KD (Newburger et al., 2016). The reported incidence of KD per 100, 000 children younger than 5 years varied widely among different countries: for example, from isolated case reports to 264.8 in Japan in developed countries (Fischer et al., 2007; Makino et al., 2015), and 7.06 to 55.1 in China (Du et al., 2007; Li et al., 2008). For example, in Shanghai, the largest city of China, there has been about 3-fold increase in KD incidence (from 16.8 per 100,000 in 1998 to 50.5 per 100,000 in 2012) in the last two decades in a longitudinal survey (Chen et al., 2016; Huang et al., 2006). The etiology of KD is commonly believed to be an exaggerated immune and/or inflammatory response to infectious or environmental agents in genetically susceptible individuals (Rowley, 2011). Recent studies suggested that environmental triggers, such as air pollution and extreme temperatures, may also serve as risk factors (Jung et al., 2016).

Ambient air contains particulate matter and various gaseous pollutants. The strong oxidizing property of air pollutants gives them the potential to induce KD through exaggerated inflammatory response, which is heavily involved in the pathophysiologic process of KD development (Kelly, 2003). Several studies have explored the associations between air pollution and KD, but the results remained controversial (Jung et al., 2016; Rodó et al., 2014; Zeft et al., 2016). And, the existing evidence is all reported in developed countries, and few studies have been conducted in developing countries (such as China) where air pollution levels are much higher.

Seasonal trends of KD incidence have been widely observed, but varied globally, for example, there was a winter/spring peak in Japan whereas a summer/spring peak in China (Burns et al., 2013). The seasonal patterns may be driven by differences in infectious disease activity and presence of environmental allergens, as well as by the independent influences of ambient temperature. However, these studies merely made seasonal comparisons, and even few directly evaluated the potential effects of ambient temperature on KD occurrences (Burns et al., 2005; Checkley et al., 2009). Thus, the objective of the current study was to evaluate the associations between ambient air pollution and temperature changes and KD incidence in children over a 10-year period (2001–2010) in Shanghai, China.

2. Materials and methods

2.1. Data source

This study utilized the epidemiological survey database of Kawasaki disease from major pediatric hospitals in urban areas of Shanghai from 1 January 2001 to 31 December 2010 (Chen et al., 2016; Huang et al., 2006; Ma et al., 2010) (see Fig. S1 in supplementary information). KD cases were diagnosed by the 5th revised edition of diagnostic criteria for KD, issued by the Japan Kawasaki Disease Research Committee at the 7th International Kawasaki Disease Symposium in 2002 (Ayusawa et al., 2005). Cases were included in the study if the patients had at least five of the following six clinical manifestations or at least four signs together with coronary abnormalities documented by echocardiography or coronary angiography: (1) fever persisting 5 days or longer (inclusive of those cases in whom the fever has subsided before the 5th day in response to therapy); (2) bilateral conjunctival congestion; (3) changes of lips and oral cavity, such as reddening of lips, strawberry tongue, diffuse congestion of oral and pharyngeal mucosa; (4) polymorphous exanthema; (5) changes of peripheral extremities, such as reddening of palms and soles, indurative edema at initial stage, or membranous desquamation from fingertips at convalescent stage; and (6) acute non-purulent cervical lymphadenopathy. In addition, the cases of incomplete KD, diagnosed with referring to the guidelines for incomplete KD made by American Academy of Pediatrics and American Heart Association in 2004, were also included (Newburger et al., 2004). In our study, the date when the patient started to have a fever was considered as the first day of a KD course, and was then linked to air pollution and temperature data. Besides, the study population was restricted to residents who had permanent living addresses for at least 6 consecutive months in the urban areas of Shanghai. The study was approved by the Institutional Review Boards at the School of Public Health, Fudan University.

We collected daily mean concentrations of particulate matter with an aerodynamic diameter of <10 μm (PM_{10}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) from the Shanghai Environmental Monitoring Center. The data for these pollutants were simply averaged from six fixed-site stations located in six urban districts (Hongkou, Jing'an, Luwan, Putuo, Xuhui, and Yangpu; see Fig. S1 in supplementary information). The monitoring methods were tapered element oscillating microbalance for PM_{10}, ultraviolet fluorescence for SO_2, and chemiluminescence for NO_2. Daily weather data (mean temperature and humidity) were directly obtained from the urban station (Xujiahui) of Shanghai Meteorology Bureau.

2.2. Statistical analysis

In environmental epidemiological studies, the time-series approach is broadly applied to assess short-term associations between air pollution and temperature and adverse health outcomes (Chen et al., 2012; Ma et al., 2014). For estimating the effects of air pollutants, we applied a *quasi*-Poisson generalized additive model (GAM). Several covariates were introduced into this model: (1) a natural cubic smooth function of calendar day with 7 degrees of freedom (*df*) per year to exclude (as a linear filter) unmeasured long-term and inherent seasonal trends in KD incidence (Peng et al., 2006); (2) natural smooth functions with 6 *df* for the same-day mean temperature and 3 *df* for the same-day mean relative