

Preconceptional and Prenatal Exposure to Diurnal Temperature Variation Increase the Risk of Childhood Pneumonia

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Abstract

Background: Pneumonia is the leading cause of death and hospitalization among young children worldwide, but its risk factors are not clear.

Objective: To examine the effect of maternal exposure to diurnal temperature variation (DTV) during preconceptional and prenatal periods on childhood pneumonia.

Methods: A retrospective case-control study was conducted for pneumonia (N=699) and normal (N=811) children under age of 14 who were enrolled in the Xiangya Hospital, Central South University, Changsha, China. Demographic data (gender, age, birth season, gestational weeks, parity, mode of delivery, and parental atopy) were collected from the hospital's electronic medical records system. We calculated the individual DTV exposure during different time windows. The relationship between maternal exposure to outdoor DTV and pneumonia in children was analyzed by logic regression models.

Results: Pneumonia in children was linked to outdoor DTV exposure during one year before conception (adjusted OR=2.53, 95% CI:1.56-4.10), during entire pregnancy (adjusted OR =1.85, 95% CI:1.24-2.76), and the first and second trimesters, with statistical significance. Sensitivity analysis showed that boys exposure to outdoor DTV during prenatal period were at higher pneumonia risk than girls.

Conclusions: Preconceptional and prenatal exposure to DTV plays an important role in the development of childhood pneumonia, the first and second trimesters were the key exposure timing-windows.

Background

Pneumonia is the leading cause of death and hospitalization among children under age of 5 worldwide [1, 2]. Although pneumonia treatment have been improved significantly in the past decades, the incidence of pneumonia in children remains high, especially in developing countries [3]. According to a recent epidemiological report, pneumonia has resulted in 808,694 deaths among children in 2017, which accounts for 15% of all deaths in children under age of 5 [4]. Notably, China has a high morbidity of childhood pneumonia [5]. Pneumonia not only harms the growth and development of a child's lung, but also causes a huge burden on economy and families [6]. Therefore, it is crucial to understand the risk factors for pneumonia susceptibility, which will help to design effective prevention strategy.

Recently, there is widespread awareness that climatic variation threatens human health. Although pneumonia is an infectious disease, its development is also closely associated with climate change [7, 8]. Mounting evidences suggest that children suffer most due to climate change [9, 10]. Epidemiological studies have found an association of outdoor temperature to child pneumonia [11, 12]. Diurnal temperature variation (DTV), which reflects outdoor temperature changes, has been found to correlate with the incidence and mortality of respiratory diseases [13-18]. In particularly, a cohort study suggests that outdoor DTV is an important risk factor for pneumonia in children [19].

Exposure of harmful factors in early life may not only affect development in childhood, but also have long-term impact on late life including the onset and progression of diseases in adulthood [20, 21]. It has been suggested that early-life exposure to temperature and DTV contributes to child respiratory diseases [19, 22-24]. Interestingly, a few studies find that maternal exposure to outdoor air pollution during preconceptional period is associated with increased risk of asthma, eczema and allergic rhinitis in children [25, 26]. However, the impacts of preconceptional exposure to outdoor DTV on respiratory diseases, in particularly childhood pneumonia, have never been investigated.

We hypothesized that preconceptional and prenatal exposure to outdoor DTV could be a risk factor to pneumonia in children. To test this hypothesis and determine the susceptible time window, we have performed a large retrospective case-control study.

Methods

1. Study population

A retrospective case-control study was conducted in the Department of Pediatrics, Xiangya hospital, Central South University from May 2017 to April 2019. We recruited 699 children under age of 14 who were diagnosed with pneumonia as the case group, and 811 healthy children who registered for physical examination as the control group.

2. Demographic data

We obtained the demographic data from the electronic medical records system, including child's gender, age, birth season, gestational weeks, parity, mode of delivery, and parental atopy. Parental atopy is the history of maternal or paternal allergic diseases.

3. Exposure assessment

3.1. Exposure time windows

Exposure timing-windows included preconceptional and prenatal time periods in this study. The preconceptional exposure mainly included two time windows: one year before conception and three months before conception. The prenatal time period was defined from the first day of the mother's last menstrual period to the delivery date. The prenatal exposure was further divided into three trimesters: the first trimester (the 1st to 12th weeks of pregnancy), the second trimester (the 13th to 27th weeks of pregnancy), and third trimesters (the 28th weeks of pregnancy to birthday of child).

3.2. The data of diurnal temperature variation (DTV)

We obtained the data of daily temperature (including the mean, maximum, and minimum temperatures) of 10 regions in Changsha during 2003-2019 from China Meteorological Administration. The diurnal temperature variation was calculated as the difference between the daily maximum and minimum temperature. The 10 regions of Changsha included Kaifu district, Yuhua district, Furong district, Liuyang county, Mabing, Ningxiang county, Tianxin district, Wangcheng district, Yuelu district, Changsha county. Child's exposure was estimated by DTV at the region where the residence was located. Then individual exposure to outdoor DTV was counted by average of the daily DTV during preconceptional and prenatal period.

3.3 Exposure to outdoor air pollution

Exposure to air pollution was considered as confounding variables for pneumonia in this study. We obtained daily 24h average concentrations of three main air pollutants, including nitrogen dioxide (NO₂), sulfur dioxide (SO₂), and particulate matter ≤10 μm in diameter (PM₁₀), from 7 municipal air quality monitoring stations in Changsha from 2003 to 2019. Individual air pollution exposure during different time windows was estimated using inverse distance weight (IDW) method [27].

4. Statistical analysis

Statistical analyses were performed by SPSS software (version 23.0, SPSS Inc., Chicago, USA). The relationship between outdoor DTV exposure during preconceptional and prenatal period and childhood pneumonia was assessed by using multiple logistic regression model, and with adjusting potential variables in Table 1 and three air pollutants (NO₂, SO₂, and PM₁₀). The correlation in regression analysis was calculated by odds ratio (OR) of 95% confidence interval (95% CI). In our study, OR (95% CI) was estimated by per 1 °C increase in exposure level for outdoor DTV. $p \leq 0.05$ were considered significant.

Results

Our study included 699 children with pneumonia and 811 healthy children without pneumonia. The demographic information of covariates between the case and control groups, along with the distribution of known or suspected pneumonia risk factors, was compared (Table 1). In the case group, 62.4% of children with pneumonia were boys. The preterm birth rate was 8.9% in the pneumonia group and 3.7% in the normal group. The proportion of caesarean section was 47.6% in the pneumonia group and 38.0% in the normal group. The proportion of parental atopy was 7.6% in the pneumonia group and 3.7% in the normal group. Covariates were statistically different between the case and control groups: the prevalence of pneumonia was significantly higher in children who were boy ($p < 0.001$), children aged under 1 year old ($p < 0.001$), had premature birth ($p < 0.001$), caesarean birth ($p < 0.001$), with parental atopy ($p < 0.001$).

Table 1 Demographic information of covariates among children with (case) and without (control) doctor-diagnosed pneumonia (n=1,510).

	Case		Control		P-value
	N	(%)	N	(%)	
Total	699	(100.0)	811	(100.0)	–
Sex					<0.001
Boys	436	(62.4)	429	(52.9)	
Girls	263	(37.6)	382	(47.1)	
Age (years)					<0.001
<1	334	(47.8)	68	(8.4)	
1	130	(19.4)	193	(23.8)	
>1	235	(33.6)	550	(67.8)	
Birth season					0.048
Spring	138	(19.7)	204	(25.2)	
Summer	184	(26.3)	208	(25.6)	
Autumn	197	(28.2)	225	(27.7)	
Winter	180	(25.8)	174	(21.5)	
Parity					0.046
1 st	454	(64.9)	571	(70.4)	
2 nd – 5 th	238	(34.0)	240	(29.6)	
Gestational age (weeks)					<0.001
<37	62	(8.9)	30	(3.7)	
≥37	637	(91.1)	781	(96.3)	
Mode of delivery					<0.001
Natural labour	360	(51.5)	503	(62.0)	
Caesarean birth	333	(47.6)	308	(38.0)	
Parental atopy					<0.001
No	646	(92.4)	786	(96.9)	
Yes	53	(7.6)	25	(3.1)	

Sum of the number is not 1,510 due to missing data. The p-values < 0.05 were in bold.

DTV exposure levels in preconceptional and prenatal periods between the case and control groups were compared in Table 2. The average of individual exposure to DTV was 7.3°C in children with pneumonia, and 7.2°C in normal children during one year before conception. The average individual DTV was 7.3°C in children with pneumonia, and 7.0°C in normal children during entire pregnancy. The average individual DTV of children with pneumonia was significantly higher than normal children during all exposure time windows (p<0.001).

Table 2 Descriptive statistics for outdoor temperature and DTV during different time windows attributed to the children (n=1,510).

	Total		Case		Control		P-value
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Preconceptional							
1 year before conception	7.2	(0.5)	7.3	(0.4)	7.2	(0.5)	<0.001
3 months before conception	7.2	(0.8)	7.3	(0.7)	7.1	(0.8)	<0.001
Prenatal							
1 st trimester	7.2	(0.8)	7.3	(0.7)	7.0	(0.8)	<0.001
2 nd trimester	7.1	(0.7)	7.3	(0.7)	6.9	(0.7)	<0.001
3 rd trimester	7.1	(0.7)	7.3	(0.7)	6.9	(0.7)	<0.001
Entire pregnancy	7.1	(0.5)	7.3	(0.5)	7.0	(0.5)	<0.001
DTV(°C) =Tmax-Tmin. The p-values < 0.05 were in bold.							

The relationship between child's DTV exposure during different time windows and pneumonia was further analyzed in Table 3. We observed a significant association between pneumonia and preconceptional DTV exposure, particularly long-term exposure (one year before conception), with adjusted OR (95% CI) = 2.53 (1.56-4.10) for per 1°C increase in DTV. Childhood pneumonia was also significantly associated to prenatal outdoor DTV exposure, with adjusted OR (95% CI) = 1.85 (1.24-2.76) for per 1°C increase in DTV, especially in the first and second trimesters.

Table 3 Odds ratio (95%CI) of childhood pneumonia for exposure to outdoor DTV during different timing-windows (n=1,510).

	Crude	Adjusted model #	Adjusted model †
preconceptional			
3 months before conception	1.40(1.22,1.61)***	1.98(1.67,2.34)***	1.15(0.91,1.46)
1 year before conception	1.86(1.48,2.32)***	10.21(7.08,14.71)***	2.53 (1.56,4.10)***
Prenatal			
1 st trimester	1.72(1.50,1.97)***	2.30(1.94,2.72)***	1.63(1.32,2.00)***
2 nd trimester	1.99(1.71,2.33)***	2.55(2.12,3.07)***	1.43(1.12,1.81)**
3 rd trimester	1.88(1.62,2.18)***	2.29(1.91,2.73)***	1.20(0.96,1.51)
Entire pregnancy	4.45(3.52,5.6)***	8.36(6.21,11.27)***	1.85(1.24,2.76)**
OR (95% CI) was estimated by 1°C increase in outdoor DTV during each time window.			
# Model # was adjusted for the covariates in Table 1.			
† Model † was further adjusted for outdoor air pollution exposure during each time window based on model #.			
* p ≤ 0.05.			
** p ≤ 0.01.			
*** p ≤ 0.001.			

The relationship between maternal outdoor DTV exposure during prenatal period and pneumonia stratified by gender was showed in Fig. 1. We found that the boys exposure to outdoor DTV during prenatal period were at higher pneumonia risk than the girls.

Discussion

In this retrospective case-control study, we found for the first time an association between maternal outdoor DTV exposure one year before conception and childhood pneumonia. Such association was also observed in gestational exposure, particularly the first and second trimesters. Sensitivity analysis showed that boys were more vulnerable to pneumonia risk due to prenatal exposure to DTV than girls.

Studies suggest that DTV may play a significant role in the risk of respiratory diseases [28-30], including respiratory tract infection (RTI) and asthma in children [31-33]. However, the association between DTV and childhood pneumonia is controversial [19, 34]. Our study suggests that early-life DTV exposure may be a risk factor contributing to childhood pneumonia.

For the first time, our study indicates that DTV increase during the year prior to conception has an adverse influence on childhood pneumonia. Several other diseases in children have also been associated with preconceptional exposure. A cohort study in China suggests that preconceptional exposure to outdoor traffic and industrial air pollutants is significant risk of child asthma [26]. Eczema in children is also linked to NO₂ exposure during three months before conception [25]. Another recent retrospective research in the USA proved a significant relationship between preconceptional NO_x and SO₂ exposure and the increased risk of gestational diabetes mellitus (GDM) [35]. Furthermore, a multi-site study found that preconception exposure of PM₁₀, SO₂ and CO was connected to increased oral cleft risk [36]. Therefore, it is reasonable to believe that preconceptional outdoor DTV exposure significantly increased the risk of pneumonia in children.

In the 1990s, Professor David Barker, a British epidemiologist, first proposed the theory of the development origins of health and diseases (DOHaD): early life (pre-natal and early postnatal stages) exposure to environmental factors affects the plasticity of development, leading to the development and deterioration of various complex diseases in adulthood. Therefore, early-life was considered as a critical window of environmental exposure associated with healthy development. In this study, we observed that prenatal DTV exposure was a significant risk for pneumonia in children, which is in line with a recent cohort study from China [19]. We found that DTV exposure at the first and second trimester of pregnancy was the susceptible time windows, which was barely investigated. Exposure to outdoor DTV in the first trimester of pregnancy was found to be a risk factor for common cold in children [22]. Other studies indicate the significant association between the first trimester exposure to industrial air pollution and childhood ear infection [37]. The mechanisms underlying the association of childhood pneumonia with DTV in the first and second trimesters are unclear. Lung development starts about 4 weeks of gestation, airway branching morphogenesis occurs in the first two trimesters [38]. Long-time exposure to environmental factors during pregnancy may lead to the improper development of lung at various degree, which may affect postnatal lung function and predispose to respiratory diseases. The pathogenic mechanisms of intrauterine exposure to outdoor DTV on the development of pneumonia in children need further investigation.

We and others found that girls had less risk to the gestational DTV-associated pneumonia than boys during pregnancy [13, 19]. According to the 2017 GBD results, the prevalence of respiratory tract infections in male was generally higher than female [39]. Some scholars considered that gender difference of environmental susceptibility was mainly related to immune response [40]. In general, female was more responsive to pathogenic stimuli and vaccines than male, so female was more resistant to infectious diseases [41]. But the mechanisms of DTV effects on childhood pneumonia by gender remain unclear.

This study had several limitations for data collection and analysis. The data of child's outdoor temperature was only obtained from one meteorological station, this could result in exposure misclassification. Indoor air temperature was not considered in this study, and the expectant mother usually spent most of their time indoors. Other meteorological parameters that may affect temperature, such as precipitation, wind speed, or relative humidity, were not included.

Conclusions

This case-control study reveals that preconceptional (one year before conception) and prenatal exposure to outdoor DTV is a susceptibility factor to children, and the first and the second trimesters are the susceptible time windows. This result has clinical significance in assessing the occurrence of pneumonia in children, and providing guideline for pneumonia prevention, i.e., avoiding excessive DTVs during pregnancy (especially in the first and second trimesters), and reducing outdoor activities for women preparing for pregnancy when the outdoor temperature changes sharply.

Abbreviations

DTV: diurnal temperature variation; IDW: inverse distance weight

Declarations

Acknowledgements

Not applicable.

Authors' contributions

XR conducted the study, analyzed the data, and drafted the initial manuscript. JK collected and analyzed the data, and drafted part of the manuscript. CL conceptualized and designed the study, supervised the data analysis and the draft writing, critically reviewed the manuscript for important intellectual content. HW, RGM, MBJ, WP, MW conducted the study, analyzed the data, reviewed the revised the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to public policy restriction but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the academic ethics committee of Xiangya Hospital (201904107).

Informed consent was obtained from a parent or guardian for all individual participants included in the study.

Consent for publication

Not applicable.

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Figures

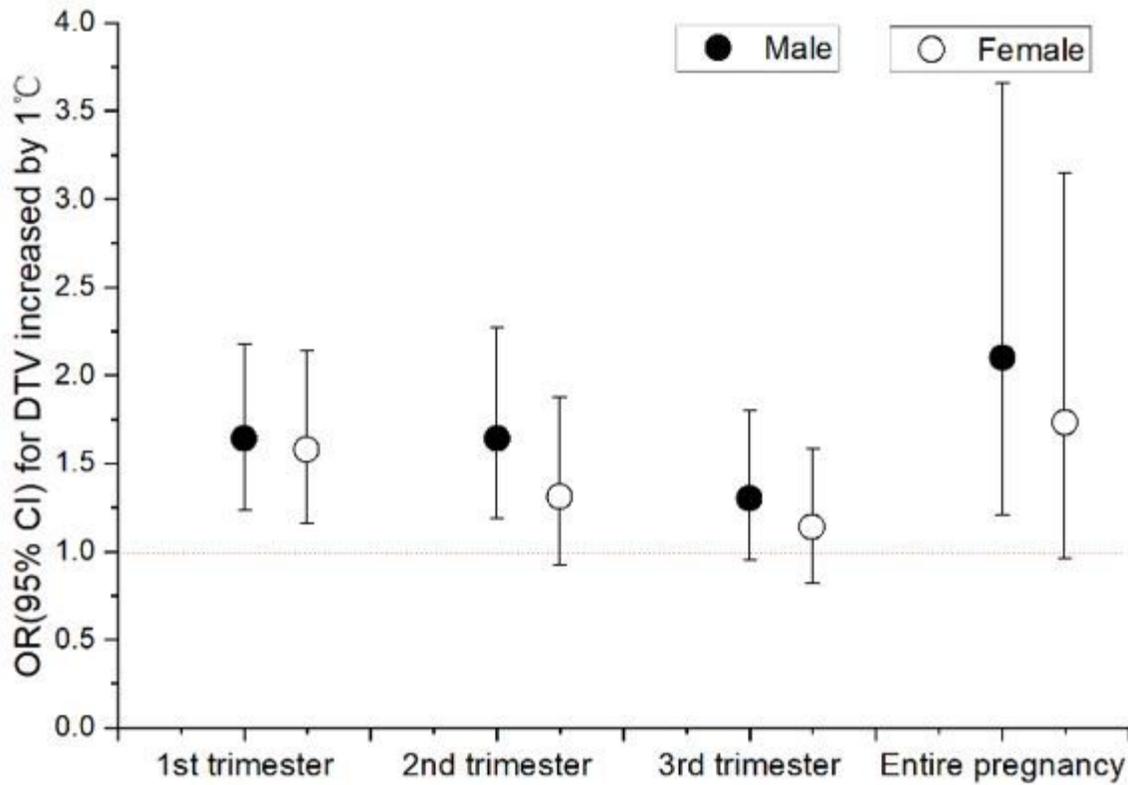


Figure 1

Odds ratio (95%CI) of childhood pneumonia for exposure to diurnal temperature variation (DTV) stratified by gender during pregnancy (n=1,510). ORs was adjusted for all covariates in Table 1 and outdoor air pollutants (PM10, SO2 and NO2).