Chemosphere 186 (2017) 817–822

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

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

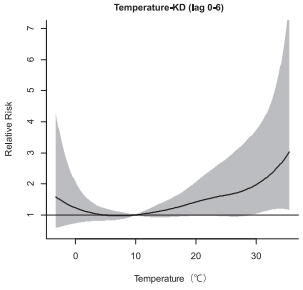
Zhijing Lin [a, 1], Xia Meng [b, 1], Renjie Chen [a], Guoying Huang [c], Xiaojing Ma [c], Jingjing Chen [c], Min Huang [d], Meirong Huang [e], Yonghao Gui [c], Chen Chu [c, *], Fang Liu [c, **], Haidong Kan [a]

[a] School of Public Health, Key Lab of Public Health Safety of the Ministry of Education and Key Lab of Health Technology Assessment of the Ministry of Health, Fudan University, Shanghai 200032, China
[b] Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta 30322, GA, USA
[c] Cardiovascular Center, Children's Hospital of Fudan University, Shanghai 201102, China
[d] Department of Pediatric Cardiology, Children's Hospital of Shanghai Jiaotong University, Shanghai 200040, China
[e] Pediatric Heart Center, Shanghai Children's Medical Center, Shanghai 200127, China

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



ARTICLE INFO

Article history:
Received 9 May 2017
Received in revised form
10 August 2017
Accepted 11 August 2017
Available online 12 August 2017

Handling Editor: A. Gies

Keywords:
Air pollution
Temperature

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%

* Corresponding author. Children's Hospital of Fudan University, 399 Wan Yuan Road, Shanghai 201102, China.
** Corresponding author. Children's Hospital of Fudan University, 399 Wan Yuan Road, Shanghai 201102, China.
E-mail addresses: chickenchu@163.com (C. Chu), liufang@fudan.edu.cn (F. Liu).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.chemosphere.2017.08.054

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

humidity to exclude potential nonlinear confounding effects of weather conditions; (3) an indicator for the day of week to adjust for temporal variation of KD cases within a week. Three pollutants were introduced into the model one at a time. We estimated the effects of air pollutants on the present day (lag 0), the previous day (lag 1) and the previous 2 day (lag 2), because previous studies have indicated an immediate effect of air pollution on human health (Chen et al., 2012; Dominici et al., 2006). Estimates were presented as the percent increase in daily KD incidence and its 95% confidence intervals (CIs) associated with a 10 $\mu g/m^3$ increase in air pollutant concentrations.

Because previous studies showed potentially nonlinear and lagged associations between ambient temperature and adverse health outcomes (Ma et al., 2014), we combined the distributed-lag nonlinear model (DLNM) to the GAM to estimate the effects of temperature on KD incidence. The DLNM allows simultaneous estimation of the non-linear effect of temperature at each lag after accounting for the collinearity across lags and of the cumulative effects of temperature over multiple lags. To be specific, we established a flexible cross-basis by a natural cubic spline for the space of temperature with three internal knots at equally spaced temperature percentiles. For the space of lags, we defined a natural cubic spline with two internal knots at equally spaced log-values of lags (plus intercept) to allow for more flexible lag effects at short delays (Guo et al., 2014). In the GAM, we also added a natural cubic smooth function of calendar day with 7 *df* per year and an indicator of day of week. We further controlled for PM_{10}, SO_2, and NO_2 using the polynomial distributed lag models with a maximum lag of 3 days to adjust for the potential confounding effects of air pollution. We first plotted the relative risks (RRs) in the temperature-KD association curves. To obtain a quantitative risk estimate, we then calculated the RRs comparing the 1st percentile of temperature (as the extreme cold temperature) and the 99th percentile (as the extreme hot temperature) to the referent temperature, respectively. Given the uncertainty in determining the maximum lag in estimation, we used multiple maximum lags from 1 to 10 days. In order to determine the "best" maximum lag, we evaluated the model fit based on three statistics: Akaike information criterion (AIC), generalized cross validation (GCV) and coefficient of determination (R^2).

We also conducted several sensitivity analyses to evaluate the robustness of our results for the association between ambient temperature and KD. First, we re-analyzed the data after dividing our dataset into odd (2001, 2003, 2005, 2007, 2009, and 2011) and even (2002, 2004, 2006, 2008, and 2010) years. Second, we re-analyzed the data stratified in either hot (April to September) or cold (October to March) periods separately.

The statistical tests were two-sided, and values of $P < 0.05$ were considered as statistically significant. All models were performed using R software (Version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) with the GAM using the "mgcv" package and the DLNM using the "dlnm" package.

3. Results

3.1. Descriptive results

Table 1 summarizes the descriptive statistics on daily KD cases, air pollution and weather conditions. There were no missing daily values for both environmental and health data. During the study period of 2001–2010 (3652 days), we recorded a total of 2344 KD cases in urban areas of Shanghai, with their ages ranging from 1 month to 18.8 years (median: 2.35 years) and boys accounting for 69.5%. The annual average values of daily mean concentrations of PM_{10}, SO_2 and NO_2 were 92.9 $\mu g/m^3$, 46.0 $\mu g/m^3$ and 62.3 $\mu g/m^3$, respectively, which were well above the World Health Organization Air Quality Guidelines (WHO, 2006). There were almost downward trends of air pollution levels in these years (see Fig. S2 in supplementary information). The annual mean temperature and relative humidity were 17.6 °C (range, −3.3 °C–35.5 °C) and 71.1% (range, 25.0%–97.0%), respectively, reflecting the typical subtropical climate of Shanghai. There was a similar seasonal pattern (i.e., peak in summer and trough in winter) in daily temperature and KD incidence (see Fig. S3 in supplementary information). Air pollutants were highly correlated with each other (Pearson $r > 0.65$) and moderately correlated with temperature and humidity.

3.2. Regression results

Table 2 provides the effect estimates of a 10 $\mu g/m^3$ increase of air pollutant concentrations on daily KD incidence in single lags of 0–2 days. We observed consistently positive but statistically insignificant associations between air pollutants and KD.

The exposure-response relationship curves were almost J shaped with higher risks at hot temperatures, which varied little across different lags. A referent temperature of about 10 °C was selected by visualizing these curves. For example, as depicted in Fig. 1, the risks of KD gradually increased when temperature was above 10 °C and became statistically significant when temperature was above 20 °C; the risks of KD were statistically insignificant when temperature was less than 10 °C.

Table 3 summarizes the cumulative risk estimates of extreme cold and hot temperatures using different maximum lag days. There were positive but statistically non-significant risks of extreme cold temperature using all lags we examined. Noteworthy was that the risks increased drastically at lags 0–6 days or longer. For the extreme hot temperature, the risk estimates increased gradually up to lags 0–7 days; became statistically significant from lags 0–4 days to 0–8 days; and lost statistical significance at longer lags. According to the three model fit statistics, the lag of 0–6 days was determined to be the main lag in this analysis because it could lead to the smallest AIC/GCV and the highest R^2. Based on this lag, we obtained a RR of 1.27 (95% CI: 0.60, 2.69) for extreme cold temperature and of 1.91 (95% CI: 1.13, 3.23) for extreme hot temperature.

Fig. 2 illustrates the lag structures in the effects of extreme hot temperature on KD over lags 0–10 days. The RRs increased from lag 0 day to lag 6 days, and then decreased slightly thereafter.

Results from sensitivity analyses of temperature and KD demonstrated that the effect estimate was similar in either odd or even years (data not shown). Additionally, the estimated effect increased slightly in hot period while kept unchanged in cold period.

4. Discussion

The present study in Shanghai, China suggested that high temperature was significantly associated with increased incidence of KD, but air pollutants were positively but not significantly associated with KD. To the best of our knowledge, this was the first attempt to assess the impacts of ambient air pollution and temperature on KD in Mainland China.

Recently, attention has been paid on the role of ambient air pollution in triggering KD. Although the exact mechanisms are unclear, some human studies have demonstrated that this association was somewhat plausible. For example, short-term exposure to air pollutants may damage endothelial cells, impair vascular function, stimulate systemic inflammation response, increase oxidative stress, and induce cardiac ischemia and repolarization abnormalities (Brook et al., 2010; Chen et al., 2015; Kelly, 2003), consequently contributing to the development of KD. However, we

Table 1
Descriptive statistics of daily KD cases, weather conditions and air pollution in Shanghai, China (2001–2010).

	Mean	SD	Min	P_1	P_{25}	P_{50}	P_{75}	P_{99}	Max
KD	0.7	0.9	0	0	0	0	1.0	4.0	9.0
Weather conditions									
Temperature (°C)	17.6	8.9	−3.3	0.3	10.0	18.5	25.1	32.4	35.5
Humidity (%)	71.1	11.9	25.0	41.0	64.0	71.8	80.0	94.0	97.0
Air pollutants									
PM_{10} (μg/m^3)	92.9	54.5	11.5	23.8	53.4	79.8	118.0	274.1	600.0
SO_2 (μg/m^3)	46.0	26.7	5.0	10	25.8	40.0	60.2	131.2	189.4
NO_2 (μg/m^3)	62.3	23.3	11.2	19.2	46.4	59.2	75.4	130.1	167.0

Abbreviations: KD, daily Kawasaki disease cases; SD, standard deviations; PM10, particulate matter with air aerodynamic diameter of <10 μm; SO2, sulfur dioxide; NO2, nitrogen dioxide.

Table 2
Percent increases (means and 95% confidence intervals) in daily KD cases associated with a 10 μg/m^3 increase of air pollutant concentrations on the present day (lag 0), the previous day (lag 1) and the previous 2 day (lag 2).

Pollutant	Lag day	KD
PM_{10}	0	−0.04 (−1.34, 1.34)
	1	1.05 (−0.31, 2.43)
	2	1.48 (−1.07, 1.89)
SO_2	0	2.36 (−0.85, 5.57)
	1	2.07 (−1.21, 5.32)
	2	2.11 (−2.70, 4.41)
NO_2	0	2.54 (−0.87, 5.90)
	1	3.73 (−0.20, 7.65)
	2	3.27 (−0.51, 7.01)

Definitions of abbreviations as in Table 1.

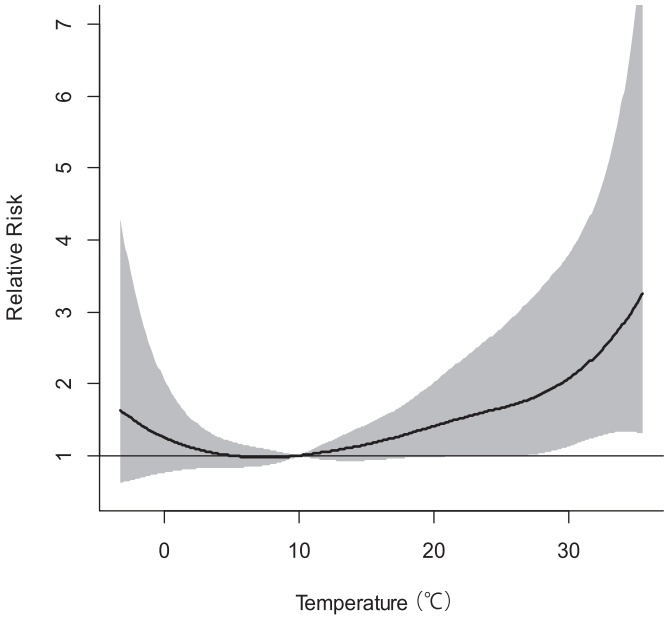


Fig. 1. The nonlinear curve for the association between daily mean temperature (°C) and KD over lag 0–6 days. The black line is the mean relative risk, and the gray area is the 95% confidence intervals of risk estimates.

found positive but statistically insignificant effects of air pollutants on KD, which were still consistent with all three previous investigations. For example, one study in Japan assessed SO_2, oxidants, nitrogen oxides, carbon monoxide and non-methane hydrocarbon as potential causes of KD, and reported positive but statistically insignificant findings (Rodó et al., 2014). A case-crossover study in United States evaluated fine particulate matter ($PM_{2.5}$) as a potential cause of KD (indicated by the onset of KD-related fever) and also obtained non-significant results (Zeft et al., 2016). Another case-crossover analysis in Taiwan evaluated the associations between PM_{10}, SO_2, NO_2, carbon monoxide and ozone and KD hospitalization, but merely found significant effects of ozone (Jung et al., 2016). The lack of robust evidence to date may be

Table 3
The cumulative relative risks (means and 95% confidence intervals) of extreme cold and extreme hot temperatures on KD over different lag days, compared with the referent temperature (10 °C).[a]

Lag	Extreme cold	Extreme hot	AIC	GCV	R^2
0–1	1.09 (0.63, 1.88)	1.24 (0.98, 1.56)	7565.72	1.132	0.126
0–2	1.09 (0.74, 1.60)	1.27 (0.98, 1.64)	7571.64	1.132	0.126
0–3	1.04 (0.65, 1.69)	1.45 (0.98, 2.13)	7569.80	1.134	0.126
0–4	1.07 (0.68, 1.72)	1.62 (1.01, 2.61)*	7568.37	1.133	0.126
0–5	1.08 (0.68, 1.74)	1.81 (1.21, 2.72)*	7566.09	1.135	0.126
0–6	1.27 (0.60, 2.69)	1.91 (1.13, 3.23)*	7555.14	1.130	0.131
0–7	1.26 (0.77, 2.05)	2.40 (1.21, 4.74)*	7559.86	1.133	0.128
0–8	1.29 (0.78, 2.14)	2.08 (1.02, 4.23)*	7565.63	1.136	0.126
0–9	1.34 (0.80, 2.25)	2.00 (0.76, 3.73)	7566.39	1.129	0.126
0–10	1.30 (0.74, 2.28)	1.96 (0.70, 3.81)	7560.01	1.131	0.126

*P < 0.05.; Abbreviations: AIC, Akaike Information Criterion; GCV, Generalized Cross Validation; R^2, R-square.

[a] Extreme cold: 1st percentile of temperature, 0.3 °C; extreme hot: 99th percentile of temperature, 32.4 °C.

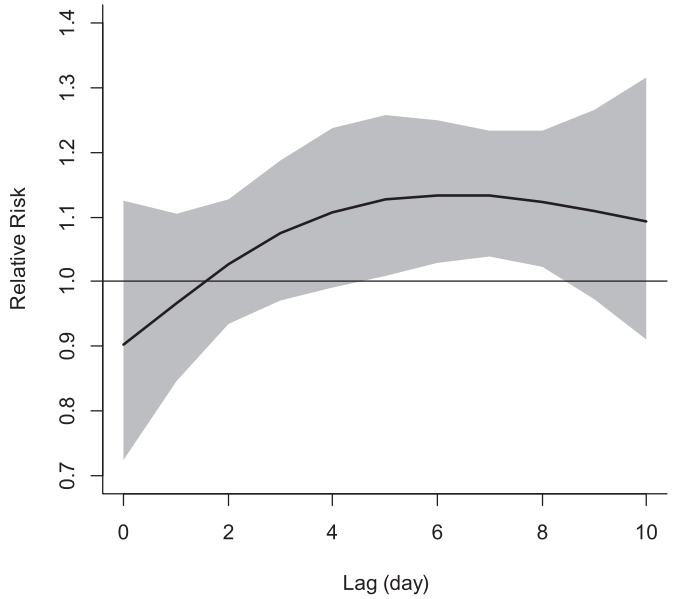


Fig. 2. The lag structure in the relative risks of KD by comparing the extreme hot temperature (99th percentile, 32.4 °C) with the referent temperature (10 °C). The black line is the mean relative risk, and the gray area is the 95% confidence intervals of risk estimates.

due to the limited statistical power associated with the small size of daily KD cases and the unmeasured residual confounding. More large-scale studies, especially longitudinal studies, were needed to confirm whether the occurrence of KD was associated with air pollutants.

The incidence of KD has a striking seasonal variation, with different patterns reported in several countries and areas (Burns et al., 2013; Chen et al., 2016; Du et al., 2007; Fischer et al., 2007; Li et al., 2008; Ma et al., 2010). For example, there is a winter/spring peak in developed countries (Holman et al., 2010; Lin et al., 2010; Nakamura et al., 2012), but a summer/spring peak in China (Chen et al., 2016; Du et al., 2007; Huang et al., 2006; Li et al., 2008; Ma et al., 2010; Ng et al., 2005). However, few epidemiological studies have directly explored the role of ambient temperature as a risk factor after adjusting for inherent time trends. Our results suggested that there was a "J-shaped" exposure-response curve for the association between daily temperature and KD incidence, and temperature higher than 10 °C might significantly increase the risk of KD. Our present findings supported the evidence of high temperature as a potential risk factor of KD. It was biologically plausible that high temperature could increase the risk of KD in terms of the infection hypothesis (Principi et al., 2013; Rowley, 2011). First, high temperature may improve the spread of infectious agents (e.g. fungi and bacteria) or its activity, which result in a high exposure level of these infectious agents. Second, children tend to spend more time outside when temperature is high or moderate (typically > 10 °C), which increase the exposure to these infectious agents. Third, high temperature can trigger the release of inflammatory mediators from the airway epithelial cell and in the vessel wall, and thereafter the consequent systemic inflammatory response and vascular endothelial dysfunction may exacerbate the risk of vascular diseases including KD (Burns et al., 2000; Rowley et al., 2000; Zhang et al., 2014).

The limitations of our study should be noted. First, it is not easy to determine the true timing of the occurrence of KD, which might result in inaccurate matching of exposure and health data; we hereby used a relatively long lag structure to explore the effects. Second, limited by the data availability, we did not evaluate $PM_{2.5}$ and O_3 that might have larger effects on KD than three pollutants we currently examined (Jung et al., 2016; Rodó et al., 2014). Third, as done in previous time-series studies, we used the data of air pollution and temperature from fixed-site monitoring stations as the representatives of individual exposures, therefore, measurement errors were inevitable. However, this kind of non-differential error may lead to an underestimate on the effects (Zeger et al., 2000). Fourth, this is inherently an ecological analysis, which cannot control for individual-level confounders. Finally, we failed to conduct a stratification analysis by hospitals due to the low number of daily KD cases.

5. Conclusions

In summary, as the first study to evaluate the association between ambient temperature and KD incidence in Mainland China, this investigation showed that a short-term exposure to high temperature might significantly increase the incidence of KD in Shanghai, China. Our analysis did not show robust evidence linking daily air pollution exposure and increased incidence of KD. Further studies with larger sample size are needed to investigate the association between air pollution, ambient temperature and KD occurrence, as well as to explore their underlying pathological mechanisms.

Conflict of interest

None.

Acknowledgements

This work was supported by Shanghai Natural Science Foundation (15ZR1404300), Developing Discipline of Shanghai Municipal Commission of Health and family Planning (Pediatrics) 2016 ZB0101, China Medical Board Collaborating Program (13-152), and Shanghai 3-Year Public Health Action Plan (GWTD2015S04). The authors thank all of the hospitals and investigators involved in this survey.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemosphere.2017.08.054.

References

Ayusawa, M., Sonobe, T., Uemura, S., Ogawa, S., Nakamura, Y., Kiyosawa, N., et al., 2005. Revision of diagnostic guidelines for kawasaki disease (the 5th revised edition). Pediatr. Int. Official J. Jpn. Pediatr. Soc. 47, 232–234.
Brook, R.D., Rajagopalan, S., Pope 3rd, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., et al., 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the american heart association. Circulation 121, 2331–2378.
Burns, J.C., Kushner, H.I., Bastian, J.F., Shike, H., Shimizu, C., Matsubara, T., et al., 2000. Kawasaki disease: a brief history. Pediatrics 106, E27.
Burns, J.C., Cayan, D.R., Tong, G., Bainto, E.V., Turner, C.L., Shike, H., et al., 2005. Seasonality and temporal clustering of kawasaki syndrome. Epidemiology 16, 220–225.
Burns, J.C., Herzog, L., Fabri, O., Tremoulet, A.H., Rodo, X., Uehara, R., et al., 2013. Seasonality of kawasaki disease: a global perspective. PLoS One 8, e74529.
Checkley, W., Guzman-Cottrill, J., Epstein, L., Innocentini, N., Patz, J., Shulman, S., 2009. Short-term weather variability in chicago and hospitalizations for kawasaki disease. Epidemiology 20, 194–201.
Chen, J.J., Ma, X.J., Liu, F., Yan, W.L., Huang, M.R., Huang, M., et al., 2016. Epidemiologic features of kawasaki disease in shanghai from 2008 through 2012. Pediatr. Infect. Dis. J. 35, 7–12.
Chen, R., Kan, H., Chen, B., Huang, W., Bai, Z., Song, G., et al., 2012. Association of particulate air pollution with daily mortality: the China air pollution and health effects study. Am. J. Epidemiol. 175, 1173–1181.
Chen, R., Zhao, Z., Sun, Q., Lin, Z., Zhao, A., Wang, C., et al., 2015. Size-fractionated particulate air pollution and circulating biomarkers of inflammation, coagulation, and vasoconstriction in a panel of young adults. Epidemiology 26, 328–336.
Dodds, S., Nguyen, L., Bergeron, E.J., 2011. An overview of kawasaki disease. U. S. Pharm. 36. HS-15–HS-22.
Dominici, F., Peng, R.D., Bell, M.L., Pham, L., McDermott, A., Zeger, S.L., et al., 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 295, 1127–1134.
Du, Z.D., Zhao, D., Du, J., Zhang, Y.L., Lin, Y., Liu, C., et al., 2007. Epidemiologic study on kawasaki disease in beijing from 2000 through 2004. Pediatr. Infect. Dis. J. 26, 449–451.
Fischer, T.K., Holman, R.C., Yorita, K.L., Belay, E.D., Melbye, M., Koch, A., 2007. Kawasaki syndrome in Denmark. Pediatr. Infect. Dis. J. 26, 411–415.
Guo, Y., Gasparrini, A., Armstrong, B., Li, S., Tawatsupa, B., Tobias, A., et al., 2014. Global variation in the effects of ambient temperature on mortality: a systematic evaluation. Epidemiology 25, 781–789.
Holman, R.C., Belay, E.D., Christensen, K.Y., Folkema, A.M., Steiner, C.A., Schonberger, L.B., 2010. Hospitalizations for kawasaki syndrome among children in the United States, 1997-2007. Pediatr. Infect. Dis. J. 29, 483–488.
Huang, G.Y., Ma, X.J., Huang, M., Chen, S.B., Huang, M.R., Gui, Y.H., et al., 2006. Epidemiologic pictures of kawasaki disease in shanghai from 1998 through 2002. J. Epidemiol. 16, 9–14.
Jung, C.R., Chen, W.T., Lin, Y.T., Hwang, B.F., 2016. Ambient air pollutant exposures and hospitalization for kawasaki disease in taiwan: a case-crossover study (2000-2010). Environ. Health Perspect. 125, 670–676.
Kelly, F.J., 2003. Oxidative stress: its role in air pollution and adverse health effects. Occup. Environ. Med. 60, 612–616.
Li, X.H., Li, X.J., Li, H., Xu, M., Zhou, M., 2008. Epidemiological study of kawasaki disease in sichuan province of China. J. Trop. Pediatr. 52, 133–136.
Lin, Y.T., Manlhiot, C., Ching, J.C., Han, R.K., Nield, L.E., Dillenburg, R., et al., 2010. Repeated systematic surveillance of kawasaki disease in ontario from 1995 to 2006. Pediatr. Int. Official J. Jpn. Pediatr. Soc. 52, 699–706.
Ma, W., Chen, R., Kan, H., 2014. Temperature-related mortality in 17 large Chinese cities: how heat and cold affect mortality in China. Environ. Res. 134, 127–133.
Ma, X.J., Yu, C.Y., Huang, M., Chen, S.B., Huang, M.R., Huang, G.Y., et al., 2010. Epidemiologic features of kawasaki disease in shanghai from 2003 through 2007. Chin. Med. J. Engl. 123, 2629–2634.
Makino, N., Nakamura, Y., Yashiro, M., Ae, R., Tsuboi, S., Aoyama, Y., et al., 2015. Descriptive epidemiology of kawasaki disease in Japan, 2011-2012: from the

results of the 22nd nationwide survey. J. Epidemiol. 25, 239–245.
Nakamura, Y., Yashiro, M., Uehara, R., Sadakane, A., Tsuboi, S., Aoyama, Y., et al., 2012. Epidemiologic features of kawasaki disease in Japan: results of the 2009-2010 nationwide survey. J. Epidemiol. 22, 216–221.
Newburger, J.W., Takahashi, M., Gerber, M.A., Gewitz, M.H., Tani, L.Y., Burns, J.C., et al., 2004. Diagnosis, treatment, and long-term management of kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis and kawasaki disease, council on cardiovascular disease in the young, american heart association. Circulation 110, 2747–2771.
Newburger, J.W., Takahashi, M., Burns, J.C., 2016. Kawasaki disease. J. Am. Coll. Cardiol. 67, 1738–1749.
Ng, Y.M., Sung, R.Y., So, L.Y., Fong, N.C., Ho, M.H., Cheng, Y.W., et al., 2005. Kawasaki disease in Hong Kong, 1994 to 2000. Hong Kong Med. J. 11, 331–335.
Peng, R.D., Dominici, F., Louis, T.A., 2006. Model choice in time series studies of air pollution and mortality. J. Roy. Stat. Soc. a Stat. 169, 179–198.
Principi, N., Rigante, D., Esposito, S., 2013. The role of infection in kawasaki syndrome. J. Infect. 67, 1–10.
Rodó, X., Curcoll, R., Robinson, M., Ballester, J., Burns, J.C., Cayan, D.R., et al., 2014. Tropospheric winds from northeastern China carry the etiologic agent of kawasaki disease from its source to Japan. Proc. Natl. Acad. Sci. U. S. A. 111, 7952–7957.
Rowley, A.H., Shulman, S.T., Mask, C.A., Finn, L.S., Terai, M., Baker, S.C., et al., 2000. Iga plasma cell infiltration of proximal respiratory tract, pancreas, kidney, and coronary artery in acute kawasaki disease. J. Infect. Dis. 182, 1183–1191.
Rowley, A.H., 2011. Kawasaki disease: novel insights into etiology and genetic susceptibility. Annu. Rev. Med. 62, 69–77.
WHO, 2006. Air Quality Guidelines-global Update 2005 : Particulate Matter, Ozone, Nitrogen Dioxide, and Sulfur Dioxide. WHO Regional Office for Europe, Copenhagen, pp. 9–19.
Zeft, A.S., Burns, J.C., Yeung, R.S., McCrindle, B.W., Newburger, J.W., Dominguez, S.R., et al., 2016. Kawasaki disease and exposure to fine particulate air pollution. J. Pediatr. 177, 179–183 e1.
Zeger, S.L., Thomas, D., Dominici, F., Samet, J.M., Schwartz, J., Dockery, D., et al., 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108, 419–426.
Zhang, X., Lu, J., Zhang, S., Wang, C., Wang, B., Guo, P., et al., 2014. Effects of simulated heat waves on cardiovascular functions in senile mice. Int. J. Environ. Res. Public Health 11, 7841–7855.