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Key Words: Temperature, heat, mortality, epidemiology, cities, climate

How urban characteristics affect vulnerability to heat and cold: a multi-country analysis

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Abstract

Background

The health burden associated with temperature is expected to increase due to a warming climate. Populations living in cities are likely to be particularly at risk, but the role of urban characteristics in modifying the direct effects of temperature on health is still unclear. In this contribution, we used a multi-country dataset to study effect modification of temperature-mortality relationships by a range of city-specific indicators.

Methods

We collected ambient temperature and mortality daily time-series data for 340 cities in 22 countries, in periods between 1985 and 2014. Standardized measures of demographic, socioeconomic, infrastructural, and environmental indicators were derived from the Organisation for Economic Co-operation and Development (OECD) Regional and Metropolitan Database. We used distributed lag non-linear and multivariate meta-regression models to estimate fractions of mortality attributable to heat and cold (AF%) in each city, and to evaluate the effect modification of each indicator across cities.

Results

Heat and cold-related deaths amounted to 0.54% (95%CI: 0.49% to 0.58%) and 6.05% (5.59% to 6.36%) of total deaths, respectively. Several city indicators modify the effect of heat, with a higher mortality impact associated with increases in population density, fine particles ($PM_{2.5}$), gross domestic product (GDP), and Gini index (a measure of income inequality); while higher levels of green spaces was linked with a decreased effect of heat.

Conclusions

This represents the largest study to date assessing effect modification of temperature-mortality relationships. Evidence from this study can inform public health interventions and urban planning under various climate change and urban development scenarios.

Keywords

Temperature, heat, mortality, epidemiology, cities, climate

Key messages

1. Urban populations may experience higher risks due to exposure to non-optimal temperature, particularly in a changing climate, but the role of urban characteristics in modifying such direct health effects is still unclear.
2. This represents the largest study to date assessing effect modification of temperature-mortality relationships, performed by comparing different cities across the world and using standardized indicators.
3. The effects of heat on mortality is higher in cities characterised by a higher level of inequalities, higher air pollution exposure, lower green spaces, and lower availability of health services.
4. Evidence from this study can inform public health interventions and urban planning under various climate change and urban development scenarios.

Introduction

Several studies have evaluated the relationship between ambient temperature and mortality, consistently reporting increased risks at high and low temperatures [1-3]. These risks are associated with a substantial health burden across populations living in different parts of the world, indicating that exposure to non-optimal temperature represents an important global contributor to excess mortality [1-3]. The situation is not likely to improve in the context of climate change, as the health burden associated with non-optimal temperature is projected to increase in a warming planet [4]. In addition, scenarios of socioeconomic pathways suggest that future susceptibility is likely to increase with ageing population, rapid urbanisation and growing inequalities [5].

Populations living in cities are particularly vulnerable to non-optimal temperature. The structure of urban areas could enhance temperature-related health risks through a combination of higher exposures (e.g., urban heat island effect) and higher vulnerability (e.g., population density and socio-economic differentials) [6, 7]. Evidence of this excess health burden, particularly during extreme events as in Chicago in 1995, Paris in 2003, and Moscow in 2010, have motivated the development of public health measures to reduce preventable mortality and morbidity (e.g Heat Health Watch Warning System). Several Heat Health Watch Warning System (also called heat warning systems" (HWSs) or "heat health warning systems" (HHWS)) have been implemented in several countries (e.g. USA, Italy, Germany, France, Spain, Portugal, UK, Australia, Canada, South Korea, and China), some of which attempt to target potentially vulnerable groups in urban communities[8, 9]. In this context, identifying aspects that modify the susceptibility to the impacts of non-optimal temperatures can help improve health protection programs and contribute to the development of city-level mitigation and adaptation strategies, including urban planning and design.

A number of studies have contribute to this topic, investigating potential effect modifiers of temperature-mortality associations. In particular, some studies have adopted ecological study designs to assess community-level factors, such as urbanisation, amount of green areas or vegetative covering [10-19]. However, most of the published studies included homogeneous populations, and only a few compared regions with different geographic and climatic conditions, and populations with highly variable socio-economic and demographic characteristics.

In this study, we used data from the Multi-City Multi-Country (MCC) collaborative network (http://mccstudy.lshtm.ac.uk/) to evaluate the role of cities' characteristics in modifying susceptibility to high and low temperatures. The MCC database includes time series data for hundreds of cities in 22 countries, and provides a unique opportunity to compare health effects across highly heterogeneous populations. Specifically, we linked the MCC data with standardized measures of contextual factors at the city level, and analysed their effect modification for mortality risks associated with both heat and cold.

Materials and Methods

MCC data

The analysis is restricted to 340 cities or metropolitan areas (from now on generally referred to as cities) available in the MCC dataset, distributed across 22 countries. For each location, the dataset comprises time series of daily mean temperature and mortality counts for all causes or non-external causes only (International Classification of Diseases – ICD-9: 0-799; ICD-10: A00-R99) in largely overlapping periods ranging from 1st of January 1985 to 31st December 2014. The full list of cities, together with additional information, can be found in Supplementary Material A and B.

Indicators

OECD Regional and Metropolitan database

We collected data on several city-specific socio-economic indicators and urban development from the Organisation for Economic Co-operation and Development (OECD) Regional and Metropolitan database[20, 21]. The OECD Regional Database provides a set of comparable statistics and indicators on about 2,000 regions, and 281 OECD metropolitan areas in 34 OECD member countries and other economies (http://stats.oecd.org/Index.aspx). They include yearly time series, from 2000 to 2014, for around 40 indicators of demography, economic, labour market, social, environmental and innovation themes. Details on the regional and metropolitan OECD database can be found in a specific OECD publication[22]. OECD follows a strict Quality Framework for Statistical Activities [23]. The OECD quality framework define two dimensions: the quality of national statistics OECD receives and the quality of OECD internal processes for collection, processing, analysis and dissemination of data and metadata. OECD statistics have a high reputation for quality and integrity throughout the world and we are confident that the data we used have a high level of accuracy.

First, 136 cities in the MCC database were linked with the OECD Metropolitan Database at the metropolitan area (MA) level. In addition, all 340 MCC cities were linked with the OECD Regional database both at small regions (SR) and large regions (LR) geographical levels. The former represents provinces or prefectures, the latter administrative regions or small states [20]. In total, a set of 14 indicators were selected from OECD Regional and Metropolitan Databases. These indicators encompass demographic, socioeconomic, health system and urban characteristics (Table 1). For each indicator, we used the data collected at the smallest geographical level available, using the value measured in a single year or averaged across multiple years in order to minimize the amount of missing data. The definition of each OECD indicator considered in this analysis is provided in Table 1.

[Table 1 here]

The set of indicators related to urbanisation (e.g. urbanised area, green area, concentration of population in the core, Sprawl index) is available for 136 MCC cities that are in the OECD metropolitan area (MA) database. A subset of socioeconomic indicators (e.g. Gini index, educational level) is available for OECD country members, but not for OECD country partners (e.g. China, Brazil, Colombia, Iran, Moldova, Philippines, Viet Nam). Other indicators (e.g. GDP, % population ≥ 65 years, Unemployment rate) were available also among some OECD country partners (Brazil, China, Colombia). For each indicator the list of countries with available information is reported in the Supplementary Table 1.

Air pollution indicators

To characterise long-term air pollution exposures in each city, we used global estimates of annual fine particulate ($PM_{2.5}$) levels of the Data Integration Model for Air Quality (DIMAQ) available for year 2014[24], and global annual mean ground-level nitrogen dioxide (NO_2) concentrations (3-years running mean for year 2001), developed by Geddes and colleagues [25]. Both global estimates were calculated for grid cells with a spatial resolution of 0.1° for latitude and longitude.

We linked the 340 MCC cities with the databases containing the $PM_{2.5}$ and the NO_2 global estimates. Specifically, for each city we assigned the $PM_{2.5}$ and NO_2 level of the grid cell (spatial resolution (0.1° × 0.1°), which is approximately 11km x 11km at the equator) including the coordinates of the city as defined by the World Cities database (https://simplemaps.com/data/world-cities) [26].

Population and density data

The World Cities database was used to retrieve population and density indicators for year 2015. The former is an estimate of the city's population, while the latter is defined as population per square kilometre.

Weather variables

For each city, we calculated the average daily mean temperature and daily mean temperature range from the observed daily temperature distribution in the MCC dataset, in the city-specific observation period (between 1985 and 2014). These were used as basic indicators to avoid confounding by weather/climatological conditions.

Statistical methods

Description of the indicators

We summarise distribution of indicators by country with the median, standard deviation and interquartile range. The relationships between indicators were examined first through the correlation matrix among all pairs of indicators. To remove the between-countries effects from the correlation, for all cities of a given country, the original indicator value was scaled by the country average indicator value. The country-adjusted correlation matrix was used as input of a principal component analysis (PCA). The PCA is a statistical method that identify factors (principal component) that best explain the co-variability of the data. The principal components show groups of indicators that co-vary similarly in most cities, as can be illustrated in a score plot.

Association between the indicators and temperature-mortality impacts

We adopted a three-step approach to evaluate the association between the indicators and temperature-mortality impacts. Briefly, in the first-stage we calculated the city-specific temperature-mortality associations, followed by the estimation of the corresponding heat and cold attributable fractions, and in the last step we fitted meta-regression models to evaluate the association between each indicator and heat and cold AF%. The three steps are described in more details below.

First-stage time series analysis

We estimated the city-specific temperature-mortality associations through quasi-Poisson regression [27] and distributed lags non-linear models (DLNMs) [28]. We modelled the cross-basis function of daily mean temperature with a natural cubic spline function for the temperature dimension with 3 internal knots at the 10th, 75th and 90th percentile of the city area-specific temperature distributions, and natural cubic spline with an intercept and 2 internal knots placed in equally-spaced values in the log scale for the lag dimension. We extended the lag period to 21 days to capture the long delay in cold-mortality associations. We included a natural cubic B-spline function with 8 degrees of freedom (df) per year to control for long-term trends and seasonality, along with an indicator for day of the week. The model selection was based on previous work using a similar dataset [3]. We tested these modelling choices in a sensitivity analysis.

Estimation of city specific heat and cold attributable fraction

To estimate the city-specific temperature at which mortality was minimal (called minimum mortality temperature, MMT) with greater precision, we applied a shrinkage procedure that borrows information across cities in the same country with similar climate. Details of this method are given in previous work [3]. We estimated attributable fractions (AF%, in percentage) using the first-stage (unshrunk) cumulative exposure-response associations, following a procedure described elsewhere [29]. In summary, we computed mortality attributable to cold and heat by summing the temperature-related deaths occurring in days with temperatures lower or higher than the MMT, and then dividing by the total number of deaths. We calculated empirical standard error (SE) using Monte Carlo simulations [29], assuming a multivariate normal distribution of the first-stage reduced coefficients.

Association between the indicators and heat and cold attributable fraction

We estimated whether the city-specific estimated temperature-mortality associations differed by city characteristics. For each indicator we used the set of cities with available information, and two separate meta-regression models were used to evaluate the association between the indicator and heat and cold AF% including indicators for countries, and average and range of daily mean temperature as meta-predictors. We tested and reported residual heterogeneity using the Cochran Q test and I^2 statistic, respectively [30].

Results

Description of the sample

Descriptive statistics of mortality and temperature data are reported in Table 2. Almost 50 million deaths were observed in the study period. The 340 cities are located in 22 countries, 13 of which, according to the International Monetary Fund, are developed countries while 9 are developing countries (Table 2). Figure 1 shows the geographical distribution of the 340 cities and their average daily mean temperature, illustrating how this study covers various regions and climatic areas across the world.

[Table 2 here]

[Figure 1 here]

Descriptive statistics of the 18 indicators considered in the analysis are shown in Table 3. Cities considered in this analysis show highly variable socio-economic, demographic, urban characteristics, and air pollution levels.

[Table 3 here]

Weather variables, country and attributable mortality

Overall, we estimated that 0.54% (95%CI: 0.49% to 0.58%) and 6.05% (5.59% to 6.36%) of mortality in the 340 MCC cities were attributable to heat and cold, respectively (Supplementary Table 2). Larger between-city heterogeneity was observed for heat AF% (I^2=85.4%) than for cold AF% (64.2%). Country explained 15.7% and 10.9% of heterogeneity for heat AF% and cold AF%, respectively. In total, weather variables explained a further 22% of cold AF% heterogeneity, while heat AF% heterogeneity decreased by only 2.3%.

Demographic, socio-economic, environmental and urban indicators and attributable mortality

Associations between the indicators and heat and cold-related AF% are reported in Figure 2 and Supplementary Table 3. Results are expressed as AF% variation for a SD increase of the indicator (provided in Table 3). No indicator is associated with cold-related AF. For heat, among demographic indicators, high life expectancy and high population density predicted high AF. Regarding the socio-economic indicators, GDP and educational level were positively associated with heat-related AF%. An inverse association was observed between number of hospital beds pro-capita and heat-related AF%. Cities with more inequalities (higher Gini index) had a larger mortality impact attributable to heat. Among the urban and environmental indicators considered, cities surrounded by a predominantly rural region and those with a larger green surface showed lower heat-related AF%, while $PM_{2.5}$ was positively associated with heat AF%.

[Figure 2 here]

To give some insight on the inter-relationship between indicators and their association with attributable mortality, we performed a principal component analysis. Supplementary Figures S1 and S2 show the correlation matrix and the results of the analysis. The first two principal components explained 44.4% of the total inertia. The first component seems characterised by the economic development of the MCC cities: high positive loading scores (represented by arrows) were observed for GDP, educational level and life expectancy. All these three variables showed a positive association with heat-related AF%. The second component characterised cities with higher level of air pollution ($PM_{2.5}$ and NO_2), unemployment rate, inequalities (Gini index), poverty gap, population and density. $PM_{2.5}$, Gini index and density were all positively associated with heat-related AF%.

Discussion

This study is based on the largest dataset ever collected to assess city-level modifiers of the temperature–health associations, which include more than 50 million deaths in 22 countries. The analysis allows investigating the heterogeneity of temperature-attributable mortality across 340 cities with a wide range of demographic, socioeconomic, and urban characteristics. Strengths of the study are the use of a standardised set of indicators, as well as the application of flexible statistical methods. Our findings suggest that more developed cities are perhaps surprisingly characterized by higher mortality attributable to heat, as indicated by the significant association with GDP, life expectancy and educational level. Furthermore, a second pattern emerged, with higher impact of heat on mortality in cities characterised by high population density, inequalities, and pollution, levels and less green spaces.

Cities have been centres of innovation and growth and the engines of economic development, but they are particularly vulnerable to the effects of climate change [6, 31, 32]. The nature of urban infrastructure creates microclimates that affect temperature; the urban heat island effect is an example, where cities are warmer than their surrounding hinterlands due to the thermal storage capacity of the built environment [33]. In our results, urban density is associated with an increased heat effect, which is also shown in other contextual studies [5, 14, 19].

We used the OECD regional typology to characterise the region surrounding the urban setting considered in the analysis. This indicator is based on population density, degree of rurality and size of the urban centres located within the region. This indicators allows to identify 63 cities in predominately rural regions (mainly based in US and Spain), and 84 in intermediate (both rural and urban regions) more evenly distributed across countries. These cities show a lower heat effect, a result that could be explained by a lower urban heat island effect, and that is consistent with increased heat effect observed for urban density.

Additional factors contribute to the vulnerability of cities. Among those of particular relevance are demographic structure, low socioeconomic status and social inequity. In our study, we found a positive association between the Gini index of the city's region (an indicator of inequality) and heat impact. This result is consistent with those observed in contextual [10, 11, 19, 34] and individual studies [35] showing a higher heat effect on communities or subjects with lower socio-economic status. Poorer housing condition, lower prevalence of air conditioning, poorer health status, and limited access to health care has been suggested as factor responsible for the increased heat effect in more deprived communities [10, 11, 19]. Elderly are more sensitive to non-optimal temperatures due to their higher prevalence of debilitating diseases, such as heart conditions, Alzheimer's disease and dementia [36], that are associated with an increased effect of temperature on mortality [19]. In our study, we did not observe evidence of an association between proportion of people aged more than 65 years and heat (or cold) attributable fraction. These results could be partially explained by the limited range of variation in age distributions across areas within the same country, as shown in our study, where the IQR range of the country-centered proportion aged more than 65 years was (-1.8%; 1.1%) on average within countries. Moreover the proportion of elderly population is higher in less urbanized and dense cities (+2.5% (+1.5%; +3.5%)). Limited range of the exposure, and possible confounding effect of urbanisation could have limited in our study the power to detect the modifier role of age on heat effect. We also note that our data are community-level, and that future work with individual-level data is more suited to investigate these issues.

Urbanisation is part of the development process and is generally associated with higher income, education and productivity level [33]; this relationship is shown in our study with a positive correlation (r=0.33) between GDP and city density. At the individual level, higher income and education have been associated with lower heat related mortality [35] due to higher quality of housing, and better access to information. In our study, however, heat-related impacts are higher in cities with a higher economic development characterised by a higher GDP, productivity, educational level, and life expectancy. Using GDP as an indicator Anderson and Bell [10] observed a similar positive contextual association in 107 US urban communities, while Hajat and colleagues [37] found a negative association with GDP when meta-regressing heat coefficients across studies internationally. No association was observed at a contextual level in three other studies [13, 34, 38]. The increased impacts of heat on cities with higher GDP, educational level and life expectancy are not necessarily due to those cities being more unequal, as the correlation of those indicators with GINI are low. One explanation might be an association between economic development with features of urbanisation such as the urban heat island, but further studies, including individual-level socio-economic indicators, are needed to clarify this.

The vulnerability of cities to climate change has motivated the development of city-level adaptation measures [6, 39], among which urban planning and design including for instance cooling by greening and ventilation. Several studies have evaluated the modification effect of urban landscape characteristics on temperature-mortality association [40-49]. They used different neighbour-level indicators related to urban land use and land cover (e.g. impervious surface, open space, vegetation abundance), with some evidence of a protective effect of vegetation to reduce the heat effect on mortality [41, 44, 49]. These results are consistent with the negative association between green areas and heat AF% observed in our multi-city study.

Air pollution is also a well-known public health risk factor. Fine particles (PM_{10}, $PM_{2.5}$), ozone, nitrogen dioxide, and sulphur dioxide have been linked with increases in morbidity and mortality [50]. There has been an increasing interest on the synergist effect of temperature and pollution on morbidity and mortality[51, 52]. Suggested mechanisms under the synergy hypothesis are, among others, that episodes of air pollution can increase vulnerability to the effects of temperature (e.g. respiratory diseases) and that elderly population with deficiency of thermoregulation might suffer from high pollution levels[53]. The synergistic effect of pollutants and temperature have been studied mostly using case-only or time-series studies, with some evidence of increased effect of PM at higher temperature[51, 52]. In our study, we found a tendency of a higher AF% for heat in cities with higher level of pollution as measured by $PM_{2.5}$ and NO_2; Benmarhnia and colleagues [11] found a similar contextual association between NO_2 and heat effect in Paris. These results need to take into account possible ecological confounding, as in our dataset the chronic level of pollutant exanimated ($PM_{2.5}$.and NO_2) is correlated with the city population and density, and share with these urban density indicators the tendency to increase the measured heat AF%.

Few studies have evaluated the role of healthcare access to reduce the temperature-related mortality [13, 34, 37]. Our finding of reduced heat AF in cities with more hospital beds provides some evidence that an increased level of health services is an important component of adaptive capacity in an urban context.

Few studies have evaluated the role of area-level indicators as modifiers of cold-effects on mortality with inconsistent results[10, 12-14, 19, 54]. In our analysis climate variables explain 22% of the heterogeneity suggesting for cold-related effects a greater role of acclimatization. Moreover more complex mechanisms for cold-related effects have been described [55] that may not be well captured by our set of indicators. Further research is needed in this area, possibly increasing the number of cities or the set of indicators, or with addition data such as individual-level data.

This study has several advantages. It represents the first investigation in which modifiers to both cold and heat-effect at the city level were simultaneously assessed in a wide multi-country setting through a common study design and statistical framework. Previous multi-country studies [34, 35, 37, 38] relied on simplifications of the exposure-response function [34, 37, 38], or qualitatively reviewed the evidence [35]. The statistical framework used in this analysis is based on a two-stage design that incorporates DLNMs and multivariate meta-regression to flexibly characterize complex temperature–health dependencies at a local level and to investigate their variations across cities [56]. We used the OECD Regional and Metropolitan Database as a source for defining socio-demographic indicators at city level. This choice ensures a set of indicators collected using standardised criteria. We must also acknowledge some limitations. The observational period, and data collection procedures are not uniform across all countries. Logistical constraints hinder perfectly consistent data streams across the globe as different countries have various protocols for data acquisition and maintenance. However, our study design is not sensitive to potential biases arising from these differences, and can appropriately pool information from data obtained from different sources. Specifically, our two-stage analytical framework includes indicators for countries as meta-predictors in the second-stage meta-regression. This means that implicitly the comparison is based on variations across locations within the same country, as any structural difference across countries is accounted for by the fixed-effects indicators. These differences include potential variations due to non-overlapping periods. The time frame of data collection varied for some variables, and the reference period used for indicators varied between 2000 and 2014. Moreover some of the indicators were measured after the actual city-specific time period of investigation. As a consequence there could be some measurement errors on the level of the indicator associated to each city for the observational period. Under the hypothesis of no systematic bias within a country this measurements error should lower the association under study toward a conservative error. However, we found a high correlation between indices at different years (data not shown), consequently this conservative error should be minor. The dataset includes several regions around the world, including developed and developing countries, but entire areas of the world are not covered, and there is a lack of information from countries with a lower degree of socioeconomic development. Results might therefore not be globally representative. In our analysis we considered each indicator as an explanatory variable in a meta-regression model adjusted by country and weather variables. We did not attempt a multivariable model, as many indicators exhibited collinearity, as shown in the principal component analysis. Although, it is an interesting research area we did not plan sub-group analyses by climate zones or geographical regions. Further work increasing the number of locations, hopefully including developing countries, are needed to address this research question.

In conclusion, this study identifies several city characteristics that modify the vulnerability of urban populations to heat. These results can be used for determining health burden projected in the future under specific climate change and socio-demographic scenarios, and for the implementation of urban development plans to mitigate the risk.

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Bibliography

1. Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. *Environmental Health* 2009; **8**: 40.
2. Basu R, Samet JM. Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence. *Epidemiologic reviews* 2002; **24**: 190-202.
3. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015; **386**: 369-75.
4. Gasparrini A, Guo Y, Sera F, et al. Projections of temperature-related excess mortality under climate change scenarios. *The Lancet Planetary Health*; **1**: e360-e7.
5. Hajat S, O'Connor M, Kosatsky T. Health effects of hot weather: from awareness of risk factors to effective health protection. *The Lancet* 2010; **375**: 856-63.
6. Carter JG, Cavan G, Connelly A, Guy S, Handley J, Kazmierczak A. Climate change and the city: Building capacity for urban adaptation. *Progress in Planning* 2015; **95**: 1-66.
7. van den Bosch M, Sang ÅO. Urban natural environments as nature-based solutions for improved public health–A systematic review of reviews. *Environmental Research* 2017; **158**: 373-84.
8. Kalkstein LS, Sheridan SC, Kalkstein AJ. Heat/health warning systems: development, implementation, and intervention activities. *Biometeorology for adaptation to climate variability and change*: Springer; 2009. p. 33-48.
9. Toloo G, FitzGerald G, Aitken P, Verrall K, Tong S. Evaluating the effectiveness of heat warning systems: systematic review of epidemiological evidence. *Int J Public Health* 2013; **58**: 667-81.
10. Anderson BG, Bell ML. Weather-related mortality: how heat, cold, and heat waves affect mortality in the United States. *Epidemiology* 2009; **20**: 205.
11. Benmarhnia T, Oulhote Y, Petit C, et al. Chronic air pollution and social deprivation as modifiers of the association between high temperature and daily mortality. *Environmental Health* 2014; **13**: 53.
12. Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA. Temperature and mortality in 11 cities of the eastern United States. *Am J Epidemiol* 2002; **155**: 80-7.
13. Huang Z, Lin H, Liu Y, et al. Individual-level and community-level effect modifiers of the temperature-mortality relationship in 66 Chinese communities. *BMJ Open* 2015; **5**: e009172.
14. Medina-Ramon M, Schwartz J. Temperature, temperature extremes, and mortality: a study of acclimatisation and effect modification in 50 US cities. *Occup Environ Med* 2007; **64**: 827-33.
15. Medina-Ramon M, Zanobetti A, Cavanagh DP, Schwartz J. Extreme temperatures and mortality: assessing effect modification by personal characteristics and specific cause of death in a multi-city case-only analysis. *Environ Health Perspect* 2006; **114**: 1331-6.
16. O'Neill MS, Zanobetti A, Schwartz J. Modifiers of the temperature and mortality association in seven US cities. *Am J Epidemiol* 2003; **157**: 1074-82.
17. Stafoggia M, Forastiere F, Agostini D, et al. Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis. *Epidemiology* 2006; **17**: 315-23.
18. Yu W, Vaneckova P, Mengersen K, Pan X, Tong S. Is the association between temperature and mortality modified by age, gender and socio-economic status? *The Science of the total environment* 2010; **408**: 3513-8.
19. Zanobetti A, O'Neill MS, Gronlund CJ, Schwartz JD. Susceptibility to mortality in weather extremes: effect modification by personal and small-area characteristics. *Epidemiology* 2013; **24**: 809-19.
20. OECD. *Regional Statistics (database).*
21. OECD. Metropolitan areas. 2013.
22. OECD. Regions at a Glance 2016. OECD Publishing: Paris; 2016.

23. OECD. *Quality framework and guidelines for OECD statistical activities*: OECD; 2011.
24. Shaddick G, Thomas ML, Green A, et al. Data integration model for air quality: a hierarchical approach to the global estimation of exposures to ambient air pollution. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 2018; **67**: 231-53.
25. Geddes JA, Martin RV, Boys BL, van Donkelaar A. Long-term trends worldwide in ambient NO2 concentrations inferred from satellite observations. *Environmental health perspectives* 2016; **124**: 281.
26. SImplemaps. *World Cities Database*.
27. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *International journal of epidemiology* 2013; **42**: 1187-95.
28. Gasparrini A. Modeling exposure–lag–response associations with distributed lag non-linear models. *Statistics in medicine* 2014; **33**: 881-99.
29. Gasparrini A, Leone M. Attributable risk from distributed lag models. *BMC medical research methodology* 2014; **14**: 55.
30. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002; **21**: 1539-58.
31. Habitat U. Cities and climate change: Global report on human settlements 2011. *London: Earthscan* 2011.
32. Schauser I, Otto S, Schneiderbauer S, et al. Urban Regions: Vulnerabilities, Vulnerability Assessments by Indicators and Adaptation Options for Climate Change Impacts. *European Topic Centre on Air and Climate Change (ETC/ACC): Bilthoven* 2010.
33. Kamal-Chaoui L, Robert A. Competitive cities and climate change. *OECD Regional Development Working Papers* 2009; **2009**: 1.
34. Leone M, D'Ippoliti D, De Sario M, et al. A time series study on the effects of heat on mortality and evaluation of heterogeneity into European and Eastern-Southern Mediterranean cities: results of EU CIRCE project. *Environmental Health* 2013; **12**: 55.
35. Romero-Lankao P, Qin H, Dickinson K. Urban vulnerability to temperature-related hazards: A meta-analysis and meta-knowledge approach. *Global Environmental Change* 2012; **22**: 670-83.
36. Feigin V. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *The lancet* 2016; **388**: 1459-544.
37. Hajat S, Kosatky T. Heat-related mortality: a review and exploration of heterogeneity. *Journal of Epidemiology & Community Health* 2010; **64**: 753-60.
38. McMichael AJ, Wilkinson P, Kovats RS, et al. International study of temperature, heat and urban mortality: the 'ISOTHURM' project. *Int J Epidemiol* 2008; **37**: 1121-31.
39. Georgi B, Swart R, Marinova N, Van Hove B, Jacobs C, Klostermann J. *Urban adaptation to climate change in Europe: Challenges and opportunities for cities together with supportive national and European policies*: EEA; 2012. Report No.: 929213308X.
40. Eisenman DP, Wilhalme H, Tseng CH, et al. Heat Death Associations with the built environment, social vulnerability and their interactions with rising temperature. *Health & place* 2016; **41**: 89-99.
41. Harlan SL, Brazel AJ, Prashad L, Stefanov WL, Larsen L. Neighborhood microclimates and vulnerability to heat stress. *Soc Sci Med* 2006; **63**: 2847-63.
42. Harlan SL, Declet-Barreto JH, Stefanov WL, Petitti DB. Neighborhood effects on heat deaths: social and environmental predictors of vulnerability in Maricopa County, Arizona. *Environ Health Perspect* 2013; **121**: 197-204.
43. Klein Rosenthal J, Kinney PL, Metzger KB. Intra-urban vulnerability to heat-related mortality in New York City, 1997-2006. *Health & place* 2014; **30**: 45-60.
44. Madrigano J, Ito K, Johnson S, Kinney PL, Matte T. A Case-Only Study of Vulnerability to Heat Wave-Related Mortality in New York City (2000-2011). *Environ Health Perspect* 2015; **123**: 672-8.

45. Rey G, Fouillet A, Bessemoulin P, et al. Heat exposure and socio-economic vulnerability as synergistic factors in heat-wave-related mortality. *European journal of epidemiology* 2009; **24**: 495-502.
46. Smoyer KE, Rainham DG, Hewko JN. Heat-stress-related mortality in five cities in Southern Ontario: 1980-1996. *Int J Biometeorol* 2000; **44**: 190-7.
47. Tan J, Zheng Y, Tang X, et al. The urban heat island and its impact on heat waves and human health in Shanghai. *Int J Biometeorol* 2010; **54**: 75-84.
48. Uejio CK, Wilhelmi OV, Golden JS, Mills DM, Gulino SP, Samenow JP. Intra-urban societal vulnerability to extreme heat: the role of heat exposure and the built environment, socioeconomics, and neighborhood stability. *Health & place* 2011; **17**: 498-507.
49. Xu Y, Dadvand P, Barrera-Gomez J, et al. Differences on the effect of heat waves on mortality by sociodemographic and urban landscape characteristics. *Journal of epidemiology and community health* 2013; **67**: 519-25.
50. WHO. *Review of evidence on health aspects of air pollution - REVIHAAP Project: Technical Report*. Copenhagen; 2013.
51. Analitis A, De' Donato F, Scortichini M, et al. Synergistic Effects of Ambient Temperature and Air Pollution on Health in Europe: Results from the PHASE Project. *Int J Environ Res Public Health* 2018; **15**.
52. Chen F, Fan Z, Qiao Z, et al. Does temperature modify the effect of PM10 on mortality? A systematic review and meta-analysis. *Environmental pollution (Barking, Essex : 1987)* 2017; **224**: 326-35.
53. Lam CKC. Air Pollution, Heat and Mortality in Urban Populations. *Reinvention: an International Journal of Undergraduate Research* 2014; **7**.
54. Hajat S, Kovats RS, Lachowycz K. Heat-related and cold-related deaths in England and Wales: who is at risk? *Occupational and environmental medicine* 2007; **64**: 93-100.
55. Kinney PL, Schwartz J, Pascal M, et al. Winter season mortality: will climate warming bring benefits? *Environmental Research Letters* 2015; **10**: 064016.
56. Gasparrini A, Armstrong B, Kenward M. Multivariate meta-analysis for non-linear and other multi-parameter associations. *Statistics in medicine* 2012; **31**: 3821-39.

Table 1. OECD Regional and Metropolitan database indicators included in the analysis: definition, years and geographical level of observation.

Indicator	Definition	Years	MA[1]	SR[2]	LR[3]
Demographic					
% population ≥65 years	% old population (65 years or more)	2000	136	147	37
Life Expectancy (years)	Life expectancy at birth (years)	2005-2006; 2010-2011			288
Socioeconomic					
GDP (US$)	GDP per capita (US$) (current prices, current PPP)	2001; 2010	136	59	130
Labour productivity (US$)	Labour productivity (GVA per worker) (current prices, current PPP)	2005; 2009-2010			280
Educational level (%)	Share of labour force with at least secondary level education	2000			265
Unemployment rate (%)	Unemployment rate (%)	2001; 2010	136	130	41
Gini index	Gini (disposable income, after taxes and transfers); high index means high inequality	2009-2014			280
Poverty gap	Poverty rate after taxes and transfers; the poverty line reflects 60% of the national median income	2009-2014			280
Health system					
Hospital bed rates	Hospital bed rates (hospital beds per 10 000 population)	2008-2010			279
Urban characteristics					
Type of surrounding region (rural/urban)	The OECD regional typology is based on the following criteria: Population density, degree of rurality and size of the urban centres located within a region: Predominantly Urban = 1 Intermediate = 2 Predominantly Rural = 3 Predominantly Rural close to a city = 4 Predominantly Rural remote = 5	2000		272	
Urbanised area share (%)	Urbanised area share (%): Share of the urbanised area over total land of a metropolitan area	2000-2001; 2006	136		

Green Area (square meters per million person)	Land in the metropolitan area covered by vegetation, forest and parks in 2000 (source: MODIS MCD12Q1), divided by the population of the metropolitan area and then multiplied by million.	2000	136		
Concentration of population in the core (%)	Share of population living in the core areas over the total metropolitan population.	2000	136		
Sprawl	The sprawl index measures the growth (over the period 2000-06 and 2000-12, except Japan [1997-2006] and USA [2001-06 and 2001-11]) in built-up area adjusted for the growth in city population.	2006	100		

[1]MA = City/Metropolitan area
[2]SR = Small region
[3]LR = Large region

Table 2. MCC dataset. Number of cities, deaths, period of observation, and mean daily average temperature by Country.

Country	Cities	Level of development*	Deaths	Period	Daily average temperature (Celsius degree) Mean [Range]
Australia	3	Advanced economy	1 177 950	1988-2009	18.1 [5.6; 35]
Brazil	18	Developing economy	3 401 136	1997-2011	24.6 [3.6; 33.5]
Canada	26	Advanced economy	2 989 901	1986-2011	6.8 [-39.7; 32.1]
Chile	4	Developing economy	325 462	2004-2014	13.7 [-1.7; 27.5]
China	15	Developing economy	950 130	1996-2008	15.1 [-23.7; 36.4]
Colombia	5	Developing economy	956 539	1998-2013	23.4 [10.5; 31.1]
Finland	1	Advanced economy	130 325	1994-2011	6.2 [-22.9; 25.5]
France	18	Advanced economy	1 197 555	2000-2010	12.6 [-11.6; 32.4]
Iran	1	Developing economy	121 585	2004-2013	16.0 [-14.7; 33.3]
Italy	16	Advanced economy	645 420	2001-2010	15.7 [-10.7; 39.5]
Japan	7	Advanced economy	3 123 487	1985-2009	15.0 [-12.0; 33.1]
Mexico	10	Developing economy	2 980 086	1998-2014	18.8 [0.4; 35.3]
Moldova	4	Developing economy	59 906	2001-2010	10.7 [-25.0; 32.6]
Philippines	4	Developing economy	274 516	2006-2010	28.2 [21.8; 33.3]
South Korea	7	Advanced economy	1 726 938	1992-2010	13.7 [-15.7; 33.0]
Spain	51	Advanced economy	3 479 881	1990-2010	15.5 [-10.9; 36.8]
Sweden	1	Advanced economy	201 197	1990-2010	7.2 [-21.5; 26.8]
Switzerland	8	Advanced economy	243 638	1995-2013	10.4 [-14.9; 29]
Taiwan	3	Advanced economy	765 893	1994-2007	24.0 [8.1; 33.0]
UK	1	Advanced economy	1 325 902	1990-2012	11.6 [-5.5; 29.1]
USA	135	Advanced economy	22 953 896	1985-2006	14.9 [-31.4; 41.4]
Vietnam	2	Developing economy	108 173	2009-2013	27.1 [14.4; 33.9]

*International Monetary Fund Advanced and Developing Economies List. World Economic Outlook, April 2016, p. 148; "World Economic Outlook, April 2015, pp.150-153". Retrieved 2015-06-26; "World Economic Outlook, Database—WEO Groups and Aggregates Information, April 2015". Retrieved 2015-06-26.

Table 3. Descriptive statistics of the 18 city-specific indicators considered in the analysis.

Indicator	Number of cities	Median	IQR Range	Range	SD
Demographic					
Population	340	418 800	[174 184; 1 416 981]	[7678; 26 174 599]	3 068 757.2
Density (population/km^2)	339	2771.0	[1282.6; 5638.6]	[9.3; 49 045.1]	7289.3
% population ≥ 65 years	320	12.8%	[10.4%; 15.1%]	[3.1%; 27.2%]	4.7%
Life Expectancy (years)	288	80.3	[78.5; 81.6]	[70.6; 85.0]	2.3
Socioeconomic					
GDP (US$)	325	37 660	[27 096; 47 585]	[3168; 78 444]	15 838.5
Labour productivity (US$)	280	70 450	[64 019; 79 388]	[14 647; 366 027]	29 071.5
Educational level (%)	265	21.5%	[19.8%; 25.6%]	[9.0%; 39.3%]	5.3%
Unemployment rate (%)	307	6.5%	[4.4%; 9.4%]	[2.5%; 29.7%]	5.2%
Gini index	280	0.355	[0.315; 0.398]	[0.253; 0.484]	0.047
Poverty gap	280	22.1%	[18.2%; 26.3%]	[9.2%; 40.0%]	6.0
Health system					
Hospital bed rates	279	29.0	[23.8; 35.3]	[1.6; 192.0]	23.0
Urban characteristics					
Type of surrounding region (rural/urban)	272	Predominantly Urban = 125 Intermediate = 84 Predominantly Rural = 63			
Urbanised area (%)	136	13.8%	[8.9%; 24.1%]	[0.2%; 68.7%]	13.4%
Green Area (m^2 per million person)	136	196.6	[37.6; 824.6]	[0.01; 6660.6]	1042.9
Concentration of population in the core (%)	136	83.5%	[72.8%; 93.4%]	[22.6%; 100.0%	16.0%
Sprawl	100	-0.99	[-2.71; 1.79]	[-12.13; 10.97]	4.0
Air pollution					
$PM_{2.5}$ (μg/m^3)	340	9.6	[8.2; 13.9]	[4.7; 103.1]	13.2
NO_2 (ppb)	339	2.37	[1.08; 4.47]	[0.04; 23.3]	3.16

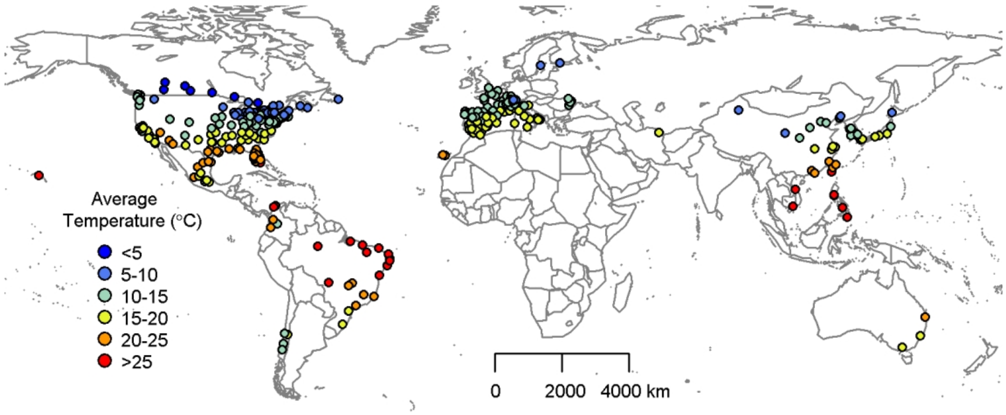

Figure 1. Average daily mean temperature in 340 MCC cities.

139x89mm (300 x 300 DPI)

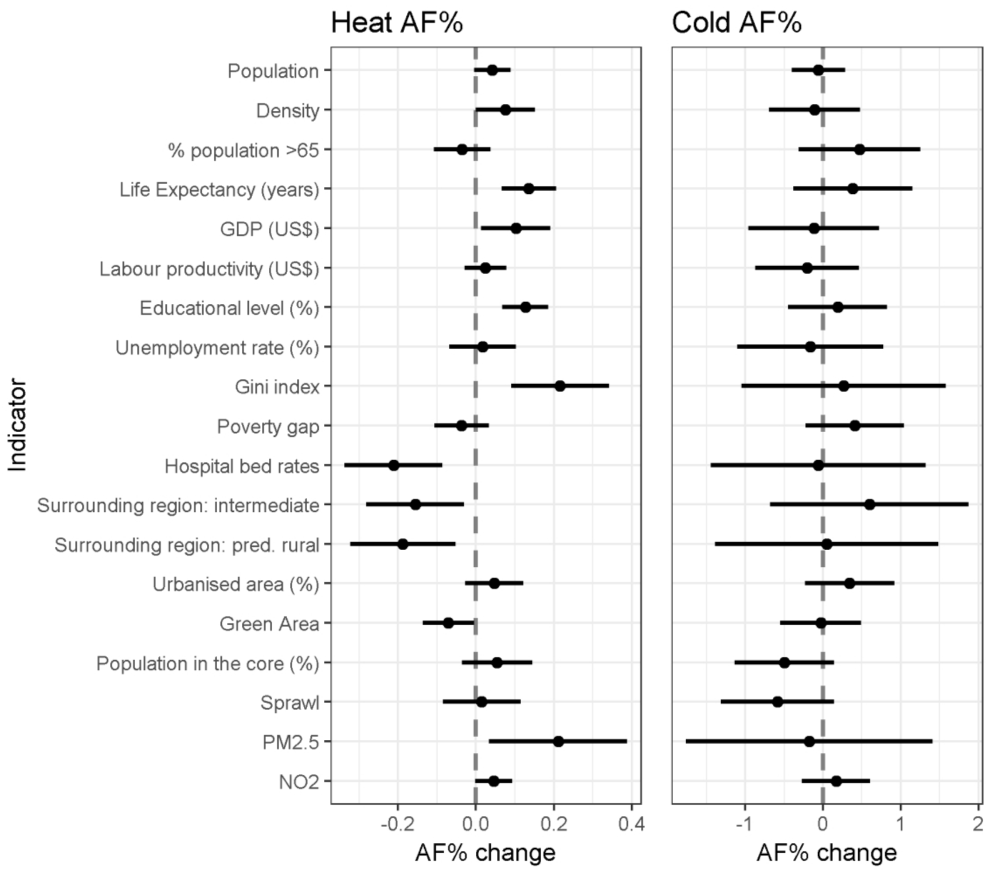

Figure 2. Associations between the indicators and heat and cold AF%. Coefficients and 95%CI calculated from a meta-regression model adjusted by country and weather variables. Results are expressed as AF% change for SD increase of the indicators. The estimates of the coefficients and 95%CI are reported in supplementary table S3.

159x139mm (300 x 300 DPI)