Impact of ambient temperature on children’s health: A systematic review

Zhiwei Xu\textsuperscript{a}, Ruth A. Etzel\textsuperscript{b}, Hong Su\textsuperscript{c}, Cunrui Huang\textsuperscript{a}, Yuming Guo\textsuperscript{a}, Shilu Tong\textsuperscript{a}\textsuperscript{*}

\textsuperscript{a} School of Public Health and Social Work & Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, 4059, QLD, Australia.

\textsuperscript{b} Department of Public Health and Environment, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland.

\textsuperscript{c} Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, Hefei, Anhui, China.

\textsuperscript{*Correspondence to:} Shilu Tong, School of Public Health and Social Work & Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, Qld. 4059, Australia. Tel: +61 7 3138 9745; fax: 61-7-3138 3369. Email address: s.tong@qut.edu.au
Abstract

Children are vulnerable to temperature extremes. This paper aimed to review the literature regarding the relationship between ambient temperature and children’s health and to propose future research directions. A literature search was conducted in February 2012 using the databases including PubMed, ProQuest, ScienceDirect, Scopus and Web of Science.

Empirical studies regarding the impact of ambient temperature on children’s mortality and morbidity were included. The existing literature indicates that very young children, especially children under one year of age, are particularly vulnerable to heat-related deaths. Hot and cold temperatures mainly affect cases of infectious diseases among children, including gastrointestinal diseases, malaria, hand, foot and mouse disease, and respiratory diseases.

Paediatric allergic diseases, like eczema, are also sensitive to temperature extremes. During heat waves, the incidences of renal disease, fever and electrolyte imbalance among children increase significantly. Future research is needed to examine the balance between hot- and cold-temperature related mortality and morbidity among children; evaluate the impacts of cold spells on cause-specific mortality in children; identify the most sensitive temperature exposure and health outcomes to quantify the impact of temperature extremes on children; elucidate the possible modifiers of the temperature and children’s health relationship; and project children’s disease burden under different climate change scenarios.

Keywords: Climate change, temperature, child health, mortality, morbidity
Funding sources

ZX was funded by a China Scholarship Council Postgraduate Scholarship and Queensland University of Technology fee waiving scholarship; ST was supported by a National Health and Medical Research Council Research Fellowship (#553043).
1. Introduction

Global climate change is affecting and will increasingly influence human health and wellbeing. Temperature extremes, which are projected to become more frequent and intense as climate change continues (Meehl and Tebaldi, 2004), have become a great public health concern. In healthy individuals, an efficient heat regulation system enables the body to cope effectively with thermal stress (Guyton and Hall, 2000). Within certain limits, thermal comfort can be maintained by appropriate thermoregulatory responses so that physical and mental activities can be pursued without any detriment to health (Guyton and Hall, 2000). Temperatures exceeding these limits, both with respect to heat and cold, substantially increase the risk of disease and death (Díaz et al., 2002; Pan et al., 1995). There are substantial differences among different populations’ vulnerability to temperature stress (Kalkstein and Greene, 1997). It appears that the elderly are most sensitive to heat- and cold-related deaths, with children representing another high-risk group (Díaz et al., 2004).

There has been increasing interest in assessing the impact of ambient temperature on children’s health as climate change continues. Nevertheless, to date, no review has specifically focused on the relationship between temperature and children’s health. We try to fill this knowledge gap and elucidate the effects of hot and cold temperatures on children’s mortality and morbidity. In this review, we adopted part of the American Academy of Pediatrics definition and consider children as a heterogeneous group of five development stages: newborn (birth to 2 months of age), infant/toddler (2 months to <2 years of age), preschool child (2 to <6 years of age), school-age child (6 to <12 years) and adolescent (12 to 18 years) (American Academy of Pediatrics Committee on Environmental Health, 2003).

2. Methods
2.1 Data sources

Empirical studies regarding ambient temperature and children’s mortality and morbidity published up to February 1st 2012 were retrieved using the electronic databases PubMed, ProQuest, ScienceDirect, Scopus and Web of Science. References of the identified papers were examined to make sure that all relevant papers were included.

2.2 Inclusion criteria

We restricted our search to peer-reviewed English journal articles. Children aged 0-18 years are the target population of this review. Thus, exposure to temperature extremes during fetus period and its impact on birth outcomes are not included in this review. Our primary search used the following U.S. National Library of Medicine’s Medical Subject Headings (MeSH terms) and keywords: “climate change”, “temperature”, “heat wave”, “heatwave”, “cold spell”, “child health”, “morbidity”, “hospitalization”, “emergency department visit”, “death” and “mortality”. Eligibility included any empirical studies which used original data and appropriate effect estimates (e.g., regression coefficient, relative risk, odds ratio, percentage change in morbidity, and morbidity or excess morbidity following heatwaves); where ambient temperature was a main exposure of interest, and where children’s morbidity or mortality were analysed. The effect estimates (e.g., relative risks, confidence intervals) were recorded from the papers identified.

3. Results

We identified 743 papers in the initial search. According to the inclusion criteria, 33 studies were included in the final review (Figure 1). Among them, 20 examined the relationship between temperature and children’s morbidity, 10 investigated the impact of temperature on
children’s mortality, and three assessed the impact of temperature on both morbidity and mortality in children.

3.1 Impacts of ambient temperature on children’s mortality

Studies found that temperature has had a significant impact on children’s mortality in Australia (Nitschke et al., 2007; Nitschke et al., 2011), Austria (Hutter et al., 2007), Brazil (Gouveia et al., 2003), China (Huang et al., 2010), England (Hajat et al., 2005), France (Fouillet et al., 2006), India (Hajat et al., 2005), Mexico (O’Neill et al., 2005), South Korea (Kysely and Kim, 2009), Spain (Basagaña et al., 2011; Díaz et al., 2004) and the USA (Basu and Ostro, 2008), most of which are high-income countries (Table 1). Hutter et al. found that the relative risk of heat waves was highest in children aged under one year in Vienna, Austria (Hutter et al., 2007). In California, elevated mortality risks were found in high ambient temperature, also for children one year of age and under (Basu and Ostro, 2008). In Catalonia, Spain, Basagaña et al. found a significant increase in mortality during heat waves among children aged under one year (Basagaña et al., 2011). Fouillet et al. investigated the effect of 2003 heat waves on mortality in France, and found that mortality increased among male children aged under one year (Fouillet et al., 2006).

Nitschke et al. explored the impacts of heat waves on morbidity and mortality during 1993-2006 and 2008-2009 in Adelaide, Australia, and found that there were mortality rises among children aged 0-4 years in heat waves of the two periods (Nitschke et al., 2007; Nitschke et al., 2011). However, in Shanghai, China, Huang and colleagues quantified the effect of 2003 heat wave on mortality, but did not find significant increase in mortality among children aged 0-4 years in heat waves (Huang et al., 2010). In South Korea, Kysely et al. examined the effect of heat waves on daily mortality during 1991 - 2005 and they reported that the relative
mortality increase during the heat waves in 1994 was larger in children aged 0-14 years than in any other age group (Kysely and Kim, 2009). Hajat et al. investigated the impact of high temperature in Delhi (India), São Paulo (Brazil), and London (England). They found that during periods of high temperatures, a high proportion of Delhi deaths (48%) occurred in children aged 0-14 years. This incidence was much greater than the proportion in São Paulo (10%) and London (1%) (Hajat et al., 2005). Another study in São Paulo found that an increase of 1 °C in temperatures above 20 °C was accompanied by an increase of 1.5% (adults) and 2.6% (children under 15 years old) in mortality (Gouveia et al., 2003).

A relatively limited number of studies found evidence of cold-related mortality in children. In Madrid, Díaz and colleagues showed that the impact of ambient temperature on mortality among children aged 0-9 years was limited to those winter days with maximum temperatures lower than 6°C (Díaz et al., 2004). O’Neill et al. found that in Mexico City, children’s total mortality increased by 10.9% on cold days (apparent temperature < 11°C) (O’Neill et al., 2005). They also found that in Monterrey, total mortality among children aged 0-15 years increased by 5.5% on hot days. To date, no study examined the relationship between cold temperature and cause-specific mortality among children.

3.2 Impacts of ambient temperature on children’s morbidity

Table 2 illustrates the studies regarding ambient temperature and children’s morbidity. Linares and Díaz investigated the effect of high temperature on hospital admissions in Madrid, and they found that hospital admissions due to non-external causes (all causes excluding injury, poisoning and external causes) increased by 0.32 (95% confidence interval: 0.12–0.52) among children aged 0-10 years for each degree that the maximum temperature surpassed 36 °C (Linares and Díaz, 2008). The incidences of hand, foot and
mouth disease, renal disease, fever and electrolyte imbalance among children increased significantly for high temperatures. Hand, foot, and mouth disease is a common viral infection whose main clinical symptoms include fever, mouth ulcers, and vesicles on the hands, feet, and mouth, mainly among children (Ruan et al., 2011). In a study conducted in Fukuoka, Japan, the weekly number of hand, foot, and mouth disease cases increased by 11.2% (95% CI: 3.2–19.8) for every 1 °C increase in average temperature (Onozuka and Hashizume, 2011). Notably, the effects of temperature and humidity on hand, foot, and mouth disease infection were most significant in children under the age of 10 years, which demonstrated that temperature had a significant influence on the incidence of children’s hand, foot, and mouth disease infections (Onozuka and Hashizume, 2011).

Paediatric renal disease is an important adverse consequence of heat waves. Nitschke et al. found significant rise of renal hospital admission in the 5-14 year age group during heat waves in Adelaide, Australia (Nitschke et al., 2011). A study conducted by Kovats et al. found emergency hospital admissions for renal disease increased during heat waves, mostly in children aged under five years (Kovats et al., 2004). Leonardi et al. investigated the relationship between heat wave and calls to the National Health Service Direct-a nurse-led helpline which provides health-related information and advice and directs callers to the appropriate health service and self care. They found a large increase in calls for fever among children aged 0-4 years in Greater London and South East regions (Leonardi et al., 2006). Maximum daily temperature was reported as a significant risk factor for fever among children younger than six years old (Lam, 2007). Knowlton and colleagues conducted a study in California and found that emergency department visits of electrolyte imbalance increased rapidly among the age group of 0-4 years during heat waves (Knowlton et al., 2008).
Low temperature enhances skin irritability (Uter et al., 1998), causes impairment of inflammatory and irritant dermatoses (Sauer and Hall, 1996; Uter et al., 1998), and affects eczema (Kramer et al., 2005). Kramer et al. investigated the influence of temperature on eczema symptoms among children aged under six years old, and found that children of winter-type eczema seemed to be more sensitive to deviations in temperature (Kramer et al., 2005).

Paediatric infectious diseases, including gastrointestinal diseases, malaria, and respiratory diseases, are both sensitive to hot and cold temperatures. For a 1°C increase in ambient temperature, childhood diarrheal admissions increased by 8% in Peru (Checkley et al., 2000). The increased hospital admissions for diarrheal in children caused by increasing temperature was also found in Bangladesh (Hashizume et al., 2007). Chou et al. reported that maximum temperature contributed to approximately 50% of diarrheal among children aged 0-14 years in Taiwan (Chou et al., 2010). Though some researchers found that the prevalence of diarrheal disease in children increased when temperature increased in hot days (Cama et al., 1999), others found that increases in ambient temperature had a more significant effect on hospital admissions for childhood diarrheal during the winter than the summer (Checkley et al., 2000). In addition to daily temperature, weekly and monthly temperature was also reported to be associated with diarrheal disease (D'Souza et al., 2008). An increase in monthly average maximum temperature raised the prevalence of diarrheal while an increase in monthly minimum temperature reduced diarrheal illness (Bandyopadhyay et al., 2012).

Some other paediatric gastrointestinal diseases are also associated with ambient temperature. In New South Wales, Australia, Lam found that maximum temperature was positively and significantly associated with emergency presentations for gastroenteritis among children.
younger than six years old (Lam, 2007). A study in Japan indicated that the temperature-
infectious gastroenteritis had an inverted shape, with fewer cases at temperature lower and
higher than 13 °C among children aged under 15 years (Onazuka and Hashizume, 2011).
Green et al. reported that intestinal infectious disease admissions among children aged 5-18
years increased with apparent temperature in nine California counties (Green et al., 2010).

Ambient temperature has been found to be one of the sensitive predictors for malaria
incidence, even though it is still controversial about which temperature indicator is the best.
Yé et al. reported that mean temperature was the best predictor of clinical malaria among
children aged under five in Burkina Faso (Yé et al., 2007). Gernaat et al. found a negative
correlation between maximum temperature and monthly malaria incidence among children
under 15 years in Nchelenge, Zambia (Gernaat et al., 1998), and Loevinsohn found the
relationship only between minimum temperature and the monthly malaria incidence among
children aged 2-9 years in Rwanda (Loevinsohn, 1994).

Paediatric respiratory diseases are also susceptible to hot and cold temperatures. During the
cold months there was a significant increase in paediatric hospitalisations due to viral acute
lower respiratory infections (Viegas et al., 2004). Tchidjou et al. found that low temperatures
were directly associated with an increase in the frequency of hospitalization for acute
respiratory infections (Tchidjou et al., 2010). Low temperature was also associated with
paediatric respiratory consultation in Santiago (Avendaño et al., 1999). Apart from cold, heat
can also result in respiratory disease in children (Kovats et al., 2004). Green et al. found that
the effects of elevated ambient temperature were highest for children under five years for all
respiratory diseases (Green et al., 2010).
Childhood asthma is a widespread health problem as asthma affects more than 300 million people worldwide, starting in childhood in a large proportion of cases (Baena-Cagnani and Badellino, 2011). The effects of ambient temperature on asthma have been somewhat controversial in previous studies (Larsson et al., 1998; Yuksel et al., 1996). Higher temperature and a rapid decrease of temperature within a 3-day period were positively associated with an increase in paediatric asthma emergency visits in Tokyo (Hashimoto et al., 2004). Another study in Japan also found that within day temperature change was associated with asthma among children under 12 years (Ueda et al., 2010). In Singapore, Loh et al. reported that paediatric asthma admissions were negatively correlated with maximum temperature (Loh et al., 2011). Nastos et al. also found a negative association between hospital admissions for asthma and monthly air temperature among children aged 0–4 years in Greece (Nastos et al., 2008).

4. Discussion

This review presents the main paediatric diseases or conditions which are sensitive to temperature extremes, and the subgroups of children vulnerable to heat- and cold-related mortality. Children’s vulnerability to high and low temperatures can be potentially explained by the following reasons: (i) Physiological modality: children have a greater body surface area-to-mass ratio compared to adults, allowing greater temperature transfer between the environment and the body (Blum et al., 1998). Also, their less developed regulating body systems mean that children are more likely to be affected by extreme temperature. (ii) Metabolic modality: children’s greater metabolic rate may render them more sensitive to extreme temperature (Bunyavanich et al., 2003). (iii) Cardiovascular modality: previous study found that children produce somewhat lower cardiac output values than adults (Turley and Wilmore, 1997). Besides, children, especially infants, have a higher heart rate than adults,
which may result in their vulnerability to extreme temperature. (iv) Behaviour modality: compared with adults, children spend more time outdoors and participate in more vigorous activities, which result in an increased exposure to outdoor heat and cold (Sheffield and Landrigan, 2010). (v) Self-care ability modality: children, especially neonates, infants, and children less than one year, cannot take care of themselves, and they are dependent on others to protect them from unsafe environments. A study of heat-stressed infants hospitalized for treatment found that 68% of the infants’ caretakers were unaware of the need for increased fluid intake by their infants during hot weather and had underestimated the seriousness of the infants’ initial symptoms (Danks et al., 1962). (vi) Life expectancy modality: more expected future years of life provide them with more time for exposure to environmental hazards (eg. temperature extremes) (Sheffield and Landrigan, 2010). If children were harmed by environmental hazards, they may be more prone to suffer from long-term adverse impact (Landrigan et al., 1999; Perera, 2008).

Existing studies regarding the impact of ambient temperature on children’s health have found that very young children, especially children aged under one year old, are particularly vulnerable to heat-related deaths. As body temperatures increase, blood flow shifts from the vital organs to underneath the skin’s surface to facilitate cooling (Astrand et al., 2003). When too much blood is diverted, the body’s capacity to regulate its temperature may be hindered, which puts increased stress on the critical organs such as heart and lungs (King, 2004).

Increased blood viscosity, elevated cholesterol levels associated with higher temperatures, and a higher sweating threshold may also induce heat-related mortality (Astrand et al., 2003). Most previous studies which found the adverse impact of hot temperature on children’s mortality are from high-income countries. It illustrated that all children with less resources, even in high income countries, are vulnerable to the adverse impact of temperature extremes.
Research is urgently needed to evaluate the health risks of extreme heat events among children in developing countries.

Regarding the heat-mortality threshold among children, Gouveia observed a 2.6% increase in children’s mortality for an increase of 1°C in temperatures above 20°C in a subtropical city (Gouveia et al., 2003). Due to different adaptation abilities worldwide, the temperature-mortality threshold in children varies from place to place (Henry and Rees, 1991; Leonard et al., 2002). Apart from biological adaptability, some other factors, including caregiver behaviour, air conditioning use (Ostro et al., 2010), nutritional status, vaccination status and access to environmental infrastructures (Bandyopadhyay et al., 2012), may also contribute to the different temperature exposure cut-offs which are largely location-specific.

The main paediatric diseases or conditions affected by heat waves include renal disease, fever, and electrolyte imbalance. Heat-related dehydration appears to promote acute renal failure (Semenza et al., 1999). Exposure to extreme hot weather can induce heat-related conditions including hyperthermia and heat stress in children (Semenza et al., 1999). The mechanism is that heat exposure causes blood to be redistributed away from splanchnic and renal vascular beds, placing stress on the kidneys and compromise the function of the renal system.

Fever can be considered a response to the change of temperature for children when they are overheated (Hay et al., 2005). When the hypothalamus receives information that the temperature is lower than the setting of the thermostat, thermoregulatory responses to conserve or produce heat are put into action. Heat is generated by shivering and is conserved by vasoconstriction. If the temperature is higher than the thermostat setting, heat is lost by vasodilatation and increased sweating. Other responses include extracellular fluid volume
regulation via arginine vasopressin, and behavioral responses such as seeking a warmer or cooler environmental temperature (Feld and Jeffrey, 2005). If body is involved in a sustained heat environment (eg, heat wave) and cannot seek a cooler environment, fever occurs. During heat waves, as a consequence of hyperthermia and dehydration, the body’s physiological mechanisms attempt to regulate electrolyte and water imbalance. Children may face electrolyte imbalance if their thermoregulatory systems fail. If electrolyte imbalance continues to exist, heat exhaustion or heat cramps may occur (Jardine, 2007). For parents, caregivers, and school personnel, focusing on hydration for children is a critical intervention to avoid paediatric morbidity during heat waves. Previous research has found that skin temperatures of the arms and hands were significantly lower and the rates of decrease in skin temperature for the hands and feet were significantly greater during cold exposure in children than in adults (Tsuzuki et al., 2008), indicating that children may face more challenges in cold environment compared with adults. Some diseases are likely to be associated with cold, but the occurrence of these diseases may not necessarily be due to the cold, but rather seasonal patterns. Influenza and influenza-like conditions among very young children, which largely contribute to paediatric mortality (Alberdi et al., 1998; Bhat et al., 2005; Eng and Mercer, 1998), are reported to occur more often in cold seasons because of seasonal patterns rather than cold effects (Mackenbach et al., 1992). Literature has indicated that children’s infectious diseases, including gastrointestinal diseases, malaria, hand, foot and mouse disease, and respiratory diseases, are more likely to be affected by both hot and cold. Diarrheal disease is one of the three main causes of child death globally, estimated consistently to cause around 21-22 per cent of all under-five deaths (Black et al., 2003; Bryce et al.). Low temperatures increase the transmission of viral diarrheal disease
(Blaser et al., 1995; D'Souza et al., 2008; Konno et al., 1983), and high temperatures increase the number of admissions for bacterial diarrheal disease (Cama et al., 1999). High temperatures increase exposure to bacterial and parasitic diarrheal, and lengthen survival of bacteria such as enterotoxigenic escherichia coli in contaminated food (Blaser et al., 1995). High temperatures may also indirectly affect behaviour patterns, such as increased consumption of water and lax hygiene, which may promote diarrheal transmission (Chou et al., 2010). Rotavirus can remain viable outside the human body from several hours to several months, depending on the environment, and the ideal environment for its survival is one of low temperature (Cama et al., 1999).

Some researchers found that the incidence of paediatric gastrointestinal disease was positively associated with ambient temperature (Green et al., 2010; Lam, 2007), while some others argued that there were fewer cases at temperatures lower and higher than a fixed temperature value (Onazuka and Hashizume, 2011). This inconsistency could be due partly to the different mechanisms that cause paediatric infectious gastrointestinal diseases. Norovirus is more prevalent in the winter period (Kwan et al., 2008; Nakata et al., 2000), and rotavirus is more prevalent in spring (Inouye et al., 2000), which may result in the association between cold temperature and infectious gastrointestinal diseases. The bacteria-related gastrointestinal diseases are more likely to increase in high temperature because bacteria which contaminates food is more prevalent during summer (Gillespie et al., 2005). The impact of temperature extremes on gastrointestinal diseases has particular public health significance because climate change may increase the incidence of food-borne and water-borne diseases (Rose et al., 2001).

Current literature has illustrated that malaria among children is also affected by temperature extremes. Ambient temperature plays a major role in the life cycle of the malaria vector. The
development of the parasite within the mosquito (sporogonic cycle) is dependent on temperature. The sporogonic cycle takes about 9 to 10 days at temperatures of 28°C, but stops at temperatures below 16°C (Lindsay and Birley, 1996). The daily survival of the vector is dependent on temperature as well. At temperatures between 16°C and 36°C, the daily survival is about 90%. This survival drops rapidly at temperatures above 36°C. The highest proportion of vectors surviving the incubation period is observed at temperatures between 28°C and 32°C (Craig et al., 1999). The gonotrophic cycle, which is the time between two blood meals of the vector, is short at higher temperatures because the digestion speed increases (Reeves, 1963).

Increases in respiratory diseases are generally attributed to cross-infection from indoor crowding, to the adverse effects of cold on the immune system’s resistance to respiratory infection (Ophir and Elad, 1987; Tyrrell et al., 1989), and to the fact that low temperatures assist survival of bacteria in water droplets (Handley and Webster, 1995). Susceptibility to pulmonary infections may increase through bronchoconstriction, caused by breathing cold air (Schaanning et al., 1986). Very young children’s susceptibility to respiratory diseases during high temperature may be due partly to their undeveloped respiratory system and poor adaptation abilities (Sheffield and Landrigan, 2010). Understanding how high temperature influences respiratory disease is an area where further research and development are clearly needed, because the burden of such diseases is expected to grow in developed countries (Mannino and Buist, 2007). Childhood asthma is one of the major paediatric respiratory diseases affected by high and low temperatures. Over short (daily) time periods, low temperatures can have a direct effect on acute exacerbations of asthma, and warmer average temperatures are also associated with an increase in asthma prevalence (Yuksel et al., 1996). The reasons for this are not well known, but higher temperatures can enhance growth of
indoor allergens such as moulds, mites and cockroaches. In contrast, the abrupt cooling of air
temperature can trigger an asthma attack directly or indirectly through viral infection in the
airway (Yuksel et al., 1996).

5. Knowledge gaps

The impact of ambient temperature on children’s health has become an important public
health issue, but there are still several knowledge gaps in this area. First, no study has focused
on the impacts of cold spells on cause-specific mortality among children, which may be due
partly to the relatively limited number of deaths among children. Large scale study analysing
children by cause-specific outcomes in temperature extremes would be beneficial for making
future adaptation strategies.

Second, limited studies have focused on the specific optimum temperature for children.
Previous literature has illustrated that U-, V-, or J-shaped patterns with the minimum
morbidity or mortality at a certain temperature or temperature range, with increased
morbidity or mortality below and above the threshold (Kovats et al., 2004; Liang et al., 2008;
Lin et al., 2009; O’Neill et al., 2005), however, in some regions, the temperature thresholds
for children in terms of mortality or morbidity remain unknown. It may be impossible to
explore a uniform optimum temperature for children worldwide due to different
characteristics in different regions, but identifying different temperature thresholds for
children in various geographic regions may be possible.

Third, previous studies tended to consider children under 15 years old as a single group.
However, children aged one year or under may be more sensitive to temperature extremes. As
a group, children are heterogeneous both physiologically and behaviourally, and they should
be considered with more in-depth when assessing their vulnerability to temperature extremes.

Fourth, most previous studies used daily or monthly mean, maximum or minimum
temperature as an indicator of exposure in evaluating temperature effects on children’s health.
However, diurnal temperature range is also a risk factor of mortality, which has not been
thoroughly investigated (Kan et al., 2007). Temperature variation rather than absolute
temperature, such as temperature variations with-in one or two days (Guo et al., 2011), could
be a future research focus.

Fifth, to date, most studies used mortality or morbidity as the outcomes to measure the effect
of ambient temperature on children’s health. Meanwhile, they treated deaths and diseases
amongst children, adults and elderly as equally important. Yet, if most deaths were in the
very elderly, who had only a life expectancy in a few years, the burden of temperature
extremes on human well-being would have less public health importance (Huang et al., 2012).
Years of life lost and disability-adjusted life years could be sensitive outcome measures
giving greater weight to deaths and diseases at younger age (Lopez et al., 2006).

Sixth, the modifying effects of some socioeconomic factors in the relationship of temperature
extremes and children’s health still remain unclear (Basu and Ostro, 2008; Gouveia et al.,
2003). Checkley and Chou have indicated the possible effects of some factors in the
temperature-diarrheal relationship, such as behaviour patterns, vaccination coverage, immune
system and dietary habits (Checkley et al., 2000; Chou et al., 2010). Nonetheless, more
studies in some low-income regions focusing on the effect of socioeconomic factors are
urgently needed.
Finally, no research has focused on the projections of the impact of climate change on children’s mortality and morbidity patterns. Projecting the change in main disease burdens under different climate change scenarios will have a great potential for future children’s disease control and prevention, planning and intervention.

6. Conclusions

Due to physiological, metabolic and behavioural characteristics, children are more sensitive to hot and cold temperatures than adults. Children under one year of age are at high risk of heat-related mortality. Temperature extremes are prone to cause more morbidity among children with regards to infectious diseases and allergic diseases. Future studies should focus on: 1. The balance of hot- and cold-temperature related mortality and morbidity among children in different regions; 2. Impacts of cold spells on cause-specific mortality in children; 3. Differences in threshold temperature between children and adults in various regions; 4. The most sensitive index of temperature exposure for children; 5. Sensitive outcome measures to quantify the impact of temperature extremes on children; 6. The modified effects of socioeconomic factors in the relationship between temperature extremes and children’s health; and 7. Projections of children’s disease burden under different climate change scenarios.

Acknowledgements

We thank Yan Bi, Xiaoyu Wang and Lyle R. Turner for their valuable comments and suggestions.
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Virus) Are the Most Prevalent Cause of Gastroenteritis Outbreaks among Infants in
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Figure/Table Legends

Figure 1. The flow chart of literature selection process

Table 1. Characteristics of studies about ambient temperature and children’s mortality

Table 2. Characteristics of studies about ambient temperature and children’s morbidity
<table>
<thead>
<tr>
<th>Studya</th>
<th>Location and time</th>
<th>Research design and statistical analysis</th>
<th>Main temperature exposure variable(s)</th>
<th>Outcome(s)</th>
<th>Key findings</th>
<th>Effect estimates</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gouveia et al. 2003</td>
<td>São Paulo, Brazil, 1991-1994</td>
<td>Time-series; Poisson GAM</td>
<td>Daily mean, maximum and minimum temperature</td>
<td>Total and cause-specific mortality</td>
<td>An increase of 1°C in temperatures above 20°C was accompanied by an increase of 2.6% in the total mortality among children aged under 15 years</td>
<td>Percent change: 2.6% (95% CI: 1.6% – 3.6%)</td>
<td>Examined temperature and total and cause-specific mortality; air condition was controlled for</td>
</tr>
<tr>
<td>Díaz et al. 2004</td>
<td>Madrid, Spain, January 1, 1986-December 31, 1997</td>
<td>Time-series; Poisson regression</td>
<td>Daily maximum and minimum temperature</td>
<td>Total mortality</td>
<td>The impact of temperature on mortality among children aged 0-9 years was limited to those winter days with maximum temperature values lower than 6°C</td>
<td>RR: 1.23 (95% CI: 1.13 – 1.32)</td>
<td>Specifically examined temperature and child mortality; air pollution was controlled for</td>
</tr>
<tr>
<td>Hajat et al. 2005</td>
<td>Delhi (India), São Paulo (Brazil), and London (England), January 1991 – December 1994</td>
<td>Time-series; Poisson GLM</td>
<td>Daily maximum and minimum temperature</td>
<td>Total and cause-specific mortality</td>
<td>During high temperatures, a high proportion of Delhi deaths (48%) occurred in children under 15 years. This incidence was much greater than the proportion in São Paulo (10%), which in turn was substantially greater than the proportion in London (1%).</td>
<td>1). Delhi: Lag 0 Percent change: 3.2% (95% CI: 1.8% – 4.5%); 2). São Paulo: Lag 0 Percent change: 0.6% (95% CI: -0.5% – 1.7%); 3). London: Lag 0 Percent change: -2.2% (95% CI: -6.7% – 2.6%)</td>
<td>Cities in high-, middle- and low-income countries were selected; temperature and child mortality relationship varied in cities.</td>
</tr>
<tr>
<td>Study</td>
<td>Location and time</td>
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<td>O’Neill et al. 2005</td>
<td>Mexico City, 1996-1998 and Monterrey, 1996-1999, Mexico</td>
<td>Time-series; Poisson regression</td>
<td>Daily apparent temperature</td>
<td>Total mortality</td>
<td>In Mexico City, total mortality among children aged 0-15 years increased by 10.9% on cold days (fully adjusted); In Monterrey, total mortality among children aged 0-15 years increased by 5.5% on hot days (fully adjusted)</td>
<td>1). Mexico: Percent change: 10.9% (95 CI: 5.4% – 16.7%); 2). Monterrey: Percent change: 5.5% (95% CI: -10.7% – 16.8%)</td>
<td>Study from a middle-income country; season, day of week, public holidays, respiratory epidemics and air pollution were controlled for</td>
</tr>
<tr>
<td>Fouillet et al. 2006</td>
<td>France, 2000-2003</td>
<td>Descriptive study</td>
<td>Heat wave periods compared with non-heatwave periods</td>
<td>Total mortality</td>
<td>During heat waves, significant excess mortality was observed for male children aged less than one year</td>
<td>Observed mortality/expected mortality: 1.3 (95% CI:1.0-1.6)</td>
<td>Cause-specific mortality was analysed.</td>
</tr>
<tr>
<td>Hutter et al. 2007</td>
<td>Vienna, Austria, May-September, 1998-2004</td>
<td>Time-series; Poisson GAM</td>
<td>7 heat waves compared with non-heatwave periods</td>
<td>Total mortality</td>
<td>The relative risk of deaths during heat wave days was the highest in children under one year old</td>
<td>RR: 1.25 (95% CI: 0.82 – 1.90)</td>
<td>Examined temperature and mortality in a cold region; air pollution was not controlled for</td>
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<td>Study</td>
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<tr>
<td>Nitschke et al. 2007</td>
<td>Adelaide, Australia, 1993-2006</td>
<td>Case-series study</td>
<td>Heat wave periods compared with non-heatwave periods</td>
<td>Hospital admissions, emergency department presentations and mortality</td>
<td>During heat waves: 1). Respiratory diseases among children aged 0-4 years decreased; 2). Mortality in children aged 0-4 years increased; 3). Mortality in children aged 5-14 years increased;</td>
<td>1). IRR:0.86 (95% CI: 0.76-0.97); 2). IRR:1.19 (95% CI: 0.82-1.71); 3). IRR:1.15 (95% CI: 0.58-2.29).</td>
<td>Three health endpoints were used.</td>
</tr>
<tr>
<td>Basu and D. Ostro 2008</td>
<td>Nine California counties, USA, May-September, 1999-2003</td>
<td>Case-crossover; Conditional logistic regression</td>
<td>Daily apparent temperature</td>
<td>Total and cause-specific mortality</td>
<td>Increased mortality risk in high apparent temperature was especially pronounced in children under one year old and children under five years</td>
<td>1). Under one year old: Percent change: 4.9% (95% CI: 1.8% – 11.6%); 2). Under five years Percent change: 4.2%</td>
<td>Apparent temperature was used as exposure measure; air pollution was not considered</td>
</tr>
<tr>
<td>Kysely et al. 2009</td>
<td>South Korea, 1991-2005</td>
<td>Descriptive study</td>
<td>20 heat waves compared with non-heatwave periods</td>
<td>Total and cardiovascular-cause mortality</td>
<td>During the heat wave in 1994, the relative increase in mortality was larger in children aged 0-14 years than in any other age group</td>
<td>Excess deaths: 183 (95% CI: 133 – 234)</td>
<td>Heat index was used; the results from 1994 heat wave were quite exceptional compared with other heat waves</td>
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<tr>
<td>Huang et al. 2010</td>
<td>Shanghai, China, June 15-September 15, 2003</td>
<td>Descriptive study</td>
<td>Heat wave periods compared with non-heatwave periods</td>
<td>Total and cause-specific mortality</td>
<td>No significant mortality increase was found in children aged 0-4 years during heat waves</td>
<td>RR: 0.67 (95% CI: 0.24, 1.87)</td>
<td>One of the few English studies regarding the impact of heat waves in China.</td>
</tr>
<tr>
<td>Basagaña et al. 2011</td>
<td>Catalonia, Spain, May 15-October 15, 1983-2006</td>
<td>Case-crossover</td>
<td>Heat wave periods compared with non-heatwave periods</td>
<td>Total and cause-specific mortality</td>
<td>In children aged under one year, the effect of heat waves was observed on the same day and was detected only for conditions originating in the perinatal period</td>
<td>RR: 1.53 (95% CI: 1.16 – 2.02)</td>
<td>Cause-specific mortality in children aged under one year was analysed.</td>
</tr>
<tr>
<td>Nitschke et al. 2011</td>
<td>Adelaide, Australia, July 1993–March 2009</td>
<td>Case-series study; Negative binomial regression</td>
<td>38 heat waves compared with non-heatwave periods</td>
<td>Hospital admissions, emergency department presentations and mortality</td>
<td>During heat waves, there were: 1). Significant rise of renal hospital admission in 5-14 year age group; 2). Significant rise of emergency department presentations in 0-4 and 5-14 year old groups; 3). Significant rise of mortality in 0-4 year old group</td>
<td>1). RR: 2.64 (95% CI: 1.47 – 4.73); 2). 0-4: RR: 1.02 (95% CI: 0.92 – 1.13); 5-14: RR: 1.04 (95% CI: 0.95 – 1.14); 3). RR: 3.23 (95% CI: 1.30 – 7.99)</td>
<td>Three health endpoints were used.</td>
</tr>
</tbody>
</table>
These studies are ordered by the date of publication and the first author.

Both mortality and morbidity were included in these studies.

Abbreviations: CI, confidence interval; GAM, generalized additive models; GLM, generalised linear models; IRR, incidence relative risk; RR, relative risk.
Table 2. Characteristics of studies about ambient temperature and children’s morbidity

<table>
<thead>
<tr>
<th>Studya</th>
<th>Location and time</th>
<th>Research design and statistical analysis</th>
<th>Main temperature exposure variable(s)</th>
<th>Outcome(s)</th>
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</thead>
<tbody>
<tr>
<td>Checkley et al. 2000</td>
<td>Lima, Peru, January 1, 1993–December 31, 1998</td>
<td>Time-series; Poisson GAM</td>
<td>Daily mean temperature</td>
<td>Hospital admissions for non-cholera diarrheal disease</td>
<td>A 1°C increase in mean ambient temperature had a greater effect on the number of daily diarrheal admissions among children under 10 years old during the cooler months of May to November than during the warmer months of December to April</td>
<td>1). Cold: RR: 1.12 (95% CI: 1.10 – 1.14); 2). Hot: RR: 1.04 (95% CI: 1.02 – 1.05)</td>
<td>The effect of El Niño on morbidity has been examined; air pollution was not controlled for</td>
</tr>
<tr>
<td>Grech et al. 2002</td>
<td>Malta, January 1994–December 1998</td>
<td>Time-series; Poisson regression</td>
<td>Monthly mean temperature</td>
<td>Hospital admissions for asthma</td>
<td>Mean monthly ambient temperature negatively correlated with monthly admissions for asthma among children aged &lt;1, 1–4, 5–9 and 10–14 years old</td>
<td>1). &lt;1: r =-0.84 (p&lt;0.0001); 2). 1-4: r =-0.56 (p&lt;0.0001); 3). 5-9: r =-0.46 (p&lt;0.0001); 4). 10-14: r =-0.44 (p&lt;0.0001)</td>
<td>Seasonality was investigated by ARIMA method; children were classified into &lt;1 year, and 1–4, 5–9, 10–14 years old groups.</td>
</tr>
<tr>
<td>Hashimoto et al. 2004</td>
<td>Tokyo, Japan, January 3, 1998- February 28, 2002</td>
<td>Time-series; Multiple logistic regression</td>
<td>Daily mean, maximum and minimum temperature</td>
<td>Emergency visits for childhood asthma</td>
<td>Daily mean temperature was positively associated with the number of emergency visits for asthma among children aged between 2 to 15 years old</td>
<td>Regression coefficient: 0.82 (95%: 0.65 – 0.98, P&lt; 0.001)</td>
<td>Calendar month and day of week were controlled for; data for December 30 and 31, January 1–3 were not included</td>
</tr>
<tr>
<td>Study (^a)</td>
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<td>Kovats et al. 2004(^b)</td>
<td>London, UK, April 1, 1994-March 31, 2000</td>
<td>Time-series; Poisson regression</td>
<td>Daily maximum and minimum temperature</td>
<td>Total mortality and emergency hospital admissions</td>
<td>Hospital admissions increased during hot weather among children under five years old, but not among elderly and adults</td>
<td>Percent change: 0.24 (95% CI: 0.02 – 0.46)</td>
<td>Long term trend, season, day of week, public holidays, the Christmas period, influenza, relative humidity, air pollution (ozone, PM10), and over-dispersion were controlled for</td>
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<tr>
<td>Kramer et al. 2005</td>
<td>Augsburg, Germany, March-September 1999</td>
<td>Descriptive study; Mixed linear model</td>
<td>Indoor and outdoor temperature</td>
<td>Eczema symptoms</td>
<td>Among children aged 9 years old, eczema symptoms improved with higher outdoor temperatures. The mean itch was 22% lower and the mean extent was 65% lower per increase in outdoor temperature of 15°C.</td>
<td>1). Mean itch: Percent change: 22% (95% CI: 16% – 27%); 2). Mean extent: Percent change: 65% (95% CI: 54% – 72%)</td>
<td>Indoor and outdoor temperature were included as exposure; eczema of summer and winter types were analysed</td>
</tr>
<tr>
<td>Leonardi et al. 2006</td>
<td>England, December 19, 2001-May 5, 2004</td>
<td>Time-series; GLM</td>
<td>Daily maximum and minimum temperature</td>
<td>Calls to National Health Service Direct (^c)</td>
<td>During heat wave periods, the largest fever call rise was seen for children 0-4 years in Greater London and South East regions for every 10°C increase in mean temperature</td>
<td>Percent change: 2.5% (95% CI: 1.8% – 3.3%)</td>
<td>National Health Service calls to evaluate the possible morbidity; all calls and calls for selected causes were analysed; air pollution was controlled for</td>
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<tr>
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<tr>
<td>Hashizume et al. 2007</td>
<td>Dhaka, Bangladesh, January 1996-December 2002</td>
<td>Time-series; Poisson GLM</td>
<td>Daily maximum and minimum temperature</td>
<td>Weekly hospital visits for non-cholera diarrheal</td>
<td>Percentage change in the number of non-cholera diarrheal cases per week for 1°C increase in temperature at lag 0–4 weeks was only statistically significant in children ≤ 14 years old</td>
<td>Percent change: 5.7% (95% CI: 2.9% – 8.6%)</td>
<td>One hospital data was used</td>
</tr>
<tr>
<td>Lam 2007</td>
<td>Sydney, Australia, January 2001 and December 2002</td>
<td>Time-series; ARIMA</td>
<td>Daily maximum and minimum temperature</td>
<td>Hospital emergency department visits for asthma/other respiratory problems, fever, and gastroenteritis</td>
<td>Maximum daily temperature was a significant risk factor for fever and gastroenteritis</td>
<td>1). Fever: Regression coefficient: 0.37 (P&lt;0.001); 2). Gastroenteritis: Regression coefficient: 0.10 (P=0.007)</td>
<td>Only four childhood illnesses were included</td>
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<tr>
<td>Yé et al. 2007</td>
<td>Nouna, Cissé and Goni, Kossi, Burkina Faso, December 1, 2003-November 30, 2004</td>
<td>Descriptive study; Logistic regression</td>
<td>Daily mean, maximum and minimum temperature</td>
<td>Malaria cases from a survey</td>
<td>Temperatures above 27°C led to a significant decrease in clinical malaria risk among children under five years old</td>
<td>Regression coefficient: -86.9789 (95% CI: -113.4057 – -60.5521)</td>
<td>The malaria cases were collected from a random survey</td>
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<tr>
<td>Study</td>
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<td>D’Souza et al. 2008</td>
<td>Brisbane, Melbourne and Canberra, Australia, 1993-2003</td>
<td>Time-series; Log-linear regression model</td>
<td>Weekly mean temperature</td>
<td>Weekly hospital admissions for rotavirus diarrheal</td>
<td>Higher temperature in the previous week were associated with a decrease in rotavirus diarrheal admissions in children under five year of age</td>
<td>1). Canberra: Coefficient: -0.05 (P&lt;0.001); 2). Brisbane: Coefficient: -0.03 (P&lt;0.05); 3). Melbourne: Coefficient: -0.02 (P&lt;0.05)</td>
<td>Three cities in Australia were included</td>
</tr>
<tr>
<td>Knowlton et al. 2008</td>
<td>58 counties of California, USA, July 8, 2006-August 22, 2006</td>
<td>Case-crossover</td>
<td>Heatwave compared with non-heatwave period</td>
<td>Hospital admissions and emergency department visits</td>
<td>During heat wave periods, emergency department visits for electrolyte imbalance increased rapidly among 0-4 year age children</td>
<td>RR: 1.05 (95% CI: 1.04 – 1.07)</td>
<td>No air pollution was controlled for. Three age categories were used in the analysis: 0-4 years, 5–64 years, and ≥ 65 years of age.</td>
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<tr>
<td>Linares and Díaz 2008</td>
<td>Madrid, Spain, May-September, 1995-2000</td>
<td>Time-series; ARIMA</td>
<td>Daily maximum temperature</td>
<td>Hospital admissions</td>
<td>Hospital admissions due to organic causes (all causes excluding injury, poisoning and external causes) increased among children aged 0-10 years for each degree that the maximum temperature surpassed 36 °C</td>
<td>Excess hospital admissions: 0.32 (95% CI: 0.12–0.52)</td>
<td>Several air pollutants, including PM_{10}, NO_{x}, and O_{3}, were controlled for</td>
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<tr>
<td>Study&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Nastos et al. 2008</td>
<td>Athens, Greece, 1978-2000</td>
<td>Time-series; Poisson GLM</td>
<td>Monthly air temperature</td>
<td>Hospital admissions for paediatric asthma</td>
<td>Paediatric asthma hospital admissions were negatively correlated with monthly air temperature among children aged 0-4 years.</td>
<td>Regression coefficient: -0.0376 (P&lt;0.001)</td>
<td>Data covered more than 20 years</td>
</tr>
<tr>
<td>Chou et al. 2010</td>
<td>Taiwan, 1996-2007</td>
<td>Time-series; Poisson regression model</td>
<td>Monthly maximum temperature</td>
<td>Hospital admissions for diarrheal</td>
<td>The maximum temperature contributed approximately more than 50% morbidity of diarrheal among children aged 0–14 years</td>
<td>Regression coefficient: 0.039 (P=0.012)</td>
<td>A subtropical place in Asia was studied</td>
</tr>
<tr>
<td>Green et al. 2010</td>
<td>Nine California counties, USA, May to September 1999–2005</td>
<td>Case-crossover; Conditional logistic regression, meta-analysis</td>
<td>Daily mean apparent temperature</td>
<td>Hospital admissions for cardiovascular disease, respiratory disease, diabetes, dehydration, heat stroke, intestinal infectious diseases, and acute renal failure</td>
<td>The effects of ambient temperature are highest for those under five years for all respiratory diseases, and the highest effects of ambient temperature on dehydration and intestinal infectious disease were seen in children aged 5-18 years</td>
<td>1) Dehydration: Percent change: 19.7% (95% CI: 6.4%–34.7%); 2) Intestinal infectious disease: Percent change: 21.3% (95% CI: 5.2%–39.8%)</td>
<td>O&lt;sub&gt;3&lt;/sub&gt; and PM&lt;sub&gt;2.5&lt;/sub&gt; were controlled for; Lag effect of temperature was examined; GIS methods were used to improve exposure assessment</td>
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<tr>
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<tr>
<td>Tchidjou et al. 2010</td>
<td>Yaounde, Cameroon, January 2006-November 2007</td>
<td>Descriptive study; Negative binomial regressions</td>
<td>Daily maximum and minimum temperature</td>
<td>Hospital admissions for acute respiratory infections</td>
<td>Maximum and minimum temperature were directly associated with frequency of hospital admissions for acute respiratory infection among children aged under 18 years</td>
<td>1). Hot: RR: 1.94 (95% CI: 1.34 – 2.81); 2). Cold: RR: 0.72 (95% CI: 0.59 – 0.87)</td>
<td>One hospital data was used</td>
</tr>
<tr>
<td>Ueda et al. 2010</td>
<td>Fukuoka, Japan, 2001-2007</td>
<td>Time-stratified case-crossover; Conditional logistic regression</td>
<td>Hourly maximum, minimum and mean temperature</td>
<td>Hospitalizations for paediatric asthma</td>
<td>Larger changes in temperature- regardless of direction-were related to a higher risk of asthma hospitalization. The ORs corresponding to an increase of 1°C in T(<em>{\text{drop03}}) and T(</em>{\text{rise03}}) were 1.033 and 1.027, respectively</td>
<td>1). T(<em>{\text{drop03}}): OR: 1.033 (95% CI: 1.005 – 1.063); 2). T(</em>{\text{rise03}}): OR: 1.027 (95% CI: 0.995 – 1.060)</td>
<td>Temperature fluctuation was the main temperature indicator</td>
</tr>
<tr>
<td>Loh et al. 2011</td>
<td>Kadang Kerbau, Singapore, August 4, 2003 – December 28, 2008</td>
<td>Time-series; ARIMA</td>
<td>Daily mean, maximum and minimum temperature</td>
<td>Hospital admissions for paediatric asthma</td>
<td>Paediatric asthma admissions were negatively correlated with maximum temperature</td>
<td>Regression coefficient: -1.363 (P&lt;0.01)</td>
<td>A tropical place in Asia was studied</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Onozuka and Hashizume 2011</td>
<td>Fukuoka, Japan, 2000-2008</td>
<td>Time-series; Negative binomial regression</td>
<td>Daily mean temperature</td>
<td>Hospital admission for infectious gastroenteritis</td>
<td>Among children aged under 15 years, every 1 °C increase in temperature below 13 °C was associated with a 23.2% infectious gastroenteritis increase, while every 1 °C increase in temperature above 13 °C was associated with an 11.8% infectious gastroenteritis decrease</td>
<td>1). Hot: Percent change: 11.8% (95% CI: 6.6% – 17.3%); 2). Cold: Percent change: 23.2% (95% CI: 16.6%– 30.2%)</td>
<td>Specifically focused on infectious gastroenteritis in children aged under 15 years</td>
</tr>
<tr>
<td>Onozuka and Hashizume 2011</td>
<td>Fukuoka, Japan, 2000-2010</td>
<td>Time-series; Negative binomial regression</td>
<td>Weekly mean temperature</td>
<td>Hand, foot and mouth disease data from 120 sentinel medical institutions</td>
<td>A significant increase in the risk of paediatric hand, foot and mouth disease was associated with an increase in temperature. The time between the temperature increase and the occurrence of paediatric hand, foot and mouth disease involved lag periods between 0 and 3 weeks</td>
<td>Percent change: 11.2% (95% CI: 3.2% – 19.8%)</td>
<td>Lag effect of weekly temperature was examined by distributed lag non-linear model</td>
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<tr>
<td>Bandyopadhyay et al. 2012</td>
<td>14 Sub-Saharan African countries, 1992-2001</td>
<td>Time-series; Random effect model</td>
<td>Monthly average maximum and minimum temperature</td>
<td>Diarrheal cases from a survey</td>
<td>An increase in monthly average maximum temperature raises the prevalence of diarrheal while an increase in monthly minimum temperature reduces diarrheal illness in children under three year of age</td>
<td>1). Maximum temperature: Coefficient: 1.013 (P&lt;0.01); 2). Minimum temperature: Coefficient: -0.475 (P&lt;0.01);</td>
<td>Monthly temperature was used; 14 African countries were studied</td>
</tr>
</tbody>
</table>
These studies are ordered by the date of publication and the first author.

Both mortality and morbidity were included.

A nurse-led helpline which provides health-related information and advice and directs callers to the appropriate health service or self care.

Maximum daily temperature drop during the period from the day of hospitalization to 3 days prior to hospitalization

Maximum daily temperature rise during the period from the day of hospitalization to 3 days prior to hospitalization

Abbreviations: ARIMA, Autoregressive Integrated Moving Average model; CI, confidence interval; GAM, generalized additive models; GIS, geographic information system; GLM, generalised linear models; NOx, nitrogen oxides; OR, odds ratio; PM$_{2.5}$, particles on the order of ~2.5 micrometers or less; PM$_{10}$, particles on the order of ~10 micrometers or less; RR, relative risk.
Figure 1 The flow chart of literature selection process

1. Potentially relevant studies in the initial searching (n=743)

2. 522 excluded due to irrelevant titles

3. Studies after reviewing the titles (n=221)

4. 176 did not meet inclusion criteria according to abstract

5. Studies retrieved for more detailed evaluation (n=45)

6. 17 articles excluded (12 no appropriate effect estimate; 5 no original data)

7. Studies met inclusion criteria (n=28)

8. 5 articles added by inspecting reference lists

9. Studies included in final review (n=33)