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All-Cause and Cause-Specific Risk of Emergency Transport Attributable to Temperature

A Nationwide Study

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Abstract: Although several studies have estimated the associations between mortality or morbidity and extreme temperatures in terms of relative risk, few studies have investigated the risk of emergency transport attributable to the whole temperature range nationwide.

We acquired data on daily emergency ambulance dispatches in all 47 prefectures of Japan from 2007 to 2010. We examined the relationship between emergency transport and temperature for each prefecture using a Poisson regression model in a distributed lag nonlinear model with adjustment for time trends. A random-effect multivariate meta-analysis was then applied to pool the estimates at the national level. Attributable morbidity was calculated for high and low temperatures, which were defined as those above or below the optimum temperature (ie, the minimum morbidity temperature) and for moderate and also extreme temperatures, which were defined using cutoffs at the 2.5th and 97.5th temperature percentiles.

A total of 15,868,086 cases of emergency transport met the inclusion criteria. The emergency transport was attributable to nonoptimal temperature. The median minimum morbidity percentile was in the 79th percentile for all causes, the 96th percentile for cardiovascular disease, and the 92th percentile for respiratory disease. The fraction attributable to low temperature was 6.94% (95% eCI: 5.93–7.70) for all causes, 17.93% (95% eCI: 16.10–19.25) for cardiovascular disease, and 12.19% (95% eCI: 9.90–13.66) for respiratory disease, whereas the fraction attributable to high temperature was small (all causes = 1.01%, 95% eCI: 0.90–1.11; cardiovascular disease = 0.10%, 95% eCI: 0.04–0.14; respiratory disease = 0.29%, 95% eCI: 0.07–0.50). The all-cause morbidity risk that was attributable to temperature was related to moderate cold, with an overall estimate of 6.41% (95% eCI: 5.47–7.20). Extreme temperatures were responsible for a small fraction, which corresponded to 0.57% (95% eCI: 0.50–0.62) for extreme low temperature and 0.29% (95% eCI: 0.26–0.32) for extreme high temperature. The same trends were observed for cardiovascular and respiratory diseases.

The majority of temperature-related emergency transport burden was attributable to lower temperature. The effect of extremely high or low temperatures was markedly lower than that attributable to moderately nonoptimal temperatures.

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Abbreviations: CI = confidence interval, ICD = International Classification of Diseases, MMP = minimum morbidity percentile, RR = relative risk.

INTRODUCTION

The relationship between temperature and mortality or morbidity is of increasing public health concern throughout the world.[1] Previous studies have provided evidence that high and low temperatures are associated with increased risk of mortality or morbidity in a wide range of climates and countries.[2,3] Mortality related to extreme temperature is expected to increase as the frequency, intensity, and duration of extreme events increase due to climate change.[4] Most studies have particularly focused on extreme weather events or aimed to define exposure–response associations between temperature and mortality. For example, previous studies have indicated that extremely high and low temperatures are associated with a substantial increase in all-cause and cause-specific mortality, such as cardiovascular and respiratory diseases.[5] However, few quantitative studies have investigated the risk of emergency transport related to temperature.

Emerging evidence suggests that extreme temperatures might be an important factor in emergency transport.[6–8] However, most studies have focused on quantifying the association in terms of the relative risk, and it is necessary to assess the potential burden of morbidity in the population. In relation to strategies to prevent or control for temperature-related emergency transport, public health officials are required to investigate the actual impact of temperature. Thus, estimation of the relationship between the temperature range and emergency transport burden is essential for the effective management of emergency medical care systems.

Attributable risk measures the potential impact of a prevention strategy within a population.[9] The attributable fraction combines the relative risk and prevalence of exposure to measure the public health burden of a risk factor by estimating the proportion of disease cases that would not have occurred in the absence of the exposure, and it has long held an important place in public health. However, few studies have investigated the risk of emergency transport that is attributable to the range of temperatures nationwide or compared the contribution of moderate temperatures. Moreover, the relationships between extreme and moderate temperatures and morbidity can be affected by the

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cause of morbidity and by regional, climatological, socioeconomic, demographic, and infrastructural factors.[10–12] In addition, the optimal temperatures that correspond to minimal temperature effects on major disease groups have not been elucidated.

Here, we investigated the all-cause and cause-specific risk of emergency transport that is attributable to nonoptimal temperature and the relative contributions of low and high temperatures for ~ 4 years in the 47 prefectures of Japan using flexible and advanced statistical approaches based on multivariate meta-regression models with time-varying distributed lag nonlinear models. To our knowledge, this study is the first report to quantify the all-cause and cause-specific risk of emergency transport that is attributable to temperature in Japan.

METHODS

Data Sources

In Japan, municipal governments provide emergency medical services via ~800 fire stations with dispatch centers under the Fire Service Act. All of the emergency ambulance dispatch data were obtained for all 47 prefectures of Japan from 2007 to 2010. The Tokyo metropolitan area was excluded from all analysis, due to a lack of data on emergency transport. Morbidity data were obtained from the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications of Japan, which included the date of the emergency transport and the main cause of the disease according to the *International Classification of Diseases*, 10th revision (ICD-10). In Japan, registration of emergency transport data is required under the Fire Service Act and is considered to be complete across the country. Eligible cases that involved individuals who were transported to a medical institution were assessed for possible enrollment according to the inclusion criteria (Fig. 1). Data on the daily mean temperature and relative humidity as measured by representative monitoring stations in each prefecture were obtained from the Japan Meteorological Agency. The daily mean temperature was selected as the main exposure index.

The study was approved by the ethics committee at Kyushu University Graduate School of Medical Sciences. This study was an observational study that used national registry data. The requirement for written informed consent was waived.

Statistical Analysis

We first examined the associations between all-cause and cause-specific emergency transport and temperature using a time-series quasi-Poisson regression model in a distributed lag nonlinear model separately in each prefecture.[13–15] Emergency transport from all causes (ICD-10: A00-Z99), cardiovascular disease (ICD-10: I00–I99), and respiratory disease (ICD-10: J00–J99) were analyzed. The distributed lag nonlinear model was developed on the basis of a cross-basis function, which allows for the simultaneous estimation of possible nonlinear associations across lag periods.[13–15] We defined a cross-basis function by a natural cubic spline for the space of temperature. A natural cubic B-spline with 8 degrees of freedom per year for time was included to allow for seasonality and long-term trend. The categorical variable for day of the week and the indicator variable of public holidays were incorporated into the model. A cross-basis composed of a quadratic B-spline for the temperature-morbidity relationship with 3 internal knots at prefecture-specific temperature percentiles (10th, 75th, and 90th) was selected. We also fitted a natural cubic B-spline for the lag-response curve with an intercept and 3 internal knots, which are equally spaced log-values of lag. Although the association between prefecture and temperature-induced morbidity is usually evaluated by using an absolute temperature scale, temperature ranges and distributions vary across the 47 prefectures of Japan. Thus, the combination of temperature–morbidity relationship across the 47 prefectures by using nonoverlapping temperature ranges is not appropriate. Moreover, the overall effects of temperature on morbidity might be more reliable in relative temperature scales than absolute temperature scales due to adaptation to climate change among populations. Therefore, we estimated the overall cumulative temperature–morbidity relationship by standardizing the prefecture-specific absolute temperatures to prefecture-specific temperature percentiles. We considered lag periods of up to 21 days to include the delayed effects of low temperatures and to exclude the harvesting effect.

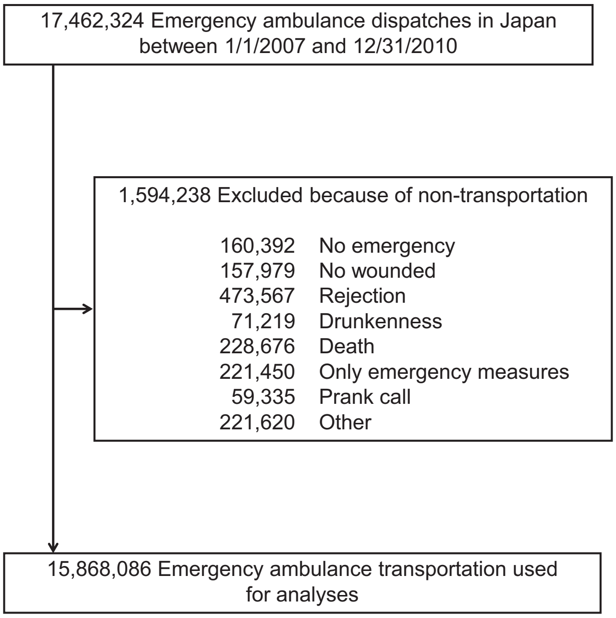

FIGURE 1. Emergency transport used for analyses.

In summary, the time-series model for each prefecture took the following form (1).

$$\log[E(Y)] = a + cb + dow + hol + NS\ (time, df) \tag{1}$$

where $E(Y)$ denotes the expected daily morbidity, cb denotes the cross-basis matrix for the daily mean temperature, dow denotes the categorical variable for the day of the week, hol denotes the indicator variables for public holidays, $NS\ (time,\ df)$ denotes the natural cubic spline function of time, and df denotes the degrees of freedom per year for time, with 8 df used to allow for seasonality and long-term trend.[16] Plots of partial autocorrelation functions of the residuals (Supplementary data, Figure S1, http://links.lww.com/MD/A571) suggested that this model had an adequate amount of adjustment for seasonal trends.

The estimated prefecture-specific associations were then pooled using multivariate random-effects meta-regression models that were obtained following the reduction of time series regression model to estimate the nonlinear temperature–morbidity relationship at the national level.[17] Multivariate random-effects meta-regression analyses were performed to assess national, pooled estimates based on the maximum likelihood. Residual interprefecture heterogeneity was evaluated by the Cochran Q test and the I^2 index.[18]

We fitted multivariate random-effects meta-regression models to estimate the best linear unbiased prediction of pooled relations between temperature and morbidity for all 47 prefectures. The optimal linear unbiased prediction means a trade-off between the prefecture-specific association that is obtained from time-series model and the prefecture-pooled association. This approach enabled prefectures with small daily morbidity counts to make use of information from larger populations that have similar characteristics.[16,18] The minimum morbidity temperature was estimated from the best linear unbiased prediction of pooled relations between temperature and morbidity in each prefecture. This value was referred to as the optimum temperature in each prefecture and was regarded as the reference for calculating the attributable risk by re-centering the quadratic B-spline. This method has been described in detail elsewhere.[16,19]

Population attributable risks to low and high temperatures were calculated by summing the subsets corresponding to days with temperatures lower or higher than the minimum morbidity temperature. Moreover, these attributable risks were divided into moderate and extreme temperatures. Motivated by a recent study, extremely low temperatures were defined as those that were below the 2.5th location-specific percentile, and extremely high temperatures were defined as those that were above the 97.5th location-specific percentile.[16] The choices of these cut-offs are consistent with previous definitions of extreme temperatures.[20–22] Moderate temperatures were defined as those temperatures that fall between the optimal temperature and these cut-offs. Empirical confidence intervals (eCIs) were calculated using Monte Carlo simulations, assuming a multivariate normal distribution of the best linear unbiased predictions of the reduced coefficients. We used 999 Monte Carlo replications to estimate the significance levels of the results. This method is described in more detail elsewhere.[16,19]

In sensitivity analysis, modeling selections were tested by controlling for different degrees of freedom for seasonal and long-term trends (6 and 10 df per year) and relative humidity for the 47 prefectures. All of the statistical analyses were conducted with the R software system (version 3.2.0), using the packages *dlnm* and *mvmeta* (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptive Analysis

Of 17,462,324 emergency ambulance dispatches between January 1, 2007 and December 31, 2010, of the 47 prefectures of Japan, we evaluated 15,868,086 cases that met the inclusion criteria; 9.1% were excluded (Fig. 1, Table 1). The daily mean temperature was 15.7 °C, and the populations in different prefectures experienced a broad range of temperatures, with the prefecture-specific mean ranging from 9.6 °C in Hokkaido Prefecture to 23.4 °C in Okinawa Prefecture (Supplementary data, Table S1, http://links.lww.com/MD/A571).

Exposure–Response Associations

Fukuoka Prefecture was selected as a representative prefecture due to its large population. Figure 2 shows the overall cumulative exposure–response curves (best linear unbiased predictions) between all-cause and cause-specific morbidity

TABLE 1. Descriptive Statistics: Study Periods, Total Number of Emergency Transports, and Daily Emergency Transport Distribution

Cause of Death (ICD-10 Codes)	Total Case Number	Mean Prefecture-Specific Cases (Range)	
All causes (A00-Z99)	15,868,086	231.1	(15.5–1022.9)
Cardiovascular diseases (I00-I99)	2,139,220	31.2	(2.3–115.5)
Respiratory diseases (J00-J99)	975,594	14.2	(1.2–64.8)

ICD = International Classification of Diseases.

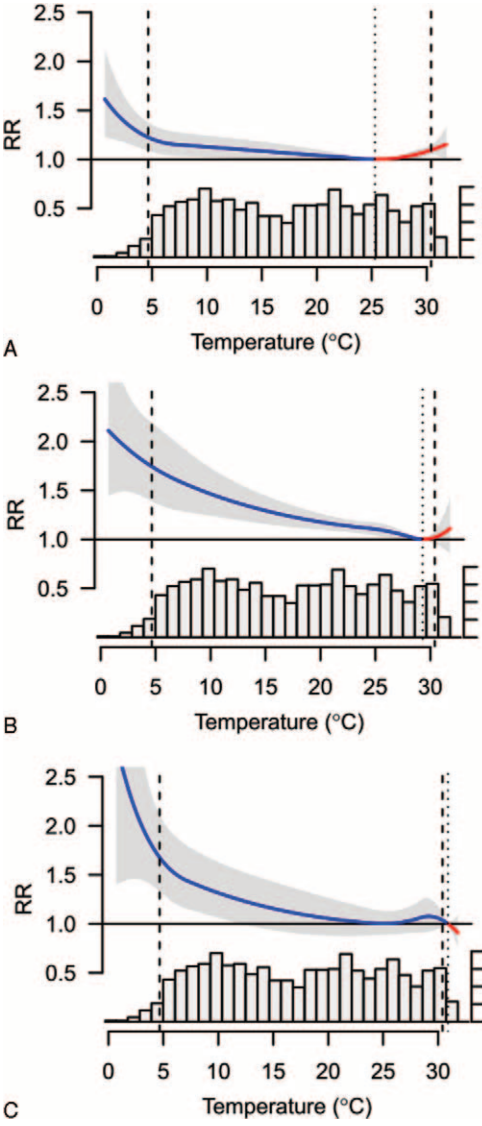

FIGURE 2. Overall cumulative exposure–response associations between the RRs (95% CI) for all-cause and cause-specific morbidity and temperatures in Fukuoka Prefecture, Japan: (A) all causes; (B) cardiovascular diseases; (C) respiratory diseases. Exposure–response associations expressed as the best linear unbiased prediction (with 95% empirical CI, shaded gray), with the related temperature distributions. The solid gray lines indicate the minimum mortality temperatures, and the dashed lines indicate the 2.5th and 97.5th percentiles. CI = confidence interval, RR = relative risk.

TABLE 2. Attributable Emergency Transport Computed as the Total and as Separate Components for Low and High Temperatures. The Data are the Median Percentile or % (95% Empirical CI)

Cause of Death (ICD-10 Codes)	MMP	Total (%)		Low Temperature (%)		High Temperature (%)	
All causes (A00-Z99)	79th	7.95	(6.90–8.84)	6.94	(5.93–7.70)	1.01	(0.90–1.11)
Cardiovascular diseases (I00-I99)	96th	18.02	(16.32–19.32)	17.93	(16.10–19.25)	0.10	(0.04–0.14)
Respiratory diseases (J00-J99)	92th	12.48	(10.30–14.10)	12.19	(9.90–13.66)	0.29	(0.07–0.50)

CI = confidence interval, ICD = International Classification of Diseases, MMP = minimum morbidity percentile.

and temperatures for this prefecture, with corresponding minimum morbidity temperature and cutoffs used to define extreme temperatures. Morbidity risks of emergency transport generally increased slowly and linearly for low temperatures below the minimum morbidity temperature, although different patterns of respiratory disease were observed in some prefectures. The corresponding graphs for different causes of morbidity in all 47 prefectures are also reported in the Supplementary data (Figure S2–S4, http://links.lww.com/MD/A571).

Attributable Risk

The median minimum morbidity percentile was in the 79th percentile for all causes, the 96th percentile for cardiovascular disease, and the 92th percentile for respiratory disease across all prefectures. Morbidity attributable to nonoptimum temperature was 7.95% (95% eCI: 6.90–8.84) for all causes, 18.02% (95% eCI: 16.32–19.32) for cardiovascular disease, and 12.48% (95% eCI: 10.30–14.10) for respiratory disease (Table 2). Heterogeneity between prefectures was significant for all causes (Cochran Q test, $P < 0.001$; $I^2 = 43.6\%$), cardiovascular disease (Cochran Q test, $P < 0.001$; $I^2 = 27.5\%$), and respiratory disease (Cochran Q test, $P = 0.008$; $I^2 = 19.5\%$). Low temperature was responsible for most of the burden, and the fraction that was attributable to low temperature was 6.94% (95% eCI: 5.93–7.70) for all causes, 17.93% (95% eCI: 16.10–19.25) for cardiovascular disease, and 12.19% (95% eCI: 9.90–13.66) for respiratory disease. In contrast, the fraction attributable to high temperature was small (total estimate = 1.01%, 95% eCI: 0.90–1.11; cardiovascular disease = 0.10%, 95% eCI: 0.04–0.14; respiratory disease = 0.29%, 95% eCI: 0.07–0.50).

The attributable risks, separated into components related to moderate and extreme temperatures, are shown in Table 3. The all-cause morbidity risk that was attributable to temperature was related to moderate low temperature, with an overall estimate of 6.41% (95% eCI: 5.47–7.20). Extreme temperatures were responsible for a small fraction, which corresponded to 0.57% (95% eCI: 0.50–0.62) for extreme low temperature and 0.29% (95% eCI: 0.26–0.32) for extreme high temperature. The same trends were observed for cardiovascular and respiratory diseases. Sensitivity analysis showed that these results were not dependent on the modeling assumptions (Supplementary data, Tables S2–S3, http://links.lww.com/MD/A571).

DISCUSSION

Our nationwide analysis yielded several notable findings. Most importantly, our results suggest that temperature accounted for a substantial fraction of emergency transport. Morbidity burden was mostly attributed to low temperatures. Specifically, most emergency transport was caused by exposure to moderately high or low temperatures, and the contribution of extremely high and low temperatures was relatively small. These findings indicate that low temperatures cause more cases of emergency transport than high temperatures.

Our results showed that 7.95% of emergency transport was attributable to nonoptimal temperature. More temperature-attributable emergency transport was caused by low than high temperature, and morbidity attributable to moderately nonoptimal temperatures substantially outnumbered that attributable to extreme temperatures. The most probable explanation for our findings is that the frequency of moderate low temperature days is much higher than that of moderate high or extreme temperature days. Our results are consistent with the findings of previous studies, which suggested that the number of ambulance dispatch calls increases on days of high and low temperature.[6–8] Moreover, all-cause mortality attributable to heat was between 0.37% and 1.45% in London, Budapest, and Milan.[20] Another study in London reported that the population attributable fraction per 1 °C drop <15 °C was 5.4%, but there was none attributable to heat in 1986 to 1996.[23] Furthermore, a recent multicountry observational study found that cold-related mortality outnumbered heat-related mortality, and mortality

TABLE 3. Attributable Emergency Transport Computed as the Total and as Separate Components for Moderate and Extremely Low and High Temperatures. The Data are the Median Percentile or % (95% Empirical CI)

Cause of Death (ICD-10 Code)	Extreme Low Temperature (%)		Moderate Low Temperature (%)		Moderate High Temperature (%)		Extreme High Temperature (%)	
All causes (A00-Z99)	0.57	(0.50–0.62)	6.41	(5.47–7.20)	0.74	(0.64–0.83)	0.29	(0.26–0.32)
Cardiovascular diseases (I00-I99)	1.08	(0.95–1.15)	16.92	(15.15–18.25)	0.02	(0.00–0.04)	0.08	(0.04–0.11)
Respiratory diseases (J00-J99)	1.07	(0.93–1.15)	11.19	(8.91–12.71)	0.23	(0.02–0.41)	0.08	(0.03–0.12)

CI = confidence interval, ICD = International Classification of Diseases.

attributable to moderately nonoptimal temperatures substantially outnumbered that attributable to extreme temperatures.[16] Our findings suggest that nonoptimal temperature is associated predominantly with substantial increases in emergency transport.

We also found that 18.02% of emergency transport for cardiovascular disease was attributable to nonoptimal temperature. Most attributable emergency transport for cardiovascular disease was associated with low temperature, and emergency transport attributable to moderately nonoptimal temperatures substantially outnumbered that attributable to extreme temperatures. Our results are consistent with the findings of previous studies, which suggested that hospitalization for cardiovascular disease increases during low temperatures.[24] Another study also reported negative associations between high ambient temperature and emergency transport for aneurysm, hemorrhagic stroke, and hypertension.[25] These results might be due to low temperatures being associated with cardiovascular stress by affecting factors, such as blood viscosity and inflammatory responses.[26,27] High excess risks for heart failure, arrhythmia, and atrial fibrillation have also been reported during periods of low temperature.[28,29] In contrast, previous studies also suggested that heat stress exacerbates already impaired physiological responses, such as higher sweating thresholds, decreased skin blood flow, increased blood viscosity and coagulation, reductions in cerebral perfusion, attenuated vasoconstrictor responsiveness, elevated cholesterol levels and reduced cardiac output and that these changes could affect the increased mortality risk.[30–32] These discrepancies in our study might be due to the health and age profile of the study populations. Although the exact mechanism remains unclear, our findings highlight the need for further studies on the effects of temperature on cardiovascular disease.

Emergency transport for respiratory diseases showed that 12.48% was attributable to nonoptimal temperature. Low temperatures accounted for 12.19% of the overall emergency transport for respiratory diseases, whereas high temperatures accounted for only 0.29%. Emergency transport for respiratory diseases attributable to moderately nonoptimal temperatures substantially outnumbered those attributable to extreme temperatures. Our results are consistent with the findings of previous studies, which suggested that mortality caused by respiratory diseases increased significantly during periods of low temperature.[33] In a single-city study from Spain, for example, the daily mortality increased during the days that had a temperature under the 5th percentile in winter.[34] Bronchoconstriction induced by low temperature is associated with impairment of mucociliary clearance and a variety of other immune responses, which induces a local and systemic inflammatory response and increases the risk of acute upper respiratory tract viral infections.[35] These physiological responses attributable to low temperature can be observed with longer term compared with those attributable to high temperature.[26] These results are in support of the suggestions that most of the temperature-related emergency transport burden was attributable to low temperature. In addition, the compensatory effects suggest that cold-related mortality might most strongly impact those whose health status is already compromised and is often terminal.[10,36] Short-term harvesting effects might also play a role in morbidity due to respiratory disease.

Using multivariate meta-regression models, we observed significant heterogeneity between prefectures for all-cause, cardiovascular, and respiratory diseases. These results might reflect differences in socioeconomic status, population demographics, geographical factors, underlying disease risk, vulnerable subpopulations, physiological acclimatization, and local adaptations in addition to weather patterns. Although we could not identify all of these factors, our results suggest that populations might adapt to local weather patterns in terms of physiology, behavior, and technology. Further investigation is required to apply these variables as meta-predictors.

Although recent studies suggest that the risk of temperature-related mortality is distributed across a wide range of causes, such as endocrine, digestive system, genitourinary system, mental, nervous system, and external causes,[3,21] few studies have investigated the morbidity risk of emergency transport that is attributable to high and low temperatures on specific causes. Our findings highlight the importance of further investigation of morbidity risk that is attributable to temperatures from a variety of causes in different regions and populations for longer periods.

We are confident that major selection biases did not affect this study; the registration of emergency transport was almost complete. However, our study has several limitations that warrant mentioning. First, we did not consider factors such as acclimatization, susceptibility, resilience, socioeconomic status, community characteristics, road closures due to extreme weather events, or the proportion of the population that consists of unwell, young, and elderly people, which might affect the temperature-related effects on emergency transport. These factors must be considered in explanation of the heterogeneity between prefectures. To apply these variables as metapredictors, further study would be important. Second, we did not control for air pollution; however, a recent multicountry study suggested that this lack of control is unlikely to have materially altered the pattern of results.[16] In addition, a previous study provided evidence of increased mortality, due to elevated apparent temperatures with no confounding or effect modification due to air pollution.[37] However, a recent study indicated that the $PM_{2.5}$ concentration was associated with ischemic heart disease mortality and morbidity.[38] Further investigation to examine the effects of air pollution and temperature on mortality would be critical for future studies. Third, social, environmental, and biophysical adaptations between prefectures can affect the vulnerability of a population to extreme temperatures. Several studies have reported reduced short-term mortality due to extreme temperatures in areas where the population has adapted to highly variable ambient temperatures.[23,39] Better housing and public health systems, behavioral and physiological adaptation and heightened awareness are associated with extreme temperatures.[12] In addition, increased car ownership, climate-controlled transportation and shopping facilities, and improved clothing fabric are also likely to have reduced potentially dangerous outdoor exposure to hot and cold weather.[23] These factors might indicate a need for more precise modeling of any effects of temperatures on emergency transport and are critical topics for future study. Fourth, the definition of extreme temperatures would be important. Although a variety of approaches have been used to define extreme temperatures, there is no universally accepted definition based on specific temperatures. Additionally, it is often difficult to obtain stable and correct estimates near the extreme values of a distribution (boundary problem). Our findings highlight the importance of comprehensive assessment in the definition of extreme temperatures across space and time.

The practical implications of the present findings suggest that a better understanding of the relationships between high and low temperatures and emergency transport is crucial for public health officials to identify specific factors that affect susceptibility to high and low temperatures and to explore differences in susceptibility. Recently, the demand for the use of emergency ambulances in Japan has almost exceeded capacity, and public health officials have been required to reduce the use of emergency ambulances and develop mitigation strategies.[40] The results of this study could help public health officials predict temperature-related emergency transport and prepare for the effects of climatic change on emergency transport through the development of public health intervention strategies, such as timely public health and medical advice, improvements to housing and urban planning, early warning systems, health education, and health care system preparedness.[41]

In conclusion, we found evidence that most of the temperature-related emergency transport burden was attributable to the contribution of low temperature. The effect of extreme temperature was substantially less than that attributable to moderate but nonoptimal temperature. Our results suggest that public health interventions aimed at controlling temperature-related morbidity could be more effective when accounting for the effects of the entire range of temperatures.

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