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The Combined Effects of Long-Term Mixture Exposure to Temperature and Relative Humidity on Asthma in China

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ABSTRACT:

Background: Few previous studies have examined the joint effect of long-term exposure to temperature and relative humidity (RH) on asthma. This study endeavors to explore the combined association between long-term co-exposure to temperature and RH and asthma in China.

Methods: The individual data of asthma were collected from the wave 1 to wave 3 (2007-2019) of the Study on global AGEing and adult health in China. Meteorological factors data were obtained from the European Center for Medium-range Weather Forecasts Reanalysis 5 (ERA5) and extracted from the corresponding interpolated grid according to individual residential latitude, longitude and survey time. Individual and joint association of long-term exposure to annual mean temperature and RH with asthma were estimated using Cox regression model and Quantile-Based g-Computation model (Qgcomp), respectively. Then, the joint effects of different temperature-RH compound events were further estimated.

Results: We observed negative association between both temperature and RH with asthma. In individual effect analysis, for 1°C or 1% decrease in 3-year average temperature and RH, asthma increased 4.44% (95%CI:1.76-7.05) and 6.45% (95%CI:2.79-9.98), respectively. The joint effect of long-term exposure to temperature and RH on asthma was also negative. For each percentile decreasing of both temperature and RH, asthma decreased 1.50% (95%CI: 0.85%-2.15%) in total population. People <60 years old and female were more susceptible to mixture exposure to low temperature and low RH. We also observed a higher risk of asthma in dry-cold event (HR=2.44, 95%CI: 1.67-3.55) than wet-cold, wet-hot and dry-hot events.

Conclusion: Long-term exposure to temperature and RH may jointly associate with asthma, and low RH and cold may have higher risk on asthma onset.

KEYWORDS: Asthma; Temperature; RH; Quantile-Based g-Computation model, Joint effect;

The Combined Effects of Long-Term Mixture Exposure to Temperature and Relative Humidity on Asthma in China

1. INTRODUCTION

Asthma is a major chronic respiratory disease affecting both children and adults with most related deaths in low- and middle-income countries[1]. According to the results of 2019 Global Burden of Disease (GBD) study, a total of 0.46 million deaths and 21.5 million disability adjusted life years (DALY) could be attributed to asthma globally[2]. In China, asthma ranked the 8th out of the DALYs' burden of 369 diseases[3]. Moreover, the prevalence of asthma in China was 4.2%, which represents 45.7 million Chinese suffering from asthma[4]. Thus, the prevention and control of asthma wields immense public health advantages.

There are many risk factors involving in asthma onset. Out of them, environmental factors such as weather conditions, aeroallergens (pollen, mold) and air pollutants play important roles in asthma onset[5-8]. With climate change, several studies have investigated the associations between asthma and weather factors[9]. For example, Xu et.al conducted a systematic review and reported that there was significant association between temperature and childhood asthma[10]. A review reported that each 1 °C decrement in temperature increased 15% asthma risk[11]. Several studies also examined the association between RH and asthma[12-14]. A study reported that every 1% rise in RH (lag 0–12 days) was associated with a 1.89% rise in asthma admissions in hot season[14]. However, all of those studies focused on short-term effect of temperature or RH on asthma, there was no study on the joint effect of long-term exposure to temperature or RH on asthma. Therefore, further investigation was necessary to comprehensively understand the impact of prolonged exposure to temperature and RH on asthma.

The joint health effects of environmental factors have raised great concern, and recently several previous studies have examined the joint effects of multiple environmental factors using advanced statistical methods like weighted quantile sum (WQS) regression, Bayesian kernel machine regression (BKMR) models and Quantile-Based g-Computation (Qgcomp)[15, 16]. The WQS requires the effects of exposures on health outcome should be in the same direction and linear[17]. Nevertheless, previous studies reported that the effects of meteorological factors on asthma were commonly non-liner[14]. In addition, BKMR was limited applicable to large dataset for running slowly[16, 18]. The Qgcomp approach could be employed in large dataset without linear hypothesis. Therefore, it was an ideal model framework in the assessment of joint effects of multiple weather factors exposure on health[19].

To fill the knowledge gaps, this study first examined the individual effects of long-term exposure to temperature and RH on asthma based on a prospective study on global AGEing and adult health (SAGE) in China. Then, the joint effects of temperature and RH on asthma were estimated using Qgcomp model. Finally, we estimated the joint effects of different temperature-RH compound events on asthma. Our findings may help understand the risk of long-term exposure to multiple meteorological factors on asthma, which will provide useful information for asthma clinical management and prevention in the context of climate change.

2. MATERIAL AND METHOD

2.1 Study Population

The data from wave 1 to wave 3 (2007-2019) of the World Health Organization's SAGE(WHO-SAGE) in China was used in this analysis. SAGE is a longitudinal study in six low- and middle-income countries (China, Ghana, India, Mexico, Russia and South Africa) with nationally representative samples of persons aged 50+ years[20]. Stratified random sampling strategy was carried out in all countries and then the sampling unites were stratified by region and location[21]. In China, 8 provinces were selected including Guangdong, Yunnan, Hubei, Shanxi, Shanghai, Shandong, Zhejiang and Jilin Province (Fig.S1). Information of participants were collected by face-to-face interview using structured household and individual questionnaires[22].

A total of 18,361 participants aged 50 years or older was included in the WHO-SAGE study in China. The exclusion criteria in this study were as follows: People who had asthma before the first wave (901 participants); loss to follow-up (7530 participants); missing asthma information (127 participants); missing information on age and sex (133 participants); abnormal information of address (23 participants) and missing data on follow-up years (138 participants). Finally, this study based on data of 9509 participants with three times follow-ups for 8184 participants and twice follow-ups for 1325participants (Fig.S2) after excluding participants who meet the exclusion criteria above.

2.2 Environmental data

As a long-term developing chronic respiratory disease, asthma have been estimated the effect of long-term exposure to air pollution using 3-year averages in previous study[23]. Therefore, for understanding the effect of long-term exposure to temperature and RH on asthma, three-year averages of temperature and RH was regarded as indicator. In current analysis, temperature, RH, windy speed, pressure and precipitation from 2007 to 2019 were collected from the ERA5 which was the fifth generation European Center for Medium-range Weather Forecasts (ECMWF) atmospheric reanalysis of the global climate and have been validated and employed in previous studies[24-26]. $PM_{2.5}$ and O_3 were collected from National air quality forecast information release system in China, and they were covariates when fitting the association of temperature and RH with asthma[23]. Temperature, RH, windy speed, pressure, precipitation, $PM_{2.5}$ and O_3 (Fig.S3 shown the correlation of environmental factors) were extracted from the corresponding interpolated grid according to individual residential latitude, longitude and survey time.

2.2 Outcome variable definition and Covariates

The questions of asthma status in questionnaire were "have you ever been diagnosed with asthma (an allergic respiratory disease)?" and "have you been taking any medications or other treatment for asthma?". If the answer was "Yes" for anyone of the two questions, the participant was diagnosed as asthma by a doctor or taking asthma-related therapies within the past 12 months, then we defined the participant as asthma case which was consistent with previous SAGE studies[27].

Covariates included the following variables: wind speed, air pressure, precipitation, O_3, $PM_{2.5}$, sex (male or female), age (<60 years old, 60– years old), region (urban, rural), marital status (currently married, other), household income (high income, low income), body mass index (<18.5, 18.5-, 24- and 28- kg/m^2), smoking status (yes, no), alcohol use (yes, no), household fuel (clean, unclean).

2.3 Statistical analysis

2.3.1 Descriptive analyses

We conducted descriptive analyses on the asthma, environmental factors, and socio-demographic characteristics of participants with means and standardized deviation for continuous variables and proportion for categorical variables. The chi-square test was used to test the difference between subgroups of age, sex and etc.

2.3.2 Modelling the individual effects of temperature and RH on asthma.

In the follow-up survey, the variables will change over time, thus time-varying covariance occurs. In order to identify both internal variation and external variation of variables, Cox regression model was employed in our analysis, which was consistent with previous studies[28]. The model formula was as follow [29]:

$$f = \beta_{\mathrm{TRH}} ns(X_{\mathrm{TRH}}, df) + \beta_{cov} X_{cov}$$
$$\mathrm{h}(t, asthma) = h_0(t)\exp(f)$$

Asthma is a categorical variable (yes=1, no=0). The $h_0(t)$ is the baseline hazard function and β_{TRH} is the regression coefficient of temperature or RH. Other covariates are wind speed, air pressure and precipitation, O_3, $PM_{2.5}$, sex, age, region, marital status, body mass index, smoking, drinking and household fuel[4] (model choice in Table S2). ns is the natural cubic spline function; df is the degree of freedom, and we used 2 as the degree of freedom for temperature and RH according to minimum AIC, and the sensitive analysis of different df of temperature or RH also shown in Fig. S4.

2.3.3 Modelling the joint effect of temperature and RH with asthma

To reduce the influence of collinearity, Quantile-Based g-Computation model had been employed to explore the association of temperature and RH with asthma, and Qgcomp have been used in studies about environmental exposure with health[30, 31]. In this study, we fitted a linear model as follows[19]:

$$Y_i = \beta_0 + \psi \sum_{i=1}^{n} w_i X_i^q + Z + \varepsilon_0$$

$$Y_i = \beta_0 + \sum_{i=1}^{n} \beta_i X_{ij}^q + Z + \varepsilon_j$$

In this model, the quantile format X_i^q coded from 1 to 100.The $\sum_{i=1}^{n} \beta_i$ means the change in all meteorological factors for a one-percent change in mixture exposures of them. Z is the confounders and ε_j is the error term. When assuming directional homogeneity, ψ is given as $\sum_{i=1}^{n} \beta_i$ which is the sum of the regression coefficients of all exposures and w_i is each exposure weight which is given as $w_i = \beta_i / \sum_{i=1}^{n} \beta_i$ (all the weights are from 0 to 1 positively or negatively). As the directional homogeneity on the outcomes are not hold, the weights will be redefined to be negative and positive weights. And then ψ is become a parameter of a marginal structural model estimated using g-computation and variance also can be calculated via nonparametric bootstrap which have proved in previous study[32]. Then this approach is extended to Cox proportional hazards model to estimate survival outcomes[19].

2.3.4 Modelling joint effects of different temperature-RH compound events on asthma.

In order to explore the different joint effects of temperature and RH on asthma in real world, we further estimated the different temperature-RH compound events on asthma. The 50% percentile of temperature or RH was used to distinguish low temperature/high temperature, low RH/high RH. If a day with high temperature and high RH, we defined that day as wet-hot day; a day with high temperature and low RH was classified as dry-hot day; a day with low temperature and low RH was defined as dry-cold day; and a day with low temperature and high RH was defined as wet-cold day. The joint effect of low RH and cold on asthma was estimated based on Cox regression model using wet-hot day as a reference[33].We further conducted subgroup analysis by sex (male, female) and age (<60 years old, 60- years old).

2.4 Sensitivity analysis

To assess the robustness of our results, we carried out the effects from different long-term exposure (current year, 2-year average and 4-year average) to temperature and RH. Additionally, effects of the different df of temperature, RH, $PM_{2.5}$ or O_3 also were reported. More details have shown in Table S3, Fig.S4, S5 and S6 in supplementary material.

All the statistical analyses were conducted using R4.1.0 (https://www.r-project.org/). R packages of "survminer", "survival"and "qgcomp" were used to explore individual and joint effects.

3. RESULTS

3.1Descriptive analysis

Table 1 shows the characteristics of asthma incidence and environmental factors. There were 9509 participants with 509 asthma cases. The prevalence for people aged below 60 years old (4.03%) was lower than that for the elderly ≥60 years old (6.72%). Female (5.39%) had similar prevalence to that for male (5.32%). The 3-year averages of temperature, RH, wind speed, air pressure, precipitation, $PM_{2.5}$ and O_3 were 14.55℃, 71.03%, 0.74 m/s, 96.31 kpa, 3.05 mm, 46.83μg/m^3 and 51.69μg/m^3, respectively (Table S1).

Table 1. The characteristics of asthma incidence in Chinese participants of SAGE study

Groups		Asthma		Incidence (%)	P-value
		Yes	No		
Total	All	509	9000	5.35	
Age(year)	<60	195	4644	4.03	<0.01
	60–	314	4356	6.72	
Sex	Female	268	4707	5.39	0.91
	Male	241	4293	5.32	
BMI (kg/m^2)	28-	64	1019	5.91	0.81
	24-	164	2955	5.26	
	18.5-	257	4577	5.32	
	<18.5	20	394	4.83	
Region	Rural	231	5152	4.29	<0.01
	Urban	278	3848	6.74	
Marital Status	Yes	421	7834	5.10	0.01
	Other	88	1165	7.02	
Smoking	No	335	6037	5.26	0.58
	Yes	174	2960	5.55	
Drinking	No	348	5942	5.53	0.58
	Yes	157	2846	5.23	
Household income	High	244	4486	5.16	0.27
	Low	256	4235	5.70	

Household fuel	Clean	289	4989	5.48	0.59
	Unclean	219	3990	5.20	

Note: the chi-square test was used to test the difference between subgroups of age, sex and etc.

3.2 The individual effects of long-term exposure to temperature and RH on BP

Figure 2 shows the estimated effects of three-year average temperature (Fig. 2 A) and RH (Fig. 2 B) on asthma. Generally, there was negative association of temperature with asthma, but U-shaped association of RH with asthma. Subgroup analysis by sex (male, female) and age (<60 years old, 60- years old) were shown in Fig. S7 and S8.

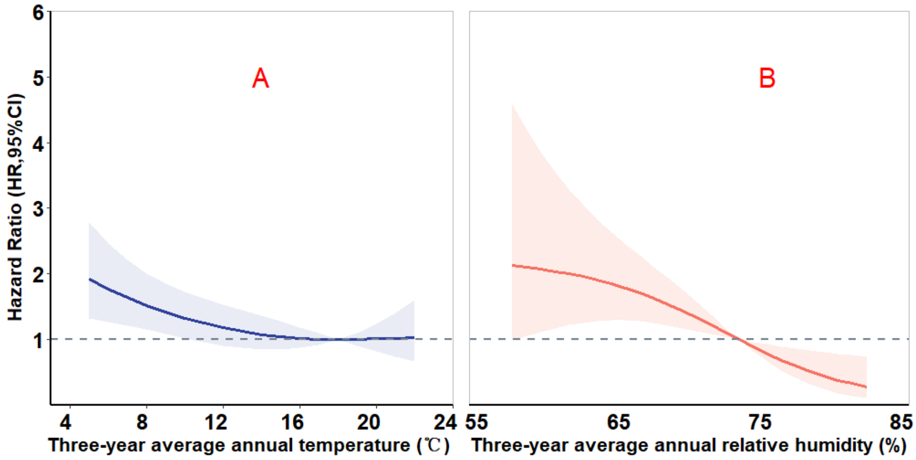

Fig.1 The individual association of 3-year average annual temperature or RH with asthma after adjusting for covariates (wind speed and precipitation, O_3, $PM_{2.5}$, sex, age, region, marital status, body mass index, smoking, drinking and household fuel).

We further quantified the excess risk (ER) of temperature and RH on asthma after linearization. For 1°C,1% decreasing in three-year average annual temperature or RH, asthma increased 4.44%(95%CI:1.76%-7.05%) and 6.45% (95%CI:2.79%-9.98%), and people ≤60 years old (For temperature: ER=5.06%, 95%CI: 1.22%-8.75%; For RH: ER=9.33%, 95%CI: 3.61%-14.71%) and female (For temperature: ER=6.56%, 95%CI: 2.98%-10.01%; For RH: ER=9.28%, 95%CI: 4.12%-14.15%) had a higher risk than their counterparts with statistically insignificant difference.

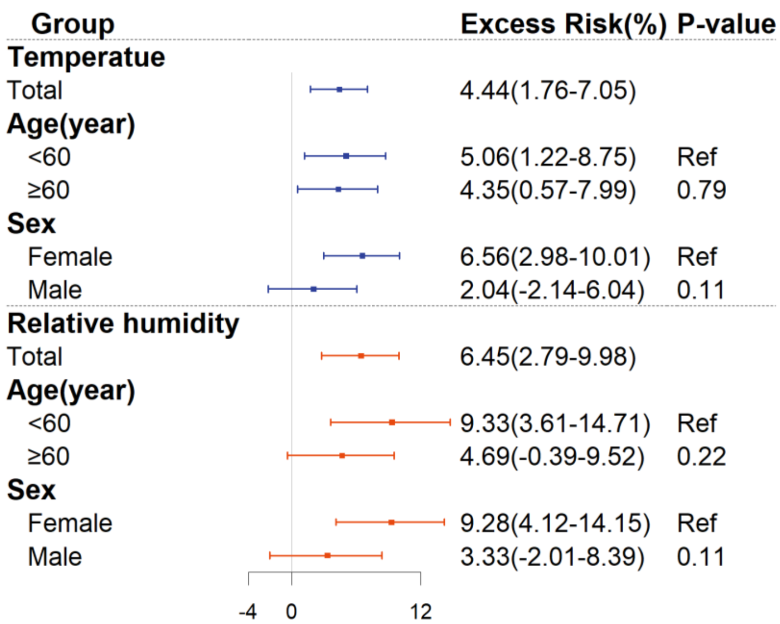

Fig.2 The excess risk (%) for 1°C decrement of temperature or 1% decrement of RH on asthma after adjusting for covariates (wind speed, pressure and precipitation, O_3, $PM_{2.5}$, sex, age, region, marital status, body mass index, smoking, drinking and household fuel). Two-sample z test was used to estimate the difference between subgroups by age, sex.

3.3 The joint effects of long-term exposure to temperature and RH on asthma

The joint effects of temperature and RH on asthma in total population were estimated by Qgcomp model. We observed that there was negative association of exposure to temperature and RH with asthma (Fig.3). For 1% percentile decreasing in three-year average annual temperature and RH, asthma increased 1.50% (95%CI: 0.85%-2.15%) (for 1% percentile decreasing in temperature, ER=0.82%, 95%CI: 0.37%-1.27%; for RH, ER=1.47%, 95%CI: 0.85%-2.09%). Subgroup analysis by sex and age were presented in Fig. S9.

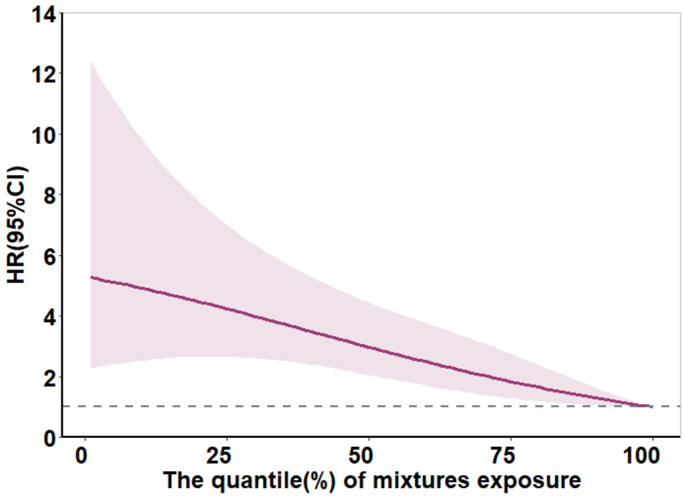

Fig.3 The joint effect of exposure to temperature and RH on asthma after adjusting covariates (wind speed, pressure and precipitation, O_3, $PM_{2.5}$, sex, age, region, marital status, body mass index, smoking, drinking and household fuel).

3.4 The joint effects of different temperature-RH compound events on asthma

We observed that dry-cold event (HR=2.44, 95%CI: 1.67-3.55) had a higher risk than wet-cold event (HR=1.64,95%CI:1.10-2.46), dry-hot event (HR=1.87, 95%CI:1.13-3.09) compared with wet-hot event. In stratified analyses by sex or age, we observed similar results for all age groups and female. While for male, dry-hot event was at the highest risk than other events.

Table 2. The joint effects of different temperature-RH compound events on asthma

Groups		HR (95%CI)
Total	Wet-hot	Ref
	Wet-cold	1.64(1.10-2.46)
	Dry -hot	1.87(1.13-3.09)
	Dry-cold	2.44(1.67-3.55)
Age(year)		
<60	Wet-hot	Ref
	Wet-cold	2.49(1.5-4.12)
	Dry-hot	2.36(1.27-4.37)
	Dry-cold	2.68(1.71-4.2)
60-	Wet-hot	Ref
	Wet-cold	0.94(0.47-1.88)
	Dry-hot	1.37(0.64-2.95)
	Dry-cold	2.22(1.33-3.72)
Sex		
Male	Wet-hot	Ref
	Wet-cold	1.98(1.19-3.28)
	Dry-hot	2.63(1.45-4.76)
	Dry-cold	2.01(1.2-3.35)

Female	Wet-hot	Ref
	Wet-cold	1.33(0.69-2.53)
	Dry-hot	1.56(0.8-3.04)
	Dry-cold	2.42(1.55-3.78)

3.5 Sensitivity analysis

Sensitivity analyses showed that our findings were generally stable when changing the freedom of degree and periods of long-term exposure to temperature and RH, and changing freedom of degree of $PM_{2.5}$ and O_3. (Table S3, Fig.S4, S5 and S6 in supplementary material).

4. DISCUSSION

In the present study, we investigated the long-term association of temperature and RH with asthma in China. Both individual effect of temperature and RH on asthma were negative, and the joint effect of the two weather factors on asthma was also negative. Moreover, dry-cold event might have a higher risk on asthma onset than their counterparts. Our findings provided new insights on the health effects of long-term exposure to temperature and RH, which might be useful for developing adaptation measures to extreme weather events in the future.

In the context of global warming, the association of weather with asthma has attracted increasing interest[34]. In the current study, we observed an inverse association between long-term exposure to temperature and asthma, which was consistent with a previous study on the effect of short-term exposure to temperature on asthma onset [11]. However, several other studies reported that both short-term exposure to heat and cold increased asthma risk [10, 35]. We did not find any studies on the effects of long-term exposure to temperature, and the possible mechanism for the association observed in our study was also unclear. Possibly, when long-term exposure to cold, airway cooling in cold days could exacerbate inflammation leading to a narrowing of airways[36], which might increase the occurrence of asthma. The same relationship between long-term exposure to RH and asthma was observed. For low RH, a previous study reported that it might dry the mucosal membrane along the airway and induced asthma[34], and another study also presented increased sneezing in allergic rhinitis model when researchers kept mice in dry weather condition[37].

Although several studies have investigated the association between individual meteorological factor and asthma, no study has examined the joint effect of multiple meteorological factors on asthma. However, people usually expose to weather factors at the same time in a real world[19]. Therefore, it is very necessary to understand the joint effects of simultaneous exposure to temperature and RH. In the study, we first reported that there was a negative joint effect of temperature and RH on asthma. Although we did not find literature on the joint effects of the two weather factors, there were studies reporting the joint effects of ambient air pollutants on pediatric asthma exacerbations[38, 39]. The joint effects of temperature and RH on asthma might attribute to complex interaction of temperature and RH. Koskela et.al reported that the long-term airway responses might develop in condition with repeated and long-standing cooling and drying of the airways, usually in endurance athletes[40].

We further explored the joint effects of different temperature-RH compound events no asthma. The results showed that dry-cold event had higher risk on asthma onset compared with wet-hot event. Chu et.al reported that long-term exposure to dry-cold weather represented a significant environmental stress to the airways which causes inflammation and remodeling in peripheral airway[41]. Our finding might explain higher asthma prevalence in northern China (6.8% in Shandong, Shaanxi and Jilin provinces in the study) than that in southern China (4.6% in Guangdong, Hubei, Shanghai, Yunnan and Zhejiang provinces in current study), because northern China usually had cold and dry weather in winter (in this study, the mean 3-year average temperature and RH in northern regions was 10.3℃ and 10.3%, respectively; the corresponding temperature and RH in southern regions was 17.1℃ and 40.1%, respectively)[41]. On the other hand, a study reported that heating the air to increase body temperature and simultaneously saturated air could completely prevent airway obstruction from occurring[42], which may explain our findings that lower risk on asthma for wet-hot weather.

In the stratified analysis, female had a greater risk on asthma than male, which was consistent with previous studies[43], and it might be attributable to bronchial hyper-responsiveness which was more prevalent in women than in men[44]. We also observed that younger population were more susceptible than the elderly, which confirms the result of a time series study conducted in Hong Kong[34]. Younger population were more vulnerable to weather factors as they were working population and likely had more outdoor activities than the elderly, which might increase their exposure to environmental triggers leading to the onset of asthma[34].

To the best of our knowledge, this is the first study to demonstrate the association of long-term exposure to temperature and RH on asthma in China based on a prospective cohort study. In addition, we also first estimated the joint effect of temperature and RH on asthma. There are also several limitations. First, the individual exposure of temperature and RH was unavailable, and we used the values from weather monitoring stations as exposures, which may lead to exposure misclassification bias. Second, the participants in our study were ≥50, which will be cautious when extrapolating our results to the general population. Thirdly, despite controlling for several covariates, there were still unmeasured confounders including genetic component, pest allergens, mold and endotoxin, which may bias our analyses.

In the context of climate change, people were likely to suffer more from extreme weather events. With rising in temperature and a decrease in summer precipitation, the frequency, severity and intensity of people long-term exposure to droughts would increase and also cold spells were projected to increase, which might increase asthma risk[45]. This study explored the joint effects of long-term exposure to temperature and humidity on asthma onset and provided information for the public to take measures preventing asthma in nonoptimal weather conditions.

5. CONCLUSION

In summary, we observed that long-term exposure to temperature and RH were significantly associated with asthma, and dry-cold event might have higher risk. Our findings will inform useful information for effectively adapting to ambient weather condition in the context of climate change.

Author Contributions: Zhongguo Huang: Methodology, Software, Formal analysis, Visualization, Writing-Original Draft. Tao Liu and Yan Shi: Formal analysis, Data Curation, Validation, Writing-Original Draft & Editing. Yanfei Guo, Guanhao He, JianXiong Hu, Xiaomei Dong and Jianpeng Xiao: Investigation, Resources, Formal analysis. Ziqiang Lin: Methodology, Resources, Data curation. Fan Wu: supervision and draft revision. Wenjun Ma: Conceptualization, Supervision, Project administration and draft revision.

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Conflicts of Interest: The authors declare that there are not competing financial
interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations:

RH: Relative humidity
ERA5: European Center for Medium-range Weather Forecasts Reanalysis 5
Qgcomp: Quantile-Based g-Computation model
GBD: Global Burden of Disease
DALY: Disability adjusted life years
WQS: Weighted quantile sum regression
BKMR: Bayesian kernel machine regression
SAGE: Study on global AGEing and adult health
ECMWF: European Center for Medium-range Weather Forecasts

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