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Impact of ambient temperature on morbidity and mortality: An overview of reviews

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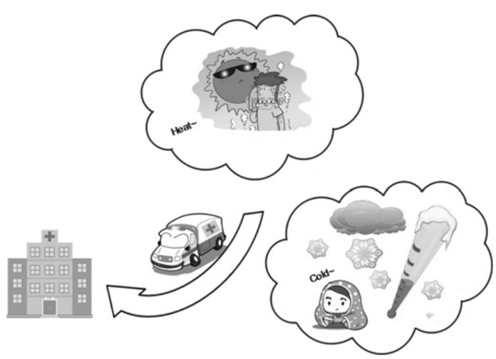
HIGHLIGHTS

- Heat exposure increased risk of cardiovascular and cerebrovascular mortality.
- Risk of cold-induced cardiovascular morbidity increased in the elderly.
- Definitions of temperature exposure included various indicators and thresholds.

GRAPHICAL ABSTRACT



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ABSTRACT

The objectives were (i) to conduct an overview of systematic reviews to summarize evidence from and evaluate the methodological quality of systematic reviews assessing the impact of ambient temperature on morbidity and mortality; and (ii) to reanalyse meta-analyses of cold-induced cardiovascular morbidity in different age groups. The registration number is PROSPERO-CRD42016047179. PubMed, Embase, the Cochrane Library, Web of Science, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Global Health were systematically searched to identify systematic reviews. Two reviewers independently selected studies for inclusion, extracted data, and assessed quality. The Assessment of Multiple Systematic Reviews (AMSTAR) checklist was used to assess the methodological quality of included systematic reviews. Estimates of morbidity and mortality risk in association with heat exposure, cold exposure, heatwaves, cold spells and diurnal temperature ranges (DTRs) were the primary outcomes. Twenty-eight systematic reviews were included in the overview of systematic reviews. (i) The median (interquartile range) AMSTAR scores were 7 (1.75) for quantitative reviews and 3.5 (1.75) for qualitative reviews. (ii) Heat exposure was identified to be associated with increased risk of cardiovascular, cerebrovascular and respiratory mortality, but was not found to have an impact on cardiovascular or cerebrovascular morbidity. (iii) Reanalysis of the meta-analyses indicated that cold-induced cardiovascular morbidity increased in youth and middle-age (RR = 1.009, 95% CI: 1.004–1.015) as well as the elderly (RR = 1.013, 95% CI:

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1.007–1.018). (iv) The definitions of temperature exposure adopted by different studies included various temperature indicators and thresholds. In conclusion, heat exposure seemed to have an adverse effect on mortality and cold-induced cardiovascular morbidity increased in the elderly. Developing definitions of temperature exposure at the regional level may contribute to more accurate evaluations of the health effects of temperature.

1. Background

Substantial evidence has been presented suggesting climate change affects human health and may be associated with an increased risk of disease in a large number of populations (Costello et al., 2009; McMichael et al., 2006). Over the past 30 years, trends in warming and precipitation due to anthropogenic climate change have been identified as responsible for over 150,000 deaths annually (Patz et al., 2005). Furthermore, the Intergovernmental Panel on Climate Change (IPCC) reported that global climate change has led to increased occurrence of extreme weather events (IPCC, 2013). At present, extreme temperatures have become a public health hazard, contribute to a substantial burden of disease (Empana et al., 2009; Huynen et al., 2001; Shaposhnikov et al., 2014; Turner et al., 2013) and pose great threats to the well-being of increasingly ageing populations (McMichael, 2013).

Numerous epidemiologic studies have reported ambient temperature to be associated with mortality, often exhibiting a J-, V-, or U-shaped association (Analitis et al., 2008; Ballester et al., 2011; Gasparrini et al., 2015). Mortality rates have been found to be lowest in optimal temperature zones and increased in areas with hot or cold temperatures (McMichael et al., 2006). Humans have efficient thermoregulation systems that facilitate appropriate responses to thermal stress. Within certain temperature limits, thermoregulatory responses can maintain thermal comfort. However, once levels of heat or cold surpass these limits, the risks of morbidity and mortality have been found to increase substantially (Guyton and Hall, 2000). At present, heat exposure, cold exposure, heatwaves, cold spells, and diurnal temperature ranges (DTRs) have been the most frequently studied temperature exposures.

Two systematic reviews, which were both published in 2016, reported cold-related cardiovascular morbidity (Bunker et al., 2016; Phung et al., 2016). Debatable results for the association between cardiovascular morbidity and cold exposure were identified in the general and elderly populations. Elevated risks of cold-induced cardiovascular (RR = 1.028, 95% CI: 1.021–1.035) morbidity were identified in the general population (Phung et al., 2016). However, no associations between cold exposure and cardiovascular (RR = 1.000, 95% CI: 0.993–1.007) morbidity were observed in the elderly (Bunker et al., 2016). Assuming the results of these two systematic reviews were reliable, we inferred that cold exposure had no effect on cardiovascular morbidity in the elderly but could elevate the risks of morbidity in middle-aged individuals, youth or children. The conclusion seemed problematic because a series of studies have suggested that the elderly were more vulnerable to the effects of temperature (Goggins et al., 2012; Lian et al., 2015; Pitsavos et al., 2005). Therefore, assessing the effects of cold exposure on cardiovascular morbidity in different age groups is necessary and essential.

Numerous systematic reviews assessing the effects of ambient temperature on health have been published; however, the study designs and methodological quality of these studies have varied. An overview of systematic reviews may thus be used to summarize the available evidence on a given topic, which may support leaders in making decisions based on adequate information (Smith et al., 2011). The objectives were (i) to conduct an overview of systematic reviews to summarize evidence from and evaluate the methodological quality of systematic reviews assessing the association between ambient temperature and cause-specific morbidity or mortality; and (ii) to reanalyse meta-analyses of cold-induced cardiovascular morbidity in different age groups.

2. Method

The protocol for this overview was published online and is available on PROSPERO (International Prospective Register of Systematic Reviews). The registration number is CRD42016047179.

2.1. Inclusion and exclusion criteria

Systematic reviews of any design that evaluated the association between ambient temperature and cause-specific morbidity or mortality were included in this overview. The eligibility criteria were as follows: (i) studies that evaluated the association between ambient temperature and cause-specific morbidity or mortality and (ii) studies that were systematic reviews. A review was considered to be a “systematic review” if it met the following three criteria: had a specific research question, had a predefined search strategy and had predefined eligibility (inclusion and exclusion) criteria (Gamble et al., 2015). (iii) The publication language was restricted to English. The exclusion criteria were as follows: (i) studies that evaluated indoor, body or workplace temperatures as exposure variables; (ii) studies that predicted future temperature-related morbidity or mortality; and (iii) studies that focused on seasonality rather than ambient temperature.

Studies that evaluated cold-induced cardiovascular morbidity and conducted sensitive analyses of age were included in this reanalysis of meta-analyses. Only English publications were considered. Cold exposure was defined as studies presenting effect estimates below threshold temperatures, linear effects with no threshold, or comparisons between two temperatures as a linear increase/decrease. Studies reporting risk estimates not convertible to 1 °C reduction in temperature were excluded in meta-analyses. The criteria defining study designs and time-series span were different in the two systematic reviews. One had a wider scope and included the general population, compared to the other review, which focused on the elderly only (Bunker et al., 2016; Phung et al., 2016). (i) study designs in review of the general population were required to be appropriate for examining the short-term effects of temperature change, while review focused on the elderly were case-crossover and time-series studies. (ii) Studies were required to have analysed a minimum of three consecutive years or seasons in review focused on the elderly, while no time-series span was required in the review of the general population. To explore differences between these two systematic reviews, we chose criteria with a wider scope for study design and time-series span.

2.2. Search strategy

PubMed, Embase, the Cochrane Library, Web of Science, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Global Health were systematically searched to identify studies published from inception to March 14, 2016. The following U.S. National Library of Medicine's Medical Subject Headings (MeSH) terms and keywords were used in the primary search: (climate change* OR temperature*) AND (morbidit* OR hospitalisation* OR hospitalization* OR death* OR mortalit* OR outpatien*) AND review* (Table S1). In addition, we manually searched the reference lists of included studies to identify additional relevant studies.

2.3. Study selection and data extraction

Two investigators (Xuping Song and Yu Liu) independently screened titles and abstracts to identify eligible studies. Studies whose relevance could not be determined by their titles and abstracts underwent full-text screening. Any conflicts were adjudicated by a third investigator (Jinhui Tian). Two reviewers (Xuping Song and Tingting Zhang) independently extracted data from the included systematic reviews. Study characteristics were extracted using a standardized form that included but was not limited to the following items: author, year of publication, disease, outcome, databases searched, and number of included studies. Disagreement was resolved by consensus and the opinion of a third reviewer (Jinhui Tian).

For the two systematic reviews in the reanalysis of meta-analyses, Xuping Song and Jinhui Tian independently extracted data from the included studies. We recalculated summary statistics (relative risks, odds ratios, or percentage), which were converted to relative risks (RR) per 1 °C decrease in temperature. The following formula was used to calculate the standardized risk estimates:

$$RR_{(\text{standardised})} = RR_{(\text{original})}^{\text{Increment}(10)/\text{Increment}(\text{original})} \quad (1)$$

Reanalysis were performed for two age groups: (i) the elderly; and (ii) youth and middle-age. We regard youth and middle-age as a single group because the included studies did not analyse youth and middle-age separately. In addition, only one study (Chan et al., 2013) performed an analysis for children. Therefore, we could not include children as an age group. Definition of elderly was consistent with reanalysed systematic reviews (Bunker et al., 2016). 65+ was defined as elderly and slightly younger age groups (50+) were also included to minimise data loss. For reviews that did not provide a risk estimate based on age, we attempted to contact the corresponding author and first author via email.

2.4. Quality assessment

Two reviewers (Xuping Song and Tingting Zhang) independently assessed the quality of included systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. The AMSTAR is a measurement tool assessing the methodological quality of systematic reviews and consists of 11 items, each with yes, no, cannot answer and not applicable options (Shea et al., 2007). The maximum score on the AMSTAR is 11. Consistent with previous overviews, we considered studies with a score between 0 and 4 to be of low quality, 5 and 8 to be of moderate quality, and 9 and 11 to be of high quality (Jaspers et al., 2011; Monasta et al., 2010).

2.5. Statistical analysis

Descriptive and quantitative analyses were conducted. We summarized the characteristics of included systematic reviews and determined the number of systematic reviews assessing heat exposure, heatwaves, cold exposure, cold spells and DTRs. We extracted the temperature-exposure thresholds defined in the included systematic reviews. Risk estimates were converted to RR per 1 °C change in temperature. In addition, we plotted the pooled risk estimates and 95% confidence intervals (CIs). When a review presented both individual and combined estimates of overall and cause-specific risk of disease, the combined estimates were plotted.

On account of the anticipated significant heterogeneity between studies due to different study designs and locations, random-effects model was performed in the meta-analyses. Heterogeneity between trials was assessed by the Chi-square test and the extent of inconsistency was evaluated by the I^2. To evaluate the heterogeneity and compare two systematic reviews, we conducted stratified analyses of time-series span and disease classification (cardiovascular disease including stroke versus excluding stroke) in the elderly group. Disease classification was analysed because stroke was included as the cardiovascular disease in the review of the general population. However, stroke was considered a cerebrovascular disease in the review focused on the elderly. In addition, we performed a sensitive analysis on geographical location (Europe, America and Asia) in the elderly. Subgroup analyses on study design were not conducted because all included studies met the narrow criteria. All analyses were performed using Stata software (Version 12.0, Stata Corp, College Station, TX, USA). Statistical significance was taken as a two sided $p < 0.05$.

3. Results

We initially identified 2252 studies in the overview of reviews, and 89 studies were reviewed in depth. Sixty-one studies were excluded after full-text screening (Table S2). Ultimately, 28 reviews (Amegah et al., 2016; Åström et al., 2011; Basu, 2009; Basu and Samet, 2002; Beltran et al., 2014; Bhaskaran et al., 2009; Bunker et al., 2016; Burkart et al., 2014; Carlton et al., 2015; Carolan-Olah and Frankowska, 2014; Cheng et al., 2014; Fan et al., 2015; Li et al., 2015; Lian et al., 2015; Martiello and Giacchi, 2010; Phung et al., 2016; Poursafa et al., 2015; Ramesh et al., 2013; Ryti et al., 2016; Strand et al., 2011; Turner et al., 2012; Viana and Ignotti, 2013; Witt et al., 2015; Ye et al., 2012; Xu et al., 2012; Xu et al., 2016; Xu et al., 2014; Yu et al., 2012) met the criteria in the overview (Fig. 1). Eleven reviews (Beltran et al., 2014; Carlton et al., 2015; Carolan-Olah and Frankowska, 2014; Fan et al., 2015; Li et al., 2015; Phung et al., 2016; Poursafa et al., 2015; Ramesh et al., 2013; Turner et al., 2012; Viana and Ignotti, 2013; Ye et al., 2012) evaluated morbidity, 5 reviews (Basu, 2009; Basu and Samet, 2002; Burkart et al., 2014; Xu et al., 2016; Yu et al., 2012) evaluated mortality, and 12 reviews (Amegah et al., 2016; Åström et al., 2011; Bhaskaran et al., 2009; Bunker et al., 2016; Cheng et al., 2014; Lian et al., 2015; Martiello and Giacchi, 2010; Ryti et al., 2016; Strand et al., 2011; Witt et al., 2015; Xu et al., 2012; Xu et al., 2014) evaluated both morbidity and mortality (Table 1). The first systematic review (Basu and Samet, 2002) identified that evaluated the health effects of temperature was published in 2002 (Table 2). Of the 28 included reviews, only 4 (Phung et al., 2016; Ramesh et al., 2013; Ryti et al., 2016; Witt et al., 2015) were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The median [interquartile range (IQR)] number of databases searched was 3 (2.25), while the median (IQR) number of included studies was 28 (16.75) (Fig. S1). Fig. S2 shows the distribution of temperature exposures in systematic reviews with and without meta-analyses, which indicated that systematic reviews evaluating heat and heatwave exposure outnumbered those evaluating cold exposure and cold spells.

Twenty-four studies (Bhaskaran et al., 2010; Giang et al., 2014; Goggins et al., 2013; Goggins et al., 2012; Gomes et al., 2015; Hajat and Haines, 2002; Hong et al., 2003; Kyobutungi et al., 2005; Lee et al., 2010; Lee et al., 2014; Liang et al., 2008; Mostofsky et al., 2014; Panagiotakos et al., 2004; Pitsavos et al., 2005; Son et al., 2014; Tanigawa-Sugihara et al., 2013; Turner et al., 2012; Urban et al., 2014; Vasconcelos et al., 2013; Wang et al., 2013; Wang and Lin, 2014; Wang et al., 2012; Webb et al., 2014; Wolf et al., 2009) were included in the review of the general population and ten (Alessandrini et al., 2011; Bhaskaran et al., 2010; Chan et al., 2013; Ebi et al., 2004; Giang et al., 2014; Hajat and Haines, 2002; Silva and Ribeiro, 2012; Vasconcelos et al., 2013; Wichmann et al., 2011; Wichmann et al., 2012) were included in the review focused on the elderly, four of which (Bhaskaran et al., 2010; Giang et al., 2014; Hajat and Haines, 2002; Vasconcelos et al., 2013) were included in both reviews. Therefore, thirty studies were initially identified in the reanalysis of meta-analyses. Of these thirty studies, fourteen studies in the review on the general population were excluded due to the following reasons. Seven studies (Liang et al., 2008; Turner et al., 2012; Urban et al., 2014;

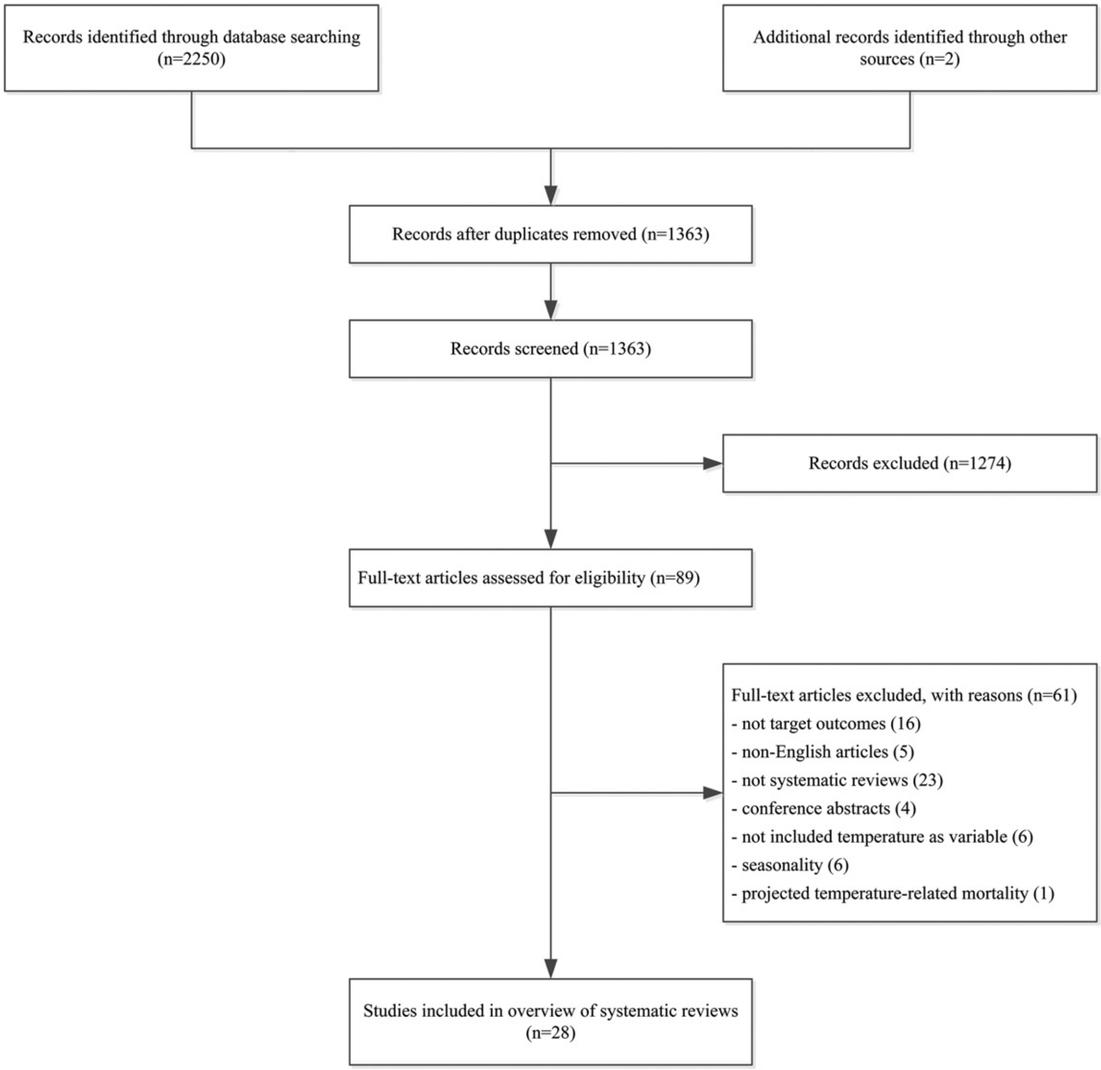

Fig. 1. Flow diagram of literature screening process.

Wang et al., 2013; Wang and Lin, 2014; Wang et al., 2012; Wolf et al., 2009) did not perform analyses based on age. Three studies (Mostofsky et al., 2014; Son et al., 2014; Webb et al., 2014) did not offer stratified risk estimates based on age. 2 studies (Gomes et al., 2015; Kyobutungi et al., 2005) presented risk estimates not convertible to 1 °C reduction in temperature and other 2 studies (Lee et al., 2010; Panagiotakos et al., 2004) did not provide 95% confidence intervals (CIs). Ultimately, sixteen studies (Alessandrini et al., 2011; Bhaskaran et al., 2010; Chan et al., 2013; Ebi et al., 2004; Giang et al., 2014; Goggins et al., 2013; Goggins et al., 2012; Hajat and Haines, 2002; Hong et al., 2003; Lee et al., 2014; Pitsavos et al., 2005; Silva and Ribeiro, 2012; Tanigawa-Sugihara et al., 2013; Vasconcelos et al., 2013; Wichmann et al., 2011; Wichmann et al., 2012) met our criteria for the reanalysis of meta-analyses.

3.1. Quality assessment on systematic reviews

The AMSTAR scores of systematic reviews with and without meta-analyses are presented in Fig. S1. The median (IQR) AMSTAR scores were 7 (1.75) for quantitative reviews and 3.5 (1.75) for qualitative reviews. The quality assessment results suggested that only one review was of high quality (AMSTAR score >8). In addition, the AMSTAR score was higher for quantitative than qualitative reviews. Thirteen (72.22%) qualitative reviews were of low quality (AMSTAR score lower than 5), while most quantitative reviews ($n = 9$, 90.00%) were of moderate quality (AMSTAR score: 5–8).

3.2. Definitions of temperature exposure

Of the 28 included systematic reviews, 14 (Amegah et al., 2016; Åström et al., 2011; Basu, 2009; Basu and Samet, 2002; Burkart et al., 2014; Carolan-Olah and Frankowska, 2014; Li et al., 2015; Lian et al., 2015; Phung et al., 2016; Ryti et al., 2016; Turner et al., 2012; Xu et al., 2016; Xu et al., 2014; Yu et al., 2012) listed or described the precise definitions of temperature exposures used(heat exposure, heatwave, cold exposure, cold spell), 9 (Beltran et al., 2014; Bhaskaran et al., 2009; Bunker et al., 2016; Martiello and Giacchi, 2010; Poursafa et al., 2015; Strand et al., 2011; Witt et al., 2015; Ye et al., 2012; Xu et al., 2012) did not report or only partially presented these definitions, and 4 (Carlton et al., 2015; Fan et al., 2015; Ramesh et al., 2013; Viana and Ignotti, 2013) did not analyse the effects of any temperature exposures. To obtain a comprehensive understanding of the threshold effects of temperature exposures, we summarized the definitions of these four temperature exposures, as reported in the 14 systematic reviews that provided definitions (Table S3). In addition, we did not summarize the definitions of DTR because this term was considered to be explicit and only two included reviews (Cheng et al., 2014; Phung et al., 2016) reported the effect of DTR.

Table 1
Characteristics and quality assessment of included systematic reviews.

Author	Disease	Times cited	PRISMA	Age	Outcome	Databases searched	Software	No. of included studies	Meta analysis	AMSTAR score
Turner et al. (2012)	Cardiovascular disease, respiratory disease.	57	N	All	Morbidity	4	WinBUGS	21	Y	8
Cheng et al. (2014)	All cause	12	N	All	Morbidity, mortality	3	NR	25	N	4
Lian et al. (2015)	Stroke	1	N	All	Morbidity, mortality	5	Excel and STATA	20	Y	9
Yu et al. (2012)	All cause	69	N	≥65 years	Mortality	2	WinBUGS	15	Y	6
Yu et al. (2012)	Diarrhoea	3	N	All	Morbidity	4	STATA	26	Y	8
Fan et al. (2015)	Dengue fever	6	N	All	Morbidity	6	STATA	33	Y	7
Phung et al. (2016)	Cardiovascular disease	1	Y	All	Morbidity	1	NR	64	Y	7
Xu et al. (2012)	All cause	62	N	≤18 years	Morbidity, Mortality	5	NR	33	N	3
Ryti et al. (2016)	All cause[a]	8	Y	All	Morbidity, Mortality	4	R	26	Y	8
Xu et al. (2016)	All cause	1	N	All	Mortality	5	STATA	60	Y	5
Xu et al. (2014)	All cause	29	N	<18 years	Morbidity, Mortality	5	NR	12	N	3
Bhaskaran et al. (2009)	Myocardial infarction	134	N	≥25 years[b]	Morbidity, mortality	3	NR	19	N	5
Witt et al. (2015)	Respiratory disease	1	Y	All	Morbidity, mortality	3	SPSS	33	N	2
Li et al. (2015)	All cause	10	N	All	Morbidity	2	NR	33	N	4
Basu (2009)	All cause	391	N	All	Mortality	1	NR	36	N	2
Amegah et al. (2016)	All cause diseases except for vector-borne diseases	0	N	All	Morbidity, mortality	3	NR	23	N	5
Martiello and Giacchi (2010)	All cause	41	N	All	Morbidity, mortality	2	NR	113	N	4
Bunker et al. (2016)	All cause	1	N	≥50 years	Morbidity, mortality	3	R	60	Y	7
Ye et al. (2012)	Non-communicable diseases	156	N	All	Morbidity	1	NR	40	N	3
Åström et al. (2011)	All cause	118	N	≥50 years[c]	Morbidity, mortality	1	NR	30	N	3
Carolan-Olah and Frankowska (2014)	Preterm birth	13	N	All	Morbidity	5	NR	7	N	5
Basu and Samet (2002)	All cause	803	N	All	Mortality	1	NR	49	N	3
Strand et al. (2011)	Preterm birth, birth weight, stillbirth.	81	N	All	Morbidity, mortality	3	NR	14	N	3
Beltran et al. (2014)	Hypertensive disorders in pregnancy, preterm birth, birth weight.	38	N	All	Morbidity	2	NR	38	Y	6
Poursafa et al. (2015)	Preterm birth, low birth weight.	6	N	All	Morbidity	4	NR	6	N	6
Ramesh et al. (2013)	Trachoma	4	Y	All	Morbidity	5	NR	4	N	7
Viana and Ignotti (2013)	Dengue fever	20	N	All	Morbidity	4	NR	20	N	3
Burkart et al. (2014)	All cause	32	N	All	Mortality	3	NR	32	N	4

Abbreviations: PRISMA: preferred reporting items for systematic reviews and meta-analyses; NR: not report; Y: yes; N: not.
[a] Disease: Ryti (2016) included all or all nonaccidental causes.
[b] Age: Bhaskaran (2009) included adult humans, but did not give an accurate age. The youngest age of included study was 25 years.
[c] Age: Åström (2011) included the eldly, but did not give an accurate age. The youngest age of included study was 50 years.

Different exposure indicators, including mean temperature, maximum temperature, minimum temperature, apparent temperature, humidex and heat index, were used to define temperature exposures in different studies. For the definitions of heat and cold exposure, temperature percentiles and values were commonly adopted to define thresholds; however, these definitions differed by study. For example, McMichael et al. defined a temperature above the 95th percentile as the heat threshold and below the 5th percentile as the cold threshold, while Azongo et al. used the 75th and 25th temperature percentiles as heat and cold thresholds, respectively (Azongo et al., 2012; McMichael et al., 2008). Furthermore, definitions of heatwaves and cold spells had greater variety and differed by exposure indicators, thresholds and durations of temperature (Anderson and Bell, 2011; Gasparrini and Armstrong, 2011; Hutter et al., 2007).

3.3. Findings from overview of reviews

Twenty-eight systematic reviews were included in our overview. Ten studies (Beltran et al., 2014; Bunker et al., 2016; Carlton et al., 2015; Fan et al., 2015; Lian et al., 2015; Phung et al., 2016; Ryti et al., 2016; Turner et al., 2012; Xu et al., 2016; Yu et al., 2012) were quantitative systematic reviews, of which 3 (Beltran et al., 2014; Carlton et al., 2015; Fan et al., 2015) only conducted meta-analyses of the association between temperature and cause-specific mortality and did not perform analyses of the effects of specific temperature exposures. Therefore, these reviews were not included in the forest plots for the effects of heat exposure, cold exposure, heatwaves, cold spells, or DTRs.

3.3.1. Impacts of ambient temperature on morbidity

Within the 7 quantitative systematic reviews (Bunker et al., 2016; Lian et al., 2015; Phung et al., 2016; Ryti et al., 2016; Turner et al., 2012; Xu et al., 2016; Yu et al., 2012) assessing the association between morbidity and temperature exposure, a total of 383 estimates for this association were reported. Pooled estimates of the risk of morbidity in association with the following four types of temperature exposures were reported: (i) heat exposure (n = 238 estimates); (ii) cold exposure (n = 96 estimates); (iii) heatwave (n = 23 estimates); and (iv) DTR (n = 26 estimates).

Table 2
Summary characteristics of included systematic reviews.

Characteristics	All reviews [n (%)]	No meta-analysis [n (%)]	Meta-analysis [n (%)]
Year			
2002	1 (3.57)	1 (5.56)	0
2009	2 (7.14)	2 (11.11)	0
2010	1 (3.57)	1 (5.56)	0
2011	3 (10.71)	3 (16.67)	0
2012	3 (10.71)	1 (5.56)	2 (20.00)
2013	2 (7.14)	2 (11.11)	0
2014	5 (17.86)	4 (22.22)	1 (10.00)
2015	6 (21.43)	3 (16.67)	3 (30.00)
2016	5 (17.86)	1 (5.56)	4 (40.00)
No. of databases searched			
1	5 (17.86)	4 (22.22)	1 (10.00)
2	4 (14.29)	2 (11.11)	2 (20.00)
3	7 (25.00)	6 (33.33)	1 (10.00)
4	5 (17.86)	2 (11.11)	3 (30.00)
5+	7 (25.00)	4 (22.22)	3 (30.00)
No. of included studies			
≤15	6 (21.43)	5 (27.78)	1 (10.00)
16–30	9 (32.14)	5 (27.78)	4 (40.00)
31–45	8 (28.57)	6 (33.33)	2 (20.00)
46-60	3 (10.71)	1 (5.56)	2 (20.00)
>61	2 (7.14)	1 (5.56)	1 (10.00)
AMSTAR[a] score			
0–4	13 (46.43)	13 (72.22)	0
5-8	14 (50.00)	5 (27.78)	9 (90.00)
9–11	1 (3.57)	0	1 (10.00)

n = number of systematic reviews.
[a] AMSTAR: assessment of multiple systematic reviews checklist.

Fig. 2 shows the pooled estimates for the association between morbidity and heat exposure. Three systematic reviews (Bunker et al., 2016; Phung et al., 2016; Turner et al., 2012) reported the presence of no significant association between heat exposure and cardiovascular morbidity. Turner et al. (2012) (RR = 0.995, 95% CI: 0.970–1.021) Phung et al. (2016) (RR = 0.997, 95% CI: 0.994–0.999) investigated the effect of health exposure on general population, while Bunker et al. (2016) investigated the effect of heat exposure on the elderly (RR = 1.002, 95% CI: 1.000–1.004). Similar associations were observed between cerebrovascular morbidity and heat exposure. In addition, heat exposure was significantly associated with respiratory morbidity in the elderly (RR = 1.017, 95% CI: 1.011–1.022), which had no impact on the general population (RR = 1.032, 95% CI: 0.968–1.010) (Bunker et al., 2016; Turner et al., 2012). By contrast, a limited number of quantitative reviews reported cold-related morbidity (Fig. 3). Debatable results for the association between cardiovascular morbidity and cold exposure were identified in the general and elderly populations. Therefore, a reanalysis of meta-analyses was performed on it.

Several reviews investigated the associations between temperature extremes and birth outcomes. Carolan-Olah and Frankowska (2014) showed that increased temperature was associated with preterm birth, while Poursafa et al. (2015) indicated that exposure to heat and cold were both associated with preterm birth. Furthermore, Strand et al. (2011) examined the effects of temperature on birth outcomes and reported that heat exposure was more strongly associated with the occurrence of abnormal birth weight than the occurrence of preterm birth.

Adverse health impacts of heatwaves on morbidity were noted, and this association was consistent in the included reviews (Li et al., 2015; Ye et al., 2012) (Fig. 4).

Åström et al. (2011) reported that heatwaves were associated with increased respiratory morbidity. In Phung et al. (2016) study, the risk of cardiovascular morbidity increased by 2.2% (1.006, 1.039) for each 1 °C increase in temperature during a heatwave. In addition, 2 reviews (Beltran et al., 2014; Carolan-Olah and Frankowska, 2014) indicated that heatwaves might be associated with an increased number of

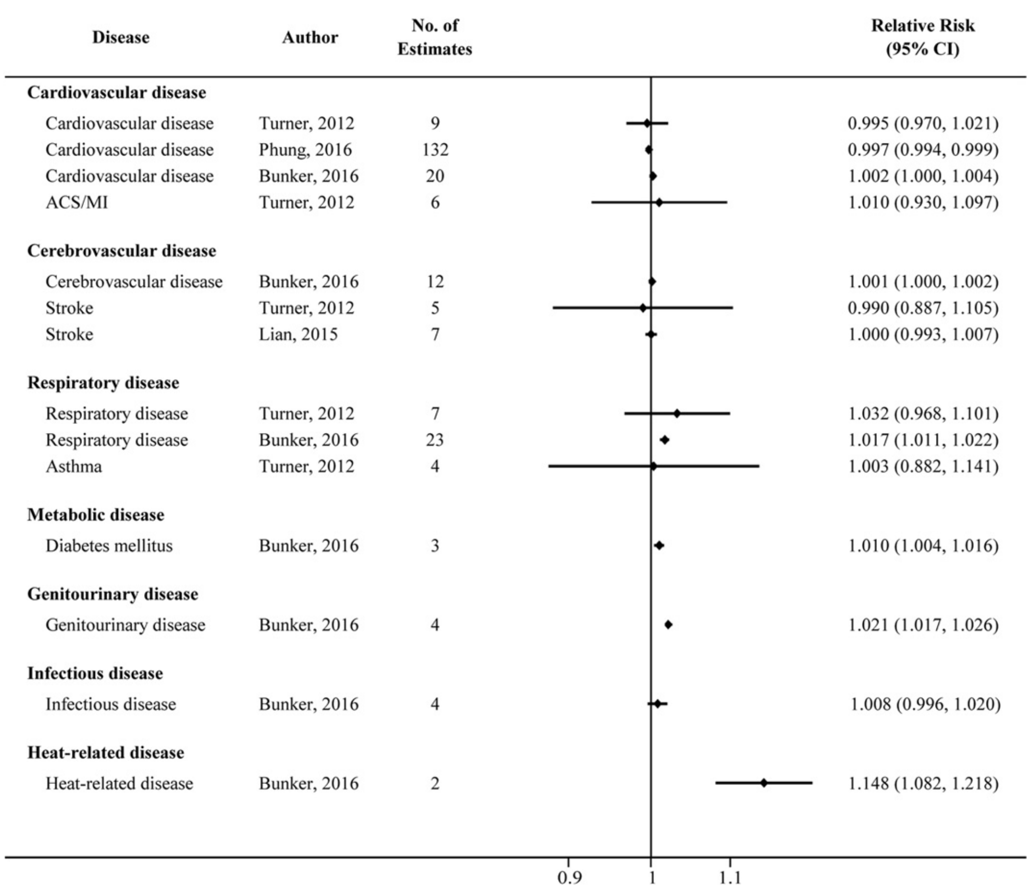

Fig. 2. Forest plot for the effect of heat exposure on morbidity.

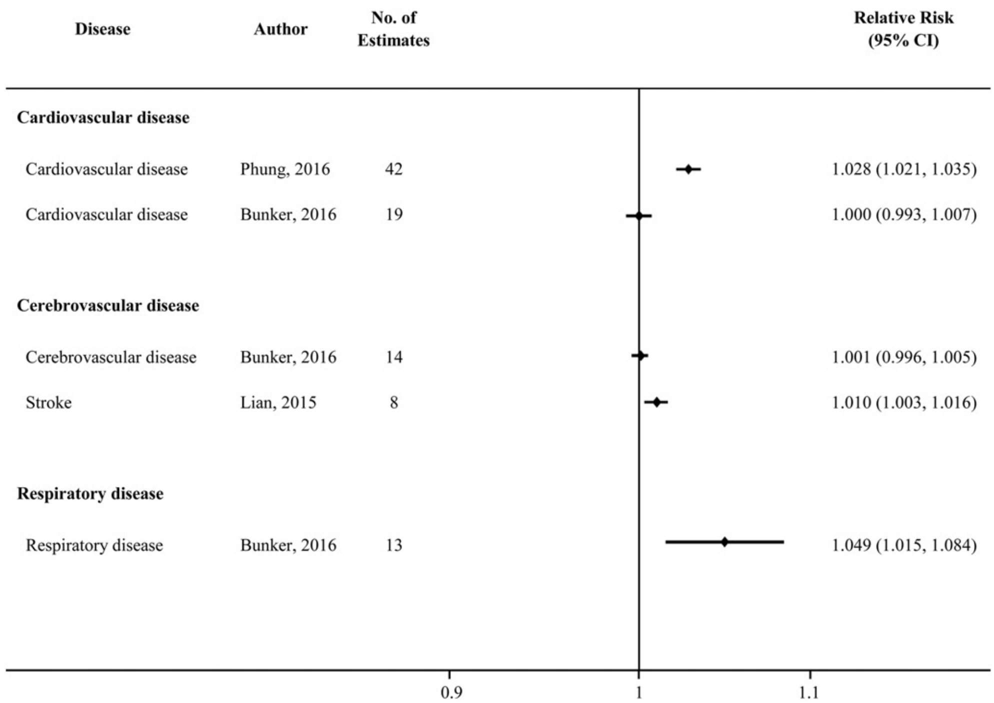

Fig. 3. Forest plot for the effect of cold exposure on morbidity.

preterm births. Furthermore, Xu et al. (2012) observed that morbidities related to fever, renal disease, and electrolyte imbalances increased significantly in children following heatwave exposure.

Only 2 reviews (Cheng et al., 2014; Phung et al., 2016) reported the effect of DTRs, one of which conducted a meta-analysis (Fig. 4). Phung et al. (2016) reported that an elevated risk of cardiovascular morbidity (RR = 1.007, 95% CI: 1.002–1.012) was associated with each 1 °C increase in DTR. In addition, Cheng et al. (2014) indicated that the presence of a significant association between DTR and morbidity, particularly for cardiovascular and respiratory diseases.

Four reviews (Carlton et al., 2015; Fan et al., 2015; Ramesh et al., 2013; Viana and Ignotti, 2013) assessed the association between overall

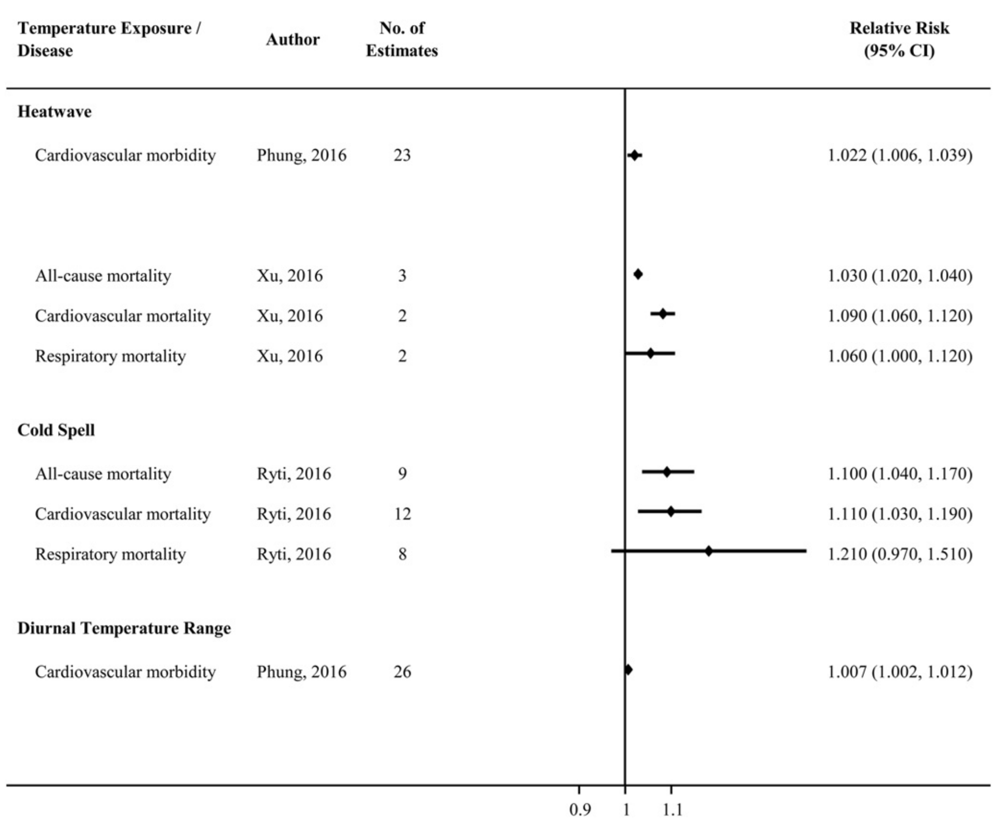

Fig. 4. Forest plot for the effect of heatwaves, cold spells and diurnal temperature ranges on morbidity and mortality.

temperature and morbidity, but did not analyse the effect of specific temperature exposures. Ramesh et al. (2013) reported that temperature has been found to play a role in the transmission of acute trachoma. A review conducted by Carlton et al. (2015) assessing the association between temperature and diarrhoeal diseases showed that temperature was associated with all-cause diarrhoea and bacterial diarrhoea but not viral diarrhoea. In addition, two other reviews (Fan et al., 2015; Viana and Ignotti, 2013) investigated the association between temperature and dengue fever. Viana and Ignotti (2013) reported that dengue fever had been found to be associated with temperature in Brazil. In addition, another study illustrated that compared to the associations with minimum and maximum temperatures, a stronger association was observed between dengue fever and mean temperature (Fan et al., 2015).

3.3.2. Impacts of ambient temperature on mortality

Within the 7 quantitative systematic reviews assessing the associations between mortality and temperature exposures, a total of 360 estimates were reported for this association (Bunker et al., 2016; Lian et al., 2015; Phung et al., 2016; Ryti et al., 2016; Turner et al., 2012; Xu et al., 2016; Yu et al., 2012). Pooled estimates of the risk of mortality in association with each of the four types of temperature exposure were reported as follows: (i) heat exposure (n = 175 estimates); (ii) cold exposure (n = 149 estimates); (iii) heatwave (n = 7 estimates); and (iv) cold spell (n = 29 estimates).

Striking increases in the risks of cardiovascular, cerebrovascular and respiratory mortality in association with heat exposure were observed in the included reviews (Fig. 5). One quantitative review (Bunker et al., 2016) (cardiovascular mortality: RR = 1.034, 95% CI: 1.031–1.038; respiratory mortality: RR = 1.036, 95% CI: 1.032–1.040) and 2 qualitative reviews (Basu, 2009; Burkart et al., 2014) reported that heat exposure was associated with increased cardiovascular and respiratory mortality. In addition, 3 reviews (Basu, 2009; Bunker et al., 2016; Lian et al., 2015) illustrated an increased risk of heat-induced cerebrovascular mortality.

Pooled estimates extracted from the included reviews showed that cold exposure was associated with an elevate risk of mortality (Fig. 6). Bunker et al. (2016) indicated that statistically significant increases in cold-related cardiovascular (RR = 1.017, 95% CI: 1.012–1.021), cerebrovascular (RR = 1.012, 95% CI: 1.007–1.018) and respiratory (RR = 1.029, 95% CI: 1.018–1.040) mortality were observed. In addition, another review (Yu et al., 2012) found that all-cause mortality in the elderly was substantially increased during periods of hot and cold temperatures. Furthermore, Xu et al. (2012) reported that an increased risk of heat-related mortality had been identified in young children, especially children under one year of age. The included systematic reviews reported that subgroups with increased vulnerability to mortality in association with heat exposure included women, people of lower socioeconomic status, people with pre-existing illnesses and the elderly (Basu, 2009; Basu and Samet, 2002; Martiello and Giacchi, 2010).

Evidence extracted from 2 reviews (Åström et al., 2011; Xu et al., 2016) demonstrated that heatwaves may be associated with an elevated risk of cardiovascular mortality. In addition, the observed effects of heatwaves on respiratory mortality showed that increased risks were found in children, the elderly or people with pre-existing illnesses (Åström et al., 2011; Witt et al., 2015; Xu et al., 2014). No association (RR = 1.060, 95% CI: 1.000–1.120) was observed in the general population (Xu et al., 2016).

On the other hand, a limited number of reviews evaluated the effects of cold spells and DTRs. Two reviews (Burkart et al., 2014; Ryti et al., 2016) assessing the association between cold spells and mortality were identified. One review (Ryti et al., 2016) performed a meta-analysis and found cold spells to be associated with increased risk of cardiovascular and all-cause mortality; however, the other review (Burkart et al., 2014) did not provide a concrete conclusion. In addition, DTR was found to be associated with increased mortality in Cheng's study (Cheng et al., 2014).

Some reviews have evaluated the health effects of temperature in specific climates or geographic regions. Burkart et al. (2014) performed a review investigating the association between temperature and mortality in tropical climates and observed that high temperatures were associated with adverse effects in terms of cardiovascular and respiratory mortality. In addition, a review (Amegah et al., 2016) conducted in Sub-

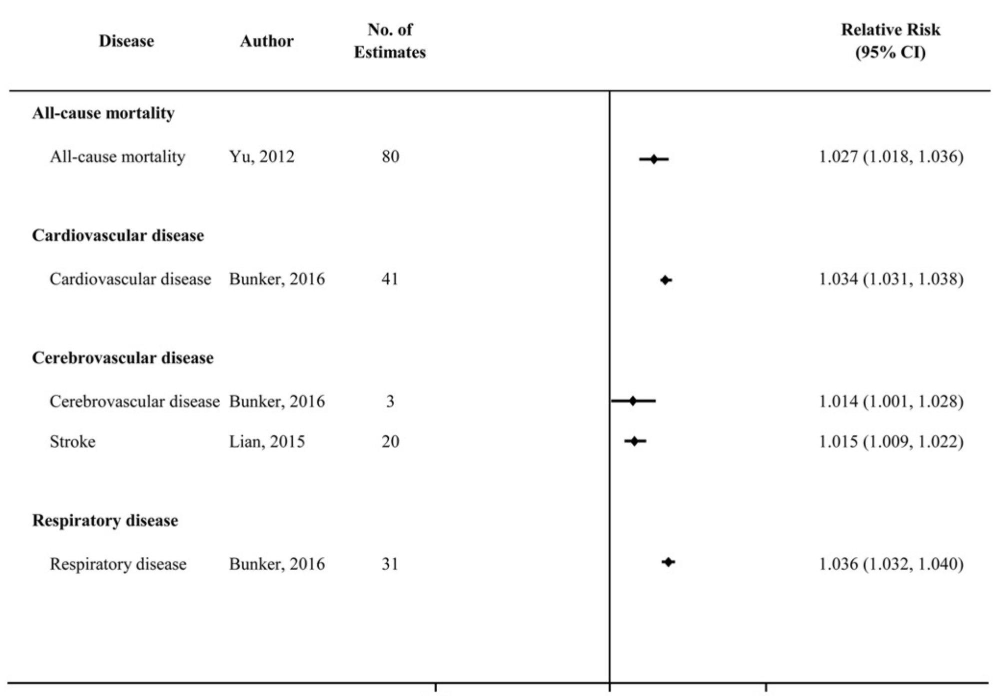

Fig. 5. Forest plot for the effect of heat exposure on mortality.

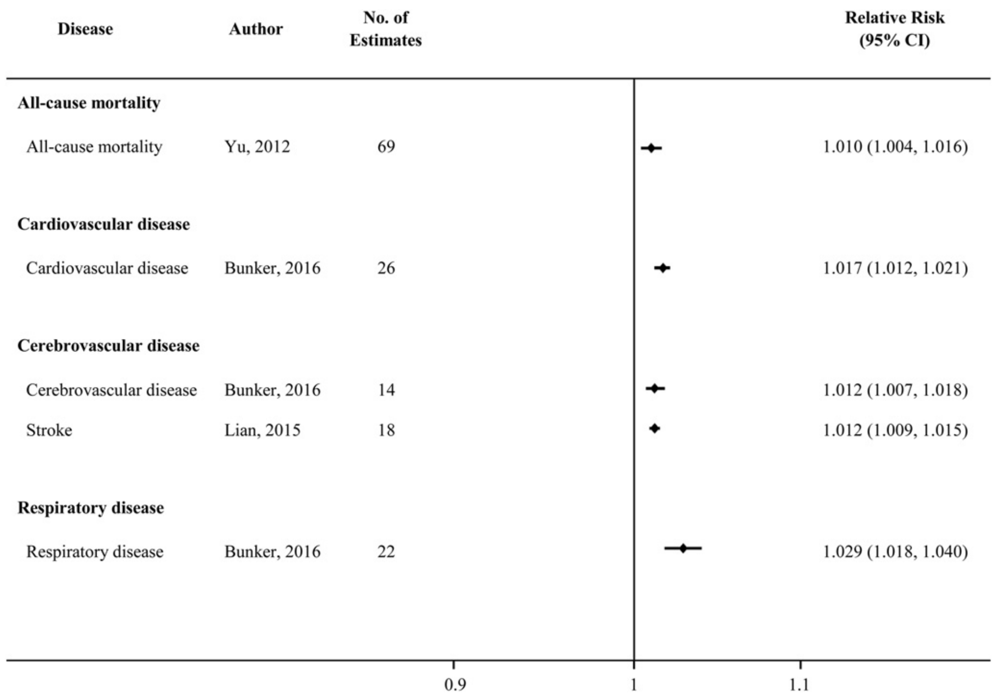

Fig. 6. Forest plot for the effect of cold exposure on mortality.

Saharan Africa reported that exposure to hot and cold temperatures was associated with increased risk of all-cause and cardiovascular mortality.

3.4. Findings from reanalysis of meta-analyses

16 studies met our criteria for reanalysis of meta-analyses. Details of included studies in the reanalysis of meta-analyses see Table S4.

3.4.1. Overall analysis

The pooled estimates for the association between cold exposure and cardiovascular morbidity included a 0.9% increase (RR = 1.009, 95% CI: 1.004–1.015) in youth and middle-age as well as a 1.3% increase (RR = 1.013, 95% CI: 1.007–1.018) in the elderly per 1 °C decrease in temperature.

3.4.2. Subgroup analysis

To compare the two systematic reviews, stratified analyses were performed. Two studies (Goggins et al., 2012; Hong et al., 2003) evaluated stroke and one study (Misailidou et al., 2006) analysed one year data. After adjusting for time-series span and disease classification, we observed that a 1 °C temperature reduction increased cardiovascular morbidity in youth and middle (RR = 1.011, 95% CI: 1.006–1.017) as well as the elderly (RR = 1.011, 95% CI: 1.005–1.016).

The subgroup analysis on geographical location in the elderly indicated that Asia (RR = 1.037, 95% CI: 1.030–1.045) showed a stronger association compared with Europe (RR = 1.010, 95% CI: 1.003–1.017). However, no association was found in America (RR = 0.993, 95% CI: 0.984–1.002) (Fig. 7).

4. Discussion

This is the first overview of systematic reviews investigating the health effects of ambient temperature. A comprehensive search of six electronic databases was performed using a well-defined search strategy. Ultimately, we included 28 systematic reviews assessing the association between temperature and cause-specific morbidity or mortality. Reanalysis of meta-analyses provided several significant points on methodology for further research.

4.1. Health impact of temperature exposure

The impact of temperature on cardiovascular and cerebrovascular events has been identified as a cause for extensive concern owing to substantial associated disease burden (Mendis et al., 2011; Ward et al., 2012). Heat exposure was identified as being associated with an increased risk of cardiovascular and cerebrovascular mortality but was found to have no impact on cardiovascular and cerebrovascular morbidity. Heatwaves, regarded as extended periods of heat exposure, were found to be significantly associated with an elevated risk of cardiovascular mortality. A limited number of quantitative reviews reported cold-related morbidity. Reanalysis of meta-analyses showed that elevated risks of cold-induced cardiovascular morbidity were identified in the general and elderly populations. On the other hand, DTRs reflect global climate change and weather stability (Kalnay and Cai, 2003). Some reviews have reported that DTRs might be associated with elevated cardiovascular morbidity risk (Cheng et al., 2014; Phung et al., 2016).

Respiratory diseases are common causes of morbidity and mortality worldwide. An elevated risk of respiratory mortality in association with heat exposure was observed in our study. Nevertheless, the association between heat exposure and respiratory morbidity remains poorly defined (Bunker et al., 2016; Turner et al., 2012). Pooled estimates showed that compared with the general population, the elderly were more vulnerable to respiratory morbidity in association with heat exposure.

4.2. Populations vulnerable to extreme temperatures

Populations vulnerable to heat exposure were mentioned more frequently than were populations vulnerable to other temperature exposures in the included reviews. Populations described as having increased vulnerability to increased temperatures included the elderly, young children, infants, and people with a low socioeconomic status and pre-existing illnesses (Basu, 2009; Basu and Samet, 2002; Li et al., 2015; Martiello and Giacchi, 2010; Ye et al., 2012; Xu et al., 2012; Xu et al., 2016). Children and infants have been identified as the groups most vulnerable to these heat-related effects (Balbus and Malina, 2009). In addition, included reviews illustrated that children, and

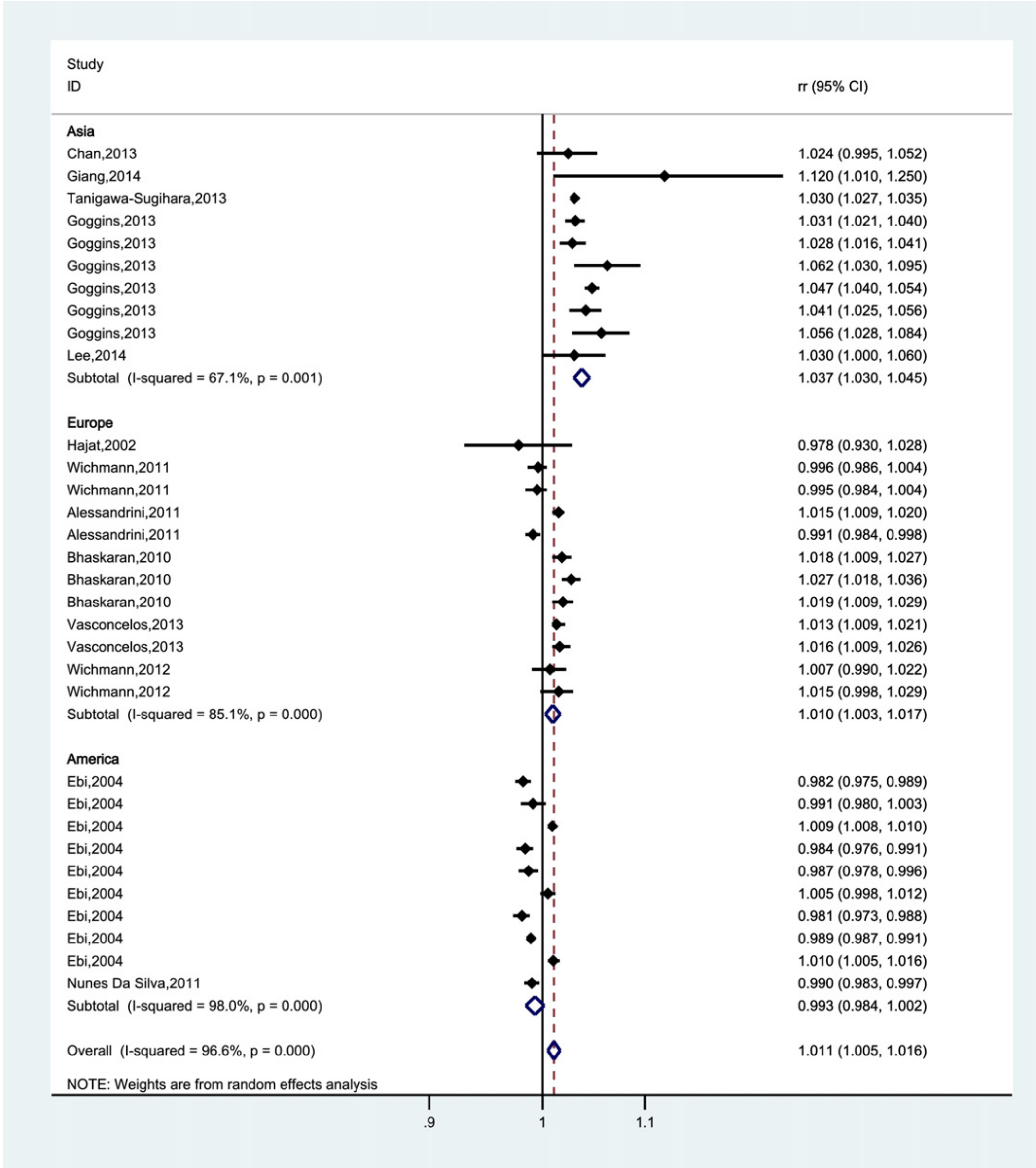

Fig. 7. Subgroup analysis stratified by geographical location on cold-induced cardiovascular morbidity in the elderly.

especially infants, were more susceptible to renal disease, fever, and electrolyte imbalances during heatwaves (Xu et al., 2012; Xu et al., 2014). However, populations vulnerable to cold exposure remain ambiguous, and few studies have focused on this vulnerability.

Subgroup analysis on geographical location illustrated that increased risk of cardiovascular morbidity were found in Asia compared with Europe and America. This analysis indicated that ethnic variations possibly exist in the effects of ambient temperature on health. A study conducted in the northern territory of Australia found the indigenous population was more vulnerable to temperature change than the non-indigenous population (Webb et al., 2014). Furthermore, a 32% increase in ischemic heart disease was noticed in an indigenous female population on hot days. No additional investigations on comparisons of different ethnicities have been found so far, which is possibly due to the limited amount of medical data that could be obtained by researchers. Therefore, evidence is needed to examine whether temperature-related health risks varied according to ethnicity. On the other hand, some studies have found spatial variability of heat vulnerability across regions (Bai et al., 2016; Christenson et al., 2016; Reid et al., 2009). Bai conducted a county-level heat vulnerability assessment for urban and rural residents in Tibet, China. The research showed there was generally a higher vulnerability in high-altitude counties (Bai et al., 2016). In addition, a study performed in United States found higher vulnerability in the Northeast and Pacific Coast and the lowest in the Southeast (Reid et al., 2009).

4.3. Urgent need to develop definitions of temperature exposure

There is an urgent need to reach a consensus on the definitions of temperature exposures at the regional level. Various definitions of temperature exposure were used in different studies, and the reasons for these differences may include author preferences and locational differences. The health effects of temperature have been evaluated by numerous studies. However, inappropriate temperature indicators, thresholds, and durations could result in overestimation or underestimation of the risk of disease. Therefore, it is necessary to reach a consensus regarding this issue. Although completely consistent definitions of temperature exposure may be unachievable owing to climate differences, developing definitions at the regional level is reasonable and achievable through international collaborations (Xu et al., 2016). Temperature thresholds are factors fundamental to the development of these definitions. Cunningham et al. (2013) postulated that a temperature threshold should be defined as the temperature inflexion point, which may not, in actuality, be the commonly used temperature percentiles (e.g., 5th or 1st percentile for cold spells).

Humidity plays a significant role in the health effects of ambient temperature. Prior studies have shown that humidity could elevate risks of angina pectoris and visits to mental health emergency departments increased with humidity (Abrignani et al., 2012; Vida et al., 2012). However, mean and maximum daily temperatures were the most commonly adopted indicators in the included studies, which did not indicate the effect of humidity on health. Apparent temperature, heat index and humidex are commonly used synthetic indices for evaluating the association between meteorology and human health. These indices incorporate temperature, humidity and sometimes wind speed, which could reflect relative human discomfort from heat and cold. Therefore, the apparent temperature, heat index and humidex are considered to be better temperature exposure metrics than temperature alone, especially for the effects of heat exposure on morbidity or mortality (Ho et al., 2016; Nguyen et al., 2014; Ye et al., 2012).

Specific definitions of temperature exposure could present sufficient and essential information to policymakers. For example, the visualization of heatwave and cold spell could enable local governments to raise awareness and allocate resources before the events happened (Wolf et al., 2015). Governors could arrange hospitals and institutions for disease control and prevention that are prepared in advance. Furthermore, specific definitions of temperature exposure for vulnerable populations and communities may be conducive to the development of effective warning systems, which could protect more people from the adverse effects of ambient temperatures.

4.4. Potential mechanism for the effects of temperature on diseases

Abundant evidence regarding the possible mechanism behind the association between temperature and cardiovascular disease has been presented. Physiopathological regulation generally occurs through sympathetic reactivity, the renin-angiotensin system (RAS), dehydration, and the systemic inflammatory response (Liu et al., 2015). Enhanced sympathetic reactivity to cold temperature could contribute to increased risks of hypertension and cardiovascular disease in overweight individuals (Kuniyoshi et al., 2003; Park et al., 2012). Elevated angiotensin-II levels in plasma were observed during cold exposure both in cardiovascular or cerebrovascular patients and in control groups (Sun, 2010; Zhang et al., 2014). It indicated that the RAS was activated, while RAS could lead to increased blood pressure. The biological mechanism behind the association between temperature and respiratory disease may be associated with the effect of increased temperature on enhanced growth of allergens such as moulds, mites and pollen. Temperature could also affect the transmission of viruses, and respiratory viruses are primary causes of respiratory diseases (Pica and Bouvier, 2014). Studies from 85 countries showed that influenza virus transmission in temperate climates correlated with a low temperature (Azziz Baumgartner et al., 2012). In addition, high rates of respiratory syncytial virus infection were associated with colder weather (Weber et al., 1998). On the other hand, air pollutants, including fine particulate matter, ozone, and carbon monoxide, have been observed to cause or exacerbate respiratory diseases and have often been linked to high environmental temperatures (Amegah et al., 2016; Basu, 2009).

Children and infants are the most vulnerable to heat-related effects (Balbus and Malina, 2009). Possible reasons for this finding may be the physical and physiological characteristics of and presence of self-care deficits in these populations. In addition, the risk of abnormal birth weight and preterm birth appeared to be higher during times of increased temperature, especially heatwaves. Abnormal birth weight and preterm birth may lead to death and can influence health later in adult life. Abnormal birth weight infants have been found to be at increased risk of obesity, diabetes, and even lower intelligence scores in later life (Gillman et al., 2003; Matte et al., 2001; Singhal et al., 2003). Researchers have identified links between preterm birth and the risk of some disorders, including developmental delays, cerebral palsy, and hearing and seeing problems (NIH, 2013). Some researchers have hypothesized that maternal heat stress may result in the release of hormones, which may induce labour (Basu et al., 2010; Lajinian et al., 1997; Yackerson et al., 2008). Furthermore, Basu reported that increased temperature could trigger inadequate thermoregulation in expectant mothers. Pregnant women may become dehydrated under these conditions, leading to labour (Basu et al., 2010). Although the presence of an association between higher temperature and increased risk of preterm birth has been supported by a considerable number of studies, consensus regarding the specific mechanisms by which this association occurs has not yet been established (Carolan-Olah and Frankowska, 2014).

4.5. Significant points on methodology for further research

Several weaknesses on methodology were found in included systematic reviews on health effects of ambient temperature, which should be concerned in the future.

First, the PRISMA checklist or other principles should be followed by authors to improve the reporting of systematic reviews and meta-analyses (Moher et al., 2009). Transparent reporting is conducive to a better understanding of how the research was conducted. Cochrane systematic reviews are conducted according to the Cochrane Handbook and published in the database of systematic reviews in the Cochrane library (Green and Higgins, 2011; Wiley, 2014). Methodological Expectations of Cochrane Intervention Reviews (MECIR) required that all Cochrane reviews must include PRISMA study flow diagram (Moher et al., 2009).

Second, a comprehensive literature search is essential because it helps authors find as much available evidence as possible. AMSTAR indicated that at least two electronic databases should be searched (Shea et al., 2007). Therefore, researchers should make a judicious and comprehensive decision when choosing databases. On the other hand, reasons for full-text article exclusion should be provided for the repeatability of systematic reviews, which have been a part of the Cochrane systematic reviews. In the reanalysis of meta-analyses, missing three eligible studies (Goggins et al., 2013; Lee et al., 2014; Tanigawa-Sugihara, 2013) in the review on the elderly (Bunker et al., 2016) led to no association being found between cold exposure and cardiovascular morbidity. We did not know the missing studies were excluded by reviewers or were not included by the database that was searched. Therefore, reanalysis of meta-analyses illustrated that missing eligible studies could lead to over or underestimation and even change the results of the effects of temperature on health.

Third, sensitive analyses based on age and disease should be performed in the original studies and reviews to assess the effects of meteorological factors on health. It could help researchers confirm vulnerable population and disease of extreme meteorological conditions. In the overview of reviews, debatable results for the association between cardiovascular morbidity and cold exposure were identified in the general and elderly populations. Policymakers would not obtain scientifically accurate evidence if further reanalysis was not conducted. Therefore, stratified analyses on age, gender, and other major characteristic should be conducted.

4.6. Limitations

Some limitations to our overview should be noted. Firstly, the evidence summarized in this overview is weakened to some extent by the limited number and methodological limitations of included reviews. Secondly, the majority of reviews were not restricted by climatic conditions or geographical area. Thus, the conclusions of these reviews may not be generalizable to all climatic conditions and regions. Thirdly, the definitions of temperature exposures differed in the original studies that were included in the systematic reviews, which led to heterogeneities in the meta-analyses and influenced, to some extent, the veracity of our evaluation of the association between ambient temperature and disease.

5. Conclusions

This overview of systematic reviews summarized evidence from and evaluated the quality of systematic reviews assessing the association between risk of disease and ambient temperature. The present overview of systematic reviews may inform the development of a high-quality systematic review on the health impact of temperature.

Systematic reviews evaluating heat and heatwave exposure outnumbered those evaluating cold exposure and cold spells with global warming accelerating. Heat exposure seemed to have an adverse effect on mortality. Risks of cold-induced cardiovascular morbidity increased both in youth and middle-age as well as the elderly. In addition, developing definitions of temperature exposures at the regional level may facilitate more accurate evaluation of the health impact of temperature.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2017.01.212.

Conflict of interest

We declare that all authors have no competing interests.

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