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Longer-Term Outdoor Temperatures and Health Effects: A Review

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Abstract

Purpose of review—Our goal was to assess current literature and knowledge on associations between characteristics (mean, variability, extremes) of ambient temperatures and human health. We were motivated by concerns that climate change, which operates on a time frame of decades or longer, may influence not only shorter-term associations between weather and health (daily/weekly) but also have enduring implications for population health. We reviewed papers published between 2010 and 2017 on the health effects of longer-term (3 weeks to years) exposures to ambient temperature. We sought to answer: 'What health outcomes have been associated with longer-term exposures?' We included studies on a diverse range of health outcomes, with the exception of vector borne diseases such as malaria. Longer-term exposures were considered to be exposures to annual and seasonal temperatures and temperature variability.

Recent findings—We found 26 papers meeting inclusion criteria, which addressed mortality, morbidity, respiratory disease, obesity, suicide, infectious diseases and allergies among various age groups. In general, most studies found associations between longer-term temperature metrics and health outcomes. Effects varied by population subgroup. For example, associations with suicide differed by sex and underlying chronic illness modified effects of heat on mortality among the elderly.

Summary—We found that regional and local temperatures, and changing conditions in weather due to climate change, were associated with a diversity of health outcomes through multiple mechanisms. Future research should focus on evidence for particular mechanistic pathways in order to inform adaptation responses to climate change.

Keywords

temperature; review; epidemiology; climate change

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Introduction

The new Intergovernmental Panel on Climate Change (IPCC) report re-affirms the mounting threat of climate change[1], with strong evidence that CO_2 emissions will lead to warmer temperatures, and to more extreme heat and cold events. The frequency of extreme heat waves is expected to increase in a warmer climate, resulting in greater variance of surface temperatures.[2–7]

Numerous analyses have shown that cold and hot temperatures, as well as average temperature and temperature extremes, are associated with increased risks for a number of health outcomes. [8–10] For example, increased mortality has been linked not only to heat wave episodes[11–13] but also to exposure to cold.[11,13,14].

Studies investigating associations between temperature and cardiac risk factors such as blood pressure,[15–17] markers of inflammation,[18,19] and cholesterol[20–23] have shown divergent results, suggesting that mechanisms for heat-related cardiovascular deaths are uncertain. Some studies have hypothesized potential reasons for this variation, and have shown evidence of adaptation to usual temperatures.[24–29]

Moreover, greater susceptibility to morbidity[30–33] and mortality[8,24–26,34–36] to extreme heat has been reported by gender and among the elderly; children; lower socio-economic status (SES) populations [24,35,37–39]; pregnant women; people with chronic health conditions (e.g., diabetes, mobility and cognitive constraints); and outdoor workers[40]. Additionally, heat and health associations differ by home characteristics and access to air conditioning. [25, 32, 35, 37, 41, 42]

A summary of evidence relating temperature variability, health outcomes, and adaptation strategies to cold weather found that the populations most vulnerable to variations in cold winter weather are the elderly, rural and, generally, populations living in moderate winter climates. [43] Other reviews have addressed the epidemiological evidence of the short term effects of temperature and specific outcomes. Ye and co-authors found a significant short-term effect of ambient temperature on total and cause-specific morbidities. [44] Another review found increased risk of acute myocardial infarction associated with exposure to air pollution and cold temperatures. [45] An article on the health impacts of climate change among older people found that heat, temperature variability, and air pollution were associated with increased mortality risk, especially from cardiovascular and respiratory diseases. Zhang and co-authors reported that the current evidence for adverse effects on birth outcomes was stronger for heat than for cold.[46] (••) Another review summarized current evidence on ambient temperature and overall stroke occurrence and found that larger temperature changes were associated with higher stroke rates in the elderly.[47] A systematic review and meta-analysis found elevated risks for the elderly for temperature-associated cerebrovascular, cardiovascular, diabetes, genitourinary, infectious disease, heat-related, and respiratory outcomes.[48] Changes in temperature due to global climate change can also increase the risk of diarrheal diseases.[49] Regarding vulnerability to heat-related mortality, Benmarhnia and co-authors found strongest evidence of heat-related vulnerability for the elderly ages >65 and >75 years and low SES groups. [50]

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Substantial scientific literature describes health impacts linked with the short-term (0 to 7 days) temperature exposures, with outcomes not limited to heat and cold-related mortality or morbidity, in all age groups and by SES. These findings related to shorter term exposures have important implications for understanding the health effects of weather. However, with climate change impacting both temperature and weather extremes and variability over much longer time horizons, understanding how these longer-term exposures may impact health is important.

This article presents a review of published papers on the long-term effects of temperature on health. We focus on annual and seasonal temperatures and temperature variability to characterize the longer-term effects of changing temperature patterns.

Methods

We conducted a literature search in the National Library of Medicine's MEDLINE/PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/). The inclusion criteria were designed to identify original population-based research articles on health impacts of long-term exposure to ambient temperature.

We defined long-term as average exposure periods ranging from 3–4 weeks to up to one or more years. Exposure was defined as average temperature, temperature variability or other heat and cold indices over the selected long term periods. We included studies from all continents, with no restrictions on the method used, and published in English from 2010 to 2017.

We did not specify the health outcomes except to exclude vector-borne diseases such as malaria and dengue. We also excluded studies which examined temperature as an effect modifier, and the studies which applied climate model projections to estimate future temperature-related mortality.

We used the following key words: annual, yearly, monthly, summer, and long term for temperature and temperature variability together with health, effects, risks, chronic effects, mortality, and admissions.

Results

Using various combinations of the key words, the search yielded a total of 395 articles. Most of the articles did not involve humans (n=158), studied vector-borne diseases (n=18), or examined short term effects (n=92). Removing those, together with the ones not in English, reviews or duplicates, reduced this number to 106. We then reviewed the abstracts in relation to exclusion criteria and reviewed the full texts of the final 26 articles.

Table 1 presents all the selected studies. For each study we extracted information on location, each study's time frame, population description with sample size, exposure type, health outcome, methods and results.

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Among the 26 papers, 11 studies were conducted in the United States (U.S.), 6 were from Asia, 6 from Europe, 1 from South America, 1 from Africa, and one included 12 countries worldwide. Regarding the outcomes, 11 studies examined mortality. Of these, 2 examined fetal death rates, 2 suicide, while the others focused on non-accidental mortality. Three studies focused on obesity, 3 studies examined respiratory diseases including respiratory allergies. The other 9 studies examined specific health endpoint: cancer; basal cell carcinoma; birth weight; visits for heat illness; hand, foot and mouth disease; metabolic syndrome; DNA methylation; dialysis; and diarrhea.

In terms of time frame, the shortest study included 1 year (data were from the 2011 Behavioral Risk Factor Surveillance System), 3 studies included 2 years, and then the number of years covered in studies increased with a total of 18 papers with less than 20 years and 9 studies including between 20 and 60 years of data (from the mid-1900s to mid-2000s). The two longest studies included 111 years from 1749 to 1859, and 258 years between 1751 and 2008. In terms of the exposure type, 12 studies examined mean annual temperature (MAT), one study used mean summer temperature, 1 monthly averages, 1 study used 3-week average temperature, 1 used the 20 years average of summer temperature, 2 studies used yearly (one of these also monthly) mean temperature anomalies defined as the sum of yearly mean temperature minus the mean temperature during the previous 30 years. Among all the studies, 5 examined temperature variability defined as the standard deviation of temperature, one study used the standard deviation of yearly temperature, while the others computed the standard deviation of summer and winter months. Two of these studies examined also the average summer and winter temperature. Finally, three studies used annual summaries of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature. For example the Annual cold degree-days (DD_{COLD}) were defined as the sum over the year of daily values: $DD_{COLD} = Thresh_{COLD}$ - Temp, where $Thresh_{COLD}$ is the threshold below which cold impacts on mortality are believed to begin (or the minimum mortality temperature (MMT)), and Temp is the mean daily temperature.

In some studies, temperature was not the only exposure examined; other weather parameters or pollutants were considered as well. However, for this review, we report only the results for long-term temperature.

Summary of findings

Most of the studies found an association between the outcome and temperature. We discuss findings for each outcome category in detail next.

Respiratory disease

Metintas and co-authors [51] in Turkey examined asthma and wheezing and eczema in schoolchildren using parents' questionnaire responses and found an association between mean annual temperature with the prevalence of asthma and wheezing in both sexes, and with eczema in girls.

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Miller and co-authors [52] found that changes in average annual temperature did not influence the prevalence of otitis media or respiratory allergy. The authors conclude that even though global warming continues to affect our environment, childhood otolaryngologic disease prevalence may not be directly influenced.

Another study [53] (•) used data from the 2007 National Survey of Children's Health and found that children residing in states with a higher quartile mean annual temperature had increased prevalence of HF compared with that in states with the lowest quartile; and that the third- and fourth-quartile mean temperatures were associated with higher HF prevalence in all seasons. The authors also found that hay fever increased with mean total pollen counts, suggesting that climate factors and pollen counts could aggravate HF, resulting in chronic disease. This study provides evidence of the influence of climate on the US prevalence of childhood hay fever.

Obesity

Three studies, one in Spain [54], one in the US [55] and one in Korea [56] (•), examined the association between obesity prevalence and MAT. The studies used very different data, populations and methods but they all found an association with obesity, waist circumference or BMI. The study carried out in the US used data from the Behavioral Risk Factor Surveillance System and presented a parabolic relationship between MAT and prevalence of obesity by counties, with higher proportions of obese population for counties with temperatures between 5 and 20 °C, consistent with the results from a quantile regression showing lower median BMIs at the extremes of each temperature category.

Other health outcomes

In the US, Sharma and co-authors [57] (•) found a negative correlation between average annual temperature and cancer incidence rate at all anatomical sites. These results suggest that living in a colder county in the United States might confer a higher risk of cancer, irrespective of cancer type.

In a study population of white participants from the U.S. Radiologic Technologists' cohort, the authors[58] did not find a significant trend in the association between average lifetime summer ambient temperature and basal cell carcinoma (BCC) risk. However, they found that BCC risk rose slightly as ambient temperature increased, except in the hottest areas. The authors suggest that failure to find a dose-response relationship could be due to limitations in the exposure assessment, and they recommend to explore temperature and skin cancer in other population-based studies.

Hess and co-authors [59] in the US found a significant correlation between annual temperature anomalies and annual population-based rates of acute heat illness visits to emergency departments.

Molina and Saldarriaga [60] (••) examined birth weight in 86,021 children from the Demographic and Health Survey in the Andean region. The exposure was defined as the standard deviation of temperature for the trimesters before pregnancy and found that an increase of one standard deviation in temperature variability was associated with reduction in birth weight of around 20 grams and a 0.7% increased probability that a child was born with low birth weight. In China, Liao and co-authors [61] examined hand, foot and mouth disease (HFMD) in the population in Sichuan Province, They found that the annual HFMD incidence was positively associated with the average annual temperature.

Two studies [62,63(•)] used data from the Normative Aging Study in the US New England region, which includes older male veterans. Bind and co-authors [62] examined DNA methylation and found that the 3-week average of temperature was associated with methylation on tissue factor (F3), intercellular adhesion molecule 1 (ICAM-1), toll-like receptor 2 (TRL-2), carnitine O-acetyltransferase (CRAT), interferon gamma (IFN-γ), inducible nitric oxide synthase (iNOS), and glucocorticoid receptor, LINE-1, and Alu, genes related to coagulation, inflammation, cortisol, and metabolic pathway. This suggests that DNA methylation in blood cells may reflect biological effects of temperature and relative humidity. Wallwork and co-authors [63] examined metabolic syndrome and its components and found that annual average temperature was associated with higher risk of developing elevated fasting blood glucose. They conclude that men living in neighborhoods with higher temperatures (and $PM_{2.5}$ levels) showed increased risk of developing metabolic dysfunctions.

In Ethiopia, high risk periods and seasonal patterns influenced childhood diarrhea (CDD) and increased temperature was associated with increased rate of childhood diarrhea morbidity. [64(••)]

Ogata and Yorioka [65] in Japan found that the average annual temperatures influenced the 1-year survival of new dialysis patients, and they suggest that the survival of dialysis patients may be influenced by environmental factors that cannot be controlled medically after the initiation of dialysis.

Mortality

In a population-based cohort study in Japan, Fakuda and co-authors [66] found a significant positive association between yearly temperature differences and sex ratios of fetal deaths, but a negative association between temperature differences and sex ratios of newborn infants from 1968 to 2012. This suggests that temperature fluctuations in Japan seem to be linked to a lower male:female sex ratio of newborn infants, partly via the mechanism of increased male fetal deaths.

In Uppsala, Sweden, which has a relatively small population and number of yearly deaths, Schumann and co-authors [67] obtained 111 years of data and found associations between higher springtime temperatures and decreased annual mortality, while higher summer temperatures were associated with an increased death toll.

Two studies focused on suicide. In Finland [68], among 94,356 deaths from suicide over a 258-year period, the authors found a positive correlation between annual temperature variability and suicide rates, with temperature variability explaining more than 60% of the total suicide variance up until the initiation of a national suicide prevention program.

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The other study [69] examined suicide rates in Greece in association with MAT, finding that temperature was a determinant of male suicides, and also suicide attempt rates among women, but less so than for males.

Lim and co-authors [70] (•) studied 32 cities in Taiwan, China, Japan, and Korea and found increasing heat-related mortality in cities with lower gross domestic product (GDP) *per capita*. They found no association between average summer temperature and heat-related mortality in cities with high GDP.

Three studies [71–73] examined the chronic effect of temperature variability on survival among individuals aged 65 and older. All three used Medicare data and applied a Cox proportional hazards model. The first one published [71] focused on mortality in elderly with previous congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction or diabetes-related hospitalizations and found that long-term increases in temperature variability may increase the risk of mortality in different subgroups of susceptible older populations. The other 2 studies from the same group used US Medicare data in New England [73] (••) and in Southeastern states [72] (••) and analyzed in the same model both the average and the variability of summer and winter temperature. Both studies found that summer mean temperature was linked to increased mortality, while during winter, an increase in temperature was associated with reduced mortality. Moreover, increases in temperature standard deviations (SDs) for both summer and winter were associated with increased mortality risk.

Three papers, one in Hong Kong [74] (•), one in London [75] (••) and one using data from across the world [76] used a time series approach with the unit of analysis being the year instead of day; this method is extensively used when examining short term effects. The outcome was defined as the annual count of mortality (one paper used age-standardized mortality rates) and the exposures were annual summaries of heat and cold using a degree-day approach, that is, the mean annual degrees above/below minimum mortality temperature. Goggins and co-authors [74] in Hong Kong found that annual frequency of both hot and cold temperatures influenced annual mortality rates, and that a proportion of these deaths occurred in people who would have been expected to live at least several months longer in the absence of these exposures. In London, Rehill and co-authors [75] (••) found that colder years were associated with increased mortality, but did not find an association with heat, suggesting that most deaths related to cold were among individuals who would not have died in the next 6 months.

The world-wide paper of Armstrong and co-authors [76] (••) is the largest study estimating the association between annual mortality and annual summaries of heat and cold in 278 locations from 12 countries across the world. The authors found, on average over all countries, a positive association of mortality with mean annual degrees of heat and cold. The authors then replaced the summaries of heat and cold with the exposure defined as the estimated fractions of deaths attributed to heat and cold to understand whether the associations to heat and cold previously found in daily analyses indicate short-term displacement. Even with the presence of some heterogeneity among the countries, the results suggest that most lives were shortened by at least one year. This suggests that the adverse

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health effects of high and low temperatures are a significant public health concern and not merely short-term displacement of times of death.

Discussion

This review on the longer-term effects of temperature on health outcomes uncovered a diverse range of studies, varying by region, outcome, and study population. While most examined annual temperature, a few examined temperature anomalies or shorter term (weeks to months) exposures, temperature variability or annual summaries of heat and cold.

Most studies found that warmer temperatures, both annual and in the summer, were associated with increased adverse health outcomes, not limited to mortality. Temperature variability was also an important health-relevant exposure.

Temperature has seasonal patterns and extremes are very important as determinants of health outcomes, especially the direct effects of hot and cold temperature exposures at the extremes of the distribution in any given area. Annual averages of temperature vary less across time and space, and therefore the use of an annual metric limits statistical power to detect effects and results are not always easily interpretable. Estimation of chronic effects associated with seasonal mean or variability of temperature can be more meaningful.

Short term studies have found a U or J shaped relationship between daily mortality and daily temperature [77]. Studies using mortality and temperature constructs summarized on an annual basis inherently cannot capture this kind of dose response. However, three studies extended the time series analysis approach to annual counts of mortality and defined exposure as annual summaries of heat and cold using a degree-day approach (mean annual degrees above/below minimum mortality temperature) as a way of capturing trends across longer time frames.

Most daily time-series studies do not address whether the association between temperature and mortality represents life shortening or short-term displacement of deaths (harvesting). These recent analyses go a step further than the short term effect studies, as the findings can provide evidence as to whether most of the deaths associated in daily analyses with heat and cold are displaced by 6 months to a year. These three studies have found that the cold- and heat associated excess deaths reported in daily studies have been displaced by 6 months to one year and strengthens the evidence that policies aimed at reducing vulnerability to cold (e.g., home insulation) can be beneficial to health, and specifically life expectancy.

The studies we reviewed addressed a diversity of health outcomes. The majority addressed health outcomes (e.g., mortality, heat illness) that are associated with direct exposure to temperature or weather conditions, typically estimated using outdoor monitors. Several biological mechanisms have been posited and explored for the physiological response to extreme temperatures or temperature variability, as previously reviewed. [78] Other outcomes, such a hay fever, are hypothesized to be influenced by more distal effects of temperature trends, including the presence of pollen and other allergens that may be affected by changes in growing season and other temperature-related phenomena.

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Regardless of mechanism, the patterns of association observed in these and other studies support the importance of longer term temperatures for human health.

Conclusions

Recent literature shows that a diverse range of outcomes are affected by longer term exposures to temperature and temperature variability. Study designs employed range from ecological studies evaluating disease prevalence and weather conditions at various geographic scales to time series studies using vital statistics data on morbidity, mortality and birth outcomes. The mechanisms explaining these associations are diverse, and range from direct effects of temperature exposure and temperature variability on the cardiovascular and respiratory systems, to proliferation of infectious agents at different temperature and temperature variabilities, to changes in population behavior (e.g., more time spent indoors) that impact patterns and prevalence, to physiological responses to prevailing climate conditions (obesity).

In light of this diversity of study designs and outcomes, it is difficult to make broad conclusions regarding this literature review. However, results suggest that regional and local temperatures, and changing conditions in weather due to climate change, are associated with multiple health outcomes through a variety of plausible mechanisms. Continued study of this phenomenon with careful elucidation of mechanistic pathways, and evaluation of evidence for particular ones, will be useful for building the evidence base that can inform adaptation to climate change across the globe.

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Conflict of Interest

Antonella Zanobetti reports grants from National Institutes of Health NIH/NIEHS and grants from US EPA, during the conduct of the study.

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46••. Zhang Y, Yu C, Wang L. Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence. Environ. Pollut. [Internet]. 2017; 225:700–12. [cited 2017 Dec 20] Available from: http://linkinghub.elsevier.com/retrieve/pii/S026974911730074X This review indicates that high temperatures are a risk factor for preterm birth, low birth weight, and stillbirth, while less evidence was reported for cold-related effects. Given the projected changes in the global climate, these findings may have great implications in public decision-making regarding maternal and child health to reduce temperature-related adverse birth outcomes. Due to inconsistencies among temperature indicators used in different studies, the authors recommend that more well-designed studies are needed in more diversified climate zones, to ascertain the association between temperature and birth outcomes.

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53(•). Silverberg JI, Braunstein M, Lee-Wong M. Association between climate factors, pollen counts, and childhood hay fever prevalence in the United States. Mosby; 2015. 135Available from: http://linkinghub.elsevier.com/retrieve/pii/S0091674914011154 This study used the National Survey of Children's Health to examine the impact of specific climate factors and pollen counts on the US prevalence of hay fever and statewide variation in prevalence. this study provides evidence of the influences of climate on the prevalence of HF, suggesting that climate factors and pollen counts likely aggravate HF, resulting in chronic disease. [cited 2017 Dec 18]

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55. Voss JD, Masuoka P, Webber BJ, Scher AI, Atkinson RL. Association of elevation, urbanization and ambient temperature with obesity prevalence in the United States. Int. J. Obes. (Lond). [Internet]. 2013; 37:1407–12. [cited 2018 Jan 17] Available from: http://www.nature.com/articles/ijo20135.

56(•). Yang HK, Han K, Cho J-H, Yoon K-H, Cha B-Y, Lee S-H. Meyre D, editor [cited 2018 Jan 17] Ambient Temperature and Prevalence of Obesity: A Nationwide Population-Based Study in Korea; PLoS One [Internet]. 2015. e0141724Available from: http://dx.plos.org/10.1371/journal.pone.0141724 Excess body weight is an important risk factor for mortality and morbidity. It is known that unhealthy diets and sedentary lifestyle are major contributors to the increasing prevalence of obesity. But few studies examined other conditions such as genetic, biological and environmental factors. This study demonstrate a significant association between ambient temperature and prevalence of obesity among the Korean population and suggest that a possible explanation could be cold-induced thermogenesis.

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58. Michal Freedman D, Kitahara CM, Linet MS, Alexander BH, Neta G, Little MP, et al. Ambient temperature and risk of first primary basal cell carcinoma: A nationwide United States cohort study. J. Photochem. Photobiol. B. [Internet]. 2015; 148:284–9. [cited 2018 Jan 30] Available from: http://linkinghub.elsevier.com/retrieve/pii/S1011134415001487.

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60(••). Molina O, Saldarriaga V. The perils of climate change: In utero exposure to temperature variability and birth outcomes in the Andean region. Econ. Hum. Biol. [Internet]. 2017; 24:111–24. [cited 2018 Jan 17] Available from: http://linkinghub.elsevier.com/retrieve/pii/S1570677X1630212X This study is one of the first to examine the adverse effects of temperature variability on health conditions of newborns by investigating how in utero exposure to temperature variability, measured as the fluctuations relative to the historical local temperature mean, affects birth outcomes in the Andean region. The finding that temperature variability is associated with decreased birth weight is important, and sheds light on the adverse effects of temperature variability on health conditions of newborns. Moreover, the authors find some evidence that these results can be explained by food insecurity and health care during pregnancy that arise due to increased temperature variability.

61. Liao J, Qin Z, Zuo Z, Yu S, Zhang J. Spatial-temporal mapping of hand foot and mouth disease and the long-term effects associated with climate and socio-economic variables in Sichuan Province, China from 2009 to 2013. Sci. Total Environ. [Internet]. 2016; 563–564:152–9. [cited 2018 Jan 17] Available from: http://linkinghub.elsevier.com/retrieve/pii/S0048969716305836.

62. Bind M-AM-AM-A, Zanobetti A, Gasparrini A, Peters A, Coull B, Baccarelli A, et al. Effects of Temperature and Relative Humidity on DNA Methylation. Epidemiology [Internet]. 2014; 25:561–9. [cited 2014 May 12] Available from: http://www.ncbi.nlm.nih.gov/pubmed/24809956.

63(•). Wallwork RS, Colicino E, Zhong J, Kloog I, Coull BA, Vokonas P, et al. Ambient Fine Particulate Matter, Outdoor Temperature, and Risk of Metabolic Syndrome. Am. J. Epidemiol. [Internet]. 2017; 185:30–9. [cited 2017 Dec 16] Available from: https://academic.oup.com/aje/article-lookup/doi/10.1093/aje/kww157 Metabolic syndrome is an urgent public health concern that affects 10%-25% of the global population and is associated with increased risk of cardiovascular disease, asthma, sleep apnea, and selected malignancies and with higher total and cause-specific mortality. This is the first study to examine and find an association between long-term exposures to outdoor temperatures with increased risk of developing elevated fasting blood glucose. The authors suggest that this could be due to the role of adipose tissue in adaptation to temperature differences. Specifically, people exposed to comparatively higher temperatures burn fewer calories to maintain body temperature, have less brown adipose tissue, and therefore may be more prone to developing insulin resistance.

64(••). Azage M, Kumie A, Worku AC, Bagtzoglou A, Anagnostou E. Shaman J, editor [cited 2018 Jan 30] Effect of climatic variability on childhood diarrhea and its high risk periods in northwestern parts of Ethiopia; PLoS One [Internet]. 2017. e0186933Available from: http://www.ncbi.nlm.nih.gov/pubmed/29073259 In Ethiopia the burden of childhood diarrhea is high and diarrhea is the second leading cause of childhood deaths in the country. This study found an association between climatic factors and the occurrence of childhood diarrhea, and recommend that local health departments should develop appropriate climate-change adaptation and preparedness for diarrhea prevention and control strategies.

65. Ogata S, Yorioka N. Environmental factors influencing the survival of chronic dialysis patients. Clin. Exp. Nephrol. [Internet]. 2011; 15:405–9. [cited 2018 Jan 30] Available from: http://www.ncbi.nlm.nih.gov/pubmed/21249416.

66. Fukuda M, Fukuda K, Shimizu T, Nobunaga M, Mamsen LS, Yding Andersen C. Fertil. Steril. [Internet]. Vol. 102. Elsevier; 2014. Climate change is associated with male:female ratios of fetal deaths and newborn infants in Japan; 1364–1370.e2. Available from: http://www.sciencedirect.com.ezp-prod1.hul.harvard.edu/science/article/pii/S0015028214018408?via%3Dihub [cited 2017 Dec 13]

67. Schumann B, Edvinsson S, Evengård B, Rocklöv J. The influence of seasonal climate variability on mortality in pre-industrial Sweden. Glob. Health Action [Internet]. 2013; 6:20153. [cited 2018 Jan 17] Available from: https://www.tandfonline.com/doi/full/10.3402/gha.v6i0.20153.

68. Helama S, Holopainen J, Partonen T. Temperature-associated suicide mortality: contrasting roles of climatic warming and the suicide prevention program in Finland. Environ. Health Prev. Med. [Internet]. 2013; 18:349–55. [cited 2018 Jan 17] Available from: http://link.springer.com/10.1007/s12199-013-0329-7.

69. Fountoulakis KN, Savopoulos C, Zannis P, Apostolopoulou M, Fountoukidis I, Kakaletsis N, et al. Climate change but not unemployment explains the changing suicidality in Thessaloniki Greece

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(2000–2012). J. Affect. Disord. [Internet]. 2016; 193:331–8. [cited 2018 Jan 17] Available from: http://www.ncbi.nlm.nih.gov/pubmed/26796233.

70(•). Lim Y-H, Bell ML, Kan H, Honda Y, Guo Y-LL, Kim H. Economic status and temperature-related mortality in Asia. Int. J. Biometeorol. [Internet]. 2015; 59:1405–12. [cited 2018 Jan 17] Available from: http://link.springer.com/10.1007/s00484-014-0950-1 This study found that in cities with low GDP per capita, heat risk increases with higher summer temperature but not in cities with high GDP per capita. These findings may indicate a greater heat-related risk in hotter cities if economic resources are insufficient, possibly due to poor individual- or city-level adaptation or mitigation efforts.

71. Zanobetti A, O'Neill MSMSS, Gronlund CJJCJ, Schwartz JDJDD. Summer temperature variability and long-term survival among elderly people with chronic disease. Proc. Natl. Acad. Sci. [Internet]. 2012; 109:6608–13. [cited 2012 Apr 11] Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1113070109.

72(••). Shi L, Liu P, Wang Y, Zanobetti A, Kosheleva A, Koutrakis P, et al. Chronic effects of temperature on mortality in the Southeastern USA using satellite-based exposure metrics. Sci. Rep. [Internet]. 2016; 6:30161. [cited 2018 Jan 17] Available from: http://www.nature.com/articles/srep30161 This study adds more evidence on the chronic effect of temperature on mortality. Moreover, it suggests that even in regions with hot summers and high prevalence of air conditioning like the Southeastern USA, areas with higher summer temperature or temperature variability had higher death rates. This suggests that temperature related mortality is already present at non-trivial levels, and adaptation ability is limited and therefore these locations may be particularly sensitive to rising summer temperatures in the future.

73(••). Shi L, Kloog I, Zanobetti A, Liu P, Schwartz JD. Impacts of Temperature and its Variability on Mortality in New England. Nat. Clim. Chang. [Internet]. 2015; 5:988–91. [cited 2016 Mar 18] Available from: http://www.ncbi.nlm.nih.gov/pubmed/26640524 This study, by estimating impacts of both mean temperature and temperature variability in summer and winter simultaneously, adds considerable strength to the evidence of a significant association between mortality and prolonged exposures to temperatures, especially temperature variability. Moreover this study shows that increases in temperature variability can have similar estimated effects on mortality as increases in mean temperature. Therefore the variability of atmospheric temperature emerges as a key factor for potential health impacts of climate change.

74(•). Goggins WB, Yang C, Hokama T, Law LSK, Chan EYY. Using Annual Data to Estimate the Public Health Impact of Extreme Temperatures. Am. J. Epidemiol. [Internet]. 2015; 182:80–7. [cited 2018 Jan 17] Available from: https://academic.oup.com/aje/article-lookup/doi/10.1093/aje/kwv013 This study used the annual cold-degrees days and heat-degrees days in an annual time series analysis. The results indicate that annual time periods with a greater frequency and severity of both hot and cold weather tend to have higher mortality rates than years with more moderate daily temperature; moreover the results imply that the excess mortality observed during periods of hot or cold weather is not simply due to short- or medium-term forward mortality displacement, and that a substantial proportion of these deaths occurred in people who would have been expected to live at least several more months in the absence of these exposures.

75(••). Rehill N, Armstrong B, Wilkinson P. Clarifying life lost due to cold and heat: a new approach using annual time series. BMJ Open [Internet]. 2015; 5:e005640. [cited 2018 Jan 17] Available from: http://bmjopen.bmj.com/cgi/doi/10.1136/bmjopen-2014-005640 This was the first study to apply an annual time series analysis to examine the association between long-term mortality and long-term temperature, and to use the 'heat-degrees' and 'cold-degrees' derived as the number of degrees above a threshold to summarize heat and cold day across the year.

76(••). Armstrong B, Bell ML, de Sousa Zanotti Stagliorio Coelho M, Leon Guo Y-L, Guo Y, Goodman P, et al. Longer-Term Impact of High and Low Temperature on Mortality: An International Study to Clarify Length of Mortality Displacement. Environ. Health Perspect. [Internet]. 2017; 125:107009. [cited 2018 Jan 17] Available from: http://ehp.niehs.nih.gov/EHP1756 This is the largest study estimating the association between annual mortality and annual summaries of heat and cold, with 278 locations from 12 countries around the world. This study not only found strong evidence that annual mortality was associated with the extent to which years experienced long or severe hot or cold weather, but also that most lives were shortened by at least a year, and these associations are confirmed as important public health concerns.

77. Nordio F, Zanobetti A, Colicino E, Kloog I, Schwartz J. Changing patterns of the temperature-mortality association by time and location in the US, and implications for climate change. Environ. Int. [Internet]. 2015; 81:80–6. [cited 2015 Jun 18] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25965185.
78. Gronlund CJ. Racial and socioeconomic disparities in heat-related health effects and their mechanisms: a review. Curr. Epidemiol. reports [Internet]. 2014; 1:165–73. [cited 2018 Jan 27] Available from: http://link.springer.com/10.1007/s40471-014-0014-4.
79. Fukuda M, Fukuda K, Shimizu T, Nobunaga M, Mamsen LS, Yding Andersen C. Climate change is associated with male:female ratios of fetal deaths and newborn infants in Japan. Fertil. Steril. [Internet]. 2014; 102:1364–1370.e2. Available from: DOI: 10.1016/j.fertnstert.2014.07.1213

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Table 1

List and description of the studies included in the review on longer-term outdoor temperatures and health effects.

Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
Hess JJ[59]	US	2006–2010	Nationwide Emergency Department Sample: 326,497 ED visits	Acute heat illness visits to emergency departments	Annual temperature anomalies	Correlation	Significant correlation between annual temperature anomalies and annual population-based rate for ED heat illness visits.
Freedman MD[58]	US	1970– 2000	U.S. radiologic technologists (USRT) Study, 3556 BCC cases	Basal cell carcinoma (BCC) risk	average 20 years summer ambient temperature in quintiles	Cox proportional hazard models	No significant trend between average lifetime summer ambient temperature and BCC risk, but BCC risk was lowest in the first quintile of temperature exposure and highest in the fourth quintile (Q4 vs. Q1; HR=1.18; 95% CI: 1.06–1.31), with a suggestive trend in the risk relationship
Sharma A[57]	US	2009–2013	National program of cancer registries	Cancers site-specific	Mean annual temperature (MAT)	Linear regression analysis	Negative correlation between the temperature and cancer incidence rate at all anatomical sites
Molina O[60]	Andean region (Bolivia, Columbia, Peru)	1950–2010	86,021 children Demographic and Health Survey	Birth weight	Temperature variability: SD of temperature by trimester before pregnancy (months 0–2, 3–5, 6–8 before birth)	Linear regression analysis	Increased temperature of one standard deviation: 1) lower birth weight by 19.7 g; 2) 0.7% increased probability of low birth weight

Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
Ogata S[65]	Japan	2005–2007	Japanese Society for Dialysis Therapy: 108,692 cases	Dialysis: 1-year survival rate of new dialysis patients	Mean annual temperature (MAT)	Linear regression analysis	The average annual temperatures has an influence on the survival of dialysis patients
Azage M[64]	Africa, Ethiopia	2013–2015	Health Management Information System routine surveillance system: 217,734 cases	Diarrhea in childhood (CDD)	Monthly average temperature	Linear regression analysis	Monthly average temperature was significantly associated with the rate of childhood diarrhea with an Incident Rate Ratio of 1.019 (95%CI: 1.003, 1.034)
Liao J[61]	China, Sichuan Province	2009–2013	Chinese infectious disease surveillance system: 212,267 HFMD cases	Hand, foot and mouth disease (HFMD)	Mean annual temperature (MAT)	Hierarchical Bayesian spatial-temporal models	Annual HFMD incidence positively associated with MAT with a Relative Risk of 1.17 (95%CI: 1.0435–1.3134)
Bind MA[62]	US, New England	1999–2009	Normative Aging Study: 777 elderly men	DNA methylation: LINE-1 and Alu, as well as on genes controlling coagulation, inflammation, cortisol, DNA repair, and metabolic pathway in NAS	3-week average temperature	Generalized mixed-effects models	Temperature associated with methylation on tissue factor intercellular adhesion molecule 1 (ICAM-1) with an increase of 1.09 (1.03–1.15), toll-like receptor 2 (TRL-2) with a mean rate of 0.933 (0.872–0.999), carnitine O-acetyltransferase (CRAT) with an increase of 1.053 (1.004–1.104),and LINE-1 with a change in methilation of −0.497 (−0.915 to −0.080)

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Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
Wallwork RS[63]	US, New England	1993–2011	Normative Aging Study: 587 elderly men	Metabolic syndrome and its components-abdominal obesity, elevated fasting blood glucose concentration, low high-density lipoprotein, cholesterol concentration, hypertension, and hypertriglyceridemia	Mean annual temperature (MAT)	Cox proportional hazard models	A 1°C increase in MAT associated with a 1.33 (95% CI: 1.14, 1.56) higher risk of developing elevated fasting blood glucose
Valdes S [54]	Spain	2009–2010	5061 subjects in 100 clusters from the Diabetes Study	Obesity	Mean annual temperature (MAT)	Logistic regression analysis	Association between higher ambient temperature and obesity, with odd ratios of 1.20 (1.01–1.42), 1.35 (1.12–1.61), and 1.38 (1.14–1.67) in quartiles 2, 3, and 4
Voss JD [55]	US	2011	Behavioral Risk Factor Surveillance System: 422,603 US adults	Obesity	Mean annual temperature (MAT)	GEE and quantile regression	Parabolic relationship between MAT and prevalence of obesity by counties, with higher proportion of obese population for temperature between 5 and 20 C; quantile regression show lower median BMIs at extremes of temperature category
Yang HK [56]	Korea	2009–2010	National Health Insurance System: 124,354 individuals (2.2% of the Korean population)	Obesity, BMI, waist circumference	Mean annual temperature (MAT)	*t*-tests, Mann-Whitney test or chi-squared tests	Significant associations between obesity or abdominal obesity and ambient temperature. Compared to subjects in the lower four quintiles of MAT, those in the highest

Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
							quintile had a 1.045 times higher odds of obesity (95% CI: 1.010, 1.081)
Metintas S [51]	Turkey 14 cities	1974–2004	Parents of 25,843 primary schoolchildren from questionnaire	Respiratory diseases: asthma and wheezing in both sexes, eczema	Mean annual temperature (MAT)		Mean annual temperature was significantly associated with the prevalence of asthma [OR: 1.008 (95% CI: 1.003–1.011) in males and 1.007 (1.003–1.012) in female] and wheezing in both sexes [OR: 1.012 (1.006–1.018) in males and 1.01 (1.002–1.018) in females], and with eczema in females [OR: 1.007 (1.001–1.012)]
Miller ME [52]	US	1998–2006	National Health Interview Survey: 113,067 children	Respiratory diseases: Frequent otitis media (FOM), ear infection, respiratory allergy, seizure	Mean annual temperature (MAT)	Logistic regression analysis	No effect of MAT
Silverberg JI [53]	US	2006–2007	2007 National Survey of Children's Health: 91,642 children	Respiratory diseases: Hay fever or any kind of respiratory allergy	Mean annual temperature (MAT)	Survey logistic regression	Respiratory allergy increased with second, third, and fourth quartile MAT. Residence in a state with a higher quartile mean annual temperature was associated with increased prevalence of hay fever compared with that in a state with the lowest quartile with an OR 1.43 (1.28–1.60) in the 4th quantile

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Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
							compared to 1st quantile of temperature
Armstrong B [76]	World: 278 locations from 12 countries	1972–2012	Over 75 million deaths	Mortality	Annual summaries of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature	Generalized Additive Models (GAM)	Strong evidence that most deaths associated in daily analyses with heat and cold are displaced by at least 1 year. The percent increase in annual deaths were 1.7% (95% CI: 0.3, 3.1) for heat and 1.1% (95% CI: 0.6, 1.6) for cold
Goggins WB[74]	China, Hong Kong	1976–2012	Hong Kong Census and Statistics Department	Mortality: Age-standardized mortality rates	Annual summaries of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature	GAM	Annual time periods with a greater frequency and severity of both hot and cold weather had higher mortality rates than years with more moderate daily temperature distributions. An increase of 10 hot degree-days was associated with a 1.9% (95% CI: 0.5, 3.4) increase in ASMR, while an increase of 200 cold degree-days was associated with a 3.1% (95% CI: 1.3, 5.0; P = 0.0017) increase in ASMR
Rehill N [75]	London, UK	1949–2006	Registrar General and Office of National Statistics: 3,530,280 deaths	Mortality	Annual summaries of heat and cold using a degree-day approach as mean annual degrees above/below minimum mortality temperature	Poisson regression analysis	Association of cold with mortality, suggesting that most deaths due to cold were among individuals who

Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
							would not have died in the next 6 months. All-cause mortality increased by 2.3% (95% CI 0.7% to 3.8%) for 1 degree increase in cold. Estimated association with heat was imprecise
Lim YH [70]	Asia: 32 cities in Taiwan, China, Japan, and Korea	Japan: 1979–2009 Taiwan: 1994–2007 Korea: 1992–2010 China: 1996–2008	Department of Health, Taiwan: 688,394, Municipal Center for Disease Control and Prevention, China: 977,872, National Statistics Office, Korea: 1,511,996, Ministry of Health, Labor, and Welfare, Japan: 3,793,265 deaths	Mortality	Average summer (May-September) temperatures	Generalized Additive Models Poisson	Cities with low gross domestic product (GDP) *per capita* showed increasing heat-related mortality; cities with high GDP showed null associations between average summer temperature and heat-related mortality
Schumann B [67]	Sweden, Uppsala	1749–1859	Demographic Database: population by year. In 1859 the population was 8,473 with between 100–200 deaths per year	Mortality	Mean annual and monthly temperature	Generalized Linear Models (GLM)	Higher springtime temperature linked to decreased annual mortality with a RR of 0.962 (0.923–1.003), while higher summer temperature associated with higher mortality with a RR of 1.048 (0.997–1.102).
Zanobetti A [71]	US Medicare	1985–2006	Medicare: 3,749,096 persons with	Mortality in elderly with previous CHF,	standard deviation (SD) of summer (June–August) temperatures	Cox proportional hazard models	Long-term increases in temperature

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Study	Location	Years	Population	Outcome	Exposure Assessment	Method	Findings
			COPD (50% deaths), 1,939,149 with CHF (61% deaths), 3,364,868 with diabetes (43% deaths), and 1,454,928 with MI (42% deaths)	COPD, MI or diabetes hospitalization			variability associated with risk of mortality in subgroups of susceptible older populations. For 1 degree increase in SD of temperature, the mortality hazard ratios were: 1.038 (1.024–1.052) for CHF, 1.050 (1.030–1.069) for MI, 1.048 (1.029–1.067) for COPD and 1.055 (1.035–1.076) for diabetes
Shi L [73]	US, New England	2000–2008	Medicare: 2,740,308 study subjects, 836,776 deaths	Mortality	Mean and SD of temperature for summer (June August), and winter (December February)	Cox proportional hazard models	Rise in summer mean temperature of 1 °C associated with 1.0% (95% CI: 0.6, 1.5) higher death rate; increase in winter mean temperature corresponded to 0.6% (95% CI: 0.3, 0.9) lower mortality. Increases in temperature SDs for both summer and winter linked with increased mortality risk.
Shi L [72]	US, Southeastern states	2000–2013	Medicare: 13 million study subjects, 4,740,247 deaths	Mortality	Mean and SD of temperature for summer (June August), and winter (December February) and anomalies	Cox proportional hazard models	A 1 °C increase in summer mean temperature corresponded to 2.5% (2.33,2.59) increase in death rate. A 1 °C increase in winter mean temperature was associated with decrease of 1.5% (− 1.50,− 1.42). Increases in

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							seasonal temperature SD also associated with mortality with a 0.80 % (0.40,1.20) increase in summer SD and a 0.41% (0.22,0.60) increase in winter SD.
Fountoulakis KN [69]	Thessaloniki Greece	2000–2012	Hellenic Statistics Authority: 2.7 average yearly rate of suicide per 100,000 inhabitants; 4.38 for male and 1.16 for female	Suicide by sex	Mean annual temperature (MAT)	Linear regression analysis	Temperature associated with suicides and attempts in males and females, but less for females than males
Helama S [68]	Finland	1751–2008	Statistical authorities in Finland: 94,356 deaths from suicide over the 258-year period	Suicide mortality rates	Annual temperature variability	Pearson correlation coefficients with significance levels using a Monte Carlo method	Positive correlations found between annual temperatures and suicide rates. Temperature variability explained more than 60 % of the total suicide variance up until the initiation of a national suicide prevention program
Fukuda M [79]	Japan, 15 locations	1968–2012	Vital Statistics of Japan	Yearly sex ratios of fetal deaths, yearly sex ratios of newborn infants	Yearly and monthly mean temperature anomalies (the sum of monthly mean temperature minus the mean temperature during the previous 30 years for the same month)	Pearson correlation and t-test	A statistically significant positive association was found between yearly temperature differences and sex ratios of fetal deaths; a statistically significant negative association was found between

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							temperature differences and sex ratios of newborn infants from 1968 to 2012, and between sex ratios of births and of fetal deaths

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