A systematic review on the association between total and cardiopulmonary mortality/morbidity or cardiovascular risk factors with long-term exposure to increased or decreased ambient temperature

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Highlights

- Higher/lower annual temperature-> higher annual total and cause-specific mortality
- Increased annual temperature-> increased ischemic stroke and respiratory admissions
- People living in warmer areas tend to have lower blood pressure and higher obesity
- Higher age and lower SES increase susceptibility
- The evidence base is sparse. More and better designed studies are needed

Climate change leads to increasing temperatures and more frequent heat waves. These constitute a major risk for public health.

Although short-term effects of temperature changes are known, there is little evidence on long term exposures.
We report a systematic review on the association of long-term (> 3 months) exposure to temperature extremes or temperature changes and cardiopulmonary health outcomes.

Among 34 studies reviewed, there was a large variability in design, in exposure indices and health outcomes

Temporal comparisons: Annual changes within a population

- Association of annual temperature indices for extremes and variability with annual increases in total, cardiovascular and respiratory mortality and hospital admissions.

- Lower blood pressure levels in the summer.

Geographical comparisons: what does it mean to live in a different climate?

- Few studies by investigated health outcome; hence the evidence is suggestive
- Higher mean winter temperature -> higher annual mortality in Europe
- Higher annual temperature may be associated with higher diabetes and lower IHD mortality
- Lower blood pressure, higher obesity- BMI and higher prevalence of respiratory conditions in areas with warmer climates

There is risk of bias in the exposure assessment and control for confounding in the studies reviewed

The evidence base is sparse. More and better designed studies are needed.

ABSTRACT

The health effects of acute exposure to temperature extremes are established; those of long-term exposure only recently received attention. We performed a systematic review to assess the associations of long-term (>3 months) exposure to higher or lower temperature on total and cardiopulmonary mortality and morbidity, screening 3,455 studies and selecting 34. The studies were classified in those observing associations within a population over years with changing annual temperature indices and those comparing areas with a different climate. We also assessed the risk of bias, adapting appropriately an instrument developed by the World Health Organization for air pollution. Studies reported that annual temperature indices for extremes and variability were associated with annual increases in mortality, indicating that effects of temperature extremes cannot be attributed only to short-term mortality displacement. Studies on cardiovascular mortality indicated stronger associations with cold rather than hot temperature, whilst those on respiratory outcomes reported effects of both heat and cold but were few and used diverse health outcomes. Interactions with air pollution were not generally assessed. The few studies investigating effect modification showed stronger effects among the elderly and those socially deprived. Comparisons of health outcome prevalence between areas reported lower blood pressure and a tendency for higher obesity in populations living in warmer climates. Our review indicated interesting associations between long-term exposure to unusual temperature levels in specific areas and differences in health outcomes and cardiovascular risk factors between geographical locations with different climate, but the number of studies by design and health outcome was small. Risk of bias was identified because of the use of crude exposure assessment and inadequate adjustment for confounding. More and better designed studies, including the investigation of effect modifiers, are needed.

Key words: long-term exposure; temperature; total mortality; cardiovascular outcomes; respiratory outcomes; systematic review

1. INTRODUCTION

Climate change has been a major concern among the global community over the past decades. As a result of climate change, there is an increasing trend in temperature and the frequency and intensity of extreme weather events (1). Previous studies have established the adverse impacts on health following heat waves or cold spells, especially on mortality and morbidity due to all-natural, cardiovascular and respiratory causes (2-6). Considering the reported evidence, the effects of temperature changes or extremes on health outcomes are more often reported compared to other meteorological variables and their combinations (7).

The association between daily mortality and temperature on the same or a few preceding days follows a U-shaped curve, i.e. there is a temperature point or range associated with minimum mortality whilst mortality increases when temperature gets lower or higher. This has been observed in many parts of the world (8,9), although in some cases the curve below the minimum mortality temperature follows a more complex shape (10,11). The minimum mortality temperature level differs between geographical areas with higher thresholds observed in warmer climates (5,8,9). This phenomenon indicates a possible, behavioral or physiological, adaption of the population to the local climate conditions. In some climatic zones, the attributable number of events, such as deaths, to cold temperature exceeds those attributable to heat (12).

Vicedo-Cabrera et al. (13) assessed the potential adaptive mechanisms to heat and cold across different locations and different climates in the context of global warming. Their findings showed an attenuation of the heat-related effects on mortality in the different study populations over the past decades, whilst the cold-mortality associations provided more inconsistent results. They suggest that adaptation to heat together with non-climate-driven attenuation mechanisms, such as infrastructure changes and improved health care response, have made a large contribution to the decrease of susceptibility to heat.

Studies reported to date largely investigate effects of short-term changes in exposure. However, associations between long-term exposure to ambient temperature (hereafter referred to as "temperature") and related health effects are not well-studied and have only recently received attention (14). With climate change, long-term trends in temperature levels are already observed and are expected to become more pronounced in the future. Thus, understanding how long-term changes in temperature affect health and what adaptation mechanisms may lead to mitigation of the effects gains high importance. The studies can be classified in those observing associations within a population over years with changing annual or seasonal temperature metrics (15) and those comparing areas with a different climate (16). The former type of studies is addressing the question of whether the short-term effects represent “harvesting” or result in longer-term mortality displacement and is easier to perform. The latter investigates whether living in a location with a specific climate affects health in the long-term, requires a large-scale geographical dimension and faces the difficulty of separating the effects of temperature and other meteorological variables from other population characteristics (such as SES, behavior or genetics). In the context of climate change, it is important to investigate both aspects of “climate” effect on human health. A recent review that searched for studies between 2010 and 2017 on the association of long-term outdoor temperatures and health effects (14) found that regional and local temperatures, and changing conditions in weather due to climate change, are associated with a diversity of health outcomes.

The objective of this study was to perform a systematic review of the existing evidence related to health effects and long-term (> 3 months) exposure to temperature, with a focus on total mortality and cardiopulmonary outcomes. The present review intended to extend previous literature reviews, classify the studies into those addressing temporal changes within a population and those comparing populations living under different climates, identify related research gaps and help public health authorities to implement mitigation and adaption strategies in the context of climate change.

2. METHODS

2.1 Inclusion criteria and search strategy

PRISMA guidelines (17) were followed for the review of long-term exposure (>3 months) to changes in temperature and its effects on health. The inclusion criteria were formulated according to the PECO structure described below. The review included two types of studies: a) those addressing temporal changes within a population and b) those comparing populations living under different climates. This classification is reflected in the Exposure and Comparator items in the PECO statement.

Population: Studies in the general population or in particular sensitive subgroups (e.g. elderly or people with chronic disease) were included in any geographical area.

Exposure: Since a specific temperature characterizes the ambient environment on every day and everyone is exposed to temperature, in the present context "long-term exposure to temperature" is interpreted as exposure to average temperature changes (increase or decrease) over >three months or to extremely high or low average (>3 months) temperatures compared to the usual temperature of a specific area. This can be further elaborated according to the design: For temporal studies, within one population, temperature changes reflect differences in the selected temperature index (such as annual or seasonal average) in the same area over a number of years. For geographical studies comparing populations living under a different climate, the temperature exposure is defined as the long-term (>3 months) difference in temperature indices between areas.

Comparator: For temporal studies within one population, the comparison is between the area population or the same sensitive subgroup between years characterized by colder or hotter temperature indices compared to “normal” years. For studies comparing populations living under a different climate, the comparison is between populations living in different climate (characterized by hotter or colder long-term temperature). The year can be characterized by the average annual temperature, or by the temperature during one of its seasons (the “warm” and “cold” season), or the indices defined to represent the amount of cold/hot degree-days below or above a given threshold.

Outcomes: Outcomes were selected according to the evidence that has accumulated for the effects of short-term exposures to temperature extremes. All-cause and cause-specific mortality and hospital visits or admissions were considered. Additionally, as our focus was on cardiopulmonary outcomes, hypertension, cardiovascular disease risk factors (such as obesity), hay fever, sinusitis, chronic obstructive pulmonary disease or bronchitis, asthma and respiratory symptoms were included.

Full-length articles were included that: (1) had either temporal ecological comparisons using seasonal or annual data, or ecological geographical comparisons, or cross-sectional studies with individual data, case-control or cohort design (either sample-based or administrative), (2) reporting results on a temperature index (such as mean, max, apparent, variability) and (3) was written in English. Papers were excluded if: (1) they were investigating the occurrence of vector-borne diseases such as malaria and dengue fever or other infectious diseases, (2) they examined temperature only as an effect modifier, and (3) if they applied climate model projections to estimate future temperature-related mortality (Figure 1). The search aimed to be sensitive in order to include all relevant publications. The more general scope of the search allowed checking that no relevant study was missed. The studies not meeting the inclusion criteria were excluded after screening. Reports from studies on mortality and morbidity were searched from 01/01/1990 until 31/10/2020 in *PubMed* and complemented by a search in the Web of Science and other sources (reviews and references from papers). The following search term in PubMed: *(ambient OR air OR climat* OR meteorolog* OR weather OR season* OR outdoor) AND (temperature* OR heat OR hot OR warm OR cold) AND health AND (infectio* OR disease OR hospital* OR inciden* OR prevalen* OR morbidit* OR mortalit* OR death OR outcome* OR event* OR "blood pressure" OR pregnan* OR birth OR gestation*)AND (long* OR chronic* OR annual OR yearly OR season* OR adapt* OR cohort* OR "case control" OR "case-control" OR "cross sectional" OR "cross-sectional")* was used. The term was adjusted for Web of Science according to its system of controlled vocabulary.

2.2 Data extraction

The following information was extracted from the identified publications: author, year of publication, study location(s), study period, study design, study population(s), definition and measure (incidence, prevalence, etc.) of the outcome investigated, outcome assessment method, temperature exposure metric, exposure assessment method, descriptive measure of exposure (mean, minimum, etc.), unit of exposure, type of measure of association, increment used, type of statistical analysis, effect estimates and confidence intervals (or standard errors) and whether covariate adjustment was done and for which covariates (such as age, sex, race/ethnicity, socio-economic status (SES), physical activity, smoking habits, population density, urbanization, precipitation, relative humidity, air pollutants). Effect estimates were derived from the main statistical model with the maximum number of covariates.

2.3 Assessment of Risk of Bias

The risk of bias (RoB) in the selected studies was assessed by adapting the corresponding tool developed by WHO for the review of air pollution health effects (18). The tool was adapted to address temperature effects and is described below. Risk of bias was classified as low, moderate or high based on specific study design characteristics, such as exposure assessment methods, outcome characterizations and confounding adjustment.

RoB assessment was conducted separately at the outcome level after classifying the effects of warm and cold temperatures. In the case where a primary study reported on the effects of warm and cold separately, RoB was evaluated for every exposure-outcome combination. This is because the RoB may be different depending on the warm or cold exposure and the outcome.

The domains of RoB according to the WHO Instrument (18) are Confounding, Selection Bias, Exposure Assessment, Outcome Measurement, Missing Data and Selective Reporting. For each domain, related subdomains and guidance are provided to assist raters in making a judgment about whether the study presents ‘low’, ‘moderate’, or ‘high’ RoB. To avoid ‘carrying-forward’ the ratings from one domain to the others, it is proposed that an overall judgment of bias at the study level is not appropriate. Instead, subgroup analyses are to be performed per risk of bias domain across studies, grouping studies at higher risk of bias for that domain and studies at lower risk of bias for that domain.

The Confounding and Exposure assessment domains have been adapted to the objective of the present review, while the others have been used as they appear in the WHO Risk of Bias Instrument (18).

For the confounding domain, temporal and geographical studies were considered separately. Important confounders considered for temporal comparisons were long-term trends, inconsistencies in the method of recording population size or coding outcome and, for spatial comparisons, age, sex and area-level socioeconomic status. For studies with individual level data, additional confounders such as individual-level SES or body mass index (BMI) for cardiovascular outcomes were considered as important Thus, if a major confounder was not addressed, the RoB for this domain was considered high.

Considering the exposure assessment domain, studies of the effects of long-term exposure to temperature rely on various measurement and modeling efforts. However, spatial variation in ambient temperature is likely to be small over an area (except for the Urban Heat Island- UHI) and is therefore well represented by the measurements of few meteorological sites. Some modeling efforts attempt to individualize exposure. Issues for the raters to consider were the ability of the exposure models used in the studies to adequately predict the exposure (this can be concluded if the model is adequately evaluated against measurements — low risk of bias; not evaluated against measurements — high risk of bias), and the temporal stability over time scales relevant for the long-term studies of interest (e.g., if the exposure contrast is generated for a specific year, it is representative for other years of the epidemiological study and outcome of interest — low risk of bias; it is unrepresentative — high risk of bias).

3. RESULTS

Initially 3,455 studies were screened and 232 read. Sixty-six met the inclusion criteria. However, 34 studies are used in the present work as there is a focus on total mortality/hospital admissions/visits and cardiopulmonary outcomes (Figure 1). The geographical distribution of the studies is presented in Figure 2. From the 34 studies identified from the search, 18 studies were applying temporal comparisons (between periods or seasons with varying temperature within the same populations) and 16 were doing geographical comparisons. Among the temporal studies, 11 included total mortality or hospital visits, 8 included cardiovascular outcomes (mortality, hospital admissions, hypertension) and 6 included respiratory outcomes (mortality, hospital admissions). Among the geographical comparisons, 3 studies focused on total mortality, 8 on cardiovascular outcomes and risk factors (cause-specific mortality, blood pressure, metabolic syndrome, obesity) and 5 on respiratory health outcomes (asthma mortality and prevalence of respiratory diseases and symptoms).

Among these studies, 10 were conducted in Europe (15, 19-27). Eleven studies reported associations from the US and one from Cuba (27-38). Further, 11 studies were conducted in Asia (16,40-49), while one study reported associations from areas around the World (50).

There was a variety of temperature indices used. Specifically:

- 15 studies reported on mean annual temperature or annual temperature variability (15, 23, 27-30, 33, 34, 37, 39-42, 47, 48),
- 10 studies used seasonal temperature or seasonal temperature variability (15, 16, 19, 21, 23, 31, 35, 36, 43, 46),
- 4 studies reported on annual temperature categories (24, 26, 32, 45)
- 3 studies used a degree-day approach (mean annual degrees above/below minimum mortality temperature) (25, 44, 50),
- 2 studies reported on extreme temperature indices (49) or the number of days with extreme heat events (38)

- 1 study reported on the temperature in the month of conception for the subsequent risk of developing CVD (22) and
- 1 study reported on the temperature difference between follow-up and baseline (20).

Additionally, the assessment of temperature or temperature index effects depends on the distribution of temperature in each location. Thus, what may be perceived as “hot” in one location may be within the range of usual temperature elsewhere. Several studies based their definition of “cold” or “heat” on concentration –response functions estimated in their specific location (25, 38, 44, 49, 50).

The presentation of the review results is structured by first classifying according to whether the comparisons were temporal or geographical and then by health outcome as: total mortality/ hospital admissions and visits, cardiovascular (CVD) endpoints and respiratory endpoints. In a separate section, effect modifiers that have been included in the studies assessed are presented.

3.1 Temporal studies

Table 1 presents study design features and main results of the identified studies on temporal associations of long-term temperature exposure and health by outcome studied. A summary of the main results from these studies are shown in Table 2.

3.1.1 Total mortality and hospital admissions/visits

Eleven studies investigated the association of annual mortality and annual temperature indices throughout a long period within the same city or area (Table 1). Among these studies, five used aggregated data over a year (21, 25, 33, 44, 50) and aimed at investigating whether in years characterized by high or low temperatures or temperature variability or "anomalies", such as the deviation of the annual average in a specific year from a 30-year baseline average, the cumulative effects of short-term exposures persist at an annual basis. The results indicate that deaths are at least displaced by a year or more (25, 50). Among these studies, three provided broadly comparable estimates for annual heat and cold effects using similar methodology: Armstrong et al. (50), Rehill et al. (25) and Goggins et al. (44) reported a 1.7%, 1.7%, and 1.9% increase in mortality following a one-unit increase in their heat-related index respectively; results were very consistent even though they have different geographical coverage. Goggins et al. (44) showed that if the period used to define the year varies - they use either May to April or November to October - the estimate may vary as well: using the second definition, they found the heat-related mortality to increase by 2.2%. The corresponding estimates per one-unit change in the cold-related index were 1.1%, 2.3% and 3.1% (alternative definition for Goggins et al. (44) gives an increase of 2.8%), showing stronger cold effects, also remarkably consistent. Also, Goggins et al. (44) included pollutant terms in their models but the results remained unchanged. Blagojevic et al. (21) did not find statistically significant effects in a study including residents of Belgrade.Hess et al. (33) report a significant correlation between annual temperature anomalies and the population-based rate for emergency department heat related illness visits, however, only providing a correlation coefficient without adjusting for confounders. In this design category, we can also classify the two studies which analyzed historical data from the 18th-19th centuries (15, 23). With conditions hardly comparable to today, these studies did not find statistically significant effects of annual temperature and mortality.

All cohort studies (31, 35, 36, 42) addressed the same issue as above, namely temporal changes, i.e. the long-term association of annual mortality and annual temperature indices, using individual data for exposure estimates, confounders and health outcomes. All used the mean or standard deviation of annual or season-specific temperature as the exposure index. The Japanese study (42) used data from a cohort of dialysis patients and found that in years with 1^{o}C higher average annual temperature the survival rate increased by 0.6%. The other three cohort studies were conducted in the US in subjects aged 65+ years. Zanobetti et al. (31) investigated the yearly summer temperature effects on mortality in subjects with chronic diseases and found increased mortality by 3.8 to 5.5% associated with 1^{o}C increase in the summer temperature variability as expressed by the temperature standard deviation. Adjusting for ozone levels, the results were similar (~10% lower). Shi et al. did a similar analysis in New England (35) and the South Eastern US (36) and found that increased summer temperatures were associated with increased annual mortality (1% and 2.5% per 1^{o}C , respectively), whilst increased winter temperatures are associated with a decreased annual mortality (-0.6% and -1.5% per 1^{o}C, respectively). The effect of increased standard deviation was harmful in the New England analysis but not entirely consistent in the South Eastern US.

3.1.2 Cardiovascular outcomes or established cardiovascular disease risk factors

Eight temporal studies comparing cardiovascular health outcomes in different years characterized by specific temperature indices are shown Table 1. There was a variety of assessed outcomes as three studies reported on cardiovascular mortality (21,44,25), one on cardiac and ischemic stroke hospital admissions (39), three studies reported on blood pressure (20, 43, 46). One study was based on an older birth cohort (subjects born between 1934 and 1944) in Finland (22) and assessed the effects of temperature at the time of conception on adult life cardiovascular morbidity and risk factors.

The mortality studies report that cardiovascular mortality decreased as temperature increased during cold periods (21, 25, 44) but not all associations were statistically significant. Results for temperature indices in the warm periods were more inconsistent; for example, Rehill et al. (25) reported decreasing rates of mortality with increasing temperature in the US, whereas for Hong-Kong, Goggins et al. (44) found an increase in the age-standardized cardiovascular mortality rate of around 2-3% with an increase in 10 hot degree days (mean annual degrees above minimum mortality temperature). Thus, it may be inferred that lower temperatures affect CVD mortality more consistently than warmer; however, the local conditions may be shaping the associations.

Yitshak-Sade et al. 2018 (39) showed associations between long-term exposures to temperature and an increased risk of hospital admissions due to ischemic stroke and a decreased risk of admissions due to cardiac causes. For an interquartile range (IQR) increase 2.2 °C) in the 10th (8 °C) percentile of temperature, there was a 2.15% (95% CI: 2.36, 1.93) decrease in admissions due to cardiac causes and a 7.32% (6.68, 7.96) increase in those due to ischemic stroke. The percent changes per IQR (2.2 °C) in the 90th (10.2 °C) percentile of temperature are −1.69% (−1.77, −1.60) and 0.15% (−0.04, 0.34), respectively. This study adjusted for air pollutants in the core models.

Seasonality in blood pressure levels is well known. Some studies included in this review also demonstrated seasonality in population blood pressure levels with higher values in the winter and lower in the summer (20, 43, 46). Regarding temperatures on month of conception, Schreier et al. (22) found that unusually warm month at conception time is associated with lower BMI in adult life for men, while a month of conception with average temperatures in the coldest quartile is associated with lower BMI, lower fat percentage and lower risk of obesity in adult life for women. However, they did not find any association between temperature in the month of conception and later risk of developing specific cardiovascular diseases.

3.1.3 Respiratory outcomes

Three temporal studies Blagojevic et al. (21), Rehill et al. (25) and Goggins et al. (44), investigated effects on respiratory mortality.

Goggins et al. (44) reported an increase in respiratory mortality with an increasing number of hot and cold degree days per year in Hong-Kong. An increase of 10 hot degree-days is associated with a 1.3% (95% CI: -2.1, 4.7) increase in heat-related respiratory mortality, defining the year from May to April, and a 2.7% (95% CI: 0.1, 5.4) increase, defining the year from November to October. Only the latter definition resulted in a statistically significant association. An increase of 200 cold degree-days was associated with a 4.6% (95% CI: 0.1, 9.3) and 6.3% (95% CI: 2.3, 10.5) increase in cold-related mortality, respectively.

A study conducted in the US (25) reported a 7.6% (95% CI: 2.7, 12.8) increase in respiratory mortality associated only with colder years (no association was found with heat). Blagojevic et al. (21) found no statistically significant associations of excess winter mortality with mean winter temperature.

Regarding hospital admissions, Yitshak –Sade et al. (39) reported a 6.24% (95% CI: 6.54, 5.93) and 1.37% (95% CI: 1.28, 1.47) increased rate of respiratory admissions per IQR (2.2 °C) increase in the 10th (8 °C) and 90th (10.2 °C) percentile of temperature, respectively; this suggests that the effect is more pronounced in areas with a cooler climate. This was the only study that accounted for air pollution and reported the effects of temperature adjusted for exposure to $PM_{2.5}$ (39).

Regarding the respiratory symptoms, in the US, Bhattacharyya et al. 2009 (30) reported a small increase in the prevalence of sinusitis with increasing temperature but Miller et al. (28) found no association with otitis media and respiratory allergies. No statistically significant association was reported between temperature and prevalence of chronic bronchitis (30).

3.2 Geographical comparisons

Table 3 presents study design features and main results of the identified studies with geographical comparisons of long-term temperature exposure and health by outcome studied. A summary of the main results from these studies are shown in Table 4.

3.2.1 Total mortality and hospital admissions/visits

Three studies reported on geographical comparisons in mortality excesses according to the levels of temperature indices and their rate of change. The study by Healy (19) focused on mean winter temperature across Europe and found that increased mean winter temperature is associated with an increased mortality rate, i.e. in cities with warmer winters higher excess cold mortality is observed. Lim et al. (16) reported that higher average summer temperatures were associated with higher heat-related mortality risk in cities with a low gross domestic product (GDP) per capita. The study by Yang et al (49) found that both extreme heat and extreme cold had adverse long-term effects on total mortality and suggested that the number of annual deaths per 100,000 population due to extreme temperatures in the long-term were considerably larger compared to the short-term.

3.2.2 Cardiovascular outcomes or established cardiovascular disease risk factors

Two studies provide geographical comparisons of the incidence of CVD mortality in relation to long-term temperature levels. Faeh et al. (26) found that living in areas with higher temperatures is associated with a lower rate of IHD mortality. Zhou et al. (47) reported higher diabetes mortality rates in locations with higher temperatures in China, with 5% higher rates per 1°C increase in average temperature. Six studies report geographical comparisons of the prevalence of hypertension or blood pressure levels or other CVD risk factors between areas with different long-term temperature average. Results supported a decrease in blood pressure in locations with higher long-term temperature exposure in diverse countries, such as China and France (40, 48). One study conducted in children in China (48) showed that at very high temperatures, the association was reversed and higher blood pressure values were observed. It should be noted that Li et al. (48) adjusted also for air pollutants in an additional model and found that results remained unchanged. In terms of other CVD risk factors, inconsistent results were reported in geographical comparisons of obesity measures: Voss et al. (32) in a study in the US reported no statistically significant association of annual temperature and obesity. However, Valdes et al. (24) found a statistically significant association in Spain where people living in warmer climate tend to have a higher prevalence of obesity. Similarly, Yang HK et al. (45) found a higher BMI and waist circumference in warmer areas of Hong Kong and in areas where there are fewer days with temperature below 0^{o}C. Wallwork et al. (37) found a statistically significant association of increased temperatures and higher fasting blood glucose, while the association with metabolic syndrome and the other studied components was not statistically significant.

3.2.3 Respiratory outcomes

As far as respiratory outcomes are concerned, Venero et al. 2008 (29) reported higher asthma mortality in areas with lower temperatures. Four studies (27, 34, 38, 41) reported on temperature associations with the prevalence of respiratory conditions. The association of higher temperatures with the prevalence of hay fever was reported in two US studies (34, 38). The prevalence of asthma was also found to be increasing in areas of higher temperature in a study in Turkey (41) and one in Italy (27). Pesce et al. (27) reported a 1.09% (95% CI: 0.23, 1.95) change in the prevalence of lifetime asthma per 1 standard deviation increase in average annual temperature. In Metintas et al. (41) a similar association was reported with the prevalence of wheezing and the prevalence of allergic rhinitis in females only. No statistically significant association was reported between temperature and prevalence of chronic bronchitis (27).

3.3 Effect modification

Seven of the identified studies reporting on total mortality and morbidity investigated potential effect modifiers, namely age, sex, ethnicity, population density and GDP per capita. Results of the studies by Rocklov et al. (23) and Shumann et al. (15) do not support an effect modification pattern by sex. However, Shi et al. (35, 36) reported that women were more sensitive to increased summer mean temperature but less to summer temperature variability. Several studies (25, 31, 35, 36) reported that elderly persons are more sensitive to temperature effects. Also, Zanobetti et al. (31) examined the association of summer temperature and long-term survival among people with chronic disease (chronic obstructive pulmonary disease, diabetes, congestive heart failure, and myocardial infarction) and found that 1°C increase in the summer temperature variability is associated with 3.8 to 5.5% increase in mortality as expressed by the temperature standard deviation.

Zanobetti et al. (31) also reported that there is a stronger temperature variability (measured by the standard deviation)-mortality association in cities with a higher percentage of non-white residents. Shi et al. (35, 36) reported an increased risk in black race and a decreased risk in Asian, Hispanic and `other' race group relative to the white race, which may be explained by the fact that elderly subjects in the decreased risk groups immigrated from warm areas and might be more acclimated to a warmer summer. Blagojevic et al. (21) reported higher winter-related mortality among the Roma population of Belgrade compared to the non-Roma population.

Further, Zanobetti et al. (31) also reported on significant modification of the temperature variability-mortality association by the proportion of green surfaces (associations were lower in areas with a higher proportion of green surfaces), while Shi et al. (35, 36) reported higher effect estimates in less densely populated areas for both mean and standard deviation of summer temperature. Last, Lim et al. (16) reported that only among cities with low GDP per capita, higher summer temperature was associated with increased mortality.

Regarding cardiovascular outcomes and the established risk factors, Li et al. (48) investigated age and sex as potential effect modifiers, but they did not find any modifying patterns.

None of the studies reporting on respiratory outcomes investigated potential effect modifiers. However, Metintas et al. (41) reported results separately by sex, but the coefficients were similar in magnitude.

3.4 Assessment of Risk of Bias

The assessment for the risk of bias in the associations reported from the studies on the cardiovascular outcomes is presented in Figure 3. Several (8 out of 23) associations rated a high risk of bias in the domain of possible confounding control, due either to their ecological design and inadequate adjustment for appropriate confounders (long-term trend for temporal or area level for spatial comparisons) or to not accounting for one of the critical confounders (or mediators) when analyzing individual data, usually BMI. Similarly, some associations rated moderate or high in the exposure assessment domain, because whilst they were analyzing individual data, they only used ecological exposure metrics and did not adequately describe the method itself or did not account properly for exposure contrasts.

The risk of bias assessment for the associations reported in the selected studies on the respiratory outcomes is presented in Figure 4. Some associations (7 out of 18) rated high for risk of bias mainly due to inadequate potential confounding control or inadequate adjustment for temporal trend. About one third (6 out of 18) rated high in the exposure method domain due to inappropriate description of either the exposure contrast or the method itself or inadequate estimation of individual exposure (e.g. not taking into account residential history).

4. DISCUSSION

Studies of long-term exposures to temperature are few compared to those studying effects of episodic decreased or increased temperature. The studies can be classified in two categories: those observing associations within a population over years with changing annual or seasonal temperature metrics and those comparing areas with a different climate. The former type of study is easier to perform whilst the latter requires a large-scale geographical dimension and faces the difficulty of separating the effects of temperature and other meteorological variables from other population characteristics (such as SES, behavioral or genetic).

In terms of the exposure variable, we focused in this review on the effects of temperature, as in many studies of short-term effects, temperature is highlighted as the most important health determinant compared to other meteorological characteristics. We defined as long-term those exposures exceeding three months. Most studies of those selected in this context are temporal studies comparing annual changes in the frequency of a health outcome according to annual characteristic patterns of temperature, such as annual means, seasonal means, days with extreme temperature characteristics and related metrics. Their results may be interpreted as responding to the question of whether the well-established effects of short-term temperature exposures to heat and cold are due to short-term displacement (harvesting) or are evident in the annual health event rates, especially deaths, indicating that they are at least displaced by a year or more.

Temporal studies using aggregated data indicate a 1.5% to 2% increase in mortality following a 1-unit increase in the used heat-related index, which was rather consistent although referring to different geographical areas (25, 44, 50). The quantitative estimate is shown to vary somewhat according to how the "year" was defined, i.e. from January 1st to December 31st, or alternatively e.g. from May 1st to April 30. The corresponding estimates for cold effects varied between a 1% and 3% increase in mortality. Cohort studies may investigate temporal changes (e.g. from year to year or between seasons) but they may also study geographical contrasts, using, in all cases, individual data for exposure estimates, confounders and health outcomes. Among those that investigated temporal changes, Ogata and Yorioka (42) used data from a cohort of dialysis patients and found that in years with 1°C higher average annual temperature the survival rate increased by 0.6%. The other three cohort studies, conducted in the US in subjects aged 65+ years, found increased mortality by 1 to 5.5% associated with 1°C increase in the summer temperature or summer temperature variability (31, 35, 36). Increased winter temperatures were associated with decreased annual mortality (-0.6 and -1.5% respectively). From these results it may be inferred that the short-term effects of usual temperature patterns or temperature extremes that characterize a specific year lead to premature deaths that are displaced by more than one year on average. Temporal studies investigating cardiovascular mortality found more pronounced effects of cold temperature and more inconsistent effects of heat. Respiratory mortality associations with temperature followed a similar pattern to that of total mortality.

Among the two studies comparing all-cause mortality in geographical areas with different climates, Healy (19) found that an increase in mean winter temperature is associated with increased cold-related mortality rate in Europe, which may be attributed to the smaller degree of preparedness for cold weather in countries with milder climate. Lim et al. (16) using data from Asian cities in 4 countries, reported that higher average summer temperatures were associated with higher heat-related mortality risk in cities with a lower GDP per capita. These results may be interpreted as showing higher effects in socioeconomically deprived areas where air conditioning cannot be afforded. The few geographical comparisons for cardiovascular mortality outcomes provide sparse and rather inconsistent results.

In this review studies assessing the effects of temperature on cardiovascular risk factors were also included. Temporal studies comparing seasonal difference within the same populations show that blood pressure has seasonality, with lower levels in the summer. Results from studies comparing geographical areas with different long-term temperature levels reported a decrease in blood pressure for those living in warmer areas (20, 40, 48). One study in China (48) was conducted in children and showed that at very hot temperatures the association is reversed and higher blood pressure values were observed. Geographical comparisons for the prevalence of known CVD risk factors, such as obesity, waist circumference and glucose level, were more inconsistent, however, there were indications that these factors have increased prevalence among those living in warmer climate.

A few studies (27, 34, 38, 41) reported geographical comparisons on the associations of higher temperature and higher prevalence of respiratory conditions, i.e. hay fever, asthma, wheezing, allergic rhinitis. These studies were implemented in very different geographic areas worldwide and their number is still very small to lead to conclusive results.

There were various temperature indices used in the above studies. Despite of the variety of exposure metrics, consistent patterns emerge; however, it is difficult to compare the magnitude of effects across studies, hence we opted not to combine results quantitatively even for outcomes where we had more than 3 studies.

For the above studies, some potential effect modifiers have been explored. Those identified are old age, the co-morbidity with chronic disease, and low SES areas, whilst very few studies adjusted for air pollutants, but the results did not change remarkably.

The mechanisms by which long-term exposure to different temperature affects health are not so extensively studied. They include cold –enhanced sympathetic reactivity leading to elevated blood pressure which may be linked with the development of hypertension and

CVD outcomes; cold and heat mediated dehydration leads mainly to immediate effects; and heat induced systemic inflammatory response. The fact that CVD risk factors increase after exposure to cold may contribute to the development of atherosclerosis (51).

Regarding the Risk of Bias assessment, the domains of possible confounding control and exposure assessment rated with increased or moderate risk of bias in several studies. It is true that the assessment of the risk of bias cannot be entirely standardized and includes qualitative aspects but we believe that it provides useful synthetic information. The result implies that better designed studies when it comes to adjustment for confounders and exposure assessment are needed in the future.

In conclusion, there are relatively few studies investigating the associations of long-term temperature exposure and health. Those studies which evaluate the annual or seasonal associations of temperature exposure and mortality or hospital admissions within the same area report an increasing number of health events both with increasing and decreasing annual or seasonal temperature. It follows that the short-term effects of usual temperature patterns or temperature extremes that characterize a specific year lead to premature deaths that are displaced by more than one year on average. Geographical comparisons indicate that there is more cold related excess mortality in warmer climates. Additionally, populations living in warmer climates tend to have lower levels of blood pressure and higher prevalence of obesity. Several gaps in research are identified, especially concerning geographical comparisons. However, a better understanding of the long-term exposure to higher temperature and weather-related extreme events is necessary to promote adaptation and mitigation of climate change.

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Table 1. Description of Study Design Features and Main Results of Selected Studies on Temporal Comparisons of the Association Between Changes in Long-Term Exposure to Temperature by health outcome

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
A. Total mortality/ hospital admissions-visits					
Ecological studies					
Blagojevic et al. (21)	Residents of Belgrade (Roma and non-Roma population), Serbia (1992-2007)	Mean winter environmental temperature per year(°C)/ monitoring sites	Excess winter mortality from all-causes per year/ Mortality database from the Statistical Office of the Republic of Serbia.	Annual change in excess winter mortality rate per 10,000: −0.51 (-2.69, 1.67)	Smaller but not statistically significant EWM in years with increased mean winter temperature.
Shumann et al. (15)	Population in Uppsala Doyra parish, Sweden, (1749-1859)	Annual and seasonal average temperature (°C) (winter: January and February, springtime: March to May, summer; June to August, autumn: September to November)/ measurements	Annual death counts / Demographic Database (DDB) at Umeå University	Relative Risk per 1°C increase (only statistically significant results): Spring temperature-mean: 0.959(0.921,1.000) Winter temperature in the sub-period 1749-1785: 1.049(1.003,1.098)	No statistically significant effect of annual or seasonal temperature on annual mortality was found in these historical data from the 18th-19th centuries
Hess et al. (33)	US Population , US (2006-2010)	Annual temperature anomalies (°C)/ monitoring sites	Annual ED visits for heat-related illness (ICD-9-CM 992.0–992.9)/ Nationwide Emergency Department Sample (NEDS) of the Healthcare Cost and Utilization Project	Spearman's correlation coefficient = 0.882(p-value<0.005)	Significant correlation between annual temperature anomalies and annual population-based rate for ED heat illness visits

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Rocklov et al. (23)	Population in Skelleftea parish, Sweden, (1749-1859)	Annual and seasonal average temperature (°C) (winter: January and February, springtime: March to May, summer; June to August, autumn: September to November)/ measurements	Annual death counts / Demographic Database (DDB) at Umeå University	Relative Risk per 1°C increase (only statistically significant results): Annual temperature: 10-14yrs: 0.76 (0.61-0.94), 50+yrs: 0.91 (0.85-0.97), Winter temperature: 0.97 (0.95-0.99), Spring temperature: 0.95 (0.91-0.98)	Statistically significant effect of annual temperature on annual mortality for age groups 10-14 and 50+ years (fewer deaths in warmer years) and of winter and spring temperature on annual mortality for all ages (fewer deaths in years with warmer winter or spring)
Goggins et al. (44)	Residents of Hong Kong, China (1976–2012)	Annual measures of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature (°C)/ monitoring sites	All-cause mortality/ Hong Kong Census and Statistics Department	% increase in health outcome per increase of 10 hot degree-days, or per increase of 200 cold degree-days (based on the different the definition of year (May to April or Nov to Oct): May-April: Heat: 1.9% (0.5, 3.4%), Cold: 3.1% (1.3, 5.0%) Nov-Oct: Heat: 2.2% (1.0, 3.3%), Cold: 2.8% (1.0, 4.5%)	A statistically significant association was found between an increase in annual mortality and the increase in both hot and cold degree days. The quantitative estimate is sensitive to the definition of year.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Rehill et al. (25)	London residents, UK, (October 1949 - September 2006)	Annual mean of 'Heat-degrees' per day as the number of degrees above 18°C of the daily mean temperature Annual mean of 'Cold-degrees' as the number of degrees below 18°C of the daily mean temperature. / monitoring site	All-cause mortality/ Registrar General (1949-1975), supplementing 1950–1964 data from a previous study (weekly counts), and for 1976-2006 from the Office of National Statistics (daily counts) (all-natural causes)	% increase per 1°C increase in average cold (or heat) below (above) the threshold (18°C) across each year: Cold: 2.3 (0.7, 3.8) Heat: 1.7 (-2.9, 6.5)	Cold related increase in annual mortality was identified. The authors interpret this as evidence against the hypothesis that temperature-related deaths are due to short-term "harvesting".
Armstrong et al. (50)	Residents of 278 locations from 12 countries over the world (10 to 40 years per country between 1972-2012)	Mean annual degrees above/below minimum mortality temperature (°C) / monitoring sites	Mortality/ death records	% excess relative risks per 1°C increase in the annual exposure indices: Heat: 1.7% (0.3-3.1%), Cold: 1.1% (0.6-1.6%) Daily attributable fractions: Heat 0.8 (0.2, 1.3), Cold 1.1 (0.9, 1.4)	The results provide evidence that most deaths found attributable to heat and cold in daily analyses were brought forward by at least 1 y. (High heterogeneity between countries: I^2= 67% and 72% for heat and cold effects respectively).
Cohort studies					
Ogata & Yorioka (42)	Dialysis patients/Japanese Society for Dialysis Therapy, Japan (2005-2007)	Average annual temperature (°C)/ -	The 1-year survival rate of new dialysis patients/ data from the Japan Statistics Bureau and Japanese Society for Dialysis Therapy	Change per 1 °C increase: 0.0062 (p-value<0.0001)	In years with 1°C higher temperature the survival rate is increased by 0.6%

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Zanobetti et al. (31)	US residents aged 65 +yrs, with potentially predisposing conditions (Chronic Obstructive Pulmonary Disease, Congestive Heart Failure, Diabetes, Myocardial Infarction from 135 US cities (1985-2006)	Summertime (June–August) temperature SDs in each year (°C) across all cities/ monitoring site	Mortality/ death records	Hazard ratio per 1°C increase: COPD cohort: 1.048 (1.029-1.067), Diabetes cohort: 1.055 (1.035-1.076), MI cohort: 1.05 (1.030-1.069), CHF cohort: 1.038 (1.024-1.052)	Mortality was increased in persons with COPD, Diabetes, previous MI and CHF in years with higher summertime temperatures
Shi et al. (35)	Fee-for-service Medicare beneficiaries, who were aged 65 and older in New England, US (2000-2008)	Annual summer and winter mean temperature and SD at residential zip code(°C)/ satellite-based measurements	All-cause mortality/ death certificates Centers for Medicare and Medicaid services	% increase per 1°C increase in annual indices: Annual summer mean temperature: 1.0% (0.6, 1.5%) Annual winter mean temperature: -0.6% (-0.3,-0.9%) Annual summer mean SD: 1.3% (0.2, 2.4%) Annual winter mean SD: 4.1% (3.0, 5.2%)	Long-term survival was statistically significantly associated with both seasonal mean values and standard deviations in elderly subjects. A rise in summer mean temperature was associated with higher death rate. An increase in winter mean temperature corresponded to lower mortality. Increases in temperature SDs for both summer and winter were harmful.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Shi et al. (36)	Fee-for-service Medicare beneficiaries, who were aged 65 and older in the Southeastern USA (2000-2013)	Annual summer and winter mean temperature, SD and anomaly at residential zip code(°C)/ satellite-derived surface temperature measurements	All-cause mortality/ US Medicare data.	% increase per 1°C increase in annual indices: Annual summer mean temperature: 2.46 (2.33,2.59) Annual winter mean temperature: -1.46 (-1.50,-1.42) Annual summer mean SD: 0.80 (0.40,1.20) Annual winter mean SD: 0.41 (0.22,0.60) Summer mean temperature annual anomaly: 0.96 (0.72,1.19) Winter mean temperature annual anomaly: -1.27(-1.36,-1.17) Summer SD annual anomaly: 3.71(3.21,4.22) Winter SD annual anomaly: 0.59(0.37,0.81)	An increase in summer mean temperature corresponded to an increase in the death rate. An increase in winter mean temperature was associated with a decrease in the mortality rate. Increases in seasonal temperature SD also adversely influence mortality. However, the "anomalies" indices did not yield consistent results.
B. Cardiovascular outcomes					
Ecological studies					
Blagojevic et al. (21)	Residents of Belgrade(Roma and non-Roma population), Serbia (1992-2007)	Mean winter environmental temperature (°C) per year/ monitoring sites	Excess winter mortality from cardiovascular causes per year/ Mortality database from	Annual change in excess winter mortality rate per 10,000: −0.50 (−2.09, 1.09)	Smaller but not statistically significant EWM in years with increased mean winter temperature.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
			the Statistical Office of the Republic of Serbia.		
Goggins et al. (44)	Residents of Hong Kong, China (1976–2012)	Annual measures of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature (°C)/ monitoring sites	Cardiovascular mortality/ mortality records from Hong Kong Census and Statistics Department	% increase per increase of 10 hot degree-days, increase of 200 cold degree-days (based on different definition of year (May-April and Nov-Oct): May-April: Heat: 2.3% (0.1, 4.5%), Cold: 4.4% (1.7, 7.9%) Nov-Oct: Heat: 2.9% (0.7, 4.7%), Cold: 3.7% (0.9, 6.6%)	A statistically significant association was found between an increase in annual mortality and the increase in both hot and cold degree days. The quantitative estimate is somewhat sensitive to the definition of year.
Rehill et al. (25)	London residents, UK (1949 - 2006)	Annual mean of 'Heat-degrees' per day as the number of degrees above 18°C of the daily mean temperature; annual mean of cold-degrees as the number of degrees below 18°C of the daily mean temperature/monitoring site	Cardiovascular mortality/ counts of deaths by Registrar General (1949-1975), supplementing 1950–1964 data from a previous study, and for 1976-2006 from the Office of National Statistics	% increase per 1°C increase in average cold (or heat) below (above) 18°C across each year: Cold: 2.9 (0.9, 5.0) Heat: -0.1(-5.9, 6.1)	Colder years are associated with increased cardiovascular mortality. No association found with heat.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Yitshak-Sade et al. (39)	Adults aged 65 years and older who were Medicare beneficiaries and enrolled in the fee-for-service program, New England, US (2001-2011)	Annual average temperature/ satellite-based spatio-temporally (zip code- daily) resolved models	All cardiac (ICD 9: 390-429) and ischemic stroke (ICD 9: 432-435) hospital admissions/ records	% increase per annual temperature IQR (2.2 °C) in the 10th (8 °C) and 90th (10.2 °C) percentile of temperature: All cardiac admissions: −2.15% (−2.36%, −1.93%) and−1.69% (−1.77%, −1.60%) respectively Ischemic stroke admissions: 7.32% (6.68%, 7.96%) and 0.15% (−0.04%, 0.34%) respectively	Cardiac admissions decrease but ischemic stroke admissions increase with increasing annual temperature. The magnitude of the effect is larger at the 10th temperature percentile in both cases. The associations were not modified by PM2.5.
Cohort studies					
Alperovitch et al. (20)	Population aged > 65 yrs, noninstitutionalized Bordeaux, Dijon, Montpellier, France (1999-2001)	Mean difference in temperature between 2-year follow-up and baseline, °C, seasons as: winter December 21 - March 20; spring March 21 - June 20; summer June 21 - September 20; autumn September 21 - December 20/ monitoring sites in Bordeaux, Dijon, Montpellier (French	Blood pressure (SBP,DBP mm Hg)/ field measurements using a validated digital electronic tensiometer	Temporal comparisons: Mean temperature difference between 2-year follow-up and baseline: mean change (sd) in SBP/ DBP: −15: +2.3 (21.6)/+0.5(13) −10:−1.4(20.7)/−1.2(11.9) −5:−3.2(20.8)/−2.5(12.7) 0: −3.6(21.1)/−2.2(12.9) +5:−5.7(20.1)/−2.9(12.3) +10:−8.8(20.1)/−3.8(12.2) +15:−9.7(20)/−3.7(12.7)	The study shows a strong influence of outdoor temperature on blood pressure in the elderly and a pronounced seasonality in blood pressure levels. Increased long-term temperature is associated with decreased blood pressure levels.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
		National Meteorological Office)			
Schreier et al. (22)	A random sample from The Helsinki Birth Cohort Study (includes subjects born in 1934-44), Finland (2001-2004)	Temperature of the month of conception (°C)/ monitoring site	Coronary heart (ICD10 codes: I21-25) and cerebrovascular disease (ICD10 codes: I60-69) mortality and hypertension/ Death certificates from the Death Registry and the Hospital Discharge Registry. Hypertension from antihypertensive medication from the Social Insurance Institution of Finland	Hypertension: Probability of hypertension rose from about 0.20 to about 0.25 with increasing quartiles of temperature in women (but not in men) Coronary heart and cerebrovascular disease mortality: only p-values reported (p-values > 0.05)	Warm temperatures around conception: significantly higher probability of hypertension in women. Coronary heart and cerebrovascular disease mortality were not associated with warm temperatures at month of conception.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Schreier et al. (22)	A random sample from The Helsinki Birth Cohort Study (includes subjects born in 1934-44), Finland (2001-2004)	Temperature of the month of conception (°C)/ monitoring site	BMI scores, Fat percentage and obesity (BMI ≥30 kg/m2)/ measurements from clinical examinations in 2001-2004	Only p-values reported: Obesity: p-value < 0.05 only for women BMI scores: p-values <0.05 for both men and women Fat percentage: p-value < 0.05 only for women	Unusually warm month at conception time, in men: lower BMI in adult life. Women conceived during a month with average temperatures in the coldest quartile: lower BMI, lower fat percentage and lower risk of obesity in adult life.
Cross-sectional studies					
Lewington et al. (43)	Adults aged 30-79 recruited from ten diverse urban and rural regions in China, 10 diverse regions (2004-2008)	Seasonal outdoor temperature(°C) (winter: Dec-Feb, summer: June-Aug)/ monitoring sites	Blood pressure (SBP mm Hg)/ standardized measurements by trained study personnel	On average, 22.4° C difference in seasonal temperature (summer vs winter)-> 10 mm Hg difference in SBP (summer vs winter)	Temporal comparison indicated higher blood pressure levels in the winter and lower in the summer.
Yang L et al. (46)	Adults aged 30–79 years from 10 diverse regions in China with prior CVD (2004-2008)	Seasonal outdoor temperature (°C) (winter: Dec-Feb, summer: June-Aug) / monitoring sites	Blood pressure (SBP mm Hg)/ standardized measurements by trained study personnel	On average, 21.7° C difference in seasonal temperature (summer vs winter)-> -9 mm Hg difference in SBP (summer vs winter)	Higher blood pressure levels in the winter and lower in the summer.
C. Respiratory outcomes					

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Ecological studies					
Blagojevic et al. (21)	Residents of Belgrave (Roma and non-Roma population), Serbia (1992-2007)	Mean winter environmental temperature (°C) per year/ monitoring site	Excess winter mortality from respiratory causes per year/ mortality from the Statistical Office of the Republic of Serbia.	Annual change in excess winter mortality rate per 10,000: −0.15 (-0.74, 0.43)	The association of average annual temperature per year was not associated with excess respiratory mortality.
Goggins et al. (44)	Residents of Hong Kong,China, (1976–2012)	Annual measures of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature (°C)/ monitoring sites	Respiratory mortality/ records from Hong Kong Census and Statistics Department	% increase per increase of 10 hot degree-days, increase of 200 cold degree-days based on different definition of year (May to April or Nov to Oct): May-April: Heat: 1.3% (-2.1, 4.7%), Cold: 4.6% (0.1, 9.3%) Nov-Oct: Heat: 2.7% (0.1, 5.4%), Cold: 6.3% (2.3, 10.5%)	An increase in respiratory mortality was found with increasing hot and cold degree days. The results were sensitive to the definition of year.
Rehill et al. (25)	London residents, UK (1949-2006)	Annual mean 'Heat-degrees': the number of degrees>18°C of the daily mean temperature; Annual mean of cold-degrees: the number of degrees< 18°C of the daily mean temperature. /monitoring site	Respiratory mortality/ deaths by Registrar General (1949-1975), supplementing 1950–1964 data from a previous study, and for 1976-2006 the Office of National Statistics	% increase per 1°C increase in average cold (or heat) below (above) the threshold (18°C) across each year: Cold: 7.6 (2.7, 12.8) Heat: 3.3 (-10.3, 19.0)	Colder years are associated with increased respiratory mortality. No association found with heat.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Yitshak-Sade et al. (39)	Adults aged 65 years and older who were Medicare beneficiaries and enrolled in the fee-for-service program, New England, US (2001-2011)	Annual average temperature/ satellite-based spatio-temporally (ZIP code- daily resolved models	Respiratory hospital admissions (ICD 9: 460-519) records	% increase per annual temperature IQR (2.2 °C) in the 10th (8 °C) and 90th (10.2 °C) percentile of temperature:6.24% (6.54%, 5.93%) and 1.37% (1.28%, 1.47%) respectively	Respiratory admissions increase with increasing temperature and the magnitude of the effect is larger at the 10th temperature percentile.
Cross-sectional studies					
Bhattacharyya (30)	Adult sample from the National Health Interview Survey, US (1998-2006)	Average annual US temperature (°F)/ monitoring sites	Hay fever, sinusitis and Chronic bronchitis/ Questionnaire data	Change in disease condition prevalence per 1°C increase in average annual temperature: Hay fever: -0.002 (p-value: 0.164), Sinusitis:0.004 (p-value:0.031), Chronic bronchitis:-0.001 (p-value:0.324)	No statistically significant association between annual temperature and prevalence of hay fever and chronic bronchitis. Small effect for increasing prevalence of sinusitis with increasing temperature.
Miller et al. (28)	Children 0-18 yrs from the National Health Interview Survey,US (1998-2006)	Average US annual temperature(°F)/ land-based weather stations and satellite measurements	Frequent otitis media, respiratory allergies / Aggregated data from NHIS based on questionnaire data completed by parents	Odds ratio per 1°C increase in average annual temperature: Frequent otitis media: 1.013 (0.952-1.078) Respiratory allergies 1.003 (0.961-1.048)	Changes in average annual temperature (temporal comparisons) do not influence the prevalence of otitis media nor the prevalence of respiratory allergies.

CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; MI: Myocardial Infarction; SD: Standard Deviation

Table 2. Summary of results from temporal studies by health outcome

Temporal comparisons			
Outcome	**Number of studies**	**Reference**	**Evidence for**
Total mortality/admissions/ visits	11	15, 21, 23, 25, 31, 33, 35, 36, 42, 44, 50	Higher winter temperature -> lower mortality Higher summer temperature -> higher mortality Annual Temperature anomalies -> increased heat illness emergency department visits (suggestive)
Cardiovascular Disease (CVD) mortality/admissions	4	21, 25, 44, 39	Higher winter temperature -> lower mortality Higher summer temperature -> inconsistent evidence Higher annual temperatures -> increase in rate of ischemic stroke admissions, bu decrease in all cardiac admissions
Hypertension/Blood Pressure (BP) levels	4	22, 43, 46, 20	Higher temperature/ warm season -> Lower BP Lower temperature/ cold season -> Higher BP Higher temperature around conception: increased risk of hypertension in adult life for women
Obesity/ Body Mass Index (BMI)	1	22	Higher temperature around conception: lower BMI for males/ higher BMI for females (limited evidence)
Respiratory mortality/admissions	4	21, 25, 44,39	Higher winter temperatures -> lower mortality Higher summer temperature -> inconsistent evidence Higher annual temperatures -> increase in rate of respiratory admissions
Respiratory conditions	2	28,30	Higher temperatures -> small increase in the prevalence of sinusitis No evidence of association with hay fever, respiratory allergies and chronic bronchitis

Table 3. Description of Study Design Features and Main Results of Selected Studies on Geographical Comparisons of the Association Between Long-Term Exposure to Temperature and Health Outcomes

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
A. Total mortality/ admissions-visits					
Ecological studies					
Yang et al. (49)	Residents of 70 cities in China (2002-2013)	Extreme temperature indices (5 hot,5 cold)(°C) (per year) and extreme hot/cold index (PCA) / monitoring sites	All-cause mortality/ China Regional Statistical Yearbook	Mortality change per change in rate of index: Extreme hot index: 1.435×10^{-3} (1.434×10^{-3}, 1.442×10^{-3}) Extreme cold index: 7.343×10^{-4} (7.323×10^{-4}, 7.350×10^{-4})	Both extreme heat and extreme cold had long-term effects on all-cause mortality. Annual deaths per 100,000 individuals due to long-term exposure to extreme heat and cold were considerably larger compared to the short-term.
Healy (19)	Europe, population of 14 European countries (1988-1997)	Mean winter ambient temperature(°C) in 14 different countries/ monitoring sites (weather stations)	Excess winter mortality (the surplus number of deaths during the winter season (December to March) in each country compared to the average of the non-winter seasons)/ United Nations Databank	Relative excess winter mortality per 1°C increase in temperature: 0.27 (p-value <0.001)	Countries with 1°C higher mean winter temperature were found to have an increase of 0.27 in the mortality rate.
Lim et al. (16)	Residents of 32 cities in Taiwan, China, Japan, and Korea (1996–2002)	City's average summer (May-Sep) temperature (°C) / monitoring sites	All-cause mortality per city (ICD10 codes: A00-S99)/ Department of Health in Taiwan, the Korea National	Increase in mortality in cities with 1°C higher average summer temperature: 0.025, p-	Among the cities with low GDP per capita, heat related mortality increased with higher summer temperatures,

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
			Statistics Office, the Ministry of Health, Labor, and Welfare of Japan, and the Municipal Center for Disease Control and Prevention in China	value=0.0233 (among cities with low GDP per capita)	whereas among high-GDP cities, heat-related mortality did not change by average summer temperature.
B. Cardiovascular outcomes					
Ecological studies					
Lei et al. (40)	Males 17-21 years from 6 geographic areas of China (2001)	Annual mean air temperature(°C) per area/ not reported	Blood pressure (SBP,DBP mm Hg)/ field measurements performed by using a periodically calibrated mercury sphygmomanometer	Mean change per 1°C increase in area's annual mean temperature: Coefficient: - 0.07 for SBP, - 0.055 for DBP	This study reports lower levels of blood pressure among young people living in areas with higher temperatures.
Zhou et al. (47)	People aged 20 years and older in China (2006-2012)	Average temperature(°C) of each Disease Surveillance Point System in 2010/ monitoring sites	Diabetes mortality ICD10 codes: E10-14)/ Mortality counts obtained from the China Disease Surveillance Point System.	Rate ratio per 1°C increase in average temperature: 1.05 (1.03, 1.08)	Higher mortality rates of diabetes are associated with higher temperature.
Cohort studies					
Faeh et al. (26)	All residents in Switzerland at 2000 census (2000-2008)- Spatial comparisons	Mean annual temperature (°C) (1981-1985) estimated at residence level/ modeled climate data derived from stations	Ischemic heart disease mortality (ICD10 codes: I20-25)/ individual records of the Swiss mortality registry	Hazard ratio per quintile of mean annual temperature at place of resident (lowest as reference: Q1[-3.3-8.6): 1 Q2[8.6-9.2): 1.01(0.98,1.03)	Living in areas with relatively high temperature (highest category vs lowest) is somewhat protective from Ischemic heart disease mortality. However, there is no dose-response.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
				Q3[9.2-9.6): 1.02 (0.99,1.06) Q4[9.6-10.0): 0.98(0.95,1.01) Q5[10.0-13.4): 0.96(0.92,0.99)	
Wallwork et al. (37)	Participants in the Normative Aging Study, a cohort of older men living across eastern Massachusetts, southern New Hampshire, and southern Maine,US (1993-2011)	Annual temperature (°C) estimated at the participants' addresses / satellite-based model	Risk of metabolic syndrome (MS) and its components/ MS if with 3 or more of the diagnostic criteria: abdominal obesity, high fasting blood glucose, low HDL, hypertension, or hypertriglyceridemia	Hazard ratio per 1°C increase in annual temperature at the participants' addresses: Abdominal obesity: 1.06(0.86-1.31) High fasting blood glucose: 1.33(1.14-1.56) Low HDL cholesterol: 1.01(0.85-1.20) Hypertension: 1.14(0.86-1.50) Hypertriglyceridemia: 1.07(0.92-1.24) Metabolic syndrome: 0.99(0.82-1.21)	Higher temperature at the participants' addresses was associated with higher fasting blood glucose. The HR for obesity, low HDL cholesterol hypertension and Hypertriglyceridemia were elevated but not statistically significant.
Cross-sectional studies					

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Voss et al. (32)	A representative sample of US adult population (2011)	Mean annual ambient temperature by county (°C)/ weather data interpolated from average monthly weather station data to 1 km resolution grids	Obesity (BMI ≥30 kg/m2) and median BMI scores/ data from The Behavioral Risk Factor Surveillance System (a nationwide telephone health survey)-self-reported	Odds ratio of obesity per temperature categories (highest as reference) in each county: <5: 0.96 (0.85, 1.08) 5-9.9: 1.03 (0.93, 1.13) 10-14.9: 1.00 (0.92, 1.09) 15-19.9: 1.03 (0.94, 1.13) >20: Referent Change median BMI per temperature categories (lowest as reference) in each county: <5: Referent 5-9.9: 0.20 (0.02, 0.38) 10-14.9: 0.19 (0.01, 0.37) 15-19.9: 0.16 (-0.02, 0.34) >20: 0.14 (-0.05, 0.33)	The association between prevalence of obesity and temperature categories was not statistically significant. BMI by quantile regression was similar across temperature categories with suggestion of lower median BMIs at the extremes of temperature category.
Valdes et al. (24)	A representative random sample of the Spanish population, aged 18-93 yrs (2009-2010)	Mean annual ambient temperature in each area of residence (°C)/ monitoring sites	Obesity (BMI ≥30 kg/m2)/ Information collected using an interviewer administered structured questionnaire, and a physical examination.	Odds ratio per mean annual temperature quartiles (lowest as reference) in each area: Q1(10.4-14.5): 1.00	The study reports an association between ambient temperature and obesity in the Spanish Population after adjusting for known confounders.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
				Q2 (14.5-15.5): 1.20 (1.01, 1.42) Q3 (15.5-17.8): 1.35 (1.12, 1.61) Q4 (17.8-21.3): 1.38 (1.14, 1.67)	
Yang HK et al. (45)	Subjects selected by stratified random sampling to represent the Korean population (2009-2010)	Mean annual temperature (MAT)(°C) and number of days with mean temperature < 0°C (DMT0) in 71 observation areas/ monitoring sites	Obesity (BMI ≥25 kg/m2) and abdominal obesity (WC ≥ 90 cm for men and ≥ 85 cm for women)/ Anthropometric measurements	Odds ratio of obesity per MAT quintile (the lower 4 groups as reference) and DMT0 quintile (the highest 4 DMT0 groups as reference): Obesity: MAT (Quantile 5 vs 1-4): 1.045 (1.010, 1.081) DMT0 (Quantile 1 vs 2-5): 1.027 (0.996, 1.059) Abdominal obesity: MAT (Quantile 5 vs 1-4): 1.082 (1.042, 1.124) DMT0 (Quantile 1 vs 2-5): 1.063 (1.027, 1.100)	BMI and waist circumference were positively correlated with MAT and negatively correlated with DMT0. Subjects in in the highest quintile of MAT exhibited higher odds of obesity, however there was no difference according to DMT0. Subjects in areas in the highest quintile of temperature and subjects in areas of the lowest quintile of DMT0 had higher odds for abdominal obesity.
Li et al. (48)	Primary and middle school students aged 7–18 years of Han ethnicity from 30 cities of China (2010)	Average ambient temperature(°C) of 2010 per city/ monitoring sites	Blood pressure (SBP,DBP mm Hg)/ by an auscultation method with a standardized clinical sphygmomanometer	The largest alteration of SBP: related to temperature difference from 20.4 to 9.6°C was 9.0 mmHg (8.4-9.5) and between the hottest	Decrease in ambient temperature was found to be associated with increased SBP and DBP in children within a temperature range. However,

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
				and the coldest area with difference from 24.6 to 4.5°C it was 4.1mmHg (2.8-5.3). Corresponding values for DBP: 6.1 (5.6-6.6) and 2.4 (1.3-3.5)	children living at extremely hot areas had somewhat higher blood pressure compared to those living in areas with 20°C.
C. Respiratory outcomes					
Ecological studies					
Venero et al. (29)	Population of Cuba (1989-2003)	Yearly mean temperature (°C)/ monitoring sites	Asthma mortality data from the Ministry of Public Health's National Statistics Division	Correlation coefficient: -0.273	Higher asthma mortality was found in areas with lower temperature.
Pesce et al. (27)	Subjects from the general population aged 20–44, Italy (7 centers) (2006-2010)	Average annual temperature (°C), temperature range (°C)/ monitoring sites	Lifetime asthma and Chronic bronchitis/Self-reported respiratory outcomes (GEIRD study screening (de Marco et al., 1999))	% change at prevalence of Lifetime asthma and chronic bronchitis per 1 SD increase in temperature index: Average annual temperature: 1.09 (0.23, 1.95) and 0.10 (-1.50, 1.70) respectively, Temperature range: -0.78 (-2.08, 0.54) and -1.15(-2.20, 0.11) respectively	Higher prevalence of asthma was found associated with higher annual temperature. The prevalence of chronic bronchitis was not found statistically significant associated with temperature related metrics.
Cross-sectional studies					

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Metintas et al. (41)	Parents of primary schoolchildren from 14 cities, Turkey (1947-2004)	Average annual temperature per city (°C)/ monitoring sites	Asthma, wheezing, allergic rhinitis/ questionnaires distributed to children in the primary schools and completed by the parents at home	Odds ratio per 1°C increase in city's average annual temperature: Asthma:Males: 1.008 (1.003, 1.011), Females: 1.007 (1.002, 1.012) Wheezing: Males: 1.012 (1.006, 1.018), Females: 1.010 (1.002, 1.018) Allergic rhinitis: Males: 1.008 (0.999, 1.018), Females: 1.009(1.000,1.017)	Mean annual temperature was statistically significant associated with asthma prevalence and the prevalence of wheezing. Mean annual temperature was statistically significant associated with the prevalence of allergic rhinitis only in females.
Silverberg et al. (34)	Representative sample of children aged 0 to 17 years from the 2007 National Survey of Children's Health, US (2006-2007)	Annual statewide mean values of ''time-bias''-corrected temperatures (°F) for 2006-2007/ monitoring sites	Prevalence of hay fever/self-reported doctor diagnosed hay fever or any kind of respiratory allergy	Odds ratio for each quartile of state's temperature (lowest as reference): Second(47.2-53.3): 1.13 (1.02-1.26) Third(53.4-57.5): 1.27(1.12-1.44) Fourth(59.2- 72.9): 1.43 (1.28-1.60)	Higher prevalence of hay fever was found associated with higher annual temperature.

Reference (Reference number)	Study population (Study period)	Exposure/ Exposure assessment method	Outcome/ Outcome assessment method	Estimate (P-value or 95% confidence interval)	Main result
Upperman et al. (38)	Adults aged 18 years and older in National Health Interview Survey, US (1997-2013)	Cumulative number of extreme heat events in the 12 months preceding the survey per county (days where the daily TMAX > county and calendar month specific 95th perc, calculated using 30 year of baseline data)/ monitoring sites	Hay fever / self-reported: "During the past 12 months, have you been told by a doctor or other health professional that you had hay fever?"	Odds ratio per Quartile of the cumulative number of extreme heat events in the 12 months preceding the survey in each county: Q1 (0-10 days): 1.00 (ref), Q2(11-16 days): 1.05 (1.00, 1.09) Q3(17-24 days): 1.04(1.00, 1.09) Q4(≥ 25 days): 1.07(1.02-1.11)	Statistically significant increase in prevalence of hay fever when the annual number of extreme heat events in a county is larger.

IQR: Interquartile Range; SD: Standard Deviation

Table 4. Summary of results from geographical studies by health outcome

Geographical comparisons			
Outcome	**Number of studies**	**Reference**	**Evidence for**
Total mortality	3	49, 16,19	Locations with larger changes in cold spells -> larger increase in mortality (not age-standardized) Higher mean winter temperature -> higher mortality in 14 European countries Higher summer temperature -> higher mortality only in low GDP Asian cities
Cardiovascular Disease (CVD) mortality/admissions	2	26, 47	Higher annual temperature -> higher diabetes mortality/lower rate of Ischemic Heart Disease mortality
Hypertension/Blood Pressure (BP) levels	2	40, 48	Higher annual temperature -> lower blood pressure levels
Obesity/ Body Mass Index (BMI)	4	24, 32,37,45	Higher annual temperature -> higher obesity prevalence/ higher BMI; higher fasting blood glucose (suggestive /partly inconsistent evidence)
Respiratory (asthma) mortality	1	29	Lower temperature -> higher asthma mortality
Respiratory conditions	4	27,34,38,41	Higher temperature -> higher prevalence of asthma and hay fever. Suggestive evidence for higher prevalence of allergic rhinitis and wheezing No evidence of association with chronic bronchitis

Figure 1. Flowchart for the systematic review on long-term exposure to ambient temperature and health effects

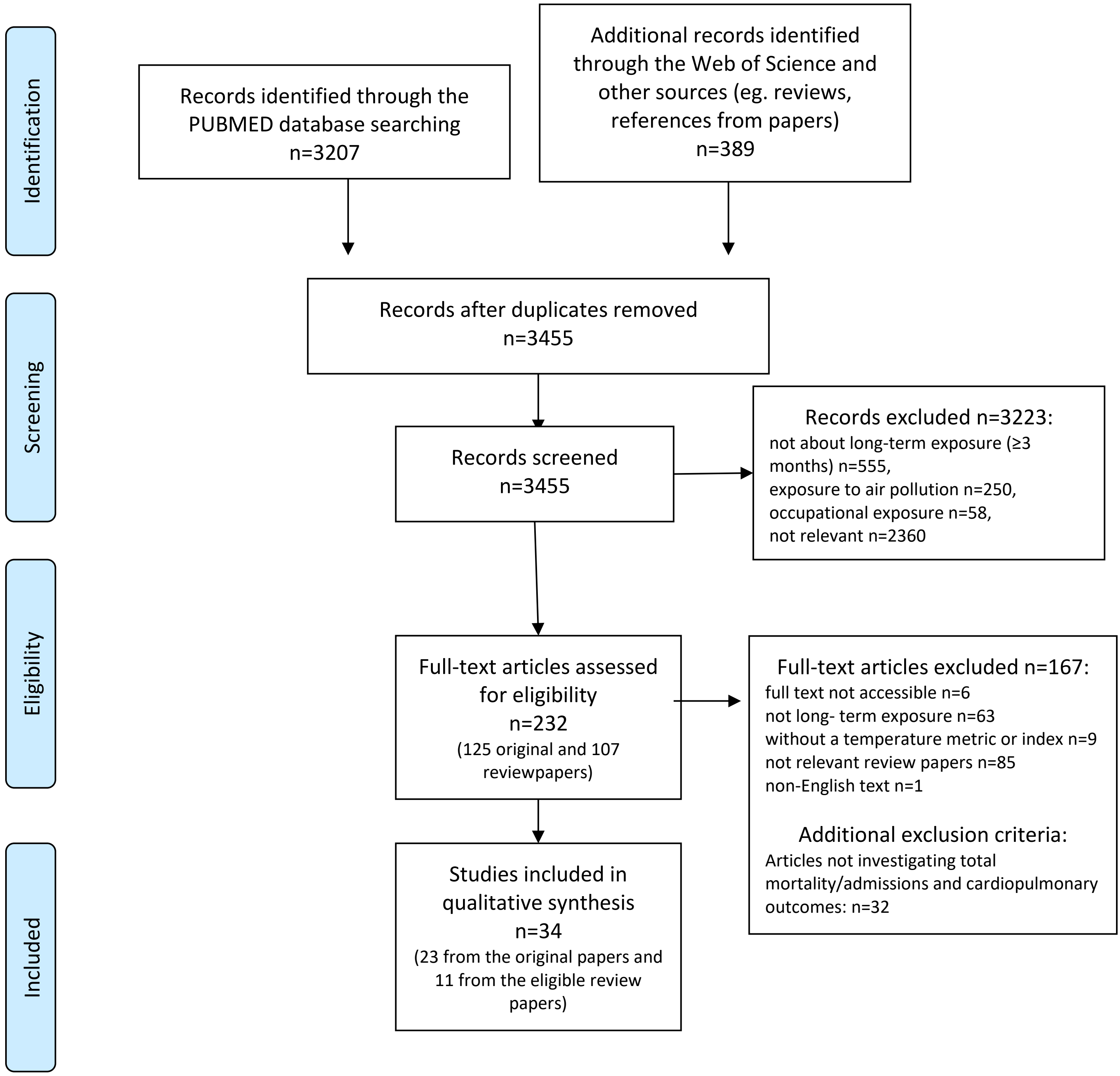

Figure 2. Geographical distribution of the 34 studies presented

Figure 3. Overall risk of bias of ratings for reported associations in the 16 studies on cardiovascular outcomes

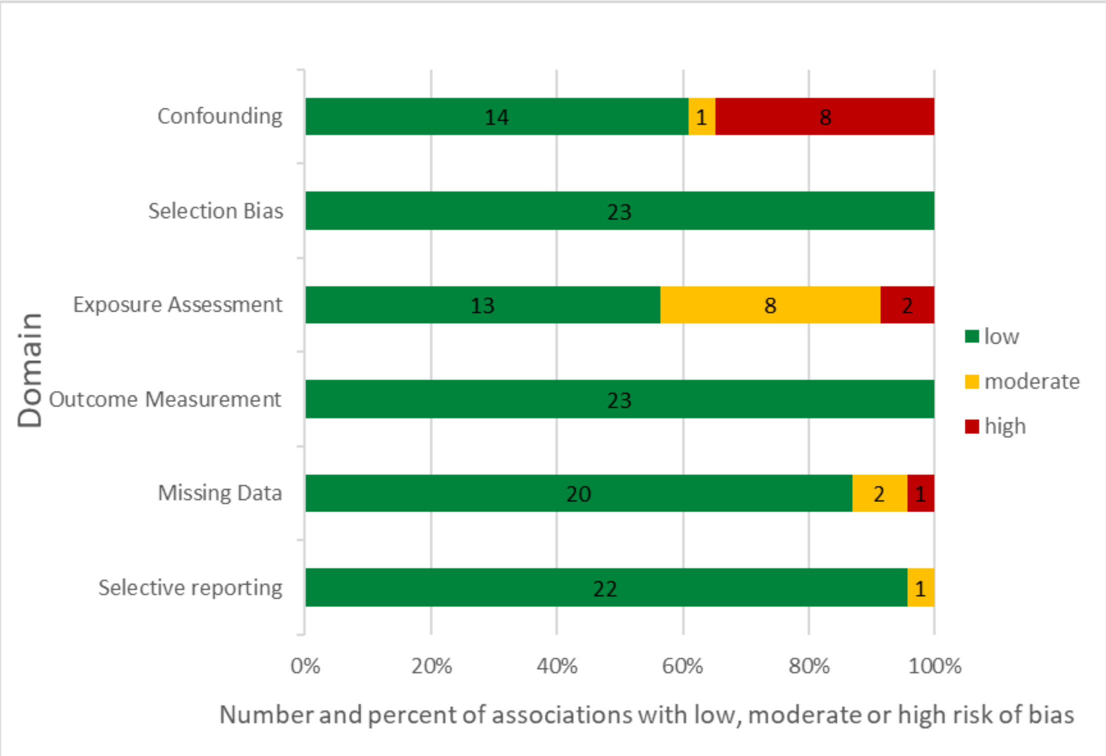

Figure 4. Overall risk of bias of the reported associations in the 11 studies on respiratory outcomes