Title page:

Type of manuscript: Original research

Title:

Different sensitivities to ambient temperature between first- and re-admission childhood asthma cases in Hong Kong – A time series study

Author list: Holly Ching Yu LAM[a], Shakoor Hajat[b], Emily Ying Yang CHAN[a], William Bernard GOGGINS III[a]

Affiliation: [a]Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR

[b] Department of Public Health, Environments and Society, London School of Hygiene & Tropical Medicine, University of London

Corresponding author for page proofs: Holly Ching Yu Lam

Address: Room 327B, JC School of Public Health and Primary Care, Prince of Wales Hospital, Shatin, Hong Kong SAR

Telephone: 852 2343 4730

E-mail: hollylam@cuhk.edu.hk

Post-publication corresponding author: William Bernard GOGGINS III, ScD

Address: Room 501, JC School of Public Health and Primary Care, Prince of Wales Hospital, Shatin, Hong Kong SAR

Telephone: 852 2252 8715

E-mail: wgoggins@cuhk.edu.hk

Running head: Sensitivity to temperature: 1st vs. re-admitted asthma

Conflicts of interest: None declared. This study received no funding support.

Acknowledgments: The authors would like to acknowledge the Hospital Authority of Hong Kong, Hong Kong Observatory and Environmental Protection Department in Hong Kong for providing the data for this study.

Funding: This study is not supported by funding.

Main Text

Abstract

Objectives

Asthma can be triggered by various factors due to different etiologies. Environmental factors remain a common trigger of asthma, especially amongst children, and such ambient exposures can be harder to avoid compared to behavioral triggers. As such, the contribution of environmental factors may be enhanced when considering repeat asthma cases compared to initial presentation. To test this hypothesis, we assessed associations between ambient temperature and hospital admissions for asthma in Hong Kong and capitalized on the regions linked system of records to stratify risk between first and repeat asthma hospitalizations.

Methods

The daily number of asthma hospitalizations among children aged 0-5 years in Hong Kong during 2007-2011 was regressed on daily mean temperature using distributed lagged nonlinear models, with adjustment for seasonal patterns, day-of-week effects, and other meteorological factors and air-pollutants. Analyses were stratified by summer/winter and by type of admission (first admission and repeated admission).

Results

About 66% of 12284 asthma hospitalizations were first admissions. Repeat admissions demonstrated higher sensitivity to high temperature in the summer. During this period, high temperatures were associated with increased risk of repeat admission but not with first admissions: RR (95% CI) comparing 31°C vs. 29°C across lags 0-15 days was 3.40 (1.26, 9.18) and 0.74 (0.31, 1.77) for repeat and first admissions respectively. In the cold season, all admissions increased with falls in temperature, with slightly stronger associations apparent for repeat admissions compared to first admission: 1.20 (1.00, 1.44) vs. 1.10 (0.96, 1.26) respectively comparing risk at 15°C vs. 12°C across lags 0-5 days.

Conclusions

To our knowledge, this is the first study to show stronger associations between ambient temperature and repeat asthma admissions compared to first admissions. The higher sensitivity among those experiencing repeat admissions may allow for more personalized disease management. Given differences in effect sizes by admission type, future studies of ambient exposures on asthma should consider analyzing the two groups separately.

Keywords: asthma, first-admission, re-admissions, temperature, ambient, children, time-series

Introduction

Asthma is a chronic respiratory condition characterized by breathing difficulties and wheezing. The fundamental causes of asthma remain largely unclear but several risk factors that trigger asthma attacks have been identified. Indoor-/outdoor- and food allergens, tobacco smoke, chemical irritants, cold air, extreme emotions, physical activities and medications can trigger asthma (1,2). Environmental factors are one of the risk factor groups that are being increasingly studied. Previous research has implicated air-pollutants and allergens as triggers of asthma (3–5), but much attention has now switched to the impact of ambient temperature on asthma morbidity (6–22), reflecting rising awareness of the dangers of climate change and this year's record-breaking temperatures across much of the globe.

However, previous studies - assessing either hospital admissions(9,11,13–15,18,22), emergency department visits (8,10,14,17,19,21) or clinic consultations (6,12,16,20) - made no differentiation between initial presentations for asthma and those that were repeat events. Among the large variety of factors that trigger asthma attacks, some are easier to avoid than others once they have been identified. For instance, although food allergen-related asthma can be fatal, most people will learn to avoid the particular food substances once they are identified(2). By contrast, environmental exposures such as ambient temperature are harder to avoid completely. Thus, asthma recurrence rates due to temperature extremes may be higher than those associated with food, medication or pets. Repeat cases, who possibly may be associated with more severe forms of asthma, may also be more vulnerable to selected risk factors, including environmental exposures. Under this hypothesis, first admission cases would include a higher proportion of asthma cases that are induced by risk factors other than ambient temperature and thus may be less sensitive to temperature, whilst recurrent cases may contain a higher proportion of temperature-induced cases and therefore more temperature-sensitive. As such, the contribution of environmental factors may be enhanced when considering repeat asthma cases compared to initial presentation.

A previous study assessing air-pollution exposure on admissions for all respiratory diseases found stronger sensitivity among re-admission cases (23), but another found no effect modification of the association of temperature with respiratory admissions in Thailand (24). To the authors' knowledge, however, no previous study has tested this hypothesis on temperature exposure and admissions specifically for asthma. By utilizing the linked system of hospital records in Hong Kong, the objective of this study was to characterize the relationship between asthma admissions and temperature among children aged 0-5 years and to determine whether effects vary between initial admissions and readmissions. We hypothesize that temperature effects are stronger amongst readmitted cases. The results of this study can inform appropriate categorization of admissions in future epidemiological studies assessing short-term associations between asthma and temperature, and possibly between other health outcomes and ambient exposures.

Methods

Data and subjects

Admission records of all public hospitals in Hong Kong between 2002 and 2011 were obtained from the Hospital Authority of Hong Kong. Children aged 0-5 years old with asthma as the principle diagnosis at discharge were included in the study (International classification of diseases 9: 493.xx). Asthma admission records between 2007 and 2011 were aggregated into time-series of daily counts and subdivided into first- and re-admission cases whichwere then used to model temperature-asthma associations. Asthma admission histories were dated back to 2002 to ensure that all previous asthma admissions among children aged 0-5 years could be identified. Daily mean temperature (°C), daily mean relative humidity (%), daily mean wind speed (km/h), daily total solar radiation (J/m^2) and daily rainfall (mm) records for the study period were obtained from the website of the Hong Kong Observatory. Daily mean concentrations of air-pollutants including respirable particulates (PM_{10} in $\mu g/m^3$), Sulfur dioxide (SO_2 in $\mu g/m^3$), nitrogen dioxide (NO_2 in $\mu g/m^3$) and ozone (O_3 in $\mu g/m^3$) collected from 10 monitoring stations were obtained from the Environmental Department website and each pollutant averaged.

Statistical analysis

Poisson Generalized Additive models (GAMs) (25) and Distributed Lagged Nonlinear models (DLNMs) (26) were used in this study. Generalized Additive models were used to adjust for trends and seasonality using flexible splines and DLNM were adopted to account for the potential non-linear associations with exposure and lagged effects. To characterize potential differences in effect estimates at different times of the year (27), analyses were stratified by season, defining the hot season from May to October and the cold season from November to April. The choice of meteorological parameters and air-pollutants assessed in this study were adopted from the results of a previous asthma study in Hong Kong (22). In the hot season, the daily number of admissions were regressed over daily levels of mean temperature, mean relative humidity, and O_3 simultaneously, whilst mean temperature and mean relative humidity were included in the cold season analysis. Same day rainfall, daily number of influenza cases, long term trends, seasonal patterns, day-of-week and public holidays were adjusted for in models in both seasons (22).

Temperature, relative humidity, ozone and influenza counts were modelled using the crossbasis() function in the dlnm() package in R(28). The maximum lags used for this study, 30 days for temperature and relative humidity and 15 days for ozone, were adopted from the previous asthma study in Hong Kong (22). The degrees of freedom (df) were chosen based on minimizing the Generalized Cross Validation (GCV) Score in the mgcv() package. This score find the appropriate balance between model fit and computation cost. The df used for the lag parameter in dlnm() was 3 and the df used for temperature, relative humidity, ozone and influenza counts were 3, 3, 2 and 2 respectively. Rainfall, long term trend and seasonal patterns were modelled using the smooth function s() in mgcv() package(25) with maximum df =2, 6 and 4 respectively. The choice of df used for the smooth functions were again based on the previous study (22). Day-of-week and holiday effects were adjusted for using indicator variables.

Partial autocorrelation functions and residual plots were generated for model assessment. Different values for maximum df, ranging from 4 to 14, were applied for long term trend as sensitivity analysis. The same analyses were performed for first admission and re-admissions separately. Cumulative relative risks (RRs) at extreme temperatures within each season (the 1^{st} or the 99^{th} percentile) were estimated. The ratio of the relative risk (RRR) was calculated to compare RRs between admission types(29).

Results

Descriptive statistics

There were a total of 12284/6331 cases during the study period 2002-2011/2007-2011, respectively. Among these, 8113/4146 (66.05%/65.49%) were first-admission cases. Descriptive statistics of the asthma admissions and temperature during the study period 2007-2011 are shown in Table 1 and Table 2. Correlations between exposure variables were at low to medium level (coefficients ranged from 0.01 to 0.51) as presented in Table 3.

Table 1 Descriptive summary of admissions and temperature during 2007-2011, Hong Kong SAR

	All	**Hot season (May-October)**	**Cold season (November-April)**
	N (%)	Median of the daily no. of cases (Interquartile)	Median of the daily no. of cases (Interquartile)
First-admissions	4146 (65.49)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)
Re-admissions	2185 (34.51)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)
Total number of cases	6331 (100)		

Table 2 Statistics of daily mean temperature during 2007-2011, Hong Kong SAR

Daily mean Temperature (°C)	**Minimum**	**25^{th} percentile**	**Median**	**Mean**	**75^{th} percentile**	**Maximum**
Hot season (May-October)	18.70	26.00	27.85	27.54	29.20	31.20
Cold season (November-April)	8.80	16.70	19.25	19.06	21.70	27.20

Table 3 Correlation table for daily exposure variables by season, 2007-2011, Hong Kong SAR

	Mean temperature	**Mean relative humidity**	**Mean ozone concentration**	**Rainfall**
Hot season (n=920)				

Mean temperature	1	-0.19**	-0.39**	-0.20**
Mean relative humidity		1	-0.47**	0.51**
Mean ozone concentration			1	-0.21**
Rainfall				1
Cold season (n=906)				
Mean temperature	1	0.32**	0.13**	0.03
Mean relative humidity		1	-0.37**	0.20**
Mean ozone concentration			1	-0.01
Rainfall				1
****p< 0.01 (2-tailed)**				

Regression models

Hot season

High temperature did not show obvious associations with first asthma admissions risk but was strongly associated with increasing asthma re-admissions. The association was most apparent for lags 0-15 days (Figure 1). The cumulative relative risks (RR) (95% confidence interval) at 31°C (the nearest integer degree to the 99^{th} percentile vs. 29°C, the threshold) at lagged 0-15 days was 3.40 (1.26, 9.18) (Figure 2). The RRR (95% confidence interval) comparing risks of re-admissions to first admissions at high temperature was 4.59 (1.23, 17.21) (Table 4).

Figure 1

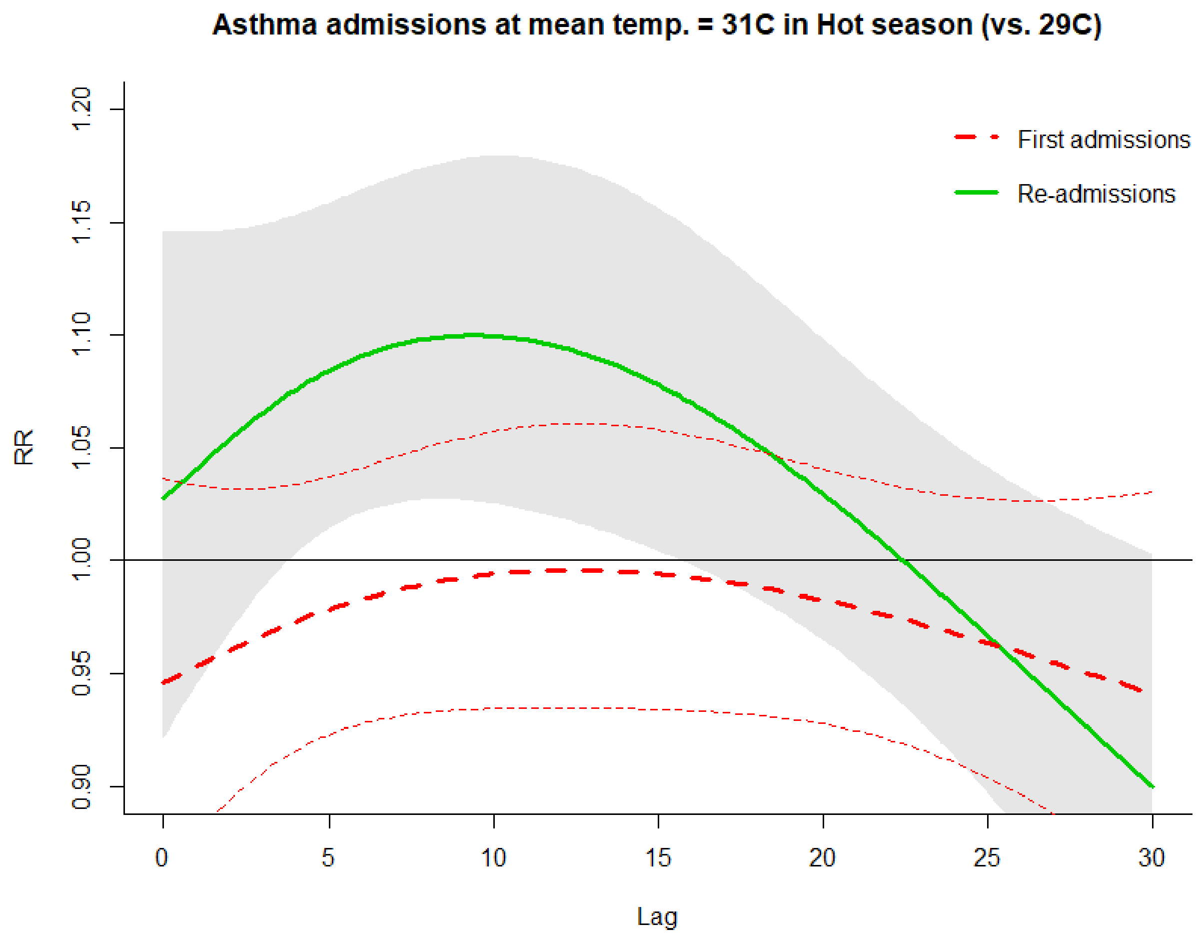
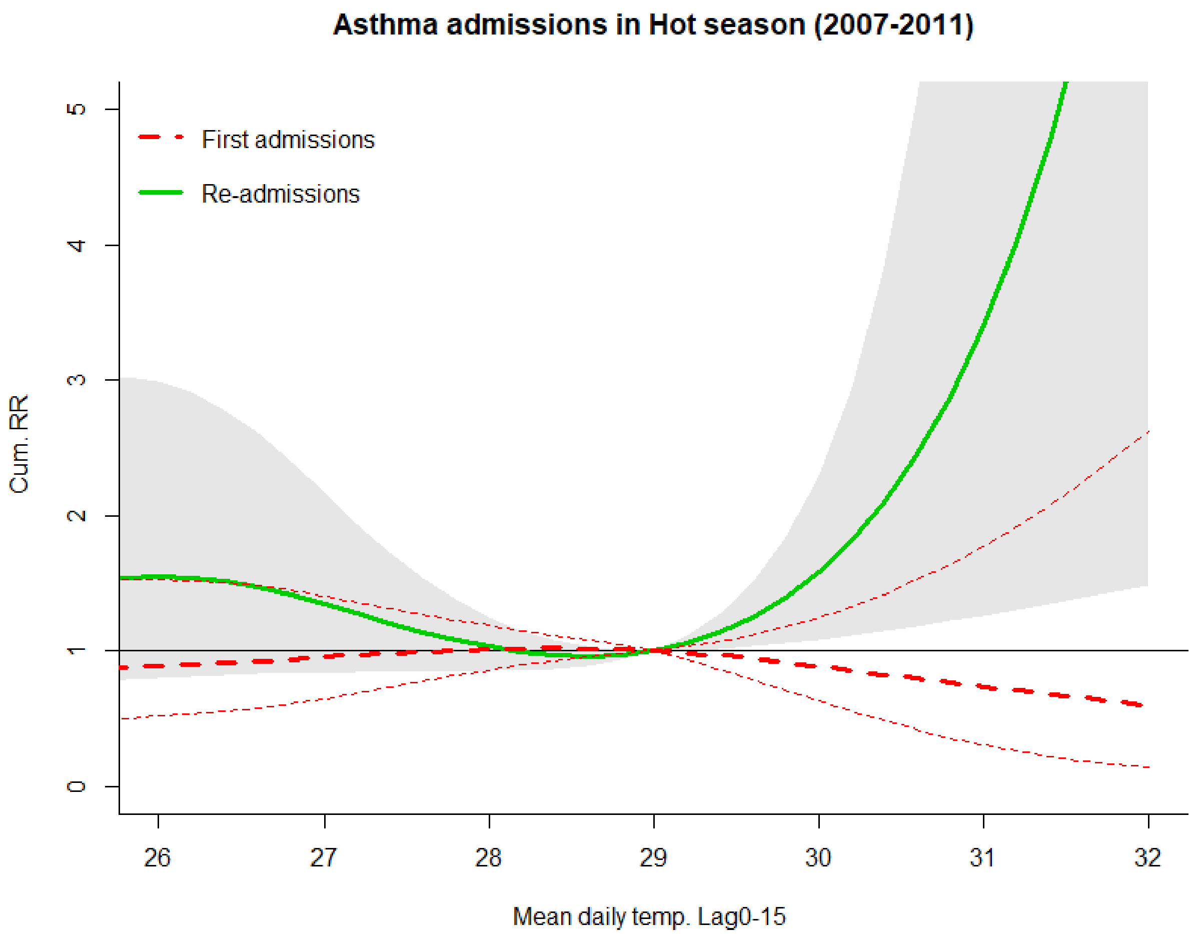

Asthma admissions at mean temp. = 31C in Hot season (vs. 29C)
First admissions
Re-admissions
RR
0.90
0.95
1.00
1.05
1.10
1.15
1.20
0
5
10
15
20
25
30
Lag

Figure 2



Asthma admissions in Hot season (2007-2011)
First admissions
Re-admissions
Cum. RR
0
1
2
3
4
5
26
27
28
29
30
31
32
Mean daily temp. Lag0-15

Table 4 Cumulative relative risk (RR) and relative risk ratio (RRR) for asthma admissions at extreme temperatures by season and admission type, 2007-2011, Hong Kong SAR

	Temperature	**RR[a] (95%CI[b]) Re-admissions**	**RR[a] (95%CI[b]) First admissions**	**RRR[c](95%CI[b]) Re-admissions vs. First admissions**
Hot season	31 vs 29°C (Lag 0-15)	3.40 (1.26, 9.18)	0.74 (0.31, 1.77)	4.59 (1.23, 17.21)
Cold season	10 vs 15°C (Lag 0-5)	1.43 (1.00, 2.04)	1.24 (0.94 1.62)	1.15 (0.74, 1.81)
	21 vs 15°C (Lag 0-5)	0.88 (0.61, 1.26)	1.27 (1.06, 1.53)	0.69 (0.46, 1.04)

a: RR – relative risk

b: CI – confidence interval

c: RRR – relative risk ratio

Cold season

In the cold season, a low temperature of 10°C - the nearest integer degree to the 1st percentile in the season, showed a raised risk with both first admissions and re-admissions, with the strongest effect in the first 5 days (Figure 3). The RRs at 10°C (vs. 15°C, the minimum overall morbidity temperature in the season) were 1.24 (0.94, 1.62) and 1.43 (1.00, 2.04) for first and re-admissions respectively (Figure 4). The risk of re-admissions was higher than that of first-admissions but the difference was not statistically significant. The RRR comparing risk of re-admission to first admission at low temperature was 1.15 (0.74, 1.81) (Table 4). The risk of first admission also increased during higher temperatures, 21-22°C, in the cold season with a lagged effect of 5 days (RR 1.27 (1.06, 1.53); 21 vs 15°C) (Figure 5). No association was found between re-admissions and warm temperature. Results from sensitivity analyses showed consistent patterns in associations with temperature between the two groups in both seasons.

Figure 3

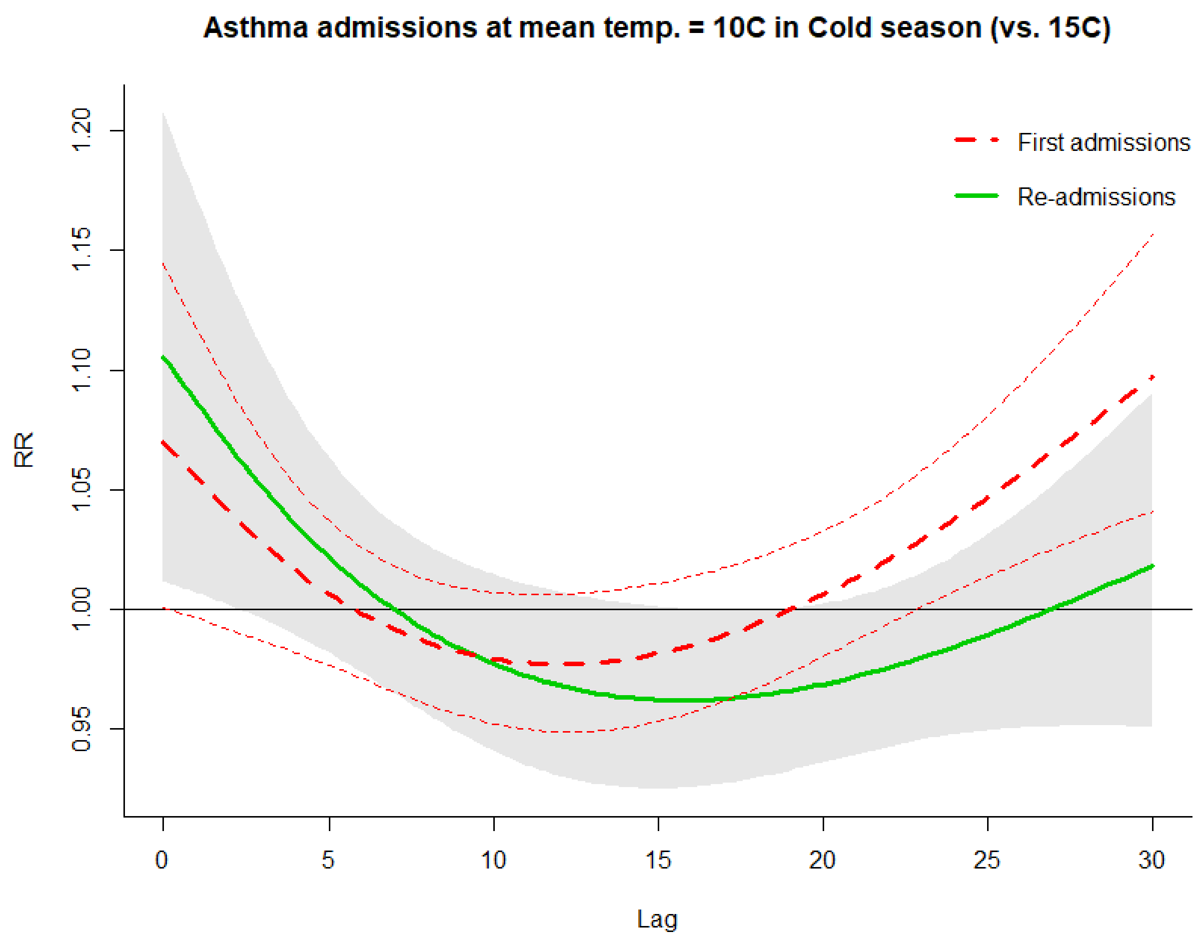
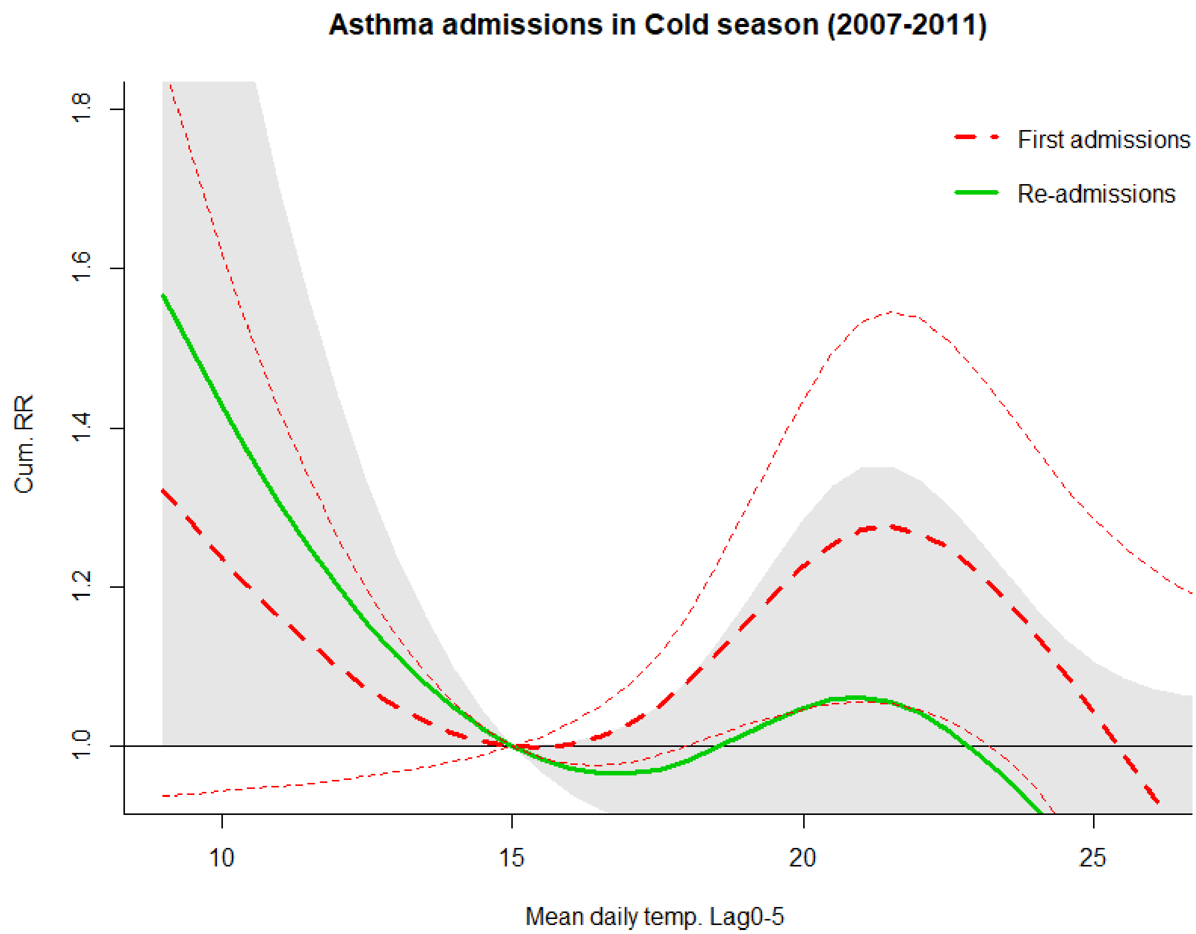
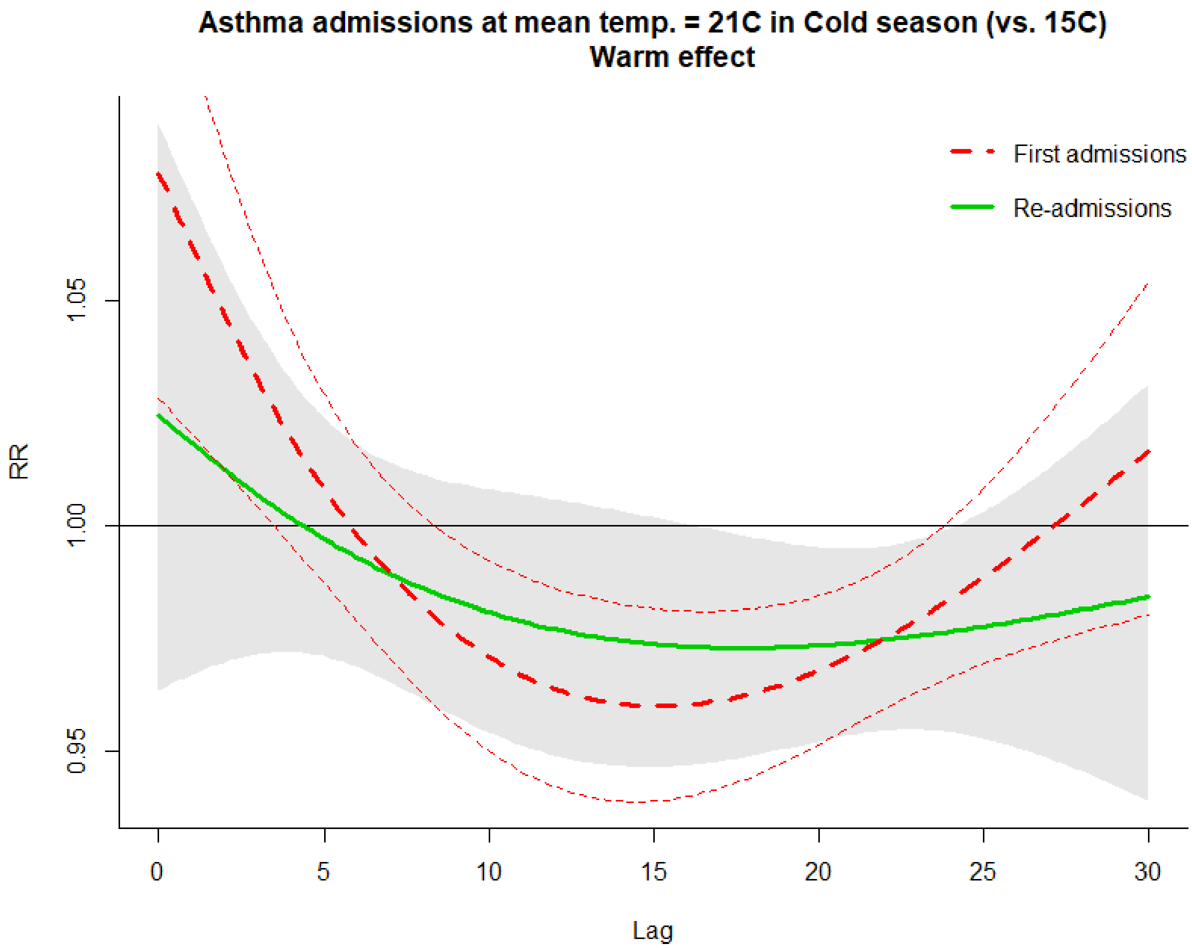

Asthma admissions at mean temp. = 10C in Cold season (vs. 15C)
First admissions
Re-admissions
RR
1.20
1.15
1.10
1.05
1.00
0.95
0
5
10
15
20
25
30
Lag

Figure 4



Asthma admissions in Cold season (2007-2011)
First admissions
Re-admissions
Cum. RR
1.0
1.2
1.4
1.6
1.8
10
15
20
25
Mean daily temp. Lag0-5

Figure 5



Discussion

This study showed that one-third of asthma admissions were readmission cases and these cases were more sensitive to temperature than first admission cases. In the hot season, re-admissions had a much higher sensitivity to high temperature than first admission cases. In the cold season, re-admissions were also more sensitive to low temperature, although the difference did not reach statistical significance. Conversely, the number of first admissions increased significantly during high temperatures during the cold season whilst re-admissions showed no association. To the best of our knowledge, no previous studies have compared the association between temperature and first and repeated asthma admissions, although a study in Canada looking at ambient air-pollution and respiratory admissions reported similar patterns to us(23). The Canadian study found a stronger association between coarse particulates and repeated respiratory admissions than first admission among the elderly(23). Previous studies evaluating short-term associations between ambient temperature and asthma morbidity, including hospital admissions (9,11,13–15,18,22), clinic visits (6,12,16,20) and emergency department visits (8,10,14,17,19,21), did not differentiate first and repeated asthma cases, although this has been done in the case of respiratory diseases in general.(24)

Several hypothesis may be considered for the different sensitivities to temperature between admission types. The nature of the disease, i.e. whether the asthma attack was triggered by medications or respiratory infections, may make a difference. Asthma caused solely by specific allergens such as pets, particular food substance and medications may be more manageable once the allergen has been identified. Therefore, compared to re-admission cases, first-admission cases may contain a higher proportion of asthma attacks that are triggered by particular allergens that are less sensitive to temperature. Of note, the severity of disease and poor disease management may also contribute to the higher sensitivity to temperature among re-admissions. Many previous studies reported previous admissions(30,31), history of other allergic/ respiratory complications(32,33) and poor disease management (34,35) as associated risk factors for re-admissions among children.

Extreme temperatures trigger asthma in various ways, including directly triggering broncho-constrictions and airway spasm(36,37), and indirect triggering through airway inflammation process(38,39) (37), lowering lung function(37,40,41), increasing neutrophil count in blood(42–44) and changing the ambient level of allergens like pollens and molds(37,45,46). Higher levels of air-pollutants associated with high temperatures may also contribute to the increased risk of triggers(37). Patients with poor disease management such as having poor medication regimes or even loss to follow-up may be more sensitive to triggers and more likely to be admitted to emergency departments due to lack of medication. Patients with more severe asthma or associated complications may also be more sensitive to triggers due to a longer history of airways inflammation.

Our study results suggest that combining first- and re-admissions cases in time-series temperature-asthma studies may underestimate the effect of temperature on asthma admissions for those groups of temperature-sensitive cases. Health guidelines and relevant promotion against temperature-associated asthma recurrence for physicians, healthcare providers, caregivers and patients should consider modification of effects among cases for more accurate risk and threshold estimation. Future studies may consider stratifying analyses by admission type based on the findings of this study. Studies for forecasting the overall asthma admission rate may use overall admissions as the primary health outcome whilst studies that aim to evaluate the specific exposure-response relationship between asthma and temperature, as well as other ambient exposures, may obtain more accurate results by considering subgroup analysis by admission type.

This study has several limitations. We only have 10-years data for both first- and re-admission cases and therefore we could only perform the analyses among children. However, young children have a lower proportion of comorbidities and better asthma control due to better diseases management strategies such as stronger medication reinforcement and being forced to stay indoor during conditions of extreme environmental conditions by caregivers. Thus studying children minimizes the complicating effects of poor disease management or comorbidities and may better reflect asthma sensitivity to temperature. Another limitation is that we were unable to consider the number of times a patient has been re-admitted rather than simply grouping subjects into first- and repeat admissions. Large differences in the number of re-admissions may point to important factors that may modify temperature sensitivity, such as disease severity, disease management and etiology. However, subgroup analysis by the number of re-admissions was not possible in this study due to the limited number of daily cases. Etiology is also a potential effect modifier which should be considered if relevant data are available. In addition, we were unable to consider potential modification by the socioeconomic characteristics of patients even though socioeconomic status has been identified as an important risk factor for repeat asthma admissions(47). Furthermore, this study has not adjusted for pollen exposures and PM2.5 due to the unavailability of such data. Also, similar to other single exposure time-series studies we assumed the same exposure for the whole population. Finally, since there is no similar study for comparison, the degree to which the different sensitivities to temperature between first- and re-admissions can be generalized to other geographic locations and other age-groups is uncertain.

Conclusions

This study showed different sensitivities to high temperatures between first- and re-admission asthma cases among young children. Physicians, parents and caregivers of young children who have already been admitted to hospital for asthma should take special care to reduce their patient's exposure to very high or very low temperatures. Health promotion guidelines against temperature-associated asthma in recurrent cases should be emphasized. Further studies looking at populations in other geographic locations and age-groups and comparing the causes of asthma between first and re-admission cases are recommended. Future time-series studies aiming to evaluate temperature-asthma associations should also consider performing subgroup analyses by admission type for potential modification of effect sizes.

Reference

1. WHO. What triggers an asthma attack?. 2011 [cited 2017 Sep 11]. Available from: http://www.who.int/features/qa/46/en/

2. Caffarelli C, Garrubba M, Greco C, Mastrorilli C, Dascola CP. Asthma and Food Allergy in Children : is There a Connection or interaction ? Front Pediatr. 2016;4(April):1–7.

3. Weinmayr G, Romeo E, DeSario M, Weiland SK, Forastiere F. Short-Term Effects of PM10 and NO2 on Respiratory Health among Children with Asthma or Asthma-like Symptoms : A Systematic Review and Meta-Analysis. Environ Health Perspect. 2010;118:449–57.

4. Guarnieri M, Balmes JR, Francisco S. Outdoor air pollutaion and asthma. Lancet. 2014;383(9928):1581–92.

5. Lee JY, Lee SB, Bae GN. A review of the association between air pollutant exposure and allergic diseases in children. Atmos Pollut Res. 2014;5:616–29.

6. Guo Y, Jiang F, Peng L, Zhang J, Geng F, Xu J, et al. The association between cold spells and pediatric outpatient visits for asthma in Shanghai, China. PLoS One. 2012 Jan;7(7):e42232.

7. Li S, Baker PJ, Jalaludin BB, Guo Y, Marks GB, Denison LS, et al. Are children's asthmatic symptoms related to ambient temperature? A panel study in Australia. Environ Res. 2014 Aug ;133:239–45.

8. Mireku N, Wang Y, Ager J, Reddy RC, Baptist AP. Changes in weather and the effects on pediatric asthma exacerbations. Ann Allergy Asthma Immunol. 2009 Sep;103(3):220–4.

9. Son J-Y, Bell ML, Lee J-T. The impact of heat, cold, and heat waves on hospital admissions in eight cities in Korea. Int J Biometeorol. 2014 Nov;58(9):1893–903.

10. Xu Z, Huang C, Hu W, Turner LR, Su H, TongS. Extreme temperatures and emergency department admissions for childhood asthma in Brisbane, Australia. Occup Environ Med. 2013 Oct;70(10):730–5.

11. Zhang Y, Peng L, Kan H, Xu J, Chen R, Liu Y, et al. Effects of meteorological factors on daily hospital admissions for asthma in adults: a time-series analysis. PLoS One. 2014 Jan;9(7):e102475.

12. Wang Y-C, Lin Y-K. Temperature effects on outpatient visits of respiratory diseases, asthma, and chronic airway obstruction in Taiwan. Int J Biometeorol. 2015 Sep 16;59(7):815–25.

13. Delamater PL, Finley AO, Banerjee S. An analysis of asthma hospitalizations, air pollution, and weather conditions in Los Angeles County, California. Sci Total Environ. 2012 May 15;425:110–8.

14. Babin SM, Burkom HS, Holtry RS, Tabernero NR, Stokes LD, Davies-Cole JO, et al. Pediatric patient asthma-related emergency department visits and admissions in Washington, DC, from 2001-2004, and associations with air quality, socio-economic status and age group. Environ Health. 2007 Jan;6:9.

15. Lin S, Luo M, Walker RJ, Liu X, Hwang S, Chinery R, et al. Extreme High Temperatures and Hospital Admissions for Respiratory and Cardiovascular Diseases. Epidemiology.

2009;20(5):738–46.

16. Yamazaki S, Shima M, Yoda Y, Oka K, Kurosaka F, Shimizu S, et al. Association of ambient air pollution and meteorological factors with primary care visits at night due to asthma attack. Environ Health Prev Med. 2013 Sep ;18(5):401–6.

17. May L, Carim M, Yadav K. Adult asthma exacerbations and environmental triggers: a retrospective review of ED visits using an electronic medical record. Am J Emerg Med. 2011 Nov;29(9):1074–82.

18. Vaneckova P, Bambrick H. Cause-specific hospital admissions on hot days in Sydney, Australia. PLoS One. 2013 Jan;8(2):e55459.

19. Abe T, Tokuda Y, Ohde S, Ishimatsu S, Nakamura T, Birrer RB. The relationship of short-term air pollution and weather to ED visits for asthma in Japan. Am J Emerg Med. 2009 Feb;27(2):153–9.

20. Hajat S, Haines A. Associations of cold temperatures with GP consultations for respiratory and cardiovascular disease amongst the elderly in London. Int J Epidemiol. 2002;31:825–30.

21. Buckley JP, Richardson DB. Seasonal modification of the association between temperature and adult emergency department visits for asthma: a case-crossover study. Environ Health. 2012 Jan;11(1):55.

22. Lam HC-Y, Li AM, Chan EY-Y, Goggins WB. The short-term association between asthma hospitalisations, ambient temperature, other meteorological factors and air pollutants in

Hong Kong: a time-series study. Thorax. 2016 Jun 24;1–13.

23. Chen Y, Yang Q, Krewski D, Burnett RT, Shi Y, Mcgrail KM, et al. The Effect of Coarse Ambient Particulate Matter on First , Second , and Overall Hospital Admissions for Respiratory Disease Among the Elderly The Effect of Coarse Ambient Particulate Matter on First , Second , and Overall Hospital Admissions for Respirato. Ihalation Toxicol. 2005;17:649–55.

24. Pudpong N, Hajat S. High temperature effects on out-patient visits and hospital admissions in Chiang Mai, Thailand. Sci Total Environ. 2011;409(24):5260–7.

25. Simon N.W. Generalized Additive Models: An Introduction with R. Chapman & Hall; 2006.

26. Armstrong B. Models for the relationship between ambient temperature and daily mortality. Epidemiology. 2006 Nov;17(6):624–31.

27. Su Q, Liu H, Yuan X, Xiao Y, Zhang X, Sun R, et al. The interaction effects of temperature and humidity on emergency room visits for respiratory diseases in Beijing, China. Cell Biochem Biophys. 2014 Nov ;70(2):1377–84.

28. Gasparrini A. Distributed Lag Linear and Non-Linear Models in R : The Package dlnm. J Stat Softw. 2011;43(8):1–20.

29. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012 Apr [cited 2016 Apr 14];41(2):514–20.

30. Mitchell EA, Bland M, Thompson JMD. Risk factors for readmission to hospital for asthma in childhood. Thorax. 1994;49:33–6.

31. Buyantseva LV, Brooks J, Rossi M, Lehman E, Timothy J, Buyantseva LV, et al. Risk factors associated with 30-day asthma readmissions. J Asthma. 2016;53(7):684–90.

32. Visitsunthorn N, Lilitwat W, Jirapongsananuru kO, Vichyanond P. Original article Factors affecting readmission for acute asthmatic attacks in children. Asian Pacific J Allergy Immunol. 2013;31:138–41.

33. Rha Y. Risk factors of readmission for childhood asthma. J Allergy Clin Immunol. 2004;113(2):S274.

34. Chen E, Bloomberg GR, Jr EBF, Strunk RC. Predictors of Repeat Hospitalizations in Children With Asthma : The Role of Psychosocial and Socioenvironmental Factors. Heal Psychol. 2003;22(1):12–8.

35. Karon A. Bedside asthma medication delivery tied to lower ED readmissions. Pediatric News. 2016 Mar 1;

36. Hayes D, Collins PB, Khosravi M, Lin R-L, Lee L-Y. Bronchoconstriction Triggered by Breathing Hot Humid Air in Patients with Asthma. Am J Respir Crit Care Med. 2012 Jun;185(11):1190–6.

37. Xu Z, Crooks JL, Davies JM, Khan AF. The association between ambient temperature and childhood asthma : a systematic review. Int J Biometeorol. 2018;62:471–81.

38. Chan PKS, Mok HY, Lee TC, ChuI MT, Lam W, Sung JJY. Seasonal Influenza Activity in Hong Kong and its Association With Meteorological Variations. J Med Virol. 2009;81:1797–806.

39. Jaakkola K, Saukkoriipi A, Jokelainen J, Juvonen R, Kauppila J, Vainio O, et al. Decline in

temperature and humidity increases the occurrence of influenza in cold climate. Environ Heal. 2014 Jan;13(1):22.

40. Koskela HH, Pekkarinen H, Kononoff A. Effect of Whole-Body Exposure to Cold and Wind on Lung Function in Asthmatic Patients *. Chest J. 1994;105(6):1728–31.

41. Donaldson GC, Seemunga lT, Jeffries DJ, Wedzicha JA. Effect of temperature on lung function and symptoms in chronic obstructive pulmonary disease. Eur Respir J. 1999;13:844–9.

42. Sampson AP. The role of eosinophils and neutrophils in inflammation. Clin Exp Allergy. 2000;30:22–7.

43. LaVoy ECP, McFarlin BK, SimpsonRJ. Immune responses to exercising in a cold environment. Wilderness Environ Med. 2011 Dec;22(4):343–51.

44. Mahima, Ingle, A. M., Verma AK, Tiwari R, Karthik K, Chakraborty S, Dhama K. Immunomodulators in day to day life a review. Pakistan J Biol Sci. 2013;16(17):826–43.

45. Tang JW. The effect of environmental parameters on the survival of airborne infectious agents. J R Soc Interface. 2009;6:S737–46.

46. Forsberg B, Bråbäck L, Keune H, Kobernus M, Krayer von Krauss M, Yang A, et al. An expert assessment on climate change and health – with a European focus on lungs and allergies. Environ Heal. 2012;11(Suppl 1):S4.

47. Liu SY. Hospital Readmissions for Childhood Asthma : The Role of Individual and Neighborhood Factors. Public Health Rep. 2009;124(February):65–78.

Figure Legends

Figure 1 Plot showing how relative risk (RR) and the 95% confidence interval (indicated by shaped area/ fine dotted lines) of asthma admissions changed along lag by comparing 31 to 29°C in hot season (May-October), 2007-2011, Hong Kong SAR

Figure 2 Plot of cummulated relative risk and the 95% confidence interval (indicated by shaped area/ fine dotted lines) of asthma admissions against temperature in hot season (May-October), 2007-2011, Hong Kong SAR

Figure 3 Plot showing how relative risk (RR) and the 95% confidence interval (indicated by shaped area/ fine dotted lines) of asthma admissions changed along lag by comparing 12 to 15°C in cold season (November-April), 2007-2011, Hong Kong SAR

Figure 4 Plot of cummulated relative risk and the 95% confidence interval (indicated by shaped area/ fine dotted lines) of asthma admissions against temperature in cold season (November-April), 2007-2011, Hong Kong SAR

Figure 5 Plot showing how relative risk (RR) and the 95% confidence interval (indicated by shaped area/ fine dotted lines) of asthma admissions changed along lag by comparing 21 to 15°C in cold season (November-April), 2007-2011, Hong Kong SAR