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RESEARCH ARTICLE

Temperature drop and the risk of asthma: a systematic review and meta-analysis

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Abstract The relationship between asthma and temperature changes remains controversial. The aim of this study was to investigate the association between temperature changes and the risk of asthma. A total of 26 studies (combined total number of subjects $N > 26$ million), covering 13 countries and Costa Rica, were identified by using a series of keywords in different combinations and searching the papers in PubMed, EMBSEA, Web of Science, MEDLINE, AIM, LILACS, and WPRIM before February 2016. Most of the papers were published in English. Random-effects meta-analyses were performed to evaluate the effect of temperature drop on risk of asthma. Several secondary analyses were also calculated based on stratification for different age, season, latitude, and region on risk of asthma. The odds ratio (OR) estimate between temperature drop and asthma was 1.05 (95% CI 1.02, 1.08) in the meta-analysis. For children, the overall OR was 1.09 (95% CI 1.03, 1.15). Dose-effect analyses showed stronger associations in asthma risk for each 1°1 °C decrement in short-term temperature (OR 1.055, 95% CI 1.00, 1.11). Further stratifications showed that winter (OR 1.03, 95% CI 1.01, 105) and low latitude (OR 1.72, 95% CI 1.23, 2.41) have a statistically significant association with the increased risk of asthma. Exposure of people to short-term temperature drop (per 1 °C decrement) was significantly associated with the risk of lower respiratory tract infections (LRTI) with asthma (OR 1.02, 95% CI 1.00, 1.04). Results suggest an adverse effect of temperature drop on asthma risk, especially in children and low-latitude areas. It may be opportune to consider the preventive actions against temperature drop, including simple face masks, to decrease the risk of asthma.

Keywords Temperature drop · Asthma · Meta-analysis · Systematic review

Introduction

Asthma is one of the major chronic non-communicable diseases that affects human health and life quality, and involves pronounced constriction of airway muscles, lung inflammation, excessive mucus production, and respiratory distress (Wasilevich et al. 2012; Shang et al. 2017). Asthma can occur at any age and has a worldwide prevalence of 5~10% (Eder et al. 2006), with an estimated 235 million people currently suffering from asthma (WHO 2013). Although the etiology of asthma still has not been fully elucidated, some evidence suggests that environment risk factors may trigger asthma (Xu et al. 2013; Darçın, 2014).

The relationship between global climate changes and their effects on respiratory health have drawn significant and increasing public attention (Paynter et al. 2010). Among the numerous climate factors, one of the biggest concerns focused on the effects of temperature (Lian et al. 2015). Temperature

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drop have been linked to a number of adverse health endpoints, including morbidity and mortality of cardiovascular and respiratory diseases (Phung et al. 2016; Beard et al. 2012; WHO 2016). Studies have shown that ambient temperature can affect inflammation pathways, airway hyper-responsiveness, airway remodeling, and facilitate bacterial growth in water droplets and resulting in airway narrowing which are all potential temperature drop triggers of asthma (Buckley and Richardson, 2012; Handley and Webster, 1995; Kaminsky et al. 2000).

Although a series of epidemiological studies suggest that ambient temperature has an effect on asthma, distinct differences have been showed by different laboratories. For example, evidence shows that temperature drop may not be a risk factor for severe respiratory symptoms in children with asthma (Li et al. 2014), while to the contrary, another study demonstrates that the relative risk of hospital admissions for asthma was associated with a lower temperature level (Zhang et al. 2014).

In order to further explore how ambient temperature changes affect risk of asthma, we performed a systemic search to collect the previously published studies, and extracted and transformed the data for meta-analysis. A statistical model was employed for meta-analysis to evaluate the effects of temperature drops on risk of asthma. In addition, the association between the changes in different windows of exposure, involving age, season, latitude and region, and risk of asthma were also explored.

Material and methods

We retrieved the published literature available online, up to February 2016, that reported on the risk of asthma in relation to temperature changes. All useful data and information sources were from papers obtained by searching the PubMed, Embase, Web of Science, Scopus, African Index Medicus (AIM), Latin American and Caribbean Health Sciences Information System (LILACS), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR), and Western Pacific Region Index Medicus (WPRIM). The keywords used in searching for articles were “temperature drop,” “ambient temperature,” “temperature,” “cold,” “warm,” “asthma incidence,” and “asthma” in different combinations. We also manually searched the references from the primary studies for additional publications. Further publications included were also identified by examining review articles.

Study selection

Inclusion and exclusion criteria

We initially screened studies and abstracts that were related to the association between asthma and ambient temperature, especially in regard to temperature drop. If studies did not address the relationship between asthma and ambient temperature, studies were excluded. Then, we marked and further evaluated the remaining studies. The criteria for inclusion were as follows: (a) the study included temperature and asthma; (b) cohort studies and cross-sectional studies were considered; (c) assumptions of literature focus on risk factor of asthma; (d) the sample size for study was comprised of more than 50 cases; (e) the study provided odds ratios (ORs) or relative risks (RRs) for asthma incidence as well as the 95% confidence intervals (CI), or information that could be used to infer these results; and (f) repeated reports, incompleted data, case study, editorial, and conference proceeding were excluded. The selection process is described and shown in detail in Fig.1.

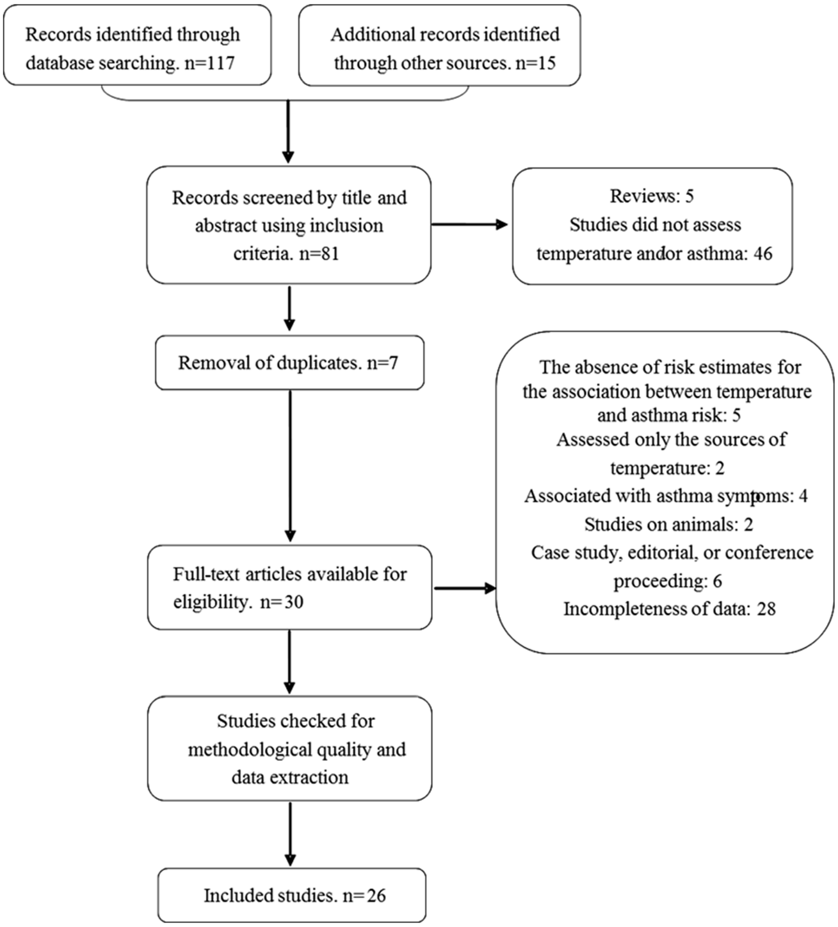
Data extraction

Information regarding publication was extracted as follows: author, source of publication, exposure period, study design, data sources, sample size, temperature measurement methods, OR or RR and 95% CI, and conclusion of publication. If a study provided association of temperature during different periods or seasons with asthma incidence, all data was extracted from full-text articles by author. Several studies assessed the risk of asthma based on different windows of exposure; we preferentially chose to evaluate articles with a cohort study, which could potentially reduce the heterogeneity between studies included in meta-analysis. In addition, estimates were extracted based on signal statistical models only if they were fully adjusted for other multiple covariates. Not all studies were adjusted for all other variables other than temperature. However, if the sample was a group that had been selected for further analysis because of other stronger risk factors for development of asthma, data were not eligible due to the inability to collect a realistic data set based on temperature drops (i.e., pollution, tobacco smoke, pet dander, and chemical irritants). Two authors of this study scrutinized extraction criteria and assessments by using a standard form that included the characteristics of the articles, and resolved all discrepancies by discussion.

Meta-analysis and statistical analysis

All study designs for the included studies were divided into different types based on different windows. Prior to performing the meta-analysis, we converted all risk estimates (OR/RR) of ambient temperature from selected studies to a uniform form of temperature drop increasing the risk of asthma, which allowed us to pool general estimates from different research studies. The logit transformation was applied in prevalence proportions for an appropriate normal distribution, and estimates of combined logit prevalence were back

Fig. 1 Flow diagram of the selection of studies for meta-analysis



transformed into their original scale for interpretation on the same basis for all the studies. Then, random-effects meta-analyses were conducted for the assessment of effect of temperature drops on asthma incidence. We also estimated the pooled effects of different time, season, latitude, and region on asthma incidence by using several secondary analyses. These analyses aimed to further explore the impact of temperature drops on asthma risk and test the impact of heterogeneity.

The varying degree of exposure effects was evaluated by comparing OR values with 95% CI at a statistical test level of 0.05 between the control and high-exposure group (Onakpoya et al. 2015). The *I*-squared (I^2) value is indicative of a significantly elevated consistency for the analyzed studies (Chen et al. 2013). An I^2 value ranging from 25 to 50% based on odds ratios is indicative that articles included for analysis have moderate inconsistency. However, if meta-analyses had I^2 values over 50%, then there were large inconsistencies in the studies. Therefore, I^2 values were determined to meet the required sensitivity of the meta-analysis by excluding individual studies of large biases and restricting the analyses to certain subgroups in a process verified by another study in which a funnel plot or Egger's graphical test could visually assess the publication bias (the Egger's test *p* value was < 0.05) (Egger et al. 1997; Fan et al. 2016). Each statistical test was two-sided, and a value of $p < 0.05$ was considered statistically significant. Data were recorded and analyzed in Excel 2010 (Microsoft Corp) and the Stata software version 12 (Stata Corp).

Definitions

For the purpose of this review, a temperature drop is defined as a lower temperature level, compared with a higher or middle temperature level, at a period of time in the same area, which is based on prior studies (Zanazzi et al. 2007; Pino et al. 2004; Wang and Lin, 2014). Risk of asthma is defined as asthma incidence or pre-existing asthma onset, which comes from self-reported or hospital/national recorded.

Results

Document search and study characteristics

We selected a total of 132 studies as potentially eligible publications. After excluding 51 studies (5 studies were reviews, and 46 studies did not assess temperature and/or asthma), 81 studies were identified for further assessment. We further excluded studies due to the absence of risk estimates for the association between temperature and asthma risk (*n* = 5); or only the sources of temperature (*n* = 2); asthma-related symptoms (asthma is uncertain) (*n* = 4); duplicate studies (*n* = 4); studies on animals (*n* = 2);, articles that were case studies, editorials, or conference proceedings (*n* = 6); and incompleteness of data (*n* = 32). Finally, 26 studies were included in this meta-analysis from 1994 to 2014, with a total population of over 26 million, of which 16 studies assessed temperature drops and 10 studies assessed temperature raises. More than 350,000 asthma cases were included in these 26 studies that assessed the association between ambient temperature and asthma risk (Wasilevich et al. 2012; Beard et al. 2012; Buckley et al. 2012; Li et al. 2014; Zhang et al. 2014; Kim et al. 2012; Epton et al. 1997; Pino et al. 2004; Lin et al. 2008; Celenza et al. 1996; Lombardi et al. 1997; Kiechl-Kohlendorfer et al. 2007; Gonzalez et al. 2008; Makinen et al. 2009; Rumchev et al. 2004; Soto-Quiros et al. 1994; Wang and Lin, 2014; Guo et al. 2012; Mi et al. 2006; Lee et al. 2005; Zanolin et al. 2004; Jacobs et al. 1997; Yamazaki et al. 2015; Villeneuve et al. 2015; Khalaj et al. 2010; Gleason et al. 2014). The included studies were conducted in China (*n* = 5), the USA (*n* = 6), South Korea (*n* = 1), New Zealand (*n* = 1), Chile (*n* = 1), the UK (*n* = 1), Austria (*n* = 1), Brazil (*n* = 1), Finland (*n* = 1), Australia (*n* = 4), Costa Rica (*n* = 1), Italy (*n* = 1), Japan (*n* = 1), and Canada (*n* = 1). An overview of these publications and the rationale for exclusion in the present meta-analysis is provided in Table 1 and Fig. 1.

Data synthesis

The results of the main extracted data

The results of different meta-analyses and the assessment of heterogeneity are summarized in Table 2. When the main extracted data from each study was combined, a statistically significant association with asthma was observed (OR 1.05, 95% CI 1.02, 1.08). A forest graph of the 21 main studies was plotted (Fig. 2). Dose-effect analyses showed stronger associations in asthma risk for each 1 °C decrement (OR 1.055, 95% CI 1.00, 1.11) and each 8 °C decrement in ambient temperature (OR 1.057, 95% CI 1.03, 1.09). The association between lower respiratory tract infections (LRTI) and temperature drops (per 1 °C decrement) was statistically significant (OR 1.02, 95% CI 1.00, 1.04) (Fig. 3). Each study did not contribute more than 8% of the total weight. When pooling the main data from all studies included, a strong evidence for heterogeneity (I^2 of 92.2%) was observed in the meta-analysis, inconsistent with the requirement for an overall meta-analysis of the extracted data. Therefore, further analyses of combined studies were carried out to explore the sources of heterogeneity by using different stratification secondary analyses.

The results of different critical windows of exposure

The corresponding pooled estimates of secondary analyses were calculated after stratification according to different windows: age (children and adult), seasons (spring, summer, fall, and winter), latitude (low (subtropical), middle latitudes), and regions (Asian, America, Europe, and Australia). The studies included in these meta-analyses are shown in Table 2.

Pool estimate of the effect of temperature drop on risk of asthma in different age groups Heterogeneity was strongly reduced and the most results for different windows of exposure were consistent. The pooled estimated risk of asthma for children was significantly increased (OR 1.087; 95% CI 1.03, 1.15) (Table 2). Dose-effect analyses for different stages of their lives showed statistically significant association between asthma incidence and temperature drops (per 1 °C decrement) during the first stages (< 12 years old) (OR 1.070; 95% CI 1.01, 1.12) (Fig. 3). However, there was no increased risk for adults when the temperature dropped (OR 1.002; 95% CI 0.93, 1.08) (Table 2).

Pool estimate of the effect of temperature drop on risk of asthma in different seasons Stratification of studies by season showed that no statistical significance was found for the increased risk of asthma in spring (OR 1.293; 95% CI 0.63, 2.64), fall (OR 1.373; 95% CI 0.67, 2.81), and summer (OR 1.226; 95% CI 0.71, 2.27). However, winter yielded a statistically significant increase in the risk of asthma (OR 1.030; 95% CI 1.01, 1.05) without evidence of heterogeneity between studies (I^2 of 3.8%).

Pool estimate of the effect of temperature drop on risk of asthma in different latitudes Stratification by absolute latitudes showed a markedly increased risk of asthma in all studies reporting “low latitude” and “middle latitude” with a low-level heterogeneity, especially in the low-latitude exposure. We further explored the risk between asthma and temperature drop with absolute latitude. “Low latitude” generated the highest increase of Meta-OR (OR 1.718; 95% CI 1.23, 2.41) without heterogeneity (I^2 of 46.4%), in contrast to other exposure latitudes. Results were less consistent for additional substratification. Significant increase of risk of asthma was observed for lower respiratory tract infections (OR 1.020; 95% CI 1.00, 1.04), but not upper respiratory tract infections (OR 0.96; 95% CI 0.940, 0.970).

Pool estimate of the effect of temperature drop on risk of asthma in different regions Stratification by geographical location showed increased Meta-OR for all groups of studies in different regions. An increased risk of asthma associated with temperature drop was observed after combining studies in Asia (OR 1.004; 95% CI 1.01, 1.16), Europe (OR 1.102;

Table 1 Characteristics of publications selected for meta-analysis

Author	Location	Study duration	Age	No. of participants	Sex	Study design	Temperature measurement method	Type of cases	OR/RR (95%CI)	Classified information
Kim et al., 2012	Soonchunhyang, South Korea (37° N)	2005–2009	19–87	2298	Both	Case-crossover study	Monitoring network data	Refractory asthma	1.06 (0.89, 1.26)	All
Epton et al., 1997	Blenheim, New Zealand (41° S)	1992–1993	17–80	139	Both	Prospective study	Monitoring data at the local airfield	Asthma	1.03 (0.88, 1.22)	All
Pino et al., 2004	Santiago, Chile (33° S)	1995–1996	4 months	504	Both	Cohort study	Monitoring network data	Wheezing bronchitis	0.94 (0.91, 0.97)	All
Lin et al., 2008	New York, USA (40° N)	1995–1999	Children	1,204,396	Both	Retrospective cohort study	Monitoring sites	Asthma	1.06 (1.00, 1.13)	All
Celenza et al., 1996	London, UK (51° N)	1994	16 or over	148	Both	Retrospective study	Meteorological office	Asthma	1.11 (1.05, 1.18)	All
Kiechl-Kohlendorfer et al., 2007	Tyrol, Austria (47° N)	1994–1999	6–10	33,808	Both	Prospective study	Temperatures decrease at a rate of 0.5–1.0 °C/100 m of altitude	Atopic asthma	1.07 (1.01, 1.12) 2.05 (1.01, 4.16) 2.22 (1.03, 4.81) 1.87 (1.00, 3.48) 2.33 (1.03, 5.27)	All Spring Summer Autumn Winter
Gonzalez et al., 2008	Pelotas, Brazil (31° S)	1982–2005	Children	5914	Both	Birth cohort study	Monitoring network data	Asthma	1.00 2.35 (1.11, 4.99) 0.79 (0.28, 2.28) 0.78 (0.21, 2.87)	January April July October
Makinen et al., 2009	Northern Finland (64° N)	2004–2006	19.6 (mean)	892	Men	Prospective study	National meteorological stations	Asthma	0.96 (0.94, 0.97) 1.02 (1.00, 1.04)	URTI LRTI
Li et al., 2014	Sydney, Melbourne, Brisbane, Adelaide, Perth, Canberra, Australia (27° S–37° S)	2007–2008	7–12	270	Both	Cross-sectional study	Air monitoring station	Asthma	1.02 (0.97, 1.02) 1.01 (0.97, 1.06) 1.01 (0.96, 1.05) 1.00 (0.96, 1.04) 1.05 (1.01, 1.10) 1.06 (1.01, 1.10) 1.05 (1.01, 1.09) 1.02 (0.98, 1.06)	Lag0 (female) Lag1 (female) Lag2 (female) Lag3 (female) Lag0 (male) Lag1 (male) Lag2 (male) Lag3 (male)
Rumchev et al., 2004	Western Australia (32° S)	1997–1999	0.5–3	192	Both	Case-control study	Tinytalk II Data Loggers	Asthma	1.07 (1.02, 1.11)	All
Soto-Quiros et al., 1994	Costa Rica (10° N)	1997–1998	5–17	2682	Both	Cross-sectional study	Meteorological office	Asthma	4.27 3.77	< 25 °C > 25 °C
Zhang et al., 2014	Shanghai, China (31° N)	2005–2012	All	23million	Both	A time-series analysis	Center for Urban Environmental Meteorology	Asthma	1.20 (1.01, 1.41)	All
Wang and Lin, 2014	Taipei, China (25° N)	2000–2009	All	1 million	Both	Cohort study	Central Weather Bureau	Asthma	2.93 (1.26, 6.97)	All
Guo et al., 2012	Shanghai, China (31° N)	2007–2009	Children	1.99million	Both	Retrospective study	Shanghai Meteorological Bureau	Asthma	1.06 (0.97, 1.17)	All
Xu et al., 2013	Brisbane, Australia (27° S)	2003–2009	0–14	13,324	Both	Retrospective study	Australian Bureau of Meteorology	Asthma	1.25 (0.80, 1.95) 1.06 (0.63, 1.77) 1.26 (0.58, 2.73) 1.41 (0.77, 3.62) 1.24 (0.73, 2.12) 1.29 (0.68, 2.44)	All 0–4 years 5–9 years 10–14 years Male Female
Mi et al., 2006	Shanghai, China (31° N)	2000	13–14	1414	Both		Data logger (Q-track)	Asthma	1.15 (0.91, 1.44)	All

Table 1 (continued)

Author	Location	Study duration	Age	No. of participants	Sex	Study design	Temperature measurement method	Type of cases	OR/RR (95%CI)	Classified information
						Cross-sectional study				
Lee et al., 2005	Taiwan, China (21° N–25° N)	1995–1996, 2001	12–15	44,104	Both	Retrospective study	Monitoring stations	Asthma	1.00	Spring
									1.02	Winter
									0.99	Summer
Zanolin et al., 2004	Italy (36° N–47° N)	1998–2000	20–40	27,000	Both	Cross-sectional study	ISAO and ARPA	Asthma	1.11 (1.06, 1.14)	All
Jacobs et al., 1997	California, USA (36° N)	1983–1992	All	3342	Both	Retrospective study	NOAA	Asthma	0.99 (0.99, 1.00)	
									1.00	Summer
									1.15 (0.97, 1.37)	Winter
									1.05 (0.91, 1.20)	Spring
									1.03 (0.87, 1.22)	Fall
Beard et al., 2012	Salt Lake City, USA (40° N)	2003–2008	All	3425	Both	Cohort study	Monitoring network data	Asthma	1.14 (1.02, 1.27)	All
Yamazaki et al., 2015	Himeji, Japan (35° N)	2010–2013	0–14	1447	Both	Case-crossover study	The Japan Meteorological Agency	Asthma	1.04 (1.01, 1.07)	All
									1.12 (1.06, 1.19)	Spring
									1.07 (0.88, 1.29)	Summer
									0.99 (0.95, 1.03)	Fall
									1.01 (0.94, 1.09)	Winter
Buckley and Richardson, 2012	North Carolina, USA (33° N–36° N)	2007–2008	> 18	53,156	Both	Case-crossover study	Stata Climate Office	Asthma	1.01 (1.00, 1.02)	All
									1.03 (1.01, 1.05)	Winter
									0.97 (0.95, 0.99)	Spring
									1.04 (0.99, 1.09)	Summer
									1.01 (0.98, 1.03)	Fall
Villeneuve et al., 2005	Ottawa, Canada (45° N)	1992–2000	2–15	1 million	Both	Case-crossover study	Monitoring network data	Asthma	0.97 (0.92, 1.01)	All
Khalaj et al., 2010	New South Wales, Australia (28° S–37° S)	1998–2006	All	1,497,655	Both	Case-only study	NSW Bureau of Meteorology	Asthma	0.92 (0.83, 1.02)	Lag0
									0.91 (0.82, 1.01)	Lag4
									0.80 (0.69, 0.92)	Average
Wasilevich et al., 2012	Detroit, USA (42° N)	2000–2001	3–18	6659	Both	Case-crossover study	NOAA	Asthma		4 h
									1.00 (0.99, 1.02)	Change
									1.01 (0.98, 1.03)	Change rate
										8 h
									1.00 (0.99, 1.01)	Change
									1.01 (0.99, 1.04)	Change rate
										12 h
									0.99 (0.99, 1.01)	Change
									1.00 (0.98, 1.02)	Change rate
										24 h
									0.99 (0.98, 1.00)	Change
									0.97 (0.95, 0.99)	Change rate
Gleason et al., 2014	New Jersey, USA (38° N–41° N)	2004–2007	3–17	21,854	Both	Case-crossover study	New Jersey weather stations	Asthma	0.89 (0.87, 0.91)	All

URTI upper respiratory tract infections, *LRTI* lower respiratory tract infections, *Lag 0* the same day, *Lag 1* previous day, *Lag 2* day before the previous day, *Lag 3* 3 days ago, *Lag 4* the day after, *ISAO* Institute of Atmospheric and Oceanic Sciences, *ARPA* Regional Agencies for the Protection of the Environment, *NOAA* National Oceanic and Atmospheric Administration'

Table 2 Meta-analysis after stratification of the different windows in the studies

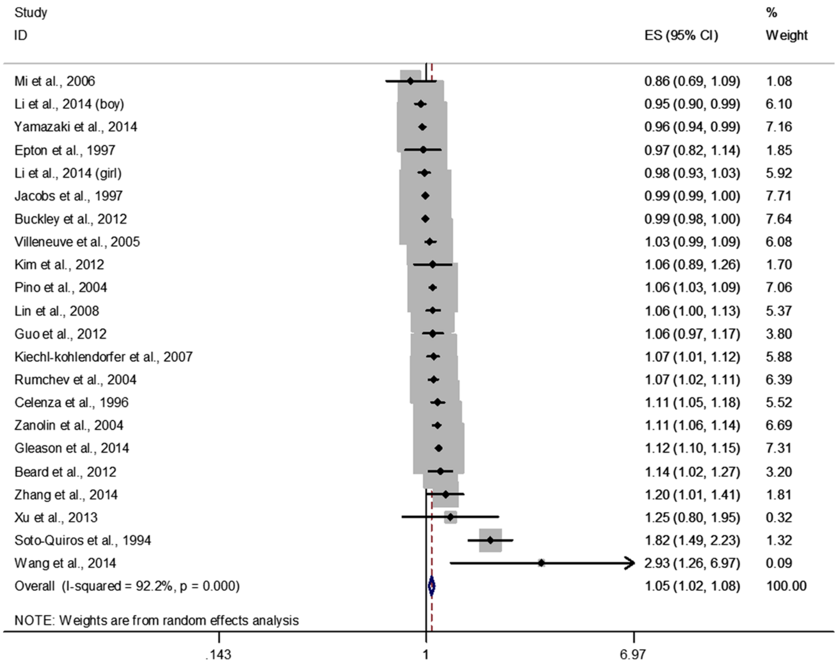
Subgroups	No. of studies	Summary OR	95% CI	x^2 Woolf	I^2 (%)	*P* for hypothesis	*P* for Egger's test	95% UI
A. The main studies	21	1.050	1.01–1.09		92.1	< 0.001	0.000	0.17–1.03
B. Exposure time windows								
(B.1) childhood	11	1.087	1.03–1.15	104.78	90.5	< 0.001	0.416	−0.58–1.27
(B.2) adult	5	1.002	0.93–1.08	55.44	55.4	< 0.001	0.843	−2.27–1.98
C. Exposure season windows								
(C.1) spring	2	1.293	0.63–2.64	4.29	4.3	0.038	–	–
(C.2) summer	2	1.373	0.67–2.81	3.71	3.7	0.054	–	–
(C.3) fall	2	1.226	0.71–2.27	3.74	3.7	0.053	–	–
(C.4) winter	2	1.030	1.01–1.05	3.84	3.8	0.050	–	–
D. Exposure latitude windows								
(D.1) low latitude	3	1.718	1.23–2.41	3.73	46.4	0.155	0.962	−7.43–7.50
(D.2) middle latitude	16	1.063	1.02–1.10	177.67	91.6	< 0.001	0.045	0.02–1.24
(D.3) Circumpolar latitude								
URTI	1	0.960	0.95–0.98	–	–	–	–	–
LRTI	1	1.020	1.00–1.04	–	–	–	–	–
E. Exposure region windows								
(E.1) Asian	6	1.004	1.01–1.16	9.33	46.4	0.097	0.039	0.03–0.71
(E.2) America	7	1.103	1.04–1.17	151.37	95.4	< 0.001	0.084	−2.38–2.68
(E.3) Europe	3	1.102	1.06–1.15	2.54	21.2	0.201	0.264	−3.15–2.20
(E.4) Australia	2	1.071	1.03–1.12	0.46	0.0	0.496	–	–

95% CI 1.06, 1.15), and Australia (OR 1.071; 95% CI 1.03, 1.12). Likewise, heterogeneities between the included studies were not observed (all $I^2 < 50\%$). Data on America revealed an increased risk of asthma after combining data (OR 1.103; 95% CI 1.04, 1.17) but inconsistency in the study was observed (I^2 of 95.4%).

Sensitivity

Sensitivity analyses in the meta-analysis showed that the pooled estimate was not significantly changed after the meta-analyses. Exclusion of the studies with more than 7% of the total weight or less than 1% of the total weight, and the lowest

Fig. 2 Forest plots of studies for temperature drops and asthma



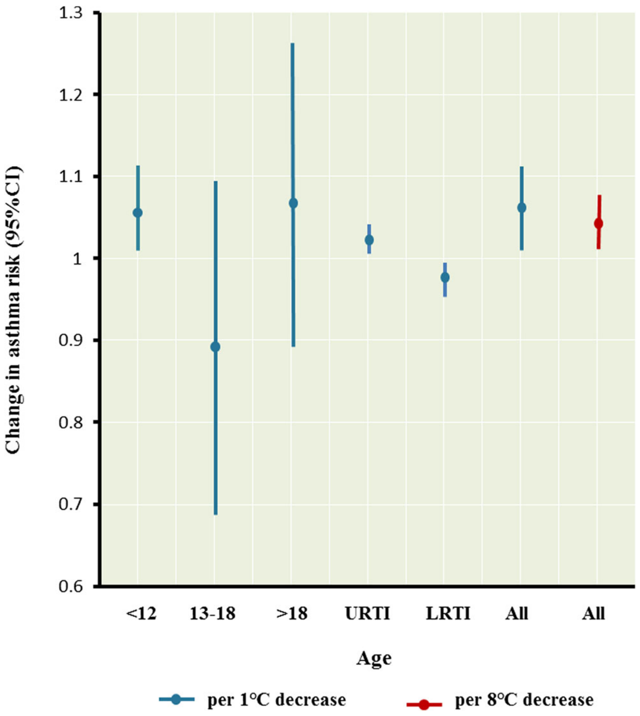


Fig. 3 Polled OR estimates between ambient temperature and asthma risk, per 1 or 8 °C decrease in temperature, different age ranges, from below 12 years old (< 12), 13 to 18 years old (13–18), and over 18 years of age (> 18). *LRTI* lower respiratory tract infections, *URTI* upper respiratory tract infections

or highest of OR, and deletion of the study reporting combined data for cross-sectional studies on ambient temperature did not substantially alter the results. Results of the meta-analyses were all similar when performed with fixed- or random-effects models.

Funnel plot and asymmetry

A funnel plot for the meta-analysis, containing 21 studies on temperature drops, was constructed (Fig. 4 and Fig. 5). Visual inspection of the funnel plot did not clearly reveal asymmetry. The statistical results provided by the linear regression using the Egger's test showed there was also no significant publication bias in most of the secondary analyses, except for the "middle latitude" and "Asian" exposure windows (Table 2).

Discussion

A summary of the evidence

This meta-analysis and systematic review examined the relevant epidemiological studies reporting an association between temperature drop and asthma. Overall, temperature drop is associated with asthma. The increased risk of asthma is also observed and did not alter the previous result when omitting some extreme values in the studies. Our conclusion is consistent with the results of previously narrative reviews (Carlsen, 2012; Kippelen et al. 2012; Fisher, 2011). Furthermore, experimental studies also showed similar results to our findings. An increase in temperature from 4 to 25 °C has been showed to limit disruption of the airway epithelium, which indicating that exposure to temperature drop could increase the risk of asthma (Bolger et al. 2011). Kippelen et al. found a lower temperature level, compared with a higher temperature level, can cause airway injury, and the repeated injury and repair process of the epithelium resulted in disorder of airway function and structure, which could be the underlying mechanism for the development of asthma (Kippelen and Anderson, 2012). Moreover, asthma exacerbation also shows a significant association with temperature drop (Hirabayashi et al. 2004; May et al. 2011; Abe et al. 2009). These results support the suggestion that temperature drop may be a potential causal factor for asthma. However, the strong evidence of heterogeneity (I^2 of 92.1%) argues against an overall meta-analysis of the data. Further analyses were therefore carried out to identify sources

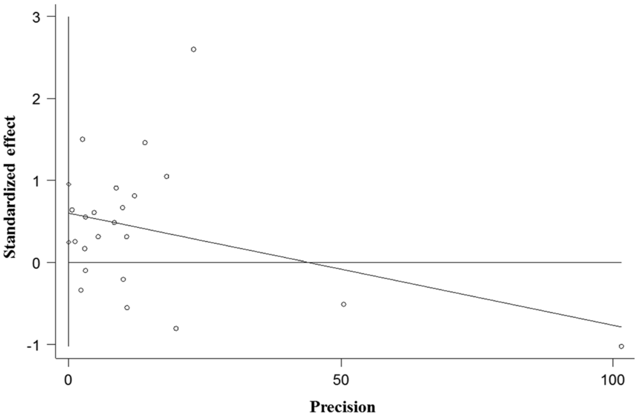


Fig. 4 Egger's publication bias plot of studies for temperature drop and asthma

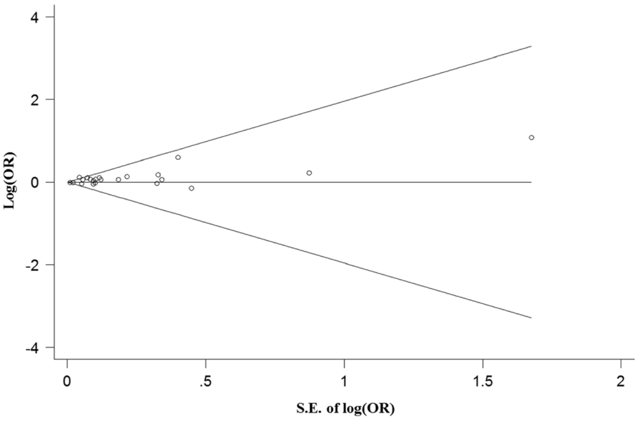


Fig. 5 Begg's funnel plot of studies for temperature drop and asthma

of heterogeneity and to improve the analysis of the data available.

Critical windows of exposure

Age

Stratification by exposure of time windows (childhood and adult) reduced the heterogeneity and showed a stronger association for exposure during childhood. This result is in agreement with the current evidence suggesting that asthma results from molecular damage that may be incurred in childhood (Tenero et al. 2016). Previous reports demonstrated that asthma in children correlates with Clara cell protein CC10 polymorphism G + 38A and levels of lower CC10 (Yang et al. 2007). It is noteworthy that Demello et al. observed that temperature drop could inhibit normal cell differentiation similar to that found for Clara cells in vivo (Demello et al. 2002). To our knowledge, investigation of cord blood IgE levels could be a predictive risk factor for asthma (Renkonen et al. 2010); the IL33-IL1RL1 pathway may play an important role in the association with persistent asthma (Savenije et al. 2014). However, the immune system of children is less mature. Moreover, studies reported that temperature drop can also suppress the immune system as well as aggravate respiratory conditions in children (Tod et al. 2016).

Seasons

Only a limited number of studies have reported data for different seasons of asthma, and the data of two studies were extracted to calculate the pooled estimates of secondary analyses. Exposure in winter shows significantly increased risk of asthma without evidence of heterogeneity. It indicates that long-term temperature drop or a lower temperature level has an impact on asthma. Heir et al. found that cold air could stimulate the parasympathetic nervous system, increasing inflammation by generation of mediators like cysteinyl1 leukotrienes, which increased contraction of the bronchial smooth muscle and induced mucus hyperescretion (Heir et al. 1995). Furthermore, cold air could gate the transient receptor potential melastain 8 (TRPM8); TRPM8 may provide a mechanistic link for the manipulation of respiratory sensations such as dyspnea or mechanisms leading to cold-induced asthma (Fisher, 2011). These evidences further reveal the adverse effect of winter. In addition, Nakaji et al. reported that seasonality affects the incidence of respiratory diseases, including asthma, pneumonia, and influenza, and the highest prevalence of these diseases occurs during winter (Nakaji et al. 2004; Hou et al. 2016).

Latitude

Data show a significant association between temperature drop at different latitudes and asthma. The risk was the highest when at low latitude without any heterogeneity. Our results are consistent with studies that latitude as a possible surrogate of climate factor could contribute to the prevalence of asthma in various countries. Areas near the equator display more frequent asthma (Hughes et al. 2011; Sole et al. 2006). Although there are no prior studies to elucidate the association between temperature drop and asthma at different latitudes, studies have revealed that latitude has an effect on asthma prevalence through climate (including temperature change) and its relation to allergens or viral infections, or vitamin D intake and ultraviolet radiation (Hughes et al. 2011; Shea et al. 2008; du Prel et al. 2009; Soebiyanto et al. 2010; Mallol et al. 2010; Wu et al. 2008; Arnedo-Pena et al. 2011). These findings suggest that in a region with higher baseline ambient temperature, a short-term temperature drop has a higher risk of asthma than in a region with lower baseline temperature. It could imply that a potential increased risk of the occurrence of asthma into the future as the global mean temperature continues to rise, when a short-term temperature drop occurs. Previous reports demonstrated that global warming and climate change can affect and adjust the ability of organisms to adapt to the changing environment, and reduce offspring fitness (Sears and Angilletta, 2011; Bartolini et al. 2013).

Regions

We observed an association between increased asthma risk and temperature drop in all regions, especially in America and Europe, which is in line with most previous studies. Currently, 8.4% of individuals in the USA have asthma contrast to 4.3% of the population worldwide (Loftus et al. 2016). Adult asthma prevalence is generally lower in Asia than in Europe (Song et al. 2014). Studies show that environment factors are more important than ethnicity in controlling asthma. Meteorological conditions, such as atmospheric pressure, temperature, humidity, and diurnal amplitude, could be important factors, for regional differences in risk of asthma (Wang, 2016). In recent years, we have also found that there is a remarkable increase in the incidence of asthma in other regions. In Asia, asthma is a major chronic disease (Thompson et al. 2013; Braman et al. 2006) and the prevalence of childhood asthma has continuously increased for decades (Wong et al. 2013). In Australia, the prevalence of asthma in children is among the highest (about 1 in 8 children) in the world, and is continuing to increase (Li et al. 2014). Studies suggested that global warming and abnormal climate events, one of the biggest concerns focused on the effect of temperature, pose an important threat to asthma and are set to trigger a surge in numbers of asthma attacks (Ault, 2004; Costello et al. 2009). However, there is not still enough evidence to explain the main cause of the regional difference of asthma attacks.

Limitations

The results of our meta-analysis have some limitations. Ideally, the highest qualitative evidence available for the association of temperature drops with asthma risk requires lower heterogeneity in the meta-analysis. However, we found high or moderate heterogeneity in our meta-analyses. These findings indicate that other factors, such as air pollution and pollen, could affect heterogeneity among the included studies. Air pollution and pollen are regarded as important risk factors of asthma; pollen transmission is related to temperature. Air pollution and pollen are not taken into account in this study due to the limited evidence. Therefore, further meta-analysis is needed to explore the sources of heterogeneity in the future.

Conclusion

Overall, this meta-analysis observed a clear association between temperature drop and risk of asthma, and children, winter and low-latitude area might be the critical windows for adverse effects. Moreover, we also observed an elevated risk of asthma in America and Europe. These results extend our understanding of the adverse effect of temperature drop on asthma, and suggest that the preventive actions against temperature drop would help to decrease the risk of asthma, especially in critical windows, which is the main conclusion and purpose of this meta-analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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