

Effects of Ambient Temperature on Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Results from a Time-Series Analysis of 143318 Hospitalizations

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Purpose: To evaluate the associations between acute exacerbations of chronic obstructive pulmonary disease (AECOPD) hospitalizations and daily mean temperature (Tmean) as well as daily apparent temperature (AT), and to explore the practical values of these two indices in policymaking and patient education.

Methods: Daily AECOPD hospitalizations and Meteorological data in Beijing were obtained between 2013 and 2016. Distributed lag non-linear model was adopted to investigate the association between daily ambient temperature and AECOPD hospitalizations. The cumulative effects of cold/hot temperature were abstracted. For the extreme and moderate low-temperature effect estimates, we, respectively, computed the RR of AECOPD hospitalizations at the 1st and 10th percentiles of temperature in comparison with that at the 25th percentile of temperature. For the extreme and moderate high temperature effect estimates, we, respectively, computed the RR of AECOPD hospitalizations at the 99th and 90th percentiles of temperature in comparison with that at the 75th percentile of temperature.

Results: During the study period, 143,318 AECOPD hospitalizations were collected. A reverse J-shape relationship was found between temperature and AECOPD hospitalizations. When comparing the effect of Tmean, higher RRs were associated with increases in AT on AECOPD hospitalizations but a lower value of Akaike's Information Criterion for quasi-Poisson (Q-AIC). The RR of extremely low temperature of Tmean and AT were 1.55 (95% CI: 1.21,2.00) and 2.08 (95% CI: 1.44,3.01), respectively. Moderate low temperature also had an adverse impact on AECOPD hospitalizations. No associations were found between high temperature and AECOPD risk. We found the females and those aged <65 years to be more susceptible to temperature change.

Conclusion: Lower temperature is associated with a higher risk for AECOPD hospitalizations. Ambient temperature is probably a better predictor in terms of quantifying risk than mean temperature when studying temperature impact on health.

Keywords: ambient temperature, distributed lag non-linear model, hospitalization

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health concern, with high prevalence and associated disability and mortality worldwide.¹ According to a nation-wide study, there are 99.9 million people living with COPD in China in 2018, and over 0.9 million people died prematurely because of COPD each year.² Acute exacerbations of COPD (AECOPD) are defined as any sustained worsening of

respiratory symptoms in COPD patients.³ Hospitalizations for exacerbations, which only account for \$ 18 billion in direct costs annually in the United States, and are associated with 1-year mortality of 21% and 5-year mortality of 55%.⁴ Identification of risk factors for exacerbation may help slow disease progression and reduce the economic and societal costs of COPD. Known risk factors for COPD exacerbations include cigarette smoking, infections, exposures to air pollutants and occupational hazards.⁵ Another potential trigger for such exacerbations is short-term exposures to extreme temperature.⁶

Extremes of temperature, both cold and hot, have also been associated with excess mortality and morbidity among patients suffering from COPD.⁷ Previously reported works have demonstrated conflicting results on the correlation of ambient temperature and COPD hospitalization, emergency room visits, and outpatient clinic visits.^{6,8–13} Several published studies suggest that a decline in ambient temperature is linked with a higher susceptibility to COPD risk.^{6,8–10} Other researches have reported higher COPD risks during high temperature.^{11–13} However, research conducted in Taiwan from 2000 to 2008 has reported a U-shaped association.¹⁴ Furthermore, previous studies on temperature and COPD have been conducted mostly in the developed regions rather than the developing ones. Therefore, high-quality evidence and large population-based study from China are certainly lacking.

Mean ambient temperature and the frequency of extreme temperature weather may increase due to climate change in the near future.¹⁵ It is, therefore, important to understand how temperature may impact COPD patients

and to find an optimal index of temperature for health environment research. Ambient daily mean temperature and apparent temperature are two commonly studied indices of thermal stress.¹⁶ This study aims to examine the relationship between ambient temperature (including Tmean and AT as indices) and AECOPD hospitalizations among residents in urban areas of Beijing between 2013 and 2016. Quantifying the effect of temperature for AECOPD hospitalizations and identifying susceptible populations could provide useful information for disease surveillance and prevention strategies.

Methods

Study Sites and Data Collection

Beijing is the capital of the People's Republic of China, the world's third most populous city, and most populous capital city. It has an urban area of 4144 km² (1600 sq mi), a population of more than 22 million in 2015. It lies in a semi-humid continental monsoon region in a warm northern temperature zone. In terms of seasons, Beijing has dry-cold winters and humid-hot summers while springs and autumns are both windy and relatively short in duration. The location and geographical properties of Beijing are shown in Figure 1.

Data on AECOPD hospitalizations in major hospitals were collected from Beijing Public Information Center between January 1, 2013, and December 31, 2016. AECOPD was defined according to the International Classification of Disease revision 10 (ICD-10: J41–J44). The study was approved by the ethical committee of

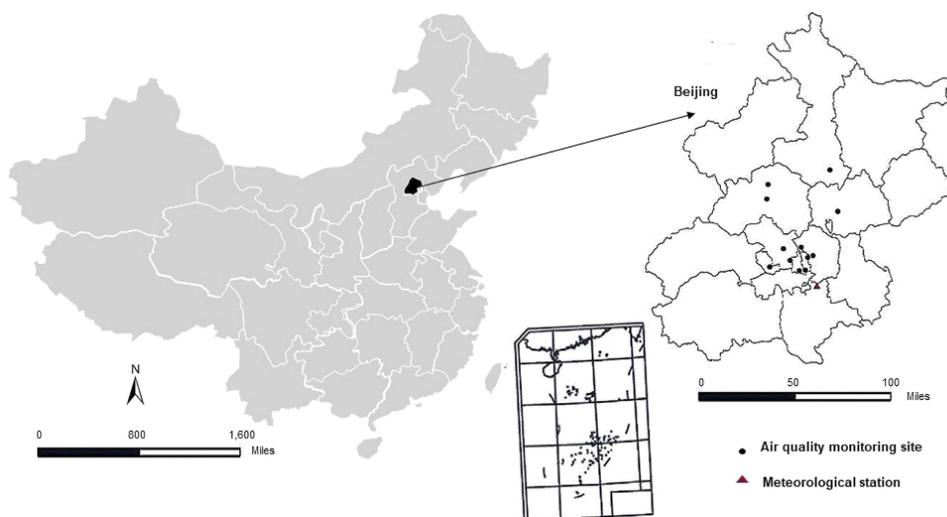


Figure 1 Location of 12 air quality monitoring sites, and one meteorological station in Beijing, China.

Peking Union Medical College Hospital. All data were fully anonymized before gathered for research purposes.

Meteorological data were obtained from Beijing Meteorological Bureau and included daily Tmean, relative humidity, wind speed, and air pressure. AT,¹⁷ an index to reflect the individual perception of combined exposure to temperature, humidity and wind speed is calculated as

$$AT = T_{\text{mean}} + 0.33 \times e - 0.70 \times WS - 4.00$$

Here, e denotes the water vapor pressure that is performed by the following formula:

$$e = RH \div 100 \times 6.105 \times \exp(17.27 \times T_{\text{mean}} \div 237.7 + T_{\text{mean}})$$

To adjust for the possible effects of air conditions on AECOPD hospitalizations, Air Quality Index (AQI) was obtained from the Beijing Environmental Monitoring Center. There was no missing data during the study period. Air pollutant data were measured at 12 monitoring stations spread across Beijing, shown in [Figure 1](#).

Statistical Analysis

Previous studies suggested that temperature usually has a delayed effect when it comes to respiratory conditions. In the study, a quasi-Poisson function combined with a distributed lag non-linear model (DLNM) was used to examine the temperature effect on AECOPD hospitalizations. This method allows us to simultaneously describe a non-linear exposure-response association and delayed or harvesting effects.^{18,19}

We controlled for the long-term trend and seasonality of daily number of hospitalizations using a natural cubic spline with 7 degrees of freedom (df) per year for time, relative humidity, wind speed, air pressure and AQI using a natural cubic spline with 3 df. To control any confounding weekly pattern, the day of the week was also included as a variable. To analyze the temperature-AECOPD hospitalization relationship, we used a natural cubic spline with 4 df, respectively, for temperature dimension and lag dimension. We placed knots at equally spaced percentiles of temperature distribution and at equally spaced log-values of lag.²⁰ A maximum lag of 30 was used to completely capture the overall temperature effect and adjust for a possible harvesting effect.²¹

Optimum temperature was used as the reference value to calculate the health risk of high and low temperature. To estimate health effects the extreme and moderate high temperature, we, respectively, computed the RR of AECOPD

hospitalizations at the 99th and 90th percentiles of temperature in comparison with 75th percentile of temperature; for the extreme and moderate low-temperature effect estimates, we, respectively, computed the RR of AECOPD hospitalizations at the 1st and 10th percentiles of temperature in comparison with 25th percentile of temperature, which was motivated by previous studies.^{22,23} Furthermore, to produce an easily interpretable effect estimates with previous studies, we further quantified the effect estimates of low and high temperature by per an absolute change (1°C) of abovementioned temperature range, for example, 1°C increase from 90th percentile of temperature to 99th percentile of temperature for the extreme temperature effect. This method of calculating temperature effects had been applied in the previous study.²³ We also examined and plotted cumulative relative risks of temperature at lag 0, lag 0–3, 0–7, 0–14 and 0–30 days to describe the acute, moderate acute, moderate delayed, delayed, and long-lasting level effects, separately.

In addition, to assess which temperature index is a better predictor for the influence of temperature on health, we compared the effect estimates of low and high temperature on hospitalizations by using Tmean and AT, and we also compared the corresponding Akaike's Information Criterion for quasi-Poisson (Q-AIC) for these two indexes, separately. And to identify the vulnerable subpopulations, we also conducted subgroup analyses that were stratified by gender (male vs. female) and age (<65 years old vs. ≥65 years old). The Z-test was applied to test the statistical significance of the differences between effect estimates by age and gender.²⁴

All analyses and modeling were conducted using the R software (version 3.4.3), with its “dlm” package. Statistical significance was set at p value <0.05.¹⁸

Results

Data Description

Summary of daily AECOPD hospitalizations and Meteorological Data are shown in [Table 1](#). A total of 143, 318 AECOPD hospitalizations were collected during the study period, with daily hospitalizations ranging from 17 to 226. The average Tmean and AT were 12.88°C and 5.85°C, respectively. The means and standard deviations (SD) of AP, RH, WS, and AQI were 1016.56±10.17 hPa, 53.43±19.86%, 9.29±4.75 m/s, and 123.65±75.17, respectively. The composition of daily hospitalizations differed by sex-and age-subgroup: Two-thirds of the patients were

Table 1 Description of Daily AECOPD Hospitalizations and Meteorological Data in Beijing, China, 2013–2016

Variables	Minimum	P25	Median	P75	Maximum	Mean±SD
Daily meteorological factors						
Mean temperature(°C)	−16	2	14	23	32	12.88±11.17
Apparent temperature(°C)	−38.07	−7	5.97	19.12	32.69	5.85±14.68
Air pressure (hPa)	994	1008	1016	1025	1044	1016.56±10.17
Humidity (%)	8	38	53	69	97	53.43±19.86
Wind speed (m/s)	3	6	8	11	34	9.29±4.75
AQI	23	68	104	159	485	123.65±75.17
AECOPD hospitalization.						
Total	17	66	98	125	226	98.10±39.42
Male	12	43	66	83	158	65.40±25.63
Female	2	21	31	42	110	32.69±15.95
People aged<65 years	0	10	17	23	47	17.07±8.22
People aged≥65 years	13	55	81	103	189	81.03±32.68

Abbreviations: P25, the 25th percentile; P75, the 75th percentile; SD, standard deviation.

male and 82.60% were 65 and older. Table 2 shows the Spearman correlation between meteorological indices. Tmean and AT estimates were strongly correlated. Tmean was positively correlated with relative humidity, while negatively correlated with the other three weather variables.

Effect of Tmean and AT on Daily Hospitalizations

Figure 2 shows the lag structures of cold and hot effects on AECOPD hospitalizations. In general, the effects of extreme cold temperature moderate cold temperature peaked at 2 days after exposure and declined slightly with a duration of 30 days, while moderate cold temperature effects appeared acutely and lasted for 14 days. The hot effects on AECOPD hospitalizations appeared after 2 days' exposure to hot temperature and peaked after about 4–5 days following the exposure to hot temperature and then leveled off in the next 4 weeks. Notably, no apparent harvesting was found for cold and hot effects. Therefore, we present the accumulative hot and cold effects along 30 days.

Figures 3 and 4 show the relationship between Tmean and AT on AECOPD hospitalizations over lag 30 days in a reverse J-shaped pattern. The optimum temperature was 9.0°C and 14.7°C for Tmean and AT, respectively. When compared with Tmean, increase in AT had higher RRs for AECOPD hospitalizations, also Q-AIC showed a lower value.

Table 3 shows the cumulative effect of cold temperature on AECOPD hospitalization by gender and age over lag 0–30 days. When compared with moderate temperature (10th vs 25th), extreme temperature (1st vs 25th) had greater effects on AECOPD hospitalization. The increased cumulative effects of extreme temperature at Tmean and AT were 1.55 (95% CI: 1.21,2.00) and 2.08 (95% CI: 1.44,3.01) respectively, while those of the moderate temperature were 1.11 (95% CI: 0.99,1.24) and 1.07 (95% CI: 0.93,1.22) respectively. However, there was no significant association between high temperature and AECOPD hospitalization (Table 4). The changing trends of CRR from the temperature in subgroups were consistent with the total population. Besides, the effect of temperature indexed by

Table 2 Spearman Correlation Coefficients Between Meteorological Data in Beijing, China, 2013–2016

Meteorological Data	AQI	Mean Temperature	Apparent Temperature	Humidity	Wind Speed	Air Pressure
AQI	1.000					
Mean temperature	−0.062*	1.000				
Apparent temperature	0.072**	0.964**	1.000			
Humidity	0.433**	0.315**	0.484**	1.000		
Wind speed	−0.471**	−0.176**	−0.419**	−0.571**	1.000	
Air pressure	−0.049	−0.872**	−0.841**	−0.287**	0.159**	1.000

Notes: *P<0.05, **P<0.01.

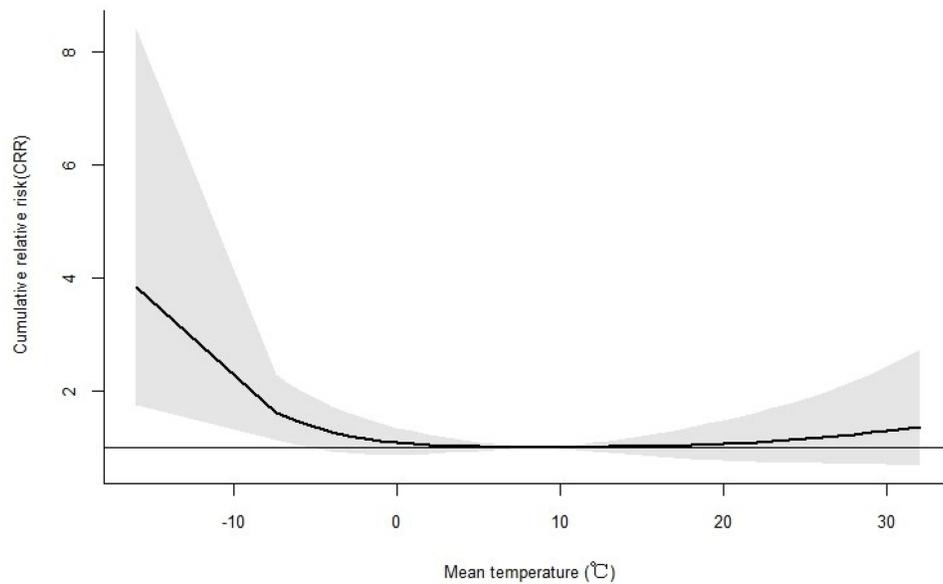


Figure 2 The cumulative effects of mean temperature on AECOPD hospitalizations over lag 30days in Beijing. The black lines are relative risks of AECOPD hospitalizations and grey regions are 95% confidence intervals.

AT on AECOPD event was greater compared to that of Tmean. The adverse effects of temperatures were more prominent for female and people aged <65 years, but the difference was statistically insignificant ($P > 0.05$).

The effect estimates of low and high temperature by per absolute change (1°C) of extreme and moderate temperature range were shown in [S-Table 1](#) and [S-Table 2](#) in Supplementary materials.

As indicated in [Figure 5](#), the association between temperature and AECOPD hospitalizations varied by lag periods. The RRs for cold and extreme cold temperatures increased with more lagged days. For cold effect, the CRR of extreme cold temperature on AECOPD hospitalizations gradually increased for up to weeks with statistical significance. Moderate low temperature also had a mild adverse impact on AECOPD hospitalizations. For hot effect, the CRR of hot temperature

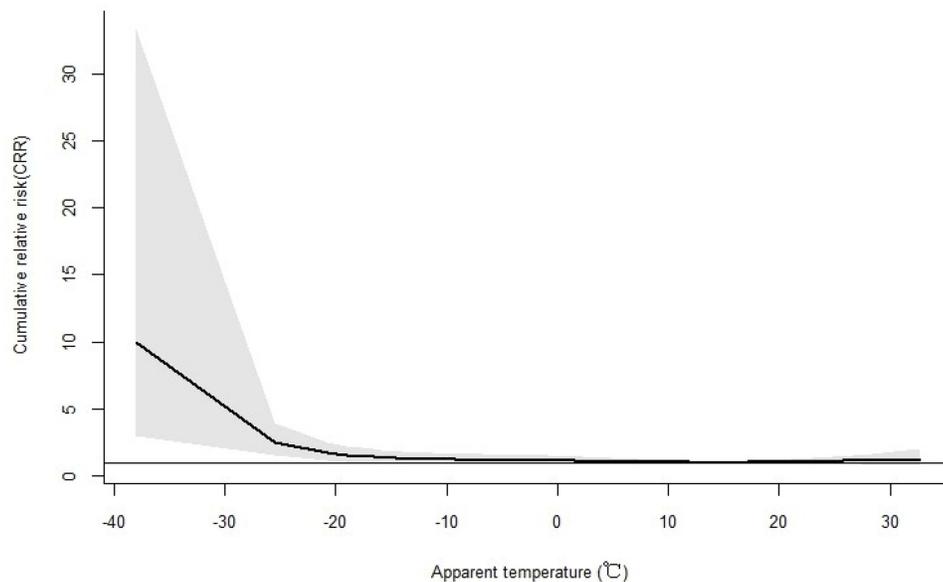


Figure 3 The cumulative effects of apparent temperature on AECOPD hospitalizations over lag 30days in Beijing. The black lines are relative risks of AECOPD hospitalizations and grey regions are 95% confidence intervals.

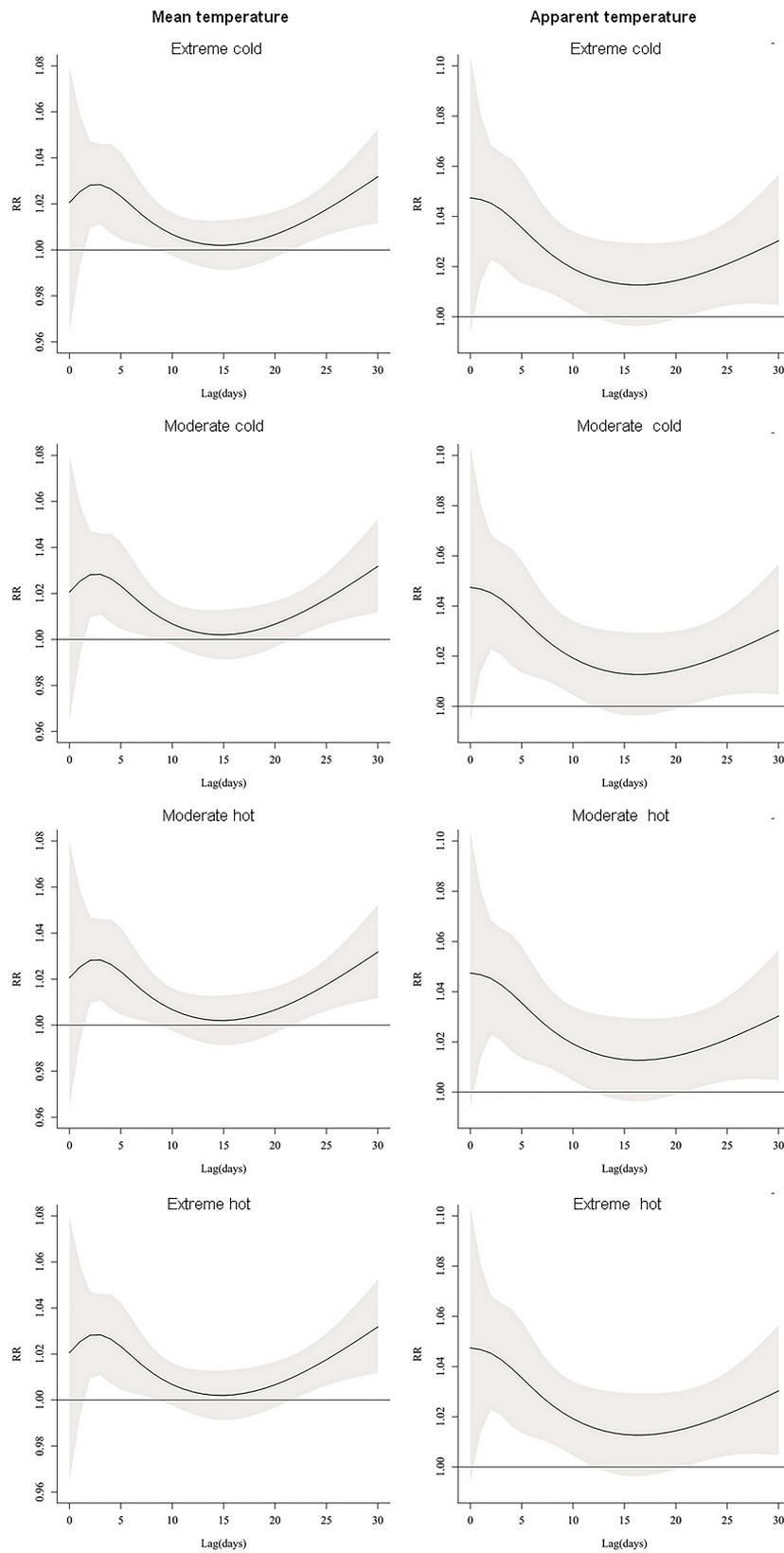


Figure 4 The effect of mean temperature (°C) and apparent temperature on AECOPD hospitalizations along days of lag. The black lines are relative risks and grey regions are 95% confidence intervals.

Notes: The definitions of extreme cold, moderate cold, moderate hot, and extreme hot temperatures are the same as those in the footnotes of [Tables 3 and 4](#).

Table 3 Relative Risks and Their 95% Confidence Intervals of Extreme and Moderate Cold Temperatures on AECOPD Hospitalizations Over Lag 30 Days by Sex and Age Groups

	Mean Temperature(°C)		Apparent Temperature(°C)	
	Extreme Cold (95% CI) ^a	Moderate Cold (95% CI) ^b	Extreme Cold (95% CI) ^c	Moderate Cold (95% CI) ^d
Total	1.55(1.21,2.00)*	1.11(0.99,1.24)	2.08(1.44,3.01)*	1.07(0.93,1.22)
Sex				
Male	1.47(1.12,1.93)*	1.08(0.96,1.23)	1.83(1.23,2.72)*	1.04(0.89,1.20)
Female	1.72(1.27,2.33)*	1.17(1.02,1.33)*	2.64(1.69,4.13)*	1.12(0.96,1.32)
Age				
<65 years	1.61(1.07,2.43)*	1.26(1.06,1.51)*	2.43(1.34,4.41)*	1.30(1.05,1.61)*
≥65years	1.53(1.19,1.97)*	1.08(0.97,1.21)	2.01(1.39,2.89)*	1.03(0.90,1.18)

Notes: *P<0.05, ^aThe first percentile of mean temperature (-7.4°C) relative to the 25th percentile of mean temperature (2.0°C). ^bThe 10th percentile of mean temperature (-2.0°C) relative to the 25th percentile of mean temperature (2.0°C). ^cThe first percentile of apparent temperature (-25.5°C) relative to the 25th percentile of apparent temperature (-7.0°C). ^dThe 10th percentile of apparent temperature (-12.8°C) relative to the 25th percentile of apparent temperature (-7.0°C).

Table 4 Relative Risks and Their 95% Confidence Intervals of Extreme and Moderate Hot Temperatures on AECOPD Hospitalizations Over Lag 30 Days by Sex and Age Groups

	Mean Temperature(°C)		Apparent Temperature(°C)	
	Extreme Hot (95% CI) ^a	Moderate Hot (95% CI) ^b	Extreme Hot (95% CI) ^c	Moderate Hot (95% CI) ^d
Total	1.17(0.88,1.54)	1.09(0.93,1.26)	1.17(0.85,1.62)	1.07(0.92,1.24)
Sex				
Male	1.19(0.88,1.60)	1.10(0.93,1.29)	1.16(0.82,1.62)	1.06(0.90,1.24)
Female	1.13(0.80,1.58)	1.06(0.88,1.28)	1.22(0.81,1.82)	1.09(0.90,1.31)
Age				
<65years	1.05(0.69,1.60)	1.03(0.82,1.30)	1.04(0.64,1.67)	1.01(0.81,1.27)
≥65years	1.20(0.90,1.58)	1.10(0.94,1.28)	1.21(0.87,1.67)	1.08(0.93,1.26)

Notes: ^aThe 90th percentile of mean temperature (27.0°C) relative to the 75th percentile of mean temperature (23.0°C). ^bThe 99th percentile of mean temperature (30.0°C) relative to the 75th percentile of mean temperature (23.0°C). ^cThe 90th percentile of apparent temperature (24.8°C) relative to the 75th percentile of apparent temperature (19.1°C). ^dThe 99th percentile of apparent temperature (30.4°C) relative to the 75th percentile of apparent temperature (19.1°C).

on AECOPD hospitalizations gradually increased with the lag days. However, the effects were statistically insignificant ($P > 0.05$).

Discussion

This large-scale population-based study showed that short-term exposure to low temperature increased the risk of AECOPD hospitalizations, while high temperature had a limited effect. We also showed that the adverse temperature effects are rather delayed, lasting up to a few weeks post-exposure. The females and patients younger than 65 years old were found to be more vulnerable to low temperature.

Our study found that low temperature, rather than high temperature, had a significant and positive correlation with AECOPD hospitalizations in Beijing. This result is consistent with previously reported studies conducted in regions with different climatic conditions. For example,

the Korean COPD subgroup study based on big data analysis has also concluded that the lowest temperature was associated with acute exacerbations.²⁵ A previous nationwide study in Taiwan reported that the risk of COPD exacerbation rate increased by over 0.8% for every 1°C rise in air temperature.⁸ Another cohort study from 1995 to 2009 in London estimated that exposure to lower temperature was associated with more severe COPD exacerbations.²⁶ In a recent study in HongKong during 2004–2011 reported that COPD hospitalization was more sensitive to cool temperatures among adults over 60.¹⁰ However, other studies have demonstrated an increase in hospitalization due to exacerbations on days with high mean temperature.¹² Although the RR curve tends to increase in hot temperature in our study, there is no statistical significance. Similarly, a study in the UK found no relation between short-term heat and total emergency room

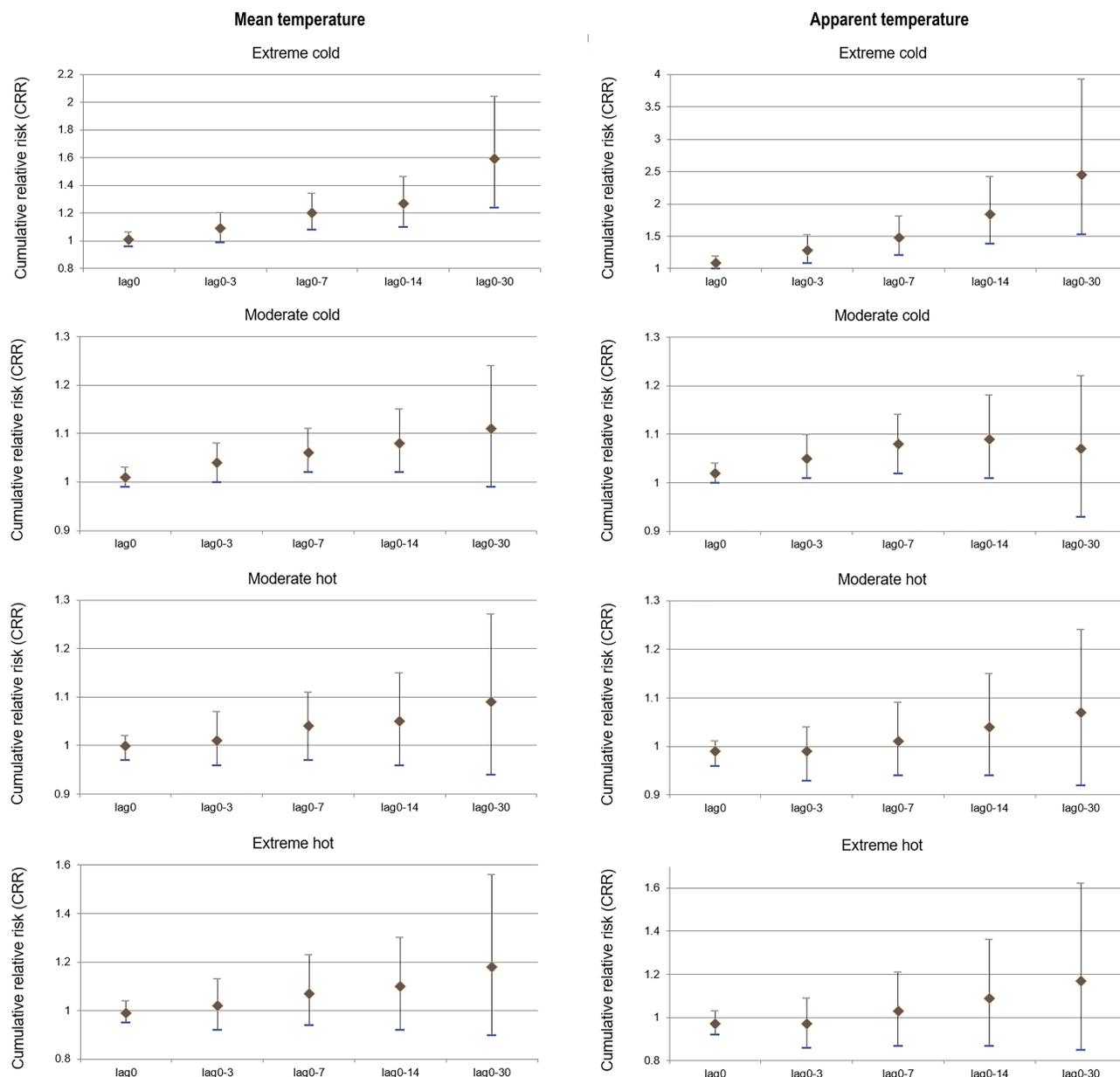


Figure 5 The cumulative relative risk and their 95% confidence intervals of cold and hot effects on AECOPD hospitalizations along different lag days in Beijing, China, 2013–2016.

Notes: The definitions of extreme cold, moderate cold, moderate hot, and extreme hot temperatures are the same as those in the footnotes of Tables 3 and 4.

visits.²⁷ We speculated that the hot temperature effect may be modified by different climates, air pollution, population sizes, and housing types. Besides, individuals in our study were vulnerable to the effects of cold temperature than hot temperature exposure may be explained by brief excursions in cold outdoor environments and gain more access to air condition in hot weather.

Several mechanisms have been proposed why cold weather is linked to increases in pulmonary diseases. Firstly,

cold temperatures were found to decrease lung function. A study conducted in East London showed FEV1 was lower in cold weeks compared to the warm ones during a 1-year epoch.⁹ Secondly, bronchoconstriction and inflammation were more robust as temperature decreases.²⁸ Thirdly, cold weather may induce mucus hypersecretion in the airway, which may induce AECOPD in the setting of cold exposure.²⁹

Previous studies showed high temperature had a short lag effect on pulmonary diseases while that of low

temperature tends to last longer.^{30–32} However, no apparent harvesting effects of temperature on AECOPD hospitalizations were observed in Beijing, China. Lin et al found that the greatest number of total emergency room visits was 0–14 days after elevated temperatures.³⁰ Baccini et al found that harvesting effect was more pronounced in the North-continental cities than in the Mediterranean cities.³³ Different regions, climatic conditions and socio-economic characteristics may have blunted the harvesting effect. Thus, our results suggest more attention to be paid on the lasting effect of extreme temperature to prevent AECOPD in Beijing.

The effects of temperature indexed by AT were greater than that of Tmean on AECOPD hospitalizations. Compared with Tmean, AT was shown to be a better predictor for the health effect assessment of temperature in Beijing. The potential explanation for this is that the perceived-temperature may be different from the actual temperature because of factors such as wind-chill or humidity. The low temperature of AT is actually colder than low temperature of Tmean. Kunst et al also suggest that AT is a better measure of human response to wind-chill related stress in cold season than simple ambient temperature or other thermal indices.³⁴ In hot weather, when humidity is high and wind speed is low, the actual apparent temperature of the environment is higher because the body cools itself at a slower rate as the environment makes it harder for the sweat to evaporate, thus greater effects on AECOPD.

Contrary to the previous studies,^{8,13,35} we found that patients under the age of 65 were more susceptible to cold temperature for AECOPD hospitalizations. In theory, the elderly are more sensitive to extreme temperature due to thermoregulation impairment, reduced respiratory function, weaken immune defenses and higher prevalence of comorbidities.³⁶ This inconsistency between theoretical results and our results may be explained by the fact that younger patients are more likely to go outdoors, which increases their exposure to cold temperature. Consistent with previously reported study,³⁵ we found that the impact of cold temperature was greater for females. Temperature-related susceptibility by gender may be due to women's special reaction to the cold exposure that they require shivering as a source of heat production earlier than men.³⁷

The study has several advantages. Firstly, the majority of research investigating the relationship between temperature and health have largely focused on numbers dying or odds of death. Contrarily, hospitalization is a more susceptible indicator to reflect the health fluctuations in

environmental factors, which contain higher counts for patients and confers a better statistical power. Secondly, distributed non-linear lag models, an advanced statistical approach, account for the delayed and non-linear effects of air pollutants and temperature flexibly and provide estimates of the lag-specific risks and cumulative effect simultaneously. Thirdly, we used only the main diagnosis of hospitalizations in metropolitan Beijing, which can avoid admission bias and reduce misclassification of outcomes.

Nevertheless, our present study has some potential limitations. Firstly, we used the average concentrations measured at fixed monitoring stations rather than personal measures for air pollution and weather exposures, which may bias our results toward the null, underestimating the RRs.³⁸ Secondly, potential confounding factors at the individual level for AECOPD, including smoking, use of air conditioning, indoor activity and pollutant patterns, could not be fully accounted for due to lack of information. Thirdly, the possible misdiagnosis of AECOPD interpreting the findings should also be taken into account. Fourthly, we could not identify the re-admissions for patients with the same AECOPD from the available data. Besides, data are only from urban areas of Beijing, with high air pollution and high population density. Also, the study period was only 4 years. It ought to be cautious when generalizing the findings to other climates and other geographic areas. Further assessment aimed at the definition of prevention programs and warning systems should research the potential added effect of specific exposures and adaptation of the population, as well as heat waves and cold spells.

Conclusion

We observed significant nonlinear and delayed effects of cold temperature on AECOPD hospitalizations in this study. Compared with the mean temperature, the apparent temperature indicating how people actually feel is more closely associated with AECOPD. The susceptible groups were females and patients under 65 years. To reduce temperature-related AECOPD hospitalizations, health authority should take measures to protect the vulnerable group and focus more on the long-lasting effect.

Abbreviations

Tmean, daily mean temperature; AT, daily apparent temperature; Q-AIC, Akaike's Information Criterion for quasi-Poisson; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; DLNM, Distributed Lag Non-linear

Model; CRR, Cumulative Relative Risk; RR, Relative Risk; CI, Confidence interval; Total, Total hospitalizations.

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Disclosure

Yongqiang Zhang reports grants from Central Public-interest Scientific Institution, during the conduct of the study. The authors report no other conflicts of interest in this work.

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