Research Paper

Effects of Air Temperature on Climate-Sensitive Mortality and Morbidity Outcomes in the Elderly; a Systematic Review and Meta-analysis of Epidemiological Evidence

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ABSTRACT

Introduction: Climate change and rapid population ageing are significant public health challenges. Understanding which health problems are affected by temperature is important for preventing heat and cold-related deaths and illnesses, particularly in the elderly. Here we present a systematic review and meta-analysis on the effects of ambient hot and cold temperature (excluding heat/cold wave only studies) on elderly (65 + years) mortality and morbidity.

Methods: Time-series or case-crossover studies comprising cause-specific cases of elderly mortality (n = 3,933,398) or morbidity (n = 12,157,782) were pooled to obtain a percent change (%) in risk for temperature exposure on cause-specific disease outcomes using a random-effects meta-analysis.

Results: A 1 °C temperature rise increased cardiovascular (3.44%, 95% CI 3.10–3.78), respiratory (3.60%, 3.18–4.02), and cerebrovascular (1.40%, 0.06–2.75) mortality. A 1 °C temperature reduction increased respiratory (2.90%, 1.84–3.97) and cardiovascular (1.66%, 1.19–2.14) mortality. The greatest risk was associated with cold-induced pneumonia (6.89%, 20–12.99) and respiratory morbidity (4.93% 1.54–8.44). A 1 °C temperature rise increased cardiovascular, respiratory, diabetes mellitus, genitourinary, infectious disease and heat-related morbidity.

Discussion: Elevated risks for the elderly were prominent for temperature-induced cerebrovascular, cardiovascular, diabetes, genitourinary, infectious disease, heat-related, and respiratory outcomes. These risks will likely increase with climate change and global ageing.

1. Introduction

Ambient temperature increase is an important public health concern, associated with substantial death and illness (Basu and Samet, 2002a). Globally, the average temperature increased by 0.85 °C between 1880 and 2012 (IPCC, 2013). Across most land areas, projections indicate an increase in the magnitude and frequency of hot days in the late 21st century (IPCC, 2013). Furthermore, across many regions, low temperatures also contribute greatly to the current burden from total mortality (Gasparrini et al., 2015). Understanding the health risks associated with high and low temperatures on elderly people is vital for preventing heat and cold-related deaths and illnesses in this vulnerable population (Basu et al., 2005). Elderly vulnerability is attributable to

physiological and social factors, including; living alone, multiple co-morbidities and high medication use, slow physiological adaptation and behavioural response to thermal stress, limited access to medical care and housing with heating or cooling.

Forecasts predict an unprecedented rate of population ageing driven by lengthening life expectancy, particularly in urban areas. The 60 + age group is expected to comprise 21.1% of the population by 2050 (United Nations, 2013). As people live longer, the global burden of chronic and degenerative disease will increase. The predominant contributors to the global burden of disease in the elderly are cardiovascular disease, malignant neoplasms, chronic respiratory diseases, musculoskeletal diseases and neurological and mental diseases (Prince et al., 2015).

Two recent reviews describe temperature effects on elderly people's health. A meta-analysis by Yu et al. report greater elderly risk (65 +) for all-cause heat-related mortality (2–5% per 1 °C increase in temperature) compared to all-cause cold-induced mortality in the 50 + age group (1–2% per 1 °C decrease in temperature) (Yu et al., 2012). The review of

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Table 1

Descriptive study characteristics. Unique study ID corresponds to locations on Fig. 2. Exposure abbreviations: Temperature = T, Maximim = Max, Minimum = Min, Apparent Daily temperature = ADT, Mean Daily Temperature = MDT, Universal Thermal Climate Index (UTCI), Diurnal Temperature Range (DTR), PET index, (temperature, humidity, mean radiant temperature, wind speed). Additional information: RR = relative risk, CI = confidence interval, Threshold t = Threshold temperature, se = standard error. References to individual studies are listed in Supplementary file 2 (S2). Disease abbreviations: Subarachnoid haemorrhage (SAH), Intracerebral haemorrhage (IntH), Haemorrhagic stroke (HS), Cerebral infarction/Ischemic stroke (IS), Other CBD (other CBD), Stroke (unspecified as haemorrhage or infarction) (Stroke), Cerebrovascular disease (CBD), Essential hypertension (Hypertension), Ischemic heart disease (IHD), Angina (Angina), Myocardial infarction (MI), Aneurysm (Aneurysm), Pulmonary embolism (PulEmb), Heart failure (HF), Coronary atherosclerosis (CorAth), Atrio-ventricular conduction disorders (AVCD), Cardiac arrhythmias (Arrhyt), Atrial Fibrillation (AtrFib), Pulmonary heart disease (PulHD), Sudden cardiac death (SuddCD), Hypotension (Hypotension), Cardiovascular disease (CVD), Influenza and pneumonia (Flu-Pneu), Respiratory infections (InfResp), Asthma (Asthma), COPD and chronic bronchitis (COPD), Chronic lower respiratory diseases (COPD + Asthma) (CLRD), Respiratory disease (RD), Cardio-respiratory disease (Cardio-Resp), Kidney stone (KidStone), Acute renal failure (AcuteRen), Renal/genitourinary disease (GUM), Gastroenteritis (Gastro), Intestinal infection (IntInf), Infectious disease (meningitis + other inflamatory diseases) (ID), Diabetes mellitus (Diab), Endocrine diseases (Endocr), Organic mental disorders (Demen), Psychoactive substance use (Psyco), Schizophrenia (Schizo), Mental diseases (Mental), Extra-pyramidal disorders (Park), Other disorders of the nervous system (DegDis), Nervous system diseases (Nervous), Digestive system diseases (Dig), Dehydration (Dehyd), Heatstroke (HStroke), Heat related disease (Heat). 13 publications are only part of the systematic review and not the meta-analysis: IDs 4,11,23,27,29,34 apply DTR as the exposure. ID 36 presents a non-linear risk at a threshold temperature, which is not comparable to per 1 °C change in temperature. IDs 56–61 present a risk estimate as a comparison of two temperatures, also not comparable to per 1 °C change in temperature.

Author, year	ID	Location	Time-series	Heat and/or cold effect	Exposure	Mortality or morbidity	Disease outcome and elderly age	Additional information
Harlan, 2014	1	Arizona, USA	2000–2008	Heat	Max ADT	Mortality	Heat, CVD, COPD/Asthma (65+)	Clarified this is not a heatwave paper, sample size
Burkart, 2014	2	26 regions, Bangladesh	2003–2007	Heat	UTCI	Mortality	CVD, ID (65+)	RR, 95% CI
Huang, 2014	3	Changsha, China	2008–2011	Heat	MDT	Mortality	CVD (65+)	No
Yang, 2013	4	Guangzhou, China	2003–2010	Heat and cold	DTR	Mortality	CVD, RD (65+)	Sample size, threshold t
Almeida, 2013	5	Lisbon and Oporto, Portugal	2000–2004	Heat	Max ADT	Mortality	CVD, RD (65+)	No
Gasparrini, 2012	6	England and Wales	1993–2006	Heat	Max DT	Mortality	CBD, IHD, MI, ChIHD, PulHD, AVCD, AtrFib, Arrhyt, HeartFail, CVD, InfResp, COPD, PulHD, Asthma, RD, Diab, Endocr, Demen, Schizo, Mental, Park, DegDis, Nervous, GUM, Renal (65+)	No
Liu, 2011	7	Beijing, China	2003–2005	Heat and cold	2-day or 15-day Mean T	Mortality	CBD, IHD, CVD, RD, Cardio-Resp (65+)	No
Wichmann, 2011	8	Copenhagen, Denmark	1999–2006	Heat and cold	Max ADT	Mortality	CVD, CBD, RD (66+)	No
Yu, 2011	9	Brisbane, Australia	1996–2004	Heat and cold	MDT	Mortality	CVD (65+)	No
Almeida, 2010	10	Lisbon and Oporto, Portugal	2000–2004	Heat	Mean ADT	Mortality	CVD, RD (65+)	No
Tam, 2009	11	Hong Kong	1997–2002	Heat	DTR	Mortality	CVD (65+)	No
Revich, 2008	12	Moscow, Russia	2000–2005	Heat and cold	MDT	Mortality	IHD, CBD, CLRD (75+)	No
Baccini, 2008	13	15 European cities	1990–2000	Heat	Max ADT	Mortality	CVD, RD (65+)	B-estimate, se, sample size, threshold t
Ishigami, 2008	14	Budapest, London and Milan	1993–2004	Heat	MDT	Mortality	CVD, RD (75+)	No
Gouveia, 2003	15	Sao Paulo, Brazil	1991–1994	Heat and cold	MDT	Mortality	CVD, RD (65+)	Sample size
Wong, 2014	16	Hong Kong	2001–2005	Cold	MDT	Mortality	RD in patients with existing hypertension (65+)	Lag, threshold t
Xu, 2013	17	Hong Kong	1998–2001	Cold	Mean ADT	Mortality	CVD, RD (65+)	No
Analitis, 2008	18	15 European cities	1990–2000	Cold	Min ADT	Mortality	CVD, CBD, RD (65+)	RR, CI, sample size
Carder, 2005	19	3 regions, Scotland	1981–2001	Cold	MDT	Mortality	CVD, RD (65+)	Sample size
Cagle, 2005	20	Washington, USA	1980–2001	Cold	MDT	Mortality	CVD (55+)	No
Condemi, 2015	21	Cuneo, Italy	2007–2010	Heat	MDT	Morbidity	KidStone (65+)	No
Han, 2015	22	Seoul, South Korea	2004–2013	Heat	Monthly MDT	Morbidity	CBD, IS, IntH (60+)	No

Table 1 (*continued*)

Author, year	ID	Location	Time-series	Heat and/or cold effect	Exposure	Mortality or morbidity	Disease outcome and elderly age	Additional information
Li, 2014	23	Ghangzhou, China	2010–2012	Heat	DTR	Morbidity	InfResp (65+)	No
Kim 2014	24	Seoul, South Korea	2007–2010	Heat and cold	MDT	Morbidity	Asthma (65+)	No
Giang, 2014	25	Thai Nguyen, Vietnam	2008–2012	Heat and cold	MDT	Morbidity	CVD (60+)	No
Anderson, 2013	26	213 USA counties	1999–2008	Heat	MDT	Morbidity	COPD, RD (65+)	No
Wang, 2013	27	Beijing, China	2009–2011	Heat	DTR	Morbidity	CVD, RD, Renal, Dig (65+)	No
Chan, 2013	28	Hong Kong	1998–2009	Heat and cold	MDT	Morbidity	RD, ID (60+)	Sample size
Qiu, 2013	29	Hong Kong	2000–2007	Heat	DTR	Morbidity	HF (65+)	No
Wichmann, 2013	30	Gothenburg, Sweden	1985–2010	Heat	Max ADT	Morbidity	AMI (66+)	No
Williams, 2012	31	Adelaide, Australia	2003–2009	Heat	Min DT	Morbidity	Renal, heat (65+)	No
Goggins, 2012	32	Hong Kong	1999–2006	Heat and cold	MDT	Morbidity	IS (65+)	Sample size
Wichmann, 2012	33	Copenhagen, Denmark	1999–2006	Heat and cold	Max ADT	Morbidity	AMI (66+)	No
Lim, 2012	34	4 cities, South Korea	2003–2006	Heat	DTR	Morbidity	Asthma (75+)	No
Basu 2012	35	California, USA	2005–2008	Heat	Mean ADT	Morbidity	CVD, Arrhyt, Aneurysm, IHD, Hypertension, HS, IS, Hypotension, RD, AcuteRen, Hstroke, IntInf, Diab, Dehyd (65+)	RR, CI, sample size
Vida, 2012	36	3 regions in Quebec, Canada	1995–2007	Heat	MDT	Morbidity	Mental (65+)	Clarified effect is not per 1 °C increase in temperature
Silva, 2012	37	Sao Paulo, Brazil	2003–2007	Heat and cold	Max DT	Morbidity	CVD, RD (60+)	RR, CI
Alessandrini, 2011	38	9 regions Emilia-Romagna, Italy	2002–2006	Heat and cold	Mean ADT	Morbidity	CVD, RD (65+)	No
Pudpong, 2011	39	Chang Mai, Thailand	2002–2006	Heat	MDT	Morbidity	RD, CVD, Diab, IntInf (65+)	Sample size
Morabito, 2011	40	Tuscany, Italy	1997–2006	Heat and cold	MDT	Morbidity	SAH, IntH, IS, Stroke (65+)	No
Hopstock, 2011	41	Tromso, Norway	1974–2004	Heat	3-day Mean T	Morbidity	MI (65+)	Sample size
Wichmann, 2011	42	Copenhagen, Denmark	2002–2006	Heat and cold	Max ADT	Morbidity	RD, CVD, CBD (66+)	No
Green, 2010	43	California, USA	1999–2005	Heat	Mean ADT	Morbidity	Flu-Pneu, IS, Dehyd, Gastro, Diab, AcuteRen (65+)	RR, CI, sample size
Lin, 2009	44	New York, USA	1991–2004	Heat	Mean ADT	Morbidity	CVD, RD (50+)	CI, sample size
Michelozzi, 2009	45	12 European cities	1990–2001	Heat	Max ADT	Morbidity	CVD, CBD, RD (65+)	No
Linares, 2008	46	Madrid, Spain	1995–2000	Heat	Max DT	Morbidity	RD (75+)	No
Kovats, 2004	47	London, UK	1994–2000	Heat	MDT	Morbidity	RD (65+)	Sample size
Koken, 2003	48	Denver, USA	19,931,997	Heat	Max DT	Morbidity	AMI, CorArth, PulHD, Arrhyt, HF (65+)	No
Liu, 2014	49	Shanghai, China	2008–2011	Cold	MDT	Morbidity	Flu-Pneu (65+)	No
Vasconcelos, 2013	50	Lisbon and Opoto, Portugal	2003–2007	Cold	PET index	Morbidity	CVD, AMI (65+)	No
Bhaskaran, 2010	51	England and Wales	2003–2006	Cold	MDT	Morbidity	MI (65+)	Sample size
Ebi, 2004	52	3 cities, California, USA	1983–1998	Cold	Max DT	Morbidity	CBD, AMI, Angina, HF (55+)	No
Hong 2003	53	Incheon, Korea	1998 2000	Cold	MDT	Morbidity	IS (65+)	No
Hajat, 2002	54	London, UK	1992–1995	Cold	MDT	Morbidity	RD, Asthma, Lower RD, Upper RD, CVD (65+)	No
Ebi, 2001	55	3 cities, California, USA	1983–1998	Cold	Min DT	Morbidity	Flu-Pneu (56+)	No
Breitner, 2014	56	Bavaria, Germany	1990–2006	Heat and cold	MDT	Mortality	CVD (75+)	No
Tian, 2012	57	Beijing, China	2000–2011	Heat and cold	MDT	Mortality	Coronary heart disease (65+)	No
Lin, 2011	58	4 regions, Taiwan	1994–2007	Heat and cold	MDT	Mortality	CVD, RD (65+)	No
O'Neill 2003	59	7 counties, Chicago, USA	1986–1993	Heat and cold	Mean ADT	Mortality	RD, CVD (65+)	No
Pan, 1995	60	Taiwan	1981–1991	Heat and cold	MDT	Mortality	IS, IHD, HS (64+)	No
Son, 2014	61	8 cities, South Korea	2003–2008	Heat and cold	MDT	Morbidity	Allergy, Asthma, RD, CVD (65+)	No

Astrom and colleagues asserts elderly people (65+) are at greater risk of mortality and morbidity during exposure to heat waves than younger people (Åström et al., 2011). Because heat and cold waves only contribute to a small proportion of excess deaths (Gasparrini et al., 2015), we focused on the association between exposure to non-optimum high and low temperatures rather than anomalous temperature events on health. Previous reviews have excluded critical epidemiological studies with information on the underlying cause of death. Cause-specific health impacts of temperature on the elderly have been reported sporadically, but coherent effort to integrate these has so far been lacking. Here we present a systematic review and meta-analysis with quantitative evidence on the effects of high and low ambient temperature (excluding heat and cold waves) on many cause-specific mortality and morbidity outcomes in the elderly.

2. Methods

2.1. Inclusion Criteria

Epidemiological studies reporting an age-stratified, quantitative association between temperature and only cause-specific, elderly mortality or morbidity (hospitalisation, emergency room admissions, general practise visits, home visits) outcomes were considered. Time-series and case-crossover design studies were included because they produce comparable effect estimates (Basu et al., 2005) for investigating temperature and mortality/morbidity associations. Only English language publications were considered.

Temperature was the primary weather exposure. Indexes combining variables including temperature, humidity and wind velocity were considered, providing comparable risk estimates were produced. Other primary environmental exposures such as air pollution (including dust) were deemed outside the scope of this review. Heat studies were defined as those presenting effect estimates per unit increase above summer or yearly threshold temperatures, or linear effects with no threshold. Cold studies were those with effect estimates per unit below a winter or yearly threshold temperature, or no threshold for linear effects. Studies presenting non-linear risk estimates [study ID 36] not convertible to a 1 °C change in temperature were considered in the systematic review, but excluded from the meta-analysis, including effect estimates given as a comparison between two threshold temperatures [study ID 56–61] (study IDs are defined in Table 1). Heat wave and cold waves were excluded because they are unique events with differing characteristics. To produce robust causal associations explaining the mechanisms linking exposure and outcome, studies were required to have analysed a minimum of three consecutive years/seasons of temperature-health associations. Studies investigating the effects of medication or binary exposures such as disasters were excluded.

A consistent definition of the elderly is yet to be applied in academic and policy discourse. Most definitions correspond with a retirement age of 65. Following this convention, we define elderly as those aged 65+ years with two caveats: to minimise information loss, studies combining the 65+ age group with slightly younger age groups (50–74, 56+, 55–69 years) and studies in low-income countries with low life expectancy where the elderly were defined as 50+ were considered in this review.

2.2. Search Strategy

Two investigators (AB and AV) conducted independent searches using Medical Subject Headings on the PubMed, Web of Science and Ovid Medline databases (Supplementary File S1). English language studies published between 1 January 1975 and 24 July 2015 in peer-reviewed journals, on the effect of temperature exposure on cause-specific mortality or morbidity in the elderly were retrieved. Titles and abstracts were scanned for fit against the inclusion and exclusion criteria. Full text documents of candidate studies were integrated into one library and details corresponding to each publication recorded systematically. The results from both reviewers were compared and disagreements resolved by consulting two senior investigators (SH and NH). A consensus was reached on papers included in the review. Authors were contacted to obtain missing information required for this analysis.

2.3. Data Management and Statistical Analysis

Cause-specific risk estimates were standardised to percent change (%) per 1 °C change in temperature. The most statistically significant effect estimate (and when unavailable, the highest effect estimate) was selected when results were presented for multiple lag days or thresholds. Unique datasets were created for each cause-specific mortality or morbidity disease outcome for heat and cold exposure. The percent change and 95% confidence interval was transformed into a beta coefficient (β) and standard error. A random-effects meta-analysis, which accounts for intra- and inter-city heterogeneity, was conducted. The two-staged analysis included; i) pooling of age-stratified risks (i.e. 65–74, 75+) in individual studies to produce one estimate (65+), ii) meta-analysis of city-specific estimates, requiring at least two effect estimates per disease category (indicated here as k > 2).

Heterogeneity was investigated using the I^2 statistic, where increasing values (ranging 0–100%) correspond to increasing heterogeneity. Subgroup analysis was performed to test if i) the risk of mortality or morbidity increased with age, and ii) pooling age-stratified effect estimates into one estimate (i.e. 65–74, 75–84, 85+ years into 65+ years) increased heterogeneity. Further sensitivity analyses explored changes in risk estimates and/or heterogeneity scores based on lag days between exposure and outcome, temperature variable, type of hospital admission, grouping cholesterol and blood pressure-related cardiovascular outcomes, and control for air pollution in studies of respiratory outcomes. Publication bias was also assessed. All analyses were carried out using the Meta package v. 4.3–2 in R.

3. Results

The systematic search retrieved 4984 mortality papers and 3777 morbidity papers. Of the 25 mortality and 35 morbidity papers that fit the inclusion and exclusion criteria, 18 mortality and 31 morbidity publications were suitable for meta-analysis (Fig. 1). The characteristics of studies investigating the effects of high and low temperature on cause-specific mortality and morbidity in the elderly are summarised in Table 1 (see also Supplementary File 2). The locations studied were dispersed across Europe, Asia, North and South America, but not Africa. We applied the Köppen–Geiger classification (Kottek et al., 2006) to further investigate geographic spread by five climate zones; 'A-Equatorial', 'B-Arid', 'C-Temperate', 'D-Snow' and 'E-Polar' (Fig. 2). Two studies [study IDs 2,39] are located in equatorial areas and one [study ID 1] in the arid zone. Clustering in the snow and temperate zones reflect the uneven distribution of study locations. The duration of the time-series ranged from 3 to 26 years. Studies used various forms of ambient temperature as the exposure. Mean daily ambient temperature was the most common exposure (28 studies). Apparent temperature (also termed heat index), a combined metric of temperature and humidity used to gauge human discomfort, was also common. Diurnal temperature range (DTR) an exposure accounting for temperature variability; the difference between daily maximum and minimum temperatures, was applied by six studies [study IDs 4,11,23,27,29,34]. A detailed analysis of exposure measures and study design/statistical modelling are in Supplementary Files 3 and 4.

Cause-specific mortality and morbidity outcomes in the systematic review and meta-analysis are reported using the International Classification of Disease (ICD 10) nomenclature and hierarchy (Supplementary File S5). A total of 13 publications were suitable for only the systematic review, including study IDs 56–61, which present risk estimates comparing two temperatures (Supplementary Table 2). The risk of cardiovascular and cerebrovascular outcomes, including cerebral infarction, cerebral haemorrhage and ischemic heart disease increased with

heat [study IDs 56–61] and cold exposure in most studies [study IDs 56–61]. Only Pan, et al. report a 0.73 lower odds of cerebral haemorrhage at 32 versus 28 °C. Respiratory deaths decreased by 2.5% with heat exposure in Chicago, USA at 29 versus 18 °C [study ID 59]. Cold exposure increased the risk of allergy [study ID 61] and respiratory mortality and morbidity [study IDs 58,59,61]. A non-linear relative risk of mental health emergency department visits ranging from 1.05 to 1.09 at 25 °C was observed across three regions of Quebec, Canada [study ID 36]. Studies applying DTR [study IDs 4,11,23,27,29,34], an exposure metric not comparable to temperature or apparent temperature was included only in the systematic review. Cardiovascular mortality and morbidity relative risk increased in all but the 75 +; 0.95 (95% CI 0.06–1.84) [study ID 4], and 65–74 group; 0.99 (0.99–1.0) [study ID 27] per 1 °C increase in DTR. Heart failure morbidity increased dramatically in Hong Kong, China [study ID 29]. Interestingly, the risk of respiratory morbidity (all respiratory, respiratory tract infection) increased with a 1 °C increase in DTR [study IDs 23,27,34], whereas mortality decreased (Basu et al., 2005). In Taiwan [study ID 27], the 75 + group exhibited slightly elevated risks per 1 °C increase in DTR for renal; 1.02 (1.0–

1.04) and digestive; 1.04 (1.02–1.05) morbidity compared with the 65 + age group.

We report mortality meta-estimates (where k > 2) for ischemic heart disease (ICD-10 codes I20–25), all cardiovascular (I00–99), all cerebrovascular (I60–69), and all respiratory outcomes (J00–99). Morbidity meta-estimates (k > 2) are presented for ischemic stroke (I63), intracerebral haemorrhage (I61), myocardial infarction (I21–23), angina pectoris (I20), heart failure (I50), asthma (J45–46), pneumonia (J09–18), diabetes mellitus (E10–14), acute renal failure (N17), intestinal infectious (A00–99), heat-related outcomes (E70–90, T66–78 and R00–99), all cardiovascular (I00–99), all cerebrovascular (I60–69), and all respiratory outcomes (J00–99). In addition, we present an 'overall' estimate for both mortality and morbidity outcomes, an amalgamation of the subgroups presented by individual studies including the 'all' category. The frequency count of each disease subgroup in the meta-analysis is given in Fig. 3. All cardiovascular disease (CVD) and all respiratory disease (RD) outweighed other mortality subgroups. A greater range of disease groups were represented by morbidity outcomes, including all RD and all CVD, followed by cerebral infarction, myocardial infarction,
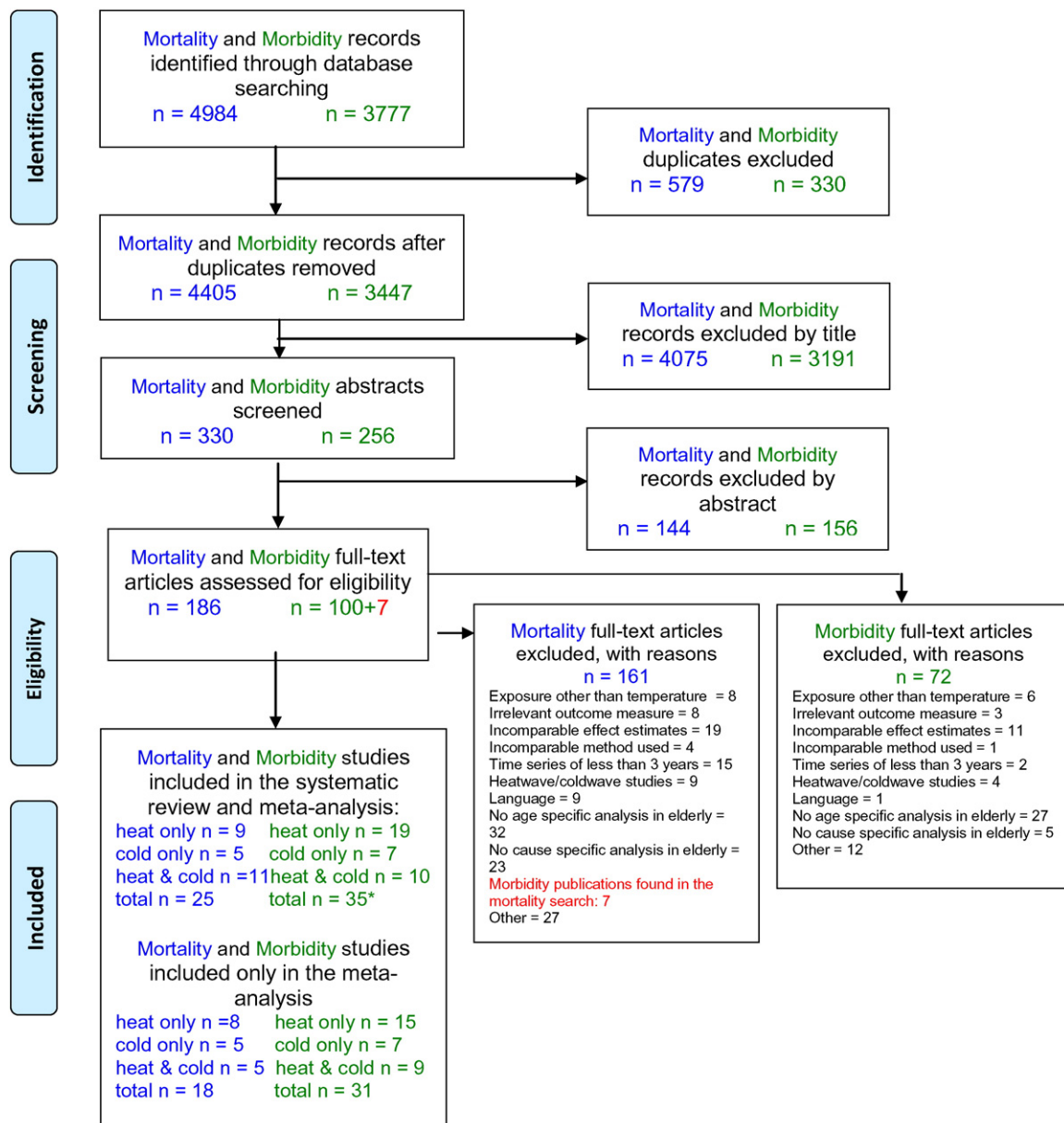

Fig. 1. Prisma diagram outlining the selection procedure for mortality and morbidity articles.
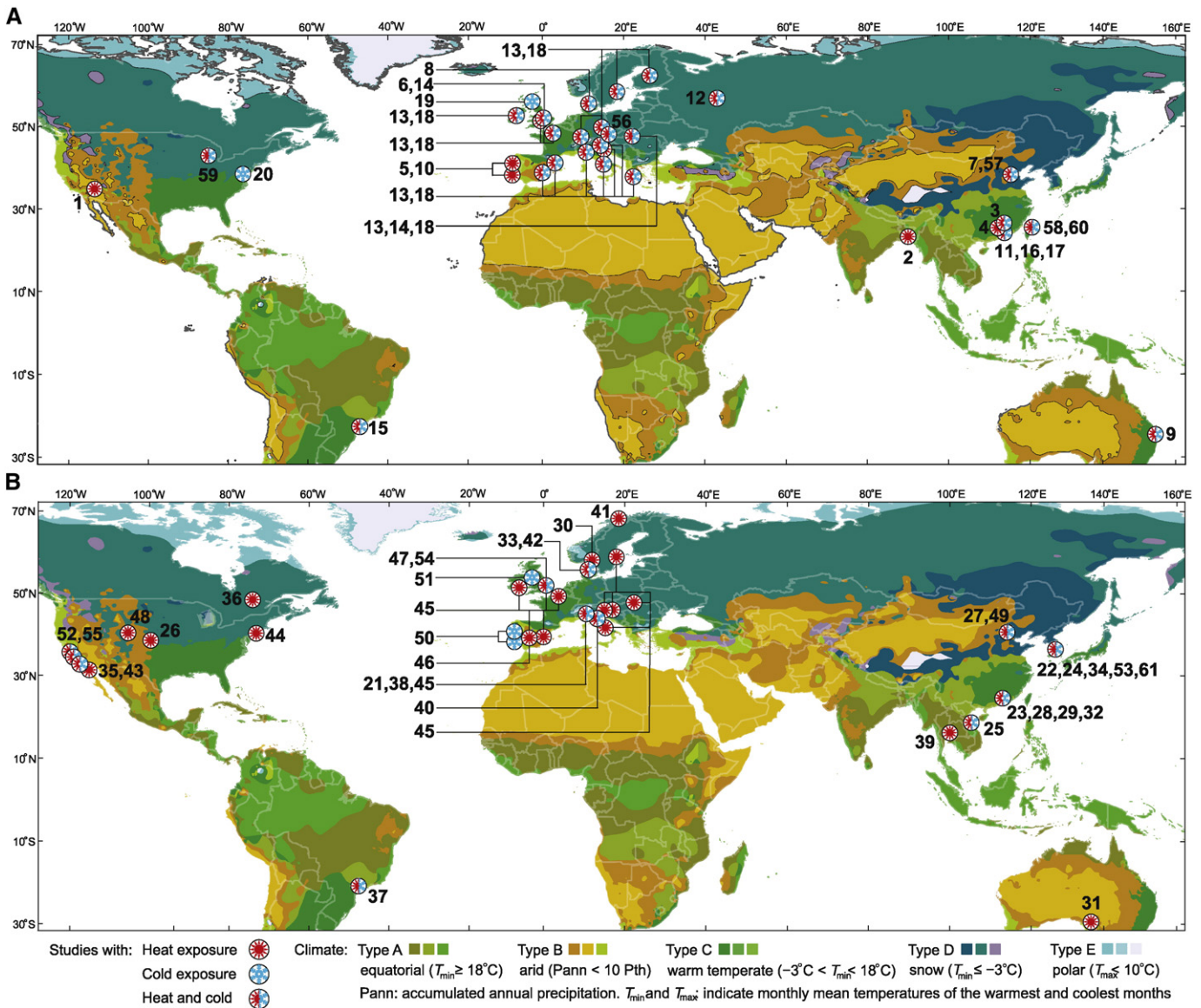
Fig. 2. Distribution of A) Mortality, and B) Morbidity studies across five Köppen Geiger climate zones (A–E). Study numbers on the map (ID) are defined in Table 1. Panel A comprises mortality studies (ID 1–20, 56–60), panel B comprises morbidity studies (ID 21–55, 61). ID 56–61 represent publications with risk estimates as a comparison between two temperatures. Repeated ID numbers on the map indicates that one study presents estimates for multiple cities.

heart failure, all genitourinary disease, intestinal infection and diabetes mellitus. Threshold temperatures were selected by individual studies based on study location. Lag times, presented as cumulative or single day lags describing the delay between exposure and outcome, varied with high and low temperature. Heat lags were shorter than cold lags, generally between lag 0–1 to 0–3 days prior to the event. Cold lags ranged between 0 to 30 days.

We observed a striking increase in the risk of all mortality outcomes, including cerebrovascular, cardiovascular and respiratory outcomes (Table 2 and forest plots in Supplementary File 6). The greatest risks were for heat-induced CVD and RD, and cold-induced RD mortality. Cerebrovascular (CBD) risks also increased with cold exposure. No protective effect (risk reduction) was found for any mortality outcome; only ischemic heart disease risk was statistically insignificant; 0.45% (95% CI −0.01–0.91) per 1 °C decrease in temperature. Compared to the universally elevated mortality risks, temperature-related morbidity risks were mixed for CBD and CVD outcomes (Table 3 and forest plots in Supplementary File 6). In warm periods, the risk of intracerebral haemorrhage, myocardial infarction and all CBD morbidity reduced per 1 °C increase in temperature. In winter, the risk of morbidity from

angina, heart failure, all CVD, and all CBD reduced per 1 °C decrease in temperature. Heat exposure led to an increase in RD morbidity by 2.76% (1.51–4.03). A statistically significant increase was noted for heat-induced diabetes mellitus 1.02% (0.43–1.62) and an even greater risk for heat-related overall genitourinary morbidity 2.12% (1.65–2.59). A 1 °C increase in temperature resulted in elevated risks for overall infectious and heat-related morbidity. The greatest statistically significant risk was associated with pneumonia; 1 °C reduction in temperature caused a 6.89% (1.20–12.99) increase in morbidity in cold periods.

We explored temporal patterns of the temperature-outcome relationship (lags) for all diseases (Supplementary File 7). We pooled heat effects as a) lag 0, 1 and 0–1, and b) above lag 2, and cold effects as a) <lag 15 b) >lag 15. The risk for heat-related CVD mortality was greatest for lag 0–1; 4.15% (3.7–4.59) relative to >lag 2 days; 2.97% (1.8–4.15). The converse was observed for heat-related CVD morbidity; a longer lag was associated with a higher risk of illness 0.27% (0.03–0.51). The risk of both heat-induced respiratory mortality (5.33%, 3.69–6.99) and morbidity (2.76%, 1.32–4.21) were greater for lag >2 days. Heat-induced cerebrovascular mortality and morbidity risk
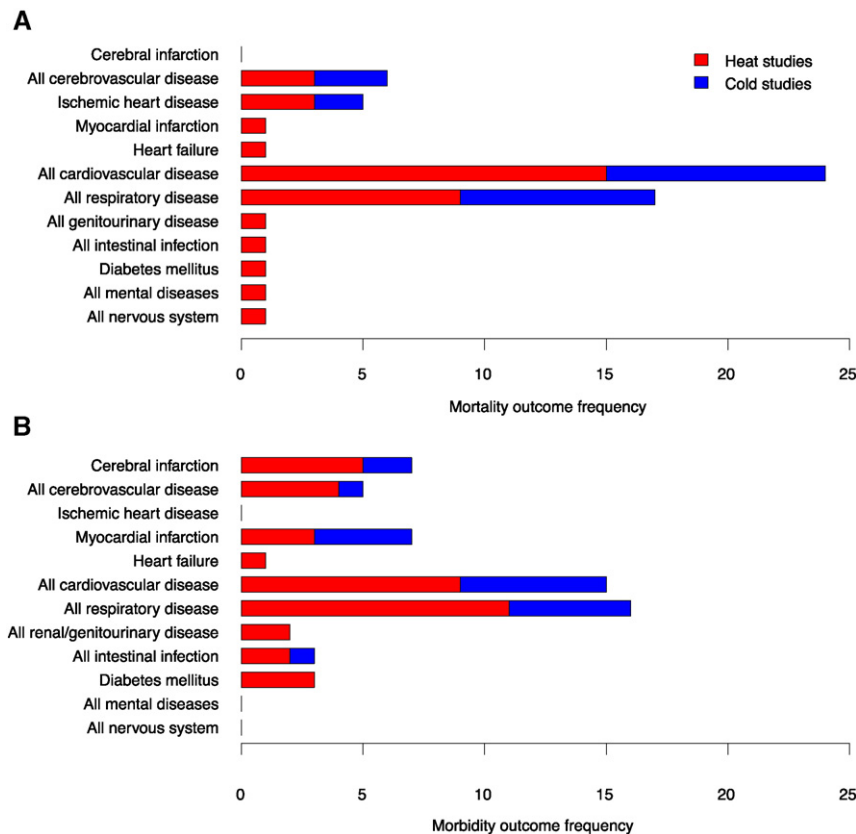
Fig. 3. Number of cause-specific A) mortality, and B) morbidity outcomes included in the meta-analysis.

estimates were elevated for the shorter lag, 0–1 days. The risks for heat-related diabetes, infectious, and renal disease morbidity were greater for the longer lag period of above 2 days. With the exception of cold-induced respiratory morbidity 6.98% (2.47–11.68, lag < 15 days), low temperatures were associated with a greater risk of mortality and morbidity for the longer lag period of above 15 days for cardiovascular and respiratory outcomes.

Publication bias was assessed with funnel plots. The asymmetrical distribution of study results suggests some level of publication bias in plots B, C, E, N, P (Supplementary File 8). These plots are characterised by few studies in the white triangle, showing that smaller, statistically insignificant results are missing. The apex of plots B, C, E, N, P are, however, dominated by studies with large sample sizes and low standard error, which can skew the plot to indicate publication bias.

Heterogeneity (I^2) was high, between 60.8 to 99.2% for mortality causes and varied from 0 to 98.6% for morbidity outcomes, supporting our use of a random-effects meta-analysis. Through an age-specific analysis, we investigated if the high heterogeneity scores were attributable to grouping risk estimates from multiple age groups. Although I^2 reduced drastically in the younger age group (65–74), heterogeneity remained high for the 75 + age group (between 59.3–94.9%) (Supplementary File 9). Regression model choice appeared to be an important determinant of heterogeneity. Pooling independent studies resulted in larger I^2 scores than pooling one study applying a consistent modelling strategy across multiple sites. Risks did not universally increase with age, as the 65–74 age group exhibited greater heat-induced all RD morbidity, all CBD mortality and cold-induced all RD mortality compared to the 75 + age group. We independently grouped heat-induced respiratory hospital admissions and emergency admissions to assess if pooling these outcomes was a cause of heterogeneity. The results were mixed; neither the relative risk nor I^2 varied greatly for overall RD, although I^2 for all RD hospital admissions dropped to 50.7% across 15 city-specific hospital admissions [study IDs 28, 37, 39, 44, 45]. We tested if pooling

cholesterol and blood pressure-related CVD outcomes altered the results. We removed the 'all CVD' estimates from the 'overall CVD' meta-estimate and grouped the remaining diseases as being related to cholesterol (1), systemic blood pressure (2), or both (3). Only heat-induced CVD mortality had more than two cholesterol and blood pressure outcomes, to enable a comparison. Heat-related mortality was higher for cholesterol 0.06% (−0.35–0.47) than blood pressure −0.87% (−4.93–3.38). There was very little difference between heat-induced overall CVD mortality (0.15%, 0.05–0.35), and cholesterol CVD mortality 0.06% (−0.35–0.47).

Compared with the original risk estimates, controlling for air pollution caused a decrease in the relative risk in two of the four outcomes; heat-induced respiratory mortality, and cold-induced respiratory morbidity. Most of these reductions in relative risk were small to moderate (less than 2% per 1 °C change in temperature). The statistical significance only changed for overall cold-induced morbidity, where controlling for air pollution reduced the relative risk to 0.83% (−2.53–4.37) per 1 °C decrease in temperature from 4.93% (1.54–8.44) (Supplementary File 10). There was no consistent trend across mortality/morbidity, heat/cold studies supporting unanimous elevated risks for either apparent temperature or air temperature as the preferred exposure (Supplementary File 11).

4. Discussion

Our systematic review and meta-analysis reveals temperature is associated with an increase in risk across every cause-specific mortality outcome and most morbidity outcomes in the elderly. The dataset comprises greater than 16 million elderly case events and is to our knowledge the largest analysis of temperature on cause-specific outcomes in a vulnerable group. Relevant publications were identified in a comprehensive search and effort was made to obtain pertinent data not included in the original publications to meta-analyse a robust

Table 2

Random-effects meta-analytic % change (and 95% confidence interval) for heat and cold related cerebrovascular, cardiovascular and respiratory mortality.

Heat outcomes correspond to percentage change per 1 °C increase in temperature above a heat threshold in summer months. Cold outcomes correspond to percentage change per 1 °C decrease in temperature below a threshold in winter months, across the year or as a linear risk. Meta-analysis is conducted when k (number of city-specific risk estimates) > 2. * indicates a statistically significant percentage change at the 5% level, arrow direction = risk increase or decrease. I^2 = heterogeneity score, p = p-value for the heterogeneity score.

Sample size was not obtainable for the following studies: Revich 2008 [a], Ishigami 2008 [b], Harlan 2014 [c], Wong 2014 [d].

ICD-10 code	Cause of death (k > 2)	Mortality heat % change (95% CI)			Mortality cold % change (95% CI)		
Cerebrovascular							
I60–I69	All cerebrovascular disease	1.40(0.06–2.75)*	↑	k = 3, I^2= 70.2%, p = 0.0349, n = 224,026	1.21(0.66–1.77)*	↑	k = 14, I^2= 60.8%, p = 0.0016, n = 95,935
I60–I69 I61–I62, I64	Overall	1.40(0.06–2.75)*	↑	k = 3, I^2= 70.2%, p = 0.0349, n = 224,026	1.21(0.66–1.77)*	↑	k = 14, I^2= 60.8%, p = <0.0001, n = 95,935
Cardiovascular							
I20–I25	Ischemic heart disease	1.62(0.24–3.03)*	↑	k = 3, I^2= 81.5%, p = 0.0045, n = 411220[a]	0.45(−0.01–0.91)	↑	k = 2, I^2= 99.2%, p = <0.0001, n = 6356 [a]
I00–I99	All cardiovascular disease	3.79(3.40–4.18)*	↑	k = 31, I^2= 99.3%, p = <0.0001, n = 1,319,818 [a,b,c]	1.84(0.85–2.84)*	↑	k = 24, I^2= 98.6%, p = <0.0001, n = 688,206 [a]
I21–23, I20, I50, I00–I99, I20–I25, I27.9, I70, I26–I28, I44, I45	Overall	3.44(3.1–3.78)*	↑	k = 41, I^2= 99%, p = <0.0001, n = 2,147,349 [a,b,c]	1.66(1.19–2.14)*	↑	k = 26, I^2= 98.9%, p = <0.0001, n = 694562[a]
Respiratory							
J00–J99	All respiratory disease	2.32(2.02–2.62)*	↑	k = 26, I^2= 92.8%, p = <0.0001, n = 367,468	2.90(1.84–3.97)*	↑	k = 22, I^2= 90.5%, p = <0.0001, n = 168,198 [a,d]
J09–J19, J40–44, J45–J46, J00–J99	Overall	3.60(3.18–4.02)*	↑	k = 31, I^2= 97.5%, p = <0.0001, n = 599,458 [c]	2.90(1.84–3.97)*	↑	k = 22, I^2= 90.5%, p = <0.0001, n = 168,198 [a,d]

sample of city-specific estimates. CBD, CVD and RD featured high sample size (n) and number of city-specific estimates (k). Endocrine, genitourinary, and infectious disease risks were elevated with heat exposure, but require further study to increase the statistical power of the estimates. Age-stratified data were combined to obtain one effect per study location using the inverse variance method. This enabled a fair comparison of effect estimates because the age groups were similar.

By excluding heat and cold wave studies, we show that temperature exposure in time-series spanning three or more years/seasons is associated with increased risk for many cause-specific health outcomes in the elderly. Adverse heat effects are concerning because an increase in mean worldwide temperatures from global warming is anticipated (IPCC, 2013). Future studies might also consider using a time-series of 30 + years to build evidence on climate change-related temperature effects on cause-specific health outcomes in the elderly. Inter-study heterogeneity (I^2) was generally high. Although I^2 exceeding 75% typically indicates considerable heterogeneity, this threshold is likely more suited for controlled epidemiological study designs. Observational studies on the temperature-health relationship, however, do not follow stringent reporting guidelines. A previous meta-analysis of temperature effects on cardiorespiratory health also reports I^2 scores ranging 89–99% (Turner et al., 2012). Heterogeneity can be attributed to several factors including differences in location, exposure variable, modelling, lag structures, threshold temperatures, adjustment for confounding variables, and grouping of different morbidity outcomes (hospital, emergency or general practitioner (GP) visits). It remains unclear, however, why I^2 reduced for hospital admissions, but not emergency admissions in our sensitivity analysis. Furthermore, inherent differences among locations including population age structure, access to medical care, social services for the elderly, housing quality and prevalence of air conditioning and heating/insulation can also increase I^2 (Basu and Samet, 2002a; Kenny et al., 2010; Medina-Ramon and Schwartz, 2007). Most studies in our meta-analysis are located in the 'C' or temperate climate zone; geographic location is unlikely to be the primary cause of heterogeneity (Turner et al., 2012). Given the physiological limits to human adaptation and climate sensitivity of local resources (i.e. crops, fisheries), populations living in regions with more extreme climates such as Africa are likely to be highly sensitive to shifts in temperature. There is need for better understanding of how the health risks vary for such groups. It proved unfeasible to obtain the original and covariate datasets for the 49 studies included here to run standardised regressions or test all causes of heterogeneity through meta-regression. We reason the studies meta-analysed here are comparable and produce meaningful results.

Risks were greatest for respiratory mortality and morbidity, with both heat and cold exposure, and longer lag periods. Heat exposure could trigger the release of inflammatory factors, increase ventilation and exacerbate chronic obstructive pulmonary disease (White, 2006; Leon and Helwig, 2010; Malik et al., 1983; Mannino and Mannino, 2011; Anderson et al., 2013), which is highly prevalent in the elderly. Anderson and colleagues also suggest that a few minutes of inhaling hot air can trigger adverse airway responses in the elderly, increasing morbidity (Anderson et al., 2013). Although indoor crowding and/or reduced ventilation during winter is thought to increase viral transmission (Hajat and Haines, 2002), alternative biological mechanisms have been proposed. Inspiration of cold air can cause bronchoconstriction and airway congestion, triggering asthma (Giesbrecht, 1995), and increase susceptibility to infection by reducing mucosal clearing (Eccles, 2002). We conclude that further research is required to establish aetiological mechanisms for how exposure to moderate cold and particularly heat cause adverse respiratory outcomes in the elderly. Sensitivity analysis revealed only a small to moderate (less than 2% per 1 °C change in temperature) difference in the relative risk for studies that controlled for air pollution, with the exception of cold-induced respiratory morbidity. Although controlling for air pollution is common in studies of temperature on health, evidence

Table 3

Random-effects meta-analytic % change (and 95% confidence interval) for heat and cold related cerebrovascular, cardiovascular, respiratory, endocrine, genitourinary, infectious and heat-related morbidity outcomes.

Heat outcomes correspond to percentage change per 1 °C increase in temperature above a heat threshold in summer months, across the year or as a linear risk. Cold outcomes correspond to percentage change per 1 °C decrease in temperature below a threshold in winter months, across the year or as a linear risk. Meta-analysis is conducted when k (number of city-specific risk estimates) >2. * indicates a statistically significant RR at the 5% level, arrows indicate risk increase or decrease, – indicates no change in risk. I² = heterogeneity score. Sample size was not obtainable for the following studies: Hajat 2002 [a], Vasconcelos 2013 [b], Alessandrini 2011 [c], Michelozzi 2009 (65–74 year age group) [d], Hopstock 2011 [e], Alessandrini 2011 [f], Williams 2012 [g].

ICD-10 code	Cause of morbidity (k > 2)	Morbidity heat % change (95% CI)		Morbidity cold % change (95% CI)	
Cerebrovascular					
I63	Ischemic stroke	0.33(−0.09–0.75)	↑ k = 5, I² = 84.9%, p = <0.0001, n = 178,487	3.63(−3.94–11.8)	↑ k = 2, I² = 85.8%, p = 0.008, n = 39,658
I61	Intracerebral haemorrhage	−0.66(−2.13–0.84)	↓ k = 2, I² = 88.6%, p = 0.0031, n = 10,739	1.49(1.04–1.94)*	↑ k = 2, I² = 0%, p = 0.3908, n = 92,991
I20–I25	All cerebrovascular	−0.17(−0.96–0.63)	↓ k = 4, I² = 46.6%,0.1318, n = 212,616 [d]	−0.46(−1.12–0.2)	↓ k = 8, I² = 98.6%, p = <0.0001, n = 552,527
I60, I61, I63, I20–I25	Overall	0.08(−0.01–0.17)	↑ k = 12 I² = 76.9%, p = <0.0001, n = 347,098 [d]	0.05(−0.37–0.47)	↑ k = 14, I² = 97.9%, p = <0.0001, n = 733,743
Cardiovascular					
I21–I23	Myocardial infarction	−0.16(−2.05–1.77)	↓ k = 3, I² = 73.4%, p = <0.0001, n = 5842 [e]	0.66(−0.14–1.48)	↑ k = 7, I² = 93%, p = <0.0001, n = 339,073 [b]
I20	Angina pectoris	NA	NA	−0.80(−2.21–0.64)	↓ k = 3, I² = 90.1%, p = <0.0001, n = 331,324
I50	Heart failure	NA	NA	−0.67(−2.15–0.83)	↓ k = 3, I² = 96.4%, p = <0.0001, n = 457,437
I00–I99	All cardiovascular disease	0.30(−0.12–0.81)	↑ k = 9, I² = 93.5%, p = <0.0001, n = 929,168 [d, f]	−0.28(−1.39–0.84)	↓ k = 6, I² = 57.3%, p = <0.0388, n = 4,371,849 [a, c]
I21–23, I20, I50, I00–I99, I20–I25, I27.9, I70	Overall	0.15(−0.05–0.35)	↑ k = 20, I² = 97.6%, p = <0.0001, n = 1,015,480 [d, e, f]	0.00(−0.67–0.66)	– k = 19, I² = 96.6%, p = <0.0001, n = 5,499,683 [a, b, c]
Respiratory					
J45–J46	Asthma	NA	NA	3.84(−9.38–18.99)	↑ k = 2, I² = 81.2%, p = 0.0212, n = 3885 [a, c]
J09–J18	Pneumonia	NA	NA	6.89(1.20–12.99)*	↑ k = 4, I² = 94.5%, p = <0.0001, n = 68,968
J00–J99	All respiratory disease	2.76(1.51–4.03)*	↑ k = 20, I² = 82.5%, p = <0.0001, n = 121,078	2.70(−0.72–6.24)	↑ k = 5, I² = 91.9%, p = <0.0001, n = 1,267,454 [f]
J00–J99, J40–J44, J09–J18, J45–46	Overall	1.65(1.09–2.21)*	↑ k = 23, I² = 81.4%, p = <0.0001, n = 2,530,203	4.93(1.54–8.44)*	↑ k = 13, I² = 97.1%, p = <0.0001, n = 1,808,820 [a, c, f]
Endocrine					
E10–E14	Diabetes mellitus	1.02(0.43–1.62)*	↑ k = 3, I² = 25.3%, p = 0.2623, n = 18,393	NA	NA
Genitourinary					
N17	Acute renal failure	2.12(1.59–2.65)*	↑ k = 2, I² = 16%, p = 0.2752, n = 26,359	NA	NA
E10–E14	Overall	2.12(1.65–2.59)*	↑ k = 4, I² = 0%, p = 0.4613, n = 26,798 [g]	NA	NA
Infectious					
A00–99	Intestinal infectious	1.00(−0.21–2.22)	↑ k = 2, I² = 0%, p = 0.05228, n = 6064	NA	NA
A00–B99, G00–G05, N70–74, N76	Overall	0.76(−0.43–1.95)	↑ k = 4, I² = 27.2%, p = 0.2487, n = 148,663	NA	NA
Heat					
E86	Dehydration	3.12(0.74–5.56)*	↑ k = 2, I² = 77.7%, p = <0.0001, n = 28,901	NA	NA
E86, T67, E70–90, X30	Overall	14.83(8.22–21.84)*	↑ k = 2, I² = 98.3%, p = <0.0001, n = 29,753 [g]	NA	NA

suggests it is indeed important to capture the entire causal effect, rendering adjustment for air pollution unnecessary in most circumstances (Buckley et al., 2014).

CBD and CVD risks were markedly elevated, but only for mortality. Heat causes an increase in cardiac output, redistributes blood flow away from core organs, attenuates vasodilatation and sweat rate, and increases the potential for thrombosis (Keatinge et al., 1986). These responses are worsened by the limited thermoregulatory capacity and high cholesterol levels in the elderly (Keatinge et al., 1986), elevating cardiovascular strain and the likelihood of acute coronary events. Furthermore, systems in the body do not act in isolation; infection or inflammation of the respiratory system can spur growth of atherosclerotic plaques and promote hypercoagulation, promoting thrombotic events (Lavallée et al., 2002). Cold exposure can also increase blood pressure, blood viscosity, systemic inflammation and thrombosis (Keatinge et al., 1984). The observed excess risk of CBD/CVD mortality compared to CBD/CVD morbidity may be attributable to short lag times where death occurs rapidly before hospitalisation. The reported cause of death may therefore be inaccurate, overlooking underlying conditions. Only a single study [study ID 14] investigated the impact of pre-existing hypertension on RD in the elderly. Furthermore, death rarely goes unreported but morbidity not leading to hospitalisation or a GP visit is likely under-reported. To more broadly capture the effect of temperature on morbidity, community-based data, such as from general practise and home visits should also be used in addition to hospitalisation data. We identified only one study that used GP data [study ID 54]. With the exception of heat-induced CVD mortality, because only cholesterol-related subgroups existed, we could not determine whether blood pressure-related risk increased with cold exposure and cholesterol-related risk increased with heat exposure. Our pooling strategy (of combining the blood pressure and cholesterol diseases) was therefore justified, considering the negligible difference between heat-induced overall CVD and cholesterol-related risk.

Diabetes and genitourinary morbidity increased with heat and longer lag periods. Chronic diseases such as diabetes can trigger metabolic, cardiovascular, neurologic and behavioural dysfunctions that impair thermoregulatory responses during heat stress (Kenny et al., 2010). Poor glucose control and neuropathy attenuate sweating responses in type 2 diabetics (Kenny et al., 2010), which is a concern as obesity and diabetes rates are projected to increase. Similarly, during heat exposure the diversion of blood from the splanchnic and renal vasculature to the periphery can stress the renal system (Semenza et al., 1999). In addition to traditional diseases (CBD, CVD, RD) this exposes a need to more rigorously understand how temperature affects under-represented diseases such as renal, endocrine and mental outcomes. Addressed in only two studies [study IDs 6,36], data for the temperature effects on elderly mental health are severely lacking, despite neurological and mental diseases contributing highly to their burden of disease (Prince et al., 2015). Moreover, the ability to sense environmental cues and take preventive action is compromised (Basu and Samet, 2002b), further endangering elderly people with mental and neurological illnesses. Few studies investigated temperature impacts on infectious disease. This bias is likely the result of geographic clustering of studies in Europe and other affluent countries, where elderly people are likely to be affected by diseases associated with longer life expectancy. To effectively capture global exposure-response effects, age-specific analysis of temperature on cause-specific mortality or morbidity in populated equatorial and arid zones are required. We found that the risk of heat-related outcomes increase with heat exposure. Unfortunately, the lack of a systematic definition of heat and cold-related deaths or illnesses is likely to have led to severe under-reporting of these causes, which are often considered only when no other cause can be determined.

Some limitations must be noted. We were unable to extend our analysis to quantify the attributable burden of risk to high and low ambient temperature. Only English language publications were considered. We present all effect estimates as originally reported irrespective of the magnitude or direction of the risk. We took precautions to exclude

heat and cold wave studies, where extreme temperature is likely to favour increased risk estimates. Regardless of these measures, we found evidence of positive publication bias.

We identify substantially elevated risks in the elderly for temperature-induced cerebrovascular, cardiovascular, and respiratory outcomes in particular. In addition, we find heat exposure-associated increases in diabetes, genitourinary, heat-related and infectious disease morbidity, all of which are anticipated to grow in importance with climate change and global ageing.

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Author contributions

AB and RS developed the research idea. RS provided supervision. The search strategy was conducted by AB and AV. Uncertainties regarding the inclusion of papers were clarified by SH and NH. Datasets were compiled by AB and verified by AV. AB conducted the statistical analysis with guidance and input from JW. Statistical expertise was provided by JW, SH and JR. NH crosschecked the results of the statistical analysis. AB wrote the manuscript. All authors contributed towards the interpretation of results and editing of the manuscript.

Competing interests

The authors declare they have no actual or potential competing financial interests.

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