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What is cold-related mortality? A multi-disciplinary perspective to inform climate change impact assessments

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ABSTRACT

Background: There is a growing discussion regarding the mortality burdens of hot and cold weather and how the balance between these may alter as a result of climate change. Net effects of climate change are often presented, and in some settings these may suggest that reductions in cold-related mortality will outweigh increases in heat-related mortality. However, key to these discussions is that the magnitude of temperature-related mortality is wholly sensitive to the placement of the temperature threshold above or below which effects are modelled. For cold exposure especially, where threshold effects are often ill-defined, choices in threshold placement have varied widely between published studies, even within the same location. Despite this, there is little discussion around appropriate threshold selection and whether reported associations reflect true causal relationships – i.e. whether all deaths occurring below a given temperature threshold can be regarded as cold-related and are therefore likely to decrease as climate warms.

Objectives: Our objectives are to initiate a discussion around the importance of threshold placement and examine evidence for causality across the full range of temperatures used to quantify cold-related mortality. We examine whether understanding causal mechanisms can inform threshold selection, the interpretation of current and future cold-related health burdens and their use in policy formation.

Methods: Using Greater London data as an example, we first illustrate the sensitivity of cold related mortality to threshold selection. Using the Bradford Hill criteria as a framework, we then integrate knowledge and evidence from multiple disciplines and areas- including animal and human physiology, epidemiology, biomarker studies and population level studies. This allows for discussion of several possible direct and indirect causal mechanisms operating across the range of 'cold' temperatures and lag periods used in health impact studies, and whether this in turn can inform appropriate threshold placement.

Results: Evidence from a range of disciplines appears to support a causal relationship for cold across a range of temperatures and lag periods, although there is more consistent evidence for a causal effect at more extreme temperatures. It is plausible that 'direct' mechanisms for cold mortality are likely to occur at lower temperatures and 'indirect' mechanisms (e.g. via increased spread of infection) may occur at milder temperatures.

Conclusions: Separating the effects of 'extreme' and 'moderate' cold (e.g. temperatures between approximately 8–9 °C and 18 °C in the UK) could help the interpretation of studies quoting attributable mortality burdens. However there remains the general dilemma of whether it is better to use a lower cold threshold below which we are more certain of a causal relationship, but at the risk of under-estimating deaths attributable to cold.

1. Introduction

Recently there has been much attention focused on the current and future effects of temperature on health. This has included debate around projected reductions in cold-related mortality burdens due to future climate warming and how these compare to increases in heat related health burdens (Woodward, 2014). Many epidemiological studies have demonstrated an increased risk of death as temperatures drop below a threshold across a number of locations (Bunker et al., 2016; Yu et al., 2012; Gasparrini et al., 2015). Within these studies, however,

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there are two distinct but linked issues which are rarely discussed, but which are integral to results obtained and their interpretation: temperature threshold choice (i.e. how 'cold' is defined) and whether the cold effects summarised in studies are indeed causal across the range of temperatures used to quantify health impacts. These are important issues. Understanding causal mechanisms can help identify downstream policy options and opportunities to prevent 'avoidable' deaths, and the magnitude of mortality burdens attributable to cold is dependent upon the threshold used in calculations. Implicit in any calculation of current or future attributable burden of mortality is that the exposure-response co-efficient used describes a causal relationship. This has particular importance for discussions regarding the extent to which reductions in future cold-related mortality will offset expected increases in mortality associated with hot weather – where impacts tend to be more direct and heat-thresholds better defined.

In this paper we explore these two related issues (and issues which inform these, such as the lagged (delayed) effect of cold on mortality), and, by integrating evidence from other disciplines, we aim to initiate a discussion around how best to interpret results from epidemiological and health impact assessment studies using a variety of cold thresholds. Of note, the metrics used both for cold exposure (e.g. mean temperature, apparent temperature, minimum temperature etc.) and for health outcomes (all-cause mortality vs cause-specific mortality or different causes of morbidity) are complex and vary across studies. For example, there is debate about whether the duration of low temperatures may be important (Barnett et al., 2012) and whether variability is important, both short term (e.g. diurnal variation in temperatures) or long term (e.g. deviation from a long-term average for that location) (Zhang et al., 2018). A wide range of health outcome measures are also used in epidemiological studies (e.g. falls and injuries, healthcare consultations such as hospital or primary care visits, acute respiratory illness in certain population groups etc.) which may have relevance to particular policy decisions but also different thresholds, time to effect and mechanisms of action.

Here, however, we focus on mean temperature as the exposure and all-cause mortality as the outcome metric, primarily because these are frequently used in both epidemiological studies of association between temperature and health outcomes (mortality is generally a more sensitive outcome in epidemiological studies) and in assessments of the potential health effects of temperature changes under climate change scenarios.

We have three main objectives:

1. To highlight some key issues around cold threshold selection – for example, the differences in temperature threshold choices between key London-based studies and the influence of threshold on the cold related mortality burden, using our own London dataset to illustrate this relationship. In doing this, we are not aiming to illustrate cold-mortality relationships for every context (we recognise that the exact relationship between temperature and mortality differs between regions and contexts (Gasparrini et al., 2015)), but aim to provide an illustration as a reference point for the evidence synthesis and discussion that follows.
2. To investigate and integrate evidence for causality across the different temperature ranges and time-periods used in studies using the Bradford Hill considerations (Hill, 1965) as a framework to do this. We appraise the range of evidence which suggests there are different health effects from extreme cold and more moderate cold conditions, with manifold mechanisms and operating over different (non-exclusive) time scales.
3. To discuss whether integrating this evidence from different disciplines can inform appropriate temperature threshold placement and interpretation of results, and to examine the policy and research implications of the preceding discussion. We consider the extent to which cold-related effects are likely to reflect causal mechanisms, and therefore how appropriate their use is in climate change risk assessments.

To address each of these objectives we use a range of different methods, described briefly below and divide our results and discussion into 3 main sections, which in turn address each of these objectives.

2. Methods

2.1. Objective 1

In order to highlight differences in common strategies used for threshold placement, we first summarise studies that analysed the relationship between daily temperature and all-cause mortality using data from Greater London. Given the aim here is not to provide a comprehensive review of the literature on the effects of cold in the UK (which has been done elsewhere (Hajat, 2017)), papers were identified through one database – Ovid Medline and were searched for combining terms for cold/low temperature and mortality. Studies which estimated the relationship between low temperature and all-cause mortality using Greater London data were selected from these, and the temperature threshold below which cold effects were estimated plotted in Fig. 1. Information about the lag period used was also noted (and summarised in Fig. 1).

In order to demonstrate the relationship between temperature and all-cause mortality in Greater London, we used mortality data provided by the Office for National Statistics (ONS). All deaths occurring in England between 1st January 1996 and December 2013 were used. We aggregated data to the Greater London conurbation level, as defined by the ONS Built-up Area codes from the 2011 census (Office for National Statistics (ONS), 2013). We used daily mean temperature (average of the daily maximum and minimum temperatures) between January 1996 and December 2013 as our main exposure variable, obtained from the UK Met Office UKCP09 gridded observation datasets (The Met Office, n.d). This dataset has the advantage of using observations from all available UK temperature stations, interpolated using inverse-distance weighting (using a regression model which includes information on longitude, latitude and importantly for Greater London, urban land use) to provide daily temperatures for 5 km^2 gridded areas.

We used a time series regression framework to analyse the risk of all-cause mortality for each 1 °C temperature decrease below a cold threshold. We controlled for the effect of season and secular trends using a cubic spline function with 7 degrees of freedom per year

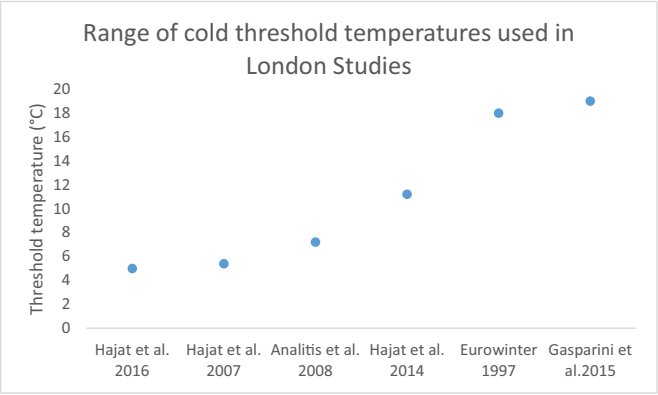

Fig. 1. Range of ambient (outdoor) cold threshold temperatures used in studies of cold related mortality in Greater London (where studies reported the threshold as a percentile of the temperature distribution, this has been converted to degrees Celsius using temperature distributions reported in the study). All studies used daily mean temeprature as the main exposure variable, with the exception of the Analitis et al. study (which used daily minimum apparent temperature). Lag periods for the included studies are as follows: Hajat et al., 2016 – 28 days, Hajat et al., 2007 – 14 days, Analitis et al., 2008 – 15 days, Hajat et al., 2014 – 28 days, Eurowinter, 1997 – 3 days, Gasparrini et al., 2015 – 21 days.

(Bhaskaran et al., 2013) and adjusted the model for over-dispersion, auto-correlation and other time varying factors such as day of the week (flu and air pollution have not been included in the model as their specific roles are addressed in Section 2 of the paper). In order to demonstrate the nature of the relationship between temperature and risk of mortality, we visualised the relationships using natural cubic splines of the temperature function, whilst controlling for time-varying factors and plotted graphs at different time lags.

To assess the impact of a change in threshold on the proportion of deaths attributable to cold, we used a distributed lag (28 days) linear model. We set the threshold at 2° intervals between 2 °C and 18 °C (to include the range of thresholds used in papers reporting the relationship between cold and mortality in Greater London). For any given threshold, the RR each 1 °C drop in temperature below that threshold was estimated. The attributable fraction of cold related deaths over the time period was calculated for each selected threshold. This was done using previously documented methods (Vardoulakis et al., 2014; Hajat et al., 2014). We made use of the specific RR from the time-series model run for each threshold and used this to calculate the risk of mortality for the number of degrees below the cold-threshold on any given day. This was used with the corresponding day's baseline mortality to calculate the cold-attributable deaths and these were totalled over the time period to give the cold-related mortality burden. Therefore changing the cold threshold changes not only the specific RR derived from the time series model, but other key inputs to the attributable mortality calculation – e.g. the number of days over the time period that are below the threshold and the change in temperature below the threshold for any given day.

2.2. Objective 2

In order to integrate information and knowledge from multiple disciplines, we used the Bradford Hill considerations as a framework to evaluate a breadth of evidence that could help determine potential causality. These were first described in 1965, when Sir Bradford Hill described nine useful considerations that can help determine whether an observed relationship is causal: coherence, plausibility, strength of association, consistency, specificity, temporality, biological gradient, experiment and analogy (Hill, 1965). Over time, these have been informally adopted as 'criteria', though Bradford Hill himself didn't intend for them to be used as such – in the original paper they are set out to allow a systematic approach to consider causality based on information and considerations in addition to the statistical measure of association. It has been argued that the considerations differ in relevance depending on context and that a nuanced approach should be taken when using them (Hofler, 2005; Phillips and Goodman, 2004), but also that the framework is still useful as a tool for data integration (Fedak et al., 2015). In this paper, we use the considerations as a framework (as opposed to a set of criteria) to investigate evidence for causality across different temperature ranges and time-periods used in studies, and discuss whether this can inform appropriate threshold placement and interpretation of results. We place more emphasis on the considerations that are most relevant to considering causality and threshold placement in this context.

Relevant literature for this section was located using the Ovid Medline database and combining appropriate search terms for two main concepts – cold (low temperature) and health outcomes (including physiological outcomes and markers along pathways that commonly lead to cardiovascular or respiratory mortality - such as increased blood pressure). We limited our search to English and to studies conducted in humans or mammals (further details available on request).

For both objectives, we have focused on mean temperature and on 'all-cause' mortality as the main exposure and outcome metrics as these are frequently used in epidemiological studies and health impact assessments of climate change. Given the majority of cold-attributable deaths are cardiovascular or respiratory deaths, we primarily consider these when integrating evidence on causality. We limit the analysis and summary of epidemiological studies to Greater London, as the aim is to provide an illustrative example of how temperature thresholds can change between studies even within one limited location, and then to use this as a reference point to interrogate causality. Further, it also removes the complication of differences in thresholds being attributed to differences in susceptibility between populations as a result of adaptation to lower temperatures.

3. Results

3.1. Current approaches to cold threshold selection and the nature of the temperature-mortality relationship

The epidemiologic relationship between ambient (outdoor) temperature and mortality is usually estimated using time–series regression (or case-crossover) analysis. These approaches require certain modelling choices, for example accounting for the length of the possible lagged effects of temperature and selection of heat and cold thresholds above or below which health effects are demonstrated. The V or U-shaped relationship between ambient temperature and daily mortality is usually characterised either by assuming a single value of temperature where mortality risk is lowest – a 'minimum mortality temperature' (MMT), which places a V-relationship constraint upon models - or by using separate thresholds for heat and cold. Typically, the risk of heat related mortality begins at a more clearly defined threshold temperature and at shorter time lags compared to cold-related mortality. The use of a single threshold in MMTs adds a further constraint to models and therefore tends to identify cold thresholds towards the upper end of the temperature distribution (i.e. cold thresholds will be influenced by the heat threshold). The rise mortality risk associated with decreasing temperature occurs more slowly compared to heat-related mortality and with a less obvious inflexion point, resulting in larger variation in threshold identification compared to for heat. The wide range of 'cold' thresholds used between studies is illustrated for papers using UK data in Fig. 1, with cold thresholds or MMTs ranging from the 5th percentile of the overall mean temperature distribution, to as high as the 90th percentile (Gasparrini et al., 2015; Analitis et al., 2008; The Eurowinter Group, 1997; Hajat et al., 2016; Hajat et al., 2007; Hajat et al., 2014) (with the higher thresholds occurring in models using an MMT value).

Fig. 2 illustrates the relationship between ambient temperature and relative risk (RR) of mortality in Greater London from all-causes over the range of (outdoor) year-round daily mean temperatures experienced during 1996–2013 (all-cause mortality) The relationship is shown at lags 0, 2 and 7 days and cumulatively at 28 days.

These data illustrate that in London, the RR of all-cause mortality associated with low temperatures becomes steeper at lags greater than zero. As the lag increases, it appears that the temperature above which cold effects appear generally increases. For example at lag 0 in Fig. 2, the 'cold' threshold (above which the RR of mortality increases) shown on the graph is between 3 and 4 °C, whereas by lag 7 it is around 8 °C. i.e. a plausible hypothesis might be that of an initial cold effect, occurring at lower temperatures and shorter lag periods and an effect which occurs at longer lags and milder temperatures; the longer the lag period, the higher the threshold above which effects occur is seen to be. This raises the question as to whether the choice of threshold selection is also dependent on the lag period considered. We do not address this point in more detail, although studies have previously reported a difference in lag structure between cardiovascular and respiratory deaths (Analitis et al., 2008), with respiratory deaths persisting over longer lag periods.

The variation in thresholds used across studies, as illustrated in Fig. 1, is important. It has an impact on the magnitude of cold-related mortality burdens since this is dependent on the number of days with temperatures below the assumed threshold. This is illustrated for Greater London data in Fig. 3. Given health burden estimations are so

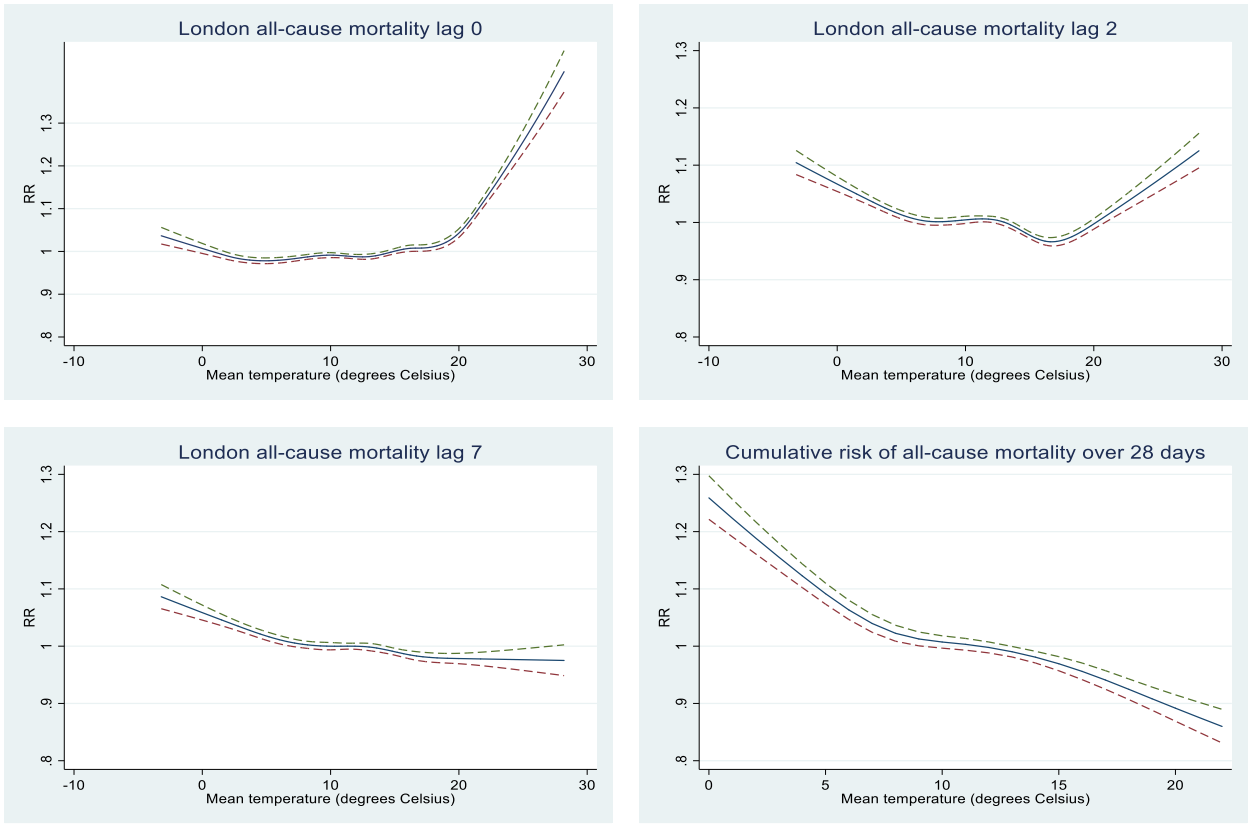

Fig. 2. Relative risk (RR) of temperature related mortality at 0, 2, and 7 day lags and over 28 days for Greater London. The solid lines represent the estimated RR of mortality, and dashed lines the upper and lower confidence intervals.

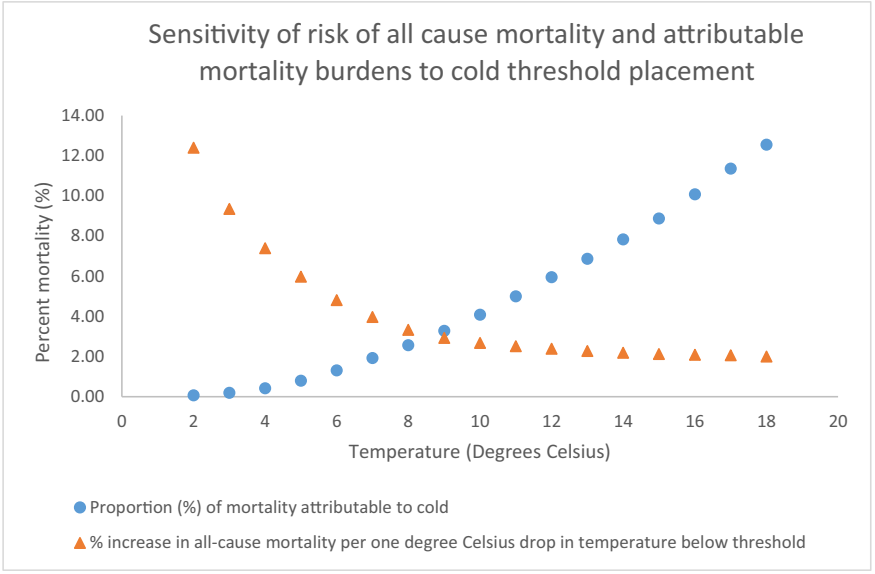

Fig. 3. Attributable fraction (AF) (%) of all-cause mortality and % increase in deaths ((RR − 1) ∗ 100) per one degree Celsius drop in temperature below a given cold threshold. Results are based on time series regression analysis of Greater London data.

highly sensitive to the choice of threshold temperature, it is notable that the rationale for the choice of threshold is often not addressed more fully in publications. Where described, most studies have taken an empirical approach to determining a threshold (e.g. by comparing model deviance). Conceptual arguments about causality are rarely used when considering implications of threshold selection and interpretation of results. Since the proportion of deaths attributable to cold deaths determines the relative importance of cold as a risk factor to health, attributable burdens influence political and economic decisions on how much to invest in policies to reduce cold-related deaths in relation to other public health strategies. Attributable burdens also contribute to the debate in the literature of the importance of climate change on heat and cold-related deaths and the 'net' effect of temperature changes due to climate change (some studies have projected a net increase in overall temperature-related mortality as heat deaths outweigh cold-related deaths under climate change projections, but others have found the

Box 1
Questions arising around cold threshold selection.

Some important questions arising around cold threshold placement:

How should we define a cold effect? And is this the same as where we place a 'cold' threshold?

- Is the effect of cold the same occurring across all temperatures, or are there different causal mechanisms occurring at different temperatures (e.g. 'extreme' and 'moderate' cold). How is this reflected in different choices of threshold placement?
- Why do we define cold thresholds? And should the purpose of the modelling affect threshold choice? E.g. are certain thresholds more useful for policy actions (e.g. defining levels at which to instigate actions or for looking at preventable deaths). Are these the same thresholds as we would use to quantify the impact of cold on mortality? I.e. should we distinguish between epidemiological thresholds and thresholds for action?

Box 2
The Bradford Hill considerations.

Bradford Hill considerations

Originally proposed by Sir Bradford Hill in 1965, these considerations are widely used in the field of epidemiology, to assess the evidence for causality for an observed association between exposure and effect. In brief they are:

- Coherence – between laboratory, physiological and epidemiological studies increases evidence for causality
- Plausibility – a plausible mechanism for the effect of the exposure would increase the evidence for causality
- Strength of association – a stronger association/larger effect of size supports evidence of causality
- Specificity – the more specific the association between exposure and effect, the more likely it is to be causal
- Temporality – the effect must occur after the exposure
- Biological gradient – generally speaking, the greater the exposure, the greater the effect within a population. However this may not always be the case
- Experiment – reversal of exposure leads to reversal of effect
- Analogy – similar factors or exposures cause similar effects

opposite) (Li et al., 2013; Doyon et al., 2008; Martens, 1998; Martin et al., 2012).

The range of cold thresholds we have demonstrated used in studies and the sensitivity of attributable burdens to threshold selection leads to a number of interesting questions (Box 1). For example, to what extent is threshold selection dependent upon regression modelling choices? Are these studies describing the same 'cold' effect or are there different 'cold' effects e.g. of 'moderate' (approximately 9–18 °C) and more 'extreme' (below 9 °C) cold, which may have different causal mechanisms and policy implications? We next explore the latter of these possibilities and examine whether threshold placement should be justified from a causal perspective. We propose that definitions of cold and interpretation of results for use in policy and risk assessments should reflect the different causal mechanisms operating.

3.2. A multi-disciplinary perspective on cold and causation

Before considering evidence of causality across a range of temperatures used as cold thresholds, some consideration should be given to whether the relationship between cold and mortality could be biased or confounded by certain time-varying factors.

There has been discussion as to whether the demonstrated association at longer lags between temperature and mortality is affected by collinearity between season and low temperatures within models (Kinney et al., 2015). This co-linearity is particularly pertinent for cold effects at longer lag periods and does not present an issue for heat estimates where effects are typically estimated at much shorter lags. However, this co-linearity between season and long lag periods would likely mean that cold effects are under-estimated rather than over-estimated. Results using simulated data (Gasparrini, 2016) indicate both distributed lag linear and non-linear models give estimates of mortality with minimal bias even at longer lag periods (models using moving averages, however, were reliable to investigate the temperature-mortality relationship only at shorter lags). This suggests that the cold effect does indeed operate at longer lags although does not help determine whether there are different mechanisms of causality operating at different lag periods.

Stanisic Stojic et al. (2016) have suggested that when controlling for the effect of air pollution (SO_2, NO_2 and soot) in a study in Belgrade, not only was the magnitude of the cold-related mortality risk reduced, but any increased risk between −5 °C (the temperature at which risk increased dramatically) and 20 °C disappeared. However, further analysis is required across different contexts and cities to determine whether this is a generalizable result. Other studies have found effect sizes in London unaltered by inclusion of air pollution in epidemiological models (Hajat et al., 2014). However, regardless of whether the effect estimate is altered by controlling for pollution is the question of where on the causal pathway pollutants lie. The potential complexity of causal pathways for specific pollutants has been discussed elsewhere (Buckley et al., 2014).

One confounder which is often included in epidemiological models, and which may have an impact on the effect of cold on mortality, is influenza. However, its potential role as a confounder again depends on where it lies on the causal pathway (see Section 2.1 for the direct effect of temperature on influenza transmission).

Assuming that the general association between cold and mortality is not due to bias or confounding, we use the Bradford Hill criteria (Box 2) as a framework to integrate evidence from different disciplines, and consider whether this supports a causal relationship across the range of temperatures used in studies of cold and mortality. In the discussion, we explore whether this can be used to inform better description of cold effects and more transparent use of epidemiological evidence to inform policy.

3.2.1. Bradford Hill criteria: plausibility and coherence

At the most extreme, cold exposure can lead to hypothermia. The drop in body temperature has a direct physiological effect on most organs, including inducing bradycardia (due to the effect on cardiac

pacemaker cells) with a resulting reduction in cardiac output and blood pressure (BP) or other cardiac arrhythmias and depression of the central nervous system. However, few deaths associated with low ambient temperatures are caused directly by hypothermia. The majority of cold-attributable deaths are cardiovascular or respiratory deaths. For this reason, we focus on plausible direct and indirect causal mechanisms and coherence between studies that relate to these causes. We consider the criteria of coherence and plausibility together, first for cardiovascular and then for respiratory mortality.

3.2.1.1. Direct and indirect mechanisms for cardio -vascular mortality. There is coherent evidence from a range of disciplines, that cold exposure can lead to an increase in cardiac risk factors (RFs) (Fig. 4).

Animal studies have demonstrated exposure to cold induces hypertension through a variety of mechanisms (Liu et al., 2015; Sun, 2010). These include cold-induced activation of the sympathetic nervous system and renin-angiotensin system in rats (Sun, 2010; Papanek et al., 1991; Fregly et al., 1989; Sun et al., 2002; Sun et al., 2003; Sun et al., 1997; Sun et al., 1995). A decrease in endothelial Nitric Oxide Synthase (eNOS) production (nitric oxide is a vasodilator involved in the regulation of BP and endothelial function) may also play a role in cold- induced hypertension in mice (Wang et al., 2005). These animal studies are typically conducted with cold exposures of 5–7 °C. Of note, one study found that mice exposed to 9 °C did not display the same increase in BP as those exposed to 5 (± 2) °C (Shechtman et al., 1990). However, other studies have found increases in cardiac RFs, including BP at temperatures of around 11 °C in mice (Luo et al., 2012).

Cold exposure has also been shown to result in a significant BP increase in human subjects. This has been demonstrated across a number of study settings and in general, the studies have shown larger increases in BP, the lower the temperature subjects were exposed to (Hintsala et al., 2013; Komulainen et al., 2000; Jevons et al., 2016; Shiue and Shiue, 2014; Leppaluoto et al., 2001; Collins et al., 1985; Inoue et al., 1992). For example, in a randomised controlled study set in Japan, Saeki et al. (Saeki et al., 2013) demonstrated that healthy adults with intensive room heating (to 22 °C), had significantly lower morning systolic and diastolic BP when compared to an experimental group with overnight heating to only 12 °C, and suggested that night-time heating could reduce the incidence of stroke by 25.5% and of mortality (all-cause) in the elderly by 12.4%. In a Scottish cross-sectional study (Shiue and Shiue, 2014), households that were heated to less than 18 °C had increased odds (OR 2.08) of increased blood pressure (compared to those heated to above 18 °C) and in those heated to less than 16 °C the odds of increased BP were higher again (OR 4.92). Leppaluoto et al. (2001) demonstrated that in healthy males exposed to temperatures of 10 °C for 2 h on 11 consecutive days, there was a significant increase in BP and Collins et al. (Collins et al., 1985) found subjects exposed to 4 h of low temperatures (6 °C, 9 °C or 12 °C), experienced significant increases in blood pressure, with the most marked effects with the coldest (6 °C) exposure.

Epidemiological studies have also established that populations have a significantly higher BP in winter months compared to summer (Modesti, 2013). Although this could in part be due to seasonal factors, such as daylight exposure and vitamin D, an increased BP has also been associated with decreased temperatures (after control for seasonal effects) (Modesti, 2013; Halonen et al., 2011a; Li et al., 2016; Madaniyazi et al., 2016; Madsen and Nafstad, 2006; Alpérovitch et al., 2009), though typically this has been seen over a broader range of temperatures than those used in physiological experimental protocols.

Human subjects exposed to low temperatures (5 °C for 3 h) have demonstrated increased activation of norepinephrine release and increase in the relative number of SP1 platelet subtypes (increasing the tendency for blood to clot) (Opper et al., 1995). Increased coagulability, mild inflammation and vasoconstriction have also been demonstrated in humans after exposure to temperatures of 11 °C for an hour, but not at pathological levels (Mercer et al., 1999). Again, these results from physiological experiments are largely supported by epidemiological biomarker studies in human populations (Schneider et al., 2008; Halonen et al., 2011b). For example, Wu et al. grouped biomarkers to represent mechanistic pathways ('indices') of systemic inflammation (e.g. coagulation, systemic oxidative stress etc.) and found an inverse association between the biomarker indices and decreasing temperature (Wu et al., 2017).

Some specific risks of cold exposure in animals have been demonstrated. Rats with reno-vascular hypertension exposed to 4 °C for 3 days were shown to have increased rates of cerebral infarction or haemorrhagic stroke (Li et al., 2014), likely linked to release of important neuro-transmitters. Cold is also known to induce cardiac hypertrophy (Liu et al., 2015; Sun, 2010; Roufai et al., 2007).

Cardiovascular events may also be brought about by a number of indirect mechanisms and events may be precipitated by preceding infection (Estabragh and Mamas, 2013; Warren-Gash and Udell, 2017; Barnes et al., 2015; Corrales-Medina et al., 2013; Smeeth et al., 2004; Wang et al., 2017). For instance, Meier et al. found an increased risk of acute myocardial infarction (AMI) in subjects with a preceding acute respiratory tract infection 10 days before (Meier et al., 1998). Plausible mechanisms for this include a number of pro-inflammatory, pro-coagulant and haemodynamic effects induced by infections, which may lead to cardiac complications. For example, increased concentrations of C reactive protein (CRP) are associated with increased risk of AMI (Kuller et al., 1996; Ridker et al., 2000)) and the systemic inflammation associated with an acute respiratory tract infection (or directly as a result of cold exposure) can result in altered endothelial function or be

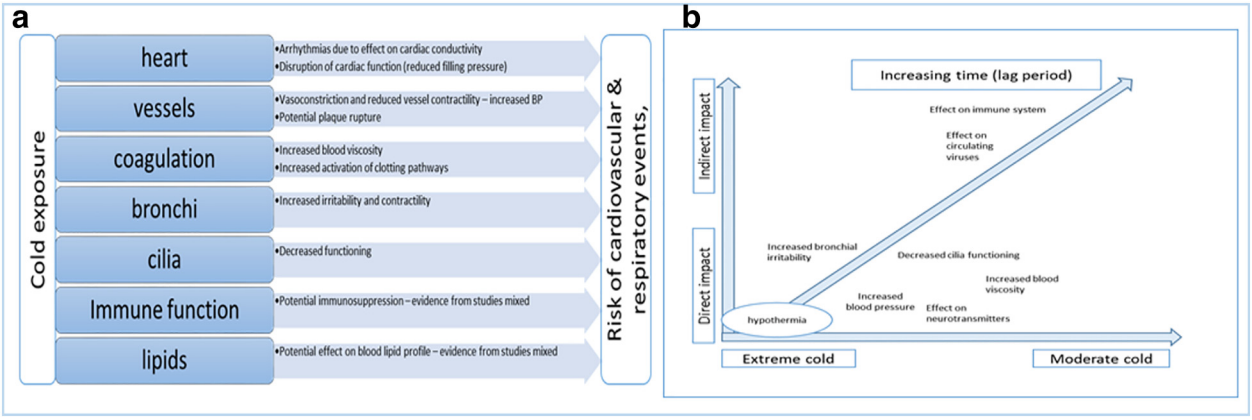

Fig. 4. a) (left) summary of coherent and plausible mechanisms for cold related cardiovascular and respiratory mortality b) (right) plausible time frames and temperatures over which these effects may occur.

associated with plaque rupture (Vallance et al., 1997). Cardiovascular events may also be triggered by indirect behavioural mechanisms, such as reduced mobility (e.g. brought about by people being less mobile in the cold, or being unwilling to move outside heated areas of homes) which can lead to deep vein thrombosis and pulmonary embolisms.

3.2.1.2. Direct and indirect mechanisms for respiratory mortality. The direct and indirect mechanisms by which cold causes an increase in respiratory mortality have not been widely discussed in the epidemiological literature and a number of plausible mechanisms exist (Fig. 4).

Facial cooling of −5 to −20 °C has been shown to reduce Forced Expiratory Volume (FEV1 – a measure of lung function) in healthy humans and those with asthma or chronic obstructive pulmonary disease (COPD) (Gavhed et al., 2000; Koskela and Tukiainen, 1995; Koskela, 2007; Koskela et al., 1996). However, the effects of breathing cold air in healthy subjects (and in animal experiments) on lung function have been mixed, with some demonstrating a positive relationship between inhalation of cold air and bronchoconstriction and others not (Koskela, 2007). In people with asthma, cold air can trigger bronchoconstriction (Deal Jr et al., 1980; Koskela et al., 1997; Nielsen and Bisgaard, 2005). Further studies have indicated the presence of cold sensitive channels in lung epithelium, that when activated (below 18 °C) increase pro-inflammatory (IL-6, IL-8) cytokine secretion (Sabnis et al., 2008). Release of these cytokines may contribute to the pathogenesis of cold-induced asthma. These findings are coherent with population based studies that have demonstrated exacerbation of symptoms in those with COPD and asthma when temperatures decrease (Tseng et al., 2013; Guo et al., 2012; Huang et al., 2015; Donaldson et al., 1999).

Studies at a population level that have examined the association between respiratory tract infections and temperatures have also demonstrated an increased risk of upper and lower respiratory tract infection with decreasing temperature (Mäkinen et al., 2009; Hajat et al., 2004). This is likely to be due to a multitude of factors, such as the effect of cold on the immune system and on pathogen transmission and reproduction within the host, and infections that follow cold-induced bronchoconstriction.

For example, decreasing temperature may result in a direct reduction on cilia motility and mucociliary clearance (and hence reduction in clearance of pathogens from the nasal passages) (Mwimbi et al., 2003). An effect of cold on the immune system (which may in turn affect mortality from respiratory and other infections) has also been demonstrated in some physiological experiments, though this has not been a consistent finding across all studies (Castellani et al., 2002).

Respiratory infection, however, also depends on exposure and rate of transmission of infective agents and their capacity to cause disease within the host. There is evidence that certain viruses (EBV, parainfluenza) persist within humans for longer in cold conditions (Mourtzoukou and Falagas, 2007). In guinea pigs, both viral shredding and transmission of influenza were increased at 5 °C compared to 20 °C (Lowen et al., 2007). Pneumococcal transmission between humans is increased in cold and dry conditions (Numminen et al., 2015) and rhinovirus replication is increased within mouse hosts at lower temperatures (Foxman et al., 2015). Further, within cold seasons, some populations may spend more time within confined spaces, which may also increase the chance of pathogen spread. This hypothesised increased exposure risk is likely to happen at any range of temperatures below which populations spend more time indoors – i.e. in the 'more moderate' temperature range.

3.2.2. Bradford Hill criteria: specificity and consistency.

Whilst the Bradford Hill criteria include specificity of effect for a given exposure, it could be argued that this is less relevant for direct temperature effects - ultimately all biological processes are affected by temperature. However, we have demonstrated that there are specific mechanistic effects of cold temperatures on the cardiac, respiratory and immune system. Some of the indirect mechanisms by which cold affects mortality (e.g. though increased respiratory illness) may also cause deaths at longer lags. Some indirect causes of mortality may also occur at milder temperatures. There is some evidence of this in population-based studies (Analitis et al., 2008), where respiratory deaths occur at longer lag periods. Cardiovascular effects could plausibly occur at short or more prolonged time frames – a quick increase in cardiac risk factors (e.g. BP, arrhythmia) may be enough to trigger a fatal cardiac event. It could be hypothesised that more extreme cold temperatures have severe enough short-term physiological effects to trigger an event. However, cardiac events could also occur due to a cumulative/prolonged effect of raised BP or at longer time periods due to the effect of inflammation or infection.

Even though the exact nature of the temperature-mortality relationship changes by location, in almost all settings and populations there is an increase in the risk of mortality below a given temperature (Gasparrini et al., 2015). Consistent findings observed in different places with different samples strengthen the evidence for a common physiological pathway, especially at lower temperatures. However, commenting on consistency as support for causality across the full range of 'cold' temperatures used is complex. The different thresholds or MMTs demonstrated between locations are often interpreted as evidence that populations differ in their susceptibility to cold and may be 'adapted' to different temperatures through a variety of mechanisms. These adaptations may range from behavioural mechanisms, to more societal level mechanisms such as the existence of public health messaging for colder weather (Public Health England, 2016), improved insulation and housing design. However, a difference in thresholds between locations may also be due, in part, to different indirect causal mechanisms between locations. For example one would expect the physiological mechanisms underlying increased mortality to remain largely consistent between locations, but that mortality related to circulating pathogens (such as influenza etc.) for example, may vary from location to location due to differences in endemic diseases which may respond differently to temperature. Another possibility is that the more consistent effects at very low temperatures are causal, but the difference in the pattern of effects at 'more moderate cold' temperatures are due to differences in confounding structures or modifying factors such as the proportion of vulnerable individuals (e.g. older adults, those with underlying co-morbidities) and behavioural differences between locations. For example, there is evidence that older populations are less able to tolerate cold and therefore may experience physiological effects at less extreme temperatures.

Generally consistent, however, is that a greater increase in risk occurs in most (but not all) locations below a lower threshold than the 'optimum' temperature (where this has been demonstrated in studies) or that the increase in mortality follows a 'double' threshold pattern, with an obvious additional upturn in risk at very low temperatures (in some settings). Consistent too is that there is a longer lag period for the mortality risk associated with cold than for heat. These two observations may support evidence that there are both direct physiological impacts of cold which occur at lower temperatures occurring across all locations (and which can occur at both short and longer time lags) and indirect (both as a result of infections and the delayed effects of immobility) affects occurring at longer lags.

3.2.3. Bradford Hill criteria: experiment, effect size and gradient, temporality and analogy

Given the multiple pathways of potential causality and variety of ways in which populations can be exposed to cold (e.g. through short exposure to decreased ambient temperatures outside or through exposure within adequately heated or insulated homes), interventions to reduce exposure to cold or its effect are varied and complex in nature.

However, a number of studies have examined the effect of interventions (in particular in the area of improved energy efficiency of

housing) to reduce cold exposure on health outcomes and these have been systematically reviewed (National Institute for Health and Care Excellence (NICE), 2014; Thomson et al., 2009).

One review found some evidence that housing interventions to improve thermal comfort (e.g. through heating, insulation, fuel poverty interventions) improve a variety of respiratory and mental health outcomes in study populations (Thomson et al., 2009). More specifically, a randomised control study investigated the effect of intensive room heating (compared to 'weak room heating') on ambulatory BP. Systolic morning BP and sleep-trough morning BP surges were significantly reduced in the intensive heating group (Saeki et al., 2013). This corroborates evidence from animal studies that one of the potential mechanisms for cardiovascular effects of cold exposure is its effect on BP. Whilst mortality is rarely an outcome in studies of this kind (due to rarity of the end point), there is evidence that respiratory morbidity can be reduced by interventions to improve housing, though the pathways through which interventions improve outcome may be multifactorial (e.g. could be a direct effect of increasing temperature or related to humidity, changes in indoor air quality or mould growth etc.) Evaluations of the effect of a telephone alert system using meteorological reports to communicate times of increased risk to patients with COPD ("Healthy Outlook") produced mixed results. Some concluded it reduced hospital admissions (Sarran et al., 2014) or mortality (Steventon et al., 2014) and some that admissions and GP visits were either unaffected or increased with the scheme (Steventon et al., 2014; Maheswaran et al., 2010; Bakerly et al., 2011). One pilot randomised controlled study examined the effect of providing thermal clothing to vulnerable groups of patients over the age of 50 (Barnett et al., 2013). However, the study was too small to determine whether the intervention was of benefit.

In some settings, the effect size at more extreme ends of the temperature distribution is observed to be larger than at more mild temperatures (Gasparrini et al., 2015), lending more support to causal mechanisms at lower temperatures. Studies in animals have also shown increased effects on cardiac risk factors with increasing intensity of cold exposure (Luo et al., 2014).

Lastly we consider temporality and analogy. In epidemiological studies of the effect of cold exposure on mortality, the criterion of temporality is easily fulfilled - reverse causality between cold temperatures and mortality cannot feasibly exist. Lagged effects of cold exposure are also seen, as previously discussed.

Analogy seems less applicable to cold exposure, compared to other environmental exposures and is not likely to be helpful in determining causation or in considering threshold choice.

4. Discussion

4.1. Can using evidence from different disciplines help in the placement of cold thresholds?

We have demonstrated the range of temperature thresholds used in studies of cold – mortality effects in Greater London, the sensitivity of attributable burdens to threshold selection, and examined evidence for a causal relationship between cold and mortality. An important question is whether the physiological and experimental evidence supports threshold temperature choices for cold-related mortality (Fig. 5) and how it can aid interpretation of evidence from epidemiological studies. Most of the experimental evidence of the direct effect of cold is from animal studies, and the exposure used is between 4 and 7 °C. This may support a lower threshold, but only if thermoregulation and body temperatures in rats and mice is deemed to be similar to humans. Some experiments in humans have used a more 'moderate' cold exposure (above 11–18 °C) – for example, one study demonstrated increases in BP in houses heated below 18 °C (Shiue and Shiue, 2014), but the majority of studies showed that effects were largest at lower temperatures, for example with exposures to indoor temperatures below 12 °C. The paucity of experiments performed at more moderate cold temperatures (taken here to mean up to 18 °C, or the 'optimum/minimum mortality' temperature used in some studies) in humans and animals does not mean that physiological effects do not occur at higher temperatures – it may just reflect experimental protocols.

It is plausible that indirect mechanisms, operating through infective pathways (Fig. 4b), may start at higher temperatures depending on how air temperature affects droplet survival and behaviour related to

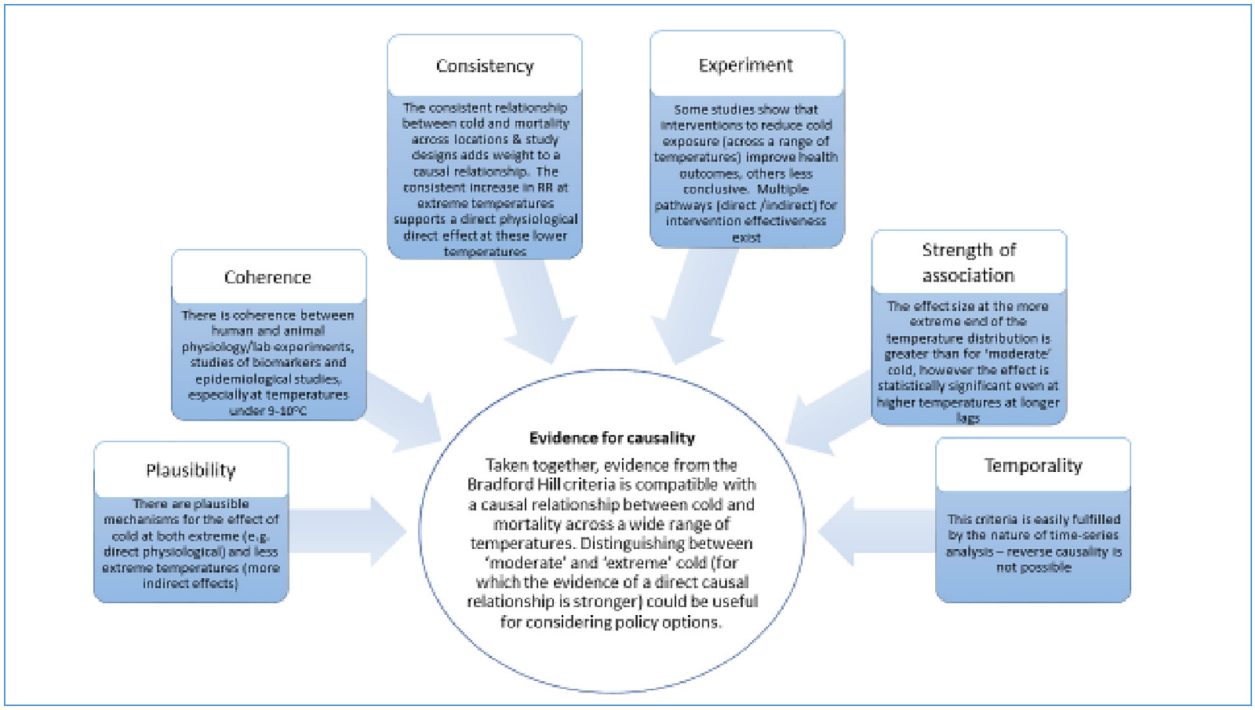

Fig. 5. Use of the Bradford Hill criteria as a framework to summarise evidence for a causal relationship across the range of low temperatures used in studies of cold related mortality.

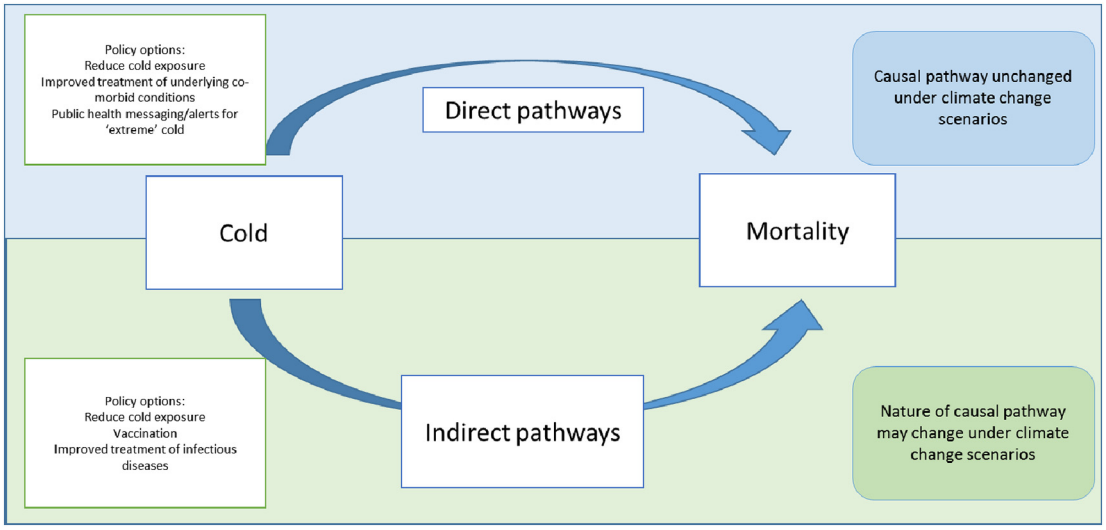

Fig. 6. Direct and indirect pathways of cold related mortality.

transmission (time spent indoors and contact with others etc.). Some indirect effects of cold due to behaviour change (e.g. reduced activity and staying in one (heated) room, increasing the risk of DVTs for example, may occur across a range of temperatures depending on affordability of heating and quality of housing stock.

One further complicating factor is that the thresholds set in epidemiological studies are usually related to outdoor air temperatures. In reality, the temperatures that populations are exposed to will vary with the amount of time spent indoors and access to heating etc. There is evidence across the UK that heating of homes is variable and depends on a number of factors (Tod et al., 2012) and also that in some settings indoor and outdoor temperatures are poorly correlated at cooler temperatures (Nguyen et al., 2014; Vadodaria et al., 2014). However, there is a paucity of studies which examine the correlation between indoor and outdoor temperatures and more work in this area would be welcomed.

4.2. Relevance to risk assessment and policy setting and conclusions

In order for attributable mortality fractions of 'cold' deaths to be valid, the underlying association between cold temperatures and mortality must be causal. Evidence from a range of disciplines appears to support a causal relationship across a range of temperatures and lag periods, although evidence is more consistent for a causal effect at lower temperatures. It is also plausible that 'direct' mechanisms for cold mortality are likely to occur at lower temperatures and 'indirect' mechanisms (e.g. via increased spread of infection) may occur at milder temperatures.

This is important when thinking about policy and future adaptation (Fig. 6). For example, if a substantive proportion deaths are attributable to moderately cold temperatures (Gasparrini et al., 2015) then alongside policies which focus on keeping active, keeping warm and reducing exposure to extremely low temperatures, policies which include reduced disease transmission (such as vaccination programmes, public health campaigns about reducing influenza spread) are also important to consider. This could be achieved by a mixture of policies including improvement of housing and affordability of heating, by activating emergency responses such as those in Public Health England's cold weather plan at relevant cold thresholds (Public Health England, 2016) and by policies which reduce infectious disease transmission. Understanding the causal mechanisms behind cold related mortality also highlights the importance of general management of risk factors for cardiac and respiratory disease within the population; improvement here may substantially reduce cold related mortality. For policy purposes it is not realistic to issue cold warnings or have policies for ambient daily mean temperatures as mild as say 18 °C (similar to 'minimum mortality temperature used in some studies). For example, Public Health England's cold weather plan (Public Health England, 2016) advocates background prevention policies are in place year-round with winter preparedness measures between November and March but more focused public health messaging and alerts are only triggered when temperatures drop below 2 °C for a period of 48 h.

Care must be taken when using epidemiological baseline estimates for projections of mortality under different climate scenarios - the validity of future estimates relies upon assumptions that the causal relationship will remain. This seems valid for mortality attributable to direct physiological mechanisms (though population adaptation to temperature extremes may negate some of this effect). However, where indirect infectious mechanisms lead to an increase in mortality, the assumption that these pathways do not change in the future is harder to justify – circulating pathogens and infections may change. Separating the effects of 'extreme' and 'moderate' cold in any given setting, may help better describe these effects and make interpreting results of studies quoting attributable mortality burdens easier. The increased evidence for causality at more extreme or increasingly cold temperatures does raise the dilemma of whether it is better to use a lower threshold (e.g. in London below 8–9 °C) to estimate cold related mortality burdens, below which we are more certain of a causal relationship, but at the risk of under-estimating deaths attributable to cold. We conclude that as a minimum, the choice of threshold be justified in this type of research, and that where appropriate (e.g. in cases where an MMT is used or where there appears to be distinct increase in risk at lower temperatures and a smaller risk at more moderate temperatures) attributable burdens are given separately for extreme cold in addition to 'moderate' or the overall cold effect. This would enable those using the research to take a more nuanced and critical approach to using the results informed by likely causal mechanisms, and for policy makers to better determine future risks of temperature to health and appropriate policy actions.

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Competing Financial Interests Declaration

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

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