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Seasonality of mortality in Japan: the role of temperature, influenza and other local characteristics

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Abstract

Objectives: To investigate the extent to which temperature and influenza explained seasonality of mortality in Japan and to examine modifications of the seasonality by prefecture-specific characteristics.

Design: We collected daily mortality from all-cause, circulatory, and respiratory disease in 47 prefectures in Japan between 1972 and 2015 and conducted time-series analysis to estimate the peak-to-trough ratio (PTR, a measure of seasonal amplitude) before and after adjusting for temperature and/or influenza. Next, we applied linear mixed effect models to investigate the association of PTR with each indicator on prefecture-specific characteristics.

Results: The nationwide unadjusted-PTRs for all-cause, circulatory and respiratory mortality were 1.29 (95% Confidence Intervals (CI): 1.28, 1.31), 1.53 (95%CI: 1.51, 1.56) and 1.51 (95%CI: 1.49, 1.54), respectively. These PTRs reduced substantially after adjusting for temperature but very little after a separate adjustment for influenza. However, in certain early years, adjusting for influenza led to larger PTR reductions in respiratory mortality. Before any adjustments, a larger PTR was associated with increases in averaged annual mean temperature, whereas a higher Gini index was surprisingly linked with a decreased PTR. Adjusting for temperature in PTR estimation reversed these associations.

Conclusion: Seasonality of mortality is primarily driven by temperature, with occasionally irregular seasonal patterns associated with influenza. Locations with warm climate and low inequality showed a large seasonal variation in mortality. Our findings can help us gain a better understanding of the mechanisms underlying seasonality of mortality and also provide important information for the management of seasonal risks.

Strengths and limitations of this study

- We investigated the contributions of temperature versus influenza to seasonal variation of different types of mortality by a common study design and statistical framework.
- We used indicators on a range of location-specific characteristics to identify locations that have larger seasonal variations in mortality.
- The study was conducted in Japan characterized by distinct seasonal weather conditions, so our results may not be generalized to locations with different climate (e.g., tropical countries).
- Our results on the contribution of influenza to seasonality of mortality can be complemented by including data on influenza subtypes and vaccination coverage.

Introduction

Seasonality of mortality is among the oldest observation across a broad range of population and geographical locations, typically entailing higher mortality in cold seasons than in warm seasons.[1–6] This epidemiological phenomenon reflects a complex interaction between environment and human.[2] The understanding of its underlying drivers is yet to be elucidated.

Some of the postulated contributors to seasonality of mortality include temperature, infectious disease, air pollution, physiological responses, and human behaviors.[1,2,7–9] Temperature is of most profound interest, with overwhelming evidence on its cold and hot effect on mortality.[10] Another well recognized contributor to seasonality is influenza, due to its strong seasonal cycle and association with inflammatory process.[11] A number of studies demonstrated an association between influenza and mortality in cold seasons.[11–15] Some of them focused on its role in temperature-mortality associations.[11,12] Other publications assessed its contribution to winter-season increase in mortality.[13–15] Although consensus exists that both temperature and influenza contribute to winter-season increase in mortality,[11–14,16] their relative importance has not been completely elucidated. Most research[11–14,16] has focused on either temperature or influenza only, and few studies have comparatively assessed their contribution to seasonality of mortality. We are aware of only one study that has compared their contributions to seasonality of all-cause mortality among people aged ≥ 75 years in Britain and suggested more seasonality was explained by temperature than influenza.[14]

The strength of seasonality in mortality varies geographically.[8] For example, a smaller seasonal amplitude was observed in areas with milder climates, suggesting that individuals living in warm areas might be more vulnerable to seasonal variations in mortality.[2] Several local characteristics on climate, demographic and socioeconomic factors, and adaptations have been linked with such spatial variation. However, only a few studies have evaluated their modifying effect on seasonality of mortality.[1,17] Another question remains unclear is if these modification effect will remain when we remove the effect of temperature and influenza from seasonal variations in mortality, given that the same local characteristics can also modify associations between influenza, temperature and mortality.[18–23]

In the current study, we collected daily mortality data between 1972 and 2015 from 47 prefectures in Japan to investigate the contribution of temperature and influenza to seasonality of mortality and to study its modifying factors by a range of prefecture-specific indicators. This study will strengthen our understanding of seasonality of mortality and provide important evidence to associate managements of seasonal risk factors to local conditions.

Method

Data collection

Hourly mean temperature (°C) and relative humidity (%) measured at a single monitoring site in the capital city of each prefecture were obtained from 1972 to 2015 from the Japan Meteorological Agency. We computed daily mean value of temperature and relative humidity for our analysis.

Daily mortality (counts) from all-cause, circulatory, respiratory disease and influenza were obtained from the Ministry of Health, Labor and Welfare of Japan between 1972 and 2015 for each prefecture in Japan. The principal cause of death statistics has been coded using the International Statistical Classification of Diseases and Related Health Problems, 8th version (ICD-8) from 1972 to 1978, the ICD-9 from 1979 to 1994, and the ICD-10 since 1995. Cause-specific mortality was defined according to the ICD system: circulatory mortality (ICD-8 codes 390-458, ICD-9 codes 390-459, ICD-10 codes I00-I99), respiratory mortality (ICD-8 and ICD-9 codes 460-519, ICD-10 codes J00-J99), mortality due to influenza (ICD-8 codes 470-474, ICD-9 codes 487-488, ICD-10 codes J09-J11). Weekly number of influenza like illness (ILI) were also obtained for each prefecture from April 1999 to 2015 from National Institute of Infectious Diseases, Japan.

Yearly data on prefecture-specific indicators was collected over the study period for each prefecture, including mean temperature, relative humidity, population density, the proportion of population aged $\geq$ 65 years, saving, income, Gini index (a measure of income inequality), consumer price index (CPI), economic power index (EPI, a measure of the wealth of a prefecture), the prevalence of air conditioning for households, and the number of registered physicians, nurses and hospital beds per 10K population. The details for data collection were described in previous studies [24,25] and summarized in supplementary material.

Data analysis

We conducted our data analysis in three steps. First, we assessed seasonality of mortality without adjustments for temperature or influenza. Then, we examined the changes in the seasonality after adjusting for temperature and influenza separately, as well as both at the same time. Lastly, we evaluated the associations between each indicator and seasonality estimates before and after adjustments.

We applied a generalized linear model with a quasi-Poisson family to assess seasonality of mortality in each prefecture without any adjustment for temperature and influenza. Day-of-year was treated as an indicator for seasonality, taking values from 1 to 366 corresponding to Jan 1st through Dec 31st for both common and leap years (from 60th day to 365th day in common years, values were taken from 61 to 366). We used a cyclic cubic spline with 4 degrees of freedom (*df*) for day of year to estimate seasonality. The days-of-year with maximum and minimum predicted mortality were identified as the peak and trough days, respectively, and were subsequently used to calculate the peak-to-trough ratio (PTR) to provide a measure of seasonality. Indicators for year, day-of-week and their interaction were used to control for the long-term trend and the effect of day-of-week. We excluded the data of the two days in our seasonality assessment: 17 January 1995 and 11 March 2011, the day of the Great Hanshin-Awaji Earthquake and Great East Japan Earthquake, respectively.

To assess the contribution of temperature and influenza to seasonality of mortality, we attempted three types of adjustment. First, we added temperature to our main model using a bi-dimensional cross-basis function to account for its non-linear and delayed effect on mortality. We modeled the exposure-response curve with a natural cubic B-spline with three internal knots at 25th, 50th, and 75th percentiles of temperature distribution, and the lag-response association with another natural cubic spline basis with 3 *df* with extended lags up to 21 days.[10,25]

Second, we removed temperature and adjusted for influenza in main model. We used as explanatory variable the count of daily deaths due to influenza as a measure of severe influenza circulating in the population, by incorporating natural log-transformed daily influenza mortality count with a natural cubic spline with 3 *df*. Third, adjustment was made using both temperature and influenza.

The prefecture-specific PTR was pooled for the whole of Japan for all-cause, circulatory and respiratory mortality, respectively, by meta-analysis with prefecture as a random factor. To explore if patterns of interest varied over time, we conducted yearly analyses for the entire country using separate quasi-Poisson regression model for each year with prefecture as a random factor.

To evaluate the modification of seasonal variation in mortality by prefecture-specific indicators, we applied linear mixed effects models (LMEMs) to investigate associations of PTR with each prefecture-specific indicator separately. We fitted LMEMs with random intercepts for prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital city of each prefecture were included to reduce spatial correlation, except for when we investigated annual mean temperature as the indicator, due to their high correlation. We conducted the analysis for all-cause, circulatory, and respiratory mortality in separate LMEMs. Results are expressed as the log(PTR) variation for a standard deviation increase of the indicator.

We performed a series of sensitivity analysis to confirm our findings. In particular, we repeated main analysis using weekly ILI cases instead of influenza mortality counts for influenza adjustment. See supplementary material for a description of modelling details.

Patient and public involvement

There was no patient or public involvement.

Results

This study included 39 913 020 deaths from all causes, 13 628 846 deaths from circulatory diseases, 5 027 271 deaths from respiratory diseases, and 32 582 deaths from influenza. Daily mean temperature for the whole country between 1972 and 2015 ranged from -14.1℃ to 33.8℃, with a mean value at 15.7℃ (Table 1). Daily deaths from influenza showed a large variation, ranging from 0 case to 77 cases with a median value at 0 (Table 1). Prefecture-specific summary was provided in Table S1.

The nationwide monthly summary of daily mean temperature and daily mortality showed a significant seasonal pattern (Figure S1). The most cases for mortality were found in cold season with a slight difference: mortality from influenza from January to March were much higher than that in December, while no significant difference from December to March was found for all-cause, circulatory and respiratory mortality.

We observed a high variability for healthcare capacity (Table S2 & S3), while a low variability for socioeconomic indicators. Most of the indicators are correlated (Figure S2). In particular, EPI was highly correlated with population density, proportion of individuals aged over than 65 years old, and numbers of physicians, nurses and hospital beds (correlation>0.70). In addition, saving is highly correlated with income (correlation>0.70). For the sake of brevity, we excluded population density, proportion of individuals aged over 65 years old, numbers of physicians, nurses and hospital beds, and saving in main analysis.

Figure 1 and Table 2 show the pooled results for the whole of Japan for seasonality of all-cause, circulatory, and respiratory mortality before and after adjustments for temperature and/or influenza. We observed a clear seasonal pattern with higher numbers of deaths in cold seasons than in warm seasons. Before any adjustments, the nationwide pooled PTR for all-cause, circulatory and respiratory mortality were 1.29 (95% confidence intervals (CI): 1.28, 1.31), 1.53 (95% CI: 1.51, 1.56) and 1.51 (95% CI: 1.49, 1.54), respectively. After adjustments for temperature and influenza, the shape of seasonality remained (Figure 1), but its amplitude reduced to different extents. Adjusting for just temperature reduced PTRs substantially in particular for all-cause and circulatory mortality to 1.08 (95% CI: 1.075,1.09) and 1.10 (95% CI: 1.08, 1.11). Adjusting for just influenza reduced PTRs only very slightly to 1.28 (95% CI: 1.27,1.30), 1.53 (95% CI: 1.50,1.55), and 1.46 (95% CI: 1.44, 1.48) for all-cause, circulatory and respiratory mortality, respectively. Notably, adjusting for temperature and influenza did not flatten the seasonal pattern or reduce the PTR to 1.

Similarly, prefecture-specific PTRs also showed a substantial reduction with temperature adjustment while a slight reduction when influenza was adjusted only, although an apparent reduction was observed in influenza-adjusted PTR for respiratory mortality (Figure 2). Furthermore, PTR for all mortality types varied across prefectures, and the spatial variation after adjustments was less apparent in particular for all-cause and circulatory mortality. Prefectures with higher latitude (northern areas), including Hokkaido, Aomori, and Akita, as well as the southernmost prefecture- Okinawa, showed a lower unadjusted-PTR and a smaller reduction after adjustments for temperature.

Our yearly analyses for the entire country showed a large reduction after adjusting for temperature while a small reduction after adjusting for influenza only for most of the years (Figure S3). For the year of 1975 and 1976, however, a larger reduction in PTR for respiratory mortality was observed when only the influenza was adjusted. Unexpectedly, PTR for all mortality types in several years, e.g., 1983, 1995 and 1999, increased when temperature was adjusted.

Figure 3 shows associations between selected indicators and PTR. Before any adjustments, PTR for all-cause mortality was positively associated with 44-year averaged annual mean temperature, whereas a negative association was observed for Gini index. After a separate adjustment for influenza, these associations remained. Adjusting for temperature, however, reversed the associations with a large confidence interval.

Similar results were observed for cause-specific mortality, with the exception of income and air conditioning prevalence: income was positively associated with unadjusted-PTR for circulatory mortality, and air conditioning prevalence was negatively associated with unadjusted-PTR for respiratory mortality. These associations remained similar when adjusting for just influenza, while moved towards null after including temperature in the adjustment.

Figures S4-S5 and Table S3 showed the results by using mortality data between 1999 April and 2015 and weekly ILI cases for influenza adjustment. The results after a separate adjustment for influenza were robust to different indicators for seasonal influenza infections. However, the results for respiratory mortality before and after any adjustments seems to be sensitive to the study period: both unadjusted- and adjusted- PTR were lower when using the subset of data between 1999 April and 2015 than by using the data between 1972 and 2015.

Discussion

In this study, we investigated the contribution of temperature and influenza to seasonal variation of mortality in 47 prefectures of Japan and evaluated the modifications of seasonality by a range of prefecture-specific indicators. Our findings show that temperature contributed substantially to seasonality of mortality in general, while influenza explained seasonal variations in certain years. In addition, seasonal amplitudes varied between prefectures. Our results suggest that individuals living in prefectures characterized by warm climate and low inequalities experienced larger seasonal variations of mortality, which may be controlled by the preventive strategies targeting the impact of temperature on mortality.

Temperature and influenza have been among the most studied drivers of seasonality of mortality.[13–16] However, most of the investigations focused on either temperature or influenza. How much of seasonality of mortality is dependent on temperature versus influenza remain unsolved. Our finding showed that most of seasonality of mortality in Japan was attributable to temperature while little was driven by influenza. Consistent with our findings, a population based cohort study in elderly British people examined month to month variation in mortality and its relationship with temperature and influenza A, and discovered that most of seasonal fluctuation was associated with cold temperature and a small component related with influenza A. Despite the smaller contribution of influenza to seasonal variation of mortality than temperature, our single-year analysis suggested that influenza was accountable for the irregularities of seasonality over years. A study[11] in 48 U.S. cities observed a link between influenza epidemic and the irregularly high winter mortality in some certain years. Evidence thus far implies that temperature contributes substantially to seasonality of mortality in general, while influenza is related with seasonal variations of mortality in certain years.

Notably, removing the effect of temperature and influenza from seasonal variation in mortality did not completely flatten the seasonal pattern of mortality, in particular, respiratory mortality.

Seasonality of mortality is resulted from complex interaction between human behavior and environment. In addition to temperature and influenza, other infectious diseases (e.g., respiratory syncytial virus), air pollutants, behavioral changes based on a seasonal basis (e.g., dietary pattern and physical activities) have been linked with seasonal variation of diseases and mortality. However, there is no direct evidence assessing their contribution to seasonality of mortality.

Our sub-period analysis suggests that seasonal amplitudes of respiratory mortality were lower in recent years. This finding may be related with changes in influenza vaccination policy in Japan: the policy from 1962 to 1987 required Japanese schoolchildren to be vaccinated against influenza, and in 1977, such vaccination policy became obligate, which was relaxed in 1987 and repealed in 1994, resulting in a substantial reduction in vaccination coverage.[26,27] In recent decade, the widespread use of neuraminidase inhibitors and increasing vaccination rates in schoolchildren and especially the elderly have led to a substantial decrease in respiratory mortality.[26] Further investigation should be conducted to confirm our hypothesis.

Despite of a similar seasonal shape across prefectures, seasonal amplitudes varied across 47 prefectures. Our findings showed that this spatial variation was related with averaged annual mean temperature and Gini index, and that these associations were reversed after adjusting for temperature. Individuals living in cold prefectures show less seasonal variation in mortality, which may be partially explained by a better cold acclimatization from the combination of habituation, metabolic adjustment, and insulative acclimatization. [8,28,29] Counterintuitively, our results suggest individuals living in prefectures with low inequality experienced larger seasonal variations in mortality. A recent multi-country analysis found a positive association between Gini index and heat effect of temperature on mortality, whereas no evidence was observed for its association with cold effect. Therefore, prefectures characterized by low inequality may be more vulnerable to heat effect, leading to a higher mortality in summer and subsequently attenuating the seasonal difference in mortality between winter and summer. Although our findings suggested averaged annual mean temperature and Gini index as the potential effect modification, adjusting for temperature reversed their associations, suggesting that the preventive strategies targeting the impact of temperature may reduce the vulnerability of individuals living in prefectures characterized by warm climate and low inequality. It is worth noting, however, that we did not consider potential confounding between indicators due to their high correlations. Therefore, our results need to be interpreted carefully, and further research at individual level or by including areas with large variation in these indicators, is merited to confirm our findings.

This study has several limitations. First, our study was conducted in Japan that has distinct seasonal weather conditions, hence our results may not be applicable to other areas with different climate (e.g., tropical countries). Second, we assumed the association of mortality with influenza and temperature did not change between 1972 and 2015. Although our main conclusion remained in our sub-period analysis by using data between 1999 and 2015, seasonality estimates for respiratory mortality seems to be sensitive to study period, and our findings from single year analysis needs to be interpreted carefully. Future investigations should be conducted by extending current datasets to those areas with different climate, and also by including more details for influenza (e.g., influenza subtype and vaccination coverage). Results from these investigations would complement our findings in current analysis.

This study presents findings from an epidemiologic analysis investigating the role of temperature, influenza and other local characteristics on seasonality of mortality across multiple locations. A strength of current study was the investigation of contributions of temperature versus influenza to seasonal variation of different types of mortality by a common study design and statistical framework, while previous studies mostly focused on either temperature or influenza only. In addition, our analysis on the effect modification provides important information for the development of interventions to attenuate seasonal effect on mortality.

This study suggests that seasonality of mortality is primarily driven by temperature, with occasionally seasonal variations associated with influenza. Furthermore, our analysis identifies several prefecture-specific characteristics that may modify the seasonality of mortality. In sum, our findings can help us to gain a better understanding of seasonality of mortality and provide important information for the management of seasonal risks.

Contributors: LM conducted the study, analyzed the data and wrote the manuscript. CN and XS helped with the statistical analysis and the discussion of the text. MT, LY and YH contributed to the final version of the manuscript. BA helped with the data analysis and the interpretation of the results. MH contributed to the study design and the discussion of the results.

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Competing interests: None declared.

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Data availability statement: Data are available upon reasonable request. The technical appendix, statistical code and data set will be available upon request from the Corresponding author.

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Figure captions:

Figure 1. Pooled seasonality of all-cause, circulatory, and respiratory mortality between 1972 and 2015 before and after adjustments (black: without any adjustment; blue: adjusted for influenza only; green: adjusted for temperature only; red: adjusted for both temperature and influenza)

The seasonality is computed as the ratio of predicted mortality at each day of the year to the predicted minimum mortality at the trough with 95% confidence intervals (95%CIs):

$$Ratio = \frac{Mortality\ prediction\ at\ day_i}{Minimum\ mortality\ prediction\ at\ the\ trough}$$

Figure 2. Prefecture-specific peak-to-trough ratio (PTR) with 95% confidence intervals (95% CI) for all-cause (left), circulatory (middle), and respiratory (right) mortality before (black) and after adjustments for influenza only (blue), temperature only (green), and both (red)

Figure 3. Associations between each indicator and PTR before and after adjusting for influenza and temperature

Coefficient and 95% confidence intervals were obtained from liner mixed effect models adjusting for latitude and longitude, except for when we investigated averaged annual mean temperature as the indicator, due to their high correlation. Results are expressed as log (PTR) change for standard deviation increase in each indicator.

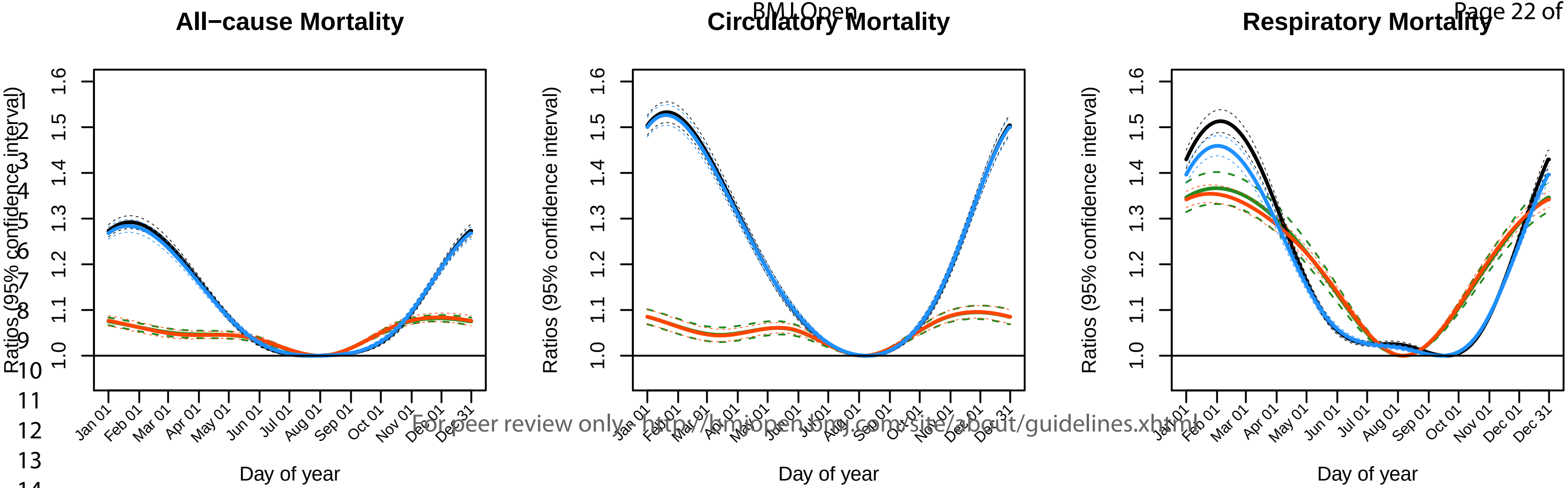
Table 1. Nationwide summary of daily mean temperature (°C) and daily death [a] (numbers of cases) between 1972 and 2015

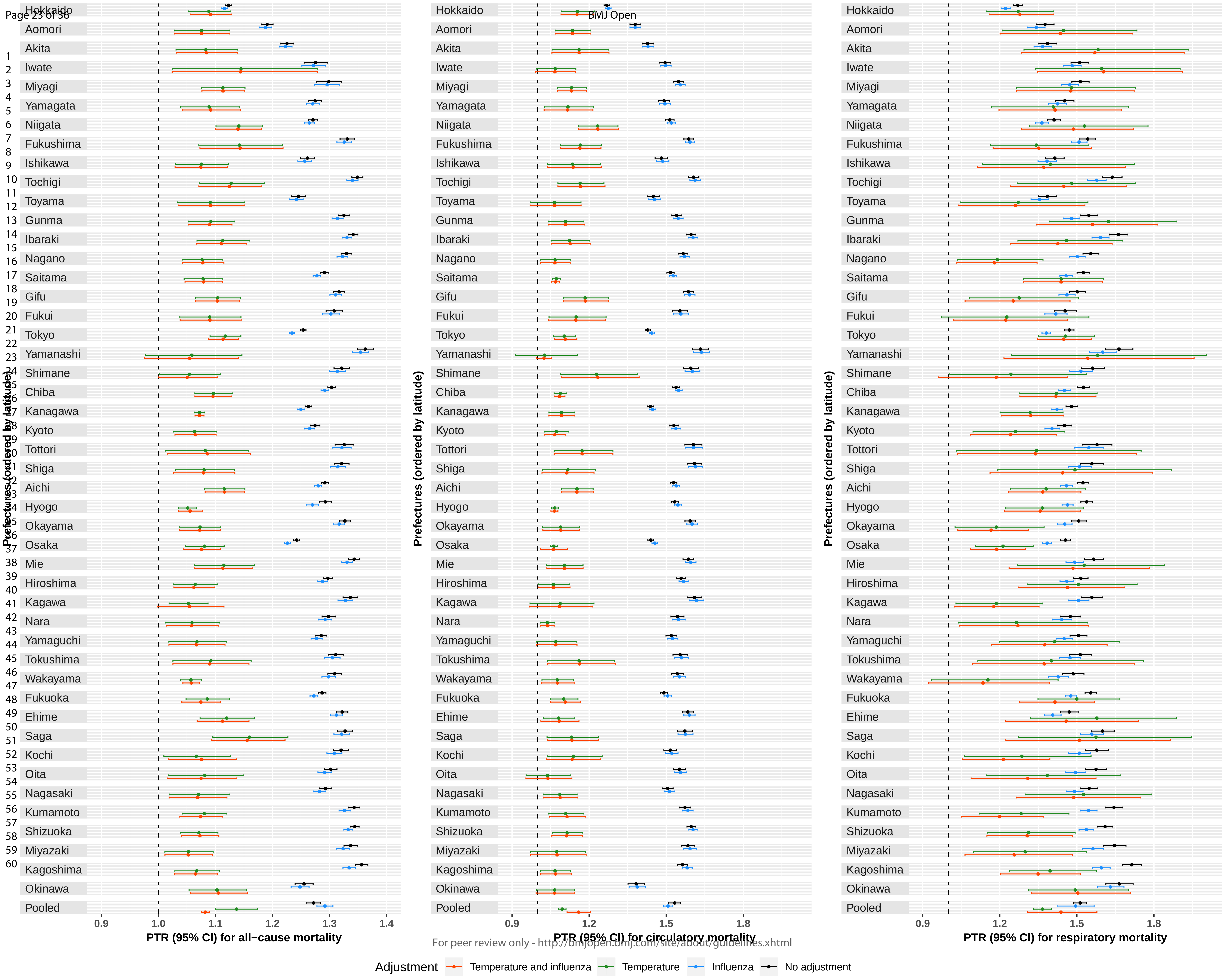
Variables	Median [interquartile range]	Mean (SD)	Range
Mean temperature	15.70 [7.70; 22.30]	15.12 (8.61)	[-14.10; 33.80]
All-cause mortality	2350 [2012; 2895]	2484.00 (587.85)	[1447; 4712]
Circulatory mortality	826 [730; 948]	848.10 (147.81)	[553; 1454]
Respiratory mortality	292 [177; 431]	292.00 (156.28)	[64; 1072]
Influenza mortality	0 [0; 1]	2.03 (5.53)	[0; 77]

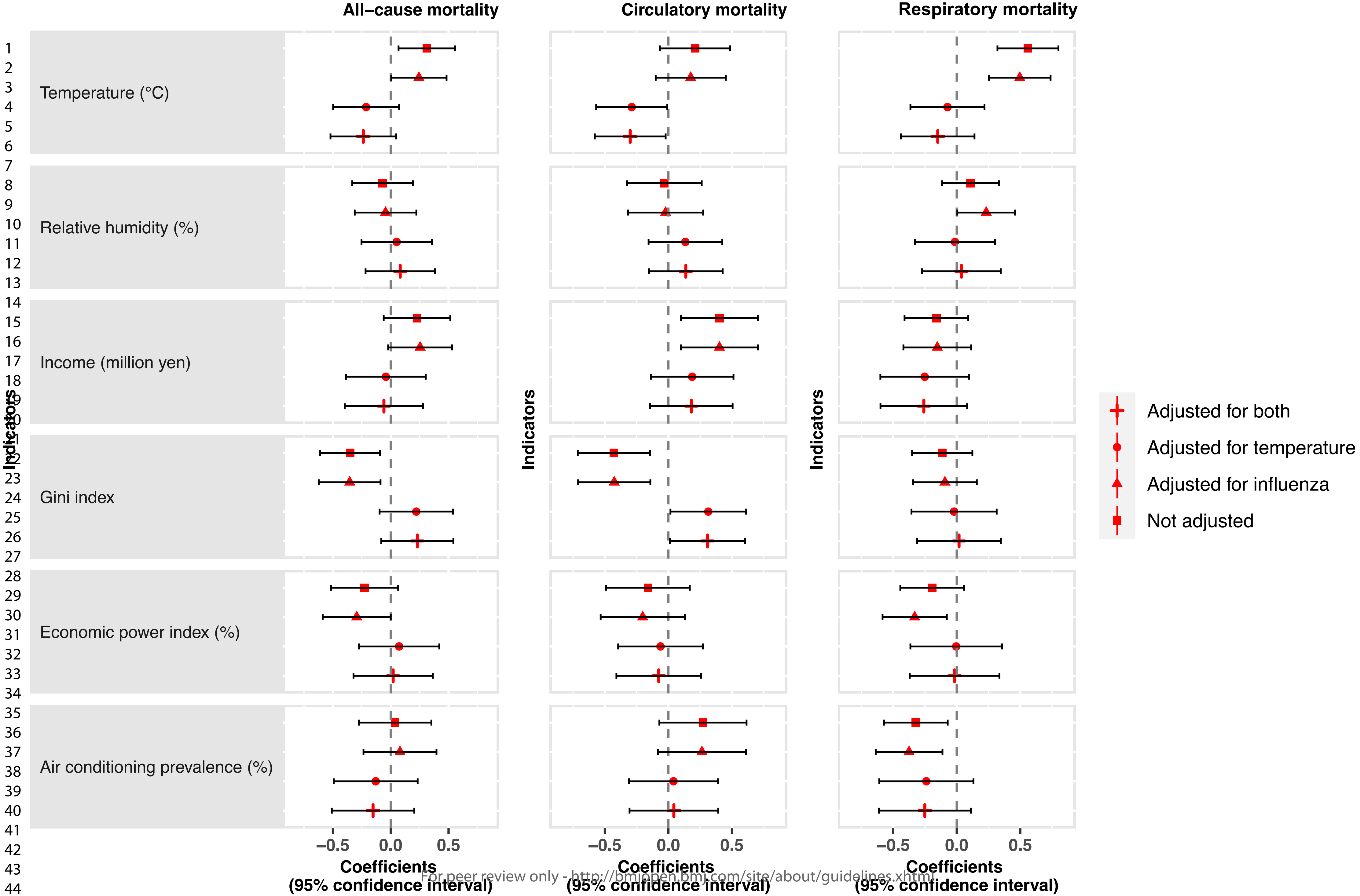
[a] We excluded the data of the two days: 17 January 1995 and 11 March 2011, the day of the Great Hanshin-Awaji Earthquake and Great East Japan Earthquake, respectively

Table 2. Nationwide pooled peak-to-trough ratio (PTR) with 95% confidence interval (95% CI) with/without adjustment for temperature and/or influenza

Adjustment	All-cause mortality		Circulatory mortality		Respiratory mortality	
	PTR	95% CI	PTR	95% CI	PTR	95% CI
None	1.29	1.28, 1.31	1.53	1.51, 1.56	1.51	1.49, 1.54
Influenza	1.28	1.27, 1.30	1.53	1.50, 1.55	1.46	1.44, 1.48
Temperature	1.08	1.08, 1.09	1.10	1.08, 1.11	1.37	1.33, 1.40
Influenza and temperature	1.08	1.08, 1.09	1.10	1.08, 1.11	1.35	1.32, 1.39


All−cause Mortality
Circulatory Mortality
Respiratory Mortality
Ratios (95% confidence interval)
1.0
1.1
1.2
1.3
1.4
1.5
1.6
Jan 01
Feb 01
Mar 01
Apr 01
May 01
Jun 01
Jul 01
Aug 01
Sep 01
Oct 01
Nov 01
Dec 01
Dec 31
Day of year


Hokkaido
Aomori
Akita
Iwate
Miyagi
Yamagata
Niigata
Fukushima
Ishikawa
Tochigi
Toyama
Gunma
Ibaraki
Nagano
Saitama
Gifu
Fukui
Tokyo
Yamanashi
Shimane
Chiba
Kanagawa
Kyoto
Tottori
Shiga
Aichi
Hyogo
Okayama
Osaka
Mie
Hiroshima
Kagawa
Nara
Yamaguchi
Tokushima
Wakayama
Fukuoka
Ehime
Saga
Kochi
Oita
Nagasaki
Kumamoto
Shizuoka
Miyazaki
Kagoshima
Okinawa
Pooled
Prefectures (ordered by latitude)
0.9
1.0
1.1
1.2
1.3
1.4
PTR (95% CI) for all−cause mortality
0.9
1.2
1.5
1.8
PTR (95% CI) for circulatory mortality
0.9
1.2
1.5
1.8
PTR (95% CI) for respiratory mortality
Adjustment
Temperature and influenza
Temperature
Influenza
No adjustment


All–cause mortality
Circulatory mortality
Respiratory mortality
Temperature (°C)
Relative humidity (%)
Income (million yen)
Gini index
Economic power index (%)
Air conditioning prevalence (%)
Indicators
Indicators
Indicators
−0.5
0.0
0.5
−0.5
0.0
0.5
−0.5
0.0
0.5
Coefficients
(95% confidence interval)
Coefficients
(95% confidence interval)
Coefficients
(95% confidence interval)
Adjusted for both
Adjusted for temperature
Adjusted for influenza
Not adjusted

Supplementary material

Seasonality of mortality in Japan: the role of temperature, influenza and other local characteristics

Table of Contents

Table S1. Summary of daily mean temperature, daily cases of all-cause, circulatory, respiratory, and influenza mortality

Prefecture/ country [a]	Daily mean temperature (℃)		All-cause mortality (n)		Circulatory mortality (n)		Respiratory mortality (n)		Influenza mortality (n)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD	Range	Mean (SD)	Range	Mean (SD)	Range
Hokkaido	8.87 (9.54)	[-14.10;30.10]	113.07 (28.91)	[49;317]	37.90 (7.99)	[10;79]	14.21 (7.43)	[0;55]	0.08 (0.34)	[0;6]
Aomori	10.33 (8.94)	[-8.70;30.10]	34.01 (9.40)	[8;79]	11.90 (3.82)	[1;33]	4.09 (2.76)	[0;19]	0.02 (0.17)	[0;4]
Akita	11.69 (9.00)	[-6.40;31.60]	30.84 (8.34)	[7;98]	11.20 (3.73)	[0;33]	3.61 (2.63)	[0;19]	0.02 (0.13)	[0;2]
Iwate	10.25 (9.32)	[-8.90;29.60]	33.35 (9.28)	[8;85]	12.65 (4.20)	[1;33]	4.27 (2.73)	[0;22]	0.02 (0.17)	[0;3]
Miyagi	12.41 (8.29)	[-5.20;31.20]	43.98 (13.14)	[13;152]	16.07 (4.99)	[2;43]	5.02 (3.40)	[0;29]	0.04 (0.21)	[0;4]
Yamagata	11.71 (9.30)	[-7.40;31.50]	31.33 (8.13)	[9;68]	11.61 (3.85)	[0;29]	3.69 (2.62)	[0;18]	0.02 (0.16)	[0;3]
Niigata	13.78 (8.67)	[-3.90;32.60]	57.84 (13.66)	[24;112]	20.77 (5.71)	[4;52]	6.69 (3.74)	[0;26]	0.05 (0.25)	[0;5]
Fukushima	13.02 (8.79)	[-5.20;31.40]	48.71 (12.56)	[18;114]	18.23 (5.45)	[3;45]	5.88 (3.68)	[0;29]	0.03 (0.20)	[0;3]
Toyama	14.03 (8.76)	[-4.40;33.80]	25.97 (7.24)	[5;59]	8.80 (3.27)	[0;25]	3.44 (2.44)	[0;16]	0.02 (0.13)	[0;3]
Nagano	11.92 (9.46)	[-7.70;30.70]	50.71 (12.47)	[16;107]	19.77 (5.64)	[4;52]	5.77 (3.64)	[0;23]	0.04 (0.22)	[0;3]
Ishikawa	14.62 (8.57)	[-3.90;32.40]	25.03 (7.09)	[6;58]	8.64 (3.27)	[0;26]	3.21 (2.34)	[0;16]	0.02 (0.14)	[0;3]
Tochigi	13.77 (8.52)	[-4.50;31.70]	41.02 (11.62)	[11;95]	15.24 (4.88)	[1;38]	5.11 (3.28)	[0;25]	0.03 (0.21)	[0;5]
Gunma	14.55 (8.47)	[-3.80;32.60]	42.13 (11.91)	[12;101]	15.17 (4.81)	[0;41]	5.73 (3.69)	[0;27]	0.04 (0.24)	[0;4]
Ibaraki	13.68 (8.14)	[-3.80;31.30]	58.95 (16.84)	[22;136]	21.16 (6.25)	[2;52]	7.05 (4.64)	[0;31]	0.05 (0.26)	[0;5]
Fukui	14.54 (8.79)	[-3.80;32.10]	18.59 (5.60)	[4;45]	6.46 (2.79)	[0;20]	2.39 (1.95)	[0;13]	0.02 (0.14)	[0;4]
Saitama	14.95 (8.36)	[-2.80;33.70]	100.88 (37.92)	[33;258]	34.09 (10.67)	[7;97]	12.51 (8.45)	[0;58]	0.08 (0.38)	[0;7]
Tokyo	16.23 (7.84)	[-0.60;33.20]	210.93 (56.25)	[100;434]	70.19 (14.77)	[32;147]	26.54 (13.62)	[1;96]	0.17 (0.62)	[0;11]
Yamanashi	14.6 (8.64)	[-4.40;31.80]	19.66 (6.10)	[3;52]	6.92 (2.96)	[0;23]	2.39 (1.92)	[0;16]	0.02 (0.16)	[0;4]
Chiba	15.73 (7.73)	[-1.40;32.20]	93.29 (33.15)	[29;216]	32.28 (9.92)	[8;88]	11.12 (7.43)	[0;58]	0.07 (0.33)	[0;6]
Tottori	14.86 (8.41)	[-5.60;32.30]	15.44 (4.87)	[1;38]	5.54 (2.57)	[0;19]	1.76 (1.55)	[0;11]	0.01 (0.11)	[0;2]
Shimane	14.85 (8.16)	[-5.30;32.20]	21.05 (5.85)	[5;118]	7.45 (3.16)	[0;23]	2.69 (1.99)	[0;14]	0.02 (0.16)	[0;3]
Gifu	15.79 (8.56)	[-3.00;32.90]	43.03 (11.81)	[14;99]	15.30 (4.82)	[2;39]	5.26 (3.57)	[0;23]	0.03 (0.20)	[0;4]
Kanagawa	15.80 (7.63)	[-1.00;32.20]	124.97 (45.15)	[35;297]	39.98 (11.29)	[12;101]	15.47 (9.76)	[0;65]	0.09 (0.38)	[0;6]
Aichi	15.75 (8.46)	[-2.90;32.70]	116.50 (33.64)	[50;236]	39.35 (9.53)	[12;80]	13.84 (8.40)	[0;52]	0.08 (0.35)	[0;7]
Kyoto	15.86 (8.61)	[-3.40;32.80]	52.80 (12.76)	[17;119]	17.85 (5.26)	[2;45]	6.55 (4.10)	[0;32]	0.04 (0.23)	[0;4]

Table S1. Continued

Prefecture/ country	Daily mean temperature (°C)		All-cause mortality (n)		Circulatory mortality (n)		Respiratory mortality (n)		Influenza mortality (n)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Shiga	14.67 (8.52)	[-3.20;31.80]	24.37 (7.44)	[5;60]	8.50 (3.35)	[0;25]	3.01 (2.32)	[0;18]	0.02 (0.16)	[0;4]
Shizuoka	16.58 (7.41)	[-0.90;31.90]	72.73 (21.16)	[29;172]	25.59 (7.17)	[6;62]	8.67 (5.23)	[0;36]	0.05 (0.29)	[0;5]
Mie	15.84 (8.15)	[-2.40;33.50]	40.22 (10.72)	[12;95]	14.36 (4.66)	[2;42]	4.73 (3.26)	[0;24]	0.04 (0.22)	[0;4]
Hyogo	16.31 (8.20)	[-4.30;32.50]	109.02 (26.72)	[44;336]	35.11 (8.74)	[9;81]	13.10 (7.75)	[0;58]	0.09 (0.39)	[0;7]
Nara	14.85 (8.43)	[-3.70;31.70]	26.76 (8.48)	[3;62]	9.19 (3.55)	[0;28]	3.34 (2.58)	[0;17]	0.02 (0.15)	[0;3]
Osaka	16.80 (8.30)	[-2.10;32.90]	157.06 (41.02)	[72;341]	48.61 (11.28)	[18;115]	20.24 (11.78)	[0;75]	0.11 (0.44)	[0;8]
Okayama	15.89 (8.58)	[-4.80;32.30]	44.59 (10.91)	[16;92]	15.26 (4.80)	[1;40]	6.26 (3.93)	[0;26]	0.04 (0.24)	[0;5]
Hiroshima	15.93 (8.30)	[-5.80;32.70]	60.47 (14.89)	[23;146]	20.01 (5.74)	[4;47]	7.91 (4.70)	[0;34]	0.04 (0.24)	[0;4]
Kagawa	15.80 (7.63)	[-1.00;32.20]	124.97 (45.15)	[35;297]	39.98 (11.29)	[12;101]	15.47 (9.76)	[0;65]	0.09 (0.38)	[0;6]
Wakayama	16.60 (8.06)	[-2.70;32.70]	27.17 (7.17)	[7;73]	9.36 (3.51)	[0;28]	3.20 (2.46)	[0;16]	0.03 (0.19)	[0;4]
Yamaguchi	15.33 (8.38)	[-5.40;31.20]	39.07 (9.61)	[14;82]	13.53 (4.35)	[2;36]	5.49 (3.46)	[0;28]	0.04 (0.22)	[0;4]
Tokushima	16.48 (7.92)	[-4.00;32.60]	21.14 (5.94)	[4;51]	7.27 (3.02)	[0;21]	2.93 (2.17)	[0;15]	0.02 (0.15)	[0;4]
Ehime	16.35 (7.97)	[-3.10;31.90]	36.86 (9.28)	[12;81]	12.95 (4.35)	[0;34]	4.70 (3.08)	[0;20]	0.03 (0.21)	[0;4]
Fukuoka	16.89 (7.84)	[-3.20;32.80]	99.34 (24.68)	[41;210]	30.77 (7.52)	[8;73]	13.35 (7.93)	[0;57]	0.09 (0.39)	[0;7]
Kochi	16.90 (7.74)	[-2.30;32.10]	22.57 (6.07)	[5;79]	8.31 (3.28)	[0;27]	3.05 (2.21)	[0;18]	0.03 (0.19)	[0;5]
Oita	16.34 (7.73)	[-3.40;31.70]	30.00 (7.60)	[9;71]	10.67 (3.83)	[0;33]	4.09 (2.77)	[0;21]	0.03 (0.21)	[0;4]
Saga	16.53 (8.16)	[-3.60;32.30]	21.08 (5.88)	[2;50]	7.07 (2.97)	[0;23]	2.83 (2.19)	[0;18]	0.02 (0.14)	[0;4]
Kumamoto	16.82 (8.25)	[-3.20;31.70]	43.14 (10.77)	[12;140]	14.88 (4.85)	[1;39]	5.89 (3.78)	[0;31]	0.06 (0.32)	[0;6]
Nagasaki	17.11 (7.61)	[-2.50;32.20]	36.71 (9.00)	[13;273]	12.49 (4.23)	[0;32]	5.06 (3.16)	[0;23]	0.03 (0.21)	[0;4]
Miyazaki	17.51 (7.44)	[-1.00;32.00]	26.77 (7.69)	[6;67]	9.53 (3.58)	[0;28]	3.64 (2.63)	[0;21]	0.03 (0.20)	[0;4]
Kagoshima	18.33 (7.50)	[-2.10;31.70]	46.72 (10.89)	[17;112]	16.59 (5.24)	[1;46]	6.66 (4.08)	[0;38]	0.06 (0.31)	[0;7]
Nationwide	15.12 (8.61)	[-14.10;33.80]	2484.00 (587.85)	[1447;4712]	848.10 (147.81)	[553; 1454]	292.00 (156.28)	[64;1072]	2.03 (5.53)	[0;77]

[a] Prefectures was ordered by latitude from high to low.

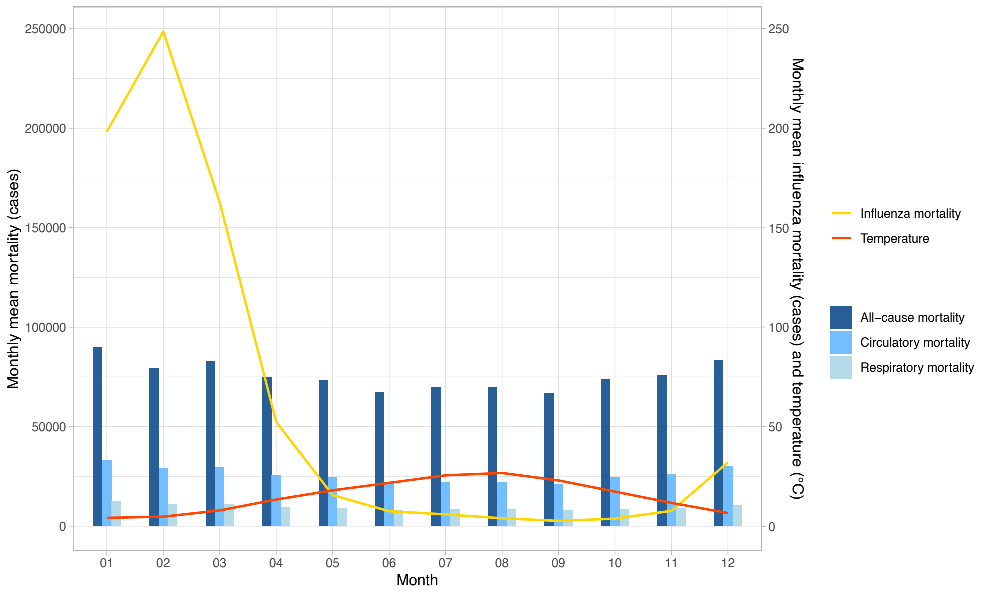


Figure S1. Nationwide monthly summary of daily mean temperature, daily mortality cases from all-cause, circulatory, respiratory disease and influenza between 1972 and 2015

Table S2. Prefecture-specific summary of annual value across the years 1972-2015 for all indicators (mean (SD))

Prefecture/ country	Temperature (℃)	Relative humidity (%)	Density (population/km^2)	% population ≥ 65 years	Savings (million yen)	Income (million yen)	CPI	Gini index	EPI (%)	Physicians (number per 10k population)	Nurses (number per 10k population)	Hospital beds (number per 10K population)	AC (%)
Hokkaido	8.82 (0.63)	69.67 (1.99	0.0056 (0.0001)	0.14 (0.06)	7.9 (3.96)	5.15 (1.42)	86.7 (16.51)	0.28 (0.01)	0.38 (0.02)	9.47 (2.73)	25.69 (12.65)	97.78 (15.51)	6.14 (5.25)
Aomori	10.28 (0.66)	74.81 (1.59	0.0015 (0.0000)	0.15 (0.06)	6.71 (3.25)	5.01 (1.42)	81.8 (17.93)	0.29 (0.02)	0.3 (0.03)	2.2 (0.39)	6.34 (2.75)	20.13 (1.42)	18.9 (17.85)
Akita	11.65 (0.59)	73.09 (1.1	0.0012 (0.0001)	0.18 (0.07)	7.42 (3.69)	5.54 (1.60)	85.72 (17.87)	0.29 (0.02)	0.27 (0.02)	1.84 (0.43)	5.37 (2.37)	16.87 (1.68)	30.72 (26.56)
Iwate	10.2 (0.61)	73.84 (1.16	0.0014 (0.0000)	0.17 (0.07)	7.99 (4.40)	5.24 (1.70)	84.96 (17.29)	0.29 (0.02)	0.29 (0.02)	2.19 (0.36)	7.4 (3.06)	19.8 (2.20)	20.36 (18.76)
Miyagi	12.36 (0.66)	71.13 (1.45	0.0022 (0.0002	0.14 (0.05)	8.25 (3.89)	5.84 (1.63)	86.25 (17.48)	0.29 (0.03)	0.51 (0.03)	3.87 (0.82)	8.18 (3.93)	24.23 (2.92)	33.43 (25.87)
Yamagata	11.67 (0.65)	74.48 (1.58	0.0012 (0.0000)	0.18 (0.06)	8.22 (4.34)	6.01 (1.99)	84.89 (17.08)	0.29 (0.02)	0.31 (0.02)	1.92 (0.55)	5.44 (2.63)	13.42 (2.13)	38.91 (28.07)
Niigata	13.76 (0.62)	71.77 (1.91	0.0024 (0.0000)	0.17 (0.06)	9.97 (5.39)	6.13 (1.97)	85.43 (17.67)	0.29 (0.02)	0.4 (0.03)	3.7 (0.71)	9.69 (4.49)	28.03 (3.52)	57.84 (30.69)
Fukushima	12.97 (0.64)	68.91 (1.19	0.0021 (0.0001)	0.16 (0.06)	8.4 (4.31)	5.7 (1.78)	83.75 (17.51)	0.3 (0.02)	0.42 (0.03)	3.15 (0.70)	7.87 (3.62)	29.92 (3.57)	33.86 (24.19)
Toyama	13.98 (0.70)	77.35 (1.88	0.0011 (0.0000)	0.17 (0.06)	11.28 (5.67)	6.74 (2.18)	86.55 (17.29)	0.29 (0.02)	0.42 (0.06)	2 (0.59)	5.51 (2.54)	17.03 (2.25)	62.83 (30.31)
Nagano	11.88 (0.60)	72.12 (1.62	0.0021 (0.0001)	0.18 (0.06)	10.63 (5.36)	6.05 (1.89)	86.18 (17.64))	0.28 (0.02)	0.44 (0.04)	3.34 (0.81)	9.19 (4.70)	23.79 (2.12)	27.96 (20.50)
Ishikawa	14.59 (0.62)	71.95 (2.16	0.0011 (0.0000)	0.15 (0.05)	11.97 (5.95)	6.57 (2.14)	87.53 (17.09)	0.28 (0.02)	0.44 (0.05)	2.55 (0.49)	6 (3.07)	19.87 (2.03)	62.88 (29.01)
Tochigi	13.71 (0.76)	69.85 (1.85	0.0019 (0.0001)	0.14 (0.05)	11.06 (5.61)	6.3 (1.90)	84.14 (18.03)	0.29 (0.01)	0.58 (0.07)	3.09 (0.94)	6.08 (3.58)	20.97 (2.26)	54.73 (30.61)
Gunma	14.49 (0.68)	63.54 (2.4	0.0019 (0.0001)	0.15 (0.05)	10.63 (5.57)	5.91 (1.78)	86.73 (17.40)	0.28 (0.02)	0.55 (0.05)	3.23 (0.84)	6.43 (3.70)	22.31 (4.36)	58.94 (28.67)
Ibaraki	13.62 (0.68)	74.47 (1.91	0.0028 (0.0002)	0.14 (0.05)	10.63 (5.34)	6.3 (2.07)	84.55 (17.08)	0.29 (0.02)	0.6 (0.07)	3.4 (1.10)	7.67 (4.47)	29.99 (5.49)	53.2 (31.75)
Fukui	14.51 (0.55)	75.11 (1.73	0.0008 (0.0000)	0.17 (0.05)	12.8 (6.39)	6.88 (2.13)	86.82 (17.30)	0.3 (0.01)	0.38 (0.04)	1.36 (0.41)	3.45 (1.76)	11.57 (1.31)	67.39 (29.30)
Saitama	14.89 (0.71)	65.68 (2.28	0.0062 (0.0009)	0.11 (0.05)	10.53 (5.32)	6.4 (1.96)	85.52 (17.58)	0.28 (0.03)	0.7 (0.06)	6.72 (2.48)	14.49 (9.58)	50.91 (15.08)	72.88 (28.12)
Tokyo	16.19 (0.64)	62.07 (2.36	0.012 (0.0005)	0.13 (0.05)	12.88 (6.13)	6.81 (1.95)	87.61 (18.28)	0.31 (0.01)	1.21 (0.14)	27.53 (7.17)	46.3 (19.26)	129.27 (7.64)	74.09 (25.50)
Yamanashi	14.54 (0.67)	65.3 (2.42	0.0008 (0.0000)	0.16 (0.05)	9.79 (4.70)	5.88 (1.77)	84.58 (17.85)	0.29 (0.02)	0.38 (0.05)	1.34 (0.41)	3.29 (1.78)	10.72 (1.18)	42.05 (26.19)
Chiba	15.67 (0.74)	68.68 (1.7	0.0054 (0.0007)	0.12 (0.05)	10.97 (5.45)	6.52 (2.01)	86.61 (17.30)	0.29 (0.02)	0.72 (0.07)	6.65 (2.40)	14.53 (8.78)	47.77 (11.38)	63.12 (30.35)
Tottori	14.82 (0.58)	73.81 (1.34	0.0006 (0.0000)	0.18 (0.05)	10.54 (5.40)	5.84 (1.78)	85.96 (17.12)	0.29 (0.02)	0.25 (0.02)	1.41 (0.28)	3.24 (1.22)	8.51 (0.66)	59.16 (29.55)
Shimane	14.81 (0.60)	75.88 (1.72	0.0008 (0.0000)	0.2 (0.06)	9.66 (5.02)	5.77 (1.81)	84.3 (17.53)	0.3 (0.02)	0.23 (0.02)	1.49 (0.44)	3.89 (1.77)	10.92 (1.54)	56.21 (30.75)
Gifu	15.74 (0.63)	67.3 (2.32	0.002 (0.0001)	0.15 (0.05)	11.78 (6.05)	6.43 (1.94)	86.03 (17.38)	0.28 (0.03)	0.49 (0.05)	2.89 (0.72)	6.34 (3.87)	20.18 (2.25)	61.7 (26.78)
Kanagawa	15.74 (0.63)	67.15 (2.33	0.0078 (0.0009)	0.11 (0.05)	12.39 (6.30)	6.74 (2.09)	85.86 (17.80)	0.29 (0.02)	0.89 (0.07)	11.61 (3.67)	25.22 (13.18)	67.12 (11.72)	65.44 (30.20)
Aichi	15.7 (0.70)	66.69 (2.66	0.0067 (0.0005)	0.12 (0.05)	12.45 (6.09)	6.56 (1.98)	86.17 (17.40)	0.3 (0.01)	0.97 (0.09)	10.41 (2.89)	22.17 (12.21)	66.6 (7.63)	73.91 (25.83)
Kyoto	15.83 (0.58)	66.19 (2.03	0.0026 (0.0001)	0.15 (0.05)	11.06 (4.97)	5.89 (1.56)	83.91 (17.87)	0.28 (0.02)	0.56 (0.07)	6.04 (1.30)	11.9 (5.37)	35.32 (4.12)	78.23 (23.06)
Shiga	14.63 (0.59)	74.18 (1.24	0.0012 (0.0002)	0.14 (0.04)	11.95 (5.60)	6.53 (1.90)	85.7 (17.12)	0.28 (0.03)	0.53 (0.07)	1.97 (0.74)	5.18 (3.26)	12.4 (2.27)	67.06 (30.01)
Shizuoka	16.55 (0.52)	67.76 (1.92	0.0036 (0.0002)	0.14 (0.06)	11.17 (5.72)	6.31 (1.97)	84.83 (17.31)	0.29 (0.01)	0.7 (0.05)	5.19 (1.47)	13.13 (6.92)	35 (6.44)	58.08 (29.97)

Table S2. Continued

Prefecture/ country	Temperature (°C)	Relative humidity (%)	Density (population/km²)	% population ≥ 65 years	Savings (million yen)	Income (million yen)	CPI	Gini index	EPI (%)	Physicians (number per 10k population)	Nurses (number per 10k population)	Hospital beds (number per 10K population)	AC (%)
Mie	15.79 (0.71)	69 (1.98)	0.0018 (0.0001)	0.16 (0.05)	11.82 (6.18)	6.28 (1.98)	83.36 (17.45)	0.28 (0.02)	0.54 (0.07)	2.78 (0.69)	6.2 (3.16)	20.57 (1.58)	68.16 (28.26)
Hyogo	16.25 (0.79)	66.45 (1.76)	0.0054 (0.0002)	0.14 (0.05)	11.62 (5.33)	6.09 (1.75)	86.97 (17.51)	0.29 (0.02)	0.55 (0.07)	9.33 (2.12)	20.08 (10.68)	59.16 (8.28)	73.09 (24.63)
Nara	14.82 (0.54)	72.75 (1.70)	0.0013 (0.0001)	0.14 (0.05)	12.46 (6.07)	6.22 (1.83)	87.62 (17.54)	0.29 (0.03)	0.39 (0.05)	2.19 (0.70)	4.61 (2.73)	13.73 (3.14)	75.27 (25.52)
Osaka	16.78 (0.59)	63.63 (1.51)	0.0087 (0.0002)	0.12 (0.06)	10.79 (4.83)	5.87 (1.67)	86.08 (18.62)	0.31 (0.03)	0.75 (0.05)	17.4 (4.12)	30.26 (15.34)	105.58 (17.53)	82.62 (20.07)
Okayama	15.85 (0.86)	68.36 (3.39)	0.0019 (0.0001)	0.17 (0.05)	11.55 (5.60)	5.88 (1.70)	85.36 (16.89)	0.29 (0.02)	0.48 (0.07)	4.09 (0.92)	10.34 (4.68)	30.91 (2.12)	70.85 (25.16)
Hiroshima	15.88 (0.86)	69.4 (2.77)	0.0028 (0.0001)	0.15 (0.05)	10.77 (5.58)	5.86 (1.72)	86.39 (16.87)	0.29 (0.02)	0.54 (0.07)	5.53 (1.36)	12.14 (5.77)	37.6 (6.37)	69.27 (24.42)
Kagawa	16.12 (0.78)	68.45 (2.68)	0.001 (0.0000)	0.17 (0.05)	12.55 (6.36)	5.89 (1.65)	85.85 (16.96)	0.29 (0.01)	0.43 (0.05)	2.01 (0.61)	5.42 (2.36)	16.98 (1.80)	74.12 (25.13)
Wakayama	16.57 (0.57)	66.37 (2.24)	0.0011 (0.0000)	0.17 (0.06)	10.75 (4.77)	5.47 (1.51)	85.86 (16.65)	0.29 (0.02)	0.3 (0.04)	2.07 (0.52)	3.74 (2.06)	14.44 (1.18)	69.89 (25.57)
Yamaguchi	15.3 (0.64)	73.61 (2.96)	0.0015 (0.0000)	0.18 (0.06)	9.96 (4.73)	5.52 (1.53)	88.13 (16.93)	0.28 (0.02)	0.41 (0.05)	2.96 (0.66)	7.44 (3.34)	26.01 (4.63)	61.49 (28.93)
Tokushima	16.46 (0.59)	66.84 (1.66)	0.0008 (0.0000)	0.18 (0.06)	10.75 (5.51)	5.7 (1.73)	86.46 (16.37)	0.32 (0.02)	0.31 (0.02)	1.94 (0.38)	4.36 (1.91)	15.55 (1.93)	65.83 (28.80)
Ehime	16.32 (0.63)	66.6 (2.36)	0.0015 (0.0000)	0.17 (0.06)	9.7 (4.74)	5.22 (1.51)	85.85 (16.37)	0.29 (0.02)	0.37 (0.04)	2.77 (0.79)	7.4 (3.70)	22.62 (2.98)	61.71 (28.66)
Fukuoka	16.85 (0.62)	68.09 (2.46)	0.0048 (0.0003)	0.14 (0.05)	8.6 (4.37)	5.47 (1.62)	86.67 (17.67)	0.3 (0.02)	0.58 (0.04)	10.79 (2.79)	24.8 (11.56)	81.53 (14.01)	69.69 (28.51)
Kochi	16.87 (0.61)	68.47 (1.70)	0.0008 (0.0000)	0.19 (0.06)	9.53 (4.99)	5.24 (1.53)	86.21 (16.81)	0.31 (0.02)	0.23 (0.02)	1.76 (0.50)	4.46 (2.15)	19.9 (1.91)	57.9 (28.56)
Oita	16.31 (0.63)	70.03 (2.79)	0.0012 (0.0000)	0.18 (0.06)	8.13 (4.17)	5.08 (1.50)	86 (16.6)	0.29 (0.02)	0.33 (0.04)	2.25 (0.65)	6.03 (2.87)	19.48 (2.58)	56.01 (29.76)
Saga	16.49 (0.54)	70.81 (2.79)	0.0009 (0.0000)	0.17 (0.05)	8.44 (4.27)	5.62 (1.81)	87.38 (17.84)	0.28 (0.02)	0.31 (0.03)	1.59 (0.43)	4.38 (2.18)	14.31 (2.25)	65.87 (30.57)
Kumamoto	16.79 (0.66)	70.79 (2.33)	0.0018 (0.0001)	0.17 (0.05)	7.65 (3.69)	5.29 (1.62)	85.89 (17.14)	0.3 (0.02)	0.36 (0.04)	3.82 (0.93)	9.99 (4.88)	34.06 (5.16)	60.83 (28.07)
Nagasaki	17.09 (0.54)	70.51 (2.11)	0.0015 (0.0001)	0.17 (0.06)	7.36 (3.72)	4.94 (1.48)	85 (17.88)	0.3 (0.03)	0.27 (0.03)	3.25 (0.63)	7.64 (3.47)	26.67 (3.76)	59.16 (32.45)
Miyazaki	17.49 (0.54)	73.72 (2.01)	0.0011 (0.0000)	0.17 (0.06)	6.75 (3.54)	4.8 (1.36)	86.52 (16.96)	0.31 (0.00)	0.29 (0.03)	1.92 (0.65)	5.55 (3.18)	19.08 (2.32)	54.65 (30.48)
Kagoshima	18.3 (0.64)	70.59 (2.68)	0.0018 (0.0000)	0.18 (0.05)	6.66 (3.53)	4.54 (1.42)	84.62 (17.48)	0.29 (0.01)	0.29 (0.02)	3.19 (0.84)	8.33 (4.92)	33.06 (4.90)	53.38 (31.06)
Okinawa	22.91 (0.51)	74.42 (2.37)	0.0012 (0.0001)	0.12 (0.04)	4.09 (1.83)	4.2 (1.13)	90.52 (10.77)	0.33 (0.02)	0.28 (0.02)	1.83 (0.89)	4.92 (3.06)	15.75 (5.83)	59.88 (25.40)
Nationwide	15.12 (2.34)	69.98 (3.61)	0.003 (0.0020)	0.16 (0.06)	9.98 (5.14)	5.83 (1.77)	85.86 (17.10)	0.29 (0.02)	0.47 (0.21)	4.55 (4.98)	10.17 (10.29)	32.29 (26.72)	57.65 (31.60)

CPI: consumer price index; EPI: Economic power index; AC: air conditioning prevalence.

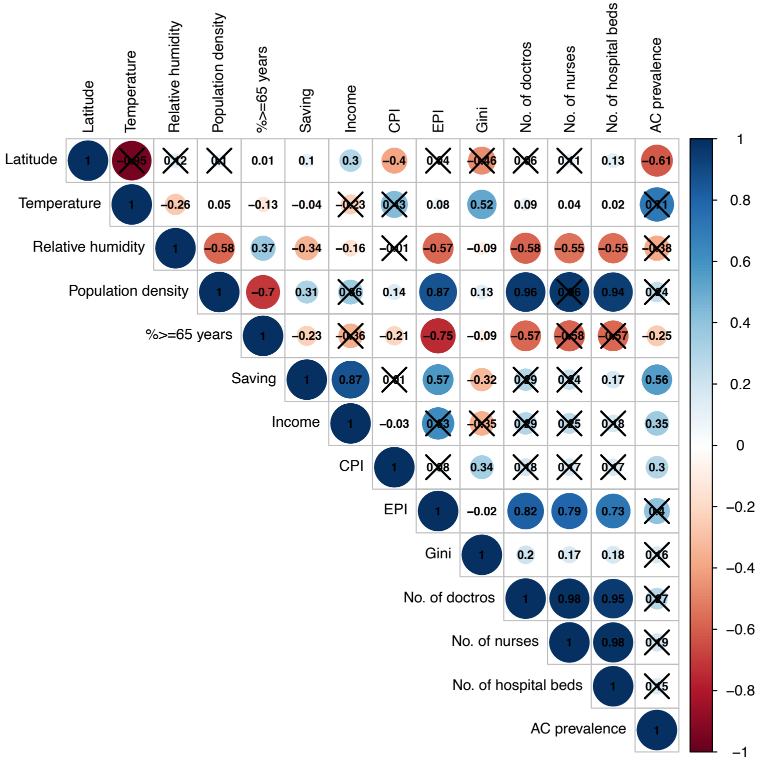


Figure S2. Correlations between the indicators.

Blue: positively associated; red: negatively associated; Cross: $p>0.05$.

RH: relative humidity; CPI: consumer price index; EPI: economic power index; AC: air conditioning prevalence

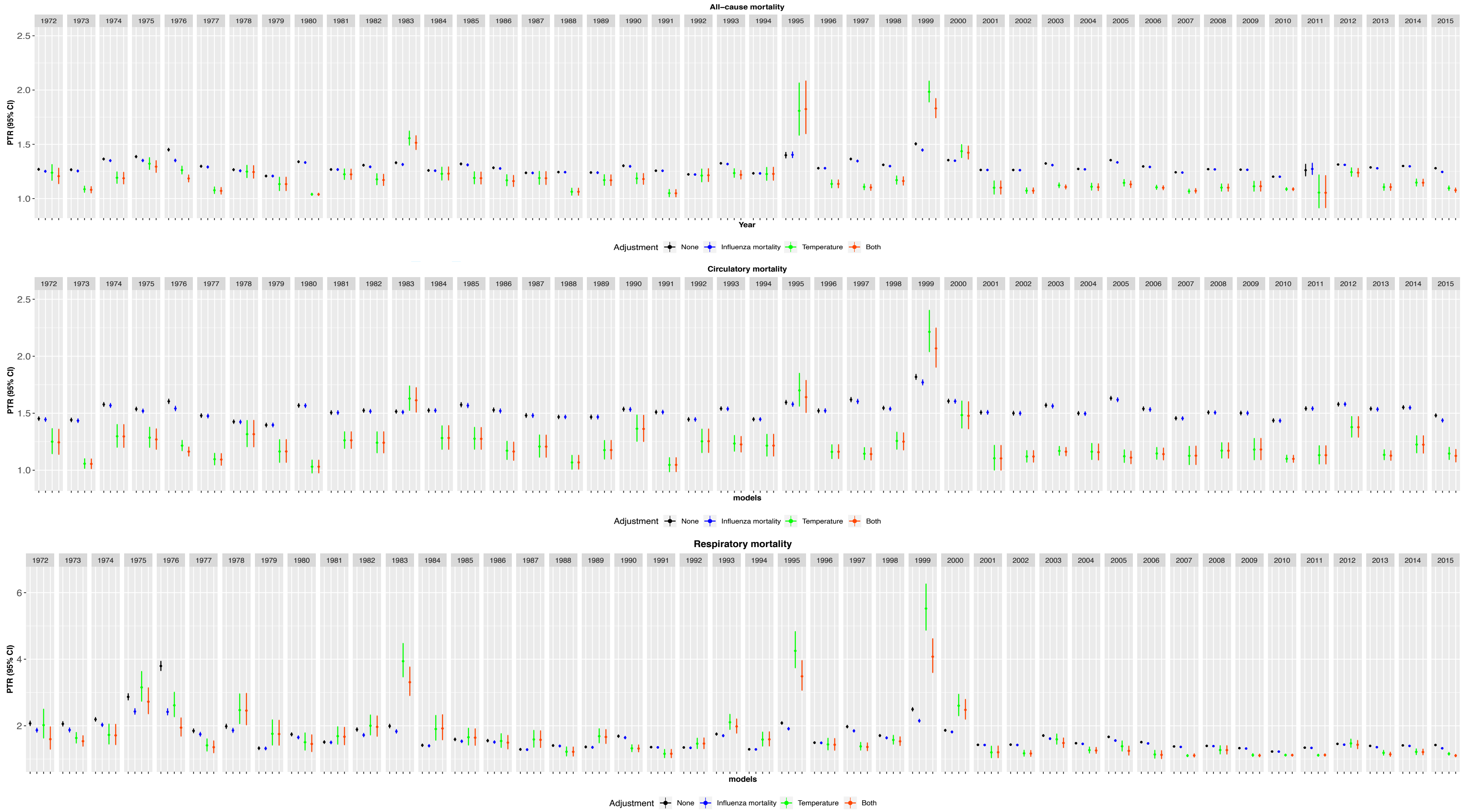


Figure S3. Peak-to-trough ratio (PTR) with 95% confidence intervals (95%CI) for each single year from 1972 to 2015 for all-cause (top), circulatory (middle), and respiratory (bottom) mortality before (black) and after adjustments for just influenza (blue), just temperature (green), and both (red)

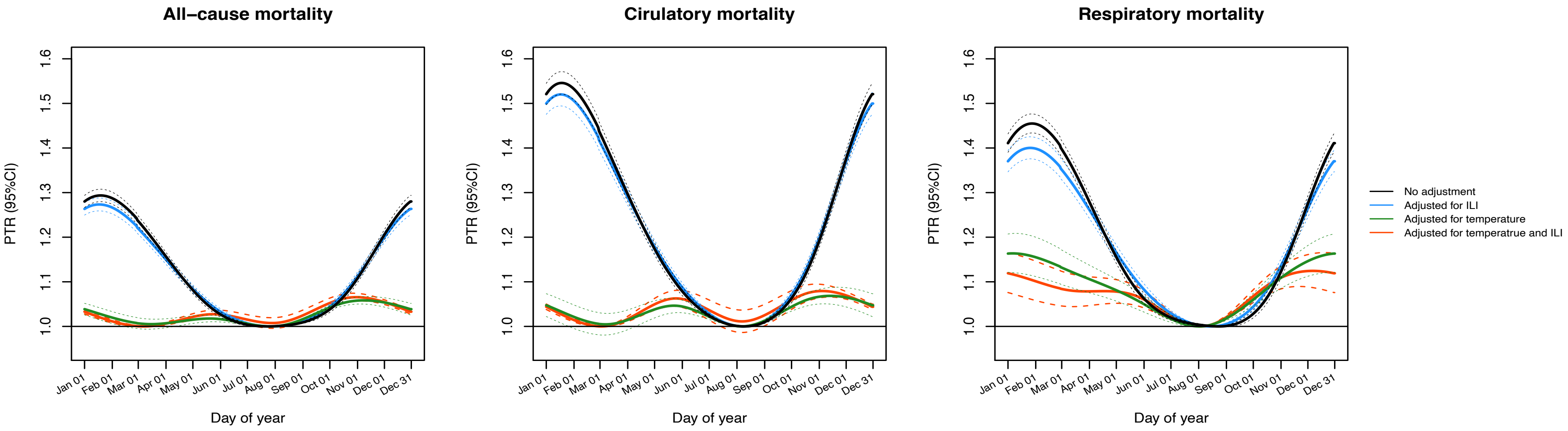


Figure S4. Pooled seasonality of all-cause, circulatory, and respiratory mortality between April 1999 and 2015 before and after adjustments, by using weekly influenza-like-illness (ILI) for influenza adjustment

(black: without any adjustment; blue: adjusted for weekly influenza like illness (ILI) only; green: adjusted for temperature only; red: adjusted for both temperature and ILI)

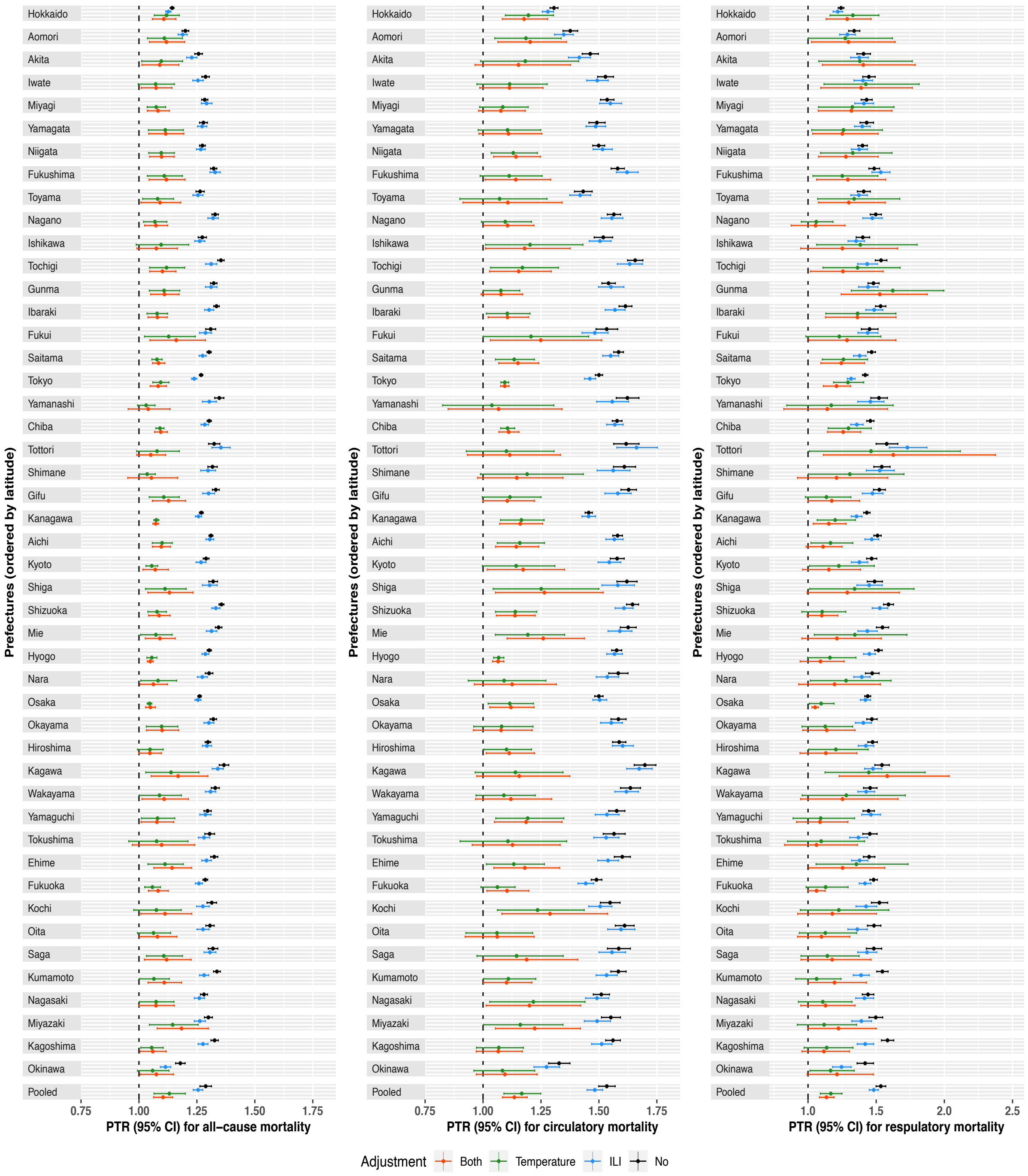


Figure S5. Pooled peak-to-trough ratio (PTR, 95% confidence intervals (95%CI)) for each prefecture between 1999 April and 2015 before and after adjustments, by using weekly influenza-like-illness (ILI) for influenza adjustment
(black: without any adjustment; blue: adjusted for just ILI; green: adjusted for just temperature; red: adjusted for both temperature and ILI)

Table S3. Pooled estimates (95% confidence interval (CI)) for peak-to-though ratio (PTR) with/without adjustment for temperature and influenza (influenza mortality or weekly ILI cases) for all-cause, circulatory, and respiratory mortality

	All-cause mortality		**Circulatory mortality**		**Respiratory mortality**	
Adjustment	PTR	95%CI	PTR	95%CI	PTR	95%CI
None (main analysis) [a]	1.29	1.28, 1.31	1.53	1.51, 1.56	1.51	1.49, 1.54
None (sub-period analysis) [b]	1.29	1.27, 1.30	1.54	1.51, 1.56	1.43	1.41, 1.45
Influenza mortality (main analysis) [a]	1.28	1.27, 1.30	1.53	1.50, 1.55	1.46	1.44, 1.48
Influenza mortality (sub-period analysis) [b]	1.28	1.27, 1.30	1.53	1.51,1.56	1.40	1.38, 1.42
Weekly ILI [b]	1.27	1.26, 1.29	1.52	1.49, 1.55	1.40	1.38, 1.43
Temperature (main analysis) [a]	1.08	1.08, 1.09	1.10	1.08, 1.11	1.37	1.33, 1.40
Temperature (sub-period analysis) [b]	1.06	1.05, 1.07	1.07	1.06, 1.08	1.13	1.09, 1.17
Temperature + Influenza mortality (main analysis) [a]	1.08	1.08, 1.09	1.10	1.08, 1.11	1.35	1.32, 1.39
Temperature + Influenza mortality (sub-period analysis) [b]	1.07	1.06, 1.07	1.14	1.08, 1.19	1.12	1.09, 1.16
Temperature + weekly ILI [b]	1.08	1.08, 1.09	1.07	1.06, 1.09	1.13	1.09, 1.17

[a] Main analysis: we used mortality data between 1972 and 2015 to assess seasonality;

[b] Subperiod analysis: we used mortality data between 1999 April and 2015 to assess seasonality and to confirm if our seasonality estimates are robust to study period or different indicators for seasonal influenza infections.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The role of temperature, influenza and other local characteristics in seasonality of mortality: a population-based time-series study in Japan

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The role of temperature, influenza and other local characteristics in seasonality of mortality: a population-based time-series study in Japan

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Abstract

Objectives: To investigate the extent to which temperature and influenza explained seasonality of mortality in Japan and to examine modifications of the seasonality by prefecture-specific characteristics.

Design and methods: We collected daily mortality from all-cause, circulatory, and respiratory disease in 47 prefectures in Japan between 1999 and 2015 and conducted time-series analysis to estimate the peak-to-trough ratio (PTR, a measure of seasonal amplitude) before and after adjusting for temperature and/or influenza like illness (ILI). Next, we applied linear mixed effect models to investigate the association of PTR with each indicator on prefecture-specific characteristics on climate, demographic and socioeconomic factors, and adaptations.

Results: The nationwide unadjusted-PTRs for all-cause, circulatory and respiratory mortality were 1.29 (95% Confidence Intervals (CI): 1.28, 1.31), 1.52 (95%CI: 1.49, 1.55) and 1.45 (95%CI: 1.43, 1.48), respectively. These PTRs reduced substantially after adjusting for temperature but very little after a separate adjustment for ILI. Furthermore, seasonal amplitudes varied between prefectures. However, there was no strong evidence for the associations of PTR with the indicators on prefecture-specific characteristics.

Conclusion: Seasonality of mortality is primarily driven by temperature in Japan. The spatial variation in seasonal amplitudes was not associated with prefecture-specific characteristics. Although further investigations are required to confirm our findings, this study can help us gain a better understanding of the mechanisms underlying seasonality of mortality.

Strengths and limitations of this study

- We investigated the contributions of temperature versus influenza to seasonal variation of different types of mortality by a common study design and statistical framework.
- We used indicators on a range of location-specific characteristics to investigate their modifying effect on seasonal variations in mortality.
- The study was conducted in Japan characterized by distinct seasonal weather conditions, so our results may not be generalized to locations with different climate (e.g., tropical countries).
- The deviance of residuals showed some autocorrelations, but it had limited impacts on our seasonality estimates.

Introduction

Seasonality of mortality is among the oldest observation across a broad range of population and geographical locations, typically entailing higher mortality in cold seasons than in warm seasons.[1–6] This epidemiological phenomenon reflects a complex interaction between environment and human.[2] The understanding of its underlying drivers is yet to be elucidated.

Some of the postulated contributors to seasonality of mortality include temperature, infectious disease, air pollution, physiological responses, and human behaviors.[1,2,7–9] Temperature is of most profound interest, with overwhelming evidence on its cold and hot effect on mortality.[10] Another well recognized contributor to seasonality is influenza, due to its strong seasonal cycle and association with inflammatory process.[11] A number of studies demonstrated an association between influenza and mortality in cold seasons.[11–15] Some of them focused on its role in temperature-mortality associations.[11,12] Other publications assessed its contribution to winter-season increase in mortality.[13–15] Although consensus exists that both temperature and influenza contribute to winter-season increase in mortality,[11–14,16] their relative importance has not been completely elucidated. Most research[11–14,16] has focused on either temperature or influenza only, and few studies have comparatively assessed their contribution to seasonality of mortality. We are aware of only one study that has compared their contributions to seasonality of all-cause mortality among people aged ≥ 75 years in Britain and suggested more seasonality was explained by temperature than influenza.[14]

The strength of seasonality in mortality varies geographically.[8] For example, a smaller seasonal amplitude was observed in areas with milder climates, suggesting that individuals living in warm areas might be more vulnerable to seasonal variations in mortality.[2] Several local characteristics on climate, demographic and socioeconomic factors, and adaptations have been linked with such spatial variation. However, only a few studies have evaluated their modifying effect on seasonality of mortality.[1,17] Another question remains unclear is if these modification effect will remain when we remove the effect of temperature and influenza from seasonal variations in mortality, given that the same local characteristics can also modify associations between influenza, temperature and mortality.[18–23]

In the current study, we collected daily mortality data between 1999 and 2015 from 47 prefectures in Japan to investigate the contribution of temperature and influenza to seasonality of mortality and to study its modifying factors by a range of prefecture-specific indicators. This study will strengthen our understanding of seasonality of mortality and provide important evidence to associate managements of seasonal risk factors to local conditions.

Method

Data collection

Hourly mean temperature (°C) and relative humidity (%) measured at a single monitoring site in the capital city of each prefecture were obtained from 1999 to 2015 from the Japan Meteorological Agency. We computed daily mean value of temperature and relative humidity for our analysis.

Daily mortality (counts) from all-cause, circulatory, respiratory disease and influenza were obtained from the Ministry of Health, Labor and Welfare of Japan between 1999 and 2015 for each prefecture in Japan. The principal cause of death statistics is coded using the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10). Cause-specific mortality was defined according to the ICD system: circulatory mortality (ICD-10 codes I00-I99), and respiratory mortality (ICD-10 codes J00-J99). Weekly number of influenza like illness (ILI) were obtained for each prefecture from April 1999 to 2015 from National Institute of Infectious Diseases, Japan.

Yearly data on prefecture-specific indicators was collected over the study period for each prefecture, including annual mean temperature, relative humidity, population density, the proportion of population aged ≥ 65 years, saving, income, Gini index (a measure of income inequality), consumer price index (CPI), economic power index (EPI, a measure of the wealth of a prefecture), the prevalence of air conditioning for households, and the number of registered physicians, nurses and hospital beds per 10K population. For each indicator, we computed the averaged value across the years 1999-2015 for each prefecture. The details for data collection were described in previous studies [24,25] and summarized in supplementary material.

Data analysis

We conducted our data analysis in three steps. First, we assessed seasonality of mortality without adjustments for temperature or ILI. Then, we examined the changes in the seasonality after adjusting for temperature and ILI separately, as well as both at the same time. Lastly, we evaluated the associations between each indicator and seasonality estimates before and after adjustments.

We applied a generalized linear model with a quasi-Poisson family to assess seasonality of mortality in each prefecture without any adjustment for temperature and ILI. Day-of-year was treated as an indicator for seasonality, taking values from 1 to 366 corresponding to Jan 1st through Dec 31st for both common and leap years (from 60th day to 365th day in common years, values were taken from 61 to 366). We used a cyclic cubic spline with 4 degrees of freedom (*df*) for day of year to estimate seasonality. The days-of-year with maximum and minimum mortality estimates from generalized liner models were identified as the peak and trough days, respectively, and were subsequently used to calculate the peak-to-trough ratio (PTR) to provide a measure of seasonality. When constructing confidence intervals for PTR, previous studies enforced the boundary constraint by truncating the lower confidence limit at one for PTR.[26,27] However, doing that may introduce a positive bias into the PTR.[28] In order to show the statistical variability in PTR, therefore, we did not truncate the lower confidence limit at one for PTR. Indicators for year, day-of-week and their interaction were used to control for the long-term trend and the effect of day-of-week. We excluded the data on 11 March 2011, the day of the Great East Japan Earthquake.

To assess the contribution of temperature and ILI to seasonality of mortality, we attempted three types of adjustment. First, we added temperature to our main model using a bi-dimensional cross-basis function to account for its non-linear and delayed effect on mortality. We modeled the exposure-response curve with a natural cubic B-spline with three internal knots at 25th, 50th, and 75th percentiles of temperature distribution, and the lag-response association with another natural cubic spline basis with 3 *df* with extended lags up to 21 days.[10,25]

Second, we removed temperature and adjusted for ILI in main model. We assumed ILI cases distributed evenly across day of week and computed daily average ILI cases. A natural cubic spline with 3 *df* was then used to control for daily ILI cases in the model. Third, adjustment was made using both temperature and influenza.

The prefecture-specific PTR was pooled for the whole of Japan for all-cause, circulatory and respiratory mortality, respectively, by meta-analysis with prefecture as a random factor. To explore if patterns of interest varied over time, we conducted yearly analyses for the entire country using separate quasi-Poisson regression model for each year with prefecture as a random factor.

To evaluate the modification of seasonal variation in mortality by prefecture-specific indicators, we applied linear mixed effects models (LMEMs) to investigate associations of PTR with each prefecture-specific indicator separately. We fitted LMEMs with random intercepts for prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital city of each prefecture were included to reduce spatial correlation, except for when we investigated annual mean temperature as the indicator, due to their high correlation. We conducted the analysis for all-cause, circulatory, and respiratory mortality in separate LMEMs. Results are expressed as the log(PTR) variation for a standard deviation increase of the indicator.

We performed a series of sensitivity analysis to confirm our findings. We tested the cyclic spline function for day of year with different *df* of *5* and *6* and adjusted temperature by changing the spline function, internal knots for temperature distribution, *df* and lag days for the lag-response associations. For influenza adjustment, we varied the number of lag days using the moving averages of the previous 7, 14, 21 and 28 days, and tested the natural cubic spline function with 2 *df*. For ILI adjustment, we tested moving average of previous 7, 14, 21 and 28 days for ILI cases, and 2 *df* for the natural cubic spline function. Overall, we did not observe substantial changes in our estimates.

The models were summarized in supplementary material including diagnostic plots. We conducted the analysis with R software, version 3.6.0 (R Development Core Team) using the dlnm and mixmeta packages.

Patient and public involvement

There was no patient or public involvement.

Results

This study included 18 985 036 deaths from all causes, 5 541 277 deaths from circulatory diseases, and 2 894 314 deaths from respiratory diseases. The nationwide time series of daily mortality showed a significant seasonal pattern (Figure S1). Daily mean temperature for the whole country between 1999 and 2015 ranged from -1.0℃ to 30.7℃, with a mean value at 15.6℃ (Table 1). ILI cases showed a large variation, ranging from 7 case to 1 652 147 cases with a median value at 7626 (Table 1). Prefecture-specific summary was provided in Table S1.

We observed a high variability for healthcare capacity (Table S2 & S3), while a low variability for socioeconomic indicators. Most of the indicators are correlated (Figure S2). In particular, EPI was highly correlated with population density, proportion of individuals aged over than 65 years old, and numbers of physicians, nurses and hospital beds (correlation>0.70). In addition, saving is highly correlated with income (correlation>0.70).

Figure 1 and Table 2 show the pooled results for the whole of Japan for seasonality of all-cause, circulatory, and respiratory mortality before and after adjustments for temperature and/or influenza. We observed a clear seasonal pattern with higher numbers of deaths in cold seasons than in warm seasons. Before any adjustments, the nationwide pooled PTR for all-cause, circulatory and respiratory mortality were 1.29 (95% confidence intervals (CI): 1.27, 1.30), 1.52 (95% CI: 1.49, 1.55) and 1.45 (95% CI: 1.43, 1.48), respectively. After adjustments for temperature and ILI, the shape of seasonality remained (Figure 1), but its amplitude reduced to different extents. Adjusting for just temperature reduced PTRs substantially in particular for all-cause and circulatory mortality to 1.06 (95% CI: 1.05,1.07) and 1.07 (95% CI: 1.05, 1.09). Adjusting for just ILI reduced PTRs only very slightly to 1.27 (95% CI: 1.26,1.29), 1.52 (95% CI: 1.49,1.55), and 1.40 (95% CI: 1.38, 1.43) for all-cause, circulatory and respiratory mortality, respectively. Notably, adjusting for temperature and ILI did not flatten the seasonal pattern or reduce the PTR to 1.

Similarly, prefecture-specific PTRs also showed a substantial reduction with temperature adjustment while a slight reduction when ILI was adjusted only, although an apparent reduction was observed in ILI-adjusted PTR for respiratory mortality (Figure 2). Furthermore, PTR for all mortality types varied across prefectures, and the spatial variation after adjustments was less apparent in particular for all-cause and circulatory mortality. Prefectures with higher latitude (northern areas), including Hokkaido, Aomori, and Akita, as well as the southernmost prefecture- Okinawa, showed a lower unadjusted-PTR and a smaller reduction after adjustments for temperature.

Our yearly analyses for the entire country showed a large reduction after adjusting for temperature while a small reduction after adjusting for ILI for most of the years (Figure S3). For the year of 2020, however, a higher PTR for all-cause and respiratory mortality was observed when temperature was included in the adjustment. We further checked the sensitivity of our estimates to temperature adjustment. Changing the lag period of 21 days in cross-basis function to 14 days reduced temperature-adjusted PTR, although it remained slightly higher than unadjusted PTR with a largely overlapped confidence intervals. The results for the other years did not change much (results not shown).

Figure S4 shows associations between the indicators and PTR. There was no strong evidence for the association between prefecture-specific characteristics and seasonality estimates. Diagnostic plots for models were included in supplementary material (Figure S5-S7).

Discussion

In this study, we investigated the contribution of temperature and influenza to seasonal variation of mortality in 47 prefectures of Japan and evaluated the modifications of seasonality by a range of prefecture-specific indicators. Our findings show that seasonal variation in mortality was substantially contributed by temperature and to a lesser extent, by influenza. In addition, seasonal amplitudes varied between prefectures. There was no strong evidence for the association between prefecture-specific characteristics and seasonal amplitudes.

Temperature and influenza have been among the most studied drivers of seasonality of mortality.[13–16] However, most of the investigations focused on either temperature or influenza. How much of seasonality of mortality is dependent on temperature versus influenza remain unsolved. Our finding showed that most of seasonality of mortality in Japan was attributable to temperature while little was driven by influenza. Consistent with our findings, a population -based cohort study in elderly British people examined month to month variation in mortality and its relationship with temperature and influenza A, and discovered that most of seasonal fluctuation was associated with cold temperature and a small component related with influenza A. Despite the smaller contribution of influenza to seasonal variation of mortality than temperature, our analysis suggested that influenza was accountable for seasonal variation, especially, for respiratory mortality. A study[11] in 48 U.S. cities observed a link between influenza epidemic and the irregularly high winter mortality in some certain years. Evidence thus far implies that temperature contributes substantially to seasonality of mortality in general, while influenza is related with seasonal variations of mortality to a less extent.

Notably, removing the effect of temperature and influenza from seasonal variation in mortality did not completely flatten the seasonal pattern of mortality, in particular, respiratory mortality. Seasonality of mortality is resulted from complex interaction between human behavior and environment. In addition to temperature and influenza, other infectious diseases (e.g., respiratory syncytial virus), air pollutants, behavioral changes based on a seasonal basis (e.g., dietary pattern and physical activities) have been linked with seasonal variation of diseases and mortality. However, there is no direct evidence assessing their contribution to seasonality of mortality.

Despite of a similar seasonal shape across prefectures, seasonal amplitudes varied across 47 prefectures. Previous studies have suggested that individuals living in cold locations show less seasonal variation in mortality, partially due to a better cold acclimatization from the combination of habituation, metabolic adjustment, and insulative acclimatization. [8,29–31] In addition, less developed locations is likely to exhibit a larger seasonal variation in mortality,[1] which can be related with high vulnerabilities to cold and heat effect of temperature because of poorer housing conditions, lower prevalence of air conditioning, and limited access to health care.[18,23] In our study, we did not observe strong evidence for any associations between prefecture-specific characteristics and seasonal variations in mortality. This could be partially explained by the limited range of variations in the indicators and possible confounding effect between them. Furthermore, our data on the indictors are population-level, and future investigations with individual-level data is recommended to examine these issues.

This study has several limitations. First, our study was conducted in Japan that has distinct seasonal weather conditions, hence our results may not be applicable to other areas with different climate (e.g., tropical countries). Second, we assumed the association of mortality with influenza and temperature did not change between 1999 and 2015, and our findings for 2000 were sensitive to temperature adjustment. Furthermore, we observed some autocorrelation in the model residuals despite our attempts to model it (Figure S6). However, sensitivity testing showed that it had limited impacts on the estimate of seasonality (Table S4). It is possible that the PTR on adjusting for influenza and temperature may be overestimated due to residual confounding as a result of error in measuring these variables.[32] However, any such overestimation would be believed to be slight, as the main error here would be of Berkson type, which does not cause bias and hence not compromise confounder control.[33] Finally, future investigations should be conducted by extending current datasets to those areas with different climate, and also by including more details for influenza (e.g., influenza subtype and vaccination coverage). Results from these investigations would complement our findings in current analysis.

This study presents findings from an epidemiologic analysis investigating the role of temperature, influenza and other local characteristics on seasonality of mortality across multiple locations. A strength of current study was the investigation of contributions of temperature versus influenza to seasonal variation of different types of mortality by a common study design and statistical framework, while previous studies mostly focused on either temperature or influenza only.

This study suggests that seasonality of mortality is primarily driven by temperature. Furthermore, seasonal amplitudes varied between prefectures. However, this spatial variation was not explained by the differences in prefecture-specific characteristics on climate, demographic and socioeconomic factors, and adaptations. Further investigations are required to confirm our findings. In sum, this study can help us to gain a better understanding of seasonality of mortality.

Contributors: LM conducted the study, analyzed the data and wrote the manuscript. CN and XS helped with the statistical analysis and the discussion of the text. MT, LY and YH contributed to the final version of the manuscript. BA helped with the data analysis and the interpretation of the results. MH contributed to the study design and the discussion of the results.

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Competing interests: None declared.

Ethics approval: This study used secondary data, with no possibility of personal identification, and an informed consent or an approval by a medical ethics board is not required.

Data availability statement: Data are available upon reasonable request. The technical appendix, statistical code and data set will be available upon request from the Corresponding author.

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Figure captions:

Figure 1. Pooled seasonality of all-cause, circulatory, and respiratory mortality between 1999 and 2015 before and after adjustments (black: without any adjustment; blue: adjusted for influenza like illness (ILI) only; green: adjusted for temperature only; red: adjusted for both temperature and ILI)

The seasonality is computed as the ratio of predicted mortality at each day of the year to the predicted minimum mortality at the trough with 95% confidence intervals (95%CIs):

$$Ratio = \frac{Mortality\ \ at\ day_i}{Minimum\ mortality\ at\ the\ trough}$$

Figure 2. Prefecture-specific peak-to-trough ratio (PTR) with 95% confidence intervals (95% CI) for all-cause (left), circulatory (middle), and respiratory (right) mortality before (black) and after adjustments for influenza like illness (ILI) only (blue), temperature only (green), and both (red)

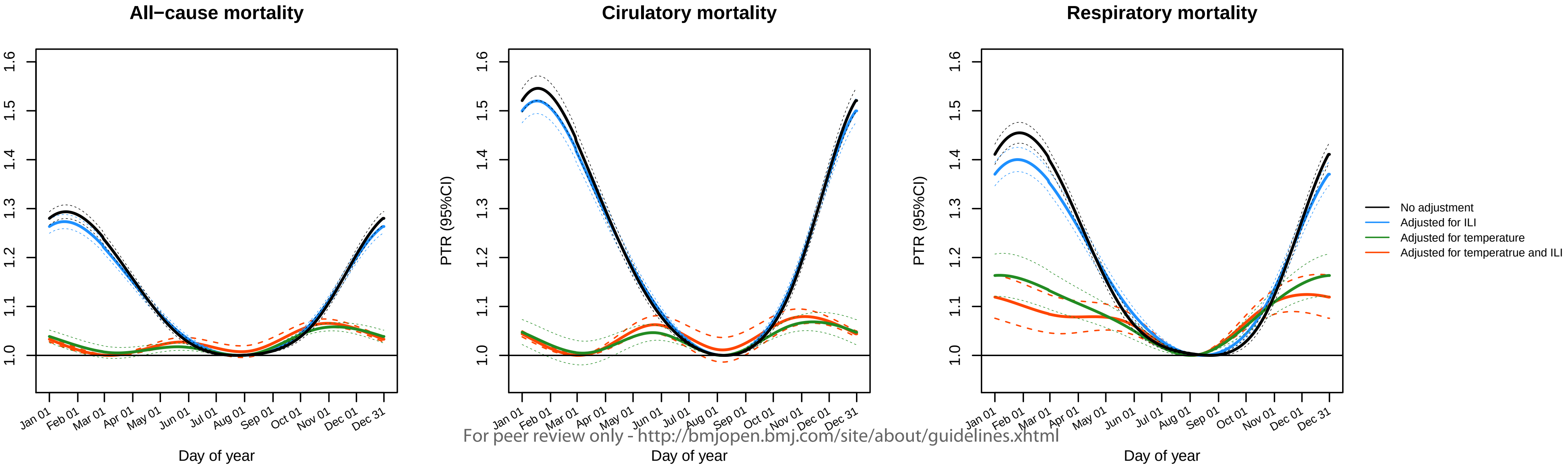
Table 1. Nationwide summary of daily mean temperature (℃), daily death (numbers of cases), and weekly influenza like illness (ILI) between 1999 and 2015

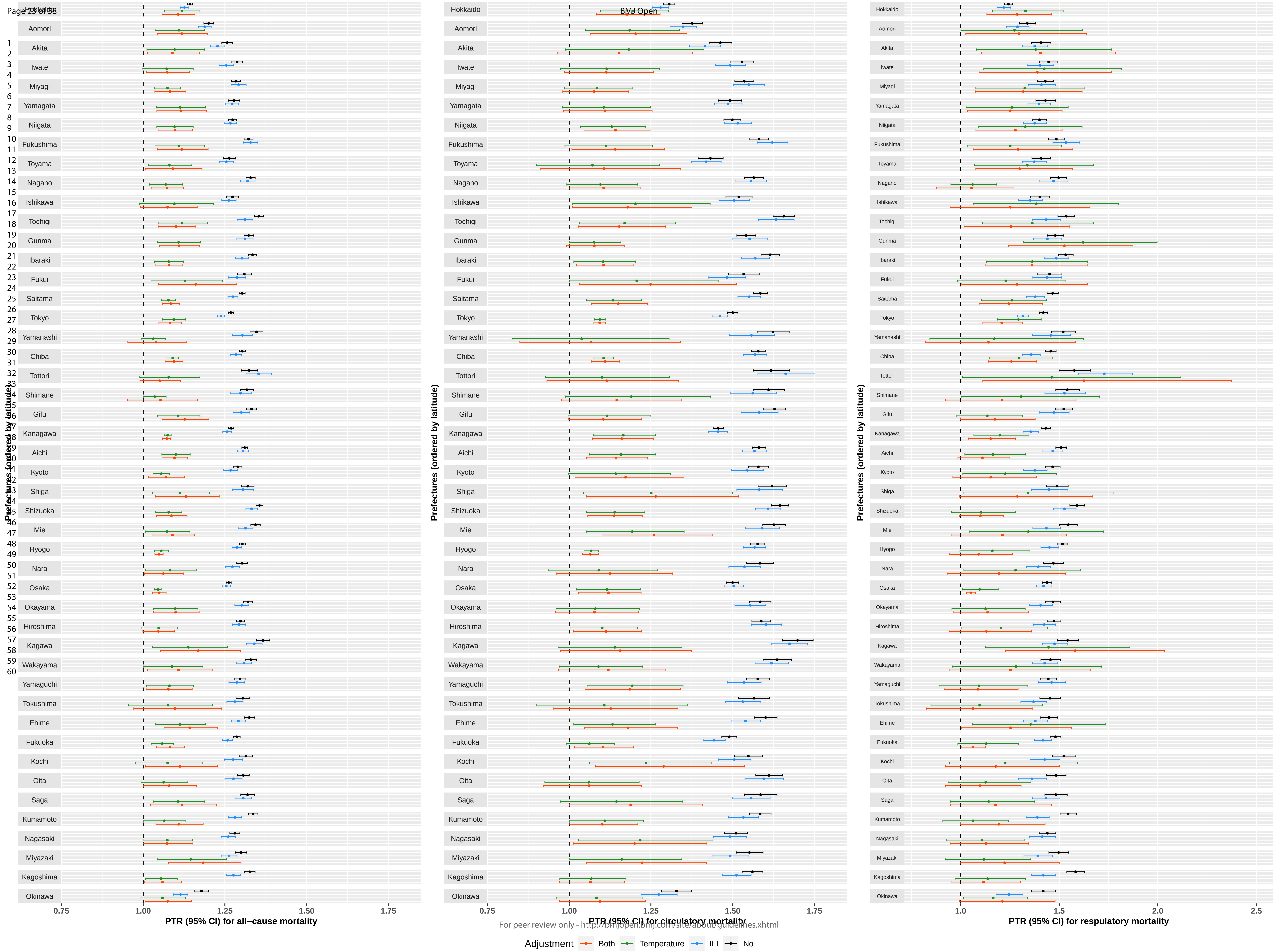
Variables	Median [interquartile range]	Mean (SD)	Range
Mean temperature	16.09 [8.04; 22.8]	15.6 (8.2)	[-1.0; 30.7]
All-cause mortality	3046 [2726; 3350]	3058 (443.7)	[2114; 4712]
Circulatory mortality	866 [768; 1003]	892.6 (157.1)	[570; 1454]
Respiratory mortality	464 [388; 535]	465.2 (105.9)	[247; 1072]
ILI	7626 [1575; 106199]	142113 (295087.3)	[7; 1652147]

Note: Daily mortality on the day of the Great East Japan Earthquake (11 March 2011) was excluded from our analysis.

Table 2. Nationwide pooled peak-to-trough ratio (PTR) with 95% confidence interval (95% CI) with/without adjustment for temperature and/or influenza like illness (ILI)

Adjustment	All-cause mortality		Circulatory mortality		Respiratory mortality	
	PTR	95% CI	PTR	95% CI	PTR	95% CI
None	1.29	1.28, 1.31	1.52	1.49, 1.55	1.45	1.43, 1.48
Temperature	1.06	1.05, 1.07	1.07	1.05, 1.09	1.16	1.12, 1.21
ILI	1.27	1.26, 1.29	1.52	1.49, 1.55	1.40	1.38, 1.43
Temperature + ILI	1.07	1.06, 1.07	1.08	1.06, 1.09	1.12	1.09, 1.16


All−cause mortality
Cirulatory mortality
Respiratory mortality
PTR (95%CI)
1.0
1.1
1.2
1.3
1.4
1.5
1.6
Jan 01
Feb 01
Mar 01
Apr 01
May 01
Jun 01
Jul 01
Aug 01
Sep 01
Oct 01
Nov 01
Dec 01
Dec 31
Day of year
No adjustment
Adjusted for ILI
Adjusted for temperature
Adjusted for temperatrue and ILI


Hokkaido
Aomori
Akita
Iwate
Miyagi
Yamagata
Niigata
Fukushima
Toyama
Nagano
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Ibaraki
Fukui
Saitama
Tokyo
Yamanashi
Chiba
Tottori
Shimane
Gifu
Kanagawa
Aichi
Kyoto
Shiga
Shizuoka
Mie
Hyogo
Nara
Osaka
Okayama
Hiroshima
Kagawa
Wakayama
Yamaguchi
Tokushima
Ehime
Fukuoka
Kochi
Oita
Saga
Kumamoto
Nagasaki
Miyazaki
Kagoshima
Okinawa
Prefectures (ordered by latitude)
0.75
1.00
1.25
1.50
1.75
PTR (95% CI) for all−cause mortality
PTR (95% CI) for circulatory mortality
1.0
1.5
2.0
2.5
PTR (95% CI) for respulatory mortality
Adjustment
Both
Temperature
ILI
No

Supplementary material

The role of temperature, influenza and other local characteristics in seasonality of mortality: a population-based time-series study in Japan

Table of Contents

Table S1. Summary of daily mean temperature, daily cases of all-cause, circulatory, and respiratory mortality, and **weekly** cases of influenza likely illness

Prefecture/ country [a]	Daily mean temperature (℃)		All-cause mortality (n)		Circulatory mortality (n)		Respiratory mortality (n)		Influenza like illness (n)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD	Range	Mean (SD)	Range	Mean (SD)	Range
Hokkaido	9.32 (9.62)	[-11;29.6]	141.36 (21.94)	[81;220]	41.47 (8.36)	[18;79]	20.49 (6.09)	[3;55]	958.26 (2040.19)	[0;15153]
Aomori	10.7 (9.06)	[-7.5;30.1]	41.56 (8.2)	[16;79]	12.64 (3.95)	[1;28]	5.94 (2.73)	[0;19]	259.68 (566.2)	[0;3591]
Akita	12.14 (9.14)	[-5.5;31.6]	37.03 (7.55)	[15;64]	11.21 (3.75)	[1;27]	5.5 (2.6)	[0;19]	241.43 (517)	[0;4180]
Iwate	10.64 (9.46)	[-8.9;29.3]	40.4 (8.44)	[15;85]	13.49 (4.37)	[1;32]	5.89 (2.68)	[0;19]	273.48 (564.55)	[0;3716]
Miyagi	12.84 (8.38)	[-4.5;31.2]	55.3 (11.21)	[22;152]	17.14 (5.11)	[2;43]	7.57 (3.26)	[0;29]	400.31 (857.1)	[0;5417]
Yamagata	12.1 (9.43)	[-5.8;30.5]	36.91 (7.58)	[13;68]	11.59 (3.81)	[0;29]	5.49 (2.63)	[0;18]	209.39 (444.9)	[0;2795]
Niigata	14.17 (8.76)	[-2.8;31.8]	68.63 (12.22)	[31;112]	21.17 (5.66)	[4;45]	9.27 (3.5)	[0;26]	467.68 (1057.89)	[0;7472]
Fukushima	13.42 (8.89)	[-4.2;31.4]	58.49 (11.3)	[23;114]	18.98 (5.55)	[5;44]	8.61 (3.43)	[0;29]	350.57 (736.63)	[0;4293]
Toyama	14.57 (8.89)	[-2.8;33.1]	30.8 (6.97)	[11;59]	8.72 (3.25)	[1;24]	4.95 (2.46)	[0;16]	197.35 (433.32)	[0;3042]
Nagano	12.28 (9.53)	[-6.7;30]	59.97 (11.51)	[26;107]	19.68 (5.61)	[4;48]	8.38 (3.48)	[0;23]	424.98 (927.86)	[0;6713]
Ishikawa	15.07 (8.66)	[-2.6;32.4]	29.71 (6.78)	[9;58]	8.78 (3.28)	[0;26]	4.65 (2.37)	[0;16]	222.14 (503.98)	[0;3450]
Tochigi	14.39 (8.56)	[-2.5;31.7]	50.11 (10.49)	[19;95]	16.02 (5.1)	[4;37]	7.32 (3.21)	[0;25]	263.1 (595.1)	[0;3112]
Gunma	15.04 (8.6)	[-1.7;32.6]	51.57 (10.8)	[20;101]	15.74 (4.96)	[0;41]	8.5 (3.55)	[0;27]	393.01 (863.12)	[0;5616]
Ibaraki	14.15 (8.23)	[-1.7;31]	73.38 (14.37)	[31;136]	22.52 (6.5)	[2;51]	10.77 (4.32)	[0;31]	395.03 (908.36)	[0;5926]
Fukui	14.87 (8.94)	[-1.8;31.9]	21.69 (5.62)	[6;45]	6.35 (2.78)	[0;18]	3.57 (2.07)	[0;13]	176.7 (401.64)	[0;3054]
Saitama	15.53 (8.47)	[-0.9;33.7]	138.85 (27.86)	[65;258]	41.24 (10.6)	[13;97]	20.3 (7.16)	[3;58]	1139.33 (2572)	[0;15454]
Tokyo	16.69 (7.93)	[0.3;33.2]	265.37 (41.16)	[166;434]	76.17 (15.73)	[36;147]	38.71 (10.36)	[11;96]	1016.52 (2578.95)	[0;18939]
Yamanashi	15.12 (8.69)	[-2.1;31.8]	23.31 (6)	[7;52]	6.82 (2.9)	[0;20]	3.46 (2.01)	[0;16]	144.31 (310.05)	[0;1812]
Chiba	16.3 (7.76)	[0.3;32.1]	126.11 (24.2)	[64;216]	38.5 (9.97)	[13;88]	17.97 (6.22)	[2;58]	891.29 (2020.46)	[0;12096]
Tottori	15.22 (8.54)	[-3.1;32]	17.86 (4.84)	[5;38]	5.38 (2.49)	[0;16]	2.54 (1.66)	[0;11]	113.05 (238.68)	[0;1543]
Shimane	15.26 (8.27)	[-3.3;32.2]	23.8 (5.83)	[6;48]	6.92 (2.91)	[0;23]	3.72 (2.07)	[0;14]	125.38 (276.71)	[0;1979]
Gifu	16.22 (8.69)	[-1.7;32.7]	52.28 (10.68)	[21;99]	15.57 (4.93)	[3;36]	8.05 (3.35)	[0;23]	339.83 (715.25)	[0;4339]
Kanagawa	16.28 (7.67)	[0.3;32.2]	170.3 (31.31)	[94;297]	47.51 (10.56)	[18;101]	24.47 (7.72)	[3;65]	1276.81 (3000.95)	[0;17813]
Aichi	16.26 (8.57)	[-1.5;32.7]	148.39 (26.39)	[81;236]	41.47 (9.81)	[16;80]	21.5 (6.99)	[5;52]	1026.52 (2284.16)	[0;12493]
Kyoto	16.23 (8.71)	[-1.2;32.6]	62.27 (11.61)	[29;119]	18.01 (5.4)	[4;45]	9.63 (3.69)	[0;32]	403.21 (882.09)	[0;5518]

Table S1. Continued

Prefecture/ country	Daily mean temperature (℃)		All-cause mortality (n)		Circulatory mortality (n)		Respiratory mortality (n)		Influenza like illness (n)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Shiga	15.1 (8.64)	[-2.1;31.8]	29.51 (7.11)	[9;60]	8.57 (3.37)	[0;22]	4.56 (2.35)	[0;18]	218.49 (484.12)	[0;2675]
Shizuoka	16.92 (7.45)	[1.7;31.9]	91.42 (18.13)	[45;172]	27.52 (7.56)	[9;62]	12.86 (4.84)	[2;36]	598.14 (1351.69)	[0;8255]
Mie	16.37 (8.21)	[-0.4;33.5]	47.71 (10.07)	[21;95]	13.97 (4.56)	[2;33]	7.12 (3.18)	[0;24]	331.76 (728.13)	[0;3989]
Hyogo	17.08 (8.24)	[-0.8;32.5]	131.5 (22.43)	[70;265]	36.03 (9.04)	[10;75]	19.74 (6.38)	[3;49]	793.55 (1722.72)	[0;10287]
Nara	15.19 (8.5)	[-1.7;30.8]	33.11 (7.65)	[12;62]	9.81 (3.76)	[0;28]	5.16 (2.56)	[0;17]	184.89 (412.67)	[0;2379]
Osaka	17.17 (8.36)	[-0.1;32.7]	195.43 (31.77)	[113;341]	52.28 (12.09)	[18;115]	30.9 (9.42)	[7;75]	1017.19 (2175.46)	[0;13525]
Okayama	16.52 (8.61)	[-1.7;32.3]	51.94 (10.18)	[19;92]	15.1 (4.7)	[1;34]	9.2 (3.64)	[0;26]	321.47 (729.3)	[0;4974]
Hiroshima	16.5 (8.43)	[-2;31.8]	72.18 (13.13)	[33;146]	20.79 (6)	[4;47]	11.62 (4.21)	[0;34]	441.89 (988.89)	[0;6087]
Kagawa	16.8 (8.37)	[-0.4;33]	28.54 (6.77)	[8;58]	8.28 (3.36)	[0;25]	5.04 (2.47)	[0;16]	187.73 (431.76)	[0;2632]
Wakayama	16.94 (8.12)	[0;32.7]	31.17 (7.11)	[9;73]	9.02 (3.47)	[0;28]	4.9 (2.48)	[0;16]	173.35 (381.83)	[0;2479]
Yamaguchi	15.79 (8.44)	[-4.5;31]	45.67 (8.95)	[20;82]	13.69 (4.43)	[2;32]	7.89 (3.25)	[0;28]	331.05 (769.8)	[0;5183]
Tokushima	16.85 (8)	[-1;32.6]	24.18 (5.89)	[8;51]	6.95 (2.88)	[0;20]	4.2 (2.26)	[0;15]	143.77 (329.5)	[0;2089]
Ehime	16.79 (8.04)	[-0.7;31.7]	42.87 (8.81)	[15;81]	13.42 (4.42)	[3;34]	6.8 (2.98)	[0;20]	263.9 (577.75)	[0;3750]
Fukuoka	17.35 (7.86)	[-0.8;32.8]	121.01 (19.83)	[69;210]	30.39 (7.36)	[11;73]	20.15 (6.46)	[4;57]	1025.85 (2276.78)	[0;12597]
Kochi	17.37 (7.75)	[-0.1;32.1]	25.27 (6.07)	[9;52]	7.92 (3.12)	[0;21]	4.2 (2.3)	[0;18]	205.81 (464.68)	[0;3201]
Oita	16.87 (7.76)	[-0.3;31.7]	34.24 (7.59)	[12;71]	10.03 (3.64)	[0;26]	5.89 (2.77)	[0;21]	316.35 (714.1)	[0;4478]
Saga	16.9 (8.22)	[-2.5;32.3]	23.97 (5.91)	[6;50]	6.67 (2.81)	[0;18]	4.1 (2.24)	[0;18]	186.74 (412.58)	[0;2778]
Kumamoto	17.31 (8.28)	[-1.8;31.7]	50.33 (10.24)	[20;95]	14.6 (4.69)	[1;35]	8.54 (3.55)	[0;31]	346.29 (811.45)	[0;5887]
Nagasaki	17.43 (7.64)	[-0.8;31.9]	41.9 (8.5)	[19;75]	11.99 (4.01)	[1;32]	7.08 (3.05)	[0;23]	337.01 (757.91)	[0;4798]
Miyazaki	17.77 (7.4)	[0.8;31.6]	31.75 (7.46)	[11;67]	9.72 (3.65)	[1;25]	5.28 (2.67)	[0;21]	356.01 (800.59)	[0;5875]
Kagoshima	18.85 (7.44)	[0.5;31.7]	53.03 (10.42)	[22;112]	16.1 (4.92)	[3;43]	9.4 (3.88)	[0;38]	436.56 (969.33)	[0;7309]
Okinawa	23.29 (4.68)	[10.3;31.1]	25.95 (6.33)	[6;53]	6.67 (2.78)	[0;21]	4.36 (2.26)	[0;15]	404.6 (716.61)	[0;5197]

[a] Prefectures was ordered by latitude from high to low.

[b] Daily mortality on the day of the Great East Japan Earthquake (11 March 2011) was excluded from our analysis.

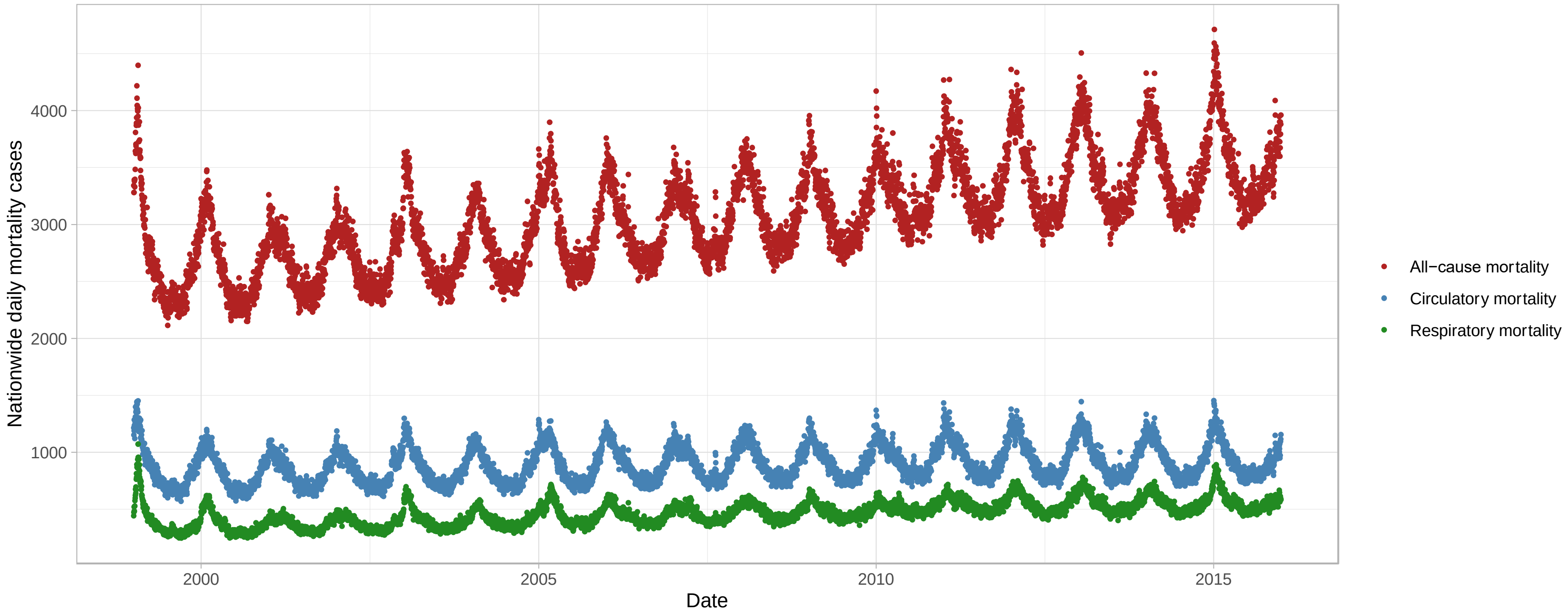

Figure S1. Time series of national wide daily mortality cases from all-cause, circulatory, respiratory disease and influenza between April 1999 and 2015

Summary of data collection on prefecture-specific indicators on climate, demographics, socioeconomic factors, and healthcare capacity

We computed the annual mean temperature and relative humidity for each prefecture averaged from 1999 to 2015. For demographic indicators, we collected yearly data on population density and the proportion of population aged ≥65 years for each prefecture for 1972-2012 from the Statics Bureau of the Ministry of Internal Affairs and Communications of Japan. We collected information on socioeconomic indicators from Statistics Bureau of the Ministry of Internal Affairs and Communications of Japan,[1,2] including saving and income available every 5 years for 1974-2009, Gini index (a measure of income inequality) available every 5 years for 1979-2009, consumer price index (CPI) from 1972 to 2009, economic power index (EPI, a measure of the wealth of a prefecture) from 2003 to 2015, and the prevalence of air conditioning for households with two persons or more from 1972 to 2009. We extracted the number of registered physicians, nurses and hospital beds per 10K population in 1975 and 2004 from the Survey of Medical Institutions and Hospital Report conducted by the Ministry of Health, Labour and Welfare.[3] For each indicator, we computed the averaged value across the years 1999-2015 for each prefecture.

1. Satistics Bureau of the Ministry of Internal Affairs and Communications of Japan. 2015. Statistics, Consumer Price Index.
2. National Survey of Family Income and Expenditure Definitions of Terms Webpage [in Japanese]. Statics Bureau of the Ministry of Internal Affairs and Communications of Japan. 2009.
3. Survey of Medical Institutions. [WWW Document]. Health Statistics Office Ministry of Health Labor and Welfare Japan. http://www.mhlw.go.jp/english/ database/db-hss/smi.html (accessed 10.1.14.). Published 2010.

Table S2. Summary of Annual Values Across the Years (1999-2015) for Each Indicator

Indicators	Mean (SD)	Median [interquartile range]	Range
Temperature (℃)	15.55 (2.34)	16.03 [14.64; 16.91]	[8.4; 23.55]
Relative humidity (%)	68.64 (3.61)	68.42 [65.52; 72.08]	[57.51; 79.96]
Density (population/km^2)	0.003 (0.002)	0.002 [0.001; 0.003]	[0.0006; 0.013]
% population ≥ 65 years	0.22 (0.06)	0.22 [0.20; 0.25]	[0.12; 0.31]
Savings (million yen)	14.49 (5.14)	14.97 [12.24; 16.47]	[5.07; 19.73]
Income (million yen)	6.88 (1.77)	6.84 [6.35; 7.45]	[4.56; 8.94]
Consumer price index	97.65 (17.1)	97.4 [96.6; 98.60]	[94.6; 103.30]
Gini index	0.30 (0.02)	0.30 [0.29; 0.31]	[0.27; 0.35]
Economic power index (%)	0.47 (0.21)	0.42 [0.31; 0.57]	[0.20; 1.41]
Physicians (number per 10k population)	5.60 (4.98)	3.60 [4.89; 5.93]	[1.62; 34.46]
Nurses (number per 10k population)	15.04 (10.29)	10.41 [7.82; 15.88]	[4.09; 68.00]
Hospital beds (number per 10K population)	34.88 (26.72)	23.81 [17.93; 36.86]	[9.11; 130.48]
Air conditioning prevalence (%)	85.9 (31.60)	92.6 [86.0; 95.7]	[8.30; 99.40]

Table S3. Prefecture-specific summary of annual value across the years 1999-2015 for all indicators (mean (SD))

Prefecture/ country	Temperature (℃)	Relative humidity (%)	Density (population/km^2)	% population ≥ 65 years	Savings (million yen)	Income (million yen)	CPI	Gini index	EPI (%)	Physicians (number per 10k population)	Nurses (number per 10k population)	Hospital beds (number per 10K population)	AC (%)
Hokkaido	9.26(0.38)	68.81(2.07)	0.0056(1e-04)	0.22(0.03)	11.64(0.15)	6.02(0.54)	97.13(1.2)	0.29(0.01)	0.38(0.02)	11.87(0.47)	37.78(4.15)	106.68(1.57)	13.23(3.46)
Aomori	10.64(0.4)	74.78(1.9)	0.0014(0)	0.23(0.03)	9.92(0.91)	5.96(0.3)	96.7(1.09)	0.3(0.01)	0.3(0.03)	2.52(0)	8.84(0.56)	19.96(0.46)	43.77(7.82)
Akita	12.11(0.28)	72.64(0.9)	0.0011(0)	0.27(0.02)	10.82(0.79)	6.51(0.62)	98.6(1.48)	0.29(0.01)	0.27(0.02)	2.2(0.06)	7.6(0.59)	17.58(0.31)	66.8(11.06)
Iwate	10.57(0.34)	73.31(1.37)	0.0014(0)	0.25(0.02)	12.29(0.23)	6.53(0.87)	97.33(0.94)	0.3(0.01)	0.29(0.02)	2.48(0.02)	10.18(0.69)	20.45(0.76)	45.5(10.4)
Miyagi	12.78(0.4)	71.22(1.25)	0.0024(0)	0.2(0.02)	11.87(0.34)	6.89(0.26)	98.05(1.4)	0.3(0.02)	0.51(0.03)	4.62(0.2)	12(1.44)	26.42(0.25)	67.99(4.46)
Yamagata	12.07(0.33)	74.27(1.31)	0.0012(0)	0.26(0.02)	12.36(0.49)	7.21(0.67)	96.85(0.84)	0.3(0.02)	0.31(0.02)	2.37(0.09)	7.94(0.69)	15.12(0.16)	76.14(6.09)
Niigata	14.19(0.29)	70.69(1.55)	0.0024(0)	0.24(0.02)	15.21(0.86)	7.38(0.64)	97.96(1.22)	0.3(0.01)	0.4(0.03)	4.34(0.09)	13.93(1.31)	30.32(0.04)	91.6(4.22)
Fukushima	13.36(0.37)	68.79(0.92)	0.0021(1e-04)	0.23(0.02)	12.46(0.38)	6.88(0.65)	97.08(1.07)	0.31(0.01)	0.42(0.03)	3.72(0.05)	11.22(1.01)	30.95(1.36)	64.27(10.34)
Toyama	14.56(0.32)	77.2(1.74)	0.0011(0)	0.24(0.02)	16.33(0.62)	8.08(0.84)	98.15(1.53)	0.3(0.02)	0.42(0.06)	2.51(0.09)	7.88(0.87)	18.34(0.01)	93.67(2.89)
Nagano	12.25(0.3)	71.31(1.55)	0.0022(0)	0.24(0.02)	15.57(0.71)	7.12(0.71)	98.11(1.21)	0.28(0.01)	0.44(0.04)	4.08(0.19)	13.78(1.49)	25.03(0.11)	54.38(7.79)
Ishikawa	15.06(0.3)	70.05(1.91)	0.0012(0)	0.21(0.02)	16.57(1.16)	7.71(0.96)	98.56(1.12)	0.29(0)	0.44(0.05)	2.9(0.12)	8.89(0.73)	20.41(0.58)	92.95(3.05)
Tochigi	14.34(0.34)	69.09(2.2)	0.002(0)	0.2(0.02)	15.62(0.66)	7.46(0.33)	96.8(1.4)	0.3(0.01)	0.58(0.07)	3.91(0.18)	9.57(1.27)	22.67(0.07)	89.19(2.63)
Gunma	14.98(0.34)	61.18(1.76)	0.002(0)	0.21(0.02)	15.58(1.06)	6.85(0.54)	98.26(1.46)	0.3(0.01)	0.55(0.05)	3.98(0.17)	10.03(1.65)	25.32(0.04)	89.03(2.93)
Ibaraki	14.08(0.39)	72.75(0.85)	0.003(0)	0.2(0.03)	15.35(0.57)	7.44(0.95)	95.5(0.98)	0.3(0.01)	0.6(0.07)	4.37(0.17)	12.01(1.43)	33.23(0.45)	89.75(3.88)
Fukui	14.85(0.28)	74.7(1.86)	8e-04(0)	0.23(0.02)	18.63(1.15)	8.19(0.72)	98.05(1.51)	0.3(0.01)	0.38(0.04)	1.72(0.05)	5.12(0.57)	12.24(0.22)	95.13(1.62)
Saitama	15.49(0.34)	64.24(2.26)	0.0071(1e-04)	0.17(0.03)	15.16(0.87)	7.38(0.62)	97.09(1.53)	0.29(0.01)	0.7(0.06)	8.95(0.71)	23.78(3.55)	61.53(1.06)	97.33(0.96)
Tokyo	16.67(0.36)	59.7(1.51)	0.0126(4e-04)	0.19(0.02)	18.18(1.42)	7.99(0.25)	99.56(1.67)	0.31(0)	1.21(0.14)	33.31(1.63)	64.5(4.94)	130.07(0.57)	96.44(1.2)
Yamanashi	15.08(0.3)	63.11(1.55)	9e-04(0)	0.22(0.02)	13.92(1.39)	6.79(0.68)	96.91(0.99)	0.29(0.02)	0.38(0.05)	1.69(0.02)	4.98(0.53)	11.52(0.33)	73.15(6.8)
Chiba	16.24(0.39)	68.32(1.6)	0.0061(1e-04)	0.18(0.03)	16.19(0.2)	7.53(0.81)	98.23(1.68)	0.3(0.01)	0.72(0.07)	8.8(0.53)	22.91(2.73)	56.24(0.03)	93.66(1.69)
Tottori	15.19(0.29)	72.91(1.3)	6e-04(0)	0.24(0.02)	15.58(0.65)	6.81(0.67)	97.94(1.25)	0.3(0)	0.25(0.02)	1.66(0.07)	4.41(0.44)	9.15(0.06)	90.29(4.57)
Shimane	15.24(0.28)	74.31(1.45)	7e-04(0)	0.27(0.02)	14.25(0.86)	6.96(0.72)	96.61(0.78)	0.3(0.02)	0.23(0.02)	1.85(0.06)	5.57(0.51)	11.97(0.21)	89.79(5.51)
Gifu	16.18(0.3)	65.69(2.68)	0.0021(0)	0.21(0.02)	17.53(0.51)	7.66(0.86)	97.35(1.76)	0.3(0.01)	0.49(0.05)	3.54(0.1)	10.18(1.01)	21.05(0.26)	90.63(4.4)
Kanagawa	16.22(0.36)	65.11(1.62)	0.0088(2e-04)	0.17(0.03)	17.92(0.65)	7.78(0.6)	97.7(1.03)	0.3(0.01)	0.89(0.07)	14.7(0.72)	37.79(3.69)	75.2(0.55)	94.64(1.46)
Aichi	16.23(0.34)	65.22(2.84)	0.0073(2e-04)	0.18(0.02)	17.99(1.16)	7.7(0.45)	97.96(1.2)	0.3(0)	0.97(0.09)	12.97(0.47)	33.84(4.21)	69.96(0.03)	96.72(0.97)
Kyoto	16.19(0.28)	64.26(2)	0.0026(0)	0.21(0.03)	15.65(0.9)	6.64(0.83)	97.09(1.02)	0.29(0.01)	0.56(0.07)	7.17(0.11)	16.99(1.48)	37.17(0.42)	97.19(1.66)
Shiga	15.07(0.26)	73.87(1.46)	0.0014(0)	0.18(0.02)	16.75(0.7)	7.42(0.54)	97.59(1.18)	0.29(0.01)	0.53(0.07)	2.63(0.18)	8.37(1.16)	14.14(0.63)	95.43(1.49)
Shizuoka	16.9(0.3)	68.26(1.74)	0.0038(0)	0.21(0.03)	16.73(0.53)	7.45(0.65)	97.06(1.33)	0.3(0.01)	0.7(0.05)	6.43(0.29)	19.68(2.15)	39.74(0.74)	90.19(3.06)

Table S3. Continued

Prefecture/ country	Temperature (℃)	Relative humidity (%)	Density (population/km^2)	% population ≥ 65 years	Savings (million yen)	Income (million yen)	CPI	Gini index	EPI (%)	Physicians (number per 10k population)	Nurses (number per 10k population)	Hospital beds (number per 10K population)	AC (%)
Mie	16.35(0.3)	67.67(2.16)	0.0019(0)	0.22(0.02)	17.55(1.8)	7.45(0.65)	96.24(0.83)	0.28(0)	0.54(0.07)	3.38(0.08)	9.3(1.17)	21.22(0.07)	94.91(1.84)
Hyogo	17.08(0.29)	65.15(1.93)	0.0056(0)	0.2(0.03)	16(0.65)	7.01(0.52)	98.18(1.95)	0.3(0.01)	0.55(0.07)	11.22(0.49)	30.33(3.37)	64.77(0.49)	95.64(1.59)
Nara	15.16(0.29)	72.17(1.47)	0.0014(0)	0.21(0.03)	18.02(1.78)	7.26(0.69)	99.24(2.2)	0.3(0.01)	0.39(0.05)	2.81(0.15)	7.23(0.82)	16.19(0.88)	97.19(1.89)
Osaka	17.19(0.32)	62.81(1.12)	0.0088(0)	0.19(0.03)	14.5(0.48)	6.62(0.7)	99.34(1.9)	0.32(0.02)	0.75(0.05)	21.07(0.69)	44.41(6.91)	113.25(3.26)	97.5(0.59)
Okayama	16.57(0.29)	65.53(1.56)	0.0019(0)	0.23(0.02)	16.77(0.56)	7.07(0.67)	97.51(0.81)	0.3(0.01)	0.48(0.07)	4.86(0.27)	14.71(1.4)	31.45(0.45)	94.55(1.98)
Hiroshima	16.48(0.28)	67.24(2.45)	0.0029(0)	0.21(0.02)	16.13(1.18)	6.9(0.34)	97.44(1.08)	0.3(0.01)	0.54(0.07)	6.7(0.16)	17.77(2.04)	42.23(0.33)	93.33(2.63)
Kagawa	16.8(0.28)	65.55(1.47)	0.001(0)	0.24(0.02)	18.52(1.26)	6.95(0.53)	97.44(1)	0.29(0.01)	0.43(0.05)	2.51(0.04)	7.55(0.52)	17.36(0.4)	96.75(1.47)
Wakayama	16.92(0.31)	64.22(1.73)	0.001(0)	0.24(0.03)	15.19(1.03)	6.24(0.7)	96.62(1.17)	0.3(0)	0.3(0.04)	2.54(0.09)	5.8(0.72)	14.84(0.25)	95.35(3.3)
Yamaguchi	15.81(0.25)	70.19(1.53)	0.0015(0)	0.25(0.02)	13.95(0.73)	6.3(0.36)	98.89(1.38)	0.29(0.01)	0.41(0.05)	3.53(0.06)	10.57(0.97)	28.29(0.22)	91.97(2.59)
Tokushima	16.86(0.3)	66.08(1.49)	8e-04(0)	0.25(0.02)	16.1(1.28)	6.77(0.58)	97.19(0.89)	0.33(0.01)	0.31(0.02)	2.26(0.05)	6.08(0.39)	16.22(0.56)	94.51(3.19)
Ehime	16.8(0.28)	65.35(2.18)	0.0015(0)	0.24(0.02)	13.8(1.41)	6.11(0.32)	97.26(0.86)	0.3(0.01)	0.37(0.04)	3.4(0.06)	10.91(0.81)	23.81(0)	92.68(3.68)
Fukuoka	17.33(0.28)	65.6(1.58)	0.0051(0)	0.2(0.02)	12.55(0.73)	6.49(0.36)	98.16(1.94)	0.31(0.01)	0.58(0.04)	13.19(0.52)	35.67(3.32)	89.87(1.1)	95.35(1.66)
Kochi	17.39(0.32)	68.63(1.23)	8e-04(0)	0.26(0.02)	13.95(2.37)	6.22(0.69)	97.43(1.26)	0.32(0.01)	0.23(0.02)	2.16(0.05)	6.48(0.71)	20.05(0.56)	88.7(4.85)
Oita	16.9(0.3)	66.88(1.82)	0.0012(0)	0.25(0.02)	12.17(0.27)	6.08(0.55)	97.08(1.06)	0.3(0.01)	0.33(0.04)	2.82(0.1)	8.78(0.95)	21.09(0.22)	88.78(4.67)
Saga	16.86(0.27)	67.71(1.68)	9e-04(0)	0.23(0.02)	12.14(1.08)	6.84(0.65)	98.58(1.54)	0.29(0.01)	0.31(0.03)	1.95(0.05)	6.44(0.57)	15.47(0.05)	93.39(4.24)
Kumamoto	17.34(0.36)	68.2(1.65)	0.0018(0)	0.24(0.02)	10.85(0.52)	6.27(0.55)	97.84(1.16)	0.31(0.01)	0.36(0.04)	4.58(0)	14.54(1.4)	36.53(0.44)	90.52(3.13)
Nagasaki	17.45(0.31)	68.71(1.9)	0.0015(0)	0.24(0.02)	11.01(0.22)	6.02(0.58)	97.86(0.97)	0.31(0.02)	0.27(0.03)	3.78(0.2)	10.92(1.21)	28.45(0.91)	93.37(2.21)
Miyazaki	17.78(0.32)	72.24(1.44)	0.0012(0)	0.24(0.02)	10.18(0.44)	5.93(0.32)	98.22(1.46)	0.31(0)	0.29(0.03)	2.49(0.07)	8.63(1.1)	19.92(0.08)	88.09(2.82)
Kagoshima	18.86(0.32)	68.12(2.12)	0.0017(0)	0.25(0.02)	10.08(0.13)	5.63(0.37)	97.42(0.72)	0.29(0.01)	0.29(0.02)	3.89(0.11)	13.17(1.27)	36.17(0.52)	89.25(6.56)
Okinawa	23.28(0.22)	72.39(2.08)	0.0014(0)	0.16(0.01)	5.58(0.44)	4.79(0.41)	97.36(1.11)	0.35(0.01)	0.28(0.02)	2.62(0.23)	7.85(0.87)	19.78(0.01)	86.45(2.78)

CPI: consumer price index; EPI: Economic power index; AC: air conditioning prevalence.

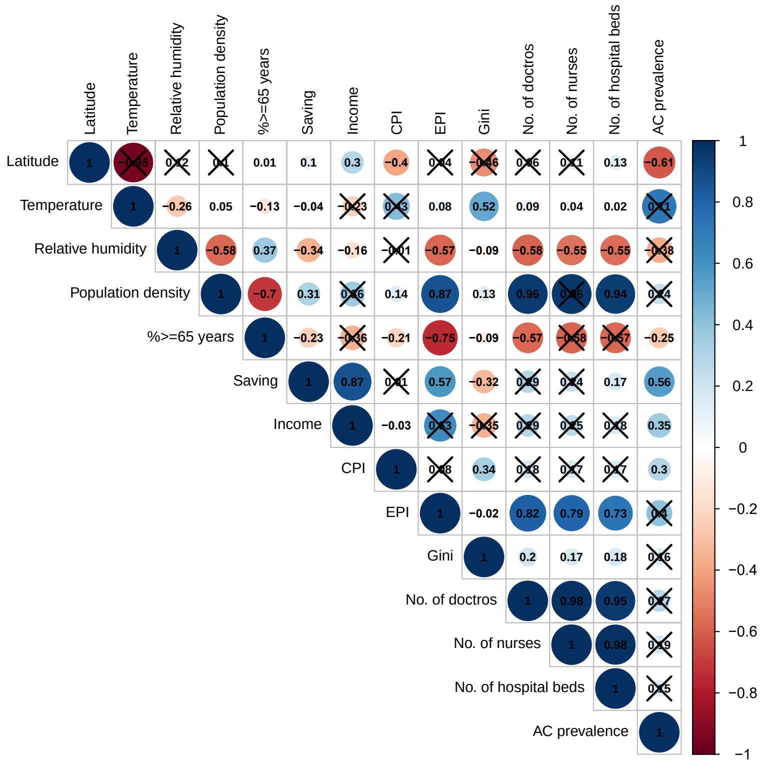

Figure S2. Correlations between the indicators.

Blue: positively associated; red: negatively associated; Cross: p>0.05.

RH: relative humidity; CPI: consumer price index; EPI: economic power index; AC: air conditioning prevalence

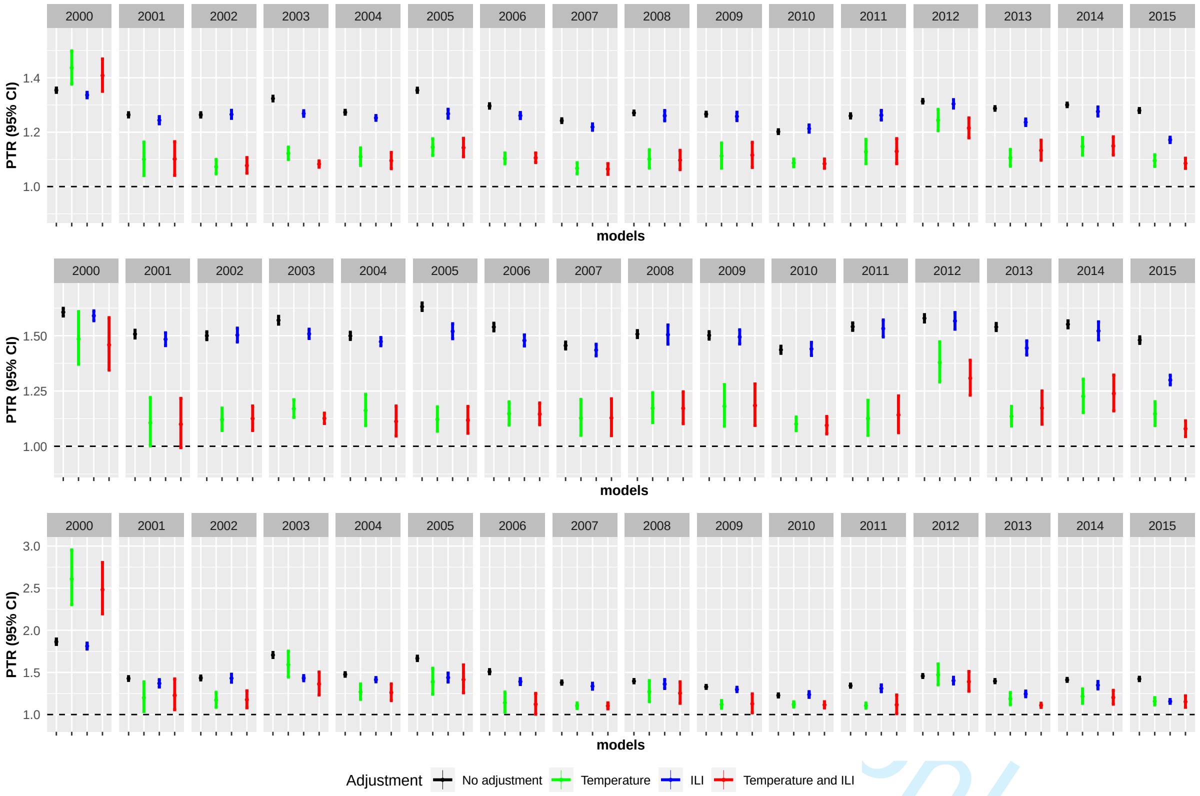

Figure S3. Peak-to-trough ratio (PTR) with 95% confidence intervals (95%CI) for each single year from 2000 to 2015 for all-cause (top), circulatory (middle), and respiratory (bottom) mortality before (black) and after adjustments for just influenza like illness (blue), just temperature (green), and both (red)

Note: The year of 1999 was excluded from our yearly analyses, as ILI data was not available until April 1999.

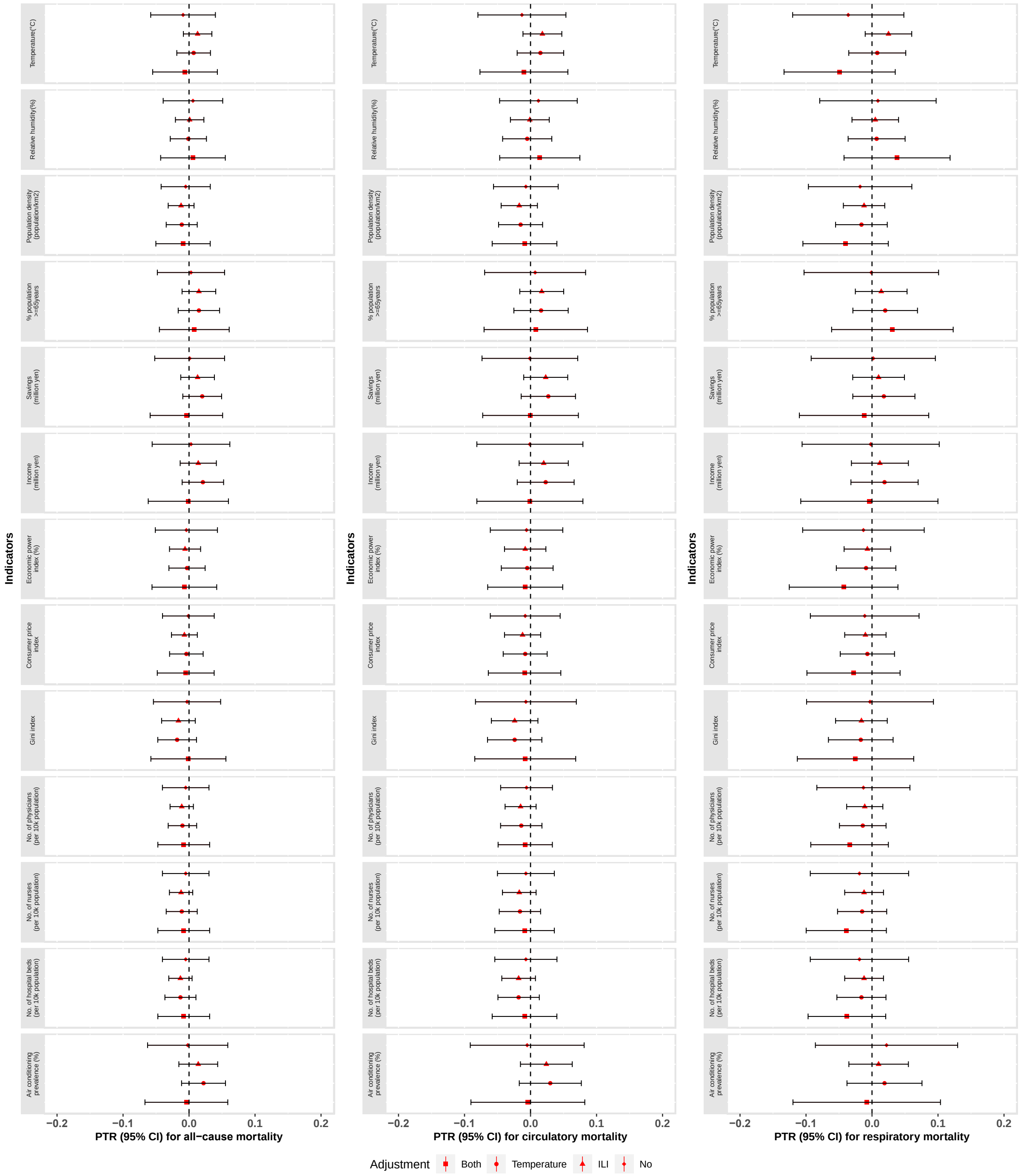

Figure S4. Associations between each indicator and PTR before and after adjusting for influenza like illness (ILI) and temperature

Coefficient and 95% confidence intervals were obtained from liner mixed effect models adjusting for latitude and longitude, except for when we investigated averaged annual mean temperature as the indicator, due to their high correlation. Results are expressed as log (PTR) change for standard deviation increase in each indicator.

Description of models

- Seasonality assessment without and with adjustments for temperature and/or influenza like illness

We applied a generalized linear model with a quasi-Poisson family to assess seasonality of mortality in each prefecture.

$$\boldsymbol{Y_t \sim Quasi - Poisson(\mu_t)}$$

Main model (without any adjustment for temperature and ILI)
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t$
Adjusting for temperature
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t + \beta Temp_{t,l}$
Adjusting for ILI
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t + ns(ILI_t, 3)$
Adjusting for both temperature and ILI
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t + \beta Temp_{t,l} + ns(ILI_t, 3)$

t: the day of the observation;
Yt: the observed daily numbers of mortality on day *t*;
β_0: the intercept;
doy: day of year, which was fitted using cyclic cubic spline with 4 degrees of freedom (*df*);
ILI_t: the daily numbers of ILI on day t, which was controlled using natural cubic spline with 3 *df*;
$Stratat$: strata defined by year, day of week, and their interaction to control for the long-term trend and the effect of day of week, and λ is the vector of coefficients;
$Tempt,l$: a matrix obtained by using cross basis function to temperature; *l* is the lag days, and β is the vector of coefficients. (For the cross-basis function, a natural cubic B-spline basis with three internal knots at the 25th, 50th, and 75th percentiles of temperature distribution was used for exposure-response association, and another natural cubic B-spline basis with 3 *df* with extended lag up to 21 days was used for the lag-response association.)

- Modification of seasonal variation in mortality by prefecture-specific indicators

We applied linear mixed effects models (LMEMs) to investigate associations of PTR with each prefecture-specific indicator separately. We fitted LMEMs with random intercepts for prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital city of each prefecture were included to reduce spatial correlation, except for when we investigated annual mean temperature as the indicator, due to their high correlation.

$$\boldsymbol{\beta_i = \alpha + \gamma Z_i + \eta + \nu_i}$$

β_i is the estimated coefficient for seasonality (i.e., log(PTR)) in prefecture *i*
Z_i is the prefecture-specific indicator for prefecture *i* (e.g., latitudes, longitudes, and averaged annual mean temperature)
α and γ are estimated using least squares regression with inverse-variance weights.
ν_i is the variation within prefecture i, with the variance as $\sigma^2_{\nu_i}$
η represents the heterogeneity among prefectures with a variance of σ^2_η estimated using the restricted maximum likelihood approach.

Model Checking and sensitivity analysis

We used scatter plot of deviance residuals vs time and partial autocorrelation function plot of the deviance residuals to check the models. In addition, sensitivity analysis was conducted to check the robustness of our estimates.
We used the largest prefecture (i.e., Tokyo) for model evaluation, as the statistical uncertainty for the estimates was small.

- Scatter plot of deviance residuals vs time

In general, the plot shows an even band of points over the time, although we observed a few spikes, for example, in 1999. This pattern did not change significantly when we use more flexible modellings for seasonality, temperature, and influenza.

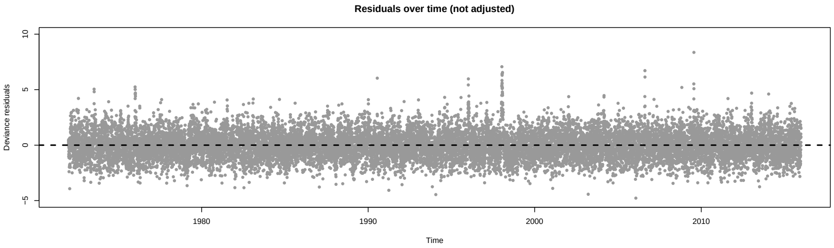

Figure S5. Deviance residuals over time from the analysis in Tokyo (without adjustment for temperature and/or influenza)

- Partial autocorrelation function (PACF) plot of the deviance residuals

PACF shows a slow decay and a high degree of autocorrelation around a 1-week lag. This pattern remained when we included temperature and/or ILI in the model. In order to reduce the autocorrelation, we tried more flexible functions for seasonality by increasing the degree of freedom, and then we added lagged deviance residuals to the model in several different ways. For example, 1-day lagged deviance residuals, 1- to 6-day lagged deviance residual, and a moving average of 6 days lagged deviance residuals, respectively. The autocorrelation remained without much reduction after many attempts, but the coefficient and its standard error from cyclic spline functions for seasonality changed very little (Table S4).

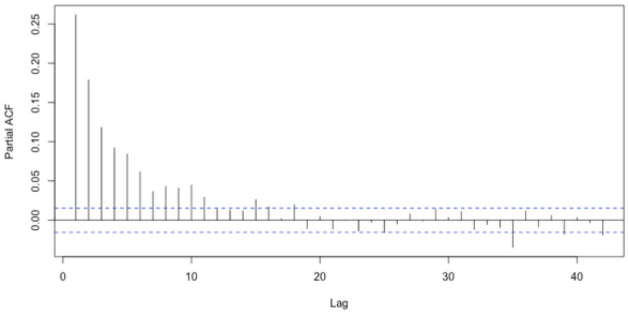

Figure S6. Partial autocorrelation function plot of the deviance residuals from the analysis in Tokyo (without adjustment for temperature and/or influenza)

Table S4. Seasonality estimates for Tokyo without adjusting for temperature and/or influenza like illness

Models	Peak-to-Trough (95% confidence interval)
Main model	1.254 (1.249, 1.259)
Model 1	1.249 (1.237, 1.255)
Model 2	1.244 (1.237, 1.252)
Model 3	1.253 (1.249, 1.258)
Model 4	1.253 (1.248, 1.257)
Model 5	1.252 (1.248, 1.257)
Model 6	1.250 (1.247, 1.254)

Main model: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t$

($Stratat$: strata defined by year, day of week, and their interaction to control for long-term trend and effect of day of week)

Model 1: $\log(\mu_t) = \beta_0 + cs(day - of - year, 5) + \lambda Strata_t$

Model 2: $\log(\mu_t) = \beta_0 + cs(day - of - year, 6) + \lambda Strata_t$

Model 3: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + Lag(residuals(main\ model), 1)$

Model 4: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + Lag(residuals(main\ model), 1) + Lag(residuals(main\ model), 2) + Lag(residuals(main\ model), 3)$

Model 5: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + Lag(residuals(main\ model), 1) + Lag(residuals(main\ model), 2) + Lag(residuals(main\ model), 3) + Lag(residuals(main\ model), 4) + Lag(residuals(main\ model), 5) + Lag(residuals(main\ model), 6)$

Model 6: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + runmean(residuals(main\ model), 6)$

- The fit of the model to the daily death counts over time

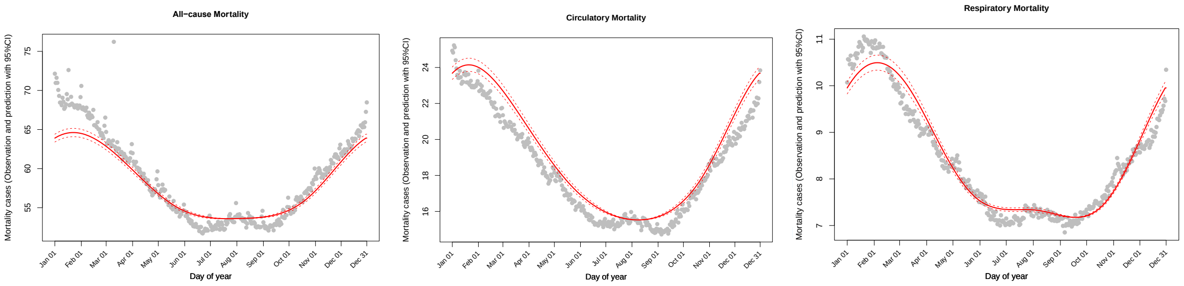

Figure S7. Daily mean number of observed aal-cause, circulatory, and respiratory mortality in Japan averaged from 47 prefectures over the study period and estimated number of daily circulatory mortality from time series regression models (Main model)

Grey dot: daily mean number of observed mortality cases averaged from 47 prefectures over the study period;
Red: pooled estimates with 95% confidence intervals obtained from prefecture-specific estimates from models without temperature adjustment

Figure S7 suggests that our models fitted seasonality of circulatory mortality better and may underestimate the seasonal variation in all-cause and respiratory mortality. The discrepancy between observed and fitted values may be explained by the risk of temperature, infectious disease, and other factors (e.g., human behaviour).

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The role of temperature, influenza and other local characteristics in seasonality of mortality: a population-based time-series study in Japan

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Secondary Subject Heading:	Public health, Epidemiology
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, PREVENTIVE MEDICINE

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The role of temperature, influenza and other local characteristics in seasonality of mortality: a population-based time-series study in Japan

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Abstract

Objectives: To investigate the extent to which temperature and influenza explained seasonality of mortality in Japan and to examine the association of the seasonality with prefecture-specific characteristics.

Design: We conducted time-series analysis to estimate the seasonal amplitude before and after adjusting for temperature and/or influenza like illness (ILI). Next, we applied linear mixed effect models to investigate the association of seasonal amplitudes with each indicator on prefecture-specific characteristics on climate, demographic and socioeconomic factors, and adaptations.

Setting: 47 prefectures in Japan

Participants: Deaths for all-cause, circulatory, and respiratory disease between 1999 and 2015

Outcome measures: Peak-to-trough ratio (PTR, a measure of seasonal amplitude)

Results: The nationwide unadjusted-PTRs for all-cause, circulatory and respiratory mortality were 1.29 (95% Confidence Intervals (CI): 1.28, 1.31), 1.52 (95%CI: 1.49, 1.55) and 1.45 (95%CI: 1.43, 1.48), respectively. These PTRs reduced substantially after adjusting for temperature but very little after a separate adjustment for ILI. Furthermore, seasonal amplitudes varied between prefectures. However, there was no strong evidence for the associations of PTR with the indicators on prefecture-specific characteristics.

Conclusions: Seasonality of mortality is primarily driven by temperature in Japan. The spatial variation in seasonal amplitudes was not associated with prefecture-specific characteristics. Although further investigations are required to confirm our findings, this study can help us gain a better understanding of the mechanisms underlying seasonality of mortality.

Strengths and limitations of this study

- We investigated the contributions of temperature versus influenza to seasonal variation of different types of mortality by a common study design and statistical framework.
- We used indicators on a range of location-specific characteristics to investigate their modifying effect on seasonal variations in mortality.
- The study was conducted in Japan characterized by distinct seasonal weather conditions, so our results may not be generalized to locations with different climate (e.g., tropical countries).
- The deviance of residuals showed some autocorrelations, but it had limited impacts on our seasonality estimates.

Introduction

Seasonality of mortality is among the oldest observation across a broad range of population and geographical locations, typically entailing higher mortality in cold seasons than in warm seasons.[1–6] This epidemiological phenomenon reflects a complex interaction between environment and human.[2] The understanding of its underlying drivers is yet to be elucidated.

Some of the postulated contributors to seasonality of mortality include temperature, infectious disease, air pollution, physiological responses, and human behaviors.[1,2,7–9] Temperature is of most profound interest, with overwhelming evidence on its cold and hot effect on mortality.[10] Another well recognized contributor to seasonality is influenza, due to its strong seasonal cycle and association with inflammatory process.[11] A number of studies demonstrated an association between influenza and mortality in cold seasons.[11–15] Some of them focused on its role in temperature-mortality associations.[11,12] Other publications assessed its contribution to winter-season increase in mortality.[13–15] Although consensus exists that both temperature and influenza contribute to winter-season increase in mortality,[11–14,16] their relative importance has not been completely elucidated. Most research[11–14,16] has focused on either temperature or influenza only, and few studies have comparatively assessed their contribution to seasonality of mortality. We are aware of only one study that has compared their contributions to seasonality of all-cause mortality among people aged ≥ 75 years in Britain and suggested more seasonality was explained by temperature than influenza.[14]

The strength of seasonality in mortality varies geographically.[8] For example, a larger seasonal amplitude was observed in areas with milder climates, suggesting that individuals living in warm areas might be more vulnerable to seasonal variations in mortality.[2] Several local characteristics on climate, demographic and socioeconomic factors, and adaptations have been linked with such spatial variation. However, only a few studies have evaluated their impact on effect on seasonality of mortality.[1,17] Another question remains unclear is if their impact effect will remain when we remove the effect of temperature and influenza from seasonal variations in mortality, given that the same local characteristics can also modify associations between influenza, temperature and mortality.[18–23]

In the current study, we collected daily mortality data between 1999 and 2015 from 47 prefectures in Japan to investigate the contribution of temperature and influenza to seasonality of mortality as well as to study the associations between prefecture-specific indicators and seasonality of mortality. This study will strengthen our understanding of seasonality of mortality and provide important evidence to associate managements of seasonal risk factors to local conditions.

Method

Data collection

Hourly mean temperature (°C) and relative humidity (%) measured at a single monitoring site in the capital city of each prefecture were obtained from 1999 to 2015 from the Japan Meteorological Agency. We computed daily mean value of temperature and relative humidity for our analysis.

Daily mortality (counts) from all-cause, circulatory, respiratory disease and influenza were obtained from the Ministry of Health, Labor and Welfare of Japan between 1999 and 2015 for each prefecture in Japan. The principal cause of death statistics is coded using the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10). Cause-specific mortality was defined according to the ICD system: circulatory mortality (ICD-10 codes I00-I99), and respiratory mortality (ICD-10 codes J00-J99). Weekly number of influenza like illness (ILI) were obtained for each prefecture from April 1999 to 2015 from National Institute of Infectious Diseases, Japan.

Yearly data on prefecture-specific indicators was collected over the study period for each prefecture, including annual mean temperature, relative humidity, population density, the proportion of population aged ≥ 65 years, saving, income, Gini index (a measure of income inequality), consumer price index (CPI), economic power index (EPI, a measure of the wealth of a prefecture), the prevalence of air conditioning for households, and the number of registered physicians, nurses and hospital beds per 10K population. For each indicator, we computed the averaged value across the years 1999-2015 for each prefecture. The details for data collection were described in previous studies [24,25] and summarized in supplementary material.

Data analysis

We conducted our data analysis in three steps. First, we assessed seasonality of mortality without adjustments for temperature or ILI. Then, we examined the changes in the seasonality after adjusting for temperature and ILI separately, as well as both at the same time. Lastly, we evaluated the associations between each indicator and seasonality estimates before and after adjustments.

We applied a generalized linear model with a quasi-Poisson family to assess seasonality of mortality in each prefecture without any adjustment for temperature and ILI. Day-of-year was treated as an indicator for seasonality, taking values from 1 to 366 corresponding to Jan 1st through Dec 31st for both common and leap years (from 60th day to 365th day in common years, values were taken from 61 to 366). We used a cyclic cubic spline with 4 degrees of freedom (*df*) for day of year to estimate seasonality. The days-of-year with maximum and minimum mortality estimates from generalized liner models were identified as the peak and trough days, respectively, and were subsequently used to calculate the peak-to-trough ratio (PTR) to provide a measure of seasonality. When constructing confidence intervals for PTR, previous studies enforced the boundary constraint by truncating the lower confidence limit at one for PTR.[26,27] However, doing that may introduce a positive bias into the PTR.[28] In order to show the statistical variability in PTR, therefore, we did not truncate the lower confidence limit at one for PTR. Indicators for year, day-of-week and their interaction were used to control for the long-term trend and the effect of day-of-week. We excluded the data on 11 March 2011, the day of the Great East Japan Earthquake.

To assess the contribution of temperature and ILI to seasonality of mortality, we attempted three types of adjustment. First, we added temperature to our main model using a bi-dimensional cross-basis function to account for its non-linear and delayed effect on mortality. We modeled the exposure-response curve with a natural cubic B-spline with three internal knots at 25th, 50th, and 75th percentiles of temperature distribution, and the lag-response association with another natural cubic spline basis with 3 *df* with extended lags up to 21 days.[10,25]

Second, we removed temperature and adjusted for ILI in main model. We assumed ILI cases distributed evenly across day of week and computed daily average ILI cases. A natural cubic spline with 3 *df* was then used to control for daily ILI cases in the model. Third, adjustment was made using both temperature and influenza.

The prefecture-specific PTR was pooled for the whole of Japan for all-cause, circulatory and respiratory mortality, respectively, by meta-analysis with prefecture as a random factor. To explore if patterns of interest varied over time, we conducted yearly analyses for the entire country using separate quasi-Poisson regression model for each year with prefecture as a random factor.

To evaluate the modification of seasonal variation in mortality by prefecture-specific indicators, we applied linear mixed effects models (LMEMs) to investigate associations of PTR with each prefecture-specific indicator separately. We fitted LMEMs with random intercepts for prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital city of each prefecture were included to reduce spatial correlation, except for when we investigated annual mean temperature as the indicator, due to their high correlation. We conducted the analysis for all-cause, circulatory, and respiratory mortality in separate LMEMs. Results are expressed as the log(PTR) variation for a standard deviation increase of the indicator.

We performed a series of sensitivity analysis to confirm our findings. We tested the cyclic spline function for day of year with different *df* of *5* and *6* and adjusted temperature by changing the spline function, internal knots for temperature distribution, *df* and lag days for the lag-response associations. For influenza adjustment, we varied the number of lag days using the moving averages of the previous 7, 14, 21 and 28 days, and tested the natural cubic spline function with 2 *df*. For ILI adjustment, we tested moving average of previous 7, 14, 21 and 28 days for ILI cases, and 2 *df* for the natural cubic spline function. Overall, we did not observe substantial changes in our estimates.

The models were summarized in supplementary material including diagnostic plots. We conducted the analysis with R software, version 3.6.0 (R Development Core Team) using the dlnm and mixmeta packages.

Patient and public involvement

There was no patient or public involvement.

Results

This study included 18 985 036 deaths from all causes, 5 541 277 deaths from circulatory diseases, and 2 894 314 deaths from respiratory diseases. The nationwide time series of daily mortality showed a significant seasonal pattern (Figure S1). Daily mean temperature for the whole country between 1999 and 2015 ranged from -1.0°C to 30.7°C, with a mean value at 15.6°C

(Table 1). ILI cases showed a large variation, ranging from 7 case to 1 652 147 cases with a median value at 7626 (Table 1). Prefecture-specific summary was provided in Table S1.

We observed a high variability for healthcare capacity (Table S2 & S3), while a low variability for socioeconomic indicators. Most of the indicators are correlated (Figure S2). In particular, EPI was highly correlated with population density, proportion of individuals aged over than 65 years old, and numbers of physicians, nurses and hospital beds (correlation>0.70). In addition, saving is highly correlated with income (correlation>0.70).

Figure 1 and Table 2 show the pooled results for the whole of Japan for seasonality of all-cause, circulatory, and respiratory mortality before and after adjustments for temperature and/or influenza. We observed a clear seasonal pattern with higher numbers of deaths in cold seasons than in warm seasons. Before any adjustments, the nationwide pooled PTR for all-cause, circulatory and respiratory mortality were 1.29 (95% confidence intervals (CI): 1.27, 1.30), 1.52 (95% CI: 1.49, 1.55) and 1.45 (95% CI: 1.43, 1.48), respectively. After adjustments for temperature and ILI, the shape of seasonality remained (Figure 1), but its amplitude reduced to different extents. Adjusting for just temperature reduced PTRs substantially in particular for all-cause and circulatory mortality to 1.06 (95% CI: 1.05,1.07) and 1.07 (95% CI: 1.05, 1.09). Adjusting for just ILI reduced PTRs only very slightly to 1.27 (95% CI: 1.26,1.29), 1.52 (95% CI: 1.49,1.55), and 1.40 (95% CI: 1.38, 1.43) for all-cause, circulatory and respiratory mortality, respectively. Notably, adjusting for temperature and ILI did not flatten the seasonal pattern or reduce the PTR to 1.

Similarly, prefecture-specific PTRs also showed a substantial reduction with temperature adjustment while a slight reduction when ILI was adjusted only, although an apparent reduction was observed in ILI-adjusted PTR for respiratory mortality (Figure 2). Furthermore, PTR for all mortality types varied across prefectures, and the spatial variation after adjustments was less apparent in particular for all-cause and circulatory mortality. Prefectures with higher latitude (northern areas), including Hokkaido, Aomori, and Akita, as well as the southernmost prefecture- Okinawa, showed a lower unadjusted-PTR and a smaller reduction after adjustments for temperature.

Our yearly analyses for the entire country showed a large reduction after adjusting for temperature while a small reduction after adjusting for ILI for most of the years (Figure S3). For the year of 2020, however, a higher PTR for all-cause and respiratory mortality was observed when temperature was included in the adjustment. We further checked the sensitivity of our estimates to temperature adjustment. Changing the lag period of 21 days in cross-basis function to 14 days reduced temperature-adjusted PTR, although it remained slightly higher than unadjusted PTR with a largely overlapped confidence intervals. The results for the other years did not change much (results not shown).

Figure S4 shows associations between the indicators and PTR. There was no strong evidence for the association between prefecture-specific characteristics and seasonality estimates. Diagnostic plots for models were included in supplementary material (Figure S5-S7).

Discussion

In this study, we investigated the contribution of temperature and influenza to seasonal variation of mortality in 47 prefectures of Japan and evaluated the modifications of seasonality by a range of prefecture-specific indicators. Our findings show that seasonal variation in mortality was substantially contributed by temperature and to a lesser extent, by influenza. In addition, seasonal amplitudes varied between prefectures. There was no strong evidence for the association between prefecture-specific characteristics and seasonal amplitudes.

Temperature and influenza have been among the most studied drivers of seasonality of mortality.[13–16] However, most of the investigations focused on either temperature or influenza. How much of seasonality of mortality is dependent on temperature versus influenza remain unsolved. Our finding showed that most of seasonality of mortality in Japan was attributable to temperature while little was driven by influenza. Consistent with our findings, a population -based cohort study in elderly British people examined month to month variation in mortality and its relationship with temperature and influenza A, and discovered that most of seasonal fluctuation was associated with cold temperature and a small component related with influenza A. Despite the smaller contribution of influenza to seasonal variation of mortality than temperature, our analysis suggested that influenza was accountable for seasonal variation, especially, for respiratory mortality. The transmission of influenza virus is most efficient under cold and dry conditions, which may lead to considerable increase in mortality during winter. For example, a study[11] in 48 U.S. cities observed a link between influenza epidemic and the irregularly high winter mortality in some certain years. Evidence thus far implies that temperature contributes substantially to seasonality of mortality in general, while influenza is related with seasonal variations of mortality to a less extent.

Notably, removing the effect of temperature and influenza from seasonal variation in mortality did not completely flatten the seasonal pattern of mortality, in particular, respiratory mortality. Seasonality of mortality is resulted from complex interaction between human behavior and environment. In addition to temperature and influenza, other infectious diseases (e.g., respiratory syncytial virus), air pollutants, behavioral changes based on a seasonal basis (e.g., dietary pattern and physical activities) have been linked with seasonal variation of diseases and mortality. However, there is no direct evidence assessing their contribution to seasonality of mortality.

Despite of a similar seasonal shape across prefectures, seasonal amplitudes varied across 47 prefectures. Previous studies have suggested that individuals living in cold locations show less seasonal variation in mortality, partially due to a better cold acclimatization from the combination of habituation, metabolic adjustment, and insulative acclimatization. [8,29–31] In addition, less developed locations is likely to exhibit a larger seasonal variation in mortality,[1] which can be related with high vulnerabilities to cold and heat effect of temperature because of poorer housing conditions, lower prevalence of air conditioning, and limited access to health care.[18,23] In our study, we did not observe strong evidence for any associations between prefecture-specific characteristics and seasonal variations in mortality. This could be partially explained by the limited range of variations in the indicators and possible confounding effect between them. Furthermore, our data on the indictors are population-level, and future investigations with individual-level data is recommended to examine these issues.

This study has several limitations. First, our study was conducted in Japan that has distinct seasonal weather conditions, hence our results may not be applicable to other areas with different climate (e.g., tropical countries). Second, we assumed the association of mortality with influenza and temperature did not change between 1999 and 2015, and our findings for 2000 were sensitive to temperature adjustment. Furthermore, we observed some autocorrelation in the model residuals despite our attempts to model it (Figure S6). However, sensitivity testing showed that it had limited impacts on the estimate of seasonality (Table S4). It is possible that temperature and influenza adjusted PTR may be overestimated due to the measurement error in temperature and influenza.[32] However, any such overestimation would be believed to be slight, as the main error here would be of Berkson type, which does not cause bias and hence not compromise confounder control.[33] Finally, future investigations should be conducted by extending current datasets to those areas with different climate, and also by including more details for influenza (e.g., influenza subtype and vaccination coverage). Results from these investigations would complement our findings in current analysis.

This study presents findings from an epidemiologic analysis investigating the role of temperature, influenza and other local characteristics on seasonality of mortality across multiple locations. A strength of current study was the investigation of contributions of temperature versus influenza to seasonal variation of different types of mortality by a common study design and statistical framework, while previous studies mostly focused on either temperature or influenza only.

This study suggests that seasonality of mortality is primarily driven by temperature. Furthermore, seasonal amplitudes varied between prefectures. However, this spatial variation was not explained by the differences in prefecture-specific characteristics on climate, demographic and socioeconomic factors, and adaptations. Further investigations are required to confirm our findings. In sum, this study can help us to gain a better understanding of seasonality of mortality.

Contributors: LM conducted the study, analyzed the data and wrote the manuscript. CN and XS helped with the statistical analysis and the discussion of the text. MT, LY and YH contributed to the final version of the manuscript. BA helped with the data analysis and the interpretation of the results. MH contributed to the study design and the discussion of the results.

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Competing interests: None declared.

Ethics approval: This study used secondary data, with no possibility of personal identification, and an informed consent or an approval by a medical ethics board is not required.

Data availability statement: Data are available upon reasonable request. The technical appendix, statistical code and data set will be available upon request from the Corresponding author.

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Figure captions:

Figure 1. Pooled seasonality of all-cause, circulatory, and respiratory mortality between 1999 and 2015 before and after adjustments (black: without any adjustment; blue: adjusted for influenza like illness (ILI) only; green: adjusted for temperature only; red: adjusted for both temperature and ILI)

The seasonality is computed as the ratio of predicted mortality at each day of the year to the predicted minimum mortality at the trough with 95% confidence intervals (95%CIs):

$$Ratio = \frac{Mortality\ \ at\ day_i}{Minimum\ mortality\ at\ the\ trough}$$

Figure 2. Prefecture-specific peak-to-trough ratio (PTR) with 95% confidence intervals (95% CI) for all-cause (left), circulatory (middle), and respiratory (right) mortality before (black) and after adjustments for influenza like illness (ILI) only (blue), temperature only (green), and both (red)

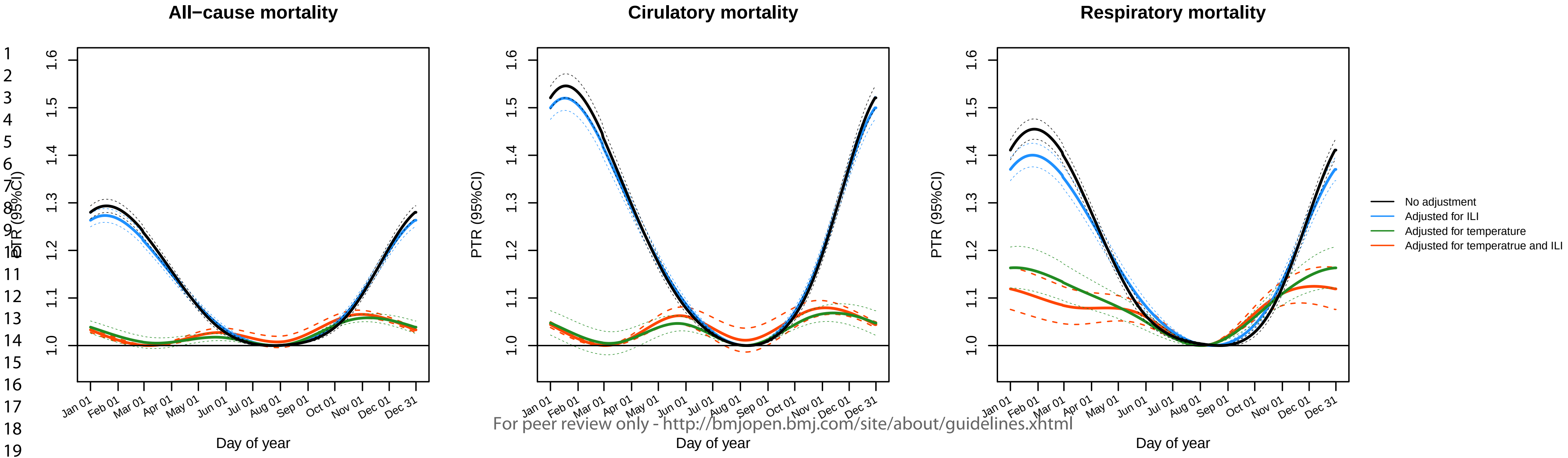
Table 1. Nationwide summary of daily mean temperature (℃), daily death (numbers of cases), and weekly influenza like illness (ILI) between 1999 and 2015

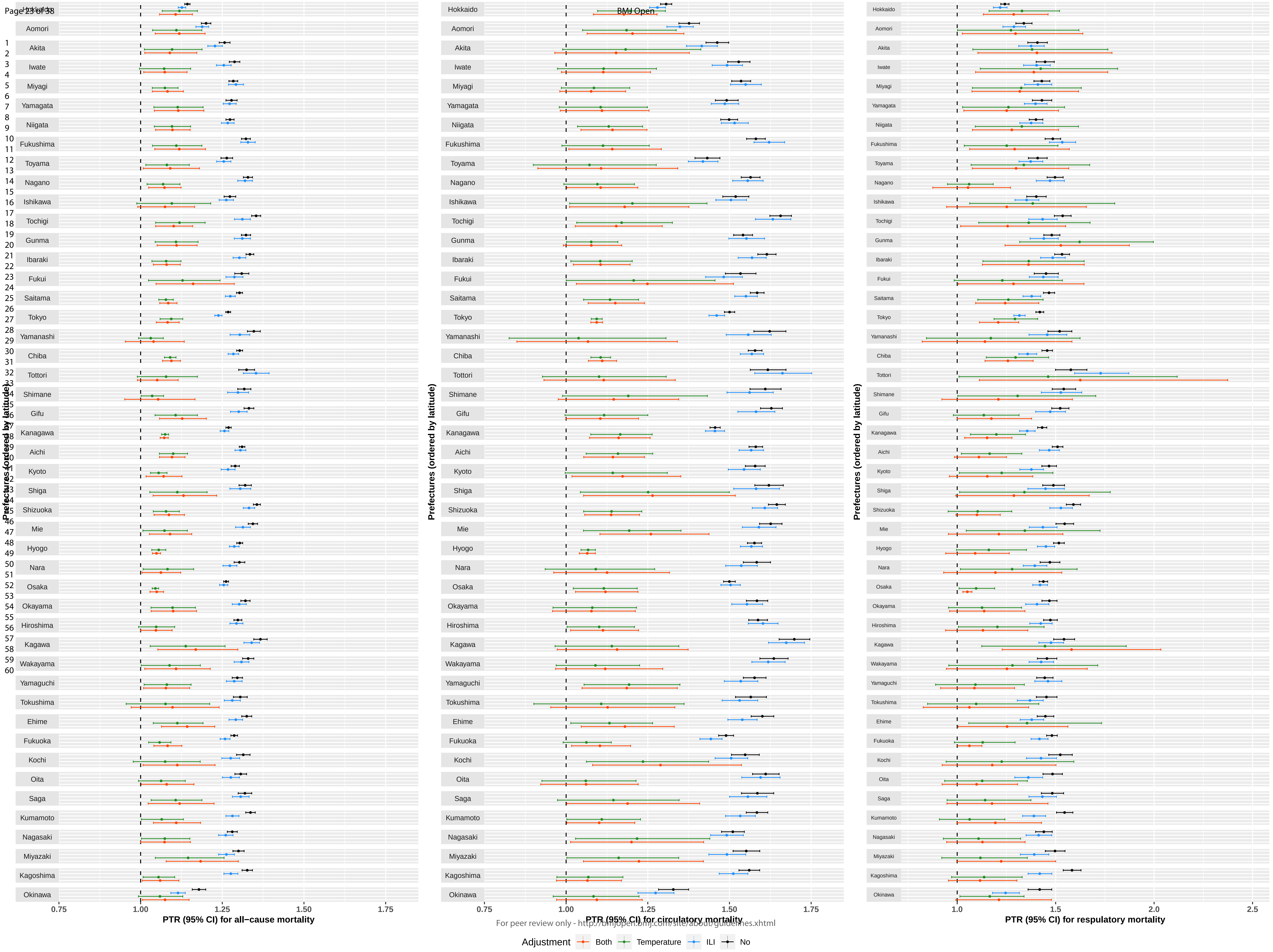
Variables	Median [interquartile range]	Mean (SD)	Range
Mean temperature	16.09 [8.04; 22.8]	15.6 (8.2)	[-1.0; 30.7]
All-cause mortality	3046 [2726; 3350]	3058 (443.7)	[2114; 4712]
Circulatory mortality	866 [768; 1003]	892.6 (157.1)	[570; 1454]
Respiratory mortality	464 [388; 535]	465.2 (105.9)	[247; 1072]
ILI	7626 [1575; 106199]	142113 (295087.3)	[7; 1652147]

Note: Daily mortality on the day of the Great East Japan Earthquake (11 March 2011) was excluded from our analysis.

Table 2. Nationwide pooled peak-to-trough ratio (PTR) with 95% confidence interval (95% CI) with/without adjustment for temperature and/or influenza like illness (ILI)

Adjustment	All-cause mortality		Circulatory mortality		Respiratory mortality	
	PTR	95% CI	PTR	95% CI	PTR	95% CI
None	1.29	1.28, 1.31	1.52	1.49, 1.55	1.45	1.43, 1.48
Temperature	1.06	1.05, 1.07	1.07	1.05, 1.09	1.16	1.12, 1.21
ILI	1.27	1.26, 1.29	1.52	1.49, 1.55	1.40	1.38, 1.43
Temperature + ILI	1.07	1.06, 1.07	1.08	1.06, 1.09	1.12	1.09, 1.16


All−cause mortality
Cirulatory mortality
Respiratory mortality
PTR (95%CI)
1.0
1.1
1.2
1.3
1.4
1.5
1.6
Jan 01
Feb 01
Mar 01
Apr 01
May 01
Jun 01
Jul 01
Aug 01
Sep 01
Oct 01
Nov 01
Dec 01
Dec 31
Day of year
No adjustment
Adjusted for ILI
Adjusted for temperature
Adjusted for temperatrue and ILI


Prefectures (ordered by latitude)
Hokkaido
Aomori
Akita
Iwate
Miyagi
Yamagata
Niigata
Fukushima
Toyama
Nagano
Ishikawa
Tochigi
Gunma
Ibaraki
Fukui
Saitama
Tokyo
Yamanashi
Chiba
Tottori
Shimane
Gifu
Kanagawa
Aichi
Kyoto
Shiga
Shizuoka
Mie
Hyogo
Nara
Osaka
Okayama
Hiroshima
Kagawa
Wakayama
Yamaguchi
Tokushima
Ehime
Fukuoka
Kochi
Oita
Saga
Kumamoto
Nagasaki
Miyazaki
Kagoshima
Okinawa
0.75
1.00
1.25
1.50
1.75
PTR (95% CI) for all−cause mortality
PTR (95% CI) for circulatory mortality
1.0
1.5
2.0
2.5
PTR (95% CI) for respulatory mortality
Adjustment
Both
Temperature
ILI
No

Supplementary material

The role of temperature, influenza and other local characteristics in seasonality of mortality: a population-based time-series study in Japan

Table of Contents

Table S1. Summary of daily mean temperature, daily cases of all-cause, circulatory, and respiratory mortality, and **weekly** cases of influenza likely illness

Prefecture/ country [a]	Daily mean temperature (℃)		All-cause mortality (n)		Circulatory mortality (n)		Respiratory mortality (n)		Influenza like illness (n)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD	Range	Mean (SD)	Range	Mean (SD)	Range
Hokkaido	9.32 (9.62)	[-11;29.6]	141.36 (21.94)	[81;220]	41.47 (8.36)	[18;79]	20.49 (6.09)	[3;55]	958.26 (2040.19)	[0;15153]
Aomori	10.7 (9.06)	[-7.5;30.1]	41.56 (8.2)	[16;79]	12.64 (3.95)	[1;28]	5.94 (2.73)	[0;19]	259.68 (566.2)	[0;3591]
Akita	12.14 (9.14)	[-5.5;31.6]	37.03 (7.55)	[15;64]	11.21 (3.75)	[1;27]	5.5 (2.6)	[0;19]	241.43 (517)	[0;4180]
Iwate	10.64 (9.46)	[-8.9;29.3]	40.4 (8.44)	[15;85]	13.49 (4.37)	[1;32]	5.89 (2.68)	[0;19]	273.48 (564.55)	[0;3716]
Miyagi	12.84 (8.38)	[-4.5;31.2]	55.3 (11.21)	[22;152]	17.14 (5.11)	[2;43]	7.57 (3.26)	[0;29]	400.31 (857.1)	[0;5417]
Yamagata	12.1 (9.43)	[-5.8;30.5]	36.91 (7.58)	[13;68]	11.59 (3.81)	[0;29]	5.49 (2.63)	[0;18]	209.39 (444.9)	[0;2795]
Niigata	14.17 (8.76)	[-2.8;31.8]	68.63 (12.22)	[31;112]	21.17 (5.66)	[4;45]	9.27 (3.5)	[0;26]	467.68 (1057.89)	[0;7472]
Fukushima	13.42 (8.89)	[-4.2;31.4]	58.49 (11.3)	[23;114]	18.98 (5.55)	[5;44]	8.61 (3.43)	[0;29]	350.57 (736.63)	[0;4293]
Toyama	14.57 (8.89)	[-2.8;33.1]	30.8 (6.97)	[11;59]	8.72 (3.25)	[1;24]	4.95 (2.46)	[0;16]	197.35 (433.32)	[0;3042]
Nagano	12.28 (9.53)	[-6.7;30]	59.97 (11.51)	[26;107]	19.68 (5.61)	[4;48]	8.38 (3.48)	[0;23]	424.98 (927.86)	[0;6713]
Ishikawa	15.07 (8.66)	[-2.6;32.4]	29.71 (6.78)	[9;58]	8.78 (3.28)	[0;26]	4.65 (2.37)	[0;16]	222.14 (503.98)	[0;3450]
Tochigi	14.39 (8.56)	[-2.5;31.7]	50.11 (10.49)	[19;95]	16.02 (5.1)	[4;37]	7.32 (3.21)	[0;25]	263.1 (595.1)	[0;3112]
Gunma	15.04 (8.6)	[-1.7;32.6]	51.57 (10.8)	[20;101]	15.74 (4.96)	[0;41]	8.5 (3.55)	[0;27]	393.01 (863.12)	[0;5616]
Ibaraki	14.15 (8.23)	[-1.7;31]	73.38 (14.37)	[31;136]	22.52 (6.5)	[2;51]	10.77 (4.32)	[0;31]	395.03 (908.36)	[0;5926]
Fukui	14.87 (8.94)	[-1.8;31.9]	21.69 (5.62)	[6;45]	6.35 (2.78)	[0;18]	3.57 (2.07)	[0;13]	176.7 (401.64)	[0;3054]
Saitama	15.53 (8.47)	[-0.9;33.7]	138.85 (27.86)	[65;258]	41.24 (10.6)	[13;97]	20.3 (7.16)	[3;58]	1139.33 (2572)	[0;15454]
Tokyo	16.69 (7.93)	[0.3;33.2]	265.37 (41.16)	[166;434]	76.17 (15.73)	[36;147]	38.71 (10.36)	[11;96]	1016.52 (2578.95)	[0;18939]
Yamanashi	15.12 (8.69)	[-2.1;31.8]	23.31 (6)	[7;52]	6.82 (2.9)	[0;20]	3.46 (2.01)	[0;16]	144.31 (310.05)	[0;1812]
Chiba	16.3 (7.76)	[0.3;32.1]	126.11 (24.2)	[64;216]	38.5 (9.97)	[13;88]	17.97 (6.22)	[2;58]	891.29 (2020.46)	[0;12096]
Tottori	15.22 (8.54)	[-3.1;32]	17.86 (4.84)	[5;38]	5.38 (2.49)	[0;16]	2.54 (1.66)	[0;11]	113.05 (238.68)	[0;1543]
Shimane	15.26 (8.27)	[-3.3;32.2]	23.8 (5.83)	[6;48]	6.92 (2.91)	[0;23]	3.72 (2.07)	[0;14]	125.38 (276.71)	[0;1979]
Gifu	16.22 (8.69)	[-1.7;32.7]	52.28 (10.68)	[21;99]	15.57 (4.93)	[3;36]	8.05 (3.35)	[0;23]	339.83 (715.25)	[0;4339]
Kanagawa	16.28 (7.67)	[0.3;32.2]	170.3 (31.31)	[94;297]	47.51 (10.56)	[18;101]	24.47 (7.72)	[3;65]	1276.81 (3000.95)	[0;17813]
Aichi	16.26 (8.57)	[-1.5;32.7]	148.39 (26.39)	[81;236]	41.47 (9.81)	[16;80]	21.5 (6.99)	[5;52]	1026.52 (2284.16)	[0;12493]
Kyoto	16.23 (8.71)	[-1.2;32.6]	62.27 (11.61)	[29;119]	18.01 (5.4)	[4;45]	9.63 (3.69)	[0;32]	403.21 (882.09)	[0;5518]

Table S1. Continued

Prefecture/ country	Daily mean temperature (℃)		All-cause mortality (n)		Circulatory mortality (n)		Respiratory mortality (n)		Influenza like illness (n)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Shiga	15.1 (8.64)	[-2.1;31.8]	29.51 (7.11)	[9;60]	8.57 (3.37)	[0;22]	4.56 (2.35)	[0;18]	218.49 (484.12)	[0;2675]
Shizuoka	16.92 (7.45)	[1.7;31.9]	91.42 (18.13)	[45;172]	27.52 (7.56)	[9;62]	12.86 (4.84)	[2;36]	598.14 (1351.69)	[0;8255]
Mie	16.37 (8.21)	[-0.4;33.5]	47.71 (10.07)	[21;95]	13.97 (4.56)	[2;33]	7.12 (3.18)	[0;24]	331.76 (728.13)	[0;3989]
Hyogo	17.08 (8.24)	[-0.8;32.5]	131.5 (22.43)	[70;265]	36.03 (9.04)	[10;75]	19.74 (6.38)	[3;49]	793.55 (1722.72)	[0;10287]
Nara	15.19 (8.5)	[-1.7;30.8]	33.11 (7.65)	[12;62]	9.81 (3.76)	[0;28]	5.16 (2.56)	[0;17]	184.89 (412.67)	[0;2379]
Osaka	17.17 (8.36)	[-0.1;32.7]	195.43 (31.77)	[113;341]	52.28 (12.09)	[18;115]	30.9 (9.42)	[7;75]	1017.19 (2175.46)	[0;13525]
Okayama	16.52 (8.61)	[-1.7;32.3]	51.94 (10.18)	[19;92]	15.1 (4.7)	[1;34]	9.2 (3.64)	[0;26]	321.47 (729.3)	[0;4974]
Hiroshima	16.5 (8.43)	[-2;31.8]	72.18 (13.13)	[33;146]	20.79 (6)	[4;47]	11.62 (4.21)	[0;34]	441.89 (988.89)	[0;6087]
Kagawa	16.8 (8.37)	[-0.4;33]	28.54 (6.77)	[8;58]	8.28 (3.36)	[0;25]	5.04 (2.47)	[0;16]	187.73 (431.76)	[0;2632]
Wakayama	16.94 (8.12)	[0;32.7]	31.17 (7.11)	[9;73]	9.02 (3.47)	[0;28]	4.9 (2.48)	[0;16]	173.35 (381.83)	[0;2479]
Yamaguchi	15.79 (8.44)	[-4.5;31]	45.67 (8.95)	[20;82]	13.69 (4.43)	[2;32]	7.89 (3.25)	[0;28]	331.05 (769.8)	[0;5183]
Tokushima	16.85 (8)	[-1;32.6]	24.18 (5.89)	[8;51]	6.95 (2.88)	[0;20]	4.2 (2.26)	[0;15]	143.77 (329.5)	[0;2089]
Ehime	16.79 (8.04)	[-0.7;31.7]	42.87 (8.81)	[15;81]	13.42 (4.42)	[3;34]	6.8 (2.98)	[0;20]	263.9 (577.75)	[0;3750]
Fukuoka	17.35 (7.86)	[-0.8;32.8]	121.01 (19.83)	[69;210]	30.39 (7.36)	[11;73]	20.15 (6.46)	[4;57]	1025.85 (2276.78)	[0;12597]
Kochi	17.37 (7.75)	[-0.1;32.1]	25.27 (6.07)	[9;52]	7.92 (3.12)	[0;21]	4.2 (2.3)	[0;18]	205.81 (464.68)	[0;3201]
Oita	16.87 (7.76)	[-0.3;31.7]	34.24 (7.59)	[12;71]	10.03 (3.64)	[0;26]	5.89 (2.77)	[0;21]	316.35 (714.1)	[0;4478]
Saga	16.9 (8.22)	[-2.5;32.3]	23.97 (5.91)	[6;50]	6.67 (2.81)	[0;18]	4.1 (2.24)	[0;18]	186.74 (412.58)	[0;2778]
Kumamoto	17.31 (8.28)	[-1.8;31.7]	50.33 (10.24)	[20;95]	14.6 (4.69)	[1;35]	8.54 (3.55)	[0;31]	346.29 (811.45)	[0;5887]
Nagasaki	17.43 (7.64)	[-0.8;31.9]	41.9 (8.5)	[19;75]	11.99 (4.01)	[1;32]	7.08 (3.05)	[0;23]	337.01 (757.91)	[0;4798]
Miyazaki	17.77 (7.4)	[0.8;31.6]	31.75 (7.46)	[11;67]	9.72 (3.65)	[1;25]	5.28 (2.67)	[0;21]	356.01 (800.59)	[0;5875]
Kagoshima	18.85 (7.44)	[0.5;31.7]	53.03 (10.42)	[22;112]	16.1 (4.92)	[3;43]	9.4 (3.88)	[0;38]	436.56 (969.33)	[0;7309]
Okinawa	23.29 (4.68)	[10.3;31.1]	25.95 (6.33)	[6;53]	6.67 (2.78)	[0;21]	4.36 (2.26)	[0;15]	404.6 (716.61)	[0;5197]

[a] Prefectures was ordered by latitude from high to low.

[b] Daily mortality on the day of the Great East Japan Earthquake (11 March 2011) was excluded from our analysis.

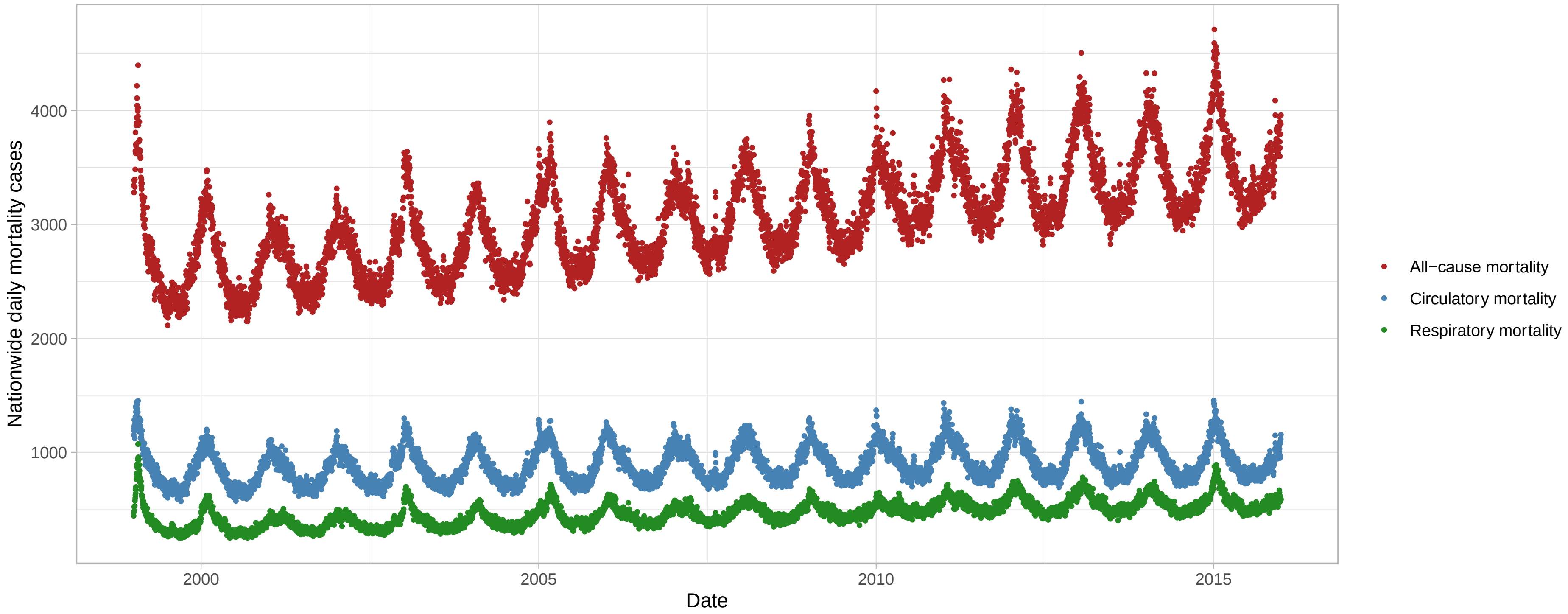


Figure S1. Time series of national wide daily mortality cases from all-cause, circulatory, respiratory disease and influenza between April 1999 and 2015

Summary of data collection on prefecture-specific indicators on climate, demographics, socioeconomic factors, and healthcare capacity

We computed the annual mean temperature and relative humidity for each prefecture averaged from 1999 to 2015. For demographic indicators, we collected yearly data on population density and the proportion of population aged ≥65 years for each prefecture for 1972-2012 from the Statics Bureau of the Ministry of Internal Affairs and Communications of Japan. We collected information on socioeconomic indicators from Statistics Bureau of the Ministry of Internal Affairs and Communications of Japan,[1,2] including saving and income available every 5 years for 1974-2009, Gini index (a measure of income inequality) available every 5 years for 1979-2009, consumer price index (CPI) from 1972 to 2009, economic power index (EPI, a measure of the wealth of a prefecture) from 2003 to 2015, and the prevalence of air conditioning for households with two persons or more from 1972 to 2009. We extracted the number of registered physicians, nurses and hospital beds per 10K population in 1975 and 2004 from the Survey of Medical Institutions and Hospital Report conducted by the Ministry of Health, Labour and Welfare.[3] For each indicator, we computed the averaged value across the years 1999-2015 for each prefecture.

1. Satistics Bureau of the Ministry of Internal Affairs and Communications of Japan. 2015. Statistics, Consumer Price Index.
2. National Survey of Family Income and Expenditure Definitions of Terms Webpage [in Japanese]. Statics Bureau of the Ministry of Internal Affairs and Communications of Japan. 2009.
3. Survey of Medical Institutions. [WWW Document]. Health Statistics Office Ministry of Health Labor and Welfare Japan. http://www.mhlw.go.jp/english/ database/db-hss/smi.html (accessed 10.1.14.). Published 2010.

Table S2. Summary of Annual Values Across the Years (1999-2015) for Each Indicator

Indicators	Mean (SD)	Median [interquartile range]	Range
Temperature (℃)	15.55 (2.34)	16.03 [14.64; 16.91]	[8.4; 23.55]
Relative humidity (%)	68.64 (3.61)	68.42 [65.52; 72.08]	[57.51; 79.96]
Density (population/km^2)	0.003 (0.002)	0.002 [0.001; 0.003]	[0.0006; 0.013]
% population ≥ 65 years	0.22 (0.06)	0.22 [0.20; 0.25]	[0.12; 0.31]
Savings (million yen)	14.49 (5.14)	14.97 [12.24; 16.47]	[5.07; 19.73]
Income (million yen)	6.88 (1.77)	6.84 [6.35; 7.45]	[4.56; 8.94]
Consumer price index	97.65 (17.1)	97.4 [96.6; 98.60]	[94.6; 103.30]
Gini index	0.30 (0.02)	0.30 [0.29; 0.31]	[0.27; 0.35]
Economic power index (%)	0.47 (0.21)	0.42 [0.31; 0.57]	[0.20; 1.41]
Physicians (number per 10k population)	5.60 (4.98)	3.60 [4.89; 5.93]	[1.62; 34.46]
Nurses (number per 10k population)	15.04 (10.29)	10.41 [7.82; 15.88]	[4.09; 68.00]
Hospital beds (number per 10K population)	34.88 (26.72)	23.81 [17.93; 36.86]	[9.11; 130.48]
Air conditioning prevalence (%)	85.9 (31.60)	92.6 [86.0; 95.7]	[8.30; 99.40]

Table S3. Prefecture-specific summary of annual value across the years 1999-2015 for all indicators (mean (SD))

Prefecture/ country	Temperature (℃)	Relative humidity (%)	Density (population/km²)	% population ≥ 65 years	Savings (million yen)	Income (million yen)	CPI	Gini index	EPI (%)	Physicians (number per 10k population)	Nurses (number per 10k population)	Hospital beds (number per 10K population)	AC (%)
Hokkaido	9.26(0.38)	68.81(2.07)	0.0056(1e-04)	0.22(0.03)	11.64(0.15)	6.02(0.54)	97.13(1.2)	0.29(0.01)	0.38(0.02)	11.87(0.47)	37.78(4.15)	106.68(1.57)	13.23(3.46)
Aomori	10.64(0.4)	74.78(1.9)	0.0014(0)	0.23(0.03)	9.92(0.91)	5.96(0.3)	96.7(1.09)	0.3(0.01)	0.3(0.03)	2.52(0)	8.84(0.56)	19.96(0.46)	43.77(7.82)
Akita	12.11(0.28)	72.64(0.9)	0.0011(0)	0.27(0.02)	10.82(0.79)	6.51(0.62)	98.6(1.48)	0.29(0.01)	0.27(0.02)	2.2(0.06)	7.6(0.59)	17.58(0.31)	66.8(11.06)
Iwate	10.57(0.34)	73.31(1.37)	0.0014(0)	0.25(0.02)	12.29(0.23)	6.53(0.87)	97.33(0.94)	0.3(0.01)	0.29(0.02)	2.48(0.02)	10.18(0.69)	20.45(0.76)	45.5(10.4)
Miyagi	12.78(0.4)	71.22(1.25)	0.0024(0)	0.2(0.02)	11.87(0.34)	6.89(0.26)	98.05(1.4)	0.3(0.02)	0.51(0.03)	4.62(0.2)	12(1.44)	26.42(0.25)	67.99(4.46)
Yamagata	12.07(0.33)	74.27(1.31)	0.0012(0)	0.26(0.02)	12.36(0.49)	7.21(0.67)	96.85(0.84)	0.3(0.02)	0.31(0.02)	2.37(0.09)	7.94(0.69)	15.12(0.16)	76.14(6.09)
Niigata	14.19(0.29)	70.69(1.55)	0.0024(0)	0.24(0.02)	15.21(0.86)	7.38(0.64)	97.96(1.22)	0.3(0.01)	0.4(0.03)	4.34(0.09)	13.93(1.31)	30.32(0.04)	91.6(4.22)
Fukushima	13.36(0.37)	68.79(0.92)	0.0021(1e-04)	0.23(0.02)	12.46(0.38)	6.88(0.65)	97.08(1.07)	0.31(0.01)	0.42(0.03)	3.72(0.05)	11.22(1.01)	30.95(1.36)	64.27(10.34)
Toyama	14.56(0.32)	77.2(1.74)	0.0011(0)	0.24(0.02)	16.33(0.62)	8.08(0.84)	98.15(1.53)	0.3(0.02)	0.42(0.06)	2.51(0.09)	7.88(0.87)	18.34(0.01)	93.67(2.89)
Nagano	12.25(0.3)	71.31(1.55)	0.0022(0)	0.24(0.02)	15.57(0.71)	7.12(0.71)	98.11(1.21)	0.28(0.01)	0.44(0.04)	4.08(0.19)	13.78(1.49)	25.03(0.11)	54.38(7.79)
Ishikawa	15.06(0.3)	70.05(1.91)	0.0012(0)	0.21(0.02)	16.57(1.16)	7.71(0.96)	98.56(1.12)	0.29(0)	0.44(0.05)	2.9(0.12)	8.89(0.73)	20.41(0.58)	92.95(3.05)
Tochigi	14.34(0.34)	69.09(2.2)	0.002(0)	0.2(0.02)	15.62(0.66)	7.46(0.33)	96.8(1.4)	0.3(0.01)	0.58(0.07)	3.91(0.18)	9.57(1.27)	22.67(0.07)	89.19(2.63)
Gunma	14.98(0.34)	61.18(1.76)	0.002(0)	0.21(0.02)	15.58(1.06)	6.85(0.54)	98.26(1.46)	0.3(0.01)	0.55(0.05)	3.98(0.17)	10.03(1.65)	25.32(0.04)	89.03(2.93)
Ibaraki	14.08(0.39)	72.75(0.85)	0.003(0)	0.2(0.03)	15.35(0.57)	7.44(0.95)	95.5(0.98)	0.3(0.01)	0.6(0.07)	4.37(0.17)	12.01(1.43)	33.23(0.45)	89.75(3.88)
Fukui	14.85(0.28)	74.7(1.86)	8e-04(0)	0.23(0.02)	18.63(1.15)	8.19(0.72)	98.05(1.51)	0.3(0.01)	0.38(0.04)	1.72(0.05)	5.12(0.57)	12.24(0.22)	95.13(1.62)
Saitama	15.49(0.34)	64.24(2.26)	0.0071(1e-04)	0.17(0.03)	15.16(0.87)	7.38(0.62)	97.09(1.53)	0.29(0.01)	0.7(0.06)	8.95(0.71)	23.78(3.55)	61.53(1.06)	97.33(0.96)
Tokyo	16.67(0.36)	59.7(1.51)	0.0126(4e-04)	0.19(0.02)	18.18(1.42)	7.99(0.25)	99.56(1.67)	0.31(0)	1.21(0.14)	33.31(1.63)	64.5(4.94)	130.07(0.57)	96.44(1.2)
Yamanashi	15.08(0.3)	63.11(1.55)	9e-04(0)	0.22(0.02)	13.92(1.39)	6.79(0.68)	96.91(0.99)	0.29(0.02)	0.38(0.05)	1.69(0.02)	4.98(0.53)	11.52(0.33)	73.15(6.8)
Chiba	16.24(0.39)	68.32(1.6)	0.0061(1e-04)	0.18(0.03)	16.19(0.2)	7.53(0.81)	98.23(1.68)	0.3(0.01)	0.72(0.07)	8.8(0.53)	22.91(2.73)	56.24(0.03)	93.66(1.69)
Tottori	15.19(0.29)	72.91(1.3)	6e-04(0)	0.24(0.02)	15.58(0.65)	6.81(0.67)	97.94(1.25)	0.3(0)	0.25(0.02)	1.66(0.07)	4.41(0.44)	9.15(0.06)	90.29(4.57)
Shimane	15.24(0.28)	74.31(1.45)	7e-04(0)	0.27(0.02)	14.25(0.86)	6.96(0.72)	96.61(0.78)	0.3(0.02)	0.23(0.02)	1.85(0.06)	5.57(0.51)	11.97(0.21)	89.79(5.51)
Gifu	16.18(0.3)	65.69(2.68)	0.0021(0)	0.21(0.02)	17.53(0.51)	7.66(0.86)	97.35(1.76)	0.3(0.01)	0.49(0.05)	3.54(0.1)	10.18(1.01)	21.05(0.26)	90.63(4.4)
Kanagawa	16.22(0.36)	65.11(1.62)	0.0088(2e-04)	0.17(0.03)	17.92(0.65)	7.78(0.6)	97.7(1.03)	0.3(0.01)	0.89(0.07)	14.7(0.72)	37.79(3.69)	75.2(0.55)	94.64(1.46)
Aichi	16.23(0.34)	65.22(2.84)	0.0073(2e-04)	0.18(0.02)	17.99(1.16)	7.7(0.45)	97.96(1.2)	0.3(0)	0.97(0.09)	12.97(0.47)	33.84(4.21)	69.96(0.03)	96.72(0.97)
Kyoto	16.19(0.28)	64.26(2)	0.0026(0)	0.21(0.03)	15.65(0.9)	6.64(0.83)	97.09(1.02)	0.29(0.01)	0.56(0.07)	7.17(0.11)	16.99(1.48)	37.17(0.42)	97.19(1.66)
Shiga	15.07(0.26)	73.87(1.46)	0.0014(0)	0.18(0.02)	16.75(0.7)	7.42(0.54)	97.59(1.18)	0.29(0.01)	0.53(0.07)	2.63(0.18)	8.37(1.16)	14.14(0.63)	95.43(1.49)
Shizuoka	16.9(0.3)	68.26(1.74)	0.0038(0)	0.21(0.03)	16.73(0.53)	7.45(0.65)	97.06(1.33)	0.3(0.01)	0.7(0.05)	6.43(0.29)	19.68(2.15)	39.74(0.74)	90.19(3.06)

Table S3. Continued

Prefecture/ country	Temperature (°C)	Relative humidity (%)	Density (population/km^2)	% population ≥ 65 years	Savings (million yen)	Income (million yen)	CPI	Gini index	EPI (%)	Physicians (number per 10k population)	Nurses (number per 10k population)	Hospital beds (number per 10K population)	AC (%)
Mie	16.35(0.3)	67.67(2.16)	0.0019(0)	0.22(0.02)	17.55(1.8)	7.45(0.65)	96.24(0.83)	0.28(0)	0.54(0.07)	3.38(0.08)	9.3(1.17)	21.22(0.07)	94.91(1.84)
Hyogo	17.08(0.29)	65.15(1.93)	0.0056(0)	0.2(0.03)	16(0.65)	7.01(0.52)	98.18(1.95)	0.3(0.01)	0.55(0.07)	11.22(0.49)	30.33(3.37)	64.77(0.49)	95.64(1.59)
Nara	15.16(0.29)	72.17(1.47)	0.0014(0)	0.21(0.03)	18.02(1.78)	7.26(0.69)	99.24(2.2)	0.3(0.01)	0.39(0.05)	2.81(0.15)	7.23(0.82)	16.19(0.88)	97.19(1.89)
Osaka	17.19(0.32)	62.81(1.12)	0.0088(0)	0.19(0.03)	14.5(0.48)	6.62(0.7)	99.34(1.9)	0.32(0.02)	0.75(0.05)	21.07(0.69)	44.41(6.91)	113.25(3.26)	97.5(0.59)
Okayama	16.57(0.29)	65.53(1.56)	0.0019(0)	0.23(0.02)	16.77(0.56)	7.07(0.67)	97.51(0.81)	0.3(0.01)	0.48(0.07)	4.86(0.27)	14.71(1.4)	31.45(0.45)	94.55(1.98)
Hiroshima	16.48(0.28)	67.24(2.45)	0.0029(0)	0.21(0.02)	16.13(1.18)	6.9(0.34)	97.44(1.08)	0.3(0.01)	0.54(0.07)	6.7(0.16)	17.77(2.04)	42.23(0.33)	93.33(2.63)
Kagawa	16.8(0.28)	65.55(1.47)	0.001(0)	0.24(0.02)	18.52(1.26)	6.95(0.53)	97.44(1)	0.29(0.01)	0.43(0.05)	2.51(0.04)	7.55(0.52)	17.36(0.4)	96.75(1.47)
Wakayama	16.92(0.31)	64.22(1.73)	0.001(0)	0.24(0.03)	15.19(1.03)	6.24(0.7)	96.62(1.17)	0.3(0)	0.3(0.04)	2.54(0.09)	5.8(0.72)	14.84(0.25)	95.35(3.3)
Yamaguchi	15.81(0.25)	70.19(1.53)	0.0015(0)	0.25(0.02)	13.95(0.73)	6.3(0.36)	98.89(1.38)	0.29(0.01)	0.41(0.05)	3.53(0.06)	10.57(0.97)	28.29(0.22)	91.97(2.59)
Tokushima	16.86(0.3)	66.08(1.49)	8e-04(0)	0.25(0.02)	16.1(1.28)	6.77(0.58)	97.19(0.89)	0.33(0.01)	0.31(0.02)	2.26(0.05)	6.08(0.39)	16.22(0.56)	94.51(3.19)
Ehime	16.8(0.28)	65.35(2.18)	0.0015(0)	0.24(0.02)	13.8(1.41)	6.11(0.32)	97.26(0.86)	0.3(0.01)	0.37(0.04)	3.4(0.06)	10.91(0.81)	23.81(0)	92.68(3.68)
Fukuoka	17.33(0.28)	65.6(1.58)	0.0051(0)	0.2(0.02)	12.55(0.73)	6.49(0.36)	98.16(1.94)	0.31(0.01)	0.58(0.04)	13.19(0.52)	35.67(3.32)	89.87(1.1)	95.35(1.66)
Kochi	17.39(0.32)	68.63(1.23)	8e-04(0)	0.26(0.02)	13.95(2.37)	6.22(0.69)	97.43(1.26)	0.32(0.01)	0.23(0.02)	2.16(0.05)	6.48(0.71)	20.05(0.56)	88.7(4.85)
Oita	16.9(0.3)	66.88(1.82)	0.0012(0)	0.25(0.02)	12.17(0.27)	6.08(0.55)	97.08(1.06)	0.3(0.01)	0.33(0.04)	2.82(0.1)	8.78(0.95)	21.09(0.22)	88.78(4.67)
Saga	16.86(0.27)	67.71(1.68)	9e-04(0)	0.23(0.02)	12.14(1.08)	6.84(0.65)	98.58(1.54)	0.29(0.01)	0.31(0.03)	1.95(0.05)	6.44(0.57)	15.47(0.05)	93.39(4.24)
Kumamoto	17.34(0.36)	68.2(1.65)	0.0018(0)	0.24(0.02)	10.85(0.52)	6.27(0.55)	97.84(1.16)	0.31(0.01)	0.36(0.04)	4.58(0)	14.54(1.4)	36.53(0.44)	90.52(3.13)
Nagasaki	17.45(0.31)	68.71(1.9)	0.0015(0)	0.24(0.02)	11.01(0.22)	6.02(0.58)	97.86(0.97)	0.31(0.02)	0.27(0.03)	3.78(0.2)	10.92(1.21)	28.45(0.91)	93.37(2.21)
Miyazaki	17.78(0.32)	72.24(1.44)	0.0012(0)	0.24(0.02)	10.18(0.44)	5.93(0.32)	98.22(1.46)	0.31(0)	0.29(0.03)	2.49(0.07)	8.63(1.1)	19.92(0.08)	88.09(2.82)
Kagoshima	18.86(0.32)	68.12(2.12)	0.0017(0)	0.25(0.02)	10.08(0.13)	5.63(0.37)	97.42(0.72)	0.29(0.01)	0.29(0.02)	3.89(0.11)	13.17(1.27)	36.17(0.52)	89.25(6.56)
Okinawa	23.28(0.22)	72.39(2.08)	0.0014(0)	0.16(0.01)	5.58(0.44)	4.79(0.41)	97.36(1.11)	0.35(0.01)	0.28(0.02)	2.62(0.23)	7.85(0.87)	19.78(0.01)	86.45(2.78)

CPI: consumer price index; EPI: Economic power index; AC: air conditioning prevalence.

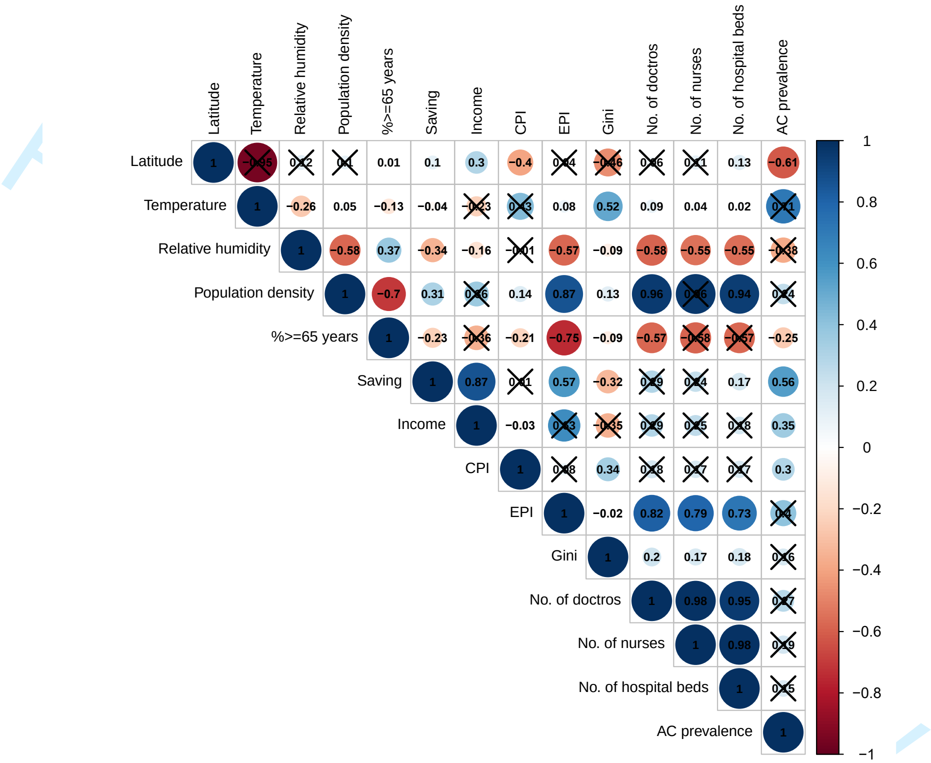


Figure S2**.** Correlations between the indicators.

Blue: positively associated; red: negatively associated; Cross: *p*>0.05.

RH: relative humidity; CPI: consumer price index; EPI: economic power index; AC: air conditioning prevalence

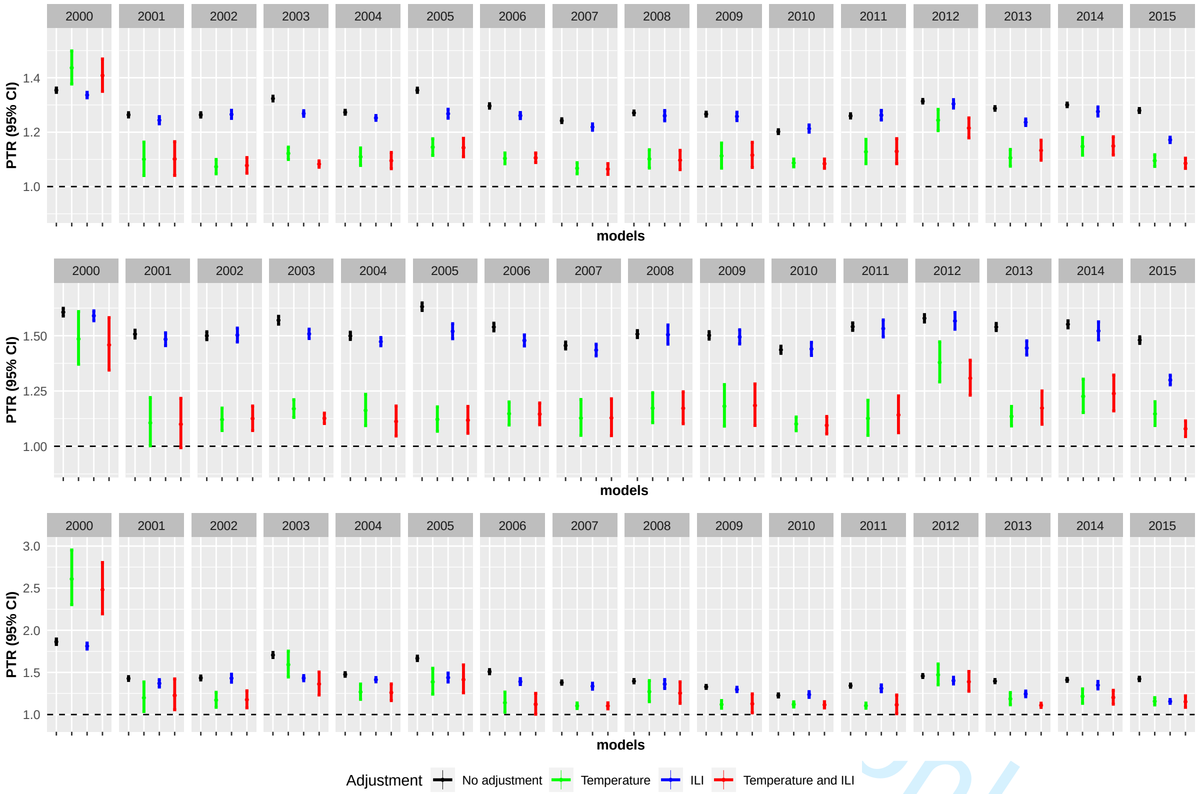


Figure S3. Peak-to-trough ratio (PTR) with 95% confidence intervals (95%CI) for each single year from 2000 to 2015 for all-cause (top), circulatory (middle), and respiratory (bottom) mortality before (black) and after adjustments for just influenza like illness (blue), just temperature (green), and both (red)

Note: The year of 1999 was excluded from our yearly analyses, as ILI data was not available until April 1999.

Figure S4. Associations between each indicator and PTR before and after adjusting for influenza like illness (ILI) and temperature

Coefficient and 95% confidence intervals were obtained from liner mixed effect models adjusting for latitude and longitude, except for when we investigated averaged annual mean temperature as the indicator, due to their high correlation. Results are expressed as log (PTR) change for standard deviation increase in each indicator.

Description of models

- Seasonality assessment without and with adjustments for temperature and/or influenza like illness

We applied a generalized linear model with a quasi-Poisson family to assess seasonality of mortality in each prefecture.

$$\boldsymbol{Y_t \sim Quasi - Poisson(\mu_t)}$$

Main model (without any adjustment for temperature and ILI)
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t$
Adjusting for temperature
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t + \beta Temp_{t,l}$
Adjusting for ILI
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t + ns(ILI_t, 3)$
Adjusting for both temperature and ILI
$\log(\mu_t) = \beta_0 + cs(doy, 4) + \lambda Strata_t + \beta Temp_{t,l} + ns(ILI_t, 3)$

t: the day of the observation;
Yt: the observed daily numbers of mortality on day *t*;
β_0: the intercept;
doy: day of year, which was fitted using cyclic cubic spline with 4 degrees of freedom (*df*);
ILI_t: the daily numbers of ILI on day t, which was controlled using natural cubic spline with 3 *df*;
$Stratat$: strata defined by year, day of week, and their interaction to control for the long-term trend and the effect of day of week, and λ is the vector of coefficients;
$Tempt,l$: a matrix obtained by using cross basis function to temperature; *l* is the lag days, and β is the vector of coefficients. (For the cross-basis function, a natural cubic B-spline basis with three internal knots at the 25th, 50th, and 75th percentiles of temperature distribution was used for exposure-response association, and another natural cubic B-spline basis with 3 *df* with extended lag up to 21 days was used for the lag-response association.)

- Modification of seasonal variation in mortality by prefecture-specific indicators

We applied linear mixed effects models (LMEMs) to investigate associations of PTR with each prefecture-specific indicator separately. We fitted LMEMs with random intercepts for prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital city of each prefecture were included to reduce spatial correlation, except for when we investigated annual mean temperature as the indicator, due to their high correlation.

$$\boldsymbol{\beta_i = \alpha + \gamma Z_i + \eta + \nu_i}$$

β_i is the estimated coefficient for seasonality (i.e., log(PTR)) in prefecture i
Z_i is the prefecture-specific indicator for prefecture *i* (e.g., latitudes, longitudes, and averaged annual mean temperature)
α and γ are estimated using least squares regression with inverse-variance weights.
ν_i is the variation within prefecture i, with the variance as $\sigma^2_{\nu_i}$
η represents the heterogeneity among prefectures with a variance of σ^2_η estimated using the restricted maximum likelihood approach.

Model Checking and sensitivity analysis

We used scatter plot of deviance residuals vs time and partial autocorrelation function plot of the deviance residuals to check the models. In addition, sensitivity analysis was conducted to check the robustness of our estimates.
We used the largest prefecture (i.e., Tokyo) for model evaluation, as the statistical uncertainty for the estimates was small.

- Scatter plot of deviance residuals vs time

In general, the plot shows an even band of points over the time, although we observed a few spikes, for example, in 1999. This pattern did not change significantly when we use more flexible modellings for seasonality, temperature, and influenza.

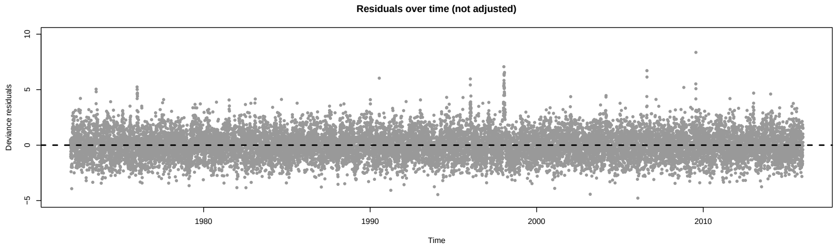


Figure S5. Deviance residuals over time from the analysis in Tokyo (without adjustment for temperature and/or influenza)

- Partial autocorrelation function (PACF) plot of the deviance residuals

PACF shows a slow decay and a high degree of autocorrelation around a 1-week lag. This pattern remained when we included temperature and/or ILI in the model. In order to reduce the autocorrelation, we tried more flexible functions for seasonality by increasing the degree of freedom, and then we added lagged deviance residuals to the model in several different ways. For example, 1-day lagged deviance residuals, 1- to 6-day lagged deviance residual, and a moving average of 6 days lagged deviance residuals, respectively. The autocorrelation remained without much reduction after many attempts, but the coefficient and its standard error from cyclic spline functions for seasonality changed very little (Table S4).

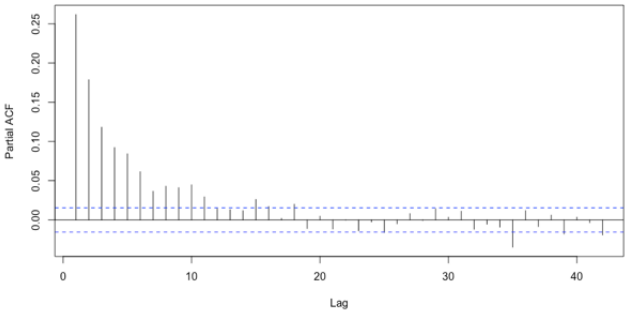


Figure S6. Partial autocorrelation function plot of the deviance residuals from the analysis in Tokyo (without adjustment for temperature and/or influenza)

Table S4. Seasonality estimates for Tokyo without adjusting for temperature and/or influenza like illness

Models	Peak-to-Trough (95% confidence interval)
Main model	1.254 (1.249, 1.259)
Model 1	1.249 (1.237, 1.255)
Model 2	1.244 (1.237, 1.252)
Model 3	1.253 (1.249, 1.258)
Model 4	1.253 (1.248, 1.257)
Model 5	1.252 (1.248, 1.257)
Model 6	1.250 (1.247, 1.254)

Main model: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t$

($Stratat$: strata defined by year, day of week, and their interaction to control for long-term trend and effect of day of week)

Model 1: $\log(\mu_t) = \beta_0 + cs(day - of - year, 5) + \lambda Strata_t$

Model 2: $\log(\mu_t) = \beta_0 + cs(day - of - year, 6) + \lambda Strata_t$

Model 3: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + Lag(residuals(main\ model), 1)$

Model 4: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + Lag(residuals(main\ model), 1) + Lag(residuals(main\ model), 2) + Lag(residuals(main\ model), 3)$

Model 5: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + Lag(residuals(main\ model), 1) + Lag(residuals(main\ model), 2) + Lag(residuals(main\ model), 3) + Lag(residuals(main\ model), 4) + Lag(residuals(main\ model), 5) + Lag(residuals(main\ model), 6)$

Model 6: $\log(\mu_t) = \beta_0 + cs(day - of - year, 4) + \lambda Strata_t + runmean(residuals(main\ model), 6)$

- The fit of the model to the daily death counts over time

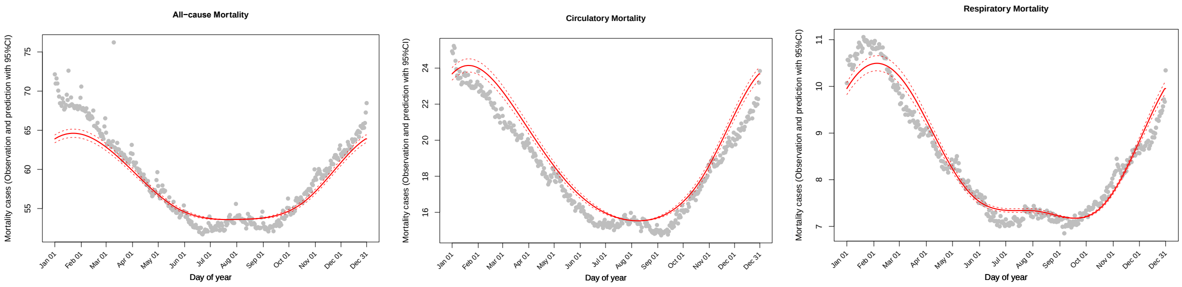


Figure S7. Daily mean number of observed aal-cause, circulatory, and respiratory mortality in Japan averaged from 47 prefectures over the study period and estimated number of daily circulatory mortality from time series regression models (Main model)

Grey dot: daily mean number of observed mortality cases averaged from 47 prefectures over the study period;
Red: pooled estimates with 95% confidence intervals obtained from prefecture-specific estimates from models without temperature adjustment

Figure S7 suggests that our models fitted seasonality of circulatory mortality better and may underestimate the seasonal variation in all-cause and respiratory mortality. The discrepancy between observed and fitted values may be explained by the risk of temperature, infectious disease, and other factors (e.g., human behaviour).

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.