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

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

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3 effect will remain when we remove the effect of temperature and influenza from seasonal
4 variations in mortality, given that the same local characteristics can also modify associations
5 between influenza, temperature and mortality.^{18–23}
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10 In the current study, we collected daily mortality data between 1972 and 2015 from 47
11 prefectures in Japan to investigate the contribution of temperature and influenza to seasonality
12 of mortality and to study its modifying factors by a range of prefecture-specific indicators. This
13 study will strengthen our understanding of seasonality of mortality and provide important
14 evidence to associate managements of seasonal risk factors to local conditions.
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22 **Method**

23 **Data collection**

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25 Hourly mean temperature (°C) and relative humidity (%) measured at a single monitoring site
26 in the capital city of each prefecture were obtained from 1972 to 2015 from the Japan
27 Meteorological Agency. We computed daily mean value of temperature and relative humidity
28 for our analysis.
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38 Daily mortality (counts) from all-cause, circulatory, respiratory disease and influenza were
39 obtained from the Ministry of Health, Labor and Welfare of Japan between 1972 and 2015 for
40 each prefecture in Japan. The principal cause of death statistics has been coded using the
41 International Statistical Classification of Diseases and Related Health Problems, 8th version
42 (ICD-8) from 1972 to 1978, the ICD-9 from 1979 to 1994, and the ICD-10 since 1995. Cause-
43 specific mortality was defined according to the ICD system: circulatory mortality (ICD-8 codes
44 390-458, ICD-9 codes 390-459, ICD-10 codes I00-I99), respiratory mortality (ICD-8 and ICD-
45 9 codes 460-519, ICD-10 codes J00-J99), mortality due to influenza (ICD-8 codes 470-474,
46 ICD-9 codes 487-488, ICD-10 codes J09-J11). Weekly number of influenza like illness (ILI)
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3 were also obtained for each prefecture from April 1999 to 2015 from National Institute of
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5 Infectious Diseases, Japan.
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8 Yearly data on prefecture-specific indicators was collected over the study period for each
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10 prefecture, including mean temperature, relative humidity, population density, the proportion
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12 of population aged ≥ 65 years, saving, income, Gini index (a measure of income inequality),
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14 consumer price index (CPI), economic power index (EPI, a measure of the wealth of a
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16 prefecture), the prevalence of air conditioning for households, and the number of registered
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18 physicians, nurses and hospital beds per 10K population. The details for data collection were
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20 described in previous studies^{24,25} and summarized in supplementary material.
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25 Data analysis

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27 We conducted our data analysis in three steps. First, we assessed seasonality of mortality
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29 without adjustments for temperature or influenza. Then, we examined the changes in the
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31 seasonality after adjusting for temperature and influenza separately, as well as both at the
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33 same time. Lastly, we evaluated the associations between each indicator and seasonality
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35 estimates before and after adjustments.
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40 We applied a generalized linear model with a quasi-Poisson family to assess seasonality of
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42 mortality in each prefecture without any adjustment for temperature and influenza. Day-of-
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44 year was treated as an indicator for seasonality, taking values from 1 to 366 corresponding to
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46 Jan 1st through Dec 31st for both common and leap years (from 60th day to 365th day in
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48 common years, values were taken from 61 to 366). We used a cyclic cubic spline with 4 degrees
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50 of freedom (*df*) for day of year to estimate seasonality. The days-of-year with maximum and
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52 minimum predicted mortality were identified as the peak and trough days, respectively, and
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54 were subsequently used to calculate the peak-to-trough ratio (PTR) to provide a measure of
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56 seasonality. Indicators for year, day-of-week and their interaction were used to control for the
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3 long-term trend and the effect of day-of-week. We excluded the data of the two days in our
4 seasonality assessment: 17 January 1995 and 11 March 2011, the day of the Great Hanshin-
5 Awaji Earthquake and Great East Japan Earthquake, respectively.
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10 To assess the contribution of temperature and influenza to seasonality of mortality, we
11 attempted three types of adjustment. First, we added temperature to our main model using a bi-
12 dimensional cross-basis function to account for its non-linear and delayed effect on mortality.
13 We modeled the exposure-response curve with a natural cubic B-spline with three internal
14 knots at 25th, 50th, and 75th percentiles of temperature distribution, and the lag-response
15 association with another natural cubic spline basis with 3 *df* with extended lags up to 21
16 days.^{10,25}
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27 Second, we removed temperature and adjusted for influenza in main model. We used as
28 explanatory variable the count of daily deaths due to influenza as a measure of severe influenza
29 circulating in the population, by incorporating natural log-transformed daily influenza
30 mortality count with a natural cubic spline with 3 *df*. Third, adjustment was made using both
31 temperature and influenza.
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39 The prefecture-specific PTR was pooled for the whole of Japan for all-cause, circulatory and
40 respiratory mortality, respectively, by meta-analysis with prefecture as a random factor. To
41 explore if patterns of interest varied over time, we conducted yearly analyses for the entire
42 country using separate quasi-Poisson regression model for each year with prefecture as a
43 random factor.
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51 To evaluate the modification of seasonal variation in mortality by prefecture-specific indicators,
52 we applied linear mixed effects models (LMEMs) to investigate associations of PTR with each
53 prefecture-specific indicator separately. We fitted LMEMs with random intercepts for
54 prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital
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3 city of each prefecture were included to reduce spatial correlation, except for when we
4 investigated annual mean temperature as the indicator, due to their high correlation. We
5 conducted the analysis for all-cause, circulatory, and respiratory mortality in separate LMEMs.
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7 Results are expressed as the log(PTR) variation for a standard deviation increase of the
8 indicator.
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11 We performed a series of sensitivity analysis to confirm our findings. In particular, we repeated
12 main analysis using weekly ILI cases instead of influenza mortality counts for influenza
13 adjustment. See supplementary material for a description of modelling details.
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15 Patient and public involvement

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17 There was no patient or public involvement.
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19 Results

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21 This study included 39 913 020 deaths from all causes, 13 628 846 deaths from circulatory
22 diseases, 5 027 271 deaths from respiratory diseases, and 32 582 deaths from influenza. Daily
23 mean temperature for the whole country between 1972 and 2015 ranged from -14.1°C to 33.8°C,
24 with a mean value at 15.7°C (Table 1). Daily deaths from influenza showed a large variation,
25 ranging from 0 case to 77 cases with a median value at 0 (Table 1). Prefecture-specific
26 summary was provided in Table S1.
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29 The nationwide monthly summary of daily mean temperature and daily mortality showed a
30 significant seasonal pattern (Figure S1). The most cases for mortality were found in cold season
31 with a slight difference: mortality from influenza from January to March were much higher
32 than that in December, while no significant difference from December to March was found for
33 all-cause, circulatory and respiratory mortality.
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36 We observed a high variability for healthcare capacity (Table S2 & S3), while a low variability
37 for socioeconomic indicators. Most of the indicators are correlated (Figure S2). In particular,
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3 EPI was highly correlated with population density, proportion of individuals aged over than 65
4 years old, and numbers of physicians, nurses and hospital beds (correlation>0.70). In addition,
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6 saving is highly correlated with income (correlation>0.70). For the sake of brevity, we
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8 excluded population density, proportion of individuals aged over 65 years old, numbers of
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10 physicians, nurses and hospital beds, and saving in main analysis.
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15 Figure 1 and Table 2 show the pooled results for the whole of Japan for seasonality of all-
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17 cause, circulatory, and respiratory mortality before and after adjustments for temperature
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19 and/or influenza. We observed a clear seasonal pattern with higher numbers of deaths in cold
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21 seasons than in warm seasons. Before any adjustments, the nationwide pooled PTR for all-
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23 cause, circulatory and respiratory mortality were 1.29 (95% confidence intervals (CI): 1.28,
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25 1.31), 1.53 (95% CI: 1.51, 1.56) and 1.51 (95% CI: 1.49, 1.54), respectively. After adjustments
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27 for temperature and influenza, the shape of seasonality remained (Figure 1), but its amplitude
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29 reduced to different extents. Adjusting for just temperature reduced PTRs substantially in
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31 particular for all-cause and circulatory mortality to 1.08 (95% CI: 1.075,1.09) and 1.10 (95%
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33 CI: 1.08, 1.11). Adjusting for just influenza reduced PTRs only very slightly to 1.28 (95% CI:
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35 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
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37 and respiratory mortality, respectively. Notably, adjusting for temperature and influenza did
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39 not flatten the seasonal pattern or reduce the PTR to 1.
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45 Similarly, prefecture-specific PTRs also showed a substantial reduction with temperature
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47 adjustment while a slight reduction when influenza was adjusted only, although an apparent
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49 reduction was observed in influenza-adjusted PTR for respiratory mortality (Figure 2).
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51 Furthermore, PTR for all mortality types varied across prefectures, and the spatial variation
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53 after adjustments was less apparent in particular for all-cause and circulatory mortality.
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55 Prefectures with higher latitude (northern areas), including Hokkaido, Aomori, and Akita, as
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3 well as the southernmost prefecture- Okinawa, showed a lower unadjusted-PTR and a smaller
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5 reduction after adjustments for temperature.
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8 Our yearly analyses for the entire country showed a large reduction after adjusting for
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10 temperature while a small reduction after adjusting for influenza only for most of the years
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12 (Figure S3). For the year of 1975 and 1976, however, a larger reduction in PTR for respiratory
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14 mortality was observed when only the influenza was adjusted. Unexpectedly, PTR for all
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16 mortality types in several years, e.g., 1983, 1995 and 1999, increased when temperature was
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18 adjusted.
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22 Figure 3 shows associations between selected indicators and PTR. Before any adjustments,
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24 PTR for all-cause mortality was positively associated with 44-year averaged annual mean
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26 temperature, whereas a negative association was observed for Gini index. After a separate
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28 adjustment for influenza, these associations remained. Adjusting for temperature, however,
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30 reversed the associations with a large confidence interval.
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33 Similar results were observed for cause-specific mortality, with the exception of income and
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35 air conditioning prevalence: income was positively associated with unadjusted-PTR for
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37 circulatory mortality, and air conditioning prevalence was negatively associated with
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39 unadjusted-PTR for respiratory mortality. These associations remained similar when adjusting
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41 for just influenza, while moved towards null after including temperature in the adjustment.
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45 Figures S4-S5 and Table S3 showed the results by using mortality data between 1999 April
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47 and 2015 and weekly ILI cases for influenza adjustment. The results after a separate adjustment
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49 for influenza were robust to different indicators for seasonal influenza infections. However, the
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51 results for respiratory mortality before and after any adjustments seems to be sensitive to the
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53 study period: both unadjusted- and adjusted- PTR were lower when using the subset of data
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55 between 1999 April and 2015 than by using the data between 1972 and 2015.
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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 study¹¹ 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.

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3 Seasonality of mortality is resulted from complex interaction between human behavior and
4 environment. In addition to temperature and influenza, other infectious diseases (e.g.,
5 respiratory syncytial virus), air pollutants, behavioral changes based on a seasonal basis (e.g.,
6 dietary pattern and physical activities) have been linked with seasonal variation of diseases and
7 mortality. However, there is no direct evidence assessing their contribution to seasonality of
8 mortality.
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11 Our sub-period analysis suggests that seasonal amplitudes of respiratory mortality were lower
12 in recent years. This finding may be related with changes in influenza vaccination policy in
13 Japan: the policy from 1962 to 1987 required Japanese schoolchildren to be vaccinated against
14 influenza, and in 1977, such vaccination policy became obligate, which was relaxed in 1987
15 and repealed in 1994, resulting in a substantial reduction in vaccination coverage.^{26,27} In recent
16 decade, the widespread use of neuraminidase inhibitors and increasing vaccination rates in
17 schoolchildren and especially the elderly have led to a substantial decrease in respiratory
18 mortality.²⁶ Further investigation should be conducted to confirm our hypothesis.
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21 Despite of a similar seasonal shape across prefectures, seasonal amplitudes varied across 47
22 prefectures. Our findings showed that this spatial variation was related with averaged annual
23 mean temperature and Gini index, and that these associations were reversed after adjusting for
24 temperature. Individuals living in cold prefectures show less seasonal variation in mortality,
25 which may be partially explained by a better cold acclimatization from the combination of
26 habituation, metabolic adjustment, and insulative acclimatization.^{8,28,29} Counterintuitively, our
27 results suggest individuals living in prefectures with low inequality experienced larger seasonal
28 variations in mortality. A recent multi-country analysis found a positive association between
29 Gini index and heat effect of temperature on mortality, whereas no evidence was observed for
30 its association with cold effect. Therefore, prefectures characterized by low inequality may be
31 more vulnerable to heat effect, leading to a higher mortality in summer and subsequently
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3 attenuating the seasonal difference in mortality between winter and summer. Although our
4 findings suggested averaged annual mean temperature and Gini index as the potential effect
5 modification, adjusting for temperature reversed their associations, suggesting that the
6 preventive strategies targeting the impact of temperature may reduce the vulnerability of
7 individuals living in prefectures characterized by warm climate and low inequality. It is worth
8 noting, however, that we did not consider potential confounding between indicators due to their
9 high correlations. Therefore, our results need to be interpreted carefully, and further research
10 at individual level or by including areas with large variation in these indicators, is merited to
11 confirm our findings.
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24 This study has several limitations. First, our study was conducted in Japan that has distinct
25 seasonal weather conditions, hence our results may not be applicable to other areas with
26 different climate (e.g., tropical countries). Second, we assumed the association of mortality
27 with influenza and temperature did not change between 1972 and 2015. Although our main
28 conclusion remained in our sub-period analysis by using data between 1999 and 2015,
29 seasonality estimates for respiratory mortality seems to be sensitive to study period, and our
30 findings from single year analysis needs to be interpreted carefully. Future investigations
31 should be conducted by extending current datasets to those areas with different climate, and
32 also by including more details for influenza (e.g., influenza subtype and vaccination coverage).
33 Results from these investigations would complement our findings in current analysis.
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48 This study presents findings from an epidemiologic analysis investigating the role of
49 temperature, influenza and other local characteristics on seasonality of mortality across
50 multiple locations. A strength of current study was the investigation of contributions of
51 temperature versus influenza to seasonal variation of different types of mortality by a common
52 study design and statistical framework, while previous studies mostly focused on either
53 temperature or influenza only. In addition, our analysis on the effect modification provides
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3 important information for the development of interventions to attenuate seasonal effect on
4 mortality.
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8 This study suggests that seasonality of mortality is primarily driven by temperature, with
9 occasionally seasonal variations associated with influenza. Furthermore, our analysis identifies
10 several prefecture-specific characteristics that may modify the seasonality of mortality. In sum,
11 our findings can help us to gain a better understanding of seasonality of mortality and provide
12 important information for the management of seasonal risks.
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23 **Contributors:** LM conducted the study, analyzed the data and wrote the manuscript. CN and
24 XS helped with the statistical analysis and the discussion of the text. MT, LY and YH
25 contributed to the final version of the manuscript. BA helped with the data analysis and the
26 interpretation of the results. MH contributed to the study design and the discussion of the results.
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36 publish, or preparation of the manuscript.
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40 **Competing interests:** None declared.
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43 **Ethics approval:** This study used secondary data, with no possibility of personal identification,
44 and an informed consent or an approval by a medical ethics board is not required.
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48 **Data availability statement:** Data are available upon reasonable request. The technical
49 appendix, statistical code and data set will be available upon request from the Corresponding
50 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):

$$\text{Ratio} = \frac{\text{Mortality prediction at day}_i}{\text{Minimum mortality prediction at the trough}}$$

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

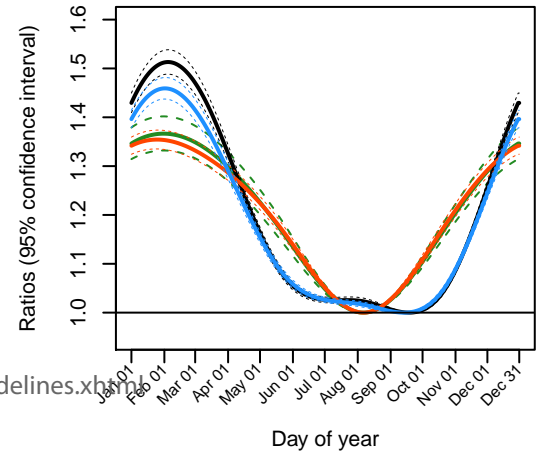
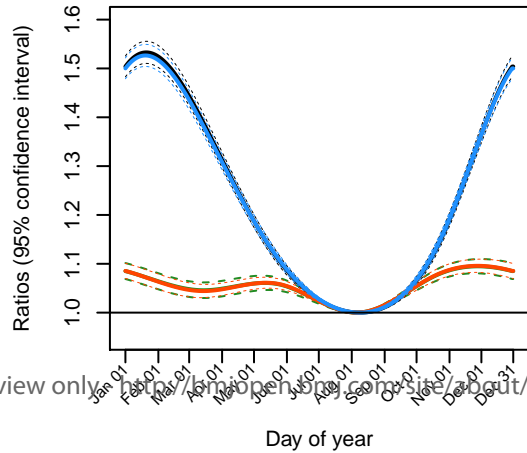
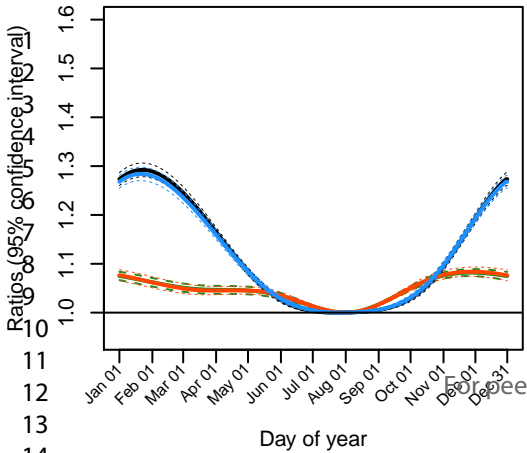
Table 2. Nationwide pooled peak-to-trough ratio (PTR) with 95% confidence interval (95% CI) with/without adjustment for temperature and/or influenza

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

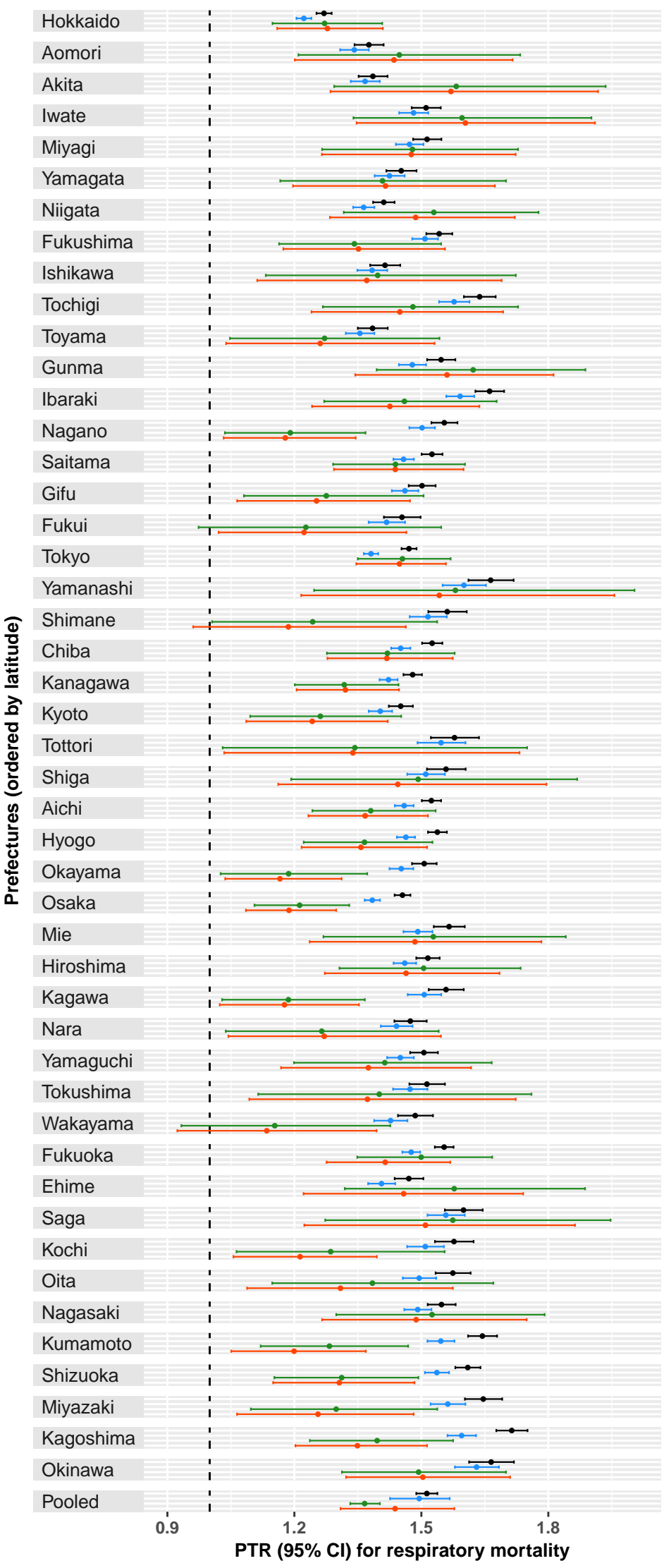
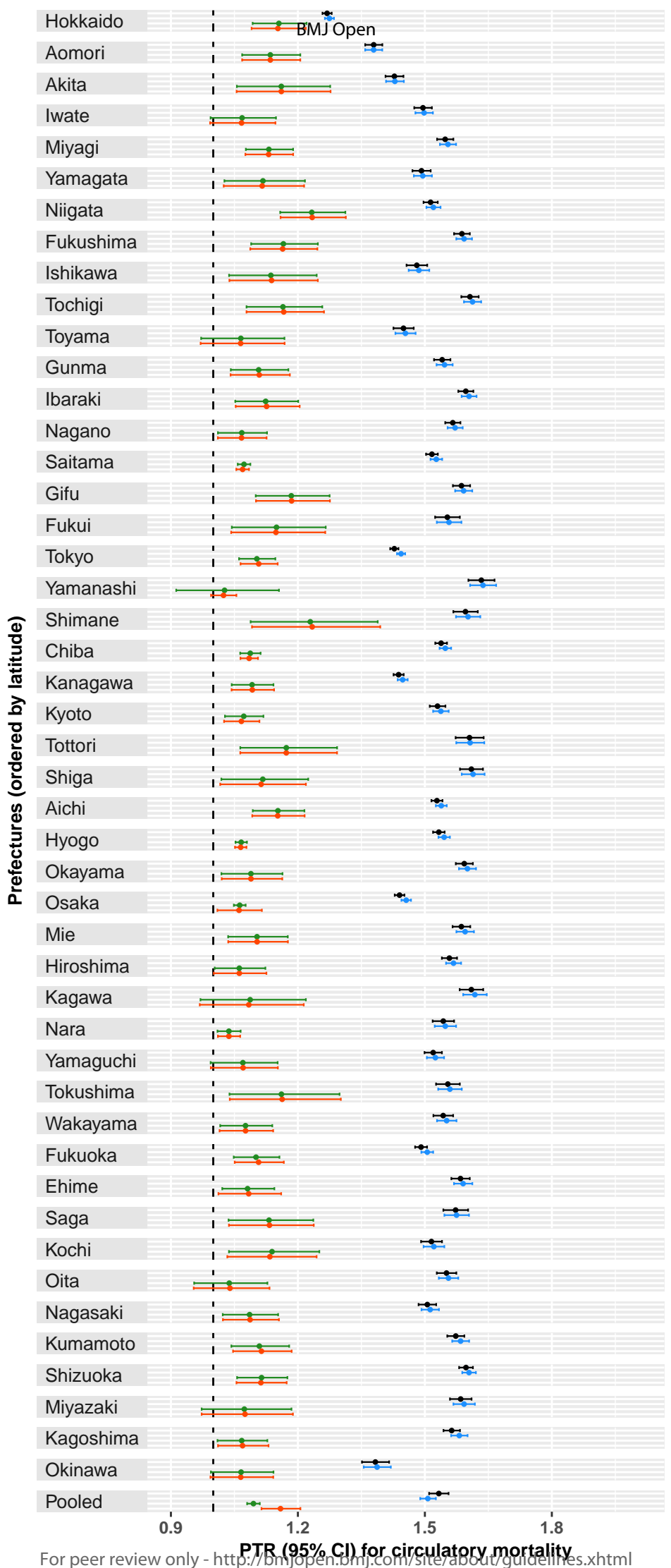
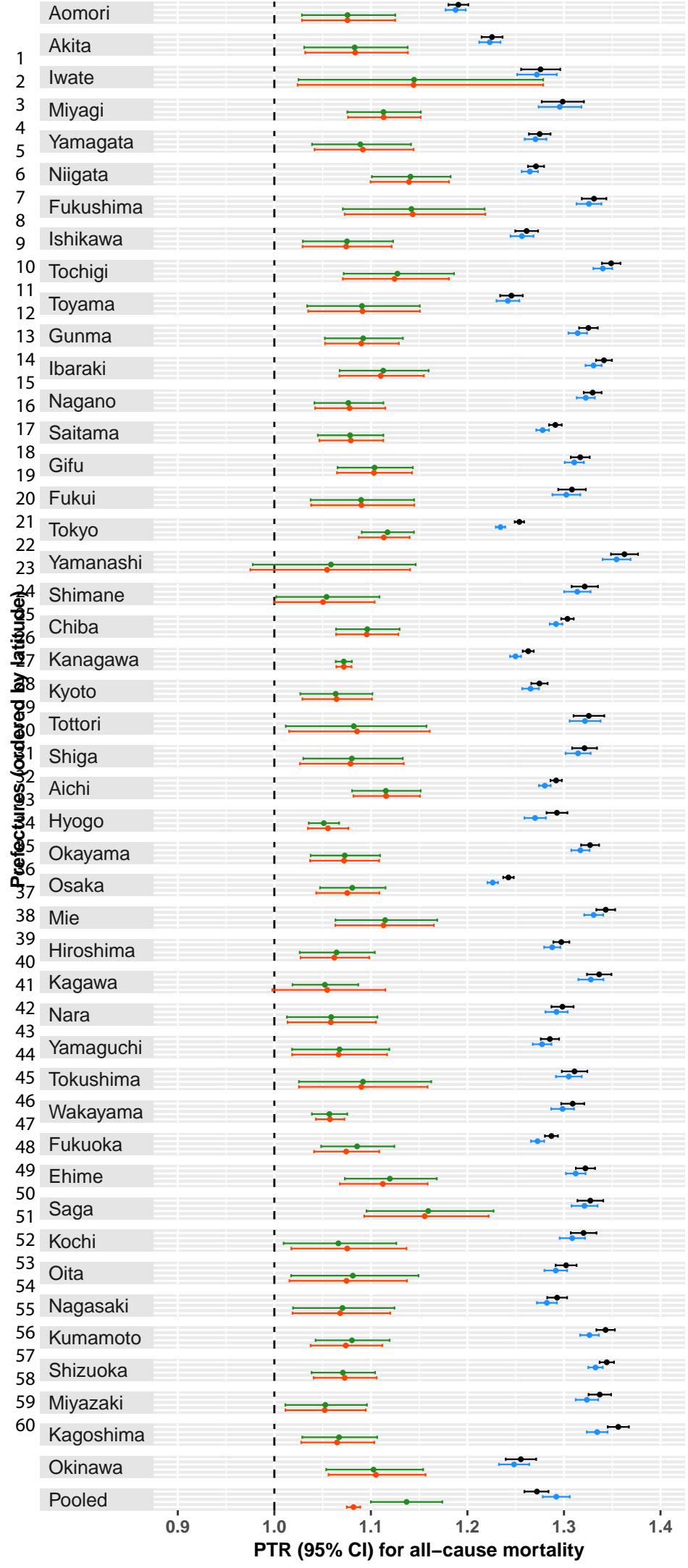
Circulatory Mortality

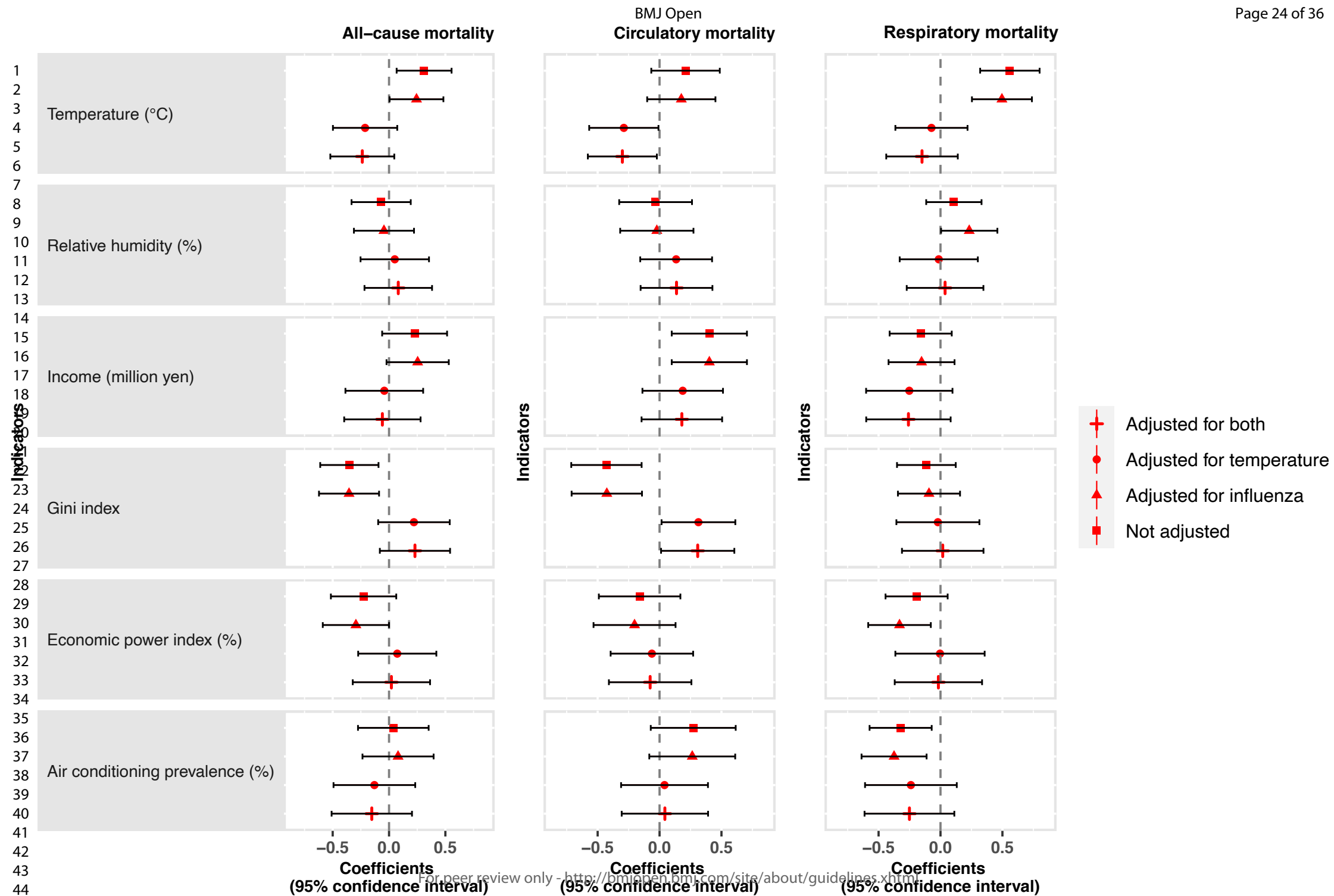
Respiratory Mortality



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Supplementary material

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

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

Prefecture/ country ^a	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
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]

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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.

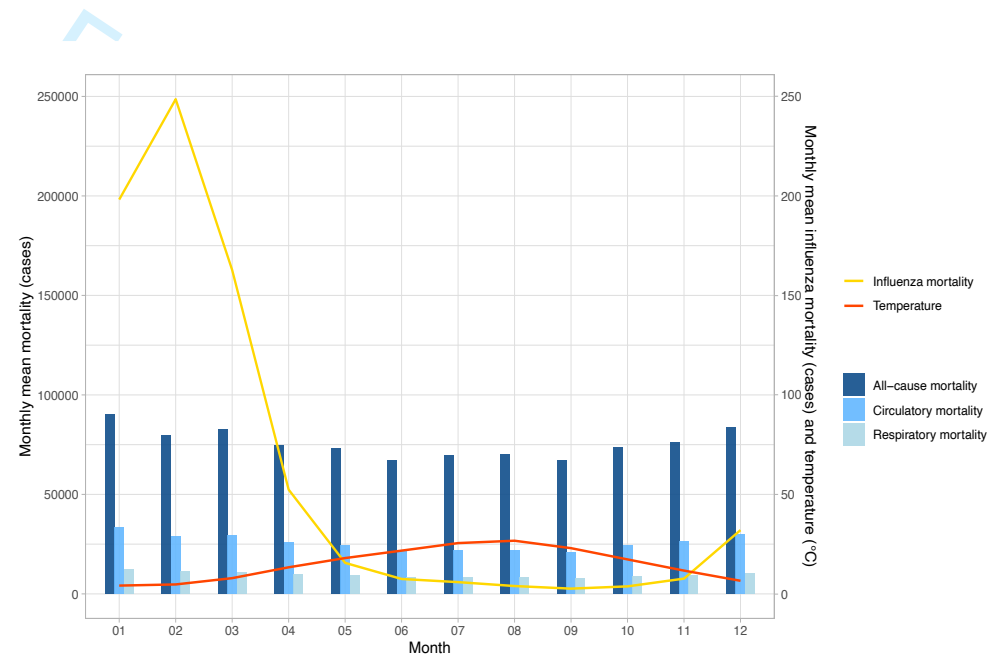


Figure S1. Nationwide monthly summary of daily mean temperature, daily mortality cases from all-cause, circulatory, respiratory disease and influenza between 1972 and 2015

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

Prefecture/ country	Temperature (°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 (%)
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/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	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.

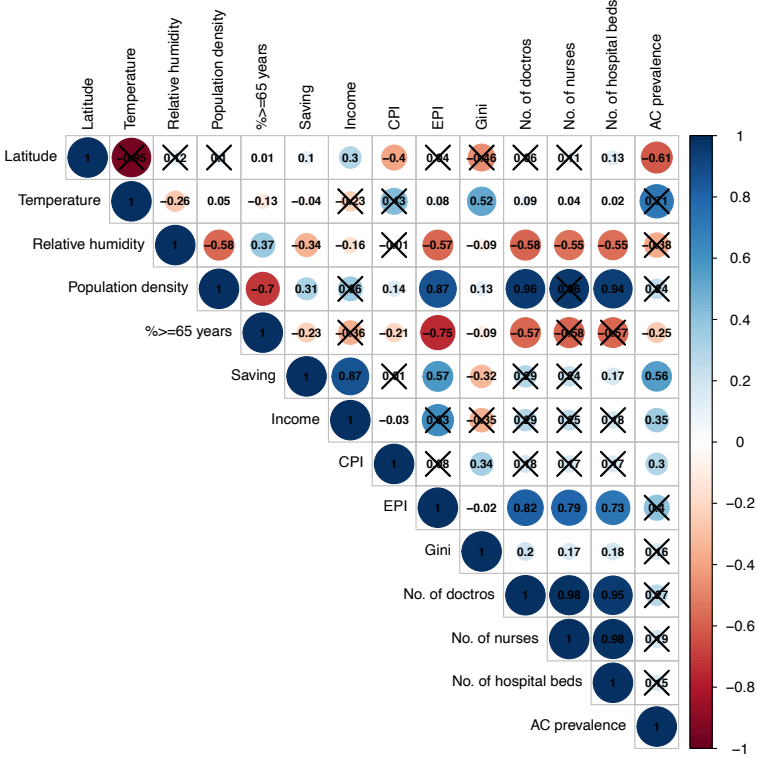


Figure S2. Correlations between the indicators.

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

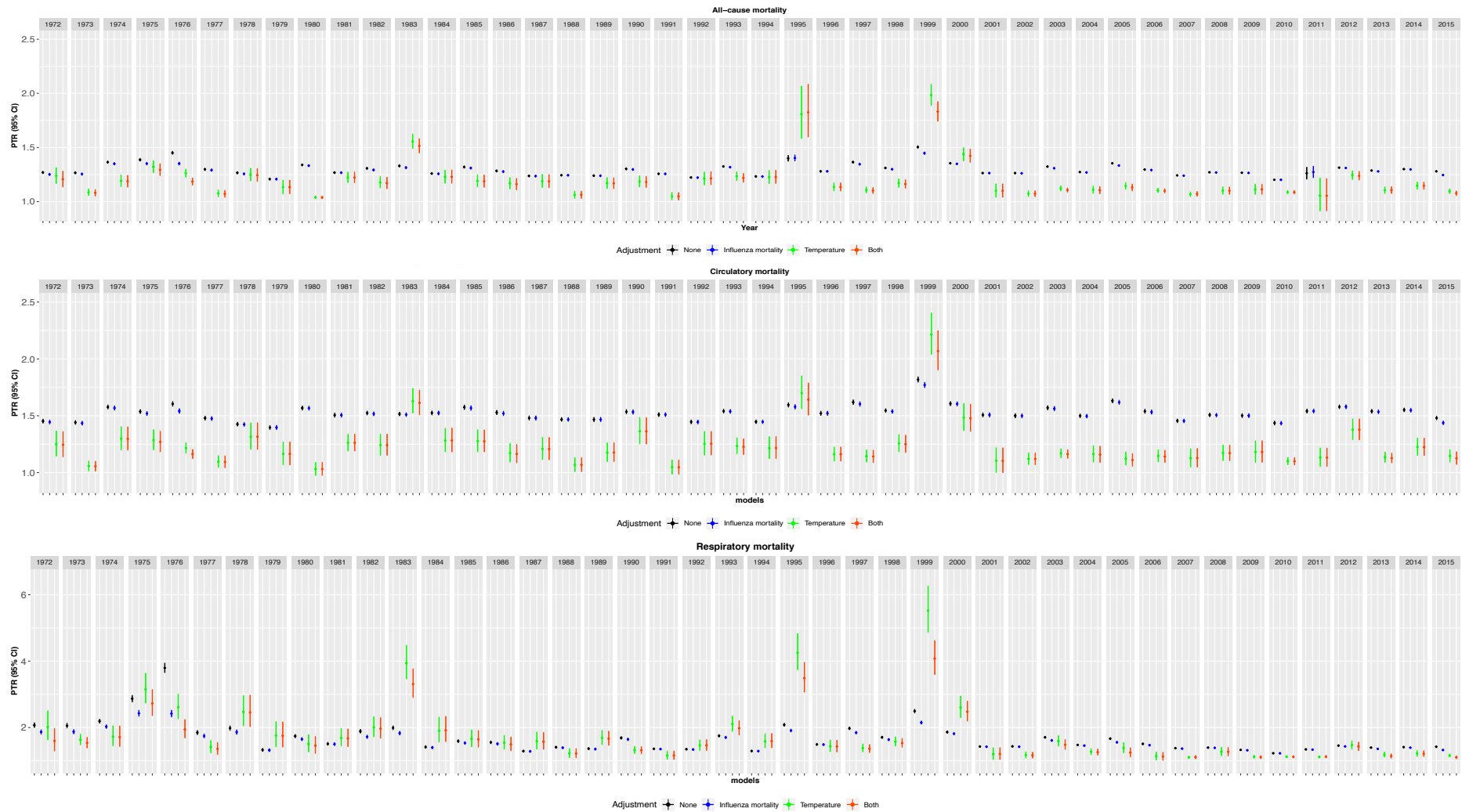


Figure S3. Peak-to-trough ratio (PTR) with 95% confidence intervals (95%CI) for each single year from 1972 to 2015 for all-cause (top), circulatory (middle), and respiratory (bottom) mortality before (black) and after adjustments for just influenza (blue), just temperature (green), and both (red)

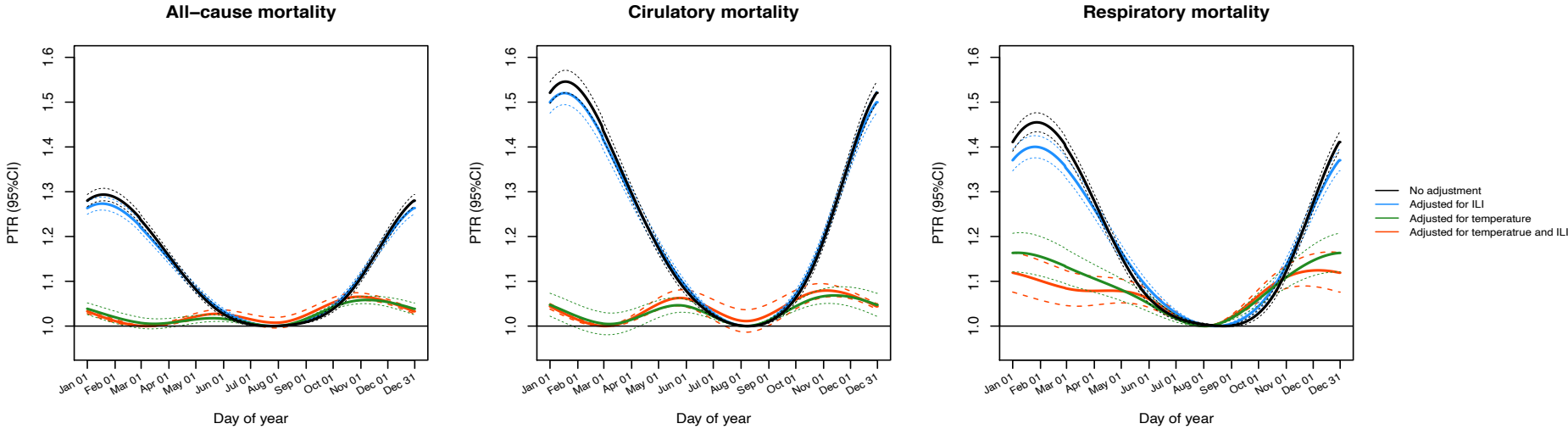


Figure S4. Pooled seasonality of all-cause, circulatory, and respiratory mortality between April 1999 and 2015 before and after adjustments, by using weekly influenza-like-illness (ILI) for influenza adjustment

(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)

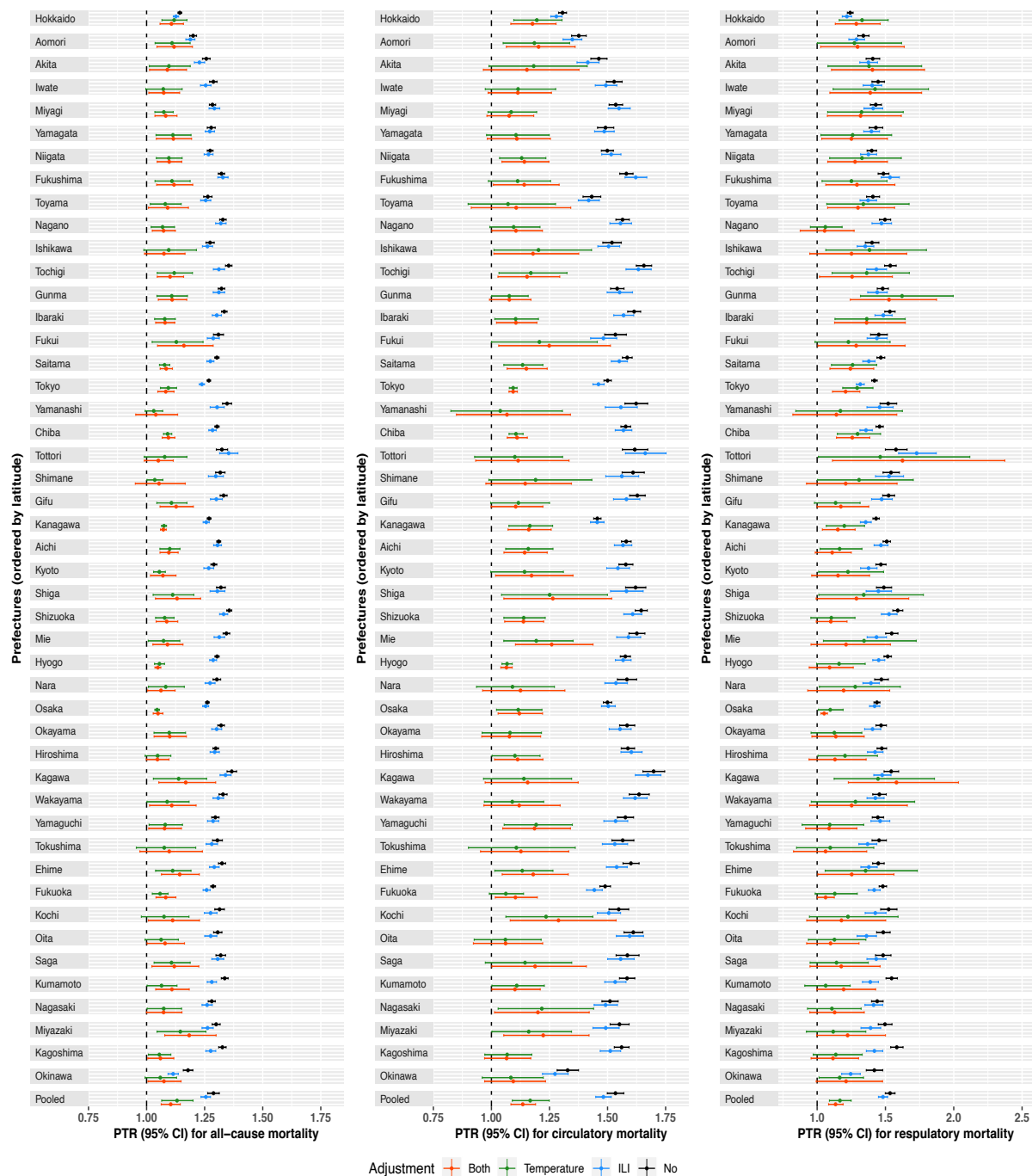


Figure S5. Pooled peak-to-trough ratio (PTR, 95% confidence intervals (95%CI)) for each prefecture between 1999 April and 2015 before and after adjustments, by using weekly influenza-like-illness (ILI) for influenza adjustment (black: without any adjustment; blue: adjusted for just ILI; green: adjusted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

Adjustment	All-cause mortality		Circulatory mortality		Respiratory mortality	
	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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	6-8

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —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.

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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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3 1 The role of temperature, influenza and other local characteristics in seasonality of mortality: a
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5 2 population-based time-series study in Japan
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8 3
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26 **Abstract**

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

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

36 Results: The nationwide unadjusted-PTRs for all-cause, circulatory and respiratory mortality
37 were 1.29 (95% Confidence Intervals (CI): 1.28, 1.31), 1.52 (95%CI: 1.49, 1.55) and 1.45
38 (95%CI: 1.43, 1.48), respectively. These PTRs reduced substantially after adjusting for
39 temperature but very little after a separate adjustment for ILI. Furthermore, seasonal amplitudes
40 varied between prefectures. However, there was no strong evidence for the associations of PTR
41 with the indicators on prefecture-specific characteristics.

42 Conclusion: Seasonality of mortality is primarily driven by temperature in Japan. The spatial
43 variation in seasonal amplitudes was not associated with prefecture-specific characteristics.

44 Although further investigations are required to confirm our findings, this study can help us gain
45 a better understanding of the mechanisms underlying seasonality of mortality.

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3 50 **Strengths and limitations of this study**
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- 5 52 • We investigated the contributions of temperature versus influenza to seasonal variation of
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8 53 different types of mortality by a common study design and statistical framework.
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11 54 • We used indicators on a range of location-specific characteristics to investigate their
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13 55 modifying effect on seasonal variations in mortality.
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16 56 • The study was conducted in Japan characterized by distinct seasonal weather conditions,
17
18 57 so our results may not be generalized to locations with different climate (e.g., tropical
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20 58 countries).
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23 59 • The deviance of residuals showed some autocorrelations, but it had limited impacts on our
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25 60 seasonality estimates.
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73 Introduction

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

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

92 The strength of seasonality in mortality varies geographically.⁸ For example, a smaller seasonal
93 amplitude was observed in areas with milder climates, suggesting that individuals living in
94 warm areas might be more vulnerable to seasonal variations in mortality.² Several local
95 characteristics on climate, demographic and socioeconomic factors, and adaptations have been
96 linked with such spatial variation. However, only a few studies have evaluated their modifying
97 effect on seasonality of mortality.^{1,17} Another question remains unclear is if these modification

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3 98 effect will remain when we remove the effect of temperature and influenza from seasonal
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5 99 variations in mortality, given that the same local characteristics can also modify associations
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8 100 between influenza, temperature and mortality.^{18–23}
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11 101 In the current study, we collected daily mortality data between 1999 and 2015 from 47
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13 102 prefectures in Japan to investigate the contribution of temperature and influenza to seasonality
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15 103 of mortality and to study its modifying factors by a range of prefecture-specific indicators. This
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17 104 study will strengthen our understanding of seasonality of mortality and provide important
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19 105 evidence to associate managements of seasonal risk factors to local conditions.
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22 106 **Method**

23 107 **Data collection**

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25 108 Hourly mean temperature (°C) and relative humidity (%) measured at a single monitoring site
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27 109 in the capital city of each prefecture were obtained from 1999 to 2015 from the Japan
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29 110 Meteorological Agency. We computed daily mean value of temperature and relative humidity
30
31 111 for our analysis.
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38 112 Daily mortality (counts) from all-cause, circulatory, respiratory disease and influenza were
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40 113 obtained from the Ministry of Health, Labor and Welfare of Japan between 1999 and 2015 for
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42 114 each prefecture in Japan. The principal cause of death statistics is coded using the International
43
44 115 Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10).
45
46 116 Cause-specific mortality was defined according to the ICD system: circulatory mortality (ICD-
47
48 117 10 codes I00-I99), and respiratory mortality (ICD-10 codes J00-J99). Weekly number of
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50 118 influenza like illness (ILI) were obtained for each prefecture from April 1999 to 2015 from
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52 119 National Institute of Infectious Diseases, Japan.
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57 120 Yearly data on prefecture-specific indicators was collected over the study period for each
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59 121 prefecture, including annual mean temperature, relative humidity, population density, the
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3 122 proportion of population aged ≥ 65 years, saving, income, Gini index (a measure of income
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5 123 inequality), consumer price index (CPI), economic power index (EPI, a measure of the wealth
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7 124 of a prefecture), the prevalence of air conditioning for households, and the number of registered
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10 125 physicians, nurses and hospital beds per 10K population. For each indicator, we computed the
11
12 126 averaged value across the years 1999-2015 for each prefecture. The details for data collection
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14
15 127 were described in previous studies^{24,25} and summarized in supplementary material.

17 128 Data analysis

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20 129 We conducted our data analysis in three steps. First, we assessed seasonality of mortality
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22 130 without adjustments for temperature or ILI. Then, we examined the changes in the
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24 131 seasonality after adjusting for temperature and ILI separately, as well as both at the same
25
26 132 time. Lastly, we evaluated the associations between each indicator and seasonality estimates
27
28 133 before and after adjustments.

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31
32 134 We applied a generalized linear model with a quasi-Poisson family to assess seasonality of
33
34 135 mortality in each prefecture without any adjustment for temperature and ILI. Day-of-year was
35
36 136 treated as an indicator for seasonality, taking values from 1 to 366 corresponding to Jan 1st
37
38 137 through Dec 31st for both common and leap years (from 60th day to 365th day in common
39
40 138 years, values were taken from 61 to 366). We used a cyclic cubic spline with 4 degrees of
41
42 139 freedom (*df*) for day of year to estimate seasonality. The days-of-year with maximum and
43
44 140 minimum mortality estimates from generalized liner models were identified as the peak and
45
46 141 trough days, respectively, and were subsequently used to calculate the peak-to-trough ratio
47
48 142 (PTR) to provide a measure of seasonality. When constructing confidence intervals for PTR,
49
50 143 previous studies enforced the boundary constraint by truncating the lower confidence limit at
51
52 144 one for PTR.^{26,27} However, doing that may introduce a positive bias into the PTR.²⁸ In order to
53
54 145 show the statistical variability in PTR, therefore, we did not truncate the lower confidence limit
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56 146 at one for PTR. Indicators for year, day-of-week and their interaction were used to control for

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2
3 147 the long-term trend and the effect of day-of-week. We excluded the data on 11 March 2011,
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5 148 the day of the Great East Japan Earthquake.
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8 149 To assess the contribution of temperature and ILI to seasonality of mortality, we attempted
9
10 150 three types of adjustment. First, we added temperature to our main model using a bi-
11
12 151 dimensional cross-basis function to account for its non-linear and delayed effect on mortality.
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14 152 We modeled the exposure-response curve with a natural cubic B-spline with three internal
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16 153 knots at 25th, 50th, and 75th percentiles of temperature distribution, and the lag-response
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18 154 association with another natural cubic spline basis with 3 *df* with extended lags up to 21
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20 155 days.^{10,25}
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25 156 Second, we removed temperature and adjusted for ILI in main model. We assumed ILI cases
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27 157 distributed evenly across day of week and computed daily average ILI cases. A natural cubic
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29 158 spline with 3 *df* was then used to control for daily ILI cases in the model. Third, adjustment
30
31 159 was made using both temperature and influenza.
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34 160 The prefecture-specific PTR was pooled for the whole of Japan for all-cause, circulatory and
35
36 161 respiratory mortality, respectively, by meta-analysis with prefecture as a random factor. To
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38 162 explore if patterns of interest varied over time, we conducted yearly analyses for the entire
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40 163 country using separate quasi-Poisson regression model for each year with prefecture as a
41
42 164 random factor.
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46 165 To evaluate the modification of seasonal variation in mortality by prefecture-specific indicators,
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48 166 we applied linear mixed effects models (LMEMs) to investigate associations of PTR with each
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50 167 prefecture-specific indicator separately. We fitted LMEMs with random intercepts for
51
52 168 prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital
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54 169 city of each prefecture were included to reduce spatial correlation, except for when we
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56 170 investigated annual mean temperature as the indicator, due to their high correlation. We
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3 171 conducted the analysis for all-cause, circulatory, and respiratory mortality in separate LMEMs.
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5 172 Results are expressed as the log(PTR) variation for a standard deviation increase of the
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8 173 indicator.

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10 174 We performed a series of sensitivity analysis to confirm our findings. We tested the cyclic
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13 175 spline function for day of year with different *df* of 5 and 6 and adjusted temperature by changing
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15 176 the spline function, internal knots for temperature distribution, *df* and lag days for the lag-
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18 177 response associations. For influenza adjustment, we varied the number of lag days using the
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20 178 moving averages of the previous 7, 14, 21 and 28 days, and tested the natural cubic spline
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22 179 function with 2 *df*. For ILI adjustment, we tested moving average of previous 7, 14, 21 and 28
23
24 180 days for ILI cases, and 2 *df* for the natural cubic spline function. Overall, we did not observe
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26
27 181 substantial changes in our estimates.

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29 182 The models were summarized in supplementary material including diagnostic plots. We
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32 183 conducted the analysis with R software, version 3.6.0 (R Development Core Team) using the
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34 184 *dlnm* and *mixmeta* packages.

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37 185 Patient and public involvement

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40 186 There was no patient or public involvement.

41 42 187 **Results**

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45 188 This study included 18 985 036 deaths from all causes, 5 541 277 deaths from circulatory
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47 189 diseases, and 2 894 314 deaths from respiratory diseases. The nationwide time series of daily
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49
50 190 mortality showed a significant seasonal pattern (Figure S1). Daily mean temperature for the
51
52 191 whole country between 1999 and 2015 ranged from -1.0°C to 30.7°C, with a mean value at 15.6°C
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54 192 (Table 1). ILI cases showed a large variation, ranging from 7 case to 1 652 147 cases with a
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57 193 median value at 7626 (Table 1). Prefecture-specific summary was provided in Table S1.

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3 194 We observed a high variability for healthcare capacity (Table S2 & S3), while a low variability
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5 195 for socioeconomic indicators. Most of the indicators are correlated (Figure S2). In particular,
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7 196 EPI was highly correlated with population density, proportion of individuals aged over than 65
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9 197 years old, and numbers of physicians, nurses and hospital beds (correlation>0.70). In addition,
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11 198 saving is highly correlated with income (correlation>0.70).

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14
15 199 Figure 1 and Table 2 show the pooled results for the whole of Japan for seasonality of all-
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17 200 cause, circulatory, and respiratory mortality before and after adjustments for temperature
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19 201 and/or influenza. We observed a clear seasonal pattern with higher numbers of deaths in cold
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21 202 seasons than in warm seasons. Before any adjustments, the nationwide pooled PTR for all-
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23 203 cause, circulatory and respiratory mortality were 1.29 (95% confidence intervals (CI): 1.27,
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25 204 1.30), 1.52 (95% CI: 1.49, 1.55) and 1.45 (95% CI: 1.43, 1.48), respectively. After adjustments
26
27 205 for temperature and ILI, the shape of seasonality remained (Figure 1), but its amplitude reduced
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29 206 to different extents. Adjusting for just temperature reduced PTRs substantially in particular for
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31 207 all-cause and circulatory mortality to 1.06 (95% CI: 1.05,1.07) and 1.07 (95% CI: 1.05, 1.09).
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33 208 Adjusting for just ILI reduced PTRs only very slightly to 1.27 (95% CI: 1.26,1.29), 1.52 (95%
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35 209 CI: 1.49,1.55), and 1.40 (95% CI: 1.38, 1.43) for all-cause, circulatory and respiratory mortality,
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37 210 respectively. Notably, adjusting for temperature and ILI did not flatten the seasonal pattern or
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39 211 reduce the PTR to 1.

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45 212 Similarly, prefecture-specific PTRs also showed a substantial reduction with temperature
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47 213 adjustment while a slight reduction when ILI was adjusted only, although an apparent reduction
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49 214 was observed in ILI-adjusted PTR for respiratory mortality (Figure 2). Furthermore, PTR for
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51 215 all mortality types varied across prefectures, and the spatial variation after adjustments was
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53 216 less apparent in particular for all-cause and circulatory mortality. Prefectures with higher
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55 217 latitude (northern areas), including Hokkaido, Aomori, and Akita, as well as the southernmost
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3 218 prefecture- Okinawa, showed a lower unadjusted-PTR and a smaller reduction after
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5 219 adjustments for temperature.
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8 220 Our yearly analyses for the entire country showed a large reduction after adjusting for
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10 221 temperature while a small reduction after adjusting for ILI for most of the years (Figure S3).
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12 222 For the year of 2020, however, a higher PTR for all-cause and respiratory mortality was
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14 223 observed when temperature was included in the adjustment. We further checked the sensitivity
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16 224 of our estimates to temperature adjustment. Changing the lag period of 21 days in cross-basis
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18 225 function to 14 days reduced temperature-adjusted PTR, although it remained slightly higher
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20 226 than unadjusted PTR with a largely overlapped confidence intervals. The results for the other
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22 227 years did not change much (results not shown).
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27 228 Figure S4 shows associations between the indicators and PTR. There was no strong evidence
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29 229 for the association between prefecture-specific characteristics and seasonality estimates.
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31 230 Diagnostic plots for models were included in supplementary material (Figure S5-S7).
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34 231 **Discussion**

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37 232 In this study, we investigated the contribution of temperature and influenza to seasonal
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39 233 variation of mortality in 47 prefectures of Japan and evaluated the modifications of seasonality
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41 234 by a range of prefecture-specific indicators. Our findings show that seasonal variation in
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43 235 mortality was substantially contributed by temperature and to a lesser extent, by influenza. In
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45 236 addition, seasonal amplitudes varied between prefectures. There was no strong evidence for
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47 237 the association between prefecture-specific characteristics and seasonal amplitudes.
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51 238 Temperature and influenza have been among the most studied drivers of seasonality of
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53 239 mortality.¹³⁻¹⁶ However, most of the investigations focused on either temperature or influenza.
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55 240 How much of seasonality of mortality is dependent on temperature versus influenza remain
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57 241 unsolved. Our finding showed that most of seasonality of mortality in Japan was attributable
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3 242 to temperature while little was driven by influenza. Consistent with our findings, a population
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5 243 -based cohort study in elderly British people examined month to month variation in mortality
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7 244 and its relationship with temperature and influenza A, and discovered that most of seasonal
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9 245 fluctuation was associated with cold temperature and a small component related with influenza
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11 246 A. Despite the smaller contribution of influenza to seasonal variation of mortality than
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13 247 temperature, our analysis suggested that influenza was accountable for seasonal variation,
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15 248 especially, for respiratory mortality. A study¹¹ in 48 U.S. cities observed a link between
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17 249 influenza epidemic and the irregularly high winter mortality in some certain years. Evidence
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19 250 thus far implies that temperature contributes substantially to seasonality of mortality in general,
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21 251 while influenza is related with seasonal variations of mortality to a less extent.

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26 252 Notably, removing the effect of temperature and influenza from seasonal variation in mortality
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28 253 did not completely flatten the seasonal pattern of mortality, in particular, respiratory mortality.
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30 254 Seasonality of mortality is resulted from complex interaction between human behavior and
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32 255 environment. In addition to temperature and influenza, other infectious diseases (e.g.,
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34 256 respiratory syncytial virus), air pollutants, behavioral changes based on a seasonal basis (e.g.,
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36 257 dietary pattern and physical activities) have been linked with seasonal variation of diseases and
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38 258 mortality. However, there is no direct evidence assessing their contribution to seasonality of
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40 259 mortality.

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45 260 Despite of a similar seasonal shape across prefectures, seasonal amplitudes varied across 47
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47 261 prefectures. Previous studies have suggested that individuals living in cold locations show less
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49 262 seasonal variation in mortality, partially due to a better cold acclimatization from the
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51 263 combination of habituation, metabolic adjustment, and insulative acclimatization.^{8,29-31} In
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53 264 addition, less developed locations is likely to exhibit a larger seasonal variation in mortality,¹
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55 265 which can be related with high vulnerabilities to cold and heat effect of temperature because
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57 266 of poorer housing conditions, lower prevalence of air conditioning, and limited access to health
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3 267 care.^{18,23} In our study, we did not observe strong evidence for any associations between
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5 268 prefecture-specific characteristics and seasonal variations in mortality. This could be partially
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8 269 explained by the limited range of variations in the indicators and possible confounding effect
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10 270 between them. Furthermore, our data on the indicators are population-level, and future
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12 271 investigations with individual-level data is recommended to examine these issues.

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15 272 This study has several limitations. First, our study was conducted in Japan that has distinct
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17 273 seasonal weather conditions, hence our results may not be applicable to other areas with
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19 274 different climate (e.g., tropical countries). Second, we assumed the association of mortality
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21 275 with influenza and temperature did not change between 1999 and 2015, and our findings for
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23 276 2000 were sensitive to temperature adjustment. Furthermore, we observed some
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25 277 autocorrelation in the model residuals despite our attempts to model it (Figure S6). However,
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27 278 sensitivity testing showed that it had limited impacts on the estimate of seasonality (Table S4).
28
29 279 It is possible that the PTR on adjusting for influenza and temperature may be overestimated
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31 280 due to residual confounding as a result of error in measuring these variables.³² However, any
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33 281 such overestimation would be believed to be slight, as the main error here would be of Berkson
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35 282 type, which does not cause bias and hence not compromise confounder control.³³ Finally, future
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37 283 investigations should be conducted by extending current datasets to those areas with different
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39 284 climate, and also by including more details for influenza (e.g., influenza subtype and
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41 285 vaccination coverage). Results from these investigations would complement our findings in
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43 286 current analysis.

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46 287 This study presents findings from an epidemiologic analysis investigating the role of
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48 288 temperature, influenza and other local characteristics on seasonality of mortality across
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50 289 multiple locations. A strength of current study was the investigation of contributions of
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52 290 temperature versus influenza to seasonal variation of different types of mortality by a common
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3 291 study design and statistical framework, while previous studies mostly focused on either
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5 292 temperature or influenza only.
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8 293 This study suggests that seasonality of mortality is primarily driven by temperature.
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10 294 Furthermore, seasonal amplitudes varied between prefectures. However, this spatial variation
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12 295 was not explained by the differences in prefecture-specific characteristics on climate,
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14 296 demographic and socioeconomic factors, and adaptations. Further investigations are required
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16 297 to confirm our findings. In sum, this study can help us to gain a better understanding of
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18 298 seasonality of mortality.
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41 307 publish, or preparation of the manuscript.
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46 309 **Ethics approval:** This study used secondary data, with no possibility of personal identification,
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48 310 and an informed consent or an approval by a medical ethics board is not required.
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51 311 **Data availability statement:** Data are available upon reasonable request. The technical
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53 312 appendix, statistical code and data set will be available upon request from the Corresponding
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55 313 author.
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58 314 **References**
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408 **Figure captions:**

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

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

$$\text{Ratio} = \frac{\text{Mortality at day}_i}{\text{Minimum mortality at the trough}}$$

416

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

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Table 1. Nationwide summary of daily mean temperature (°C), 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.

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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)

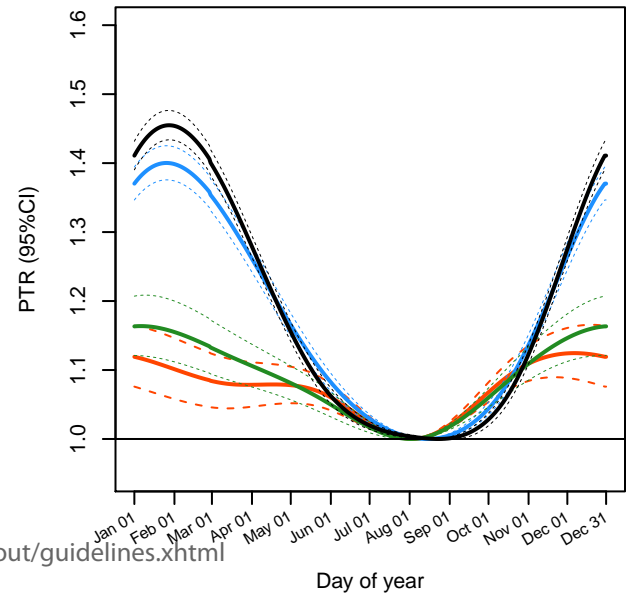
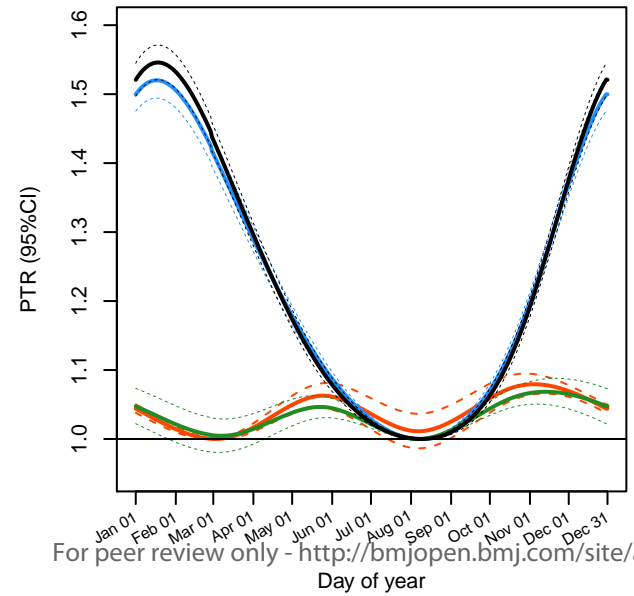
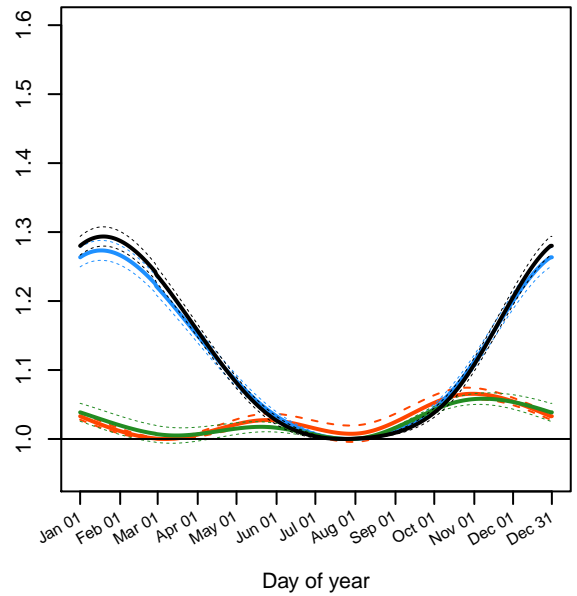
Adjustment	All-cause mortality		Circulatory mortality		Respiratory mortality	
	PTR	95% CI	PTR	95% CI	PTR	95% CI
None	1.29	1.28, 1.31	1.52	1.49, 1.55	1.45	1.43, 1.48
Temperature	1.06	1.05, 1.07	1.07	1.05, 1.09	1.16	1.12, 1.21
ILI	1.27	1.26, 1.29	1.52	1.49, 1.55	1.40	1.38, 1.43
Temperature + ILI	1.07	1.06,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

All-cause mortality

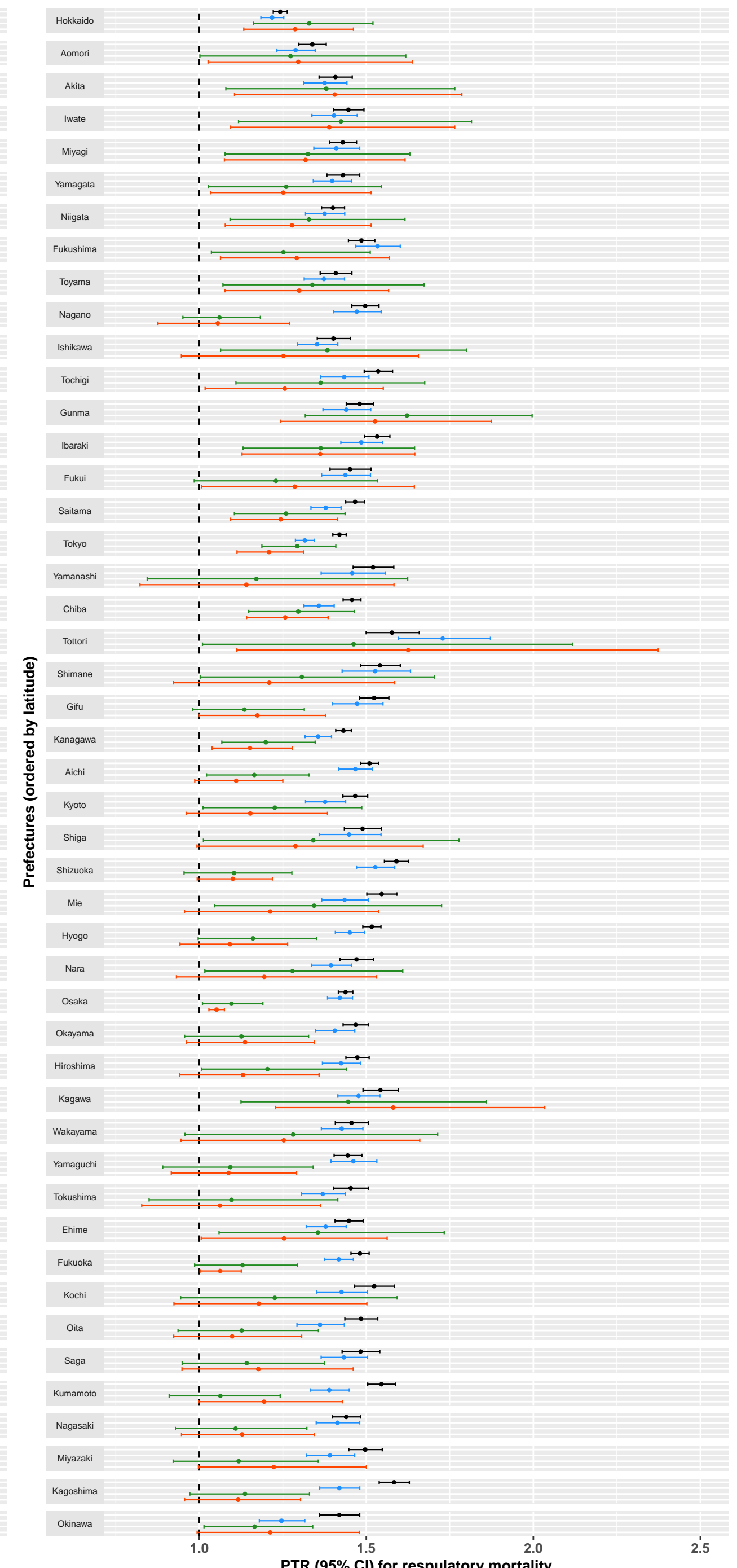
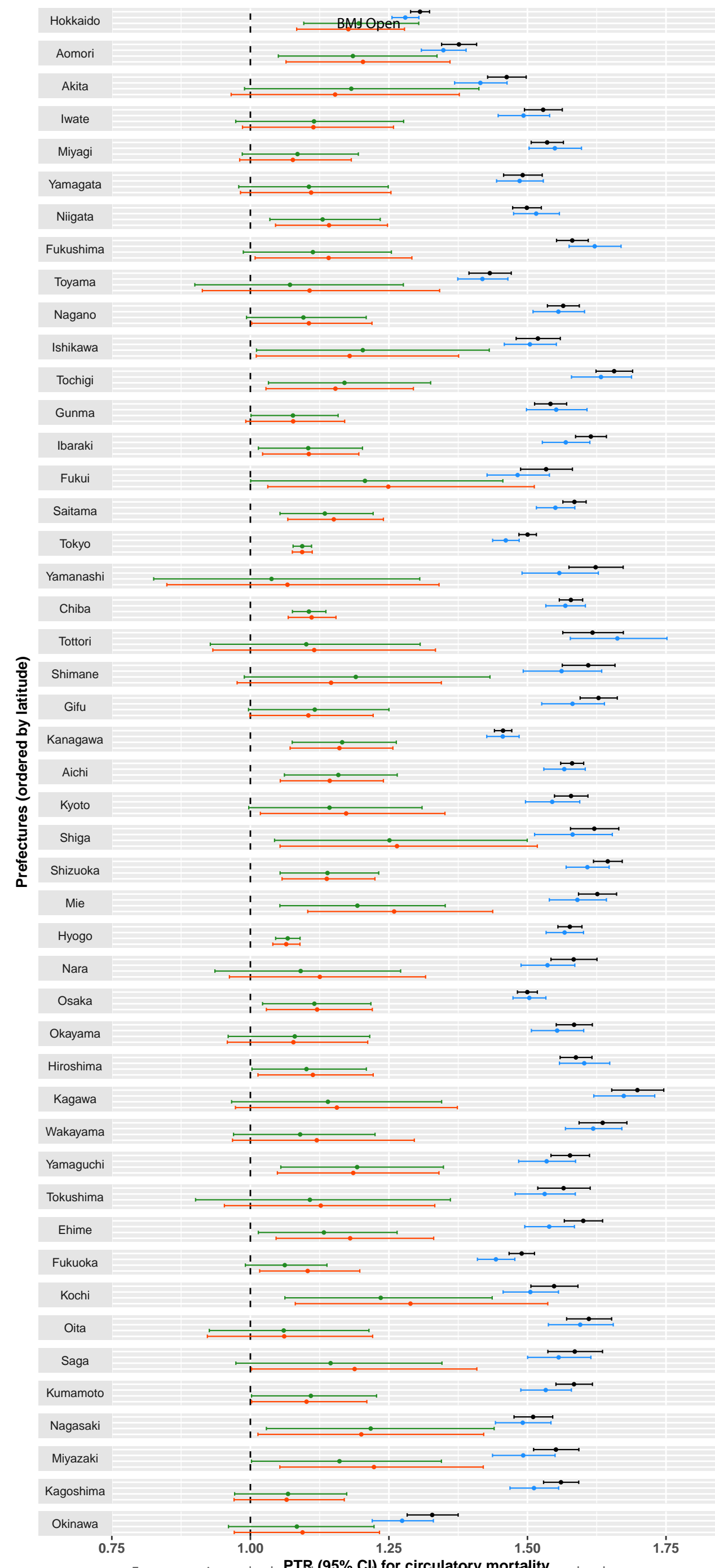
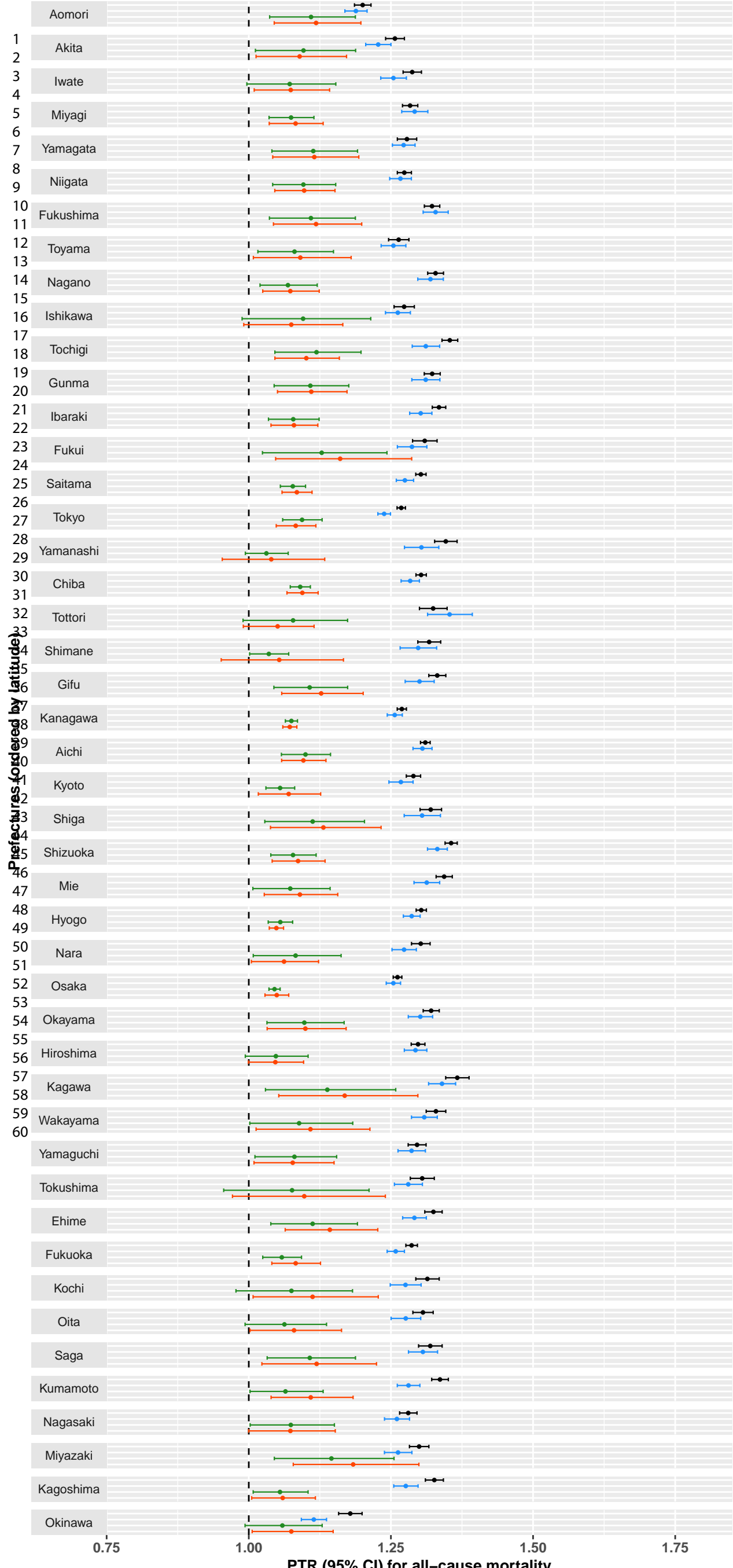
Cirulatory mortality

Respiratory mortality

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- No adjustment
- Adjusted for ILI
- Adjusted for temperature
- Adjusted for temperature and ILI



Supplementary material

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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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 (°C)		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 (°C)		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.

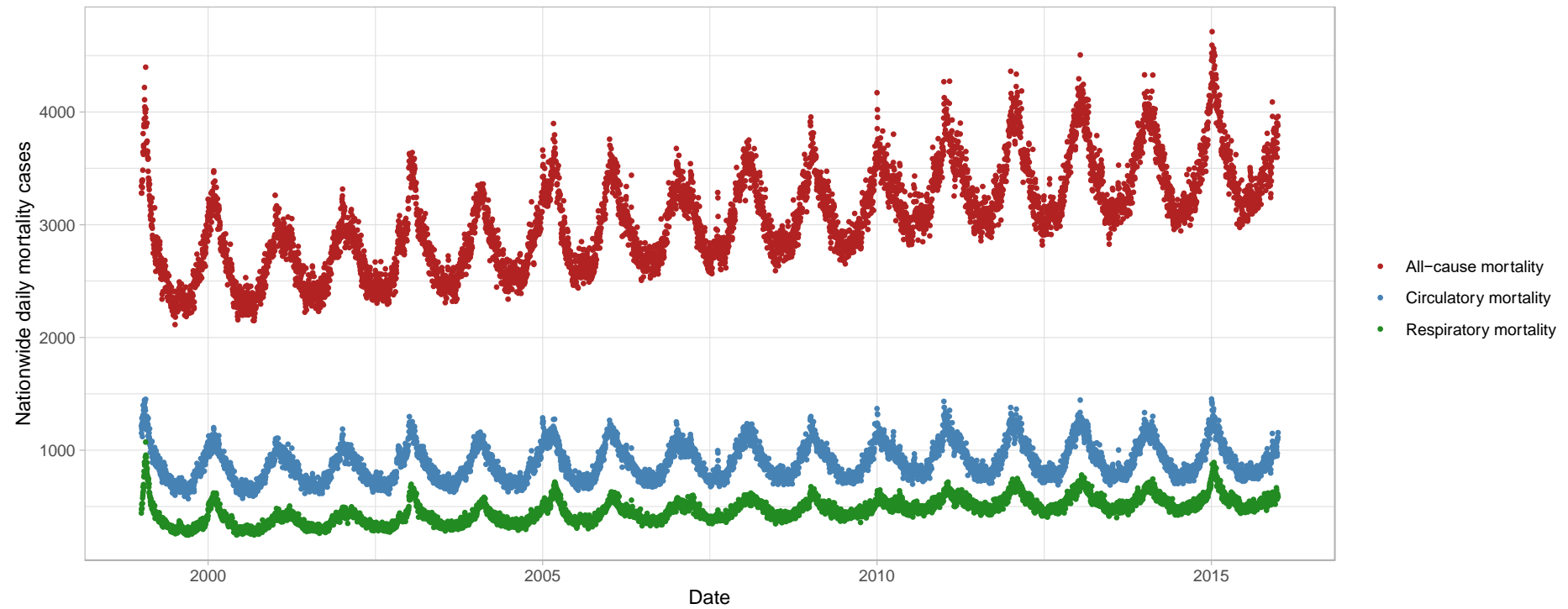


Figure S1. Time series of national wide daily mortality cases from all-cause, circulatory, respiratory disease and influenza between April 1999 and 2015

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. Statistics 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 (°C)	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]

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

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 (%)
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)

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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.

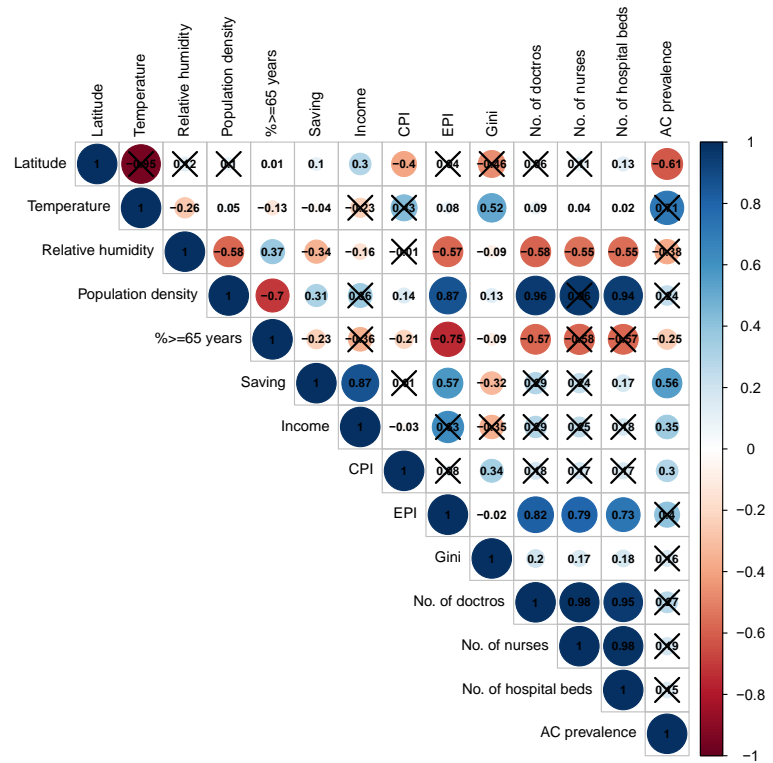


Figure S2. Correlations between the indicators.

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

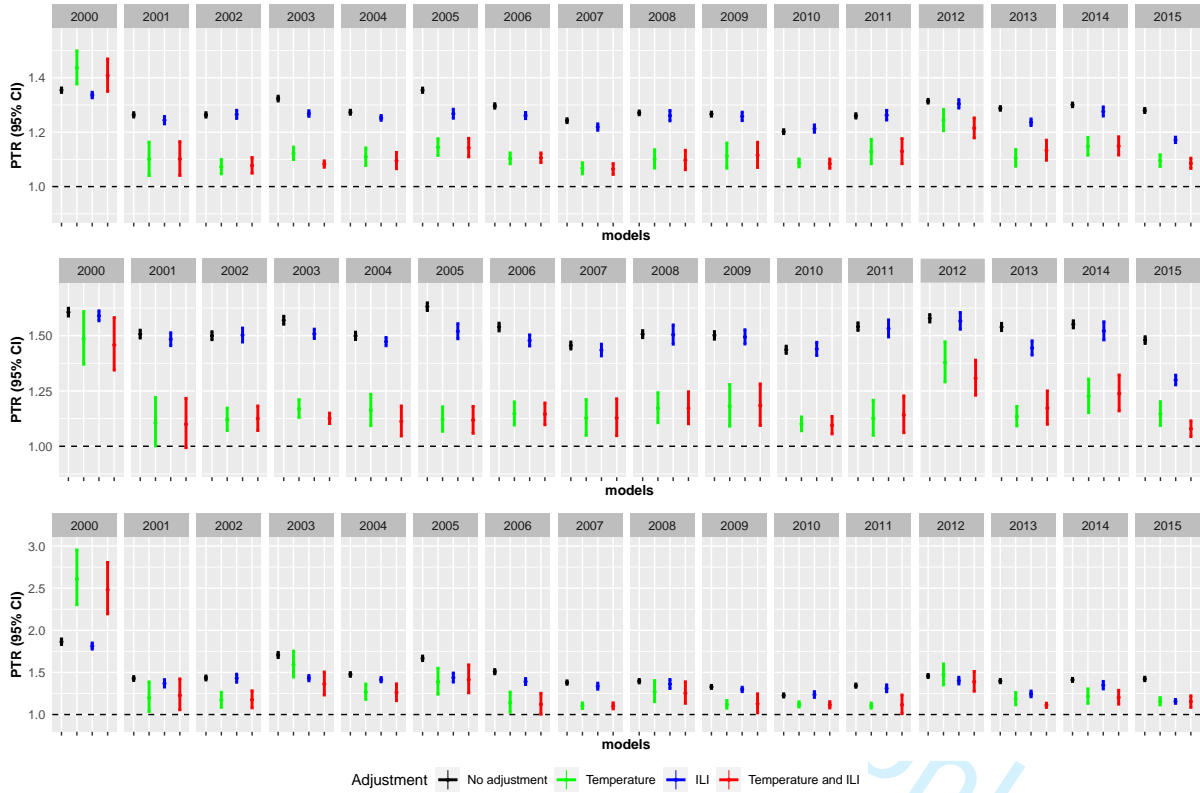


Figure S3. Peak-to-trough ratio (PTR) with 95% confidence intervals (95%CI) for each single year from 2000 to 2015 for all-cause (top), circulatory (middle), and respiratory (bottom) mortality before (black) and after adjustments for just influenza like illness (blue), just temperature (green), and both (red). Note: The year of 1999 was excluded from our yearly analyses, as ILI data was not available until April 1999.

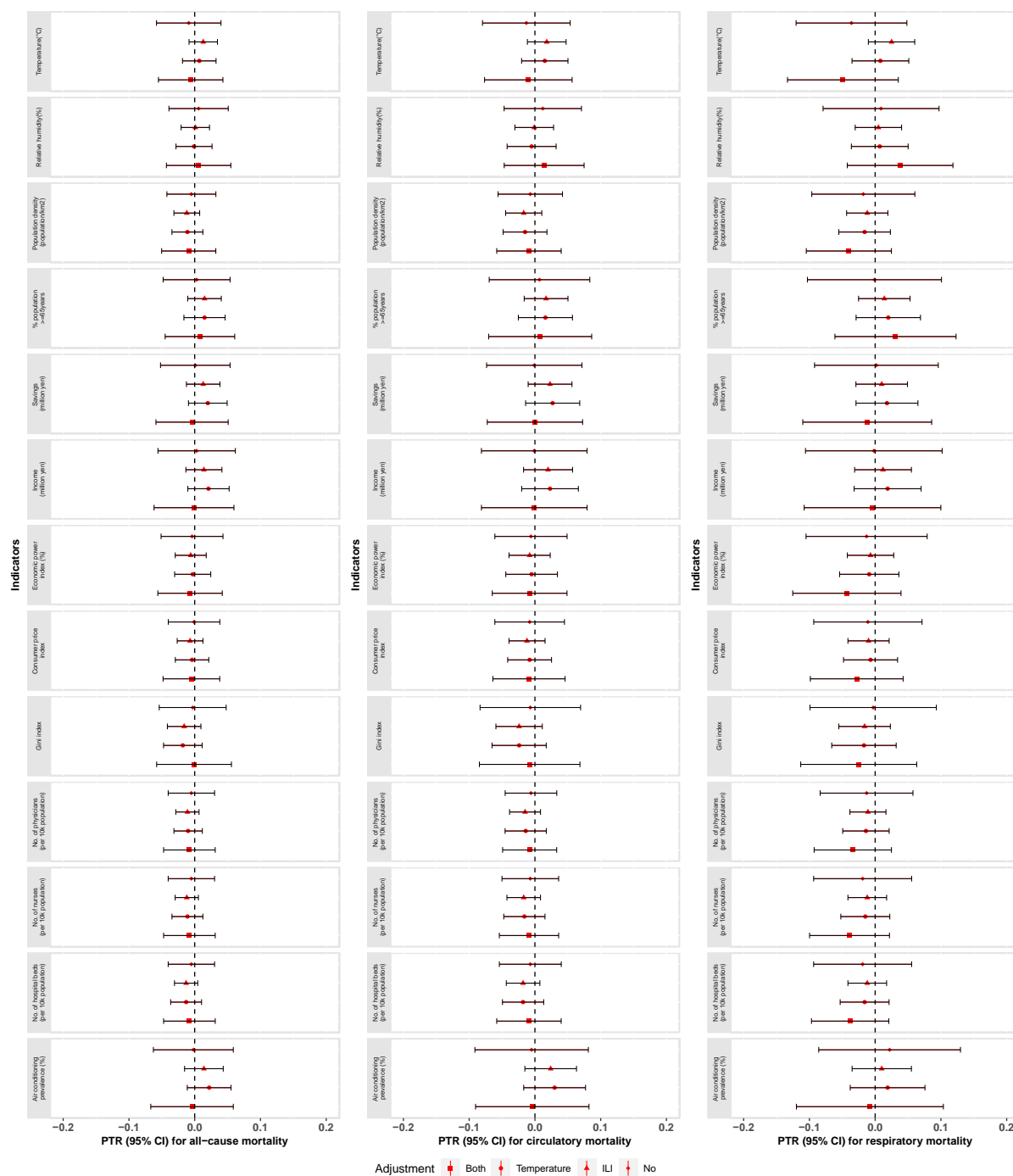


Figure S4. Associations between each indicator and PTR before and after adjusting for influenza like illness (ILI) and temperature

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.

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

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;

Y_t : 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 ;

$Strata_t$: 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;

$Temp_{t,l}$: 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.

$$\beta_i = \alpha + \gamma Z_i + \eta + v_i$$

β_i is the estimated coefficient for seasonality (i.e., $\log(\text{PTR})$) 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.

v_i is the variation within prefecture i , with the variance as $\sigma_{v_i}^2$

η represents the heterogeneity among prefectures with a variance of σ_η^2 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.

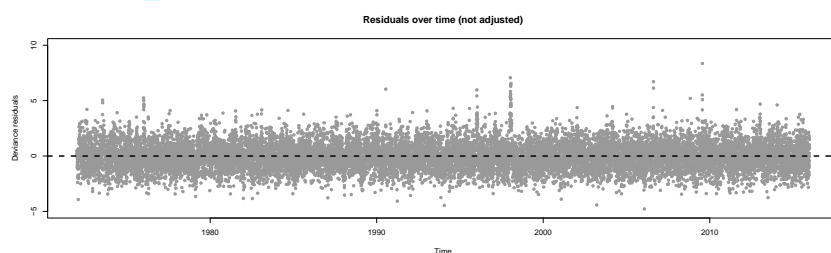


Figure S5. Deviance residuals over time from the analysis in Tokyo (without adjustment for temperature and/or influenza)

- 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).

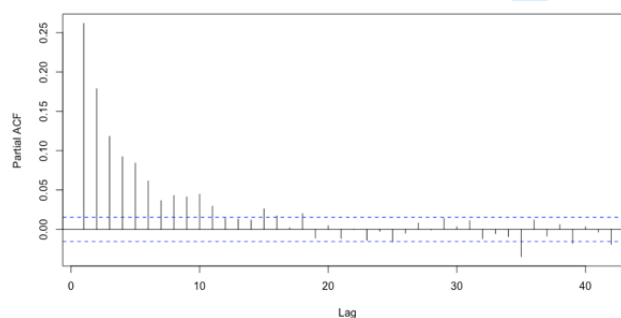


Figure S6. Partial autocorrelation function plot of the deviance residuals from the analysis in Tokyo (without adjustment for temperature and/or influenza)

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: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 4) + \lambda \text{Strata}_t$

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

Model 1: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 5) + \lambda \text{Strata}_t$

Model 2: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 6) + \lambda \text{Strata}_t$

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

Model 4: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 4) + \lambda \text{Strata}_t + \text{Lag}(\text{residuals}(\text{main model}), 1) +$

$\text{Lag}(\text{residuals}(\text{main model}), 2) + \text{Lag}(\text{residuals}(\text{main model}), 3)$

Model 5: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 4) + \lambda \text{Strata}_t + \text{Lag}(\text{residuals}(\text{main model}), 1) +$

$\text{Lag}(\text{residuals}(\text{main model}), 2) + \text{Lag}(\text{residuals}(\text{main model}), 3) + \text{Lag}(\text{residuals}(\text{main model}), 4) +$

$\text{Lag}(\text{residuals}(\text{main model}), 5) + \text{Lag}(\text{residuals}(\text{main model}), 6)$

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

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

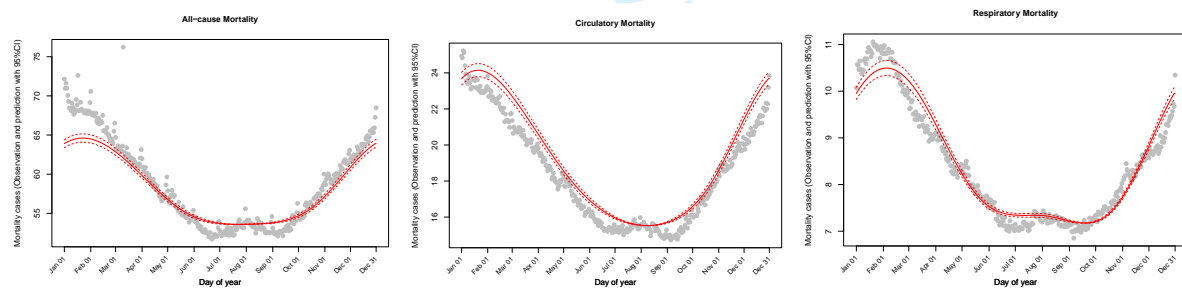


Figure S7. Daily mean number of observed all-cause, circulatory, and respiratory mortality in Japan averaged from 47 prefectures over the study period and estimated number of daily circulatory mortality from time series regression models (Main model)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	6-8

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —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.

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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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3 1 The role of temperature, influenza and other local characteristics in seasonality of mortality: a
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5 2 population-based time-series study in Japan
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25

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.

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3 49 **Strengths and limitations of this study**
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- 5 51 • We investigated the contributions of temperature versus influenza to seasonal variation of
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8 52 different types of mortality by a common study design and statistical framework.
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11 53 • We used indicators on a range of location-specific characteristics to investigate their
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13 54 modifying effect on seasonal variations in mortality.
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16 55 • The study was conducted in Japan characterized by distinct seasonal weather conditions,
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18 56 so our results may not be generalized to locations with different climate (e.g., tropical
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20 57 countries).
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22
23 58 • The deviance of residuals showed some autocorrelations, but it had limited impacts on our
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25 59 seasonality estimates.
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71 **Introduction**

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

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

90 The strength of seasonality in mortality varies geographically.⁸ For example, a larger seasonal
91 amplitude was observed in areas with milder climates, suggesting that individuals living in
92 warm areas might be more vulnerable to seasonal variations in mortality.² Several local
93 characteristics on climate, demographic and socioeconomic factors, and adaptations have been
94 linked with such spatial variation. However, only a few studies have evaluated their impact on
95 effect on seasonality of mortality.^{1,17} Another question remains unclear is if their impact effect

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3 96 will remain when we remove the effect of temperature and influenza from seasonal variations
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5 97 in mortality, given that the same local characteristics can also modify associations between
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7 98 influenza, temperature and mortality.¹⁸⁻²³
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10 99 In the current study, we collected daily mortality data between 1999 and 2015 from 47
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12 100 prefectures in Japan to investigate the contribution of temperature and influenza to seasonality
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14 101 of mortality as well as to study the associations between prefecture-specific indicators and
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16 102 seasonality of mortality. This study will strengthen our understanding of seasonality of
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18 103 mortality and provide important evidence to associate managements of seasonal risk factors to
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20 104 local conditions.
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25 105 **Method**

26 106 Data collection

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28 107 Hourly mean temperature (°C) and relative humidity (%) measured at a single monitoring site
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30 108 in the capital city of each prefecture were obtained from 1999 to 2015 from the Japan
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32 109 Meteorological Agency. We computed daily mean value of temperature and relative humidity
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34 110 for our analysis.
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40 111 Daily mortality (counts) from all-cause, circulatory, respiratory disease and influenza were
41
42 112 obtained from the Ministry of Health, Labor and Welfare of Japan between 1999 and 2015 for
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44 113 each prefecture in Japan. The principal cause of death statistics is coded using the International
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46 114 Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10).
47
48 115 Cause-specific mortality was defined according to the ICD system: circulatory mortality (ICD-
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50 116 10 codes I00-I99), and respiratory mortality (ICD-10 codes J00-J99). Weekly number of
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52 117 influenza like illness (ILI) were obtained for each prefecture from April 1999 to 2015 from
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54 118 National Institute of Infectious Diseases, Japan.
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3 119 Yearly data on prefecture-specific indicators was collected over the study period for each
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5 120 prefecture, including annual mean temperature, relative humidity, population density, the
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7 121 proportion of population aged ≥ 65 years, saving, income, Gini index (a measure of income
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9 122 inequality), consumer price index (CPI), economic power index (EPI, a measure of the wealth
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11 123 of a prefecture), the prevalence of air conditioning for households, and the number of registered
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13 124 physicians, nurses and hospital beds per 10K population. For each indicator, we computed the
14
15 125 averaged value across the years 1999-2015 for each prefecture. The details for data collection
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17 126 were described in previous studies^{24,25} and summarized in supplementary material.
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22 127 Data analysis

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25 128 We conducted our data analysis in three steps. First, we assessed seasonality of mortality
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27 129 without adjustments for temperature or ILI. Then, we examined the changes in the
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29 130 seasonality after adjusting for temperature and ILI separately, as well as both at the same
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31 131 time. Lastly, we evaluated the associations between each indicator and seasonality estimates
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33 132 before and after adjustments.
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36
37 133 We applied a generalized linear model with a quasi-Poisson family to assess seasonality of
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39 134 mortality in each prefecture without any adjustment for temperature and ILI. Day-of-year was
40
41 135 treated as an indicator for seasonality, taking values from 1 to 366 corresponding to Jan 1st
42
43 136 through Dec 31st for both common and leap years (from 60th day to 365th day in common
44
45 137 years, values were taken from 61 to 366). We used a cyclic cubic spline with 4 degrees of
46
47 138 freedom (*df*) for day of year to estimate seasonality. The days-of-year with maximum and
48
49 139 minimum mortality estimates from generalized liner models were identified as the peak and
50
51 140 trough days, respectively, and were subsequently used to calculate the peak-to-trough ratio
52
53 141 (PTR) to provide a measure of seasonality. When constructing confidence intervals for PTR,
54
55 142 previous studies enforced the boundary constraint by truncating the lower confidence limit at
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57 143 one for PTR.^{26,27} However, doing that may introduce a positive bias into the PTR.²⁸ In order to
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3 144 show the statistical variability in PTR, therefore, we did not truncate the lower confidence limit
4
5 145 at one for PTR. Indicators for year, day-of-week and their interaction were used to control for
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7
8 146 the long-term trend and the effect of day-of-week. We excluded the data on 11 March 2011,
9
10 147 the day of the Great East Japan Earthquake.

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12
13 148 To assess the contribution of temperature and ILI to seasonality of mortality, we attempted
14
15 149 three types of adjustment. First, we added temperature to our main model using a bi-
16
17 150 dimensional cross-basis function to account for its non-linear and delayed effect on mortality.
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19
20 151 We modeled the exposure-response curve with a natural cubic B-spline with three internal
21
22 152 knots at 25th, 50th, and 75th percentiles of temperature distribution, and the lag-response
23
24 153 association with another natural cubic spline basis with 3 *df* with extended lags up to 21
25
26 154 days.^{10,25}

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29 155 Second, we removed temperature and adjusted for ILI in main model. We assumed ILI cases
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31 156 distributed evenly across day of week and computed daily average ILI cases. A natural cubic
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33 157 spline with 3 *df* was then used to control for daily ILI cases in the model. Third, adjustment
34
35 158 was made using both temperature and influenza.

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38
39 159 The prefecture-specific PTR was pooled for the whole of Japan for all-cause, circulatory and
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41 160 respiratory mortality, respectively, by meta-analysis with prefecture as a random factor. To
42
43 161 explore if patterns of interest varied over time, we conducted yearly analyses for the entire
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45 162 country using separate quasi-Poisson regression model for each year with prefecture as a
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47 163 random factor.

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51 164 To evaluate the modification of seasonal variation in mortality by prefecture-specific indicators,
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53 165 we applied linear mixed effects models (LMEMs) to investigate associations of PTR with each
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55 166 prefecture-specific indicator separately. We fitted LMEMs with random intercepts for
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57 167 prefectures and the inverse of squared SE as weight. The longitude and latitude for the capital
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3 168 city of each prefecture were included to reduce spatial correlation, except for when we
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5 169 investigated annual mean temperature as the indicator, due to their high correlation. We
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7 170 conducted the analysis for all-cause, circulatory, and respiratory mortality in separate LMEMs.
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10 171 Results are expressed as the log(PTR) variation for a standard deviation increase of the
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12 172 indicator.

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14
15 173 We performed a series of sensitivity analysis to confirm our findings. We tested the cyclic
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17 174 spline function for day of year with different *df* of 5 and 6 and adjusted temperature by changing
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19 175 the spline function, internal knots for temperature distribution, *df* and lag days for the lag-
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21 176 response associations. For influenza adjustment, we varied the number of lag days using the
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23 177 moving averages of the previous 7, 14, 21 and 28 days, and tested the natural cubic spline
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25 178 function with 2 *df*. For ILI adjustment, we tested moving average of previous 7, 14, 21 and 28
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27 179 days for ILI cases, and 2 *df* for the natural cubic spline function. Overall, we did not observe
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29 180 substantial changes in our estimates.

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34 181 The models were summarized in supplementary material including diagnostic plots. We
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36 182 conducted the analysis with R software, version 3.6.0 (R Development Core Team) using the
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38 183 *dlnm* and *mixmeta* packages.

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41 184 Patient and public involvement

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43
44 185 There was no patient or public involvement.

45 46 47 186 **Results**

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50 187 This study included 18 985 036 deaths from all causes, 5 541 277 deaths from circulatory
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52 188 diseases, and 2 894 314 deaths from respiratory diseases. The nationwide time series of daily
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54 189 mortality showed a significant seasonal pattern (Figure S1). Daily mean temperature for the
55
56 190 whole country between 1999 and 2015 ranged from -1.0°C to 30.7°C, with a mean value at 15.6°C

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3 191 (Table 1). ILI cases showed a large variation, ranging from 7 case to 1 652 147 cases with a
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5 192 median value at 7626 (Table 1). Prefecture-specific summary was provided in Table S1.
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8 193 We observed a high variability for healthcare capacity (Table S2 & S3), while a low variability
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10 194 for socioeconomic indicators. Most of the indicators are correlated (Figure S2). In particular,
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12 195 EPI was highly correlated with population density, proportion of individuals aged over than 65
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14 196 years old, and numbers of physicians, nurses and hospital beds (correlation>0.70). In addition,
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16 197 saving is highly correlated with income (correlation>0.70).
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19
20 198 Figure 1 and Table 2 show the pooled results for the whole of Japan for seasonality of all-
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22 199 cause, circulatory, and respiratory mortality before and after adjustments for temperature
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24 200 and/or influenza. We observed a clear seasonal pattern with higher numbers of deaths in cold
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26 201 seasons than in warm seasons. Before any adjustments, the nationwide pooled PTR for all-
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28 202 cause, circulatory and respiratory mortality were 1.29 (95% confidence intervals (CI): 1.27,
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30 203 1.30), 1.52 (95% CI: 1.49, 1.55) and 1.45 (95% CI: 1.43, 1.48), respectively. After adjustments
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32 204 for temperature and ILI, the shape of seasonality remained (Figure 1), but its amplitude reduced
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34 205 to different extents. Adjusting for just temperature reduced PTRs substantially in particular for
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36 206 all-cause and circulatory mortality to 1.06 (95% CI: 1.05,1.07) and 1.07 (95% CI: 1.05, 1.09).
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38 207 Adjusting for just ILI reduced PTRs only very slightly to 1.27 (95% CI: 1.26,1.29), 1.52 (95%
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40 208 CI: 1.49,1.55), and 1.40 (95% CI: 1.38, 1.43) for all-cause, circulatory and respiratory mortality,
41
42 209 respectively. Notably, adjusting for temperature and ILI did not flatten the seasonal pattern or
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44 210 reduce the PTR to 1.
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50 211 Similarly, prefecture-specific PTRs also showed a substantial reduction with temperature
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52 212 adjustment while a slight reduction when ILI was adjusted only, although an apparent reduction
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54 213 was observed in ILI-adjusted PTR for respiratory mortality (Figure 2). Furthermore, PTR for
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56 214 all mortality types varied across prefectures, and the spatial variation after adjustments was
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58 215 less apparent in particular for all-cause and circulatory mortality. Prefectures with higher
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3 216 latitude (northern areas), including Hokkaido, Aomori, and Akita, as well as the southernmost
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5 217 prefecture- Okinawa, showed a lower unadjusted-PTR and a smaller reduction after
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8 218 adjustments for temperature.

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10 219 Our yearly analyses for the entire country showed a large reduction after adjusting for
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12 220 temperature while a small reduction after adjusting for ILI for most of the years (Figure S3).
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15 221 For the year of 2020, however, a higher PTR for all-cause and respiratory mortality was
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17 222 observed when temperature was included in the adjustment. We further checked the sensitivity
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19 223 of our estimates to temperature adjustment. Changing the lag period of 21 days in cross-basis
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21 224 function to 14 days reduced temperature-adjusted PTR, although it remained slightly higher
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23 225 than unadjusted PTR with a largely overlapped confidence intervals. The results for the other
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25 226 years did not change much (results not shown).

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28
29 227 Figure S4 shows associations between the indicators and PTR. There was no strong evidence
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31 228 for the association between prefecture-specific characteristics and seasonality estimates.
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33 229 Diagnostic plots for models were included in supplementary material (Figure S5-S7).

34 230 **Discussion**

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39 231 In this study, we investigated the contribution of temperature and influenza to seasonal
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41 232 variation of mortality in 47 prefectures of Japan and evaluated the modifications of seasonality
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43 233 by a range of prefecture-specific indicators. Our findings show that seasonal variation in
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45 234 mortality was substantially contributed by temperature and to a lesser extent, by influenza. In
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47 235 addition, seasonal amplitudes varied between prefectures. There was no strong evidence for
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49 236 the association between prefecture-specific characteristics and seasonal amplitudes.

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51 237 Temperature and influenza have been among the most studied drivers of seasonality of
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53 238 mortality.¹³⁻¹⁶ However, most of the investigations focused on either temperature or influenza.
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55 239 How much of seasonality of mortality is dependent on temperature versus influenza remain
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3 240 unsolved. Our finding showed that most of seasonality of mortality in Japan was attributable
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5 241 to temperature while little was driven by influenza. Consistent with our findings, a population
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7 242 -based cohort study in elderly British people examined month to month variation in mortality
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9 243 and its relationship with temperature and influenza A, and discovered that most of seasonal
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11 244 fluctuation was associated with cold temperature and a small component related with influenza
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13 245 A. Despite the smaller contribution of influenza to seasonal variation of mortality than
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15 246 temperature, our analysis suggested that influenza was accountable for seasonal variation,
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17 247 especially, for respiratory mortality. The transmission of influenza virus is most efficient under
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19 248 cold and dry conditions, which may lead to considerable increase in mortality during winter.
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21 249 For example, a study¹¹ in 48 U.S. cities observed a link between influenza epidemic and the
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23 250 irregularly high winter mortality in some certain years. Evidence thus far implies that
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25 251 temperature contributes substantially to seasonality of mortality in general, while influenza is
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27 252 related with seasonal variations of mortality to a less extent.
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29 253 Notably, removing the effect of temperature and influenza from seasonal variation in mortality
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31 254 did not completely flatten the seasonal pattern of mortality, in particular, respiratory mortality.
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33 255 Seasonality of mortality is resulted from complex interaction between human behavior and
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35 256 environment. In addition to temperature and influenza, other infectious diseases (e.g.,
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37 257 respiratory syncytial virus), air pollutants, behavioral changes based on a seasonal basis (e.g.,
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39 258 dietary pattern and physical activities) have been linked with seasonal variation of diseases and
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41 259 mortality. However, there is no direct evidence assessing their contribution to seasonality of
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43 260 mortality.
44
45 261 Despite of a similar seasonal shape across prefectures, seasonal amplitudes varied across 47
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47 262 prefectures. Previous studies have suggested that individuals living in cold locations show less
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49 263 seasonal variation in mortality, partially due to a better cold acclimatization from the
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51 264 combination of habituation, metabolic adjustment, and insulative acclimatization.^{8,29–31} In

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3 265 addition, less developed locations is likely to exhibit a larger seasonal variation in mortality,¹
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5 266 which can be related with high vulnerabilities to cold and heat effect of temperature because
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7 267 of poorer housing conditions, lower prevalence of air conditioning, and limited access to health
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9
10 268 care.^{18,23} In our study, we did not observe strong evidence for any associations between
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12 269 prefecture-specific characteristics and seasonal variations in mortality. This could be partially
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14 270 explained by the limited range of variations in the indicators and possible confounding effect
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16 271 between them. Furthermore, our data on the indicators are population-level, and future
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18 272 investigations with individual-level data is recommended to examine these issues.

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22 273 This study has several limitations. First, our study was conducted in Japan that has distinct
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24 274 seasonal weather conditions, hence our results may not be applicable to other areas with
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26 275 different climate (e.g., tropical countries). Second, we assumed the association of mortality
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28 276 with influenza and temperature did not change between 1999 and 2015, and our findings for
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30 277 2000 were sensitive to temperature adjustment. Furthermore, we observed some
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32 278 autocorrelation in the model residuals despite our attempts to model it (Figure S6). However,
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34 279 sensitivity testing showed that it had limited impacts on the estimate of seasonality (Table S4).
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36 280 It is possible that temperature and influenza adjusted PTR may be overestimated due to the
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38 281 measurement error in temperature and influenza.³² However, any such overestimation would
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40 282 be believed to be slight, as the main error here would be of Berkson type, which does not cause
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42 283 bias and hence not compromise confounder control.³³ Finally, future investigations should be
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44 284 conducted by extending current datasets to those areas with different climate, and also by
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46 285 including more details for influenza (e.g., influenza subtype and vaccination coverage). Results
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48 286 from these investigations would complement our findings in current analysis.

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52 287 This study presents findings from an epidemiologic analysis investigating the role of
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54 288 temperature, influenza and other local characteristics on seasonality of mortality across
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56 289 multiple locations. A strength of current study was the investigation of contributions of
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3 290 temperature versus influenza to seasonal variation of different types of mortality by a common
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5 291 study design and statistical framework, while previous studies mostly focused on either
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8 292 temperature or influenza only.
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10 293 This study suggests that seasonality of mortality is primarily driven by temperature.
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12 294 Furthermore, seasonal amplitudes varied between prefectures. However, this spatial variation
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15 295 was not explained by the differences in prefecture-specific characteristics on climate,
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17 296 demographic and socioeconomic factors, and adaptations. Further investigations are required
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20 297 to confirm our findings. In sum, this study can help us to gain a better understanding of
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22 298 seasonality of mortality.
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26
27 300 **Contributors:** LM conducted the study, analyzed the data and wrote the manuscript. CN and
28
29 301 XS helped with the statistical analysis and the discussion of the text. MT, LY and YH
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31 302 contributed to the final version of the manuscript. BA helped with the data analysis and the
32
33 303 interpretation of the results. MH contributed to the study design and the discussion of the results.
34
35

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37
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42
43 307 publish, or preparation of the manuscript.
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46 308 **Competing interests:** None declared.
47

48 309 **Ethics approval:** This study used secondary data, with no possibility of personal identification,
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50 310 and an informed consent or an approval by a medical ethics board is not required.
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53 311 **Data availability statement:** Data are available upon reasonable request. The technical
54
55 312 appendix, statistical code and data set will be available upon request from the Corresponding
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57 313 author.
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12 408 **Figure captions:**13
14 409 **Figure 1.** Pooled seasonality of all-cause, circulatory, and respiratory mortality between 199915
16 410 and 2015 before and after adjustments (black: without any adjustment; blue: adjusted for17
18 411 influenza like illness (ILI) only; green: adjusted for temperature only; red: adjusted for both19
20 412 temperature and ILI)21
22 413 *The seasonality is computed as the ratio of predicted mortality at each day of the year to the predicted minimum*23
24 414 *mortality at the trough with 95% confidence intervals (95% CIs):*

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$$\text{Ratio} = \frac{\text{Mortality at day}_i}{\text{Minimum mortality at the trough}}$$

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34 417 **Figure 2.** Prefecture-specific peak-to-trough ratio (PTR) with 95% confidence intervals (95%35
36 418 CI) for all-cause (left), circulatory (middle), and respiratory (right) mortality before (black)37
38 419 and after adjustments for influenza like illness (ILI) only (blue), temperature only (green),39
40 420 and both (red)41
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Table 1. Nationwide summary of daily mean temperature (°C), 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.

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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)

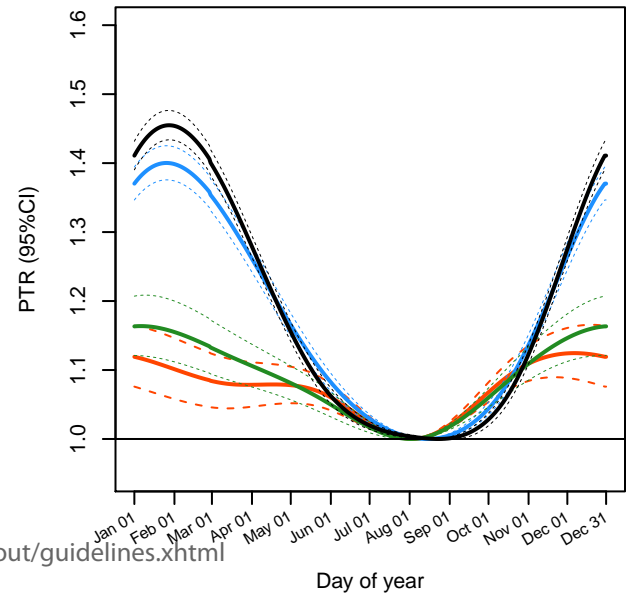
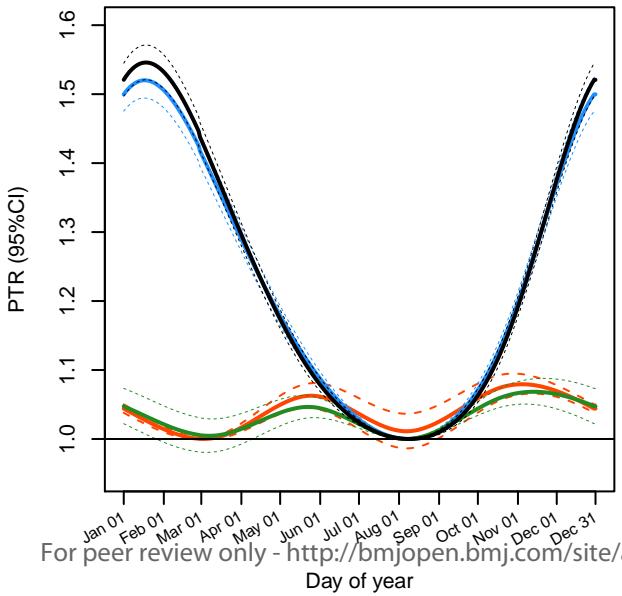
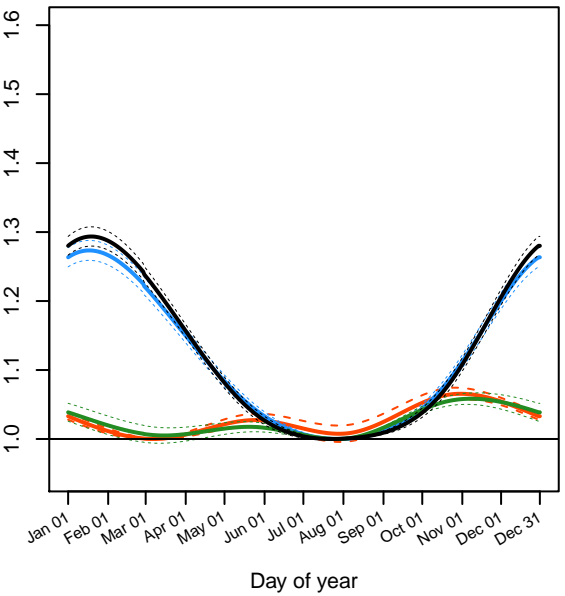
Adjustment	All-cause mortality		Circulatory mortality		Respiratory mortality	
	PTR	95% CI	PTR	95% CI	PTR	95% CI
None	1.29	1.28, 1.31	1.52	1.49, 1.55	1.45	1.43, 1.48
Temperature	1.06	1.05, 1.07	1.07	1.05, 1.09	1.16	1.12, 1.21
ILI	1.27	1.26, 1.29	1.52	1.49, 1.55	1.40	1.38, 1.43
Temperature + ILI	1.07	1.06,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

All-cause mortality

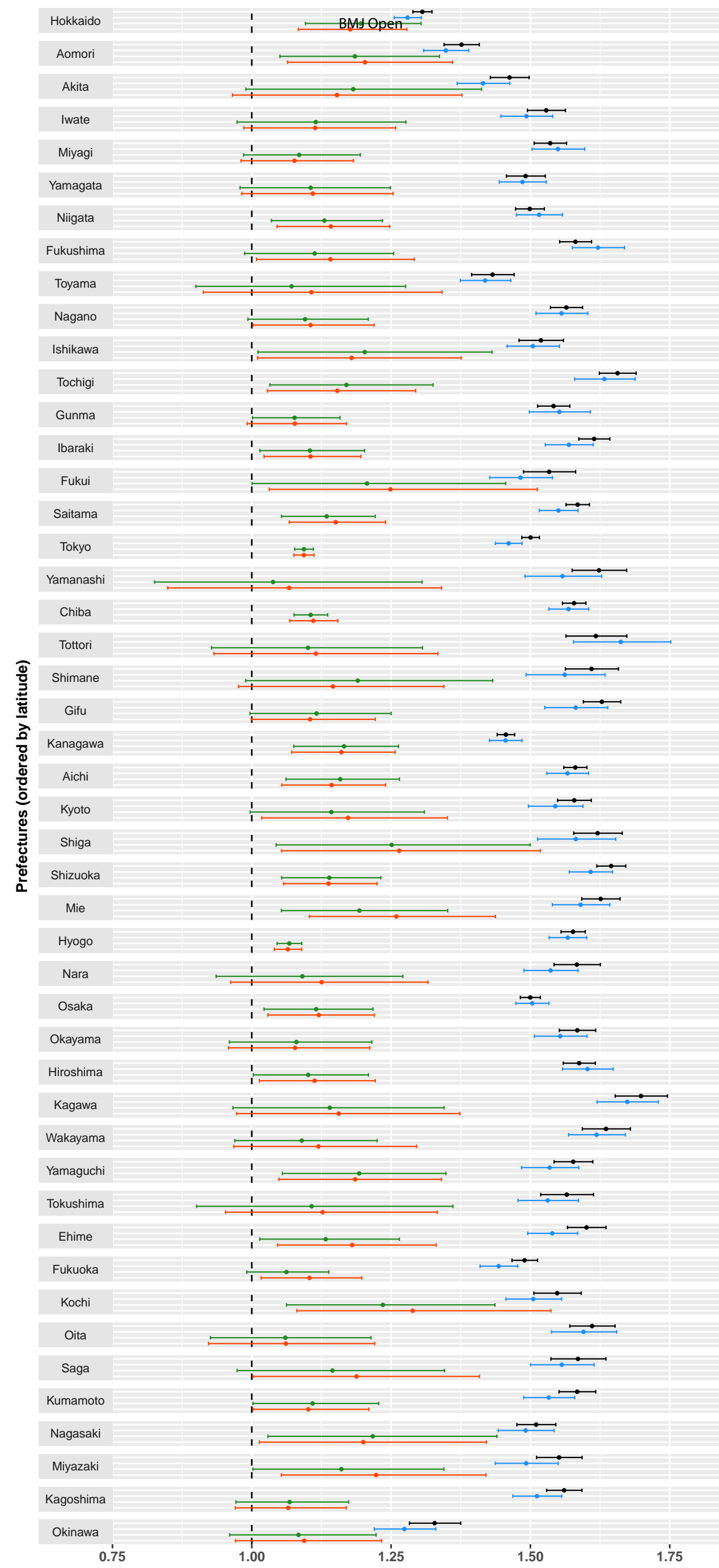
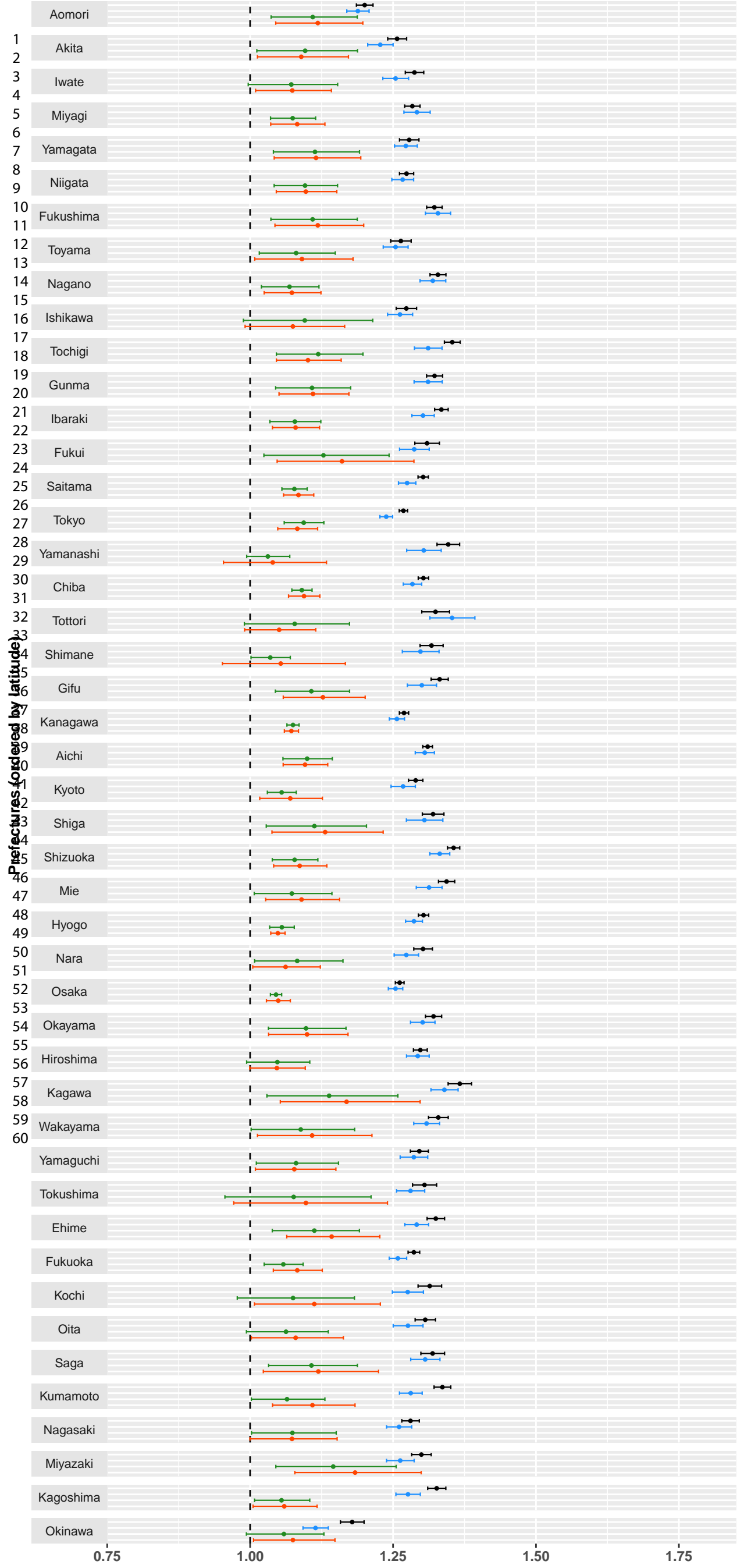
Cirulatory mortality

Respiratory mortality

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- No adjustment
- Adjusted for ILI
- Adjusted for temperature
- Adjusted for temperatruue and ILI



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Adjustment: Both (orange), Temperature (green), ILI (blue), No (black)

Supplementary material

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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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 (°C)		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 (°C)		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.

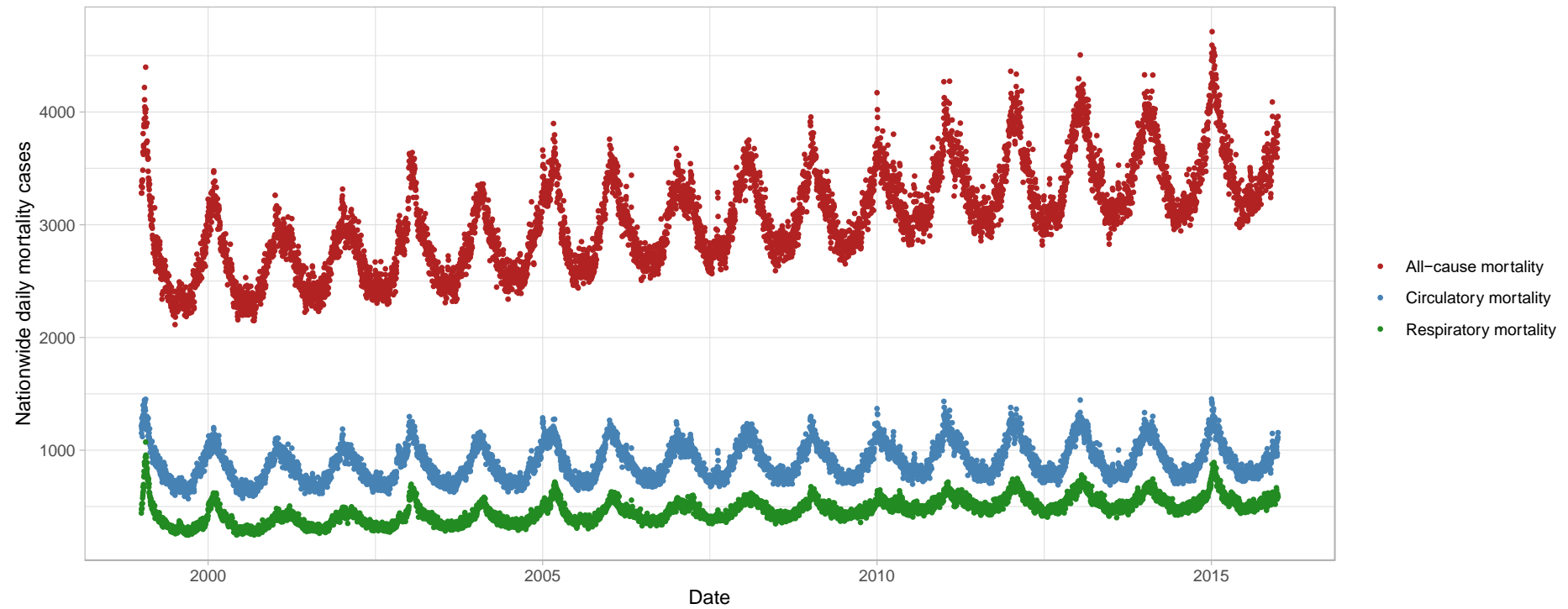


Figure S1. Time series of national wide daily mortality cases from all-cause, circulatory, respiratory disease and influenza between April 1999 and 2015

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. Statistics 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 (°C)	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]

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

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 (%)
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)

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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.

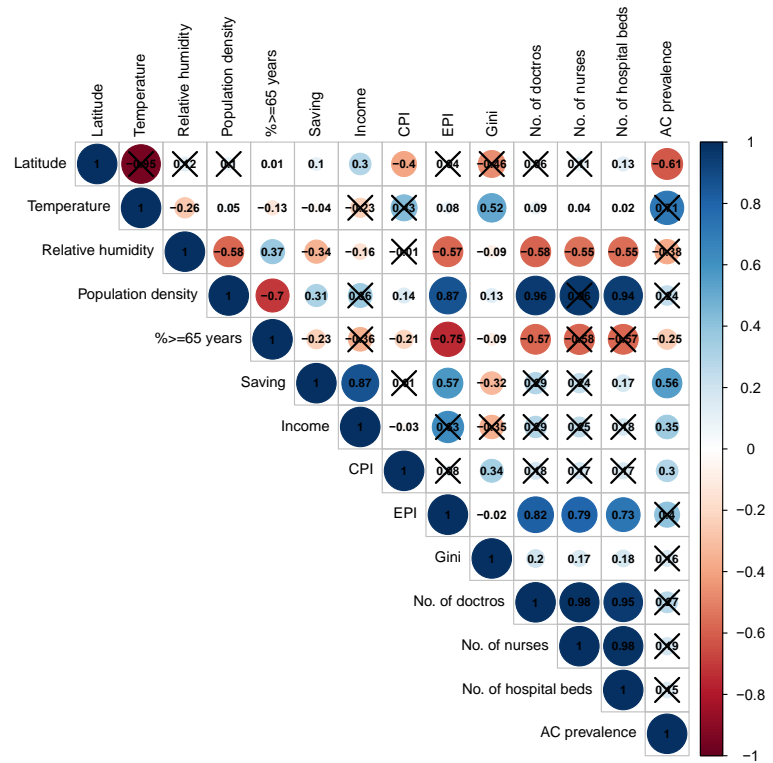


Figure S2. Correlations between the indicators.

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

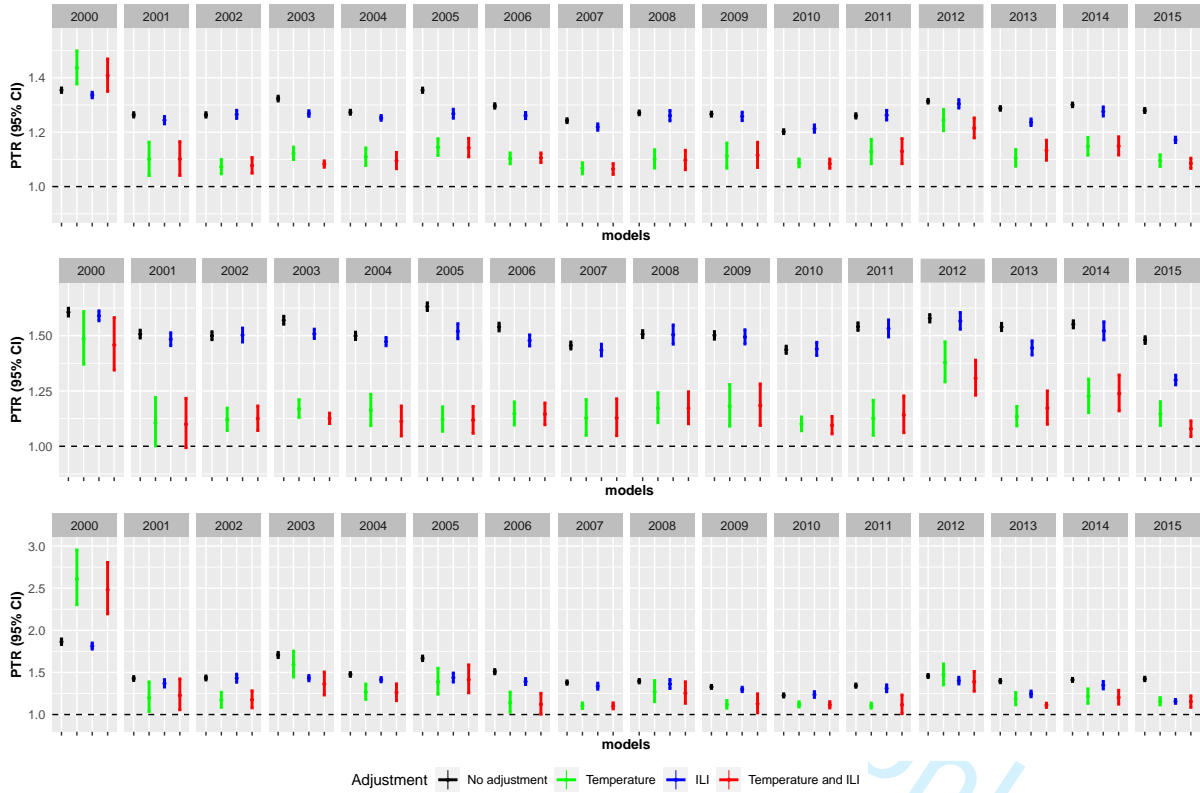


Figure S3. Peak-to-trough ratio (PTR) with 95% confidence intervals (95%CI) for each single year from 2000 to 2015 for all-cause (top), circulatory (middle), and respiratory (bottom) mortality before (black) and after adjustments for just influenza like illness (blue), just temperature (green), and both (red)
Note: The year of 1999 was excluded from our yearly analyses, as ILI data was not available until April 1999.

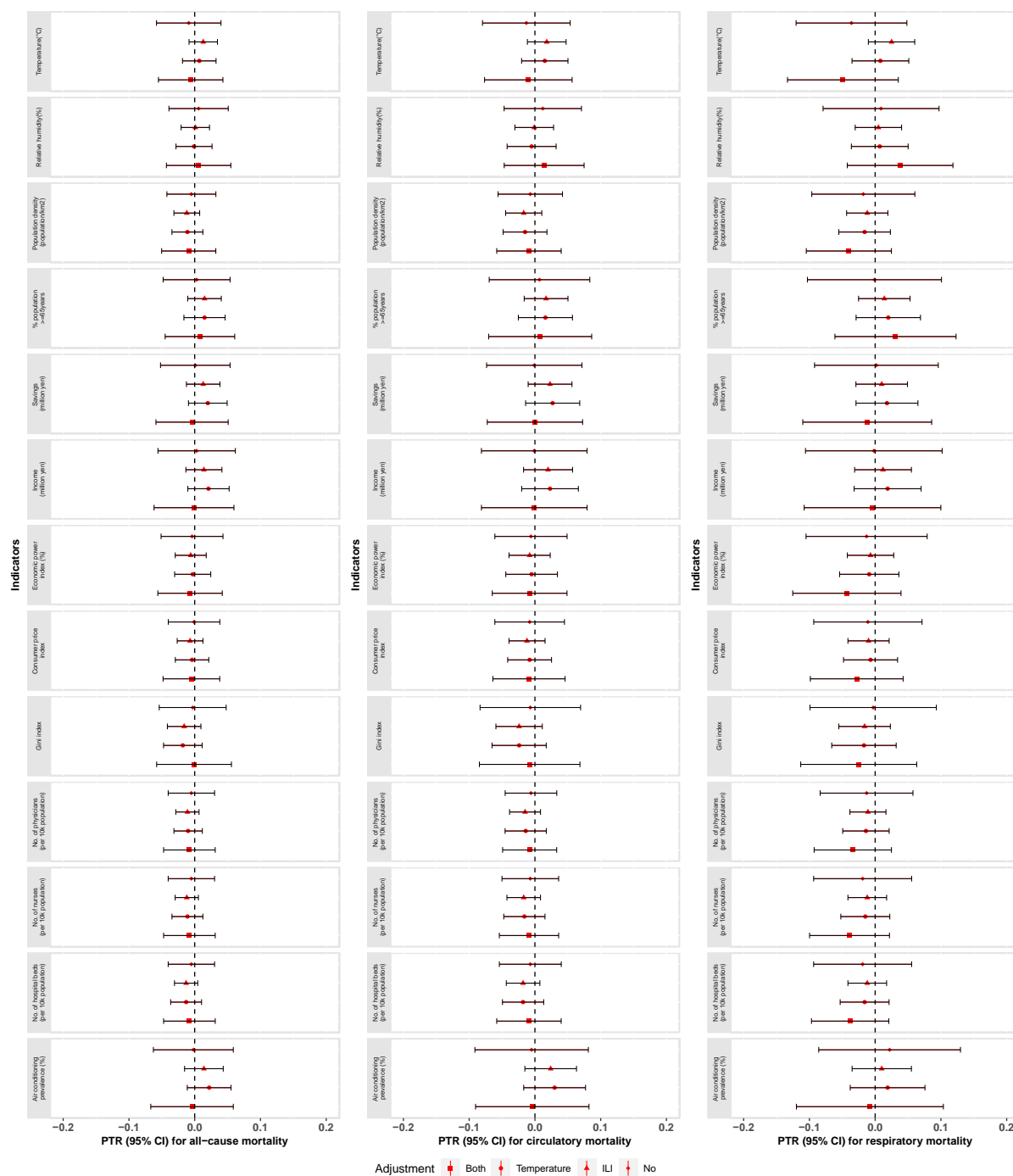


Figure S4. Associations between each indicator and PTR before and after adjusting for influenza like illness (ILI) and temperature

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.

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

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;

Y_t : 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 ;

$Strata_t$: 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;

$Temp_{t,l}$: 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.

$$\beta_i = \alpha + \gamma Z_i + \eta + v_i$$

β_i is the estimated coefficient for seasonality (i.e., $\log(\text{PTR})$) 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.

v_i is the variation within prefecture i , with the variance as $\sigma_{v_i}^2$

η represents the heterogeneity among prefectures with a variance of σ_η^2 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.

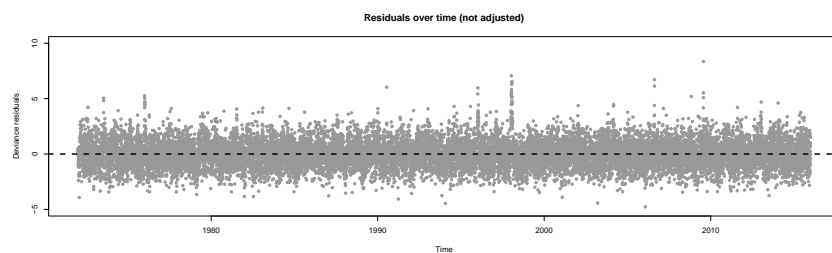


Figure S5. Deviance residuals over time from the analysis in Tokyo (without adjustment for temperature and/or influenza)

- 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).

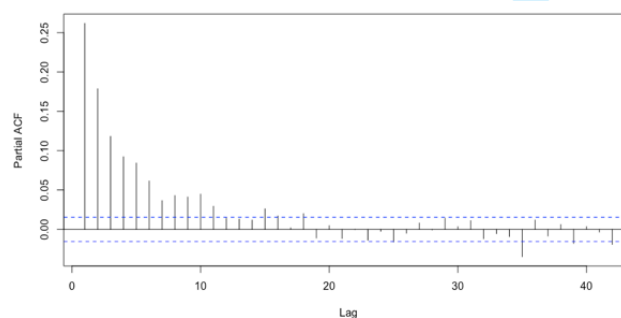


Figure S6. Partial autocorrelation function plot of the deviance residuals from the analysis in Tokyo (without adjustment for temperature and/or influenza)

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: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 4) + \lambda \text{Strata}_t$

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

Model 1: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 5) + \lambda \text{Strata}_t$

Model 2: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 6) + \lambda \text{Strata}_t$

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

Model 4: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 4) + \lambda \text{Strata}_t + \text{Lag}(\text{residuals}(\text{main model}), 1) +$

$\text{Lag}(\text{residuals}(\text{main model}), 2) + \text{Lag}(\text{residuals}(\text{main model}), 3)$

Model 5: $\log(\mu_t) = \beta_0 + cs(\text{day} - \text{of} - \text{year}, 4) + \lambda \text{Strata}_t + \text{Lag}(\text{residuals}(\text{main model}), 1) +$

$\text{Lag}(\text{residuals}(\text{main model}), 2) + \text{Lag}(\text{residuals}(\text{main model}), 3) + \text{Lag}(\text{residuals}(\text{main model}), 4) +$

$\text{Lag}(\text{residuals}(\text{main model}), 5) + \text{Lag}(\text{residuals}(\text{main model}), 6)$

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

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

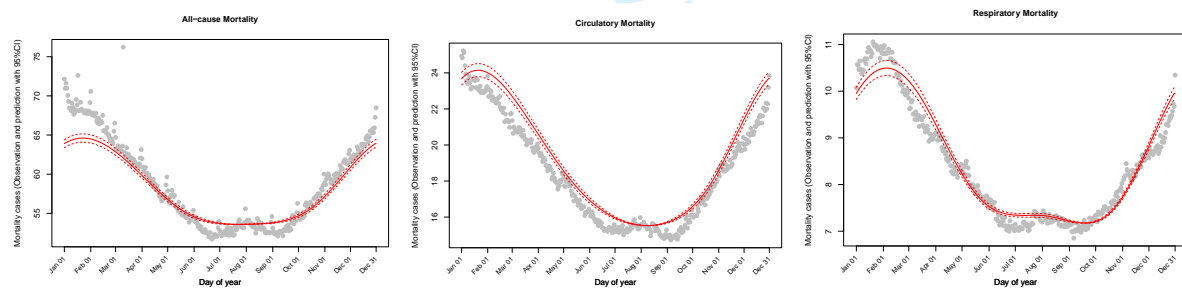


Figure S7. Daily mean number of observed all-cause, circulatory, and respiratory mortality in Japan averaged from 47 prefectures over the study period and estimated number of daily circulatory mortality from time series regression models (Main model)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	6-8

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —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.