

studies adopted either a cross-sectional and/or longitudinal design, comparing risks at different air conditioning prevalence between individuals/locations or at different times. However, they faced a number of methodologic challenges. Analyses based on the cross-sectional comparison of subjects or cities with different air conditioning use and prevalence are prone to bias, as other characteristics, such as socioeconomic or climatic conditions, can be responsible for differences in health risks. Longitudinal designs can address this issue, but they need data consistently collected over a long period of time to allow for substantial variation in air conditioning use within each location. More importantly, these studies can be affected by temporal confounding due to concurrent changes in other modifying factors, such as infrastructural changes and access to health care. Finally, the complexity of exposure–response relationships, characterised by non-linearity and temporally delayed effects, presents additional problems in modeling temperature–mortality associations. A recent investigation by Nordio et al¹⁰ partly addressed these issues by comparing estimates from several USA cities over 5 decades, while using flexible exposure–response functions and adjusting for underlying trends. However, that study was performed in a single country, and its estimates of the role of air conditioning can be affected by the lack of separation between spatial and temporal contrasts.

In this contribution, we extend the assessment to a multi-country setting and adopting sophisticated longitudinal designs to control for spatial and temporal confounding. Specifically, the analysis makes use of a unique dataset with time-series data from 331 locations in 4 countries (USA, Japan, Canada, and Spain) in the period 1972–2019, and applies novel 2-stage methods based on multilevel multivariate spatio-temporal meta-regression models.

METHODS

Data

We collated data on mortality, temperature, and air conditioning prevalence from multiple locations in the 4 countries (see eTable 1; <http://links.lww.com/EDE/B701>). For each location, the data consist of daily counts of all-cause (Canada, Japan, and Spain) or non-accidental (USA) mortality and temperature series in summer months (June to September), and air conditioning prevalence from survey data in multiple years within the study period. Table 1 lists the study locations, the observation period as well as the air conditioning variable and surveys used to derive air conditioning prevalences in the 4 countries included in this study. Across countries, air conditioning prevalence data comes from different surveys with different frequency of reporting (see eAppendix; <http://links.lww.com/EDE/B701>). More detailed information on the data collected in each country are reported in the eAppendix; <http://links.lww.com/EDE/B701>.

Statistical Methods

The analytical strategy was based on 3 steps, briefly summarized here and described in detail below. In the first

step, each country-specific study interval was split into multiple periods. Then, we fitted separate regression models to obtain estimates of heat–mortality associations for each location and period. In addition, we reconstructed location-specific air conditioning trends and assigned prevalence estimates to each location or period unit. In the second step, we pooled the set of coefficients defining the associations to evaluate changes in heat-related mortality risks by calendar year and air conditioning prevalence, accounting for both within- and between-city variations. Finally, in the third and last step, we used the coefficients of the meta-regression models to derive trends in relative risk (RR) and attributable fractions predicted using observed and alternative scenarios of air conditioning prevalence trends.

Step 1: Estimating Location and Period-specific Air Conditioning Prevalence and Risks

In the first step, for each location, we divided the observation time was divided into specific time intervals. The number and the different periods for each country are reported in eTable 2; <http://links.lww.com/EDE/B701>. Time intervals have a length of 4 or 5 years. The length of time intervals was chosen a priori to provide enough statistical power to derive period-specific estimates, and enough time points to detect changes over time. For each country and locations, using the original air conditioning data, which was assessed intermittently, we estimated the air conditioning prevalence for each period, as described in the eAppendix; <http://links.lww.com/EDE/B701>. Briefly, for the USA, Canada, and Spain, we fitted a linear mixed-effects model with a B-spline parameterization of the time variable (years), and city as grouping level. We used best linear unbiased prediction estimates were used to predict yearly air conditioning prevalence in mid-summer (1st of July) in each city of the 3 countries. For Japan, we used the original yearly data and assigned it to mid-summer. To assess if changes in reporting air conditioning prevalence over time affected the predicted trends, we performed a sensitivity analysis including an indicator that defines pre- and post-periods corresponding to implementation of the new reporting methods (see eAppendix; <http://links.lww.com/EDE/B701>).

We estimated the location and period-specific temperature–mortality associations through quasi-Poisson regression¹⁴ with distributed lag non-linear models.¹⁵ Based on previous work,¹⁶ we specified the cross-basis function of daily mean temperature using a quadratic B-spline function for the temperature dimension, with 2 internal knots at the 50th and 90th percentiles of the location and period-specific summer temperature distributions, and unconstrained parameterization over lag 0–2. To control for long-term trends and residual seasonality, we included interaction terms between a natural cubic B-spline function with 4 degrees of freedom of the day of the year and indicators of year, along with an indicator of day of the week. We tested these modeling choices in a sensitivity analysis.

TABLE 1. Geographical Boundaries, Observation Period, and Definition of Air Conditioning Prevalence in Each Country

Country	Locations	Period	Air Conditioning Variable	Survey
Canada	20 census metropolitan areas + city of Hamilton	1991–2009	Proportion of dwellings with an air conditioning system (central or with a window or room mounted air conditioning system)	Survey of Household and Energy Use (SHEU) ^a Households and Environment Survey (HES) ^b
Japan	47 prefectures	1972–2009	Proportion of households with 2 or more occupants with air conditioning	Regional statistics database ^c
Spain	52 capital cities	1990–2009	Proportion of family homes with “refrigeration”; and from 2007 proportion of “homes with air conditioning”	Population and Housing Census ^d “Life Conditions” Survey ^e
USA	211 metropolitan areas	1973–2006	Proportion of households in each metropolitan area with central air conditioning	Census of Population ^f American Housing Survey (AHS) ^g Residential Energy Consumption Survey ^h

^aEstimates at regional level in years 1993, 1997, and 2003.

^bEstimates at city level in years 2006, 2007, and 2009.

^cAsahi Newspaper Publishing (2015).

^dEstimates at city level in years 1991 and 2001.

^eEstimates at regional level in 2007.

^fEstimates before 1985 at city level.

^gAHS use a rotation sampling of cities; data available yearly from 1985.

^hUsed to estimate air conditioning prevalence in northern New England cities.

Step 2: Modeling Spatial and Temporal Variation in risk

The location and period-specific estimates obtained from the quasi-Poisson model in step 1 were then combined using multilevel multivariate spatio-temporal models that consider possible non-independence of estimates within each location.¹⁷ For each location $i = 1, \dots, m$ and year $t = 1, \dots, T_i$ (defined as mid-points of periods), we obtained a $k = 4$ length column vector of spline coefficients θ_{it} representing the temperature–mortality association cumulated over lag 0–2 in location i and period t , and associated $k \times k$ estimated (co)variance matrix S_{it} . The multilevel multivariate spatio-temporal meta-regression model for the multivariate vector response θ_{it} can be written as:

$$\theta_{it} = X_{it}\beta + Z_i b_i + \varepsilon_{it} \quad (1)$$

with $b_i \sim N(0, \Psi_1)$, and $\varepsilon_{it} \sim N(0, S_{it})$.

The matrix X_{it} in the meta-regression model in equation 1 included fixed-effect predictors, represented by indicators of country, calendar year, period-specific average and inter-quartile range of daily mean temperature, in addition to air conditioning prevalence. Temperature variables were selected following previous evidence of their role in modifying heat-related mortality risks, while a linear term for calendar year was included to control for underlying variations in risk unrelated to air conditioning use. We compared the role of different fixed-effect predictors through likelihood ratio test in models fitted with a maximum-likelihood estimator. We included random terms at city- or prefecture-level, represented by indicators Z_i with random coefficients b_i . The random coefficients have unstructured (co)variance matrices Ψ_1 . The term S_{it} represents the estimation error within location/period

combinations. A restricted maximum-likelihood estimator was used for the final model.

This modeling approach allows investigation of the independent effect of changes over time in air conditioning prevalence on the temperature–mortality association, while adjusting for country- and location-specific trends. Using random terms at location level allows the use of information both within and between locations.

Step 3: Quantifying Heat-related Risks and AC Contribution

The estimated fixed-effects coefficients $\hat{\beta}$ from the multilevel multivariate spatio-temporal meta-regression model (1) fitted in step 2 can be used to predict a set of spline coefficients $\hat{\theta}_{ct}$ that represent pooled heat–mortality association curves for any combination of country, year, and air conditioning prevalence. Specifically, associations were predicted longitudinally or at the end of country-specific study periods, either using observed values of meta-predictors or under specific scenarios of air conditioning prevalence. Results were first reported in terms of country-averaged RR, using country-specific temperature distributions and minimum mortality temperature as references. In addition, we also derived summaries corresponding to estimated mortality fractions (in percentage) attributed to summer heat for each country/sub-period, following a procedure described elsewhere.¹⁸ In brief, we computed the mortality attributable to heat first by summing the temperature-related deaths occurring in days with temperatures higher than the location specific 50th percentile of the summer distribution, and then by dividing this excess by the total number of deaths. We calculated empirical standard error using Monte Carlo simulations, assuming a multivariate normal distribution of the fixed-effects coefficients estimated in step 2.¹⁸

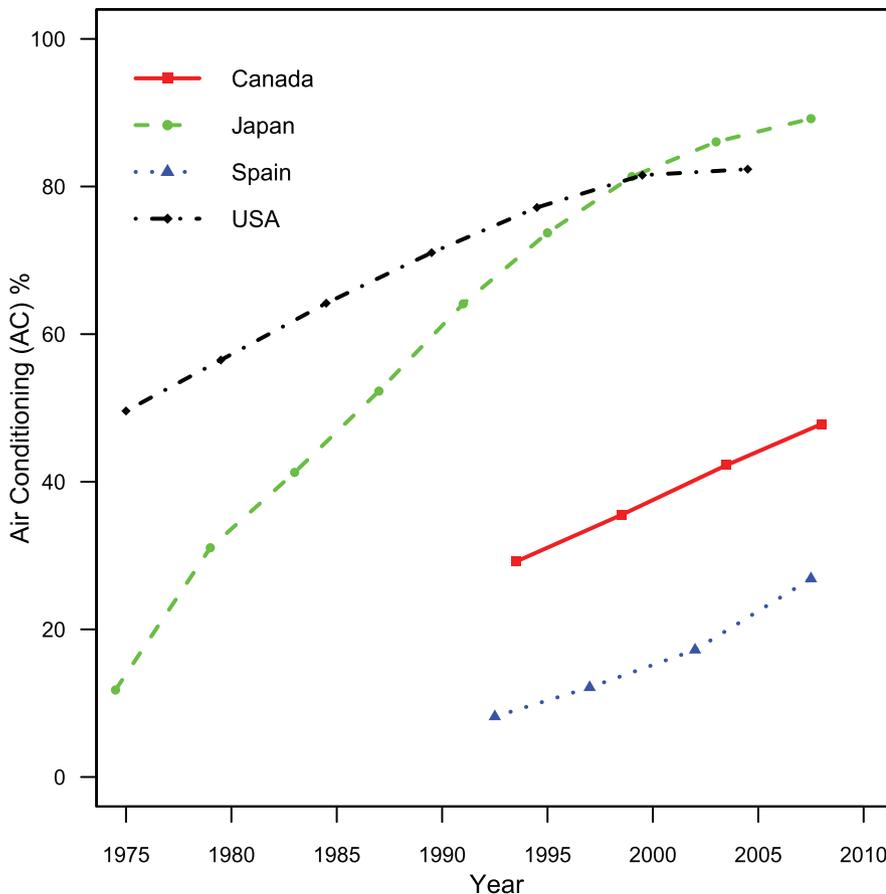


FIGURE 1. Air conditioning (AC) prevalence (%) by year in Canada, Japan, Spain, and the USA.

RESULTS

Data Description

During the study period, more than 23 million deaths were registered in the 331 locations assessed in the 4 countries. On average, air conditioning prevalence increased in all countries (Figure 1), with the highest prevalence at the end of the study period observed in Japan (89.2%), followed by the USA (82.8%), Canada (48.8%), and Spain (26.9%).

Multilevel Multivariate Spatio-temporal Meta-regression Model

The results of meta-regression models with different fixed-effects specifications are shown in eTable 3; <http://links.lww.com/EDE/B701>. In the final specification of the multilevel multivariate spatio-temporal meta-regression model, air conditioning prevalence shows an independent association with heat-related risks ($P = 0.011$), while accounting for country-specific trends and adjusting also by locations and period-specific average and interquartile range of mean temperature. We did not find strong evidence of a differential effect of air conditioning prevalence between countries ($P = 0.084$). Inspection of distribution of the residuals and their scatter plot versus time and air conditioning prevalence suggested a good fit of the model (see eFigure 3; <http://links.lww.com/EDE/B701>).

Quantification of the Heat-related Risk and its Trend

Figure 2 represents the changes in the heat-mortality association curves predicted by spatio-temporal meta-regression, at the beginning and end of the study periods in the 4 countries. Japan showed a strong attenuation in risk, with a decline of the RRs across almost all the summer temperature range. The USA and Spain also displayed a decrease in risk, although more evident at highest temperature percentiles. Canada showed little evidence of a reduction in heat-related RR over the observed period.

Table 2 presents air conditioning prevalence, estimated RR at 99th percentile of the temperature distribution versus minimum mortality temperature, and estimated excess mortality by country and calendar year. The trend is consistent with the attenuation in risk, especially in Japan where the RR declined from 1.32 to 1.08 during the period 1975–2007. In the same period, the heat-related excess deaths reduced from 3.57% to 1.10%. A reduction in RR is also evident in the USA and Spain, with a reduction of excess deaths due to heat from 0.54% to 2.78% in Spain, and 1.70% to 0.53% in the USA. In Canada, there was no evidence of reduction of the RR corresponding to the 99th temperature percentile, but we observed a decrease in mortality fraction attributable to heat, from 1.40% to 0.80%, due to an attenuation in risk at

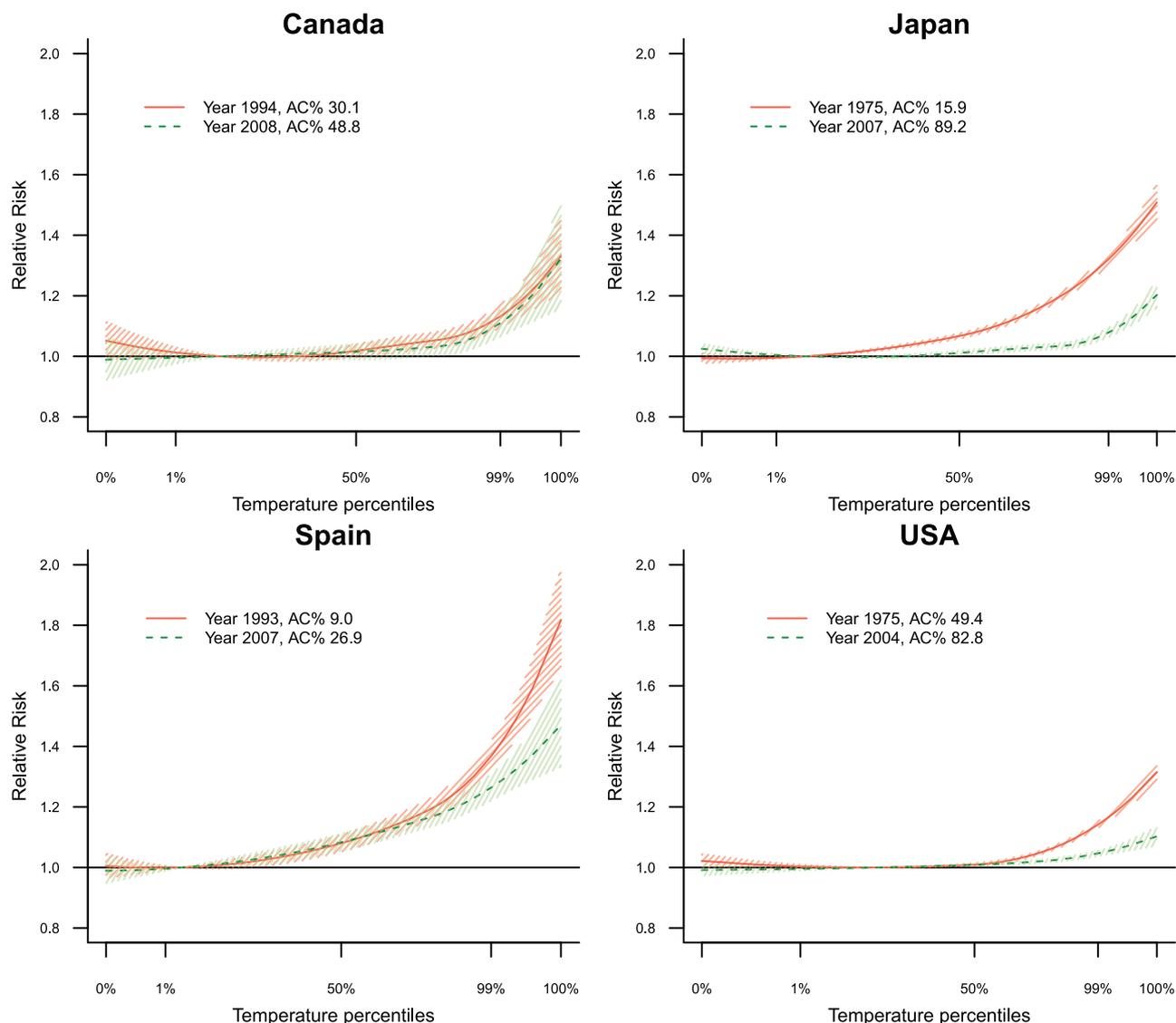


FIGURE 2. Country-average exposure–response curves (in RR) predicted at the beginning and end of the study periods in Canada, Japan, Spain, and the US. The x-axis represents relative temperatures in percentiles, but rescaled using the average distribution of absolute temperature across cities in each country.

lower temperature percentiles (90th and 50th), as shown in eFigure 2; <http://links.lww.com/EDE/B701>.

Temporal changes in temperature-related risks are generated by both variation in air conditioning prevalence and underlying trends due to other factors. To quantify the role of air conditioning, we fixed the calendar year at the end of the study period and calculated the RR at 99th temperature percentile and heat-related mortality fraction for different levels of air conditioning prevalence (Table 3). Results indicate that increasing the AC prevalence from 30% to 80% would be associated with important reduction in heat-related death: 30.2% in the USA, 24.9% in Canada, 20.3% in Japan, and 8.8% in Spain.

Finally, to separate and quantify the contribution of air conditioning prevalence from other time-varying factors in attenuating heat-related risks, we compared the excess

mortality under scenarios of observed increase or no change in air conditioning prevalence (Figure 3). The dark and light blue bars represent the excess mortality fraction calculated at the beginning and at the end of the study periods, using the actual air conditioning prevalences, with figures reported in Table 2. The middle blue bar represent instead the excess mortality fraction at the end of study period assuming no change in air conditioning prevalence: the comparison indicates that an increased air conditioning prevalence is responsible for only part of the observed attenuation, corresponding approximately to 16.7% in Canada, 20.0% in Japan, 14.3% in Spain, and 16.7% in the USA. These results suggest that other adaptation factors can be equally and, in some cases, more important for explaining the decreasing trend (see eTable 4; <http://links.lww.com/EDE/B701>).

TABLE 2. Reconstructed Air Conditioning (AC) Prevalence, RR at 99th Percentile of the Temperature Distribution Versus Minimum Mortality Temperature, and Attributed Mortality Fraction AF% with 95% Confidence Intervals (CI) by Country and Year

Country	Year	AC%	99th RR (95% CI)	AF% (95% CI)
Canada	1994	30.1	1.13 (1.09, 1.17)	1.40 (1.23, 1.55)
	1998	35.5	1.12 (1.08, 1.16)	1.33 (1.20, 1.44)
	2003	41.9	1.11 (1.08, 1.14)	1.22 (1.05, 1.38)
	2008	48.8	1.11 (1.07, 1.16)	0.80 (0.59, 0.98)
Japan	1975	15.9	1.32 (1.29, 1.34)	3.57 (3.53, 3.61)
	1979	31.1	1.28 (1.26, 1.30)	3.13 (3.10, 3.17)
	1983	41.3	1.24 (1.23, 1.26)	2.83 (2.79, 2.86)
	1987	52.3	1.21 (1.19, 1.22)	2.52 (2.49, 2.56)
	1991	64.1	1.18 (1.16, 1.19)	2.24 (2.20, 2.28)
	1995	73.7	1.15 (1.13, 1.16)	1.90 (1.86, 1.94)
	1999	81.3	1.12 (1.11, 1.14)	1.70 (1.66, 1.75)
	2003	86.0	1.10 (1.08, 1.11)	1.43 (1.39, 1.46)
	2007	89.2	1.08 (1.06, 1.10)	1.10 (1.05, 1.14)
	Spain	1993	9.0	1.37 (1.32, 1.42)
1998		12.9	1.42 (1.37, 1.46)	3.54 (3.42, 3.65)
2003		19.2	1.35 (1.32, 1.39)	3.51 (3.41, 3.60)
2007		26.9	1.26 (1.22, 1.31)	2.78 (2.63, 2.92)
USA	1975	49.4	1.14 (1.13, 1.15)	1.70 (1.67, 1.73)
	1979	56.5	1.13 (1.12, 1.14)	1.56 (1.54, 1.58)
	1984	64.1	1.11 (1.10, 1.12)	1.32 (1.30, 1.33)
	1989	71.0	1.09 (1.08, 1.10)	1.09 (1.07, 1.10)
	1994	76.8	1.08 (1.07, 1.09)	0.88 (0.87, 0.90)
	1999	80.7	1.06 (1.05, 1.07)	0.67 (0.65, 0.68)
	2004	82.8	1.05 (1.04, 1.06)	0.53 (0.51, 0.55)

CI indicates confidence interval.

DISCUSSION

Our results on air conditioning prevalence in Japan, the USA, Canada, and Spain are consistent with the hypothesis that air conditioning reduces heat-related mortality. This reduction occurs on top of variations in heat-related health risks possibly associated with planned and unplanned adaptation processes other than air conditioning use. These independent adaptation pathways were quantified and compared using alternative scenarios of air conditioning prevalence and underlying temporal trends. These scenarios indicate that while the increase in air conditioning use is associated with a reduction in heat-related mortality, this only explains a part of the decline in risk experienced in some countries, and other adaptation pathways have had a more important role in reducing the health burden.

Our results are consistent with published epidemiological investigations that have reported a substantial attenuation of heat-related health risk.^{1,2,19} In particular, similar declining trends were observed in the USA,^{6,7,10,16,20–24} Japan,^{8,9,25} Spain,²⁶ and Canada¹⁶ Similar declining trends were also observed in Sweden,²⁷ Austria,²⁸ the United Kingdom,^{29,30} Netherlands,³¹ 9 European cities,³² and Korea,^{33,34} but not in China.³⁵

TABLE 3. Predicted Relative Risk (RR) at 99th Temperature Percentile, and Attributed Mortality Fraction (AF%) with 95% Confidence Intervals (CI) Calculated at the End of the Study Period for 4 Scenarios of Air Conditioning Prevalence Levels (30%, 55%, 80%, and 100%) in Canada, Japan, Spain, and the USA. AC% indicates percent with air conditioning.

Country (Year)	AC%	99th RR (95% CI)	AF% (95% CI)
Canada (2008)	30	1.12 (1.07, 1.17)	0.93 (0.75, 1.10)
	55	1.11 (1.06, 1.15)	0.82 (0.63, 1.00)
	80	1.09 (1.05, 1.14)	0.70 (0.51, 0.89)
	100	1.08 (1.03, 1.13)	0.61 (0.40, 0.80)
Japan (2007)	30	1.12 (1.09, 1.14)	1.48 (1.41, 1.54)
	55	1.10 (1.08, 1.12)	1.33 (1.28, 1.37)
	80	1.08 (1.07, 1.10)	1.18 (1.13, 1.22)
	100	1.07 (1.06, 1.09)	1.06 (1.01, 1.10)
Spain (2007)	30	1.26 (1.22, 1.31)	2.86 (2.70, 2.99)
	55	1.24 (1.20, 1.29)	2.73 (2.58, 2.87)
	80	1.23 (1.18, 1.28)	2.61 (2.45, 2.77)
	100	1.21 (1.16, 1.27)	2.50 (2.32, 2.66)
USA (2004)	30	1.07 (1.05, 1.09)	0.82 (0.79, 0.84)
	55	1.06 (1.05, 1.07)	0.69 (0.67, 0.71)
	80	1.05 (1.04, 1.06)	0.57 (0.55, 0.59)
	100	1.04 (1.03, 1.05)	0.47 (0.45, 0.49)

Previous studies have evaluated the protective effect of air conditioning on heat-related risks. Some assessments used cohort¹² and case-control study designs,¹³ and suggested a role of AC in reducing the heat-related mortality risks in the USA. These studies were followed by 2-stage studies in which the first-stage estimates obtained through case-only¹¹ or time-series analyses⁵ in multiple cities were combined using meta-regression models with air conditioning prevalence as a contextual variable. These studies confirmed the protective effect of air conditioning in the USA, but were prone to ecological confounding as the selected cities can differ by other unmeasured characteristics (e.g., demographic, socioeconomic, and infrastructural) related to health risk. More recent studies in the USA and Japan used a longitudinal design to disentangle the effect of air conditioning as behavioral adaptive measure. In the USA, 2 studies found an independent protective effect of air conditioning,^{5,6} but Bobb et al⁷ observed no evidence of protective effect. The longitudinal study of Nordio et al¹⁰ reported independent protective effects of air conditioning while controlling for region, time trend, and mean summer temperature, using spline models in individual cities and a meta-regression approach. The 2 longitudinal studies conducted in Japan did not find evidence consistent with an independent protective effect of air conditioning over the declining heat-related risk trend.^{8,9} Differences on previous studies results can be partly explained by low statistical power, as these investigations were conducted in a single country and/or the temperature–mortality curve was summarized using simplified indices. Moreover, these studies did not jointly

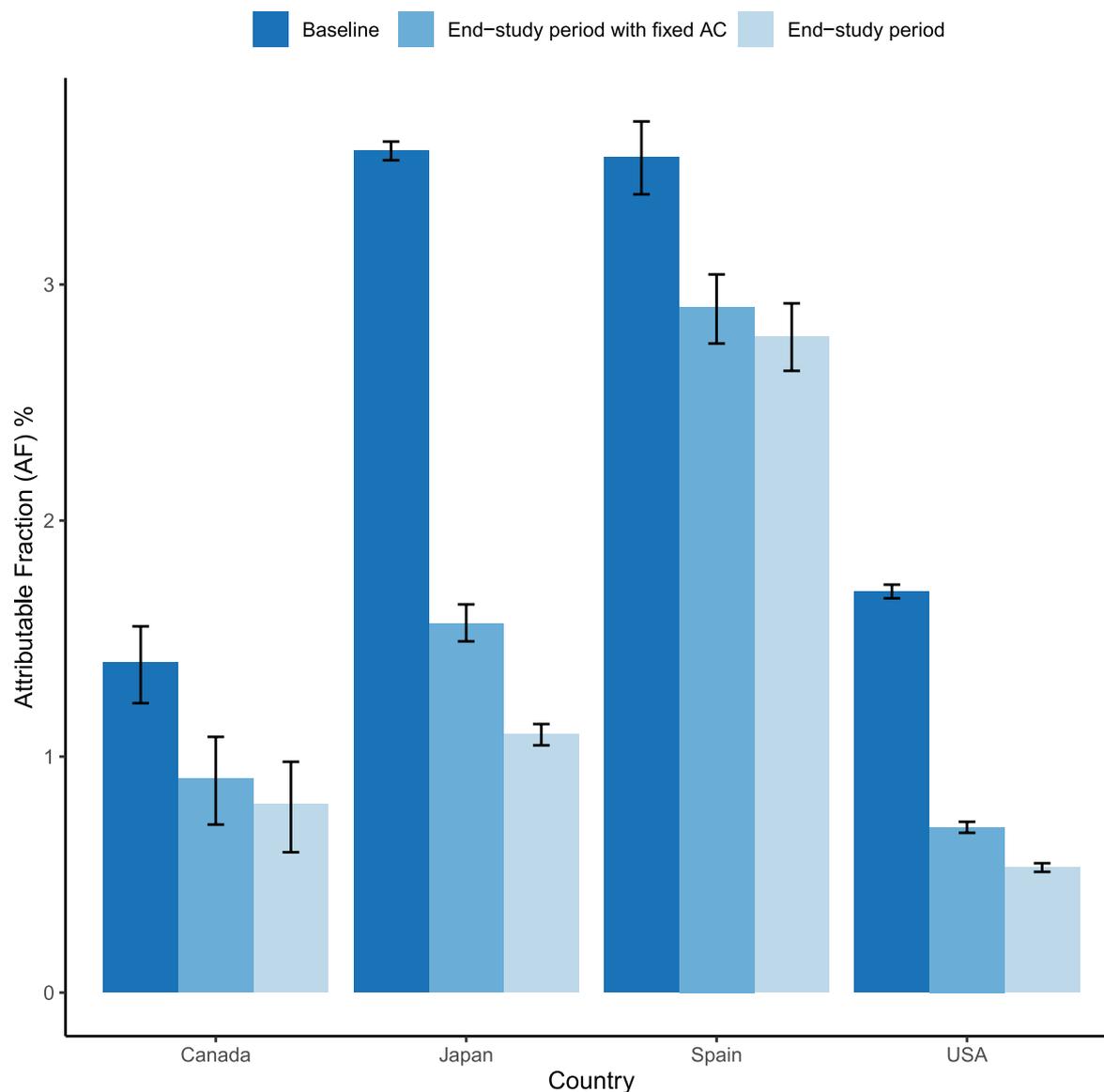


FIGURE 3. Excess mortality associated to heat reported as attributable fraction (AF%) estimated at the beginning (baseline, dark) and end of the study period assuming no change (end-study period with fixed air conditioning, medium) or with the observed change (end-study period, light) in air conditioning (AC) prevalence.

consider the longitudinal and spatial structure of the data, and the non-independence of the observations within locations.

Our study has several strengths. First, we used distributed lag non-linear modeling techniques to estimate the heat–mortality association. This modeling framework helps avoid biases due to simplification of the exposure–response association and considers possible lagged effects of heat on mortality.¹⁵ Second, we were able to collect mortality, temperature and air conditioning data for 331 locations in 4 countries for a period of 4 decades. This provided large variability in air conditioning prevalence both within and across locations, offering sufficient statistical power to isolate the impact on modifying heat–mortality relationships. Third, we used a study design based on both spatial and longitudinal comparison, reducing

the chance of ecologic bias and temporal confounding due to concurrent changes in other modifying factors, such as socioeconomic conditions and access to health care. The spatial component provides increased variability in response and exposure, while the longitudinal design compares variations in risk within a location. Finally, we used novel multilevel multivariate spatio-temporal meta-regression models that allow disentangling of the reduction in heat-related risk associated to the increase in air conditioning prevalence from underlying trends due to other adaptation pathways, while at the same time correctly accounting for correlations between repeated measures taken within the same location.¹⁷

We must acknowledge some limitations. First, the results of our study refer to developed countries with predominantly

temperate or continental climates. Caution should be used when extrapolating results to low-income countries, which are characterized by different climatic, sociodemographic, and development conditions, and where technology-based adaptation measures, such as increasing air conditioning use, may be problematic as many low-income countries already experience chronic shortages of power.² Second, we reconstructed air conditioning prevalence along the past decades by applying smoothing techniques to irregular survey data from multiple sources. However, additional analyses described in the eAppendix; <http://links.lww.com/EDE/B701> show that results are robust to this filling-up procedure. The results of the sensitivity analysis suggest that the smoothing process could have introduced some error, although it is unlikely that this is correlated with the estimated period-specific risk, and therefore can probably be assumed as random. Third, our air conditioning variable is defined as presence of air conditioning units or central air conditioning at home, but does not capture its actual use. Moreover, this measure is not informative about air conditioning use in other environments, such as on public transport, stores, workplaces, and public areas. This may induce some additional problems in the interpretation of the results.

The analysis of factors related to changes in susceptibility to temperature-related mortality is critical to inform health and climate policies. Air conditioning is a solution to regulate ambient indoor temperatures and lower the heat stress imposed on the human thermoregulatory function,³⁶ and it represents one of the most cited behavioral adaptation strategy to climate change.³⁷ The results of our analysis confirm that air conditioning is an effective adaptive measure and have contributed to reduce the burden of heat-related mortality. According to our estimates in the USA and Japan, nearly 0.09% and 0.32% of deaths during summer months were delayed by increasing the air conditioning prevalence level to more than 80%, respectively. In these countries, the air conditioning market seems to have reached a plateau, but the heat-related mortality is still substantial. However, the quantitative comparison of the contribution of increase in air conditioning prevalence, and the independent attenuation of the risk reported in Figure 3, suggest that other adaptation pathways can be equally or even more effective in reducing the health burden. In Spain and Canada, the delayed deaths during summer months were both 0.05%, suggesting a further margin on reduction of heat-related mortality, especially in Spain where the reported air conditioning prevalence reaches only 30% in 2009. In addition, increasing air conditioning use has also important negative consequences, including capital and energy cost, carbon and pollution-generating energy demand, and contribution to the heat-island effect.² However, the current rapid transition of electricity generation to carbon zero sources is likely to ameliorate the pollution impact in the next few decades. A quantitative assessment of health and economic impacts of this and other adaptive changes is critical for generating plausible scenarios of potential mitigation and adaptation benefit and costs.

In conclusion, in this study, we found a reduction over time of the heat-related health risk in Japan, the USA, and Spain. Air conditioning prevalence was factor that independently explained part of the decrease in heat-related deaths, although we estimated that other adaptive strategies accounted for a larger proportion of the attenuation. These results can be used to inform policy measures based at individual, community, and international level, and to improve and extend projections of future heat impacts on human health.

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