REVIEW

Impact of diurnal temperature range on human health: a systematic review

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Abstract Increasing epidemiological studies have shown that a rapid temperature change within 1 day is an independent risk factor for human health. This paper aimed to systematically review the epidemiological evidence on the relationship between diurnal temperature range (DTR) and human health and to propose future research directions. A literature search was conducted in October 2013 using the databases including PubMed, ScienceDirect, and EBSCO. Empirical studies regarding the relationship between DTR and mortality and morbidity were included. Twenty-five relevant studies were identified, among which, 11 investigated the relationship between DTR and mortality and 14 examined the impact of DTR on morbidity. The majority of existing studies reported that DTR was significantly associated with mortality and morbidity, particularly for cardiovascular and respiratory diseases. Notably, compared with adults, the elderly and children were more vulnerable to DTR effects. However, there were some inconsistencies regarding the susceptible groups, lag time, and threshold of DTR. The impact of DTR on human health may be confounded or modified by season, socioeconomic, and educational status. Further research is needed to further confirm the adverse effects of DTR in different geographical locations; examine the effects of DTR on the health of

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children aged one or under; explore extreme DTR effects on human health; analyze the difference of DTR effects on human health in different locations and the modified effects of potential confounding factors; and develop detailed preventive measures against large DTR, particularly for susceptible groups.

Keywords Climate change . DTR . Morbidity . Mortality

Introduction

Climate change is affecting and will increasingly influence human health (Kjellstrom and McMichael [2013](#page-12-0)). As projected by Intergovernmental Panel on Climate Change (IPCC [2007\)](#page-12-0), global surface average temperature will increase by 1.8– 4.0 °C by the end of this century. The association between increased temperature and adverse health outcomes (e.g., cardiovascular and respiratory diseases) has been extensively studied (Baccini et al. [2008](#page-12-0); Lin et al. [2009;](#page-13-0) Lin et al. [2013;](#page-13-0) Yang et al. [2012](#page-13-0)). In recent years, diurnal temperature range (DTR), another indicator of temperature, has attracted increasing research attention (Lim et al. [2012a](#page-12-0); Wang et al. [2013](#page-13-0); Xu et al. [2013a](#page-13-0)).

Defined as the difference between daily maximum and minimum temperature within 1 day, DTR is an important meteorological indicator associated with urbanization and global climate change and reflects whether the weather was stable or not (Kalnay and Cai [2003](#page-12-0)). In most regions of the world, DTR is decreasing because nocturnal minimum temperatures have risen faster than daytime maximum temperatures in the context of global climate change (Vose et al. [2005;](#page-13-0) Li and Chen [2008;](#page-12-0) Easterling et al. [1997\)](#page-12-0). For example, in central and southeastern Europe (Brazdil et al. [1996\)](#page-12-0), North America (Karl et al. [1993](#page-12-0)), and in central and south Asia (Klein Tank et al. [2006\)](#page-12-0), higher minimum temperature has

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been predicted, suggesting a lower DTR. The urban heat island effect could also contribute to the decreased DTR since increment of the daily minimum temperature was larger than daily maximum temperature (Karl et al. [1988\)](#page-12-0). However, people are still exposed to a long period of relatively large DTR (Xu et al. [2013a](#page-13-0); Lim et al. [2012c\)](#page-13-0). The change of DTR may have adverse effects on human health through its impacts on cardiovascular, nervous, and immunity system (Liang et al. [2008;](#page-12-0) Bull [1980](#page-12-0); Shinkawa et al. [1990](#page-13-0)), thus resulting in the poor ability of accommodating to the wide variations in temperature within 1 day. It has been documented that great DTR could cause the increase in blood pressure, heart rate, and oxygen take (Liang et al. [2008;](#page-12-0) Lim et al. [2012b\)](#page-13-0), then increase cardiovascular workload and induce the occurrence, even death of cardiovascular events (Imai et al. [1998](#page-12-0)). Bull argued that weather change might affect humoral or cellular immunity (Bull [1980](#page-12-0)). In order to examine the impact of DTR on human health, prior studies looking at the DTR effects on human health were mainly conducted in Asia (Luo et al. [2013](#page-13-0); Yang et al. [2013](#page-13-0); Li et al. [2013](#page-12-0); Qiu et al. [2013;](#page-13-0) Kan et al. [2007\)](#page-12-0), Oceania (Xu et al. [2013a](#page-13-0),[b\)](#page-13-0), North America (Vutcovici et al. [2013\)](#page-13-0), and Europe (Holopainen et al. [2013;](#page-12-0) Magalhaes et al. [2011\)](#page-13-0). Majority of the existing studies have reported that DTR is an independent risk factor of mortality (Luo et al. [2013;](#page-13-0) Yang et al. [2013](#page-13-0)) and is significantly associated with the occurrence of both noncommunicable diseases (e.g., cardiovascular and respiratory diseases) and communicable diseases [e.g., diarrhea and hand, foot, and mouth disease (HFMD)] (Xu et al. [2013b;](#page-13-0) Hii et al. [2011\)](#page-12-0).

In recent years, there has been increasing interest in exploring the impact of DTR on human health. However, to date, no review has specifically focused on the relationship between DTR and human health. We conducted a systematic review to assess the DTR effects on mortality and morbidity, identify knowledge gaps in this filed, and make some recommendations for further research directions.

Methods

Data sources

Empirical studies regarding the impact of DTR on mortality and morbidity published up to October 10, 2013 were retrieved using databases PubMed, ScienceDirect, and EBSCO. Titles and abstracts were screened for relevance. In addition, the reference list of each study was inspected to make sure that all relevant papers were included.

Study selection

communication, and letter to the editor, assessed the impact of DTR on human health. People of all ages are the target population of this review. The elderly are defined as humans above 65 years, with adults referring to those aged 19– 64 years, children aged 1–18 years, and infants under 1 year. Our primary search used the following US National Library of Medicine's Medical Subject Headings (MeSH terms) and keywords: "diurnal temperature range," "temperature change," "temperature variation,", "hospital," "hospitalization," "emergency room," "emergency department," "outpatient," "mortality," "death," "morbidity," "incidence." All subterms were included.

Inclusion and exclusion criteria

To clarify the relationship between DTR and mortality and morbidity, studies were included in the present review if they met the following criteria: (1) studies used the original data and appropriate quantitative effect estimates [e.g., odds ratio (OR), relative risk (RR), regression coefficient, percent change in mortality or morbidity]; (2) DTR was a main exposure of interest (e.g., daily DTR, weekly DTR) and mortality or morbidity were also analyzed; and (3) the outcome measure included the noncommunicable diseases (e.g., cardiovascular and respiratory diseases) or communicable diseases (e.g., diarrhea and HFMD). Studies were excluded if they were (1) animal or human experiments, (2) not related to DTR, (3) just focused on DTR change trend, and (4) not assessed the DTR effects on human health. The study design, first author's last name, location, study period, statistical analysis method, target population, main exposure variables, outcomes, key findings, and effect estimates [e.g., OR, RR and confidence intervals (CI)] were manually recorded by two reviewers (C.J. and Z.R.) from the identified studies. The detailed information was presented in Tables [1](#page-2-0) and [2.](#page-4-0)

Results

A total of 406 articles were identified in the initial search. According to the inclusion criteria and exclusion criteria, 25 studies were included in final review (Fig. [1\)](#page-6-0). Among them, 11 investigated the relationship between DTR and mortality, and 14 examined the impact of DTR on morbidity.

Impacts of DTR on mortality

All the studies looking at the impact of DTR on mortality were conducted in cities of Asia, North America, and Europe, including eight in China (Cao et al. [2009;](#page-12-0) Chen et al. [2007;](#page-12-0) Chu et al. [2011](#page-12-0); Kan et al. [2007;](#page-12-0) Luo et al. [2013;](#page-13-0) Song et al.

temperature range, SID sudden infant death, COPD chronic obstructive pulmonary disease

^a These studies are ordered by the date of publication These studies are ordered by the date of publication

relative risk, DTR diurnal temperature range, RTI respiratory tract infections, HF heart failure, COPD chronic obstructive pulmonary disease, ACS acute coronary syndrome, HFMD hand, foot, and mouth Telative risk, DTR diurnal temperature range, RTI respiratory tract infections, HF heat failure, COPD chronic obstructive pulmonary disease, ACS acute coronary syndrome, HFMD hand, foot, and mouth disease ^a These studies are ordered by date of publication ^a These studies are ordered by date of publication

[2008;](#page-13-0) Tam et al. [2009;](#page-13-0) Yang et al. [2013\)](#page-13-0), one in Korea (Lim et al. [2012c](#page-13-0)), one in Canada (Vutcovici et al. [2013\)](#page-13-0), and one in Finland (Holopainen et al. [2013\)](#page-12-0), most of which are highincome countries (Table [1](#page-2-0)). The significant DTR–mortality relationship was found in subtropical cities (Kan et al. [2007](#page-12-0); Luo et al. [2013](#page-13-0); Yang et al. [2013](#page-13-0); Vutcovici et al. [2013\)](#page-13-0) and temperate cities (Lim et al. [2012c](#page-13-0)). In Shanghai, China, Kan et al. [\(2007\)](#page-12-0) have found that total nonaccidential mortality was positively associated with DTR and the DTR effects were significant on both cold days $(\leq 23 \degree C)$ and warm days (≥23 °C). Later, Yang et al. [\(2013\)](#page-13-0) found a significant association between DTR and total mortality in Guangzhou, China, with 1 °C increase in DTR being associated with a 0.47 % increase in total mortality. A multicity study in Korea was conducted by Lim et al. [\(2012c](#page-13-0)) to investigate the DTR effects on deaths. They reported similar result that a 1 °C increase in DTR could result in 0.5 % increase in total mortality. Notably, the DTR effects on percent change of mortality were the greatest in fall, at 0.8 % (95 % CI, 0.5–1.2 %), followed by summer, at 0.6 % (95 % CI, 0.2–1.1 %), among four seasons. In Montreal, Canada, Vutcovici et al. [\(2013\)](#page-13-0) have specifically examined the relationship between DTR and total mortality among the elderly (\geq 65 years) and found a 11.27% increase in daily mortality was associated with an increase in DTR changing from 11.1 to 17.5 °C. Prior studies investigating DTR-related mortality just focused on the effects of high DTR, and whether low DTR, which may be linked with heat waves in summer or cold spells in winter, has marked impact on mortality remains unknown. Recently, Luo et al. [\(2013\)](#page-13-0) have further quantified the effects of extreme DTR on nonaccidential mortality and found that both extreme low DTR (defined as lower than the first percentile of DTR) and extreme high DTR (defined as higher than the 99th percentile of DTR) were significantly associated with total mortality. In addition, extreme low DTR has greater immediate effects than extreme high DTR.

Cardiovascular and respiratory diseases are the leading causes of death among people after exposure to DTR. In Shanghai and Guangzhou, China, Kan and Yang have reported that elevated cardiovascular mortality was significantly associated with DTR, with the percent change in cardiovascular mortality ranging from 0.75 to 1.86 % for per 1 $^{\circ}$ C increase in DTR (Kan et al. [2007](#page-12-0); Yang et al. [2013\)](#page-13-0). Luo et al. [\(2013\)](#page-13-0) found a significant relationship between extreme DTR and mortality from cardiovascular diseases. The extremely low DTR effects were the greatest at lag 0, subsequently declining for the following 2 days, and then rising again, while the extremely high DTR effects were the strongest at lag 0 with a decline for around 10 days, and then an increase till lag 15. With respect to the DTR effects on mortality in the elderly, Tam et al. [\(2009\)](#page-13-0) have investigated the DTR effects on cardiovascular mortality among people aged 65 or older in Hong Kong, China, and found that a 1 °C increase in DTR corresponded to a 1.7 % increase in cardiovascular mortality. The significant association between DTR and cardiovascular mortality among people aged 75 or above was found by Yang and colleagues in Guangzhou, China, with a 1 °C increase in DTR corresponding to a 0.95 % increase in cardiovascular mortality (Yang et al. [2013\)](#page-13-0). To date, limited data are available on the relationship between DTR and

cardiovascular-specific mortality. Only one study conducted by Cao et al. [\(2009\)](#page-12-0) have assessed the association of DTR and daily deaths due to coronary heart disease (CHD). They found that elevated CHD mortality was associated with the increased DTR, and the results were robust using both time-series and case-crossover analyses. A 1 °C increase in DTR corresponded to a 2.46 % increase in CHD mortality in time-series analysis, a 3.21 % increase in unidirectional case-crossover analysis, and a 2.13 % increase in bidirectional case-crossover analysis.

Respiratory mortality is another important health event after exposure to DTR. In Guangzhou, China, Luo and Yang have examined the DTR effects on respiratory mortality (Luo et al. [2013;](#page-13-0) Yang et al. [2013\)](#page-13-0). Significant relationship between elevated respiratory mortality and DTR was reported by Luo et al. [\(2013\)](#page-13-0), with the risk of respiratory mortality increasing by 40 % as DTR increased from 8 to 1.7 °C. However, Yang et al. ([2013](#page-13-0)) have not found any significant increase in respiratory mortality due to the impact of DTR. In Shanghai, China, Song et al. [\(2008](#page-13-0)) have quantified the impact of DTR on deaths from chronic obstructive pulmonary disease (COPD) and found an essentially linear DTR–COPD relationship. Specifically, for cold days $(\leq 22 \degree C)$, and for warm days ($>22 \degree$ C), an increase of 1 \degree C in DTR was associated with a 57 and a 51 % increase in COPD mortality, respectively. However, another study in Shanghai found that there was no significant increase in respiratory mortality in warm days $(>=23 \degree C)$, although the adverse effects of DTR on respiratory mortality were observed in all time (Kan et al. [2007](#page-12-0)). As those studies were conducted in subtropical cities, the potential relationship between DTR and respiratory mortality in other regions, such as in tropical and temperate regions that have different climate change scenarios, remains unknown. Focusing on mortality from chronic cardiovascular or respiratory conditions may be of great importance since these illnesses are especially common in the elderly (Vutcovici et al. [2013\)](#page-13-0).

Some prior studies have also found that DTR was linked with elevated mortality from cerebrovascular-related diseases and some other diseases, such as acute stroke death, sudden infant death (SID) and suicide. According to Luo et al. [\(2013\)](#page-13-0), the change of DTR could significantly increase the cerebrovascular mortality. Chen et al. [\(2007\)](#page-12-0) have examined DTR effects on the acute stroke death and found that DTR was positively associated with daily number of death from stroke. The relationship between DTR and SID was examined by Chu et al. ([2011](#page-12-0)). A 1 $^{\circ}$ C increase in DTR was accompanied with 1.56 % increase in SID, and DTR effect was stronger in cold days $(\leq 21 \degree C)$ than in warm days (>21 °C). Holopainen et al. ([2013](#page-12-0)) have investigated the effects of DTR on suicide in Finland and found that a higher suicide rate each spring could be linked to a higher springtime DTR.

Impacts of DTR on morbidity

Table [2](#page-4-0) presented the studies regarding DTR and causespecific morbidity, including noncommunicable diseases and communicable diseases. Existing studies have shown that DTR had a significant impact on morbidity from various diseases in China (Li et al. [2013](#page-12-0); Qiu et al. [2013](#page-13-0); Wang et al. [2013;](#page-13-0) Chen et al. [2013;](#page-12-0) Ge et al. [2013;](#page-12-0) Liang et al. [2008;](#page-12-0) Ma et al. [2010;](#page-13-0) Liang et al. [2009\)](#page-12-0), Singapore (Hii et al. [2011](#page-12-0)), Australia (Xu et al. [2013a,b](#page-13-0)), Korea (Lim et al. [2012a\)](#page-12-0), Portugal (Magalhaes et al. [2011\)](#page-13-0), and Japan (Shinkawa et al. [1990\)](#page-13-0). The main respiratory diseases affected by DTR include asthma, COPD, and respiratory tract infection (RTI). Sudden temperature change may lead to pathophysiological responses of the respiratory epithelium at a tissue level, such as bronchospasms and inflammatory changes (Graudenz et al. [2006\)](#page-12-0). Xu et al. ([2013a](#page-13-0)) have invested the DTR effects on emergency department admissions for childhood asthma during 2003– 2009 in Brisbane, Australia, and found admissions increased significantly above a DTR of 10 °C among children aged 0– 14 years. They also found that male children and children aged 5–9 years appeared to be more vulnerable to the DTR effect than female children and children of other age groups. Lim et al. [\(2012a](#page-12-0)) have examined DTR effect on hospital admissions for asthma during 2003–2006 in four cities of Korea and found that DTR was significantly associated with hospital admissions for asthma (percent change, 1.1 %; 95 % CI, 0.1–2.0 %). Meanwhile, the elderly (\geq 75 years) were more sensitive to DTR than the non-elderly. In Taiwan, China, Liang et al. [\(2009\)](#page-12-0) have explored the relationship between DTR and COPD admissions and discovered that COPD admissions to the emergency room increased by 14 % with a 3.6 °C increase in DTR. In Shanghai, China, Ge et al. [\(2013](#page-12-0)) have quantified the association between emergency room visits for RTI and DTR, and found an increase of 1 °C in the current day and 2-day moving average DTR corresponded to a 0.94 % and a 2.08 % increase in visits for RTI, respectively. Li et al. ([2013](#page-12-0)) specifically quantified the DTR effects on emergency room visits for RTI among the elderly $(\geq 65$ years) and found that a 1 °C increase in 3-day moving average DTR was associated with 2.07 % increase in visits for RTI.

DTR has also been reported to have significantly association with the increase in cardiovascular diseases. Wang et al. [\(2013\)](#page-13-0) have explored the impact of DTR on emergency room admissions for cardiovascular disease among people aged 65 and older during 2009–2011 in Beijing, China, and found that a 1 °C increase in 3-day moving average DTR was associated with 0.76 % increase in cardiovascular emergency room admissions. Furthermore, people aged 75 years and older were more strongly associated with DTR than those aged 65– 74 years. A multicity study in Korea on risk of hospital admissions for various cardiovascular diseases have found that DTR had great impact on the cardiac failure (percent change, 3.0 %; 95 % CI, 1.4–4.6 %) (Lim et al. [2012a](#page-12-0)). Similarly, in Hong Kong, China, Qiu et al. ([2013](#page-13-0)) have found adverse effects of DTR on heart failure (HF). A 1 °C increase in DTR corresponded to 0.86 % increase in emergency hospital admissions for HF and DTR had greater effects in the cool season (November to April) and on female and elderly patients (≥75 years). Magalhaes et al. [\(2011\)](#page-13-0) have invested the impact of DTR on hospital admissions for stroke stratified by stroke types and severity but did not find any DTR effects on stroke (e.g., ischemic stroke) and nonfetal stroke. However, according to Shinkawa et al. ([1990](#page-13-0)), intradiurnal temperature change was significantly correlated with the occurrence of stroke for men aged 40 years or above. Acute coronary syndrome (ACS) is one of the most common causes of death for patients with cardiovascular disease. In Taichung, China, Liang and coworkers have examined the association between DTR and ACS during 2001–2003 and found the risk of ACS admissions increased by 15 % when DTR ranged from 8.3 to 9.6 °C (reference, DTR=5.8 °C), and 34.4 % when DTR was above 9.6 °C (Liang et al. [2008](#page-12-0)).

Apart from common cardiovascular and respiratory diseases, DTR was also found to be a sensitive temperature indictor for the occurrence of communicable diseases, particular among children. In Brisbane, Australia, Xu et al. [\(2013b\)](#page-13-0) have invested the DTR effects on childhood diarrhea and found that relative risk of childhood diarrhea increased rapidly when DTR was over 10 °C. They also found an acute DTR effect on both male and female patients, with greater DTR effect on male and longer-lasting DTR effect on female. In addition to daily DTR, weekly DTR was also reported to be a potential risk factor for communicable diseases. In Hong Kong, China, Ma et al. ([2010](#page-13-0)) found a significant correlation between weekly DTR and HFMD ($r=0.4$; 95 % CI, 0.2–0.6). Furthermore, Hii and coworkers have examined the relationship between weekly DTR and HFMD in Singapore and found that elevated incidence of HFMD was positively associated with increased DTR, with 1 °C increase in weekly DTR corresponded to 41 % increase in HFMD occurrence (Hii et al. [2011](#page-12-0)). Some other health-related conditions are also associated with DTR. In Taiwan, China; Chen et al. [\(2013](#page-12-0)) have found that the risk of testicular torsion was 1.8 times higher for a DTR >6 °C than that for DTR <6 °C. In Beijing, China, Wang et al. [\(2013\)](#page-13-0) reported a significant association of DTR and digestive and genitourinary diseases among the elderly $(≥ 65 \text{ years})$, with male and people aged 75 years and older represent the higher-risk groups.

Discussion

Our review presented the main research findings in regard to the association of DTR and human health. The majority of existing studies reported the adverse effects of DTR on mortality and morbidity. Cardiovascular and respiratory diseases are the leading health-related events after exposure to DTR. Compared with adults, the elderly and children are more vulnerable to DTR effects. Furthermore, among the elderly, DTR has greater effects on people aged 75 years and older than people aged 65–74 years. DTR also appeared to be more prone to affect the occurrence of communicable diseases among children, such as diarrhea and HFMD. Regarding the effects of DTR on human health in different locations, significant DTR–mortality/morbidity relationship has been found in cities of Asia, Europe, and Oceania, with the increased DTR, the risk of DTR-associated health conditions increased accordingly.

People's vulnerability to DTR might be potentially attributed to the following causes: (1) cardiovascular modality previous studies found that great DTR could cause the increase in heart rate, oxygen uptake, blood pressure (Liang et al. [2008;](#page-12-0) Lim et al. [2012b](#page-13-0)), and thus increase cardiovascular workload (Imai et al. [1998\)](#page-12-0) and induce the occurrence of cardiovascular events; (2) respiratory modality—respiratory defense capability plays a pivotal role in offsetting external environmental hazards. The decrease in temperature of the respiratory epithelium would cause a decrease in the effectiveness of local respiratory defenses, such as mucociliary clearance and leukocyte phagocytosis (Bang [1961](#page-12-0); Diesel et al. [1991](#page-12-0)); also, sudden temperature changes could lead to pathophysiological responses of the respiratory epithelium at a tissue level, such as bronchospasms and inflammatory changes (Graudenz et al. [2006](#page-12-0)), which may trigger the increase in respiratory-related mortality or morbidity after exposure to temperature change; (3) immune modality—Bull [\(1980\)](#page-12-0) argued that weather change might affect humoral or cellular immunity. A human-based study showed that a sudden change in inhaled temperature was associated with the release of inflammatory mediators by mast cells (Togias et al. [1985\)](#page-13-0) and could cause more inflammatory nasal response (Graudenz et al. [2006\)](#page-12-0), which means that people are more likely to be influenced by DTR; (4) nervous modality—DTR could affect the balance of autonomic nervous system (Shinkawa et al. [1990\)](#page-13-0), such as sympathetic nervous system and increase the levels of blood catecholamines and fibrinolytic parameters (Mercer et al. [1999\)](#page-13-0) through the stimulation of the temperature receptors in the skin, which was associated with emergency room admissions for cardiovascular-related diseases (Liang et al. [2008\)](#page-12-0); (5) external object modality— DTR-related health effects might be not directly attributed to temperature variation, but depend partly on the external object modality. For instance, great DTR could be responsible for a dehydration of pollens resulting in a loss in mass, which permit atmospheric dispersion (Crimi et al. [2004\)](#page-12-0), thus enhancing the growth of outdoor allergens. Similarly, increased DTR might also favor the transmission of virus/bacteria attached to the dehydrated items (e.g., dust, pollen). These

will eventually result in the occurrence or aggravation of respiratory-related diseases and even death. Although DTR has marked adverse effects on human health, the heterogeneity still exists among studies in terms of study designs and statistical methods, vulnerable groups, confounding factors, lag time, and threshold of DTR.

Study designs and statistical approaches

A variety of study designs have been used to assess the association between DTR and mortality and morbidity. Time-series or case-crossover study design was mainly used in studies, even both in some articles (Cao et al. [2009;](#page-12-0) Chen et al. [2007](#page-12-0); Lim et al. [2012a](#page-12-0)). Statistical approaches varied with study designs.

Among time-series studies, general additive model (GAM) and distributed lag nonlinear model (DLNM) were commonly used to estimate the DTR effects on human health. Because the counts of daily mortality and morbidity typically follow Poisson distribution and the effects of DTR on health were potential nonlinearity, the core analysis was a GAM with loglink and Poisson error accounted for fluctuations in daily mortality and morbidity. However, Dominici et al. [\(2002\)](#page-12-0) argued that the GAM function may provide incorrect standard errors if a correlation was presented between nonlinear functions. Meanwhile, given the lagged effects of exposure factors on human health, some researchers trended to use a fully parametric model: DLNM in recent years (Yang et al. [2013](#page-13-0); Xu et al. [2013a](#page-13-0)). DLNM is developed on the basis of "crossbasis" function, which can describes simultaneously the nonlinear and delayed effects between predictors and an outcome in time-series data (Gasparrini et al. [2010](#page-12-0)). However, unlike GAM, it may be not appropriate for DLNM to explore the joint effects between environmental exposure factors on human health, such as the interaction of DTR and mean temperature (Yang et al. [2013](#page-13-0)). To date, no studies have been conducted to evaluate which model is optimal for exploring the DTR effects on human health.

Case-crossover design with conditional logistic regression (CLR) has also been widely used (Chu et al. [2011](#page-12-0); Lim et al. [2012a](#page-12-0)[,b](#page-13-0),[c\)](#page-13-0). The case-crossover approach can be regarded as a special type of case control study, in which each case can serves as his (or her) reference in this design. Compared with GAM and DLNM, many kinds of confounding factors, such as individual-level characteristics (e.g., gender, age, and race), can be effectively controlled in case-crossover study. Although the impact of DTR on health may show greater effects and/or wider CI in CLR than in other analyses sometime, such as in GAM (Cao et al. [2009](#page-12-0)) and generalized linear model (GLM) (Lim et al. [2012a\)](#page-12-0), the direction of DTR effects is identical that the risk of mortality increased with the increased DTR. CLR also appears to be more suitable for shortterm study containing a small number of cases (Chu et al. [2011](#page-12-0)). In general, as various statistical methods have its merits and demerits, it is recommended to get an appropriate model according to the characteristics and purpose of research.

Vulnerable population and confounding factors

Generally speaking, the elderly are most susceptible to the adverse impact of DTR, with children representing another high risk group. Compared with the younger population, the elderly have a lower ability to regulate body temperature and an elevated sweating threshold (Kenney and Hodgson [1987\)](#page-12-0). Big DTR may induce the increase in heart rate in the elderly (Lim et al. [2012b](#page-13-0)). Therefore, a rapid change of daily temperature may cause a sudden change in the circulation and heart rate of elderly, which may trigger the occurrence of cardiopulmonary and other diseases, and lead to fatal consequence. Tam et al. ([2009](#page-13-0)) and Kan et al. [\(2007\)](#page-12-0) have reported the significant association between DTR and total mortality and daily cardiovascular mortality among the elderly (≥ 65) . The studies of Yang et al. [\(2013](#page-13-0)) and Lim et al. ([2012a,](#page-12-0)[c](#page-13-0)) have also shown the adverse effects of DTR on total and cardiovascularrelated morbidity (e.g., cardiac failure) among people aged over 75 years. Regarding infants and children, a big DTR may be an additional environmental stress on cardiopulmonary system. For example, a sudden temperature change of inhaled air could result in the release of inflammatory mediators associated with mast cells (Togias et al. [1985\)](#page-13-0) and more inflammatory nasal responses (Graudenz et al. [2006\)](#page-12-0), which might increase cardiopulmonary workload and induce adverse health impact (Chu et al. [2011](#page-12-0)). Chu et al. [\(2011](#page-12-0)) reported that SID was significantly related to the DTR. The study of Xu et al. [\(2013a\)](#page-13-0) has shown that a great DTR was significantly associated elevated emergency room admissions for childhood asthma. However, the adverse effects of DTR on daily mortality for children (0–4 years old) were not found in the study of Kan et al. [\(2007\)](#page-12-0). Most prior studies that found the adverse impact of DTR on mortality and cause-specific morbidity among the elderly and children are conducted in highincome countries, illustrating that these people with less resource are vulnerable to the adverse impact of DTR. More analogous studies are urgently needed to assess the health risks of DTR among children and elderly in developing countries.

Many factors may confound or modify the association between DTR and human health. In order to obtain a better insight into this question, many researchers analyzed the relationship between DTR and health outcomes stratified by gender, season, and educational level, but the results among identified studies are inconsistent. Kan et al. have explored the impact of DTR on mortality during 2001–2004 in Shanghai, China, and found significant adverse effects of DTR in both male and female without a statistically significant difference between two genders (Kan et al. [2007\)](#page-12-0). However, according to Yang et al. [\(2013\)](#page-13-0) and Lim et al. ([2012c](#page-13-0)), women were more sensitive to DTR than men for the cumulative effects of DTR on total and cardiovascular mortality. Ye et al. [\(2012\)](#page-13-0) have pointed out the difference of the temperature effect on morbidity by gender was dependent on location and population and may due to differential growth rates of lung/airway size, along with immunological differences (Becklake and Kauffmann [1999;](#page-12-0) von Mutius [1996](#page-13-0)). In Shanghai and Hong Kong, China, there were greater health impacts of DTR on SID, COPD, and cardiovascular diseases in cold days than hot days (Chu et al. [2011](#page-12-0); Song et al. [2008;](#page-13-0) Tam et al. [2009\)](#page-13-0), whereas no effect modification by season was found on the association between DTR and death from coronary heart disease in Shanghai (Cao et al. [2009\)](#page-12-0). According to previous studies, DTR may present a certain trend (Xu et al. [2013b](#page-13-0); Holopainen et al. [2013\)](#page-12-0), with a greater DTR during a period time in 1 year. In addition, the effects of DTR on health, such as emergency room admissions for cardiovascular, respiratory, digestive, and genitourinary diseases (Wang et al. [2013\)](#page-13-0), were different in four seasons, which indicates the varied mechanism liking the DTR and morbidity. Up to now, the joint effects between DTR and seasons on health were rarely explored and not explicitly. Further investigation should focus on the modified effect of seasons on DTR for mortality and morbidity. Although the effect modification of temperature (e.g., heat wave and mean temperature) by socioeconomic and education level was shown in many studies (Son et al. [2012](#page-13-0); Yu et al. [2010](#page-13-0)), limited data are available on its possible impact on the relationship between DTR and mortality and morbidity. Low education attainment has been regarded as an indicator of low socioeconomic status. There was an average of 2.61 sets of air conditioning installed per household in urban areas and 1.51 in rural areas in Guangzhou in 2011 (Guangzhou Statistic Bureau [2011\)](#page-12-0). Compared with high income families, low income families with poor access to heating or cooling systems may experience higher levels of exposure to temperature change. These people with no or low education have also been reported more susceptible to DTR (Lim et al. [2012c](#page-13-0); Yang et al. [2013](#page-13-0)). When encountering a rapid change of daily temperature, those with low socioeconomic level would suffer more serious impact of DTR. Thus, detailed prevention programs targeting these high risk subgroups for impending large DTR are urgently needed to reduce the impact of DTR on human health.

Previous studies have shown that acute exposure to outdoor air pollution and weather changes was associated with mortality and morbidity. The concentrations of air pollutants, such as particulate matter with aerodynamic diameter $\leq 10 \mu m$ (PM_{10}) and ozone (O_3) , were associated with meteorological conditions in many locations (Cao et al. [2009;](#page-12-0) Xu et al. [2013a\)](#page-13-0). To examine the independent effects of DTR, both single variable model including DTR alone and multiple variable models including covariates (e.g., time trend, temperature, humidity, and air pollutants) were conducted and compared. Most studies have shown that DTR was an independent risk factor for people's health after adjusting for many potential confounding factors. For instance, according to Kan et al. [\(2007\)](#page-12-0) and Chu et al. ([2011\)](#page-12-0), humidity, temperature, PM_{10} , and O_3 did not confound the association between DTR and mortality. However, because some air pollutants, such as O_3 , present significant seasonal changes, with a high concentration in summer and a relatively low concentration in other seasons, it is essential to evaluate the effects of interaction of air pollutions and DTR in a specific season.

Lag time

In healthy individuals, an efficient temperature regulation system enables us to cope with stress from daily temperature variation within certain limits. When DTR exceeds limits, the corresponding symptoms of diseases may occur several days after exposure to DTR. In order to explore the detailed lag effects of DTR on human health, the model used in previous studies examining relationship between lag time of DTR and health events was used in two ways: single days and cumulative days. Various lag days were reported in prior studies, ranging from the same day (lag 0) of exposure (Ge et al. [2013;](#page-12-0) Yang et al. [2013](#page-13-0)) to 27 days (Luo et al. [2013](#page-13-0)), and the results were inconsistent in different studies. In Shanghai and Hong Kong, China, many studies have shown the similar trend for single-day lag effect of DTR on total nonaccidental, cardiovascular mortality, and emergency room visits for RTI (Ge et al. [2013;](#page-12-0) Kan et al. [2007](#page-12-0); Tam et al. [2009](#page-13-0)). However, the DTR effects were found to be the greatest at lag 3 for SID (Chu et al. [2011](#page-12-0)) and lag 5 for COPD death (Song et al. [2008\)](#page-13-0). Most studies also analyzed the DTR effects of cumulative days. For total and cause-specific mortality, the results from different studies were also not identical. For example, for total and cardiovascular mortality, the greatest effects of DTR were found at lag 0–2 (Chen et al. [2007;](#page-12-0) Kan et al. [2007](#page-12-0); Tam et al. [2009\)](#page-13-0), lag 0–3 (Tam et al. [2009](#page-13-0)), and lag 0–4 (Lim et al. [2012c;](#page-13-0) Yang et al. [2013](#page-13-0)). The difference existing in the effect period from exposure to DTR to health events may be partly explained by the potential different biological mechanism caused by DTR. Thus, identifying the maximum effect period for deaths from various disease or occurrence of disease may contribute to the predication of the DTR-related health risk.

Threshold effects of DTR

A nonlinear relationship, such as U-, V-, J-shape patterns, with the minimum mortality at a certain temperature and increased

mortality below and above the threshold, has been presented across different studies between temperature and health events (Lin et al. [2009](#page-13-0); Linares and Diaz [2008](#page-13-0); Baccini et al. [2008\)](#page-12-0). However, the similar relationship between DTR and mortality and morbidity has not been found.

Most of identified studies found a linear relation between DTR and health outcomes, though the relationship patterns may vary by location in different seasons (Lim et al. [2012c\)](#page-13-0). For mortality due to COPD, SID, stroke, cardiovascular, and respiratory diseases and admissions for RTI, the RR increased with the increase in DTR (Cao et al. [2009;](#page-12-0) Chen et al. [2007](#page-12-0); Chu et al. [2011](#page-12-0); Ge et al. [2013](#page-12-0); Kan et al. [2007;](#page-12-0) Song et al. [2008\)](#page-13-0). However, the dose–response curves tend to become flat at DTR levels below 5 °C, and positive nonlinear relationships were found above 5 \degree C (Kan et al. [2007](#page-12-0)). In Brisbane, Australia, Xu et al. ([2013a](#page-13-0)) have found that DTR effect on admissions for childhood asthma increased significantly above a DTR of 10 °C. The existence of nonlinear relationships could be potentially explained by the following reasons. (1) The effects of extremely high or low DTR on health events were stronger than that of moderate DTR (Luo et al. [2013\)](#page-13-0). (2) People's susceptibility may vary in different seasons. During the transitional periods of season, such as from winter to spring, the remaining population was healthier and less susceptible to daily temperature stressors, making the weaker association of health events with DTR (Lim et al. [2012c\)](#page-13-0). (3) The relationship between DTR and causespecific deaths may have different mechanisms. For example, Kan et al. [\(2007\)](#page-12-0) have shown that DTR has significant impact on total nonaccidental and cardiovascular deaths on both warm and cold days, but the relationship was only significant in cold days for respiratory deaths.

Knowledge gaps

The impact of DTR on human health has become an important public health issue, but there are still several knowledge gaps in this domain.

First, most of the identified studies were conducted in Asia, and litter evidence is available for the impact of DTR on human health in other countries, such as in North America (Vutcovici et al. [2013\)](#page-13-0). It is urgent to conduct studies to assess the DTR effects on human health in other regions.

Second, no study has focused on the impact of DTR on cause-specific mortality among children, which may be partly due to the relatively limited death counts among children. Furthermore, many researchers tended to consider children <15 years as a target group. However, few studies have focused on the DTR impact on children aged one or under. According to previous studies, infants (Basu and Ostro [2008\)](#page-12-0) were found to be at higher risk due to their inappropriate thermoregulatory response, and more studies should be conducted to assess their vulnerability to DTR with deep consideration. It would be beneficial to conduct a large-scale study to analyze the relationship between DTR and causespecific mortality for children to develop future adaptation strategies.

Third, limited studies have focused on the extreme DTR (e.g., extremely low DTR and high DTR). Previous studies have shown extremely low and high DTR have greater effects on health than moderate DTR (Luo et al. [2013\)](#page-13-0). Compared with a moderate DTR, people may pay more attention to a high DTR and take some protective measures. According to Luo et al. [\(2013\)](#page-13-0), extremely low DTR had greater effects on all types of mortality than extremely high DTR. As extremely low DTR may be associated with the duration of extreme weather, such as heat waves in summer and cold spells in winter, it could lead to adverse effects on those without much attention on low DTR. Therefore, more analogous studies were urgently warranted to explore the effects of extreme DTR on human health.

Fourth, previous studies have not shown the specific optimum DTR threshold for people in terms of mortality and morbidity. It may be impossible to explore a detailed threshold for people due to different demographic characteristics, weather patterns in different regions, but identifying the specific DTR for various geographic regions, above or below which, the impact of DTR would increase significantly, may be possible and beneficial.

Fifth, the modified effects of season, socioeconomic and educational level on the relationship of DTR and human health still remain unclear. Meanwhile, no studies have focused on the difference of DTR effect between urban areas and rural areas. There is also needed to conduct more studies to analyze DTR effect in different seasons, areas, and socioeconomic and educational level to understand the focuses of intervention.

Finally, no research has predominantly focused on improving people's ability to adapt to temperature change within 1 day, although limited studies have provided some common preventive measures against the adverse impact of a wide DTR, such as offering access to air conditioning or home heating, giving advice on adequate fluid intake in anticipation of a heat wave and on timely clothing for a rapid drop in temperature (Tam et al. [2009](#page-13-0)). How to improve the personal ability under various climate change scenarios to offset the pressure posed by DTR for different susceptible groups would be the further research direction.

Conclusions

Existing body of knowledge suggests a significant relationship between DTR and adverse health outcomes. Cardiovascular- and respiratory-related diseases are the

leading causes affecting human health after exposure to DTR. The elderly are most vulnerable to DTR, with children representing another high-risk group. Further studies should focus on: (1) confirming the adverse effects of DTR on human health in different geographical locations; (2) examining the relationship between DTR and cause-specific mortality and morbidity in children, particular for children aged 1 and under; (3) exploring the extreme DTR effects on human health; (4) identifying the specific DTR for susceptible group in distinct areas; (5) elucidating the modified effects of potential confounding factors; and (6) developing the preventive measures of improving people's ability of adapting to DTR.

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