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A systematic review and meta-analysis of the association between daily mean temperature and mortality in China

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Abstract

Purpose: We summarized the evidence on the effects of heat and cold exposures on mortality in China. We included studies published on this topic in both Chinese and English, thereby filling a gap in knowledge using data from a country that consists of one-fifth of the world's population.

Methods: We conducted a systematic search of peer-reviewed studies on the association between daily mean temperature and mortality published from 2001 up to July 2018. We searched one Chinese database (China National Knowledge infrastructure, <http://www.cnki.net>) and three English databases (PubMed, Scopus, Web of Science). We converted the effect estimates of heat/cold to rate ratios (RRs) associated with 1 degree increase/decrease beyond the heat/cold reference temperatures. For studies that provided lag-specific estimates, we used both the maximum and minimum of RR estimates. We calculated summary effect estimates for all-cause and cause-specific mortalities, as well as RRs stratified by sex, age, and socioeconomic status. We also investigated patterns of heat and cold adaptation at different latitudes, and at different reference temperatures.

Results: In total, 45 articles were included in this systematic review. For every 1 degree temperature increase/decrease beyond reference points, the rate of non-accidental mortality increased by 2% (RR, 1.02; 95% confidence interval (95% CI [1.01–1.02]) for heat and 4% (RR, 1.04; 95% CI [1.03–1.04]) for cold, respectively; the rate of cardiovascular mortality increased 3% (RR, 1.03; 95% CI [1.03–1.04]) for heat and 6% (RR, 1.06; 95% CI [1.04–1.07]) for cold; the rate of respiratory mortality increased 2% (RR, 1.02; 95% CI [1.01–1.03]) for heat and 2% (RR, 1.02; 95% CI [1.00–1.04]) for cold; the rate of cerebrovascular mortality increased 2% (RR, 1.02; 95% CI [1.02–1.03]) for heat and 3% (RR, 1.03; 95% CI [1.02–1.04]) for cold. We identified a variation in optimal temperature range related to latitude of the residential area, and differences in people's capability to adapt to heat versus cold.

Conclusion: We found consistent evidence of the association between temperature and mortality, as well as evidence of patterns in human adaptation, and we discussed the implications of our findings.

Keywords: temperature; mortality; China; systematic literature review; meta-analysis

Acknowledgements

This work was supported by EXTREMA DG ECHO project (Grant Agreement 783180).

Declarations of interest: none.

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1. Introduction

Studies of the effects of heat and cold on mortality have increased in the last two decades, due in large part to researchers' attempts to measure the impact of global climate change, which is characterized by an increase in global average surface temperature as well as an increase in the number, duration, and frequency of extreme weather events.¹ As a result, many literature reviews have examined the evidence for associations of mortality with both heat and cold,²⁻¹⁴ with recent reviews also focusing on temperature variability,¹⁰ the elderly population,⁴ vulnerabilities to temperature-related mortality,¹⁵ and rural regions.⁸ The amount of scientific evidentiary support for the associations between mortality and heat and cold varies geographically.⁹

China, which holds one fifth of the world's population, has remained difficult to include in the discussion of the effect of heat and cold on mortality, in part because of the absence of systematic summaries of existing studies and in part because of language barriers presented by studies published only in Chinese. In 2013, there was one systematic review on the association between temperature and mortality in China published in Chinese.¹⁶ In that review, the authors summarized 10 studies in 15 cities. Limited by the small number of studies and heterogeneity in study design and analytical approach, the review was not able to investigate in detail the nature of the temperature-mortality functions, the variation of association for specific causes of death, and the variation by sex, age, or other factors. In addition, because the review was in Chinese, it was not readily accessible to a wider readership. Since 2013, over 100 additional studies on this topic have been published in regard to China. However, this accumulating scientific evidence has not been systematically summarized.

In this article, we aim to fill this gap by expanding the review to include recent publications on the associations between temperature and mortality, using both English and Chinese databases. Here we present a systematic review and meta-analysis on the effects of high and low daily mean temperature on mortality. We aim to summarize the association between daily mean temperature and cause-specific mortality outcomes; summarize the temperature-mortality associations in sub-populations stratified by age, sex, and socio-economic status; identify populations of high susceptibility; identify knowledge gaps; and propose future avenues of research.

2. Methods

2.1 Data sources

We followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines in planning and conducting this review.¹⁷ We retrieved empirical studies on the impact of heat and cold on mortality in China published up to July 2018 from the databases PubMed, Scopus, Web of Science, and the Chinese database China Knowledge Infrastructure (CNKI, <http://www.cnki.net>), which is the primary Chinese database for scientific literature. We used a combination of four strings of search terms for exposure, outcome, study methods/type, and geographical

coverage. The search for exposure centered on temperature: "temperature" OR "extreme weather" OR "extreme weather events" OR "climate change" OR "extreme temperature" OR "cold" OR "heat" OR "cold temperature" OR "hot temperature" OR "cold spell" OR "heat wave." Outcome was focused on mortality: "mortality" OR "death" OR "stillbirth" OR "still-birth" OR "still birth." Study methods/type included time-series and case-crossover/review studies. Geographical coverage search terms included China, Taiwan, Hong Kong, Macau, River Delta, and a list of Chinese provinces and cities at or above the municipality levels in China. More details are available in the review protocol, accessible online at <http://www.oulu.fi/cerh/node/55435>.

2.2 Selection of articles and extraction of data

In our initial literature search, we included studies that met the following eligibility criteria: (1) they were original, peer-reviewed, with an independent study population; (2) they included information on the relationship between hot and cold temperatures and human mortality in China; and (3) they could be categorized as either time-series or case-crossover design.

The articles on temperature and mortality that we found in our initial search had various ways of measuring temperature, reported multiple causes of death, and had various study populations and study settings. Therefore, for this review and meta-analysis, we further applied the following criteria for study inclusion: (1) they used daily mean temperature as their means of measuring temperature exposure; (2) they included any of the following as causes of death: all-cause/non-accidental, cardiovascular, respiratory, or cerebrovascular; (3) they were based on general populations rather than any specific high-risk group (e.g., studies that only included patients of a pre-existing disease were not included); and (4) they provided rate ratio (RR) estimates on the effects of heat or cold, as well as reference temperature points.

We excluded studies that focused only on out-of-hospital mortality because we consider out-of-hospital mortality to be affected by healthcare delivery systems, which are not the focus of this study. Fig. 1 presents a flow diagram of the study selection process.

We screened titles and abstracts for relevance. Two investigators independently reviewed the shortlisted studies from the initial literature search and provided reasons for inclusion and exclusion. Then differences in investigators' decisions were discussed, and the articles to be included for this review were finalized. Utilizing the Cochrane Effective Practice and Organization of Care (EPOC) data collection resources guideline,¹⁸ an Excel data extraction form was created to record study information on eligibility, setting, study population, exposure, outcome, analysis, and results on the effects of heat and cold. In particular, we devised our data extraction template to allow for the recording of RRs for multiple lags. The Excel form was piloted and subsequently modified and finalized.

We sought data for quantitative information on the health effects of hot and cold temperatures. We recorded RRs for non-accidental (NACC), cardiovascular (CVD), respiratory (RESP), and cerebrovascular (CERE) mortality, as well as stratum-specific RR estimates for sex, age, and education. The estimates were obtained from the published tables, figures (when it was possible to precisely determine the estimates from the published material), through textual descriptions, and supplemental material. When information from figures was imprecise, or when there were detailed

data for the extraction table that seemed available but not provided in the article, we systematically contacted the authors to request further data. Examples for the latter included studies that generated location-specific estimates, aggregated by region, but only reported regional-level results.

Some studies reported temperature-based RRs, while other studies reported percentile-based RR estimates. When temperature based RRs were given, we recorded the reference temperature points and RR estimates associated with X degrees increase above the (higher) reference point or below the (lower) reference point. When percentile-based RR estimates were given, we recorded the percentiles used, along with the temperature points corresponding to these percentiles, and the RRs. Then we converted all RRs to RRs associated with one-degree increase/decrease above/below the reference temperature points used, assuming a log-linear relationship between mortality and temperature beyond the reference temperature points.

For studies that focused on the same city during the same time-period but stratified their analysis according to factors such as sub-regions, pollution levels, or multiple reference points, we conducted a meta-analysis to arrive at one estimate for each city for the specific time period. When both crude and adjusted estimates were given, we used the adjusted estimates.

2.3. Statistical analysis

2.3.1. Meta-analysis

We computed all-cause and cause-specific, stratum-specific RR estimates associated with hot and cold temperatures, using random-effects meta-analysis. Numerous studies included the same cities more than once. If multiple studies were using the same data, and were conducted by the same research group, we took the results for the most recent publication. If different research groups conducted the studies, we kept them all in the pooled analysis. We generated the city-specific RR estimates (non-accidental, cause-specific, stratum-specific), and then pooled all locations' RR estimates using random-effects meta-analysis. We defined socio-economic status as either education level or income status. We also calculated RRs by the five main climate groups of the Köppen climatic classification system (1976–2000 observed).¹⁹ We used I^2 to examine heterogeneity among effect estimates. I^2 statistics of 0~25, 25~50 and >50 indicated low, moderate, and significant heterogeneity, respectively. We used funnel plots to evaluate small study bias (a kind of publication bias) and used Duval and Tweedie's *Trim and Fill* procedure to examine the sensitivity of the results to small study bias.^{20,21}

To investigate the effect of adaptation, we then examined the associations between latitudes and heat/cold thresholds, and the associations between average temperatures and minimum mortality temperatures of study locations.

2.3.1.1. Lag selection for studies using distributed lag-non-linear model

The studies selected used various statistical methods, such as the generalized additive model (GAM), lag-stratified model, and the distributed lag-non-linear model (DLNM). DLNM RR estimates are temperature-specific and lag-day-specific. The direct comparison of DLNM estimates with estimates using other traditional methods is inappropriate. In addition, DLNM estimates show that heat effects occur soon, and last up to a few days, whereas cold effects can last

up to a few weeks. However, in the absence of a standard method of reporting the estimates, and informed by previous practices, we applied the following strategy: (a) if only one lagged estimate for a given cause or stratum was presented, this estimate was recorded in the data extraction table and subsequently used in the meta-analysis; (b) if more than one lag measure was presented (studies using DLNM), we used both the maximum and the minimum RR estimates, and summarized these estimates together with results that were with only one lag to generate summary estimates of RRmax and RRmin; (c) for studies using DLNM, most studies showed effect for a few days for heat and up to a few weeks for cold, so we restricted the lags for heat effects to between 0 and up to 5 days after day of exposure (cumulative RRs for lag0, lag0-1, lag0-2, lag0-3, lag0-4, lag0-5), restricted the lags for cold effects to between 2 and 3 weeks after day of exposure (cumulative RRs for lag0-13, lag0-14, ...lag0-20), selected both the maximum and the minimum RR estimates among these restricted lags (for heat and cold separately), and summarized these estimates together with the rest of studies to generate summary-effect estimates of maximum and minimum RRs of restricted lags (RRmax_rl and RRmin_rl).

2.3.1.2. Reference temperatures

For studies that used the DLNM analysis (most of the articles), the reference temperatures that were used to generate RRs for heat and cold effects varied. For example, some studies used pre-determined percentiles, some studies used thresholds informed by data, and others used minimum mortality temperature (MMT). Previous research found that beyond optimal temperatures, both heat and cold effects tend to be linear.²² Hence, we decided to simplify the presentation of results, and presented pooled results without stratifying by reference temperatures used.

2.3.2. Meta-regression

To further explore heterogeneity of effects and determinants of heterogeneity, we ran meta-regressions to investigate the associations between log-transferred RR estimates and a number of location-specific climatic, social, and economic characteristics. We considered latitude, longitude, air pressure, mean temperature, relative humidity, daily ground-level PM_{2.5}, contrast definition (i.e., extreme reference temperature vs. non-extreme), study period (i.e., median year of study period), human footprint, climate group, and whether the study adjusted for air pollution. We obtained multiyear data on meteorological variables as well as PM_{2.5} for each location using methods that were previously published.²³ We considered contrast definition because DLNM RRs are temperature-specific. We defined extreme contrasts where reference temperatures were in the 90th percentile or higher for heat effect and in the 10th percentile or lower for cold effect. The Human Footprint index reflects anthropogenic impacts on the environment, ranging from 0–50. It integrates eight types of human pressure: human population density; human land use and infrastructure, including built environments, electric infrastructure, croplands, pasture lands; and human access to roads, railways, and navigable waterways.²⁴ We downloaded the Human Footprint source data from Scientific Data (<https://datadryad.org/resource>) and summarized means of pixels in each of the studied locations using Zonal Statistics in ArcGIS 10.3.

We ran the meta-regression for each variable separately, conducted correlation analysis to assess collinearity of independent variables, and then included variables that showed little collinearity as well as moderate statistical significance (p-value≤0.20), separately for heat and cold.

We processed and analyzed the data in STATA MP 13.1 and in R software (3.5.1). We used the R packages “metaphor,” “mvmeta,” “meta,” and “data.table.” Fig. A1 was made using ArcGIS 10.3.

3. Results

3.1. Selection of Studies

We identified a total of 2356 articles in the initial search of the English databases, and a total of 550 articles in the initial search of the Chinese database. After removal of 744 duplicate records, and further elimination of 1870 obviously irrelevant articles based on title or abstract, we included 292 articles for full-text review. After applying all eligibility criteria to the full texts, 247 articles were excluded, and 45 articles were included in the final review.

3.2. Description of selected studies

The characteristics of the included studies are presented in Table 1. Among the 45 included articles, 34 were published in English, and 11 were published in Chinese (Fig. 1). Twenty studies encompassed multiple locations, including 3 studies that provided only regional estimates,²⁵⁻²⁷ and 25 studies focused on single locations (Fig. A.1). Four studies covered rural regions.^{26,70-72} The majority of the studies were conducted in the temperate zone (35 different locations/regions), the continental zone (6 different locations/regions), and the dry zone (7 different locations/regions). The tropical zone (Kaohsiung) and the polar zone (Naidong of Tibet) were each represented by just one location.

Forty-three studies were time-series by design and two studies were case-crossover by design. For exposure, 44 articles studied heat effects, while 40 studied cold effects. For outcomes, 29, 29, 17, and 12 studies investigated NACC, CVD, RESP, and CERE outcomes, respectively. In terms of statistical methods, 10 studies used traditional GAM, and 35 studies used DLNM. Thirty studies adjusted for air pollution. Twenty-two studies used the percentile-based approach, and 23 studies reported RR associated with temperature change beyond heat and/or cold thresholds.

3.3. Meta-analysis results

We present the pooled estimates of RR_{max} of restricted lags results in the main text (Table 2). We include pooled estimates of RR_{min} of restricted lags results, and we include RR_{max} and RR_{min} for unrestricted lags in the supplemental materials (Table S1–S3).

For every 1 degree of temperature increase/decrease beyond reference points, the rate of non-accidental mortality increased by 2% (RR, 1.02; 95% confidence interval (95% CI) [1.01-1.02]) for heat and 3% (RR, 1.03; 95% CI [1.03-1.04]) for cold, respectively (Table 2). The rate of cause-specific mortalities (cardiovascular, respiratory, cerebrovascular) increased between 2% and 3% for heat and between 2% and 6% for cold. RRs of cold mortality tended to be greater than that of heat mortality. Among the causes of mortality, cardiovascular seemed to have the highest RRs for both heat and cold, followed by cerebrovascular.

For non-accidental deaths associated with heat exposure, the RR difference between male (heat RR=1.03, 95% CI [1.02-1.03]) and female (heat RR=1.03, 95% CI [1.02-1.04]) was small. For non-accidental deaths associated with cold

Table 1. Study characteristics

Study	Language	Location	Data Period	Heat	Heat Exposure	Cold	Cold Exposure	NACC ^a	CVD ^b	RESP ^c	CERE ^d	Study Design	Statistical Methods	Adjusted for Air Pollution? (Y=Yes, N=No)	Air Pollutants
Wang 2018 ²⁸	ENG ^e	Multiple	2007-2012	x	DMT ^f	x	DMT	x				T-S ^g	GAM,DLNM ^h	N	
Song 2018 ²⁹	CHI ^e	Guangzhou	2011-2016	x	DMT	x	DMT	x				T-S	GAM,DLNM	Y	PM ₁₀ ⁱ , SO ₂ ^j , NO ₂ ^k , O ₃ ^l
Ban 2017 ³⁰	ENG	Multiple	2013-2015	x	DMT			x	x	x	x	T-S	GAM,DLNM	N	
Gao 2017 ³¹	ENG	Harbin	2008-2011	x	DMT			x	x		x	T-S	GAM	Y	NO ₂ , SO ₂ , PM ₁₀
He 2017 ³²	CHI	Taizhou	2014-2016	x	DMT	x	DMT		x		x	T-S	GAM,DLNM	Y	API ^m
Tang 2017 ³³	CHI	Hefei	2007-2016	x	DMT	x	DMT	x	x			T-S	GAM,DLNM	Y	NO ₂ , SO ₂ , PM ₁₀
Zhang 2017a ³⁴	ENG	Hubei	2009-2012	x	DMT	x	DMT	x				T-S	GAM,DLNM	N	
Zhang 2017b ²⁷	ENG	Multiple	2007-2012	x	DMT	x	DMT	x				T-S	GAM,DLNM	N	
Zhou 2017 ³⁵	ENG	Multiple	2009-2013	x	DMT				x			T-S	GAM,DLNM	N	
Ding 2016 ³⁶	ENG	Yuxi	2009-2014	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	N	
Li 2016 ³⁷	ENG	Chongqing	2010-2013	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Ma 2016 ³⁸	CHI	Multiple	2008-2010	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Wang 2016 ³⁹	CHI	Wuhan	2004-2008	x	DMT	x	DMT		x	x		T-S	GAM,DLNM	Y	AQI ^m
Zhang 2016 ⁴⁰	ENG	Wuhan	2003-2010	x	DMT	x	DMT	x	x	x	x	T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Chung 2015 ⁴¹	ENG	Multiple	1994-2007	x	MDMT ^f	x	MDMT	x	x	x		T-S	GAM	Y	O ₃ , PM ₁₀
Huang 2015 ²⁵	ENG	Multiple	2006-2011	x	DMT	x	DMT	x				T-S	GAM,DLNM	N	
Li 2015 ⁴²	ENG	Guangzhou	2003-2011	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	Y	PM ₁₀
Wang 2015 ⁴³	ENG	Multiple	2007-2009	x	DMT	x	DMT		x		x	T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Yang 2015a ⁴⁴	ENG	Shanghai	1981-2012	x	DMT	x	DMT		x			T-S	GAM,DLNM	N	
Yang 2015b ⁴⁵	CHI	Multiple	2008-2011	x	MDMT	x	MDMT		x			T-S	GAM	N	
Yi 2015 ⁴⁶	ENG	Hongkong	2002-2011	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	Y	PM ₁₀ , NO ₂ , SO ₂
Zhang 2015 ⁴⁷	CHI	Taian	2009-2013	x	DMT	x	DMT	x				T-S	GAM,DLNM	Y	API
Bai 2014 ⁴⁸	ENG	Multiple	2008-2012	x	DMT	x	DMT	x	x			T-S	GAM,DLNM	N	
Guo 2014 ²²	ENG	Multiple	2002-2011	x	DMT	x	DMT	x				T-S	GAM,DLNM	Y	PM ₁₀ , NO ₂ , SO ₂
Huang 2014 ⁴⁹	ENG	Changsha	2008-2011	x	DMT	x	DMT		x			T-S	GAM,DLNM	Y	API
Li 2014 ⁵⁰	ENG	Jinan	2008-2012	x	DMT	x	DMT		x	x	x	T-S	GAM,DLNM	Y	API
Wang 2014 ⁵¹	ENG	Suzhou	2005-2008	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Xie 2014 ⁵²	CHI	Multiple	2006-2009	x	DMT	x	DMT	x				C-C ^g	GAM,DLNM	N	

Zhang 2014a ⁵³	ENG	Multiple	2007-2008	x	DMT	x	DMT	x				T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Zhang 2014b ⁵⁴	ENG	Multiple	2004-2008	x	DMT	x	DMT				x	T-S	GAM,DLNM	Y	PM ₁₀ , NO ₂
Chen 2013 ⁵⁵	ENG	Multiple	2007-2008	x	DMT	x	DMT				x	T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Goggins 2013a ⁵⁶	ENG	Multiple	1999-2009			x	MDMT	x				T-S	GAM	Y	NO ₂ , SO ₂ , PM ₁₀ , O ₃
Goggins 2013b ⁵⁷	ENG	Kaohsiung	1999-2008	x	MDMT			x				T-S	GAM	Y	O ₃
Guo 2013 ⁵⁸	ENG	Multiple	2004-2008	x	DMT	x	DMT		IHD ^b			T-S	GAM,DLNM	Y	PM ₁₀ , NO ₂
Lin 2013 ⁵⁹	ENG	Multiple	1994-2007	x	DMT	x	DMT		IHD		x	T-S	GAM,DLNM	Y	NO ₂ , O ₃ , PM ₁₀
Wu 2013 ⁶⁰	ENG	Multiple	2006-2009	x	DMT	x	DMT	x				T-S	GAM,DLNM	Y	API
Chan 2012 ⁶¹	ENG	Hongkong	1998-2006	x	DMT	x	MDMT	x	x	x	x	T-S	GAM	Y	NO ₂ , SO ₂ , PM ₁₀ , O ₃
Goggins 2012 ⁶²	ENG	Hongkong	2001-2009	x	MDMT	x	MDMT					T-S	GAM	N	
Tian 2012 ⁶³	ENG	Beijing	2000-2011	x	DMT	x	DMT		CHD ^b			T-S	GAM,DLNM	N	
Yang 2012 ⁶⁴	ENG	Guangzhou	2003-2007	x	DMT	x	DMT	x	x	x	x	T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Zhang 2012 ⁶⁵	CHI	Shanghai	2001-2008	x	DMT	x	DMT	x	x	x		T-S	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂ , O ₃
Guo 2011 ⁶⁶	ENG	Tianjin	2005-2007	x	DMT	x	DMT	x	x	x		C-C	GAM,DLNM	Y	PM ₁₀ , SO ₂ , NO ₂
Liu 2011 ⁶⁷	ENG	Beijing	2003-2005	x	MDMT	x	MDMT		x	x	x	T-S	GAM	N	
Pei 2011 ⁶⁸	CHI	Multiple	1998-2008	x	DMT							T-S	GAM	N	
Yan 2011 ⁶⁹	CHI	Guangzhou	2006-2009	x	DMT	x	DMT	x	x	x		T-S	GAM	Y	NO ₂ , SO ₂ , PM ₁₀

Notes.

^a NACC: Non-accidental.

^b CVD: Cardiovascular; IHD: Ischemic Heart Diseases; CHD: Coronary Heart Disease.

^c RESP: Respiratory.

^d CERE: Cerebrovascular.

^e ENG: English; CHI: Chinese.

^f DMT: Daily Mean Temperature; MDMT: Multiple-Day Mean Temperature.

^g T-S: Time-Series; C-C: Case-Crossover.

^h GAM: Generalized Additive Model; DLNM: Distributed Lag Non-Linear Model.

ⁱ PM₁₀: Particulate Matter 10 Micrometers or Less in Diameter.

^j SO₂: Sulfur Dioxide.

^k NO₂: Nitro Dioxide.

^l O₃: Ozone.

^m API: Air Pollution Index; AQI: Air Quality Index

exposure, the RR among males (cold RR=1.04, 95% CI [1.02-1.07]) was similar to that among females (cold RR=1.04, 95% CI [1.02-1.06]).

Elderly people (age > 65 years, heat RR=1.03, 95% CI [1.02-1.04]) were more vulnerable to heat than younger people (age ≤ 65 years, heat RR= 1.01, 95% CI [1.01-1.02]). The RRs associated with cold were similar between older (age > 65 years, cold RR=1.05, 95% CI [1.02-1.08]) and younger people (age ≤ 65 years, cold RR=1.06, 95% CI [1.02-1.09]).

The RRs associated with heat were similar between populations with higher socioeconomic status (high SES heat RR=1.04, 95% CI [1.01-1.07]) and populations with lower socioeconomic status (lower SES heat RR=1.04, 95% CI [1.02-1.08]). For cold-related mortality, one-degree of change in temperature was associated with a 1% increase in cold-related mortality (heat RR=1.01, 95% CI [1.00-1.02]) among people with a higher socioeconomic status, and a 4% increase in cold-related mortality (cold RR=1.04, 95% CI [0.97-1.11]) among people with a lower socioeconomic status.

There seemed to be a variation of heat and cold effects across climate zones. The temperate zone had the highest RR for heat-related mortality, whereas the dry zone had the highest RR for cold-related mortality.

Sensitivity analysis (RRmin_rl pooled estimates, RRmax pooled estimates, RRmin pooled estimates) showed small changes, but the patterns that we observed in the results from maximum estimates of restricted lags persisted in results of minimum estimates of restricted lags and results of unrestricted lags (Table S1–S3). For example, we still saw that, for every degree of change beyond reference temperature points, cold still had higher RRs than heat, with cardiovascular having the highest RRs among three causes; elderly people still had higher RRs than their younger counterparts for heat; and people with a higher socioeconomic status still had lower RRs for both heat and cold.

We found large heterogeneity among effect estimates (all $I^2 > 50\%$). Funnel plots (Fig. A.3) showed evidence of small study bias for heat effect (Egger test p-value < 0.01) and no evidence of study bias for cold effect (Egger test p-value=0.19). For heat effect, we used Duval and Tweedie's *Trim and Fill* procedure to remove the more extreme small studies from the positive side of the funnel plot, and recomputed effect size until the funnel plot was symmetric about the (new) effect size. We used random-effects models in this procedure. We then re-displayed the funnel plot, taking into account the *Trim and Fill* adjustment (Fig. A.4). In Fig. A.6, the observed studies were shown in filled triangles, and the imputed studies were shown in filled circles.

For heat effects, the observed point estimate in log units was at 0.021 (95% CI: 0.018, 0.023), corresponding to an RR of 1.021 (95% CI: 1.018, 1.023); the imputed point estimates in log units was at 0.013 (95% CI: 0.011, 0.016), corresponding to an RR of 1.013 (95% CI: 1.011, 1.016). The “adjusted” point estimate suggested a lower RR than the original analysis, but still a statistically significant increase. For cold effects, no trimming was performed.

Higher heat thresholds were observed in populations living in lower latitudes (Fig. 2). Similarly, lower cold thresholds were observed in populations living in higher latitudes. In addition, we found that the slope for cold thresholds was higher than the slope for heat thresholds, indicating that populations studied were better at adapting to cold than to heat.

3.4. Meta-regression results

The large heterogeneity found in meta-analyses (all $I^2 > 50\%$) suggests existence of study characteristics influencing this variability. Correlation analysis found that latitude is strongly correlated with mean temperature ($r > 0.87$), relative humidity ($r > 0.67$), and climate classification ($r > 0.80$).

Table S4 presents the meta-regression results for heat effects, and Table S5 presents the meta-regression results for cold effects. We found that reference points of the 90th percentile or higher, and having higher air pressure, were significantly associated with a 1% increase in RRs for heat effects ($p\text{-value}=0.005$), and that locations having higher temperatures (being in the top tertile) were significantly associated with a 2% increase in RRs for heat effects ($p\text{-value}=0.005$). We did not find confounding adjusted to be related to RRs for heat, and we did not find relative humidity or climate group to be contributing factors to heterogeneity in the heat RRs.

4. Discussion

4.1. Main findings

In this systematic review, we assessed the published literature on the association between daily mean temperatures and mortality in China. We found that cold-related RRs are in general higher than heat-related RRs. We also found that among the causes of death (cardiovascular, respiratory, and cerebrovascular), cardiovascular diseases seem to have the highest increase in mortality rate for every 1 degree change in temperature. We found that elderly people (>65 years old) have a higher percent increase in mortality rate due to heat compared to younger people (≤ 65 years old). We also found that people who have a higher socioeconomic status are less susceptible to the effects of heat and cold.

We also identified a relationship between latitude and heat, as well as between latitude and cold thresholds. As latitudes increase from south to north (low to high), the heat thresholds decrease, and the cold thresholds increase, suggesting human adaptation. In addition, we observed that cold thresholds drops at a higher rate than heat thresholds, suggesting that humans have a greater ability to adapt to changes in cold than to heat.

Meta-regression suggested that contrast definition, higher air pressure, and higher local temperature were positively associated with heat effects.

4.2. Validity of studies

4.2.1. Validity of individual studies

We appraised the validity of the studies in the following four areas: exposure, outcome, statistical approach and confounder.

For exposure, all included studies used daily mean temperature as the exposure parameter, and they retrieved temperature data from official weather data sharing systems, either at the national or at the provincial/municipal level. Although there may be topographical variation in actual temperature exposures for people in the same study

location,^{73,74} we considered the temperature monitoring to be sufficiently consistent, and we found that there were no major biases in exposure assessment.

For outcome, all the studies obtained mortality data from China's Center for Disease Control and Prevention (or its equivalent agencies in Hong Kong and Taiwan). The healthcare system in China, especially in urban areas, is rather homogeneous. In China, death certificates are completed at the time of death, either by community doctors (for deaths at home) or by hospital doctors (for deaths in a hospital), and reported to the Center for Disease Control and Prevention. A validation study of cause-of-death statistics in urban China used expert review of medical records as the reference. The study found that the death registration system had good sensitivity in diagnosing cerebrovascular disease and average sensitivity for some major causes of adult death in China. Diagnostic misclassification appeared to balance each other at the population level.⁷⁵ We found no validation study in China that verifies cause of death using autopsy. All the studies included in the review applied the International Classification of Diseases and Health Problems (ICD) 9th revision and the ICD 10th revision codes to define non-accidental, cardiovascular, respiratory, and cerebrovascular causes of death, which enhances comparability across the studies. Noteworthy is that the majority of the studies (40 out of 45) were restricted in scope to urban areas. This is likely because the death registry is not well-established in suburban, rural, and remote areas in China.⁷⁶ Thus, the results of this review may not be representative of rural and remote areas in China.

For modelling choices, the majority of studies (35 out of 45) used DLNM, and 10 studies used GAM. It is not appropriate to make direct comparison of results from these two statistical approaches, so we addressed this uncertainty by including sensitivity analysis as part of the validity appraisal. The sensitivity analysis showed small changes in summary estimates, and the pattern we observed remained unchanged in the results of the sensitivity analysis. In terms of reporting, among studies that used DLNM, 15 out of 35 studies on heat effects reported only one lag, and 14 out of 35 studies on cold effects reported only one lag. The authors did not present sufficient justification for the choice of lag(s) reported. The individual choices of lags reported can introduce some uncertainty in our summary estimates. Hence, we propose several ways by which investigators can build upon DLNM and make methodological improvements. For example, there need to be guidelines on how to report and interpret RRs. In addition, investigators can consider generating additional effect estimate measures, for example, by calculation of the volume under the lag-temperature-RR surface of DLNM, generate an overall attributable risk. Lastly, investigators can find ways to account for the changes in pool of people with high susceptibility to avoid harvesting effects. We also call for validation studies in order to improve the comparability of various statistical methods.

The studies adjusted for confounders to different degrees. The majority of studies (30 out of 45) adjusted for air pollution. Among them, 22 adjusted for PM₁₀, 21 adjusted for NO₂, 18 adjusted for SO₂, 4 adjusted for O₃, and 5 adjusted for air pollution index. We included a variable for confounding adjustment (i.e., adjusted for air pollution? Yes or No) in the meta-regression and did not find the variable to be a significant contributor to RR heterogeneity.

4.2.2. *Validity of meta-analysis*

We appraised the validity of meta-analysis in the following three areas: literature search, publication bias, and meta-regression.

Our literature search was thorough. We included three major English literature databases and one Chinese database in our search, and updated our search to include publications up to July 2018.

We identified some study bias in heat effects but not in cold effects. We used Duval and Tweedie's *Trim and Fill* procedure to investigate the potential impact of the small study bias, and although the adjusted estimates were lower than the original analysis, they still had the same substantive implications.

For meta-regression, we included over 40 studies and over 100 locations. Although this is a large number of studies in relation to reviews of such topics, there is still the possibility that we had limited power to detect potential modifiers of the effect estimates.

4.3. Synthesis

We found in our results that cold RRs are in general greater than heat-related RRs. This is consistent with findings from an earlier meta-analysis based on a smaller number of studies.¹⁶ This finding is also consistent with a large-scale, multiyear study from the United States, and similar to results from a recently published large-scale study that includes data from 272 main Chinese cities.^{55,77}

We found that the percentage increase of cardiovascular mortality is highest for three causes of death for both heat and cold: cardiovascular, respiratory, and cerebrovascular. This finding is similar to results in a recent large Chinese study.⁵⁵ However, the same trend was not observed in a large study from the United States, which found that respiratory RRs were higher than cardiovascular RRs for both heat and cold.⁷⁸ A systematic review and meta-analysis of ambient temperature and mortality among the elderly found that for heat effects, cardiovascular RRs are the highest, followed by respiratory and then cerebrovascular RRs; for cold effects, respiratory RRs are highest, followed by cardiovascular and then cerebrovascular.⁷⁸ The difference across regions may be attributable to differences in available adaptation strategies, such as heating during winter and air conditioning use for cooling during hot seasons.^{55,79} The difference between different age groups may be attributable to differences in the physiological ability to adapt to non-optimal temperatures. In addition, there were methodological differences between our review and previous reviews. For example, previous reviews often chose lag with the most statistically significant RRs or the largest effect estimate, whereas in our analysis, we used a "restricted lags" approach complimented by a sensitivity analysis.

To date, the underlying environmental and physiological mechanisms for various lag effects of health and cold exposure remain unclear and need investigation.⁸⁰ Each mortality outcome has its own induction period in response to non-optimal thermal stress. For example, in winter, bacterial infection, which may result in respiratory mortality, usually takes a few weeks to develop. In comparison, cardiac arrest has a shorter induction period. This discrepancy suggests that the calculation of cold effects on respiratory mortality outcome would require a longer lag period than that on outcomes requiring a shorter induction period, such as cardiac arrest. We think taking into consideration the bio-plausibility of outcomes could inform lag identification for the outcomes and help make results easier to interpret.

We also have found few studies on temperature-related mortality among populations with pre-existing diseases.

Having pre-existing conditions may increase people's susceptibility to other diseases, thereby changing the induction period for various disease outcomes.

We found a clear and consistent increase in RR among people with a lower socioeconomic status, especially for cold.

Having a lower socioeconomic status may result in a lack of heating options, a lack of housing that is weatherized or insulated for cold weather, and more occupational exposure to thermal stress. Any of these conditions would result in a higher susceptibility to cold exposure.⁸³⁻⁸⁷

4.4. Further studies / gaps

For future research, we identified needs for research on temperature and health that (1) address rural populations and cover more geographical regions; (2) address sub-populations that are particularly exposed to thermal stress, such as those with occupational exposure to extreme hot or cold; (3) address sub-populations with pre-existing diseases that make them more susceptible to thermal stress; (4) differentiate specific causes of deaths in terms of induction periods based on biological plausibility; (5) use additional outcome measures, such as Years of Life Lost and measures on an absolute scale, to better convey heat and cold health impacts; (6) further explore factors that moderate the effects of non-optimal temperatures, such as greenspace and city infrastructure; (7) evaluate policies and health interventions that can help with mitigating the impact of heat and cold and the adaption to heat and cold exposures, such as early warning systems for heat and cold.

5. Conclusion

This is the first English systematic review that summarized the recent literature on daily mean temperature and mortality in China. Our review included studies in both English and Chinese. We found consistent evidence of the association between non-optimal temperature and cause-specific mortality outcomes. We found that generally cold effects are greater than heat effects, with cardiovascular mortality having the greatest percentage increase for both heat and cold exposure, followed by cerebrovascular and respiratory mortality. Consistent with previous studies, we found evidence of human adaptation to different climates, including a greater capacity in adapting to cold than to heat. We found consistent evidence of higher vulnerability to cold among people with a lower socioeconomic status. We identified some gaps in knowledge, and we proposed future avenues of research.

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Tables

Table 1. Study characteristics (embedded in text)

Table 2. Heat effects (restricted to lag 0 to lag0-3) and cold effects (lag 0-14 to lag 0-20): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen major group (maximum RRs)

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Table A.2. Heat effects (lags unrestricted) and cold effects (lags unrestricted): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen major group (maximum RRs)

Table A.3. Heat effects (lags unrestricted) and cold effects (lags unrestricted): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen major group (minimum RRs)

Table A.4. Meta-regression model investigating the predictors of log[rate ratio]s of heat-related non-accidental mortality

Table A.5. Meta-regression model investigating the predictors of log[rate ratio]s of cold-related non-accidental mortality

Table 2. Heat Effects (restricted to Lag 0 to Lag0-3) and Cold Effects (Lag 0-14 to Lag 0-20): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen Major Group (maximum RRs)

	<i>Heat Effects RR^a (95% CI^b)</i>	<i>Cold Effects RR (95% CI)</i>
Cause of Death		
Non-accidental	1.020 (1.015-1.024)	1.035 (1.026-1.045)
Cardiovascular	1.034 (1.026-1.043)	1.056 (1.039-1.073)
Respiratory	1.017 (1.009-1.025)	1.020 (0.999-1.042)
Cerebrovascular	1.021 (1.015-1.026)	1.033 (1.024-1.042)
Sex		
Male	1.023 (1.017-1.030)	1.043 (1.021-1.065)
Female	1.026 (1.015-1.038)	1.039 (1.020-1.058)
Age		
Age <65	1.014 (1.010-1.019)	1.056 (1.020-1.093)
Age ≥65	1.029 (1.017-1.041)	1.051 (1.022-1.080)
Socioeconomic status		
Low	1.043 (1.005-1.082)	1.038 (0.969-1.112)
High	1.037 (1.009-1.067)	1.011 (1.001-1.021)
Climate Zone		
Dry (Arid) climate	1.013 (1.005-1.020)	1.065 (1.001-1.133)
Temperate climate	1.025 (1.016-1.035)	1.038 (1.025-1.050)
Continental climate	1.012 (1.006-1.018)	1.025 (1.017-1.032)

^a RR: Rate ratio

^b 95% CI: 95% Confidence interval

Appendices

Table A.1. Heat effects (restricted to Lag 0 to Lag0-3) and cold effects (Lag 0-14 to Lag 0-20): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen major group (minimum RRs)

	<i>Heat Effects RR^a (95% CI^b)</i>	<i>Cold Effects RR (95% CI)</i>
Cause of Death		
Non-accidental	1.018 (1.014-1.022)	1.033 (1.025-1.042)
Cardiovascular	1.033 (1.024-1.042)	1.049 (1.035-1.063)
Respiratory	1.016 (1.008-1.025)	1.020 (0.999-1.042)
Cerebrovascular	1.021 (1.015-1.027)	1.031 (1.023-1.039)
Sex		
Male	1.023 (1.016-1.029)	1.043 (1.021-1.065)
Female	1.025 (1.013-1.037)	1.039 (1.020-1.058)
Age		
Age <65	1.014(1.010-1.019)	1.052 (1.016-1.090)
Age ≥65	1.028 (1.016-1.040)	1.048 (1.023-1.074)
Socioeconomic status		
Low	1.037 (0.995-1.080)	1.038 (0.969-1.112)
High	1.025 (0.994-1.058)	1.011 (1.001-1.021)
Climate Zone		
Dry (Arid) climate	1.012 (1.005-1.019)	1.065 (1.001-1.133)
Temperate climate	1.021 (1.015-1.028)	1.035 (1.025-1.046)
Continental climate	1.012 (1.006-1.018)	1.025 (1.017-1.032)

^a RR: Rate ratio

^b 95% CI: 95% Confidence interval

Table A.2. Heat effects (lags unrestricted) and cold effects (lags unrestricted): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen major group (maximum RRs)

	<i>Heat Effects RR^a (95% CI^b)</i>	<i>Cold Effects RR (95% CI)</i>
Cause of Death		
Non-accidental	1.017 (1.014-1.021)	1.030 (1.024-1.035)
Cardiovascular	1.036 (1.026-1.045)	1.051 (1.038-1.065)
Respiratory	1.035 (1.015-1.056)	1.028 (1.010-1.046)
Cerebrovascular	1.022 (1.016-1.027)	1.034 (1.025-1.044)
Sex		
Male	1.025 (1.018-1.032)	1.043 (1.027-1.058)
Female	1.027 (1.017-1.036)	1.043 (1.025-1.062)
Age		
Age <65	1.017 (1.011-1.024)	1.056 (1.028-1.085)
Age ≥65	1.032 (1.019-1.045)	1.060 (1.035-1.086)
Socioeconomic status		
Low	1.050 (1.019-1.081)	1.037 (1.004-1.071)
High	1.034 (1.012-1.057)	1.019 (1.010-1.028)
Climate Zone		
Dry (Arid) climate	1.012 (1.005-1.020)	1.042 (1.019-1.066)
Temperate climate	1.021 (1.015-1.027)	1.034 (1.026-1.043)
Continental climate	1.015 (1.010-1.021)	1.014 (1.006-1.022)

^a RR: Rate ratio

^b 95% CI: 95% Confidence interval

Table A.3. Heat effects (lags unrestricted) and cold effects (lags unrestricted): summary estimates of rate ratios (RRs) associated with 1 ° change beyond reference temperatures, by cause of death, sex, age, socioeconomic status, and Köppen major group (minimum RRs)

	<i>Heat Effects RR^a (95% CI^b)</i>	<i>Cold Effects RR (95% CI)</i>
Cause of Death		
Non-accidental	1.014 (1.011-1.016)	1.017 (1.012-1.022)
Cardiovascular	1.028 (1.019-1.038)	1.021 (1.011-1.030)
Respiratory	1.025 (1.004-1.046)	1.000 (0.985-1.015)
Cerebrovascular	1.019 (1.010-1.028)	1.023 (1.014-1.033)
Sex		
Male	1.022 (1.015-1.029)	1.022 (1.010-1.033)
Female	1.024 (1.015-1.033)	1.020 (1.008-1.032)
Age		
Age <65	1.013 (1.007-1.020)	1.029 (1.003-1.057)
Age ≥65	1.023 (1.008-1.038)	1.020 (1.008-1.031)
Socioeconomic status		
Low	1.039 (1.006-1.073)	1.009 (0.993-1.026)
High	1.017 (0.984-1.052)	1.006 (0.996-1.016)
Climate Zone		
Dry (Arid) climate	1.012 (1.005-1.019)	1.026 (1.004-1.048)
Temperate climate	1.015 (1.011-1.019)	1.016 (1.009-1.023)
Continental climate	1.014 (1.008-1.020)	1.008 (0.999-1.018)

^a RR: Rate ratio

^b 95% CI: 95% Confidence interval

Table A.4. Meta-regression model investigating the predictors of log[rate ratio]s of heat-related non-accidental mortality

Regressors	β (95% CI ^a , exponentiated)
Extreme reference temperature	1.012 (1.002-1.022) *
Air pressure (ref=lower half)	1.015 (1.003-1.027) *
Temperature (ref=lower two tertiles)	1.019 (1.007-1.030) *
Relative humidity (ref=lowest quartile)	0.992 (0.974-1.010)
Temperate climate (ref=arid climate)	0.999 (0.977-1.021)
Continental climate (ref=arid climate)	0.996 (0.970-1.021)
Longitude	1.000 (0.999-1.001)
Constant	1.007 (0.914-1.109)

* statistically significant (p-value<0.05)

^a 95% CI: 95% Confidence interval

Table A.5. Meta-regression model investigating the predictors of log[rate ratio]s of cold-related non-accidental mortality

Regressors	β (95% CI ^a , exponentiated)		
Extreme reference temperature	1.010	0.982	1.038
Air pressure (ref=lower half)	0.994	0.971	1.018
Temperature(ref=lower two tertiles)	0.993	0.963	1.024
Study year	1.003	0.999	1.007
Constant	0.003	0.000	5.514

^a 95% CI: 95% Confidence interval

Figures

Fig. 1. Flow diagram of study selection process

Fig. 2. Heat and cold thresholds against latitude

Figures in Appendices

Fig. A.1. Location of studies

Fig. A.2. Forest plots of rate ratios for non-accidental mortality

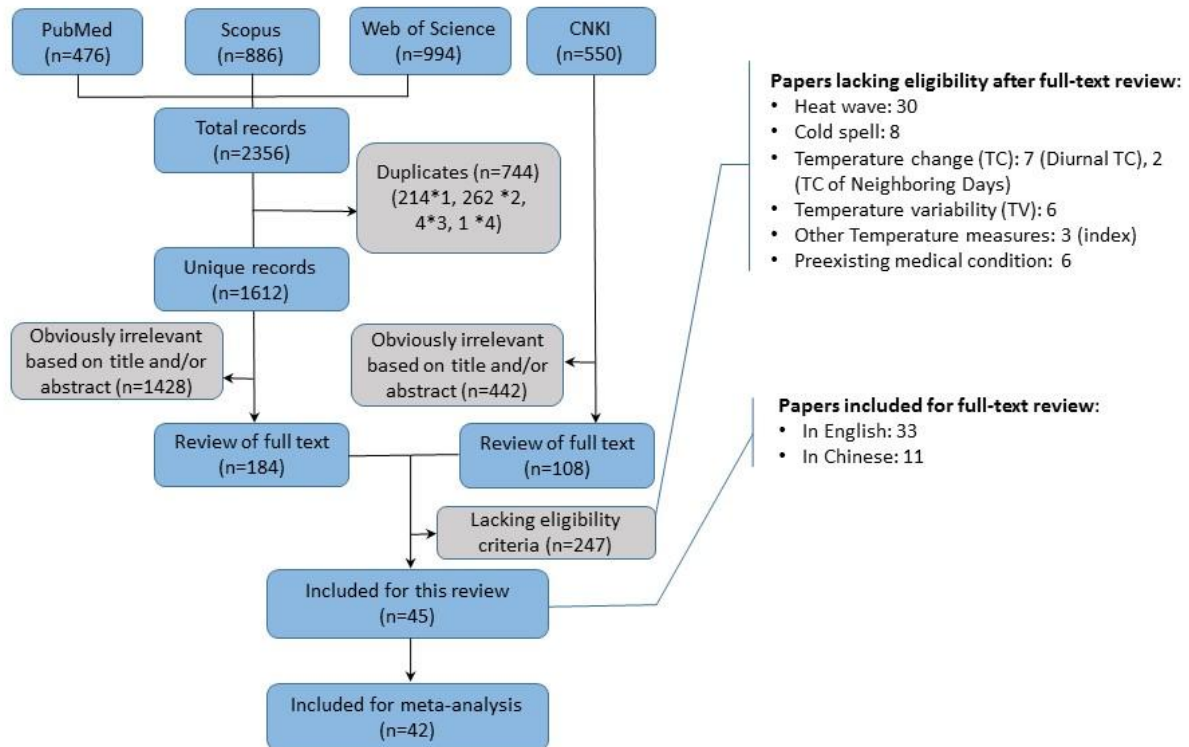
Fig. A.3. Funnel plots for non-accidental mortality (NACC)

Fig. A.4. Funnel plots of non-accidental mortality (NACC) with imputed studies

Fig. A.5. Thresholds vs. mean temperatures

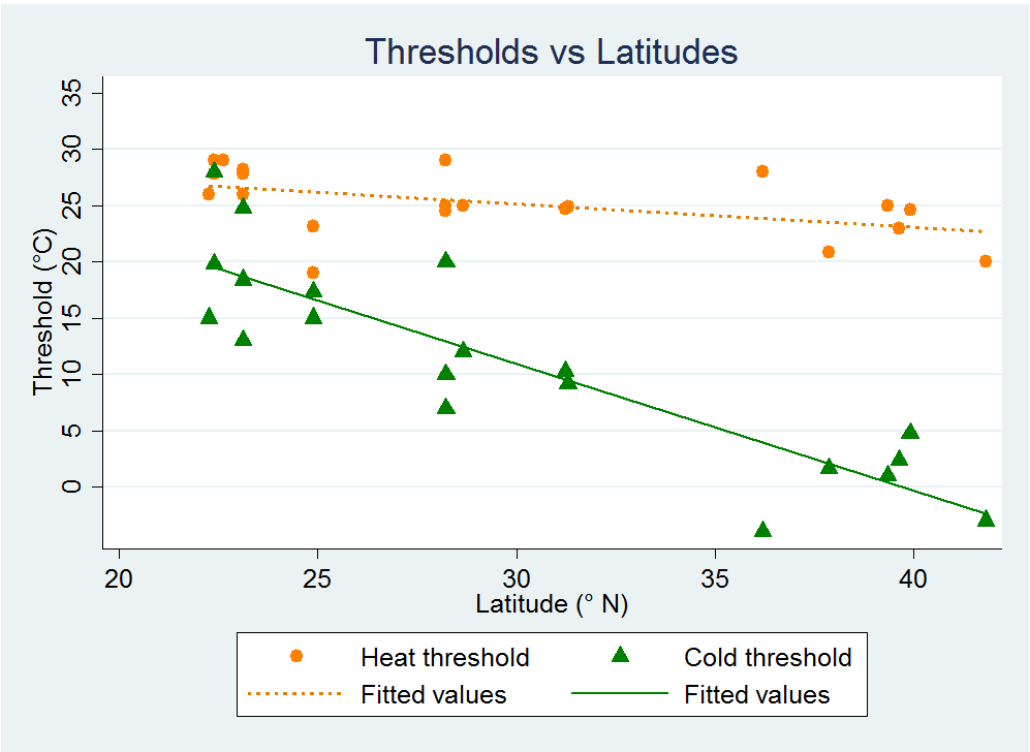
Fig. A.6. Minimum mortality temperature (MMT) vs. mean temperatures

Fig. 1. Flow diagram of study selection process. Exclusion of articles was done in three consecutive steps based on *a*) irrelevance of the title and/or the abstract, *b*) the general eligibility criteria after close inspection of the full text, and *c*) the meta-analysis eligibility criteria (meta-analysis only).



CNKI: China knowledge infrastructure

Fig. 2. Heat and cold thresholds against latitude



Appendices

Fig. A.1. Location of studies

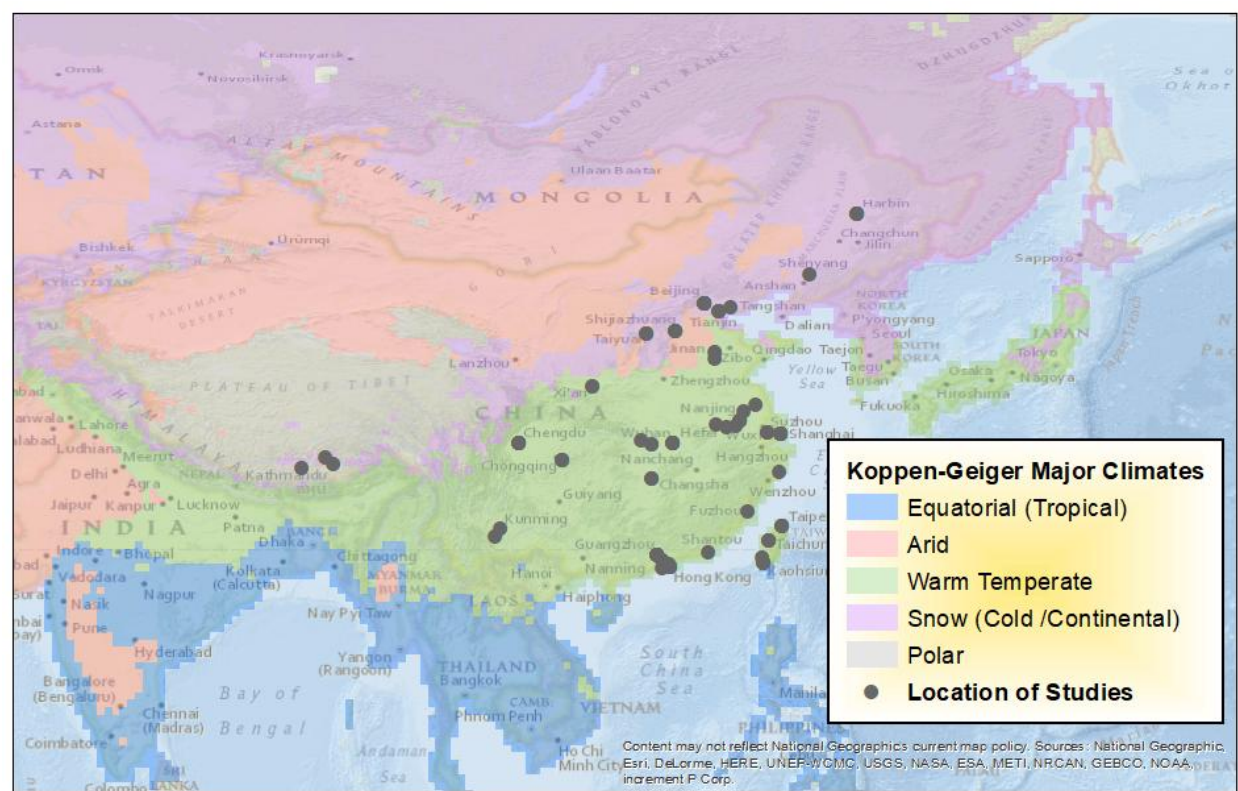
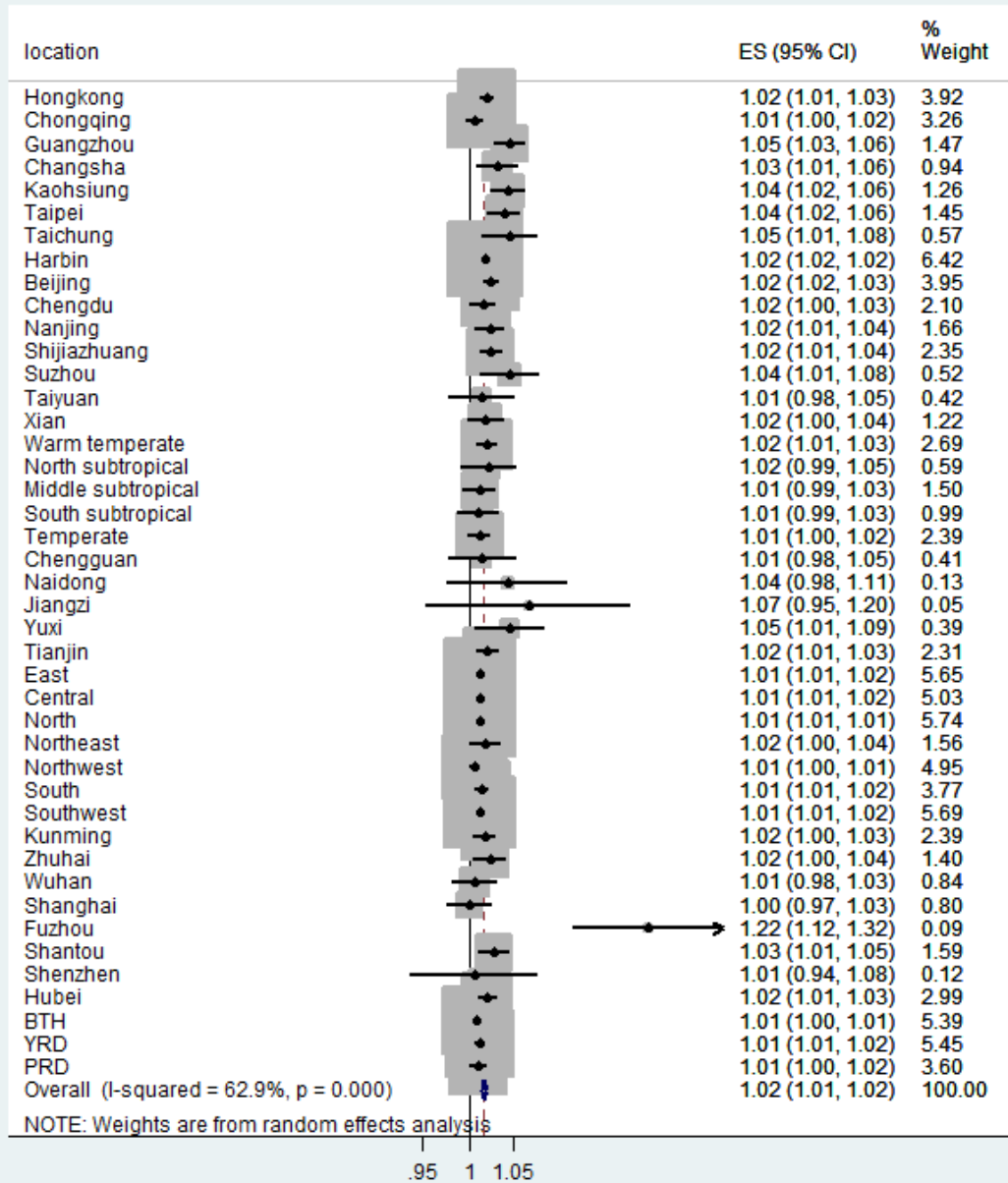


Fig. A.2. Meta-analysis of rate ratios (RR) for non-accidental mortality (NACC)

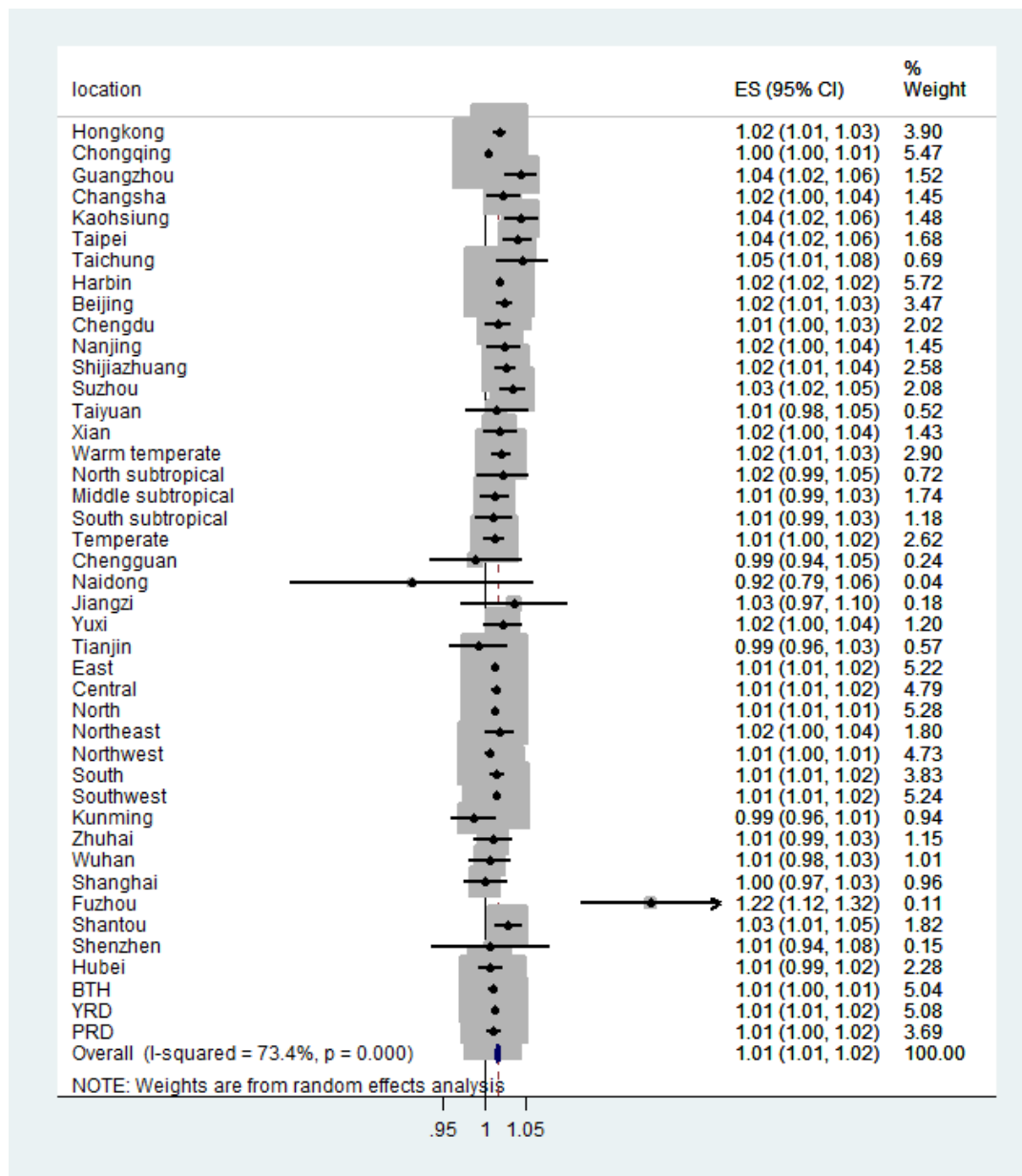
(a). Rate ratios for heat effect, maximum, restricted lags, non-accidental mortality



ES: Effect size.

95% CI: 95% confidence interval

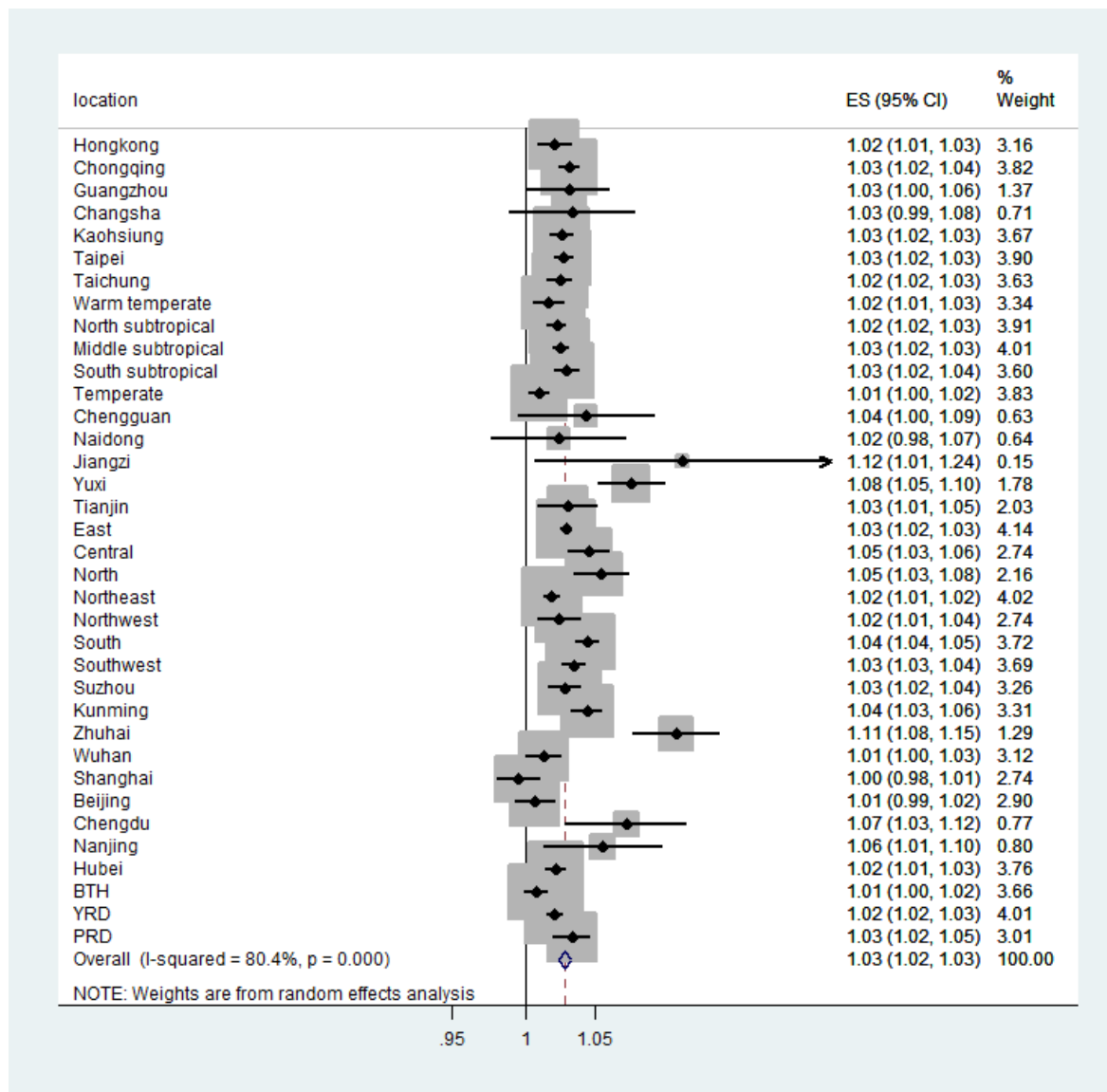
(b). Rate ratios for heat effect, minimum, restricted lags, non-accidental mortality



ES: Effect size.

95% CI: 95% confidence interval

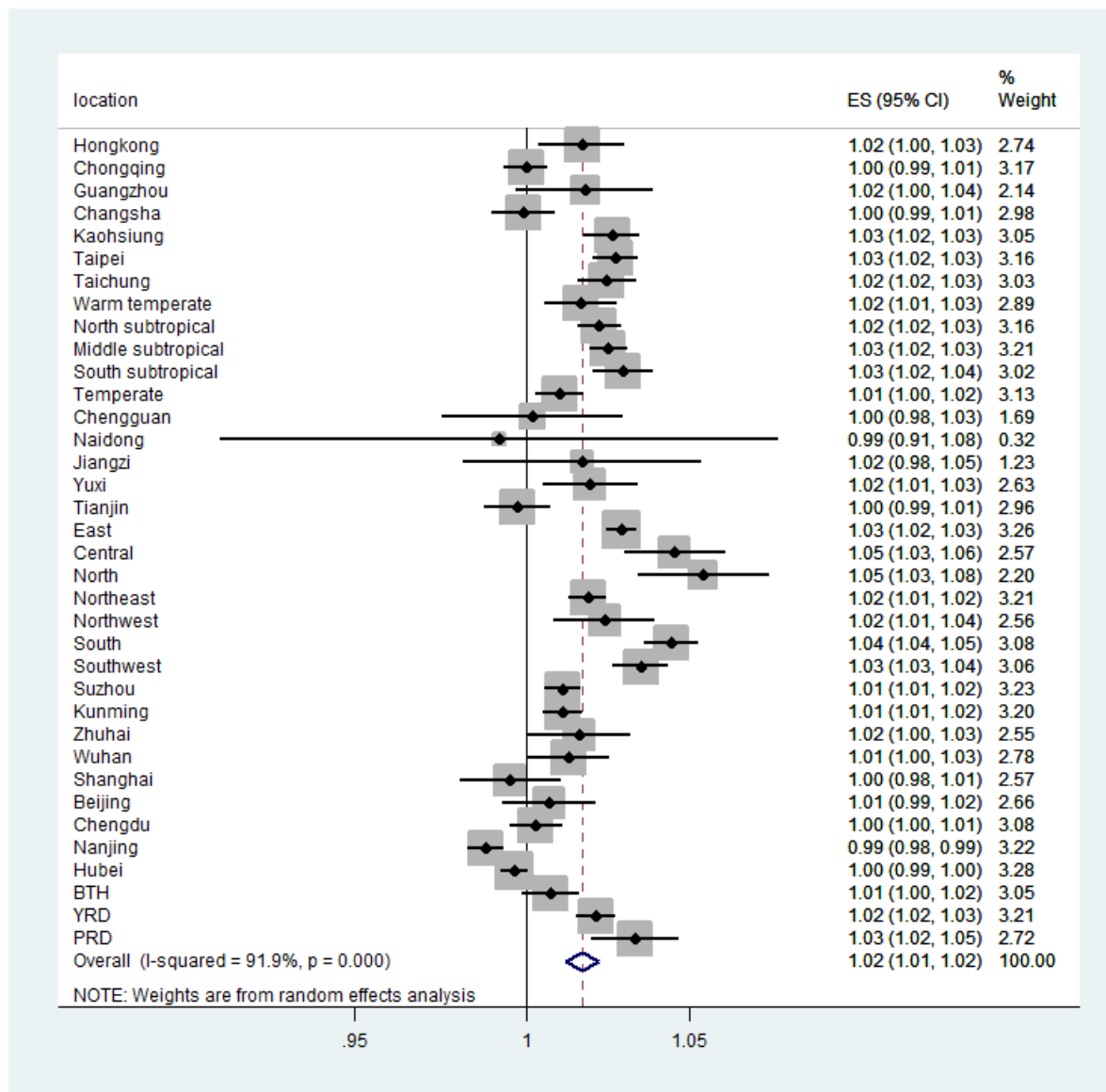
(c). Rate ratios for cold effect, maximum, restricted lags, non-accidental mortality



ES: Effect size.

95% CI: 95% confidence interval

(d). Rate ratios for cold effect, minimum, restricted lags, non-accidental mortality

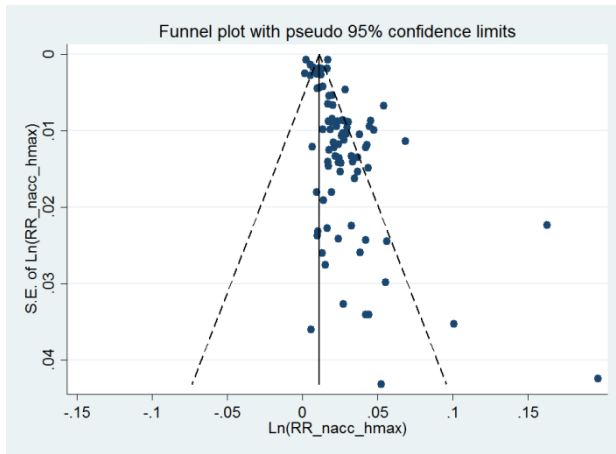


ES: effect size.

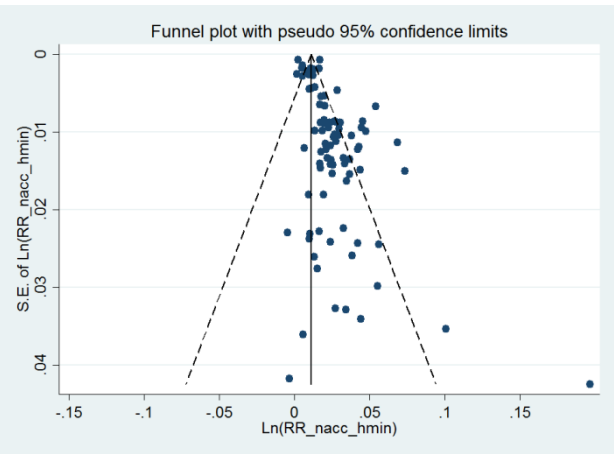
95% CI: 95% confidence interval

Fig. A.3. Funnel plots for non-accidental mortality (NACC)

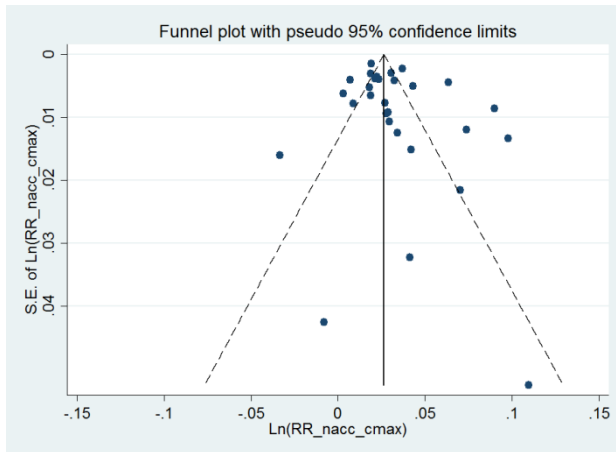
(a). Hmax_rl, NACC



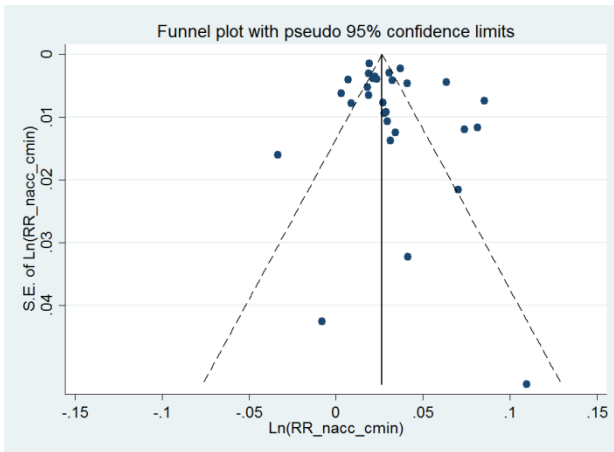
(b). Hmin_rl, NACC



(c). Cmax_rl, NACC



(d). Cmin_rl, NACC



S.E.: standard error

RR: rate ratio

Hmax_rl, NACC: heat effect, maximum, restricted lags, non-accidental mortality

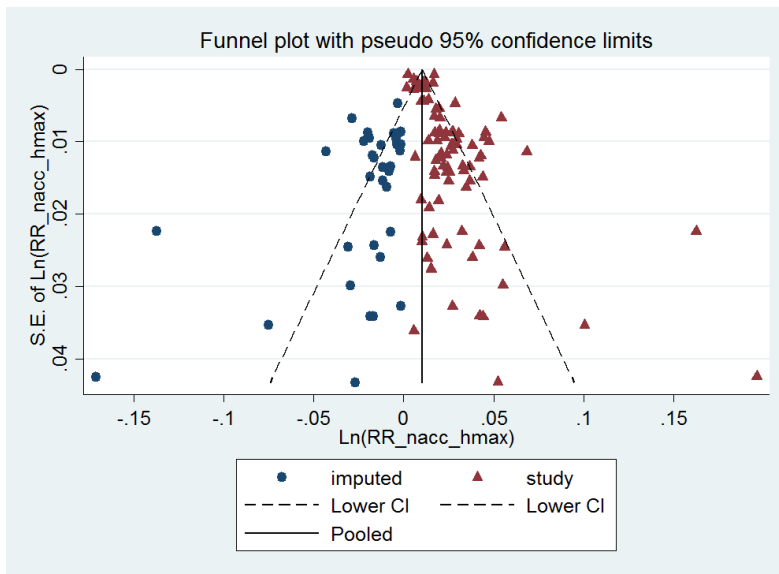
Hmin_rl, NACC: heat effect, minimum, restricted lags, non-accidental mortality

Cmax_rl, NACC: cold effect, maximum, restricted lags, non-accidental mortality

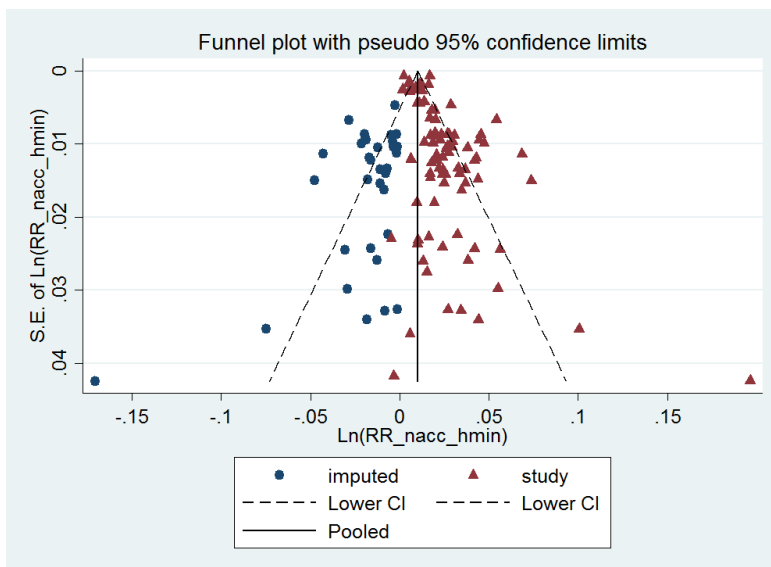
Cmin_rl, NACC: cold effect, minimum, restricted lags, non-accidental mortality

Fig. A.4. Funnel plots for non-accidental mortality (NACC) with imputed studies

(a). Hmax_rl, NACC



(b). Hmin_rl, NACC



S.E.: standard error

95% CI: 95% confidence interval

Hmax_rl, NACC: heat effect, maximum, restricted lags, non-accidental mortality

Hmin_rl, NACC: heat effect, minimum, restricted lags, non-accidental mortality

Fig. A.5. Thresholds vs. mean temperatures

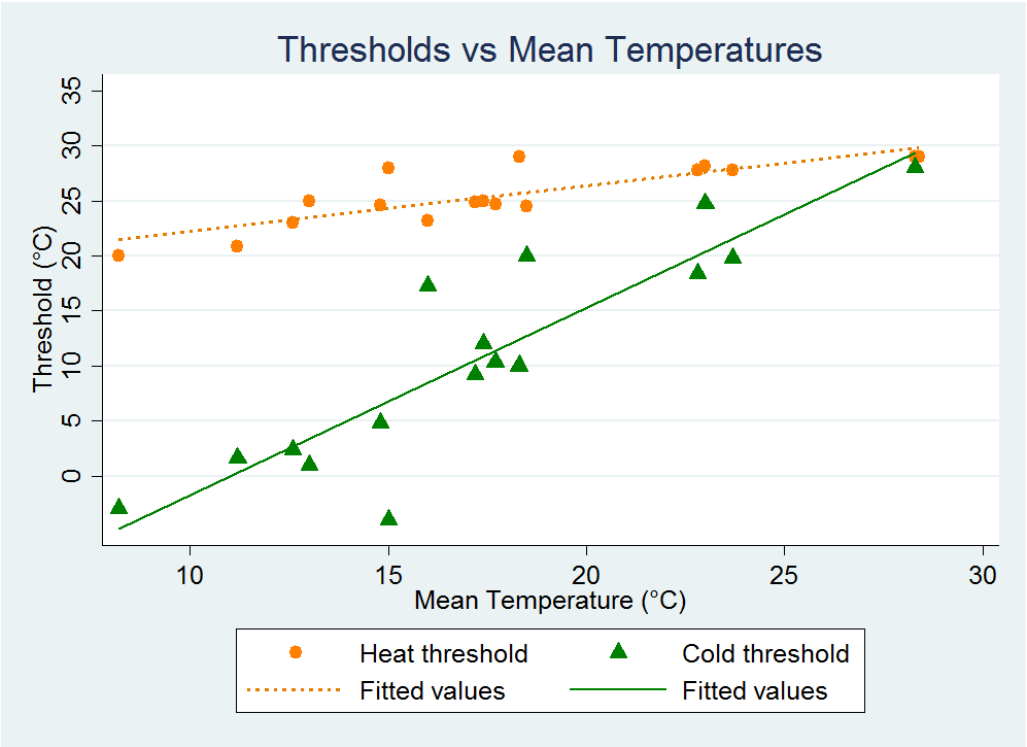


Fig. A.6. Minimum mortality temperature (MMT) vs. mean temperatures

