




Original Article

Reduced mortality during the COVID-19 outbreak in Japan, 2020: a two-stage interrupted time-series design

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Abstract

Background: Coronavirus disease 2019 (COVID-19) continues to be a major global health burden. This study aims to estimate the all-cause excess mortality occurring in the

COVID-19 outbreak in Japan, 2020, by sex and age group.

Methods: Daily time series of mortality for the period January 2015–December 2020 in all 47 prefectures of Japan were obtained from the Ministry of Health, Labour and Welfare, Japan. A two-stage interrupted time-series design was used to calculate excess mortality. In the first stage, we estimated excess mortality by prefecture using quasi-Poisson regression models in combination with distributed lag non-linear models, adjusting for seasonal and long-term variations, weather conditions and influenza activity. In the second stage, we used a random-effects multivariate meta-analysis to synthesize prefecture-specific estimates at the nationwide level.

Results: In 2020, we estimated an all-cause excess mortality of –20 982 deaths [95% empirical confidence intervals (eCI): –38 367 to –5472] in Japan, which corresponded to a percentage excess of –1.7% (95% eCI: –3.1 to –0.5) relative to the expected value. Reduced deaths were observed for both sexes and in all age groups except those aged <60 and 70–79 years.

Conclusions: All-cause mortality during the COVID-19 outbreak in Japan in 2020 was decreased compared with a historical baseline. Further evaluation of cause-specific excess mortality is warranted.

Key words: All-cause death, COVID-19, excess mortality, Japan, two-stage interrupted time-series design

Key Messages

- We estimated the all-cause excess mortality occurring in the COVID-19 outbreak in Japan in 2020 by sex and age group.
- In 2020, we estimated an all-cause excess mortality of –20 982 deaths in Japan, which corresponded to a percentage excess of –1.7% relative to the expected value.
- Reduced deaths were observed for both sexes and in all age groups except those aged <60 and 70–79 years.

Introduction

Since the early reports of an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19) has had global impact, resulting in considerable morbidity, mortality and economic burden.¹ As of 24 March 2021, the global number of confirmed cases of COVID-19 across the globe stood at 123 902 242, including 2 727 837 deaths.^{2,3}

Estimation of the excess deaths resulting from COVID-19 is an important challenge since it quantifies the overall burden of COVID-19 compared with a baseline level.⁴ Several studies have reported significant excess COVID-19 mortality in the USA and European countries.^{4–11} However, despite early exposure, high population density and ageing, and no strict quarantine or lockdown measures, Japan has had one of the lowest number of COVID-19 deaths in the world.¹² Although several studies have reported excess mortality during the COVID-19 epidemic in Japan,^{13,14} these

analyses were based on monthly or weekly data on shorter periods (from January to May or July 2020), used different reference periods (mean monthly mortality in 2 years or 3 weeks before and after a certain point for ≤ 5 years ago) and did not adjust for seasonal influenza activity, ambient temperature and temporal trends and variations in these confounding factors. The pandemic of COVID-19 is ongoing and it is difficult to cover the entire pandemic in Japan. However, to gain a better understanding of the impact of the disease on mortality in Japan, use of more detailed data over a longer period is essential. Additionally, few studies have accounted for weather factors, influenza epidemics, seasonality and long-term trends. These potential biases might affect interpretation of the results and resolving them requires quantification of excess mortality using more precise modelling methods. Understanding patterns of excess mortality in Japan offers an opportunity to identify whether Japan's unique approach to COVID-19 control, based on limited voluntary lockdowns and case isolation following

World Health Organization (WHO) guidelines, is associated with a different pattern of mortality than the approach in hard-hit nations.

Here, we examined overall excess mortality in the COVID-19 outbreak across all 47 prefectures in Japan, with stratification by sex and age group. Assessment of excess mortality was based on official mortality data obtained from the Ministry of Health, Labour and Welfare, Japan.

Methods

Data

We obtained the number of daily deaths, with stratification by sex and age group in 2015–2020 in all 47 prefectures of Japan from the Ministry of Health, Labour and Welfare. The data included complete daily totals for 2015–2019 and early-release data of 2020. Vital statistics in Japan are surveyed based on the Family Register Act and all registries of vital statistics are thought to be complete. We also obtained data on average daily temperatures in 2015–2020 from the Japan Meteorological Agency.¹⁵ For this, data were sourced from one weather station within an urban region of each prefectural capital city. Measurements were made hourly across 24 hours and averaged to yield average daily temperatures. Furthermore, we obtained national surveillance data on weekly influenza cases in 2015–2020 in all 47 Japanese prefectures from the National Institute of Infectious Diseases.¹⁶ The daily number of influenza cases was calculated by converting weekly surveillance data to daily values using a uniform distribution of events over 1 week. Mortality counts were summed by prefecture in a sex- and age-specific daily time series and were then associated with daily mean temperature and incidence of influenza cases.

Statistical analysis

We used a two-stage interrupted time-series design to estimate the time-varying excess mortality in Japan during the COVID-19 outbreak in comparison with the pre-outbreak period, which accounted for temporal trends and variations in other risk factors, as detailed elsewhere.¹⁰ In the first stage, we used a quasi-Poisson-regression model:¹⁷

$$\log[E(Y_{it})] = \alpha + b_1(\text{days from first COVID19 case}; \theta_i) + \text{date} + b_2(\text{day of the year}; \gamma_i) + \text{dow} + f(T_{it}, \ell; \beta_i) + \text{flu} + \sum_{l=1}^{28} \log(Y_{it-l})$$

where Y_{it} denotes daily deaths observed at time t in prefecture i .

The first component b_1 (*days from first COVID19 case; θ_i*) represents the spline function that models temporal excess mortality associated with the COVID-19 outbreak and was defined using a constrained quadratic B-spline system. Three equally spaced knots were used in the spline terms to control the smoothness for days from 14 January (date of first confirmed COVID-19 case) to 31 December 2020; the choice of the number of internal knots was based on the smallest Quasi-Akaike Information Criterion (QAIC) (Supplementary Table S9, available as Supplementary data at IJE online).

To deal with time-varying confounders (or nuisance variables), we included a linear term for date to control for long-term trends, a cyclic cubic B-spline with 5 degrees of freedom (df) for day of the year b_2 (*day of the year; γ_i*) to account for seasonality, as well as dummy indicators for the day of the week (*dow*) to control for weekly variation in mortality. To control for potential differences in underlying mortality arising from the non-optimal temperature between the pre-outbreak and outbreak periods, we model the complex relationship between temperature and mortality characterized by non-linearity and delayed (lagged) effects along the lag ℓ as a cross-basis term $f(T_{it}, \ell; \beta_i)$ of distributed lag non-linear models.¹⁸ In the cross-basis parameterization, we considered a natural cubic-spline function for the temperature with three internal knots, set at the 10th, 75th and 90th percentiles of prefecture-specific empirical distributions of the temperature and we considered the lags of ≤ 21 days to account for the delayed impact of temperature.¹⁹ Influenza terms with lags of ≤ 14 days (*flu*) were included to control for potential confounding of influenza epidemics and their delayed effects.^{4,11} To allow for autocorrelations, an autoregressive term of lagged deaths counts (≤ 28 days) $\sum_{l=1}^{28} \log(Y_{it-l})$ was incorporated into the models.²⁰ We checked the dispersion parameter (average of 1.066 in our data), model residuals, observed and fitted values, autocorrelation and partial autocorrelation function of the residuals to determine adequate adjustment for seasonal trends (Supplementary Figures S1–S4, available as Supplementary data at IJE online).

In the second stage, we evaluated prefecture-based coefficients θ_i that characterize the excess mortality during the COVID-19 outbreak using a random-effects multivariate meta-analysis model to synthesize the prefecture-specific estimates of coefficients θ_i at the nationwide level.²¹ We then calculated the best linear unbiased prediction (BLUP) estimated at the prefecture level $\hat{\theta}_{bi}$. The BLUP estimate represents a trade-off between specific-to-prefecture and pooled-among-prefectures associations, which enables areas with small numbers of daily cases to use information obtained from larger populations that share similar characteristics and thus stabilizes the estimates.²² The Cochran's

Q test, which asymptotically follows the chi-squared distribution with the df of 46, were used to assess the heterogeneity between prefectures. This approach has been widely studied in the two-stage time-series design or individual patient data meta-analysis.^{21–24}

Nationwide and prefecture-specific estimates were used to calculate the relative risk (RR) of excess mortality in each prefecture for every day of the outbreak period. In particular, every day of the outbreak period was represented using the quadratic B-spline system and the nationwide and BLUP prefecture-specific estimates applied to the spline values. The obtained predicted values were then exponentiated obtaining the RR of excess mortality for every day of the outbreak period. The daily number of excess deaths was calculated as $n^*(RR-1)/RR$, in which n is the number of deaths per day. We calculated empirical confidence intervals (eCIs) with 1000 Monte Carlo simulations established using a multivariate normal distribution for the BLUPs for the reduced coefficients. This approach has been tested in a similar context before.^{18,23,25} Stratified analysis was performed by sex and age groups (<60, 60–69, 70–79, 80–89 and ≥ 90 years).

Statistical analyses were performed using the packages *dlnm* and *mvmeta* in R 3.6.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Total deaths, estimated excess deaths and percentage excess in mortality during the period 13 February–31 December 2020 in Japan are summarized in Table 1. In this period, 1 190 409 deaths were registered in Japan, with an estimated excess of –20 982 deaths (95% eCI: –38 367 to –54 72) relative to the expected baseline mortality. This corresponds to a percentage excess of –1.7% (95% eCI: –3.1 to –0.5), indicating that mortality was slightly lower in 2020 than would have been expected given national trends. Among the 47 prefectures, 46

prefectures had the negative percentage of total excess mortality, with the exception of Hyogo Prefecture [0.2% (95% eCI: –1.0 to 1.3)]. Descriptive statistics before and during the COVID-19 pandemic by prefecture are reported in Supplementary Table S1 (available as Supplementary data at *IJE* online). The number of observed and estimated excess deaths (95% eCI) during the period 13 February–31 December 2020 by prefecture is shown in Supplementary Table S2 (available as Supplementary data at *IJE* online).

In the sex-stratified analysis, there were –8021 excess deaths in men (95% eCI: –15 155 to –1779), corresponding to a percentage excess of –1.3% (95% eCI: –2.4 to –0.3). The same estimate for women was –14 561 (95% eCI: –19 506 to –9685), corresponding to a percentage excess of –2.5% (95% eCI: –3.3 to –1.6).

In the age-stratified analysis, there were 2213 excess deaths (95% eCI: 386 to 3895) in the <60-years age group, –4662 (95% eCI: –7972 to –1492) in the 60– to 69-years age group, 4153 (95% eCI: 23 to 8080) in the 70– to 79-years age group, –11 995 (95% eCI: –18 517 to –6138) in the 80– to 89-years age group and –13 604 (95% eCI: –20 585 to –7189) in the ≥ 90 -years age group. The percentage of excess mortality was 3.1% (95% eCI: 0.5 to 5.6) in the <60-years age group, –4.5% (95% eCI: –7.5 to –1.5) in the 60– to 69-years age group, 1.7% (95% eCI: 0.0 to 3.4) in the 70– to 79-years age group, –2.7% (95% eCI: –4.2 to –1.4) in the 80– to 89-years age group and –3.8% (95% eCI: –5.7 to –2.1) in the ≥ 90 -years age group.

Temporal changes in excess risk of mortality during the period 14 January–31 December 2020 in Japan by sex and age group are shown in Figure 1. We found that the total excess risk of mortality started decreasing below the baseline at the beginning of January and continued to remain low. From around September, the total excess risk gradually started increasing and the peak was reached around the beginning of November. The temporal distribution of excess-mortality risk is consistent in both sex and age

Table 1 Number of observed and estimated excess deaths (95% empirical confidence interval) during the period 13 February–31 December 2020 in Japan

	Total deaths	Excess deaths	Percentage excess
Total	1 190 409	–20 982 (–38 367 to –54 72)	–1.7 (–3.1 to –0.5)
Sex			
	Males	–8021 (–15 155 to –1779)	–1.3 (–2.4 to –0.3)
	Females	–14 561 (–19 506 to –9685)	–2.5 (–3.3 to –1.6)
Age			
	<60	2213 (386 to 3895)	3.1 (0.5 to 5.6)
	60–69	–4662 (–7972 to –1492)	–4.5 (–7.5 to –1.5)
	70–79	4153 (23 to 8080)	1.7 (0.0 to 3.4)
	80–89	–11 995 (–18 517 to –6138)	–2.7 (–4.2 to –1.4)
	≥ 90	–13 604 (–20 585 to –7189)	–3.8 (–5.7 to –2.1)

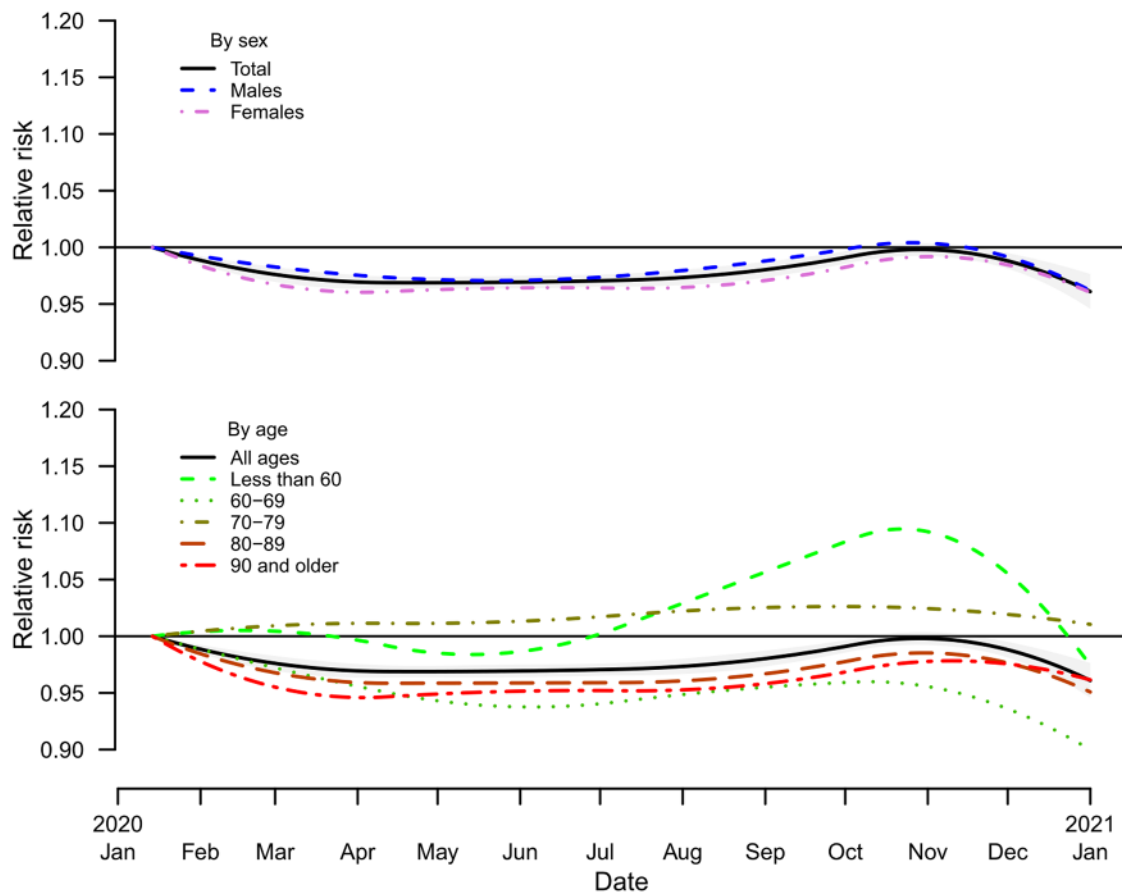


Figure 1 Trends in estimated excess risk (relative risk) during the period 14 January–31 December 2020 in Japan by sex and age groups compared with the total (band corresponds to 95% empirical confidence intervals)

groups, with an indication of an increase in the <60- and 70- to 79-years age groups. Temporal changes in excess mortality by prefectures and pooled estimates are shown in [Supplementary Figure S5](#) (available as [Supplementary data](#) at *IJE* online). Consistently with the country-pooled estimates, similar waveforms were observed for prefecture-specific estimates. The spatial distribution of percentage excess in mortality during the period 14 January–31 December 2020 in the 47 prefectures of Japan in total and stratified by sex and age groups are shown in [Figure 2](#). There was spatial heterogeneity in the excess mortality between prefectures (Cochran Q test, $p < 0.001$; $I^2 = 27.3\%$).

The dispersion parameters, plots of model residuals, observed and fitted time-series plots, autocorrelation and partial autocorrelation function of the residuals suggested that our model had an adequate amount of adjustment for seasonal trends ([Supplementary Figures S1–S4](#), available as [Supplementary data](#) at *IJE* online). We also performed sensitivity analyses to evaluate whether these findings were sensitive to the levels of control for influenza activity, ambient temperature and the number of knots (four, five and six) in the interrupted spline component. The sensitivity

analysis revealed that the temporal changes in excess mortality were consistent with the main analysis and the obtained curves identify the pandemic as one continuous until November, rather than small waves that clearly depend on the number of knots chosen ([Supplementary Figure S6](#), available as [Supplementary data](#) at *IJE* online). The estimates of excess deaths and percentage excess obtained using sensitivity analyses are reported in [Supplementary Tables S3–S8](#) (available as [Supplementary data](#) at *IJE* online). The QAICs for the main model and each sensitivity analysis are reported in [Supplementary Table S9](#) (available as [Supplementary data](#) at *IJE* online). The sensitivity analysis found that total excess deaths ranged between $-28\,834$ (95% eCI: $-33\,025$ to $-24\,510$) and $-18\,476$ (95% eCI: $-24\,939$ to $-11\,957$), corresponding to a percentage excess of -2.4 (95% eCI: -2.7 to -2.0) and -1.5 (95% eCI: -2.1 to -1.0).

Discussion

We estimated the all-cause excess mortality during the COVID-19 outbreak in Japan using a two-stage interrupted time-series design and flexible statistical methods.

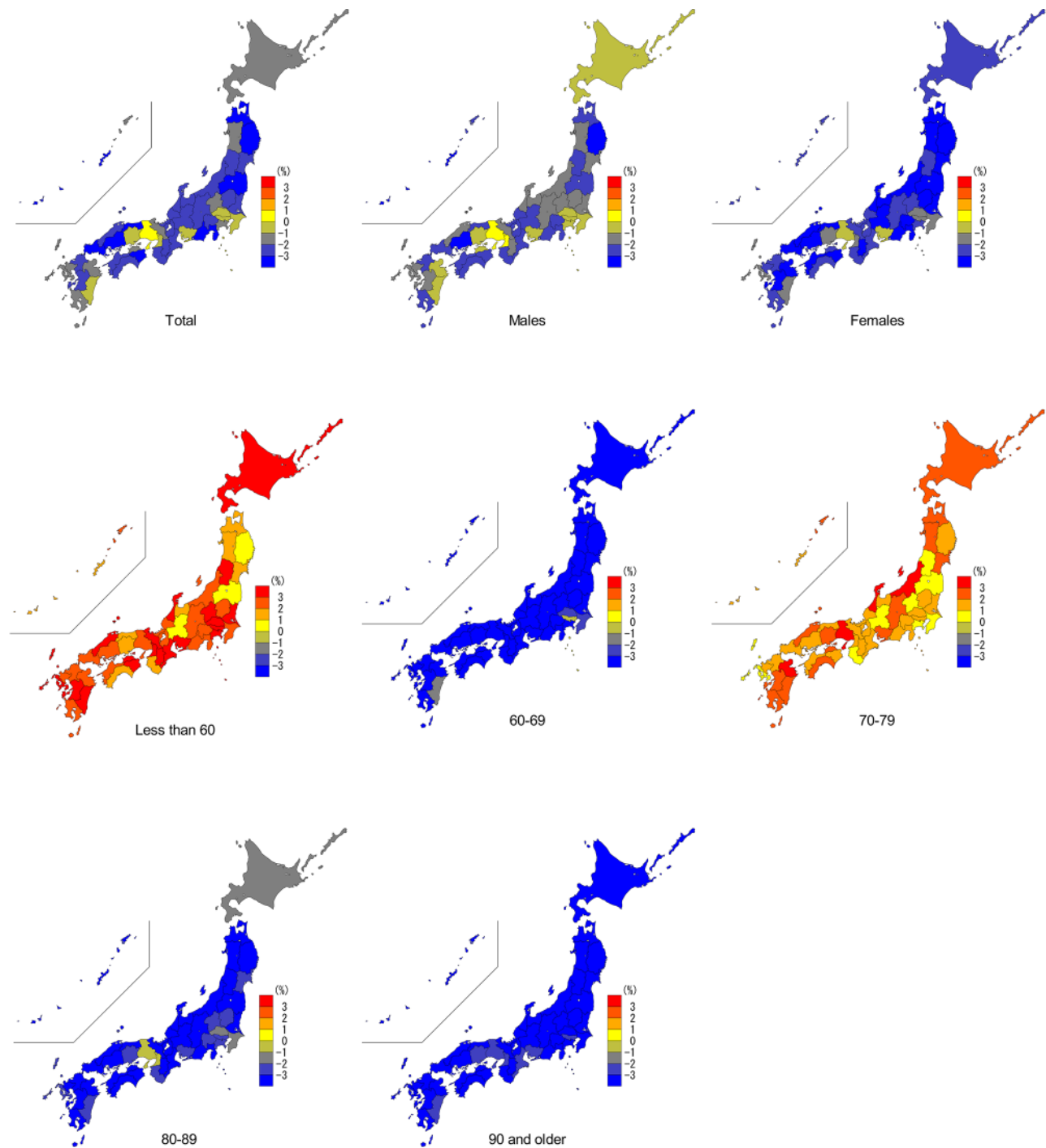


Figure 2 The spatial distribution of percentage excess in mortality during the period 14 January–31 December 2020 in the 47 prefectures of Japan in total and stratified by sex and age groups

Our models revealed a decrease in mortality during the COVID-19 outbreak in February–December 2020 in Japan. There was significant spatial heterogeneity between prefectures. The difference in the methods between our study and the previous study in Italy is that our study considered the effects of influenza activity in the main model, whereas the previous study did not.

Our findings showed that the COVID-19 outbreak may have potentially led to a decrease in deaths in Japan. These results align with a recent study that indicated a much lower overall excess-mortality burden due to COVID-19 in Japan than in Europe and the USA.¹⁴ However, that study used weekly data on a shorter period and used data for 3 weeks before and after a certain point as the reference

period. Additionally, the study did not consider variations in the effect of influenza activity and ambient temperature.¹⁴ In contrast, an advantage of our study is that we used an advanced two-stage interrupted time-series design based on daily data and considering temporal trends and variations in these confounding factors. During the first wave of the COVID-19 epidemic in Japan, the Japanese government was criticized because of not performing reverse transcriptase–polymerase chain reaction (RT-PCR) tests extensively²⁶ and the very small number of COVID-19 deaths was considered due in part to under-reporting of COVID-19 mortality. However, our results indicated that the total excess risk of mortality in Japan started decreasing below the baseline since the first COVID-19 case was confirmed and continued to remain low. Thus, the criticism that other causes were assigned to the unidentified cases of COVID-19 is not considered to be valid. Our findings suggest that Japan is one of the few countries with negative excess mortality in the world.²⁷

Our study revealed significant spatial heterogeneity in excess mortality among prefectures, suggesting the existence of regional differences in the COVID-19 situation. It is possible that regional differences may be related to changes in people's lifestyles, human behaviour and morbidity due to movement restrictions and socio-economic conditions during the COVID-19 outbreak.²⁸ Regional variations in excess mortality may be attributed to other factors such as population density, timely access to medical care and available beds, and cluster outbreaks in elderly-care facilities and medical institutions.²⁹ These factors may have contributed to the variations in excess mortality and further studies are essential to consider a variety of socio-economic and demographic factors in different regions.

Several possible mechanisms have been proposed to explain this low mortality. First, influenza activity has been at lower levels in 2020 than in previous years in Japan.³⁰ Approximately 2000 and 12 000 fewer deaths from influenza and pneumonia without COVID-19, respectively, have been reported in 2020 compared with the same period in 2019.³¹ Second, the number of road-traffic fatalities decreased from January to September 2020 in Japan, which might be due to the decrease in mobility and traffic volumes on major national highways.³² These results might be related to the reduction in all-cause deaths due to COVID-19 in Japan.

Japan saw far fewer cases and a much lower incidence rate of COVID-19 than comparable high-income countries² and its coronavirus response was broadly consistent with WHO best-practice guidelines. This reduced transmission of the virus and relative success in protecting elderly populations from infection may also have driven the low mortality rate. Regarding these points, several

hypotheses have been proposed. First, East Asian populations have a higher allele frequency of the angiotensin-converting enzyme-2 (ACE2) variants associated with higher tissue expression of ACE2.³³ Elevated plasma ACE2 is associated with increased risk of atrial fibrillation, myocardial infarction, coronary artery disease, heart failure and aortic stenosis;³⁴ thus, Japanese people may have reduced susceptibility due to increased ACE2-receptor expression. Second, countries including Japan with the mandatory bacille Calmette-Guérin (BCG) vaccination may have reduced mortality for COVID-19 compared with those that do not: among findings, BCG may boost trained immunity³⁵ and vaccination might be associated with a decrease in mortality.³⁶ The BCG vaccine also promotes the production and maturation of naïve T cells that lead to enhanced long-term trained immune protection against SARS-CoV-2.³⁷ Furthermore, small-module BCG mimics such as emetin and lopinavir inhibit the growth of SARS-CoV-2 *in vitro*, which may contribute to reduce COVID-19 mortality.³⁷ Although the exact mechanisms of remain unclear, it may result from complex and multifactorial interactions among these and other as-yet unidentified factors.

Stratified analysis showed a reduction in mortality in both men and women during the COVID-19 outbreak in Japan. Specifically, the percentage excess was -1.3% for men and -2.5% for women, with approximately twice the decline in women as in men. However, we found increases in mortality in the <60 -years age group from the middle of June 2020. This finding is consistent with a recent study which suggested that suicide rates in Japan in 2020 increased in October and November in men and in July through November in women, and that the increase was most pronounced among males aged <30 years and in females aged <30 as well as 30–49 years.³⁸ Additionally, on 1 March 2021, the Ministry of Health, Labour and Welfare, Japan, reported that the cumulative number of layoffs and suspensions related to the COVID-19 outbreak had reached 90 185 as of 26 February 2021.³⁹ Furthermore, on 16 March 2021, Japan's National Police Agency reported that juvenile suicides reached a record high of 499 in 2020 since records began to be kept in 1980.⁴⁰ These might be related to the fact that physical isolation and lockdown affect serious threats to the mental health and well-being of the general population.⁴¹ Public health emergencies due to the outbreak are associated with a range of psychosocial difficulties, including economic and financial loss from unemployment and reduced income, school and work closures, inadequate resources for suitable medical responses, domestic violence and insufficient distribution of basic necessities.⁴² Loneliness as well as social isolation also increases the risk of depression, and

children and adolescents are more likely to experience increased rates of depression and anxiety.⁴³ Although we could not access individual data on deaths, increased suicidality due to economic and mental health problems in the <60-years age group might be related to the increase in mortality.

Our study also showed that there were significant increases in mortality in the 70- to 79-year age group from February 2020 in Japan. Loneliness and social isolation in the aged are also serious public health risks.⁴⁴ Previous studies have shown that older adults are at elevated risk for morbidity and mortality due to COVID-19 and also likely to experience extended isolation.⁴⁵ Social loneliness and isolation in older adults were associated with a 50% increase in the risk of dementia⁴⁶ and a 26% increase in the risk of premature death from all causes.⁴⁷ Moreover, degraded social relationships due to social loneliness and isolation were associated with a 30% increased risk of coronary artery disease and stroke.^{48,49} These results suggest that increased risk of dementia, coronary heart disease and stroke due to social isolation might be associated with the increase in mortality in the 70- to 79-years age group. Although increased excess mortality was not observed in the 60- to 69-years age group, this might be due to the fact that many people in their 60s are working on the frontline and are an economically active population.⁵⁰ Furthermore, depression symptoms were lower among people aged 60-69 years compared with those aged >70 years during the COVID-19 pandemic.⁵¹ Further more detailed analysis of cause-specific excess mortality is needed to determine the reason for the higher excess mortality in specific age groups during the COVID-19 outbreak in Japan.

Our present results carry practical implications for the clarification or adjustment of estimates for excess deaths in public health policies for COVID-19. Our study estimates a substantial difference in excess mortality compared with other comparable high-income countries. Although the Japanese government does not have legal authority to impose lockdowns or to fine residents who ignore requests to cooperate in preventing the spread of COVID-19, most Japanese people have been following such requests. Our findings are important because there may be no need to impose strict social-distancing and social-isolation measures for COVID-19 in Japan. Further, international fora should be informed that the influence of COVID-19 on mortality varies by country and region.

There are several limitations in this study. First, we could not take account of information concerning individual factors, such as demographics or socio-economic status, due to difficulties in sourcing data. Therefore, we did not account for social or economic vulnerabilities in our estimates of excess mortality. Additionally, investigating

the role of social and demographic factors in the spread of COVID-19 would depend on data on behavioural trends in Japan. Because COVID-19 is likely spread through both human mobility and social transmission networks, these clearly require future study. Second, although the vital-statistics survey is based on the Family Register Act and the registries are considered complete, mortality data in 2020 were early-release data and there may be some differences from the actual number of deaths. This happened due to delays in reporting deaths from municipal governments to the national Ministry of Health, Labour and Welfare. This delay might be due to the overload of the health-department workers due to the COVID-19-related work. However, we suggest that this would not result in substantial bias because the death notification must be submitted to the municipal government within 7 days under the Family Register Act in Japan and the degree of delayed reporting is considered to be very low.¹⁴ Third, biases may have resulted from our inability to consider immunity to or the likelihood of person-to-person transmission as well as variations in symptoms or presentation of COVID-19 in the population at risk. Variations resulting from immunity to as well as the transmissibility of SARS-CoV-2 in the at-risk population may have biased our estimates. Fourth, although we analysed daily data spanning from 2015 to 2020, the pandemic of COVID-19 is ongoing and our data did not represent the full pandemic period in Japan. The modelling accuracy of our study would be improved by a longer study period or more detailed data. These possible biases might have in turn influenced our interpretation of the results and future studies with more precise modelling methods and detailed data are required.

In summary, our present study estimated a reduction in all-cause mortality during the COVID-19 outbreak in 2020 in Japan. Knowledge of the effects of the COVID-19 outbreak on different types of disease and areas is insufficient. Further studies with longer-term estimation of cause-specific excess deaths during the COVID-19 outbreak are warranted.

Supplementary data

Supplementary data are available at *IJE* online.

Ethics approval

The contents of this study were approved by the ethics committee of the National Institute of Infectious Diseases under authorization number 1174. As this study was conducted under a retrospective observational design that specifically included de-identified national mortality data, informed consent was not required.

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Data availability

The mortality data have been obtained through a restricted data-use agreement with the Ministry of Health, Labour and Welfare, Japan, and are therefore not available for public dissemination.

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Author contributions

D.O. made substantial contributions to the conception and design, analysed the data, wrote the first draft of the manuscript and interpreted the results. D.Y., S.N., S.G., C.N., F.S. and M.H. provided substantial scientific input into interpreting the results and drafting the manuscript. All authors were involved in data interpretation and made meaningful contributions to the final submitted manuscript. The views expressed in this paper are solely those of the authors and do not necessarily represent those of the organizations to which the authors belong.

Conflict of interest

None declared.

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