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RESEARCH ARTICLE

Maternal apparent temperature during pregnancy on the risk of offspring asthma and wheezing: effect, critical window, and modifiers

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Abstract
The objective of this study was to explore the impact of maternal AT during pregnancy on childhood asthma and wheezing, as well as the potential effect modifiers in this association. A cross-sectional study was implemented from December 2018 to March 2019 in Jinan to investigate the prevalence of childhood asthma and wheezing among aged 18 months to 3 years. Then, we conducted a case-control study based on population to explore the association between prenatal different AT exposure levels and childhood asthma and wheezing. The association was assessed by generalized additive models and logistic regression models, and stratified analyses were performed to explore potential effect modifiers. A total of 12,384 vaccinated children participated in screening for asthma and wheezing, 236 cases were screened, as well as 1445 controls were randomized. After adjusting for the covariates, childhood asthma and wheezing were significantly associated with cold exposure in the first trimester, with *OR* 1.731 (95% *CI*: 1.117–2.628), and cold exposure and heat exposure in the third trimester, with *OR*s 1.610 (95% *CI*: 1.030–2.473) and 2.039 (95% *CI*: 1.343–3.048). In the third trimester, enhanced impacts were found among girls, children whose distance of residence was close to the nearest main traffic road, and children whose parents have asthma. The study indicates that exposure to extreme AT during the first and third trimesters could increase the risk of childhood asthma and wheezing.

Keywords Apparent temperature · Asthma · Pregnancy · Effect modification · Interaction

Introduction

Asthma is a complex and heterogeneous chronic inflammatory disease of the airways and also one of the leading prevalent chronic disorders in children around the world (Asher et al. 2004; Xie and Wenzel 2013). Not only does childhood asthma impose a significant financial and public health burden on families, but also has a huge impact on children's development (Davis 2013; Stevens et al. 2003). In the USA, the prevalence of childhood asthma has steadily increased from 8.7% in 2001 to 9.3% in 2010 (Akinbami et al. 2016). Also, evidence from the International Childhood Asthma and Allergy Study suggests that the prevalence of childhood asthma in New Zealand has increased from 24.6% in 1992 to 30.2% in 2010 (Asher et al. 2008). In China, from September 2009 to August 2010, the third nationwide survey of childhood asthma was conducted in 43 cities, and the overall incidence of asthma in urban children aged 0–14 years has tripled in the past 20 years (National Cooperative Group on Childhood et al. 2013). This evidence reveals that the prevalence of childhood asthma has increased dramatically in many countries around the world over the past few decades. Therefore, there is an urgent need to study risk factors for the development of childhood asthma to provide more effective prevention strategies.

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Environmental factors have been widely accepted as critical risk factors for the development of asthma, such as ambient temperature (Buckley and Richardson 2012; Hernandez 2016). On the one hand, low temperatures can cause inflammation and narrowing of the airway (Kaminsky et al. 2000), and high temperatures can enhance the growth of indoor allergens, which may attribute to asthma (Hashimoto et al. 2004). On the other hand, compared to adults, extreme temperatures have a greater influence on children due to their absence of resistance as well as vulnerability to dramatic weather changes (McKie 2013). To date, several studies have investigated correlations between ambient temperature and childhood asthma (D'Amato et al. 2014; Xu et al. 2013a, b). A meta-analysis covering 13 countries concluded that a 1 °C decrease in short-term ambient temperature was associated with a 5.5% increase in the risk of childhood asthma (Cong et al. 2017). A large diurnal temperature range may trigger childhood asthma in Brisbane, Australia (Xu et al. 2013a, b). However, the effect of temperature on childhood asthma and its critical period was inconsistent, which might be due to differences in the age, season, and region of the study. Most previous studies were conducted in Europe, Oceania, the USA, and southern China, whereas Jinan is located in eastern China, with a temperate monsoon climate, which is notably different from the previous research locations.

Many recent studies have shown that the effects of environmental factors on the development of asthma and lung function deficits may begin in the uterus (Buteau et al. 2020; Hsu et al. 2015; Lavigne et al. 2018). Prenatal exposure to harmful environmental factors could harm organ development as well as infancy growth and could increase the risk of respiratory diseases in childhood (Gluckman et al. 2008). A study suggested that prenatal exposure to diurnal temperature variation plays an important role in the development of childhood pneumonia (Zheng et al. 2021). Also, the common cold in children was associated with prenatal exposure to air temperature variation (Lu et al. 2018). These studies indicate that extreme ambient temperature during pregnancy increases the risk of childhood respiratory disease.

In addition, since ambient temperature may not accurately describe the body's perception of outdoor temperature, Steadman (Steadman 1994) introduced apparent temperature (AT) in 1984, a composite biometeorological index that includes ambient temperature, wind speed, and relative humidity, which was believed to be a more objective indicator of the human body's thermal experiences than ambient temperature alone. A growing number of scientists have focused on the impact of different AT exposure during pregnancy on children's health. For example, exposure to a high level of AT has been reported to be associated with spontaneous preterm birth in California (Avalos et al. 2017). Additionally, an attempt to explore the association between exposure to different AT during pregnancy and term low birth weight has been conducted in California (Basu et al. 2018), whereas the relationship between AT, as a potential risk factor that may be a better fit for investigating childhood asthma than ambient temperature, and asthma in children has not been reported. In Cape Town, South Africa, a study on the association between AT and asthma was implemented in adults (Shirinde and Wichmann 2022). At high AT levels, women were more susceptible to PM_{10} and the 15–64 age group was more susceptible to NO_2 and SO_2. Although the subjects in this study were adults, it still provides potential possible for the association between AT and childhood asthma.

To our knowledge, the studies concerning the relationship between temperature, one of the most important environmental factors, during pregnancy and the risk of asthma and wheezing in children are still limited. Accordingly, we developed a case-control study based on the population of Jinan, Shandong Province, China, to evaluate the effect of AT during pregnancy and the risk of childhood asthma and wheezing. Importantly, we further explored its critical window and examined whether this association was modified by other factors. Nowadays, the impact of climatic conditions on health is receiving more attention (Abhijith et al. 2017; Lee et al. 2021). The findings of this study will give evidence on the impact of AT on the risk of asthma and wheezing in children, which could assist in the prevention of asthma and wheezing in children in the context of climate change.

Methods

Study design

There are two study designs for the present study. Firstly, a cross-sectional study was conducted from December 2018 to March 2019 in Jinan, the capital city of Shandong Province in China (36°40′N, 116°57′E). The 15 community vaccination clinics were selected in five municipal districts of Jinan (Shizhong District, Lixia District, Huaiyin District, Tianqiao District, and Licheng District), as the study sites. The locations of the five municipal districts and the distribution of the clinics were shown in Fig. 1. Children were identified as subjects from the cross-sectional study who attended the 15 community immunization clinics for vaccinations and satisfied the study's inclusion criteria, and then their mothers completed asthma and wheezing screening. Subsequently, we conducted a case-control study based on the cross-sectional population. Among the participants in the cross-sectional study, children with asthma or wheezing were screened as cases. The purpose and content of

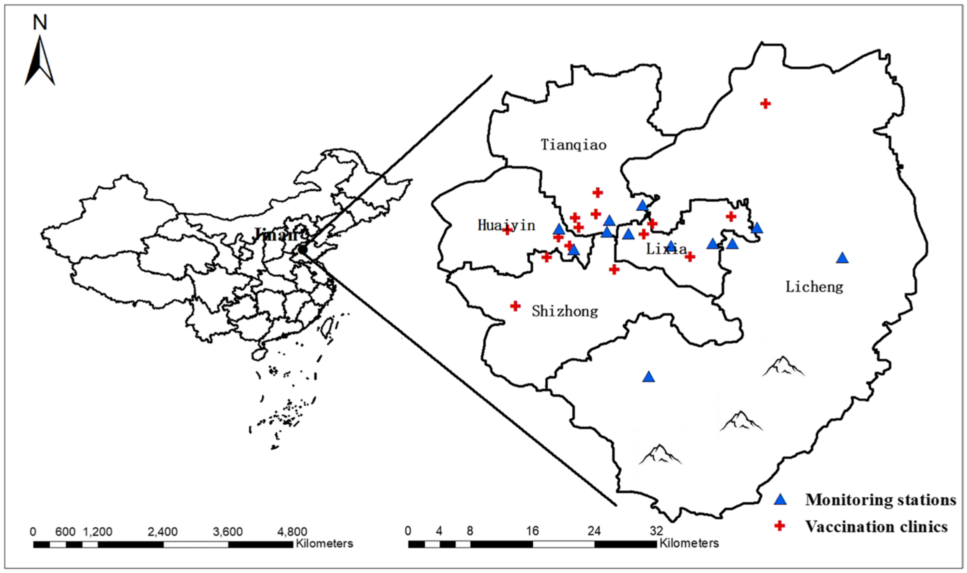


Fig. 1 The location of Jinan and the distribution of vaccination clinics

the study were explained to each mother, who then signed an informed consent form. The study was allowed by the Ethics Committee of Preventive Medicine of Shandong University (Approved number: 20170315).

Study population and data collection

Inclusion criteria for the subjects were the following: (1) singleton, (2) 18 months to 3 years old, and (3) the mothers who lived in Jinan during pregnancy in the cross-sectional study. Those who had been diagnosed by doctors with wheezing or asthma were defined as cases in the case-control study, which were reported by their mothers. After each case was identified, 1/10 children without asthma and wheezing were randomly selected as controls from vaccination clinics in the National Planned Immunization Registration System. More details, including the method of case and control selection, were presented in another paper (Bai, et al. 2022). Mother-children-pair data were collected by giving out maternal and child health questionnaires to the mothers of the children, which were completed by the children's mothers under the guidance of uniformly trained investigators. The questionnaire was adapted from the questionnaire of the International Study on Asthma and Allergies in Children (ISAAC) (Asher et al. 2006).

The definition of outcome

In our study, the outcome variable was doctor-diagnosed asthma and wheezing, which was defined by the answer to two questions: (1) Has your child ever been diagnosed with asthma by the doctor? (2) Has your child ever been diagnosed with wheezing by the doctor?

Exposure and the exposure timing windows

Exposure refers to the AT value to which the mother was exposed during pregnancy. We divided the exposure during pregnancy into 4 time windows: the first, second, and third trimesters, and the entire pregnancy, defined as the first 13 weeks of pregnancy, week 14 through 27, week 28 through birth, and the entire gestation period, respectively (Lu et al. 2020).

Exposure assessment of AT and data collection

Daily average meteorological data were obtained from the Shandong Provincial Environmental Information and Monitoring Center, including ambient temperature (° C), relative humidity (%), and wind speed (m/s). The distribution of monitoring stations was relatively concentrated (Fig. 1). The individual exposure level of 3 meteorological factors for exposure timing windows was assessed by an inverse distance weighting (IDW) method based on the subject's home address code (Bai et al. 2022). The basic idea of IDW is to weigh the level of meteorological factors based on the spatial distance between the specific address and the monitoring station. In particular, exposure levels to meteorological factors are strongly influenced by monitoring concentrations from nearby monitoring stations, but less influenced by monitoring concentrations from remote monitoring stations (Rivera-González et al. 1995). Then, the AT (°C) was calculated from the ambient temperature, relative humidity, and relative wind speed by the following equations (Steadman 1994):

$$AT = T_\alpha + 0.33 \times e - 0.70 \times Ws - 4.00 \quad (1)$$

$$e = \frac{Rh}{100} \times 6.11 \times \exp\left(17.27 \times \frac{T_\alpha}{237.7 + T_\alpha}\right) \quad (2)$$

where T_α is the ambient temperature (°C); e is actual vapor pressure (hPa); Rh is relative humidity (%); and Ws is wind speed (m/s). The AT exposure level was divided into three categories, with the extreme heat level being above the 90th percentile (> 90th), which was called heat, the extreme cold level being below the 10th percentile (< 10th), was called cold, and the moderate level being between the 10th and 90th percentile (10th-90th), was called moderate (Gasparrini and Leone 2014).

Covariates

The following variables were collected from the questionnaires as potential covariates: children's gender (male, female), children's age, mode of delivery (natural birth, cesarean delivery), preterm birth (no, yes), low birth weight (no, yes), duration of breastfeeding (no, yes), family income monthly, congenital disease (no, yes), maternal age, maternal education, maternal secondhand smoking during pregnancy (no, yes), home dampness (no, yes), the distance of residence from the nearest main traffic road (≤ 200 m, > 200 m), and parental atopy (no, yes). Following that, some covariates were given definitions in the questionnaire. Specifically, preterm birth was defined as delivery before 37 completed weeks of gestation (Vogel et al. 2018). Low birth weight was defined as a birth weight below 2500 g (Hughes et al. 2017). Congenital disease was defined as a structural and functional abnormality of the perinatal infant, which was covered by the birth defects surveillance list and diagnosed by the hospital. Maternal secondhand smoking during pregnancy was defined as the mother's exposure to tobacco smoke for 30 min or more each week during pregnancy. Home dampness was defined as the presence of at least one of the following in the home: mold, moist spots, damp clothing/bedding, condensation on windows, or musty aromas (Harville and Rabito 2018; Liu et al. 2018). Distance of residence from the nearest main traffic road was defined as the distance between the subject's residential location and a road having two or more multiple lanes (Miyake et al. 2010). Parental atopy was defined as either the father or mother having been diagnosed with an allergic disease such as asthma and eczema (O'Connor et al. 2022).

Statistical analysis

Continuous variables were described using means, standard deviations (SD), minimum value (Min), maximum value (Max), and percentiles. The Mann-Whitney U test was used to compare the differences in characteristics between the case group and the control group. Categorical variables were expressed in the form of case (percentage) [n (%)], and the Chi-square test or Fisher's exact test was performed to compare differences among groups. In our study, AT was analyzed as a continuous and categorical variable separately, with the generalized additive model (GAM) for continuous variables and the logistic regression model for categorical variables. Odds ratios (ORs) and 95% of confidence intervals (95% CIs) were calculated to express the effect of different AT exposure during pregnancy on the risk of childhood asthma and wheezing. GAM is a common method to evaluate linear and non-linear correlations, which was used to study the non-linear association between daily average temperature during pregnancy and adverse fetal outcomes (Basagana et al. 2021; Liu et al. 2019). In this study, GAM was used to evaluate the potential non-linear associations between AT during pregnancy and childhood asthma and wheezing, with the number of nodes selected based on the smallest generalized cross-validation (GCV) value. Additionally, the association between different exposure levels of AT (cold, moderate, heat) during pregnancy and childhood asthma and wheezing was evaluated by the logistic regression model. The moderate AT (10th–90th percentile) was set as a reference ($OR = 1$). Stepwise regression was used to select suitable covariates for the model to control for confounding factors. It is worth noting that previous studies have found that postnatal ambient temperature was also an important factor in asthma attacks in children (Lu et al. 2022). Therefore, we included children's AT exposure levels from birth to the day of investigation in the model for adjustment. Subsequently, we used stratified analysis to assess the potential effect modification of children's gender, mode of delivery, maternal vitamin D supplementation during pregnancy, the distance of residence from the nearest main traffic road, and parental atopy. In addition, using the relative excess risk due to interaction ($RERI$), we studied the interaction between childhood asthma and wheezing and AT as well as these factors. A statistically significant $RERI > 0$ implies the presence of supra-additivity or synergistic interaction, while a $RERI$ of 0 shows no interaction. Finally, in order to justify the appropriateness of the sample size, statistical power was evaluated using PASS software, according to the method proposed by Hsieh et al. (Hsieh et al. 1998).

Statistical analyses were performed in SPSS (version 24.0, SPSS Inc., Chicago, USA) software, R software (version 4.1.0; www.r-project.org), and PASS software. $P < 0.05$ was considered statistically significant.

Sensitivity analysis

To examine the stability of the effect of AT during pregnancy on childhood asthma and wheezing that we observed, a sensitivity analysis was implemented in two ways. Firstly, we matched the new control group to cases in the database (1:1), using children's age and children's gender as matching criteria. Based on the data of the matched case-control study, we performed a sensitivity analysis. Secondly, the code for community vaccination clinic was set as a dummy variable to investigate whether the subject's address affects the results. Since immunizations in China have a territorial management mode of 15-min community life cycle, and the vast majority of subjects will go to the nearest community vaccination clinic to be vaccinated, the clinic codes can reflect the different areas of the population.

Results

Descriptive statistics

In the study area, a total of 12,384 children and their mothers filled out asthma and wheezing screening forms with the help of instructors. The prevalence of asthma and wheezing was 2.07% among children aged 18 months to 3 years. Finally, there were 236 cases and 1445 controls in the overall material ($N = 1681$). Descriptive statistics for characteristics and the prevalence of childhood asthma and wheezing stratified by covariates are shown in Table 1. Children with asthma and wheezing were more frequently born to mothers who were older (≥ 35 years old) and more educated (college or more). Meanwhile, between the two groups, there were differences in children's age, preterm birth, low birth weight, congenital disease, family income monthly, maternal vitamin D supplementation during pregnancy, home dampness, the distance of residence from the nearest main traffic road, and parental atopy ($P < 0.05$).

Distribution of AT during pregnancy

The means, *SD*s, 10th percentile, 90th percentile, maximum, and minimum values of AT exposure level in each time window for the case group and control group are given in Table 2. For the case group, the daily means (*SDs*) of AT were 13.153 (11.004) °C, 14.902 (10.455) °C, 14.040 (11.321) °C, and 13.590 (3.656) °C in the first, second, third trimesters, and entire pregnancy, respectively. And for the control group, the daily means (*SDs*) of AT were 14.955 (9.771) °C, 13.890 (11.660) °C, 12.827 (9.828) °C, and 13.429 (3.908) °C, respectively. The mean AT exposure level in the first trimester was significantly lower in the case group than that in the control group, and the difference was statistically significant ($P < 0.05$).

The comparison of AT exposures level for the case and the control

The AT levels of the case group and control group in each time window are shown in Table 3. The 10th and 90th percentile of AT for all subjects were −0.448 °C and 27.866 °C in the first trimester, −0.695 °C and 28.655 °C in the second trimester, and −0.679 °C and 27.729 °C in the third trimester. The percentages below the 10th AT exposure in the first, second, and third trimesters were 13.5%, 8.5%, and 13.5% in the case group and 9.4%, 10.2%, and 9.4% in the control group, with no statistically significant differences among the two groups ($P = 0.128$). At the same time, the percentages above the 90th percentile of AT in the three time windows were 11.8%, 7.6%, and 13.1% in the case group and 9.7%, 10.4%, and 9.5% in the control group, with no statistically significant differences among the two groups ($P = 0.119$). In the entire pregnancy, the 10th and 90th percentiles of AT were 8.877 °C and 18.587 °C, and the percentages below the 10th AT in the two groups were 12.3% and 9.6%, with no statistically significant difference ($P = 0.205$). Likewise, the percentages above the 90th percentile of AT in the two groups were 7.2% and 10.4%, and the difference was not statistically significant ($P = 0.123$). In addition, in the first trimester, cold exposure was significantly lower in the control group than in the case group ($P = 0.008$). Meanwhile, heat exposure was significantly higher in the control group than in the case group in the second trimester ($P = 0.002$) and the entire pregnancy ($P = 0.010$).

In addition, AT exposure levels were calculated for the case and control groups from birth to the date of investigation. The daily mean (*SD*) was 12.168 (0.796) °C in the case group and 11.910 (1.387) °C in the control group. The difference between cases and controls was statistically significant ($P = 0.003$), and the AT level in case was higher than that in the control.

AT during pregnancy and asthma and wheezing

The potential non-linear associations between AT during pregnancy and childhood asthma and wheezing are provided by the GAM in Fig. 2. In Fig. 2A, when the AT exposure levels in the first trimester were lower than 7.05 °C, the positive association between ATs and the risk of asthma and wheezing was statistically significant. For example, the *OR*s were 1.689 (95% *CI*: 1.233–2.312), 1.507 (95% *CI*: 1.183–1.921), and 1.338 (95% *CI*: 1.083–1.653) when the AT was − 2 °C, 0 °C, and 2 °C, respectively, with the maximum $OR = 1.827$ (95% *CI*: 1.235–2.703) when AT = − 3.42 °C. When AT exposure levels were higher than 26.9 °C, there was also a positive association between ATs and the risk of asthma and wheezing, although it was not statistically significant. The relationship between ATs and the risk of asthma and wheezing showed a statistically significant negative

Table 1 The general characteristics of the subjects and their mothers

Covariates	Total (*n*)	Case ($n = 236$) [*n* (%)]	Control ($n = 1445$) [*n* (%)]	*P*
Infant gender				0.077
Male	897	139 (58.9)	758 (52.5)	
Female	784	97 (41.1)	687 (47.5)	
Infant age (year)				**< 0.001**
1.5	731	70 (29.7)	661 (15.7)	
2	804	122 (51.7)	682 (57.2)	
3	146	44 (18.6)	102 (7.1)	
Mode of delivery				0.149
Natural birth	839	107 (45.3)	732 (50.7)	
Cesarean delivery	842	129 (54.7)	713 (49.3)	
Preterm birth				**0.004**
No	1587	214 (89.4)	1366 (94.5)	
Yes	94	25 (10.6)	79 (5.5)	
Low birth weight				**0.031**
No	1608	219 (92.8)	1389 (96.1)	
Yes	73	17 (7.2)	56 (3.9)	
Congenital disease				**0.005**
No	1664	229 (97.0)	1435 (99.3)	
Yes	17	7 (3.0)	10 (0.7)	
Duration of breastfeeding (month)				0.274
≤ 6	280	33 (14.0)	247 (17.0)	
> 6	1401	203 (86.0)	1198 (83.0)	
Maternal age (years)				**0.001**
< 30	459	41 (17.4)	418 (29.0)	
30–34	713	121 (51.3)	592 (41.0)	
≥ 35	509	74 (31.3)	435 (30.0)	
Maternal education (year)				**0.008**
Junior or less (< 9)	218	27 (11.4)	191 (13.2)	
Senior (9–11)	351	33 (14.0)	318 (22.0)	
College or more (≥ 12)	1112	176 (74.6)	936 (64.8)	
Maternal secondhand smoking during pregnancy				0.597
No	1675	235 (99.6)	1440 (99.7)	
Yes	6	1 (0.4)	5 (0.3)	
Family income monthly (yuan, RMB)				**0.044**
< 6000	247	21 (8.9)	226 (15.7)	
6000–12,000	789	114 (48.3)	675 (46.7)	
12,000–18,000	394	64 (27.1)	330 (22.8)	
> 18,000	251	37 (15.7)	214 (14.8)	
Maternal vitamin D supplementation during pregnancy				**0.006**
No	826	96 (11.6)	730 (88.4)	
Yes	855	140 (16.4)	715 (83.6)	
Home dampness				**< 0.001**
No	1582	208 (88.1)	1374 (95.1)	
Yes	99	28 (11.9)	71 (4.9)	
Distance of residence from the nearest main traffic road				**0.018**
≤ 200	635	106 (45.0)	529 (36.6)	
> 200	1046	130 (55.0)	916 (63.4)	
Parental atopy				**< 0.001**
No	1237	148 (62.7)	1089 (75.4)	
Yes	444	88 (37.3)	356 (24.6)	

Table 2 Description of AT exposure level in each time window

Apparent temperatures (°C)	Case				Control				*P*
	Mean(*SD*)	10th	90th	Min, Max	Mean(*SD*)	10th	90th	Min, Max	
1st trimester	13.153 (11.004)	−1.255	28.174	−3.140, 29.370	14.955 (9.771)	−0.111	27.844	−3.420, 29.640	**0.025**
2nd trimester	14.902 (10.455)	−0.391	28.212	−2.970, 29.120	13.890 (11.660)	−0.720	28.677	−2.900, 30.370	0.354
3rd trimester	14.040 (11.321)	−1.197	28.771	−3.191, 30.660	12.827 (9.828)	−0.577	27.485	−3.820, 31.100	0.126
Entire pregnancy	13.590 (3.656)	8.729	18.479	7.280, 20.950	13.429 (3.908)	8.890	18.634	5.070, 22.490	0.717

Definition of abbreviations: *SD* standard deviation; *10th* the 10th percentile; *90th*: the 90th percentile; *Min* minimum value; *Max* maximum value

association when ATs were from 11.34 to 22.26 °C, with *OR*s of 0.755–0.844, with the minimum $OR = 0.755$ (95% *CI*: 0.631–0.902, $P < 0.000$) when AT = 16.63 °C. In Fig. 2C, for the third trimester, the positive association between AT and the risk of asthma and wheezing was statistically significant when AT exposure levels were lower than −0.17 °C and were higher than 24.65 °C. For instance, the *OR*s were 1.525 (95% *CI*: 1.100–2.113) and 1.653 (95% *CI*: 1.194–2.067) when the AT was −2 °C and 28 °C, respectively, with the maximum *OR* of 1.832 (95% *CI*: 1.146–2.927) when AT = −3.82 °C and 1.926 (95% *CI*: 1.208–3.070) when AT = 31.10 °C. Similarly, the relationship between ATs and the risk of asthma and wheezing showed a statistically significant negative association when ATs were from 4.87 to 17.00 °C, with *OR*s of 0.664–0.810, with the minimum $OR = 0.664$ (95% *CI*: 0.537–0.822, $P < 0.000$) when AT = 10.12 °C. However, we did not find significant effects of AT exposure in the second trimester (Fig. 2B) and entire pregnancy (Fig. 2D) on childhood asthma and wheezing.

Additionally, the association between different exposure levels of AT during pregnancy and childhood asthma and wheezing was presented by the logistic regression model in Fig. 3. In the single-factor model, with reference to the moderate temperature, childhood asthma and wheezing was significantly associated with cold exposure in the first trimester, with *OR* 1.784 (95% *CI*: 1.190–2.676), and cold exposure and heat exposure in the third trimester, with *OR*s 1.584 (95% *CI*: 1.033–2.430) and 2.303 (95% *CI*: 1.569–3.381). After adjusting for the covariates, asthma and wheezing in children was significantly related to cold exposure in the first trimester, with *OR* 1.731 (95% *CI*: 1.117–2.628). Similarly, this association remained significant in the third trimester, with *OR*s 1.610 (95% *CI*: 1.030–2.473) and 2.039 (95% *CI*: 1.343–3.048).

Effect modification on the association of AT and asthma and wheezing

The results of the stratified analysis for the first, second, and third trimesters, and the entire pregnancy are presented in Fig. 3, which had been adjusted for covariates. The results showed that there were statistically significant effect modifications by children's gender, mode of delivery, maternal vitamin D supplementation during pregnancy, the distance of residence from the nearest main traffic road, and parental atopy. Especially, in the third trimester, extreme AT exposure was found to have a stronger impact on the development of childhood asthma and wheezing among girls, children whose distance of residence was close to the nearest main traffic road, and children whose parents have asthma.

An interaction analysis on the risk of childhood asthma and wheezing was carried out among different subgroups. For the third trimester, the *RERI* estimate for the interaction effect of heat exposure and parental atopy on the risk of childhood asthma and wheezing was statistically significant, with *RERI* 2.625 (95% *CI*: 0.109–5.141). On the additive scale, during the third trimester, these indicate synergistic effects for interaction (Fig. 4).

Evaluation of statistical power

The results of statistical power evaluation showed that, with a sample size of 1681 observations, the logistic regression of a binary response variable on an independent variable achieves 0.929 statistical power when the significance level was 0.05.

Results of sensitivity analysis

The result from sensitivity analysis showed no change in the association of AT with childhood asthma and wheezing and based on the data of the matched case-control study, which is shown in Table S1. Meanwhile, we rebuilt the model which included the code for community vaccination clinics in analysis. After adjusting for the code for the community vaccination clinic, the magnitude of the association remained unchanged and was shown in Table S2.

Discussion

In recent years, several studies have explored the relationship between temperature and respiratory diseases in children (Wang 2016; Yamazaki et al. 2015). For instance, a

Table 3 The exposure level for the AT of cases and controls in each time window

Time windows	Cold (<10th)[#]						Heat (>90th)[#]					
	Number of subjects (%)			Mean (*SD*)			Number of subjects (%)			Mean (*SD*)		
	Case	Control	P^a	Case	Control	P^b	Case	Control	P^a	Case	Control	P^b
1st trimester	32 (13.5)	136 (9.4)	0.128	− .483 (0.802)	−1.872 (0.716)	**0.008**	28 (11.8)	110 (9.7)	0.119	28.704 (0.505)	28.811 (0.472)	0.376
2nd trimester	20 (8.5)	148 (10.2)		−1.551 (0.780)	−1.215 (0.575)	0.077	18 (7.6)	150 (10.4)		28.813 (0.180)	28.999 (0.272)	**0.002**
3rd trimester	32 (13.5)	136 (9.4)		−1.552 (0.828)	−1.755 (0.771)	0.366	31 (13.1)	137 (9.5)		28.851 (1.230)	29.029 (0.701)	0.900
Entire pregnancy	29 (12.3)	139 (9.6)	0.205	8.351 (0.400)	8.255 (0.675)	0.936	17 (7.2)	151 (10.4)	0.123	18.913 (0.536)	19.075 (0.501)	**0.010**

Definition of abbreviations: *SD* standard deviation; *10th* the 10th percentile; *90th* the 90th percentile

[#]For cold exposure, the threshold values (10th) of AT were −0.45 °C, −0.45 °C, − 0.66 °C, and 8.88 °C, respectively, for 1st trimester, 2nd trimester, 3rd trimester, and entire pregnancy. For heat exposure, the threshold values (90th) of AT were 27.89 °C, 28.38 °C, 27.73 °C, and 18.59 °C, respectively, for 1st trimester, 2nd trimester, 3rd trimester, and entire pregnancy

[a]Comparison of differences in extreme AT exposure between case and control groups across the three trimesters, using the Chi-square test or Fisher's exact test. Similarly, differences in extreme AT exposure between case and control groups were compared for the entire pregnancy

[b]Comparison of average AT exposure levels over 3 trimesters and the entire pregnancy, using the Mann-Whitney *U* test

prospective cohort study conducted in China among 2598 children found that prenatal exposure to diurnal temperature variation was significantly associated with the incidence of pneumonia in children aged 3–6 years (Miao et al. 2017). Similarly, Lu et al. carried out a cohort study and discovered that childhood pneumonia was significantly associated with increased exposure to diurnal temperature differences throughout the entire pregnancy (Zheng et al. 2021). Apparently, the results of these studies suggest that extreme AT during pregnancy is associated with the risk of respiratory disease in the offspring. However, studies investigating the relationship between AT during pregnancy and the risk of asthma and wheezing in children are still rare, so more relevant research evidence is necessary. In this study, we conducted a community-based case-control study in Jinan City to investigate the association between maternal exposure to extreme AT during pregnancy and the risk of asthma and wheezing in offspring aged 18 months to 3 years. We found that in the first trimester, the relationship between AT and childhood asthma and wheezing displayed an L-shaped, with low AT exposure associated with a higher risk in comparison to moderate AT exposure. Meanwhile, in the third trimester, the curve seemed to be a definite U-shaped with a bottom, with both low and high AT exposure associated with a higher risk in comparison to moderate AT exposure. After grouping the AT during pregnancy, we found essentially the same trend using a logistic regression model. Our data suggested that exposure to extreme AT during pregnancy can influence the risk of asthma in early childhood. According to the authors' limited search, this paper may be, to date, the first study to show that maternal AT exposure during pregnancy can influence asthma risk in early childhood. Meanwhile, we observed a non-linear relationship between maternal AT exposure levels during pregnancy and the risk of asthma and wheezing development in offspring.

The relationship between the critical AT exposure window in pregnancy and pregnancy outcome has been reported (Basu et al. 2016), so we wondered whether there is a critical exposure window for the relationship between AT levels during pregnancy and the development of childhood asthma. Two studies conducted in California showed that AT exposure levels in the third trimester were associated with an increased risk of LBW (Basu et al. 2016) and fetal stillbirth (Basu et al. 2018). The results of both studies reported a sensitive exposure window for the association between AT and adverse pregnancy outcomes. Our further analysis revealed that the first trimester and the third trimester were observed as crucial windows in which prenatal extreme AT exposure affected asthma and wheezing in children aged 18 months to 3 years.

Interestingly, despite the fact that AT exposure levels in the first trimester were not colder in the case group than in the control group, the children developed asthma and

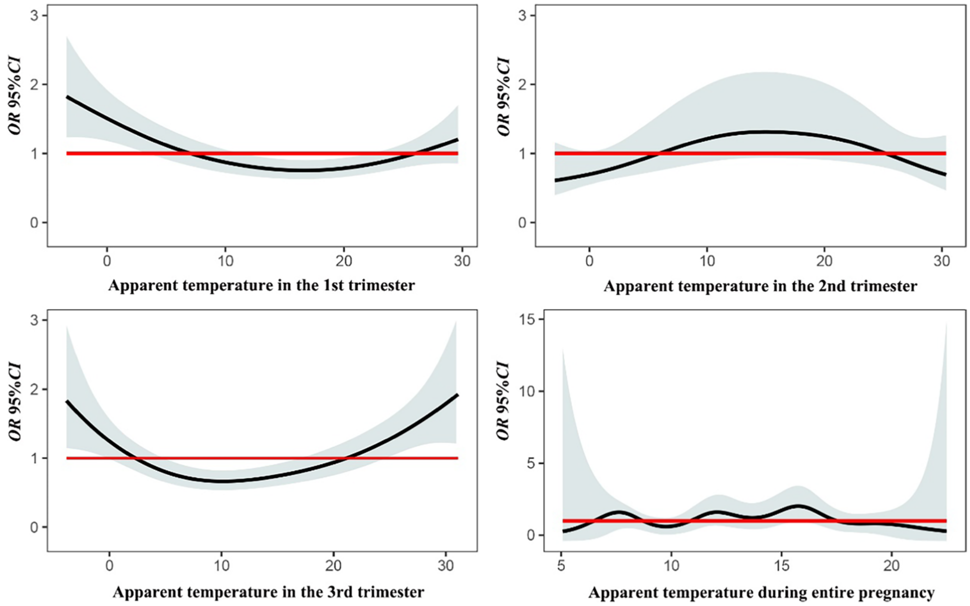
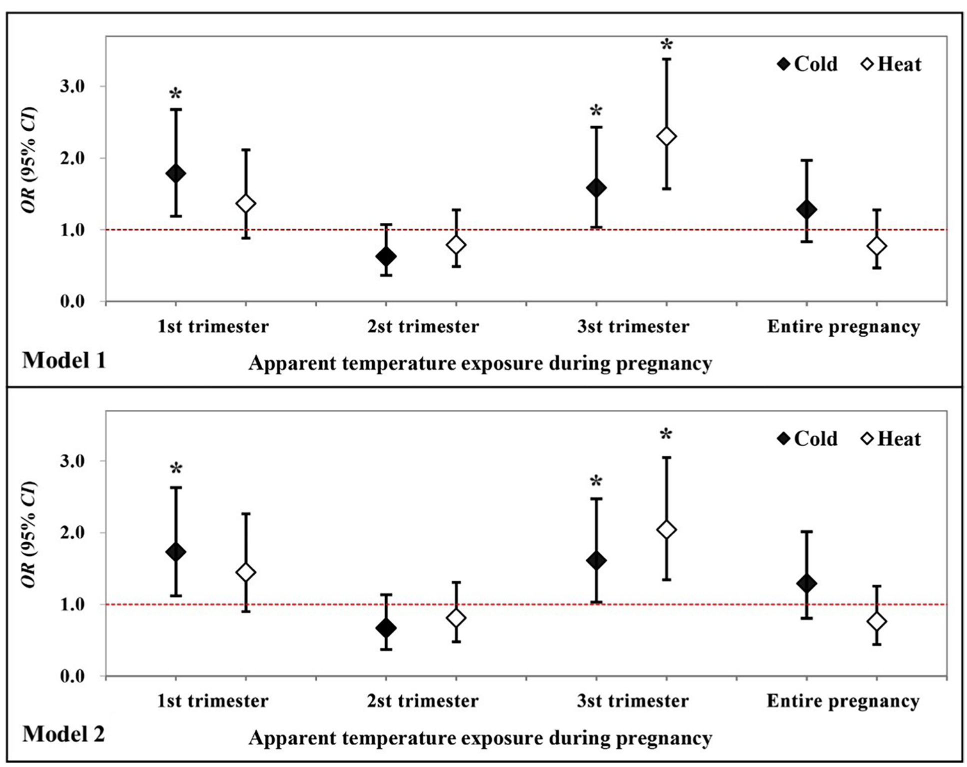


Fig. 2 Non-linear relationship between AT and childhood asthma and wheezing in each time window. The model was adjusted for children's age, children's gender, maternal age, preterm birth, low birth weight, monthly family income, congenital disease, maternal education, maternal secondhand smoking during pregnancy, the distance of residence from the nearest main traffic road, home dampness, parental atopy, and AT exposure levels after birth (from birth to the day of the investigation). **A** The relationship between AT in the first trimester and childhood asthma and wheezing. **B** The relationship between AT in the second trimester and childhood asthma and wheezing. **C** The relationship between AT in the third trimester and childhood asthma and wheezing. **D** The relationship between AT during the entire pregnancy and childhood asthma and wheezing

Fig. 3 The *OR*s and 95% *CI*s of childhood asthma and wheeze associated with AT in each exposure time window. Definition of abbreviations: cold, extreme AT exposure below the 10th percentile; heat: extreme AT exposure above the 90th percentile. Asterisk (.*) $P < 0.05$; model was performed without adjustment for the covariates; Model was adjusted for children's age, children's gender, maternal age, preterm birth, low birth weight, monthly family income, congenital disease, maternal education, maternal secondhand smoking during pregnancy, the distance of residence from the nearest main traffic road, home dampness, parental atopy, and AT exposure levels after birth (from birth to the day of the investigation)



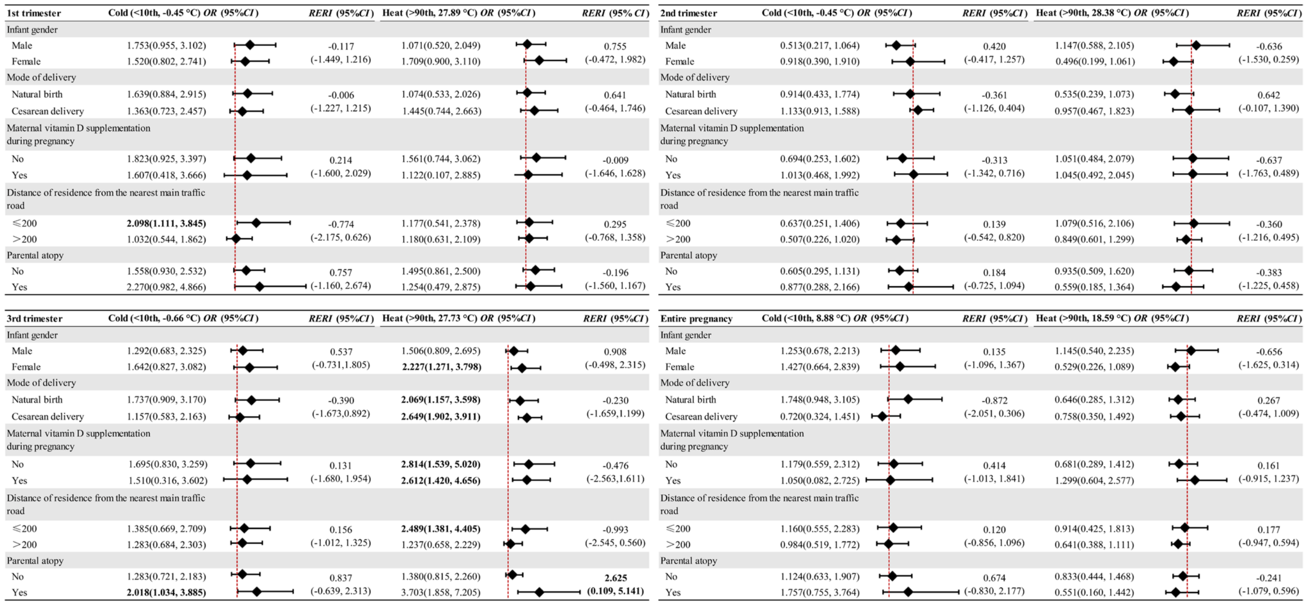


Fig. 4 Effect of AT on the risk of childhood asthma and wheezing, stratified by covariates, and the joint effects of covariates and AT on the risk of childhood asthma and wheezing, in each exposure time window. Asterisk (*) $P < 0.05$; model was adjusted for children's age, children's gender (except for stratified analyses by infant gender), maternal age, preterm birth, low birth weight, monthly family income, congenital disease, maternal education, maternal secondhand smoking during pregnancy, the distance of residence from the nearest main traffic road (except for stratified analyses by the distance of residence from the nearest main traffic road), home dampness, parental atopy (except for stratified analyses by parental atopy), and AT exposure levels after birth (from birth to the day of the investigation), in four exposure time window

wheezing. This may indicate that asthma and wheezing are the allergic constitution and are more susceptible to low temperatures. Although the mothers in the case group were not overexposed to low temperatures during pregnancy, their offspring showed hypersensitivity to extreme AT during embryonic life.

In addition, we discovered that exposure to extreme AT during pregnancy had a stronger impact on the development of childhood asthma and wheezing among children whose distance of residence was close to the nearest main traffic road, especially in the third trimester. Some studies have shown that people living in urban areas are more vulnerable, and living in wealthier urban areas may increase the risk of developing asthma, especially in children (DeVries et al. 2017). In our study, children whose mothers never took additional vitamin D supplements during pregnancy had a 28% increased risk of developing asthma and wheezing due to heat exposure (> 27.729 °C) in the third trimester compared to children whose mothers took vitamin D supplementation during pregnancy. Recent research revealed that maternal vitamin D deficiency can result in a variety of issues, including lower birth weight (Harvey et al. 2014), shorter gestation periods (Morley et al. 2006), and lower fetal blood calcium concentrations (Palermo and Holick 2014). Therefore, maternal vitamin D supplementation during pregnancy may be a smart preventive measure to avoid adverse fetal outcomes (Abreo et al. 2018; Kumar et al. 2022). We also observed that girls were more susceptible to the effects of extreme AT during the third trimester. Several studies have also reported that women are vulnerable to ambient temperature variations due to physiological factors (Yang et al. 2013; Zhou et al. 2014). Parental allergy was also found to be an effect modifier of extreme AT exposure on childhood asthma and wheezing. In the third trimester, compared to the no parental allergy group, the parental allergy group had a 1.5 times increased risk of childhood asthma and wheezing due to cold exposure (< 0.66 °C), and 2.7 times increased risk due to heat exposure (> 27.73 °C). Furthermore, we found an interaction between parental atopy and heat exposure during the third trimester on the risk of asthma development. Evidence suggested that both genetic and environmental factors contribute to asthma (Subbarao et al. 2009). A retrospective cohort study conducted in Ontario, Canada, found that a combination of maternal asthma and high levels of NO_2 exposure during pregnancy can lead to the development of asthma in children (Lavigne et al. 2018). Parental allergy has been reported to be a risk factor for childhood asthma and may increase maternal sensitivity to environmental factors and exacerbate the effects of exposure to harmful environmental factors during pregnancy (Hansen et al. 2010). We hypothesize that this effect is due to increased inflammation during pregnancy, and our data supported the theory that the development of asthma in children is caused by a coordinated effect of genetic and environmental factors. More research like this is needed to fully explore the relationship and influence of genes and environment on disease.

Several mechanisms have been hypothesized to support the relationship between AT and childhood asthma and wheezing. For the possible mechanisms for heat-related effects on childhood asthma and wheezing, on the hand, acute heat stress might cause an inflammatory response (Wu et al. 2018) and influence the endocrine system (Regnault et al. 2007), which can result in placental anomalies. On the other hand, dehydration caused by maternal heat stress can lead to a decrease in fluid flow to the uterus, which can affect the blood supply to the fetus and cause asthma in children (Wang et al. 2020). For possible mechanisms associated with the effects of cold exposure on asthma and wheezing in children, some studies suggested that low temperatures can cause vasoconstriction, which restricts blood flow to the placenta and the fetus (Lian et al. 2017). Also, hypothermia has been related to peripheral vasoconstriction and hypertensive disorders in pregnancy in several studies, which could affect uteroplacental perfusion and harm the developing fetus (Bruckner et al. 2014). Some evidence supports our conclusions for the critical exposure period. It has been claimed that lung development starts at about the 4th gestational week, after which the airway begins to branch (Herriges and Morrisey 2014). During the third trimester of pregnancy, numerous terminal vesicles keep growing into primitive alveoli (Schittny 2017), and the development and maturation of the respiratory system would be harmed if exposed to extreme temperatures during this period. The exact biological mechanisms explaining the association between extreme temperatures during pregnancy and childhood asthma are unknown, and further research is needed.

It is worth mentioning that the prevalence of asthma and wheezing was 2.07% among children aged 18 months to 3 years, in our cross-sectional study. In a cohort study in the UK, the prevalence of preschool childhood wheezing was 7.7% (Bloom et al. 2021), and in a cross-sectional investigation in Shanghai, China, the overall incidence of asthma in children aged 3–7 years was 14.6% (Hu et al. 2021). Compared to other studies, our study had a lower prevalence of asthma and wheezing, which could be attributed to differences in the age group, economic status, and diagnostic criteria. In addition, since this study was conducted from December 2018 to March 2019, both maternal exposure during pregnancy and asthma observation were not affected by the COVID-19 epidemic. Considering that people who are advised to spend less time outdoors and wear masks whenever possible reduced the actual level of maternal exposure and hence reduced childhood asthma prevalence, the prevalence of asthma and wheezing reported in this study can be used as a prevalence before the COVID-19 epidemic, which can provide a reference for post-epidemic surveys about the prevalence of asthma and wheezing.

It is important to note that the grouped case-control study, one of the most commonly used case-control study methods (Shapiro 1982), was used in our study. The benefits of this approach in exploring the etiology of the disease are obvious. Firstly, the controls were randomly selected from the vaccination system before the start of the survey. The purpose of using this method is to avoid selection bias that might result from the use of convenience samples in vaccination clinics. Secondly, the cases and the controls were investigated simultaneously in our study, which greatly reduced possible information bias due to differences in investigators and the time. This is because the controls were sampled previously, and they could be investigated at the same time as screening the cases. Thirdly, the results of the pre-survey showed the prevalence of asthma in children was low. Based on this design, a large number of non-asthmatic children in our source population were not randomly sampled and did not all participate in the survey, which resulted in substantial cost savings. Finally, one of the objectives of this study was to identify possible modifiers in the relationship between AT and asthma and wheezing. For this purpose, the grouped case-control study is more suitable for observing the effect modifications of modifiers. However, some characteristics between the case and control groups were different because they were not individually matched, which was controlled in the multi-factor model, and a 1:1 match in the sensitivity analysis was performed to validate the stability of the results. However, there are some shortcomings in the grouped case-control study. For example, it reduced the efficiency of the study compared to the matched case-control study because far more controls were sampled than the number of cases.

This research has some advantages. First, we selected the AT as the research index, which combines ambient temperature, wind speed, and relative humidity and may be more objective than ambient temperature alone. Second, we used GAM and logistic regression model to analyze the effect of different AT exposure levels during pregnancy on asthma and wheezing in children, and we think that the two models may better show the association. Combining the rough effects observed by GAM and many previous studies (Gasparrini and Leone 2014), we divided the AT exposure levels during pregnancy into 3 levels; cold, moderate, and heat, which may deeply describe the relationship between AT during pregnancy and childhood asthma and wheezing. Third, the research was based on a cross-sectional study, and the cases and controls were recruited from the same source population, ensuring good comparability. Fourth, we separated the pregnancy into 4 time windows based on gestational weeks and then explored the independent effects of each time window on the outcomes in more detail. This research also has several disadvantages. First, there was a possibility of recall bias in the diagnosis of childhood asthma and other variables, because mother-children-pair data were gathered through maternal reports, although we controlled for children aged up to 3 years to reduce maternal recall bias. Second, even though several significant confounders were controlled as soon as possible, we cannot rule out the potential confounding factors, such as maternal obesity during pregnancy, which may cause errors in the association. Third, although this study investigated the effect of AT on childhood asthma and wheezing, we only considered outside temperature and ignored the effect of indoor temperature. This is something that has to be addressed in the follow-up research and more studies are needed to investigate the association between temperature and asthma in children.

Conclusions

The study indicates that exposure to extreme AT during the first trimester and the third trimester could increase the risk of childhood asthma and wheezing. Furthermore, we found this association may be affected by effect modification factors, such as children's gender, the distance of residence from the nearest main traffic road, and parental atopy. These findings highlight the significance of conducting more research to validate the connections found here, and give further epidemiological research on the impact of meteorological conditions on childhood asthma during pregnancy.

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Author contribution Jiatao Zhang: conceptualization, formal analysis, writing—original draft. Shuoxin Bai: conceptualization, formal analysis, investigation, data curation, writing—review and editing. Shaoqian Lin: resources, investigation, data curation, writing—review and editing, validation. Liangliang Cui: resources, investigation. Xiaodong Zhao: investigation, resources. Shuang Du: conceptualization, methodology, data curation, validation. Zhiping Wang: project administration, supervision, funding acquisition, writing—review and editing.

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Data availability Due to privacy concerns of the cohort and subjects in the follow-up phase, the datasets created and/or analyzed during this study are not publically available. However, upon reasonable request, these can be obtained from the associated authors.

Declarations

Ethics approval and consent to participate The study was approved by the Ethics Committee of Preventive Medicine of Shandong University (approved number: 20170315).

Consent for publication The author confirms that neither the entire manuscript nor any part of its content has been submitted for publication elsewhere. The author consents to publish.

Competing interests The authors declare no competing interests.

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