Factors contributing to the sharp rise in excess mortality in Japan since 2021

Atsushi Takahashi

atakah7@kiui.ac.jp

Kibi International University https://orcid.org/0000-0003-3340-432X

Research Article

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Abstract

Since 2021, excess mortality in Japan has risen sharply. This study adopts an ecological approach to investigate correlations between prefectural excess mortality and factors such as demographic structure, income, medical capacity, vaccination rates, and life expectancy. The primary contributing factors identified include population aging, COVID-19 mortality, a low ratio of habitable land, a high rural population ratio, and physician shortages. In mountainous and depopulated regions, fragile medical infrastructure—worsened by depopulation, aging, and limited access to healthcare—collapsed under the pressure of the SARS-CoV-2 outbreak, contributing to elevated excess mortality. While SARS-CoV-2 vaccination initially helped suppress excess mortality until June 2022, a positive correlation has emerged since July. This may be attributable to immune imprinting caused by original strain vaccines, which results in insufficient production of neutralizing antibodies against the Omicron spike protein expressed by Omicron-based vaccines and may contribute to heightened spike protein toxicity. A shift away from urban-centric health policies and vaccine-only strategies toward multifaceted approaches aimed at strengthening herd immunity is urgently needed.

Introduction

Coronavirus Disease 2019 (COVID-19) was first reported in Wuhan, China, around December 2019 and rapidly spread worldwide[1]. As of the end of March 2025, approximately 780 million people had been infected globally, with over 7.09 million deaths. The World Health Organization (WHO) declared a pandemic on March 11, 2020, and announced the end of the “Public Health Emergency of International Concern” (PHEIC) on May 5, 2023. In Japan, the legal classification of COVID-19 under the Infectious Diseases Act was changed from “Type II equivalent” to a “Category V infectious disease” on May 8, 2023.

“Excess mortality” refers to the number of deaths exceeding the expected baseline and is often used to evaluate unrecorded impacts of infectious disease outbreaks or natural disasters. In Japan, age-adjusted excess mortality rose dramatically from approximately 26,000 in 2021 to 117,000 in 2022 and 114,000 in 2023, with the unadjusted total reaching around 600,000 by the end of 2023[2]. In 2021 in particular, excess mortality was nearly six times higher than the official COVID-19 death count, suggesting that it cannot be fully explained by COVID-19 alone.

Possible contributing factors include strain on the healthcare system, decreased physical activity, increased stress, and lifestyle changes among the elderly due to stay-at-home measures, as well as increased suicide rates linked to economic hardship in sectors such as the restaurant and transportation industries. In addition, significant rises in cerebrovascular and cardiovascular events, worsening of chronic conditions in the elderly, and sudden deaths following the start of vaccination have raised concerns about potential vaccine involvement[3]. However, most of these claims remain circumstantial, with limited quantitative or statistical validation.

The leading cause of excess deaths during this period was senility, mainly affecting individuals aged 70 and older—particularly those over 90—indicating that aging was a natural contributing factor. However, since Japan's population was already aging before 2020, the sharp rise in excess mortality from 2021 onward remains insufficiently explained.

Epidemiological research often utilizes ecological models to statistically analyze public health phenomena. Studies in Europe conducted between 2020 and 2022 found that excess mortality correlated positively with poverty and inequality indicators (e.g., Gini coefficient), and negatively with GDP per capita, healthcare expenditure, and two-dose vaccination rates[4]. These findings suggest that socioeconomic disparities, leading to limited healthcare access and lower vaccination coverage, significantly contributed to excess deaths. Did similar disparities widen in Japan after 2021?

This study employs an ecological (region-based comparative) method[5] to analyze excess mortality across Japanese prefectures. The variables examined include age composition and vaccination rates (immunological indicators); number of hospital beds and physicians per area or population (healthcare system indicators); population density (urbanization); per capita income (economic indicator); average life expectancy (overall health); and rural population ratio, habitable land ratio, and forest area ratio (geographic indicators).

The findings suggest that SARS-CoV-2 vaccination contributed to reducing excess mortality until around July 2022, but was positively correlated with increased mortality thereafter. Furthermore, in mountainous and depopulated regions—where aging populations and poor access to healthcare had already weakened the medical system—COVID-19 outbreaks triggered system collapse and contributed to increased mortality among the elderly.

Methods

We collected publicly available data for each prefecture in Japan, including excess mortality per 100,000 population; vaccination rates for the 1st to 7th doses of the SARS-CoV-2 vaccine; the percentage of the population under age 15 and aged 65 and over; the number of hospital beds and physicians per area; the number of physicians per population; population density; per capita prefectural income; average life expectancy (by sex); rural population ratio (county population) ; habitable land ratio （habitable area）; and forest coverage ratio (forest area).

Using an ecological study design[5], we analyzed the correlations between excess mortality per 100,000 people and these variables across prefectures by applying Spearman’s rank correlation coefficients. We also conducted multiple regression analyses to assess the relative influence of each factor.

Results

Since 2021, Japan has experienced six distinct waves of excess mortality through May 2024. These were defined independently of the COVID-19 epidemic waves and are referred to as Phases 1 through 6.

To identify the contributing factors to the sharp rise in excess deaths, we conducted prefecture-level ecological analyses for each phase, examining correlations with various epidemiological indicators. Multiple regression analysis was also performed to evaluate the relative strength of each factor.

Phase 1 (February 2021 – June 2021)

This phase coincided with the spread of the Alpha variant (B.1.1.7), the first Variant of Concern (VOC) designated by the WHO, and Japan's fourth wave of COVID-19.

Multiple regression analysis (Table 1) showed that both the COVID-19 mortality rate and the elderly population ratio (aged 65 and over) positively contributed to excess mortality, while the habitable land ratio (habitable area) had a negative association. In other words, prefectures with less habitable land—typically mountainous and remote areas—experienced higher rates of COVID-19-related deaths among older adults, contributing to the initial surge in excess mortality.

Phase 2 (July 2021 – January 2022)

During this period, the Delta variant (B.1.617.2) became dominant, driving Japan's fifth COVID-19 wave (June–December 2021). The Tokyo Olympics were held from July 23 to August 8, 2021. In December, the sixth wave began with the emergence of the Omicron variant (BA.1), which produced a case peak approximately four times greater than previous waves. However, Omicron generally caused less severe illness, resulting in fewer deaths.

The second-dose vaccination rate made the largest negative contribution to excess mortality (Fig. 1a, Table 1). The elderly-targeted vaccination campaign that began on April 12, 2021, likely contributed to lower infection and death rates during the fifth and sixth waves[6]. Given that cardiovascular disease was the second most common cause of excess deaths during this period, reduced COVID-19 incidence may have also helped decrease post-infection cardiovascular fatalities.

Additionally, the proportion of the population under age 15 and the habitable land ratio (Fig. 1b) were both negatively associated with excess mortality, while the rural population ratio (county population) showed a positive correlation (Table 1). In Japan, areas with limited habitable land are typically mountainous and isolated, with forests occupying much of the terrain. Indeed, the forest area showed a consistent positive correlation with excess mortality across all six phases (Fig. 2), suggesting that sparsely populated, aging, and depopulated regions experienced higher excess mortality.

Phase 3 (February 2022 – June 2022)

Excess mortality in this phase nearly doubled compared to Phases 1 and 2. The sixth COVID-19 wave continued, and from late March, the BA.2 subvariant of Omicron became dominant.

Multiple regression analysis (Table 1) revealed that a higher elderly population ratio contributed to increased excess mortality, while the third-dose (booster) vaccination rate (Fig. 3a) had a significant suppressive effect. The booster campaign, launched on December 1, 2021, appears to have reduced infections and deaths[6], thereby curbing excess mortality. The weakening of the habitable area's effect may reflect the spread of outbreaks into more urban areas.

Phase 4 (July 2022 – October 2022)

The seventh COVID-19 wave, driven by the BA.5 subvariant, caused Japan to record the highest number of new infections globally. Accumulated mutations in BA.5 weakened cross-immunity among older adults, allowing widespread infection in this previously less-affected population[6].

Excess mortality during Phase 4 exceeded that of Phase 3. The COVID-19 mortality rate (Fig. 4a) was positively correlated with excess mortality. The third-dose vaccination rate (Fig. 3b) continued to show a negative correlation, whereas the fourth-dose vaccination rate was positively associated with excess mortality (Fig. 4b, Table 1).

Because earlier analyses[6] covered only part of the seventh wave, we reanalyzed the full wave. The fourth-dose vaccination rate correlated with reduced COVID-19 prevalence (Fig. 5), mortality, and case fatality rate (CFR) (Table 2). Thus, the positive correlation between fourth-dose vaccination and excess mortality (Fig. 4b) likely reflects non-COVID-19-related factors.

During Phase 4, physician density per area (doctors per area) was negatively associated with excess mortality (Fig. 6a, Table 1). Despite longstanding concerns about physician shortages relative to population size, no significant correlation was found with physicians per capita (Fig. 6b). The explosive spread of the seventh wave—2.5 times larger than the sixth—likely overwhelmed healthcare systems, especially in depopulated rural areas, contributing to increased deaths.

Phase 5 (November 2022 – May 2023)

This phase included the eighth COVID-19 wave, driven by new subvariants such as BA.2.75, BQ.1, and recombinant strains like XBB. Despite a smaller infection scale than the seventh wave, Phase 5 saw the highest recorded excess mortality.

Multiple regression analysis indicated that the elderly population ratio (Fig. 7a), COVID-19 prevalence (Fig. 7b), and rural population ratio were all positively associated with excess mortality (Table 1).

Ecological analysis of COVID-19 outcomes during the eighth wave (Table 2) showed that the fifth-dose vaccination rate (Fig. 8a) was positively correlated with COVID-19 incidence—unlike the fourth dose, which had shown a suppressive effect (Fig. 5). This suggests a marked decline in vaccine effectiveness from the fourth to fifth dose.

Moreover, the fifth-dose vaccination rate was also positively associated with excess mortality (Fig. 9a), suggesting that increased infections contributed to more deaths.

The rural population ratio was positively associated with both COVID-19 prevalence (Fig. 8b) and mortality during the eighth wave, suggesting that spread in underserved areas exacerbated healthcare strain and fatalities.

The unprecedented level of excess mortality in Phase 5, despite a smaller COVID-19 case count than in Phase 4, may be explained by (1) reduced vaccine effectiveness and increased infection following the fifth dose, and/or (2) continued stress on rural healthcare systems, increasing both COVID-19 and non-COVID-19 deaths in older populations.

Phase 6 (June 2023 – May 2024)

After May 8, 2023, COVID-19 was reclassified as a Category V infectious disease under Japan's Infectious Diseases Act, ending mandatory case reporting. As a result, incidence data were unavailable for this phase.

Multiple regression analysis showed that the sixth-dose vaccination rate (Fig. 9b) and rural population ratio (Fig. 10a) were positively associated with excess mortality, while male life expectancy (Fig. 10b) was negatively associated (Table 1). Notably, Ishikawa Prefecture experienced a spike in excess deaths following the Noto Peninsula earthquake on January 1, 2024.

It remains unclear whether the sixth-dose vaccination contributed to increased excess mortality through elevated infection rates, as suggested in Phase 5, or through other mechanisms. Life expectancy reflects regional health and medical conditions. These findings imply that vaccination in medically underserved rural areas may have contributed to excess mortality.

Discussion

This study analyzed the increase in excess mortality in Japan from February 2021 to May 2024, categorizing it into six distinct phases. While several factors were consistently associated with excess deaths across all phases, a notable shift occurred around November 2022 regarding the impact of SARS-CoV-2 vaccination (see Table 1).

Medical collapse in mountainous and rural regions

Geographical factors contributing to excess mortality included low habitable land ratios in Phases 1–3, high rural population ratios in Phases 2, 5, and 6, and low doctors per area in Phase 4 (Table 1). Forest area was positively correlated with excess mortality throughout all phases (Fig. 2). As a mountainous island nation, Japan has many rural areas—especially in remote and highland regions—characterized by low habitable land availability and extensive forest coverage. These areas face chronic challenges, such as limited public transportation for accessing healthcare, population decline, and difficulty recruiting and retaining physicians and nurses.

Japan's regional disparity in physician distribution has worsened over time. Many doctors avoid rural assignments due to obstacles such as difficulty obtaining specialist certification, excessive workloads from night shifts, poor working conditions, limited educational opportunities for their children, and lack of family support. The 2004 revision of Japan's postgraduate clinical training system reduced the influence of universities in dispatching doctors to rural hospitals, weakening university hospitals and accelerating the withdrawal of physicians from remote areas. Administrative efforts to redistribute medical personnel have often clashed with physicians' freedom to choose their workplace, imposing burdens without improving working conditions and triggering backlash.

National health policy has promoted the consolidation and downsizing of public hospitals, reduction of infectious disease beds, and regional healthcare restructuring, primarily aimed at controlling costs and improving efficiency. As a result, regional healthcare systems were unprepared for the surge in demand brought on by the COVID-19 pandemic. The shortage of public hospitals—which play a central role in infectious disease control—was especially critical. Rural hospitals lacked adequate infection control measures, facilities, and staffing. As healthcare workers themselves became infected and patient visits declined due to public fear, many facilities curtailed outpatient services or suspended operations to secure beds, leading to financial distress and even closures. Regions with few hospital beds and specialists often depended on urban hospitals for treating severe COVID-19 cases. However, as urban hospitals became overwhelmed, patient transfers were no longer feasible. This led to a concentration of severely ill patients at under-resourced local hospitals, further increasing mortality.

In isolated rural communities, outbreaks tend to occur later than in urban centers, offering a brief window for preparation. However, once a virus spreads within such a closed population, the number of patients can quickly exceed the available caregiving capacity, resulting in critical care shortages and higher mortality[7]. Thus, in mountainous and island regions, healthcare infrastructure had already been weakened by depopulation, aging, and physician shortages. Although Japan maintained relatively low COVID-19 incidence through 2020, the spread of the Alpha and Delta variants in 2021, followed by Omicron in 2022, caused a rapid increase in cases. While urban areas retained sufficient healthcare capacity, many rural regions experienced system collapse, which significantly contributed to the rise in excess mortality.

SARS-CoV-2 vaccination

Vaccination contributed to reducing excess mortality during Phase 2 (second doses) and Phases 3–4 (third doses). However, it was associated with increased excess mortality in Phase 4 (fourth doses) and Phase 6 (sixth doses). In Phase 5, the fifth dose was positively correlated with increased COVID-19 incidence, which likely contributed to the rise in excess mortality.

Previous epidemiological studies have suggested that vaccination may transiently increase infection rates during rollout, but ultimately lowers mortality by reducing the case fatality rate[8]. Although SARS-CoV-2 vaccines provide short-term protection—typically lasting around four months—they are insufficient on their own to sustainably reduce transmission. Only the combination of infection-induced immunity and vaccine-induced immunity—so-called "hybrid immunity"[9]—can establish robust herd immunity capable of suppressing widespread transmission[6].

Epidemiological analyses of influenza interference suggest that a low-virulence SARS-CoV-2 strain may have entered Japan in mid-January[10], promoting natural immunity formation. Combined with second and third vaccine doses, this likely helped reduce excess mortality in earlier phases (Table 1). However, despite lower infection rates following the fourth dose (Table 2), excess mortality increased (Table 1), raising the possibility that adverse effects (AEs) of the vaccine may have contributed to excess deaths.

Reported AEs of SARS-CoV-2 vaccines include acute myocardial infarction, Bell's palsy, cerebral venous thrombosis, Guillain-Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, thrombocytopenia, lymphadenopathy, appendicitis, herpes zoster, neurological complications, autoimmune hepatitis, and peripheral neuropathy[11,12]. Several reports suggest that the incidence and severity of AEs and long-term symptoms may be more extensive than those reflected in official data.

The fifth dose was associated with both increased COVID-19 prevalence (Fig. 8a) and excess mortality (Fig. 9a). Epidemiological analysis suggests a change in the vaccine's effect on excess mortality between the fourth and fifth doses, a trend that continued with the sixth dose. What might explain this shift?

First, accumulating mutations in the virus may have triggered antibody-dependent enhancement (ADE)[13], whereby vaccine-induced antibodies lost their neutralizing function and instead facilitated viral entry into immune cells, exacerbating inflammatory responses[14].

Second, repeated vaccination may have led to immune tolerance in the population, weakening vaccine-induced protection. In animal models, frequent vaccinations (e.g., biweekly) induced immune tolerance beginning with the fifth dose[15]. Additionally, mRNA vaccines have been shown to increase IgG4 levels after the third dose[16], suggesting a regulatory (tolerant) immune response to spike protein exposure[17]. This could lead to reduced antiviral immunity and chronic immunosuppression[3].

Third, and perhaps most importantly, a change in vaccine composition occurred. The first four doses used mRNA encoding the spike protein of the original Wuhan strain. The fifth dose introduced bivalent vaccines targeting both the ancestral (Wuhan) and Omicron BA.1 or BA.4/5 variants. The sixth dose utilized a monovalent vaccine targeting Omicron XBB.1.5. This shift from ancestral to Omicron-based spike proteins may have introduced new immunological challenges and unintended consequences.

Free spike proteins and immune imprinting (“original antigenic sin”)

mRNA vaccines function by instructing host cells to synthesize the SARS-CoV-2 spike protein and present it on the cell surface[18]. However, the spike protein itself exhibits biological activity[19]: it binds to ACE2 and estrogen receptors on endothelial cells, potentially causing endothelial dysfunction, increased coagulation, cytokine release, and enhanced vascular permeability through glycocalyx degradation. It may also activate the complement system and promote platelet aggregation via von Willebrand factor secretion—mechanisms that may contribute to vaccine-associated AEs[20].

Although the spike protein can be detected in human plasma following vaccination, its concentration is typically far lower than levels shown to cause endothelial damage in animal models, and it generally persists for only about four weeks[21]. One study reported evidence of endothelial damage 24 hours after vaccination but not after 48 hours[22], suggesting transient toxicity.

However, spike protein expression levels may vary by tissue and individual, and localized overproduction could occur[23]. In fact, patients with post-vaccination syndrome (PVS) have demonstrated elevated levels of circulating spike protein compared to control subjects[24].

Vaccine-induced antibodies form immune complexes with circulating spike protein, which may trigger symptoms such as fever, myalgia, and vasculitis-like reactions. While these antibodies also assist in neutralizing and clearing the spike protein, some severe AEs—such as myocarditis—have been associated with elevated levels of unbound or “free” spike protein[25], implicating this form in vaccine toxicity. Myocarditis and pericarditis are more frequently observed after the second dose and less so after subsequent boosters, possibly because higher antibody titers after repeated doses help reduce free spike protein levels. Complement activation peaks when antigen levels are high relative to antibody levels[26]; therefore, boosters may reduce the relative antigen burden and dampen this inflammatory response.

“Immune imprinting”[27], also known as “original antigenic sin,” refers to the immune system’s tendency to preferentially recall responses to previously encountered antigens rather than generating new responses to novel variants. In the case of Omicron-targeted vaccines, individuals previously vaccinated with ancestral (Wuhan strain) vaccines may mount an antibody response primarily against the original spike protein[28]. As a result, they produce insufficient neutralizing antibodies against the Omicron variant. Even after receiving two doses of Omicron-specific vaccines, neutralization titers often remain low—comparable to the cross-reactivity levels seen with SARS-CoV-1 or other animal coronaviruses[28].

In bivalent vaccines that include both the original and Omicron spike antigens, immune imprinting may cause the immune system to respond predominantly to the ancestral component[28], leaving the Omicron-derived spike protein poorly neutralized. Consequently, excess Omicron spike protein may circulate in the body. Even monovalent Omicron-based vaccines may be subject to this phenomenon if imprinting is sufficiently strong. This may represent a key mechanism underlying PVS[24].

When antigen clearance mechanisms fail to eliminate toxic antigens, vaccines may pose risks. Live-attenuated vaccines, for example, are contraindicated in immunocompromised individuals. Similarly, administering Omicron spike protein to individuals unable to mount an effective neutralizing response—due to immune imprinting—could result in elevated levels of free spike protein, posing a significant safety concern.

How toxic is the Omicron spike protein? Although reduced disease severity in Omicron infections has been attributed to other viral components[29], the spike protein itself retains pro-inflammatory activity, increases vascular permeability, and induces von Willebrand factor secretion[30]. These properties suggest it may be as biologically active—and potentially toxic—as spike proteins from earlier variants.

Many elderly individuals in Japan received Omicron-targeted vaccines. Some may have overproduced spike protein and, due to immune imprinting, failed to neutralize it effectively. This may have led to elevated levels of toxic free spike protein and increased risk of severe adverse effects. Circulatory diseases were the second most common cause of death during the peaks in excess mortality, primarily affecting individuals over the age of 70. Autopsies may not have examined spike protein deposition in cardiac tissue. Thus, measuring plasma levels of free spike protein in individuals who died after receiving the fifth or sixth dose could be informative.

The impact of free spike protein on acquired immunity to SARS-CoV-2 is not yet fully understood. One study found that individuals who developed myocarditis post-vaccination had antibody and T-cell responses comparable to those in healthy controls[25]. However, the observed increase in COVID-19 incidence following the fifth dose (Table 2) suggests not only immune tolerance, but potentially an immunosuppressive effect mediated by free spike protein.

Limitations

This study has several limitations:

(i) Excess mortality is a statistical construct, which makes it impossible to determine whether specific individual deaths fall into this category. Consequently, there are inherent methodological challenges in identifying the precise causes of increased excess mortality.

(ii) The ecological study design is not well-suited for detecting the effects of variables that exhibit only small regional differences, limiting the ability to accurately assess the influence of such factors.

(iii) Epidemiological indicators change in real time, and discrepancies may exist between the timing of data collection and the actual period during which excess mortality was affected. As a result, precise measurement of correlations is difficult. However, since the primary objective of ecological studies is to identify overall correlation trends rather than to achieve absolute statistical precision, these limitations do not significantly hinder the validity of the conclusions drawn.

Conclusion

An analysis of the factors contributing to the spread of the SARS-CoV-2 pandemic suggests that, up until the third wave, high population density, insufficient urban infrastructure for airborne infection control, crowded living environments, and urban lifestyle patterns played key roles in transmission[31]. In Japan, several contextual factors may have helped to suppress infections and reduce mortality during this period. These included potential cross-immunity from prior coronavirus exposure in East Asia[32], herd immunity effects potentially induced by an influx of Chinese tourists during the Lunar New Year[10], traditional festivals that may have played a role in immunity dynamics, and the well-ventilated architecture of traditional Japanese homes—elements that may be considered examples of traditional knowledge beneficial for managing airborne viral spread.

However, beginning with the fourth wave, limited access to medical care in rural areas became a key driver of increased mortality and CFR[31]. This trend echoed patterns seen during the 1918 Spanish flu pandemic, when infections reached isolated regions and caused sudden and severe consequences[7]. In Japan, the spread of SARS-CoV-2 into underserved mountainous regions led to the collapse of fragile healthcare systems and contributed to a sharp rise in excess deaths.

Pandemics are shaped not only by virological factors but also by societal structures. While Japan was successful in suppressing transmission in urban centers, it failed to implement adequate countermeasures in rural and agricultural areas, where vaccination became the sole intervention. Ironically, this may have contributed to increased excess mortality following the fourth through sixth vaccine doses.

Vaccines developed under the U.S. government’s "Operation Warp Speed" initially raised concerns about their mid- and long-term safety profiles. In Japan, debates emerged regarding whether vaccines were essential for achieving and maintaining herd immunity. As early as 2020, studies warned that “a shortage of physicians in depopulated areas will become critical. The harmful effects of regional disparities in physician distribution will likely surface when a rise in infections dramatically increases medical demand”[33], calling for policy interventions to prevent systemic collapse. However, these academic insights have not been adequately reflected in government policy.

Although national strategies have promoted “regional revitalization” and “health promotion,” the development of healthcare infrastructure has lagged behind. Addressing physician shortages and improving medical infrastructure will require long-term vision and substantial investment. During the eighth wave, lower per capita income was associated with higher COVID-19 CFR (Table 2). In the future, healthcare policy must not only address shortages in physicians per capita but also consider physician distribution per unit area and invest in strengthening medical systems in depopulated regions. The sharp rise in excess mortality in Japan may serve as a critical warning to re-evaluate urban-centered healthcare policies.

Declarations

Competing interests

The author declares no competing interests.

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Data availability

All data are available on request.

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Tables

Table 1. Factors contributing to excess mortality (Phases 1–6)

Phase	explanatory variable	standardized partial regression coefficient	*P*-value
1	COVID-19 mortality	0.522	0.000104
	population aged ≥65	0.313	
	habitable area	-0.352	
2	county population	0.248	1.72×10^{-6}
	2nd vaccination	-0.559	
	population aged <15	-0.245	
	habitable area	-0.144	
3	population aged ≥65	0.629	0.000814
	3rd vaccination	-0.664	
	habitable area	-0.027	
4	COVID-19 mortality	0.535	1.96×10^{-8}
	4th vaccination	0.178	
	3rd vaccination	-0.280	
	doctors per area (/km^2)	-0.190	
5	population aged ≥65	0.524	2.64×10^{-11}
	COVID-19 mortality	0.330	
	county population	0.174	
6	6th vaccination	0.548	2.00×10^{-6}
	county population	0.322	
	male life expectancy	-0.190	

Table 2. Factors contributing to COVID-19 prevalence, mortality, and case fatality rate (CFR) in 7th and 8th waves

response variable	explanatory variable	standardized partial regression coefficient	*P*-value
COVID 19 7th wave (June 21–Sept 30, 2022)			
prevalence	population aged <15	0.971	1.75×10^{-15}
	population aged ≥65	0.905	
	hospital beds per area	0.573	
	4th vaccination	-0.423	
mortality	population aged ≥65	1.300	5.77×10^{-6}
	population aged <15	0.971	
	hospital beds per area	0.342	
	4th vaccination	-0.716	
	male life expectancy	-0.255	
CFR	population aged ≥65	1.194	2.61×10^{-5}
	4th vaccination	-0.843	
	female life expectancy	-0.301	
COVID-19 8th wave (October 1, 2022–Feb 28, 2023)			
prevalence	5th vaccination	0.482	9.23×10^{-6}
	male life expectancy	0.332	
	county population	0.245	
mortality	population aged ≥65	0.475	8.31×10^{-6}
	county population	0.302	
CFR	female life expectancy	-0.354	0.00290
	per capita income	-0.262	

Figures

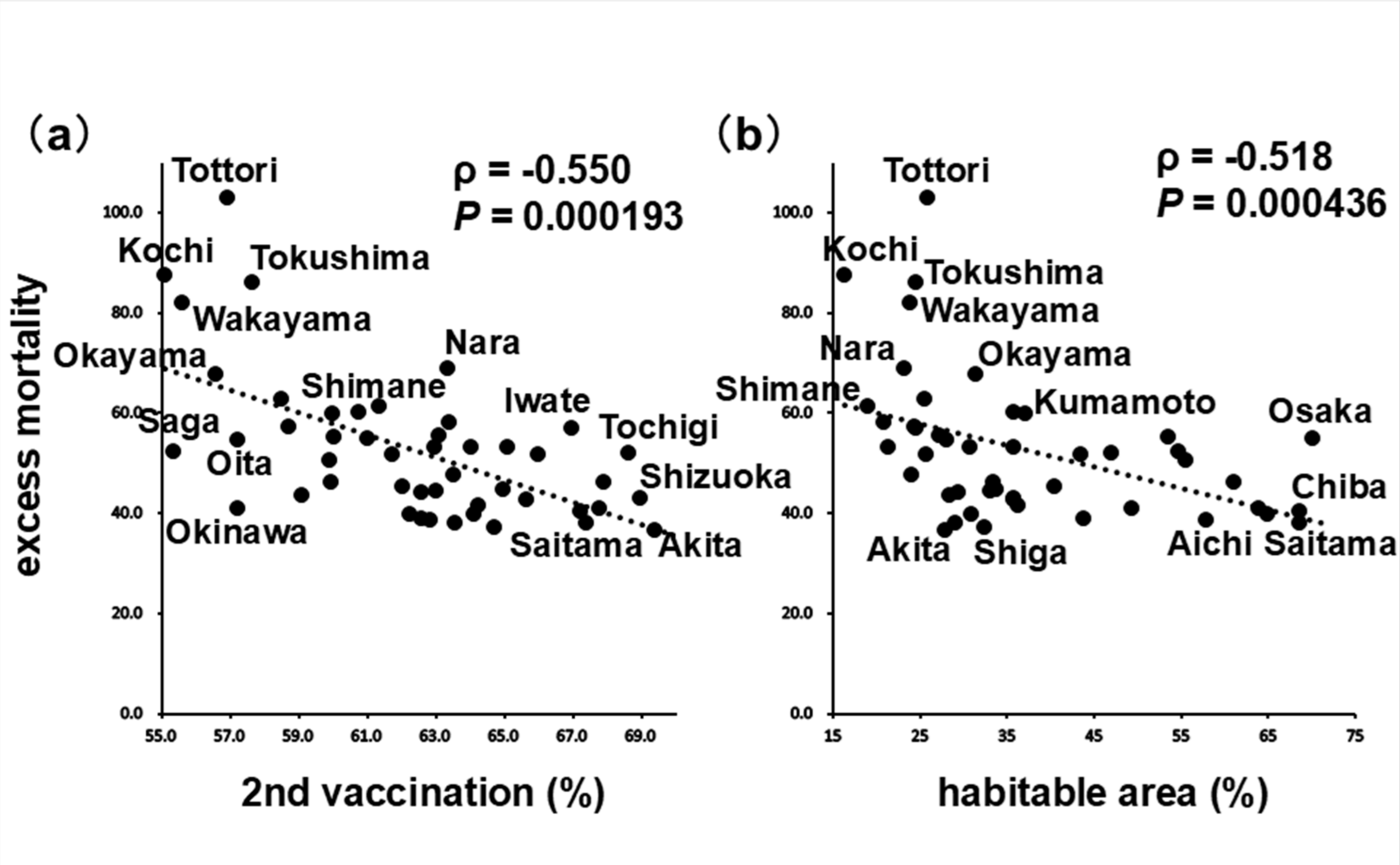

Figure 1

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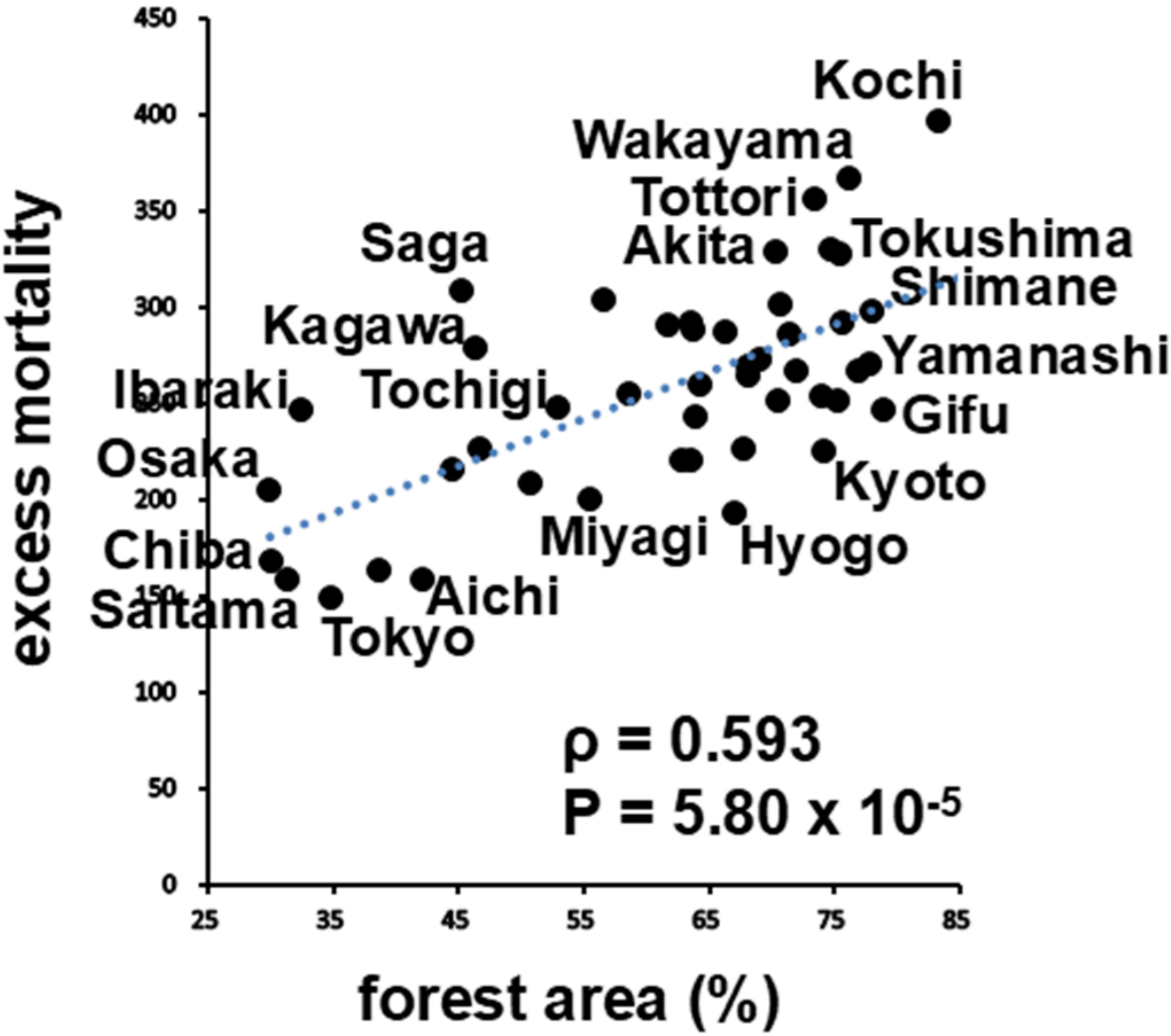

Figure 2

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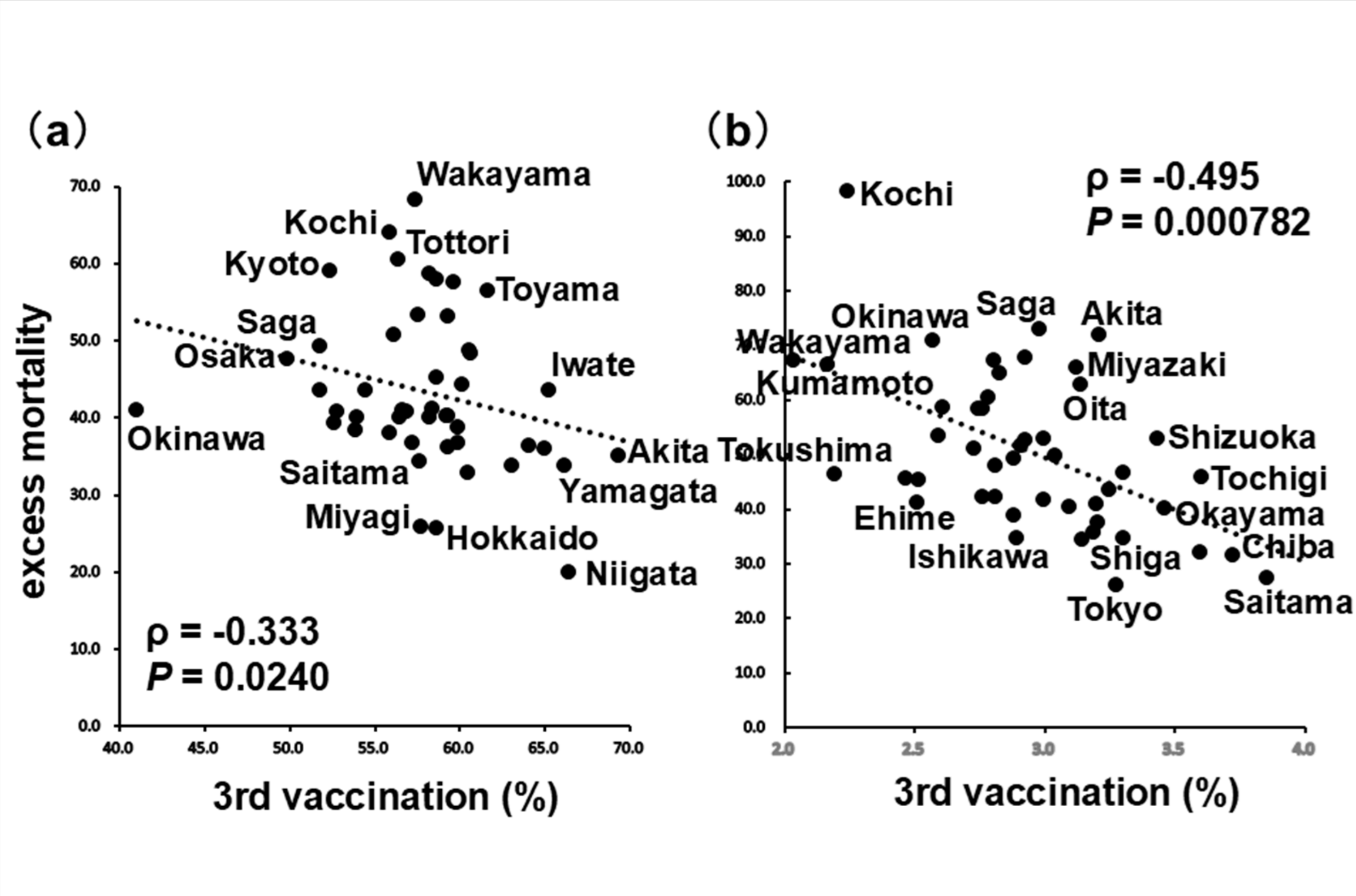

Figure 3

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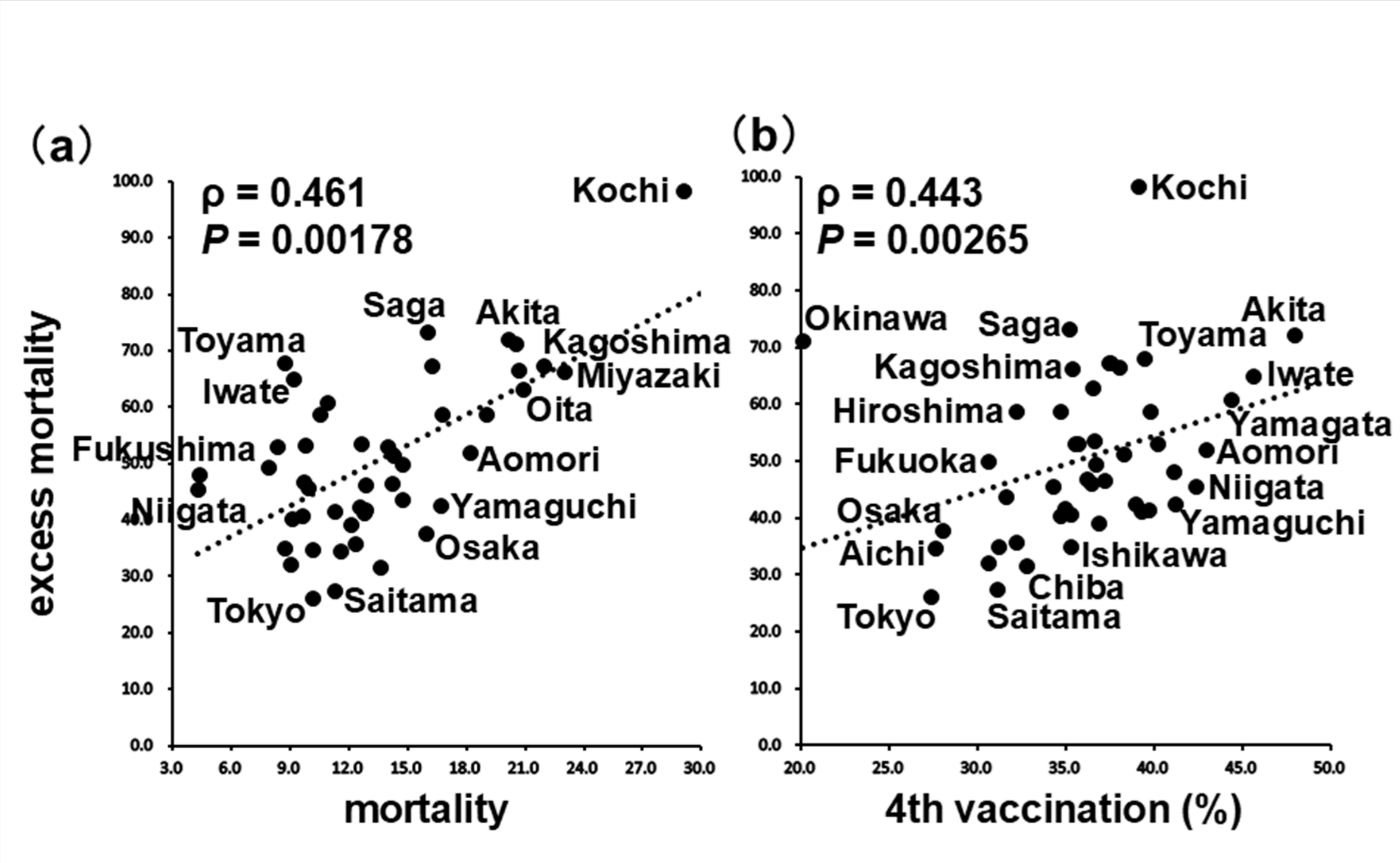

Figure 4

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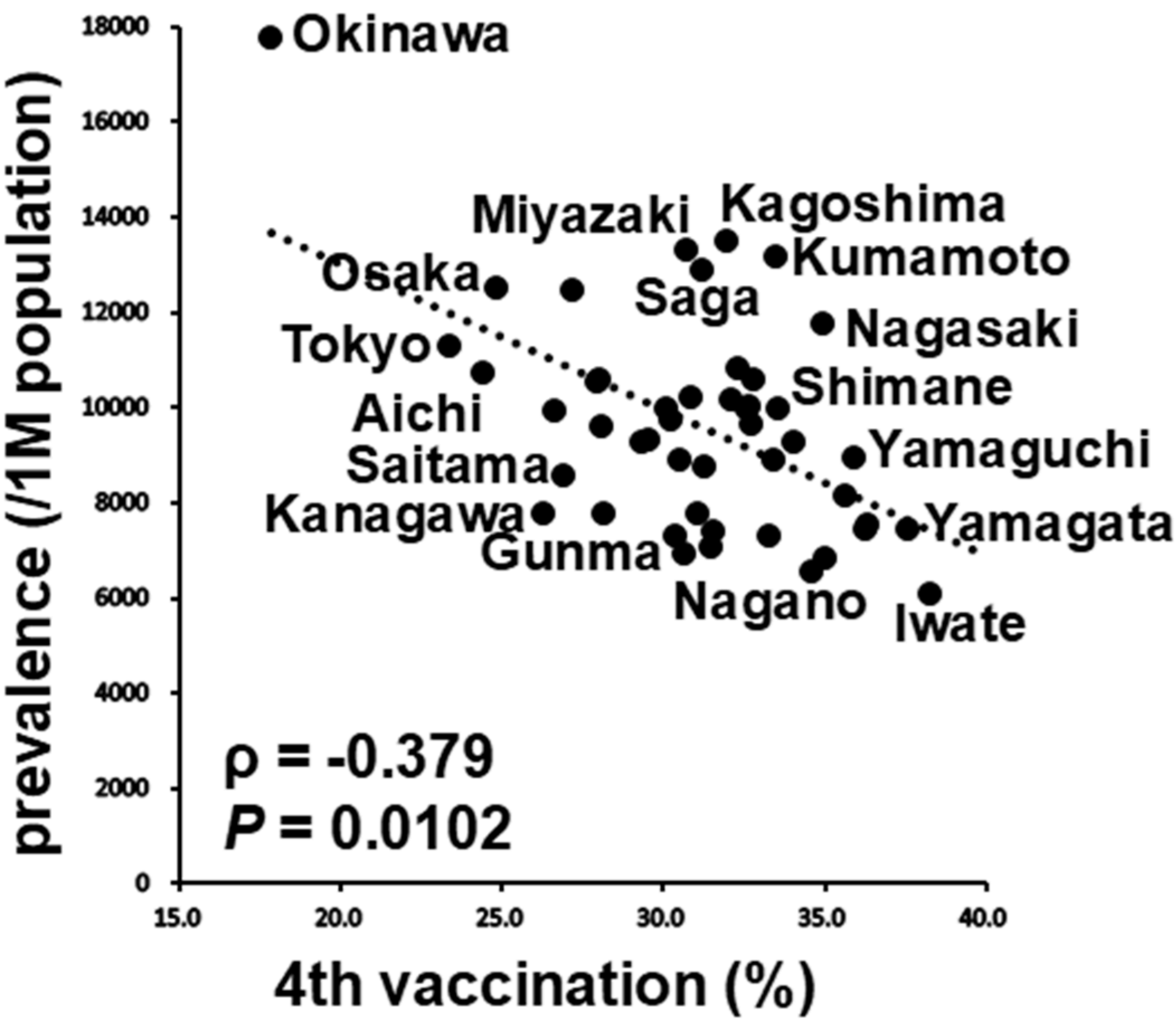

Figure 5

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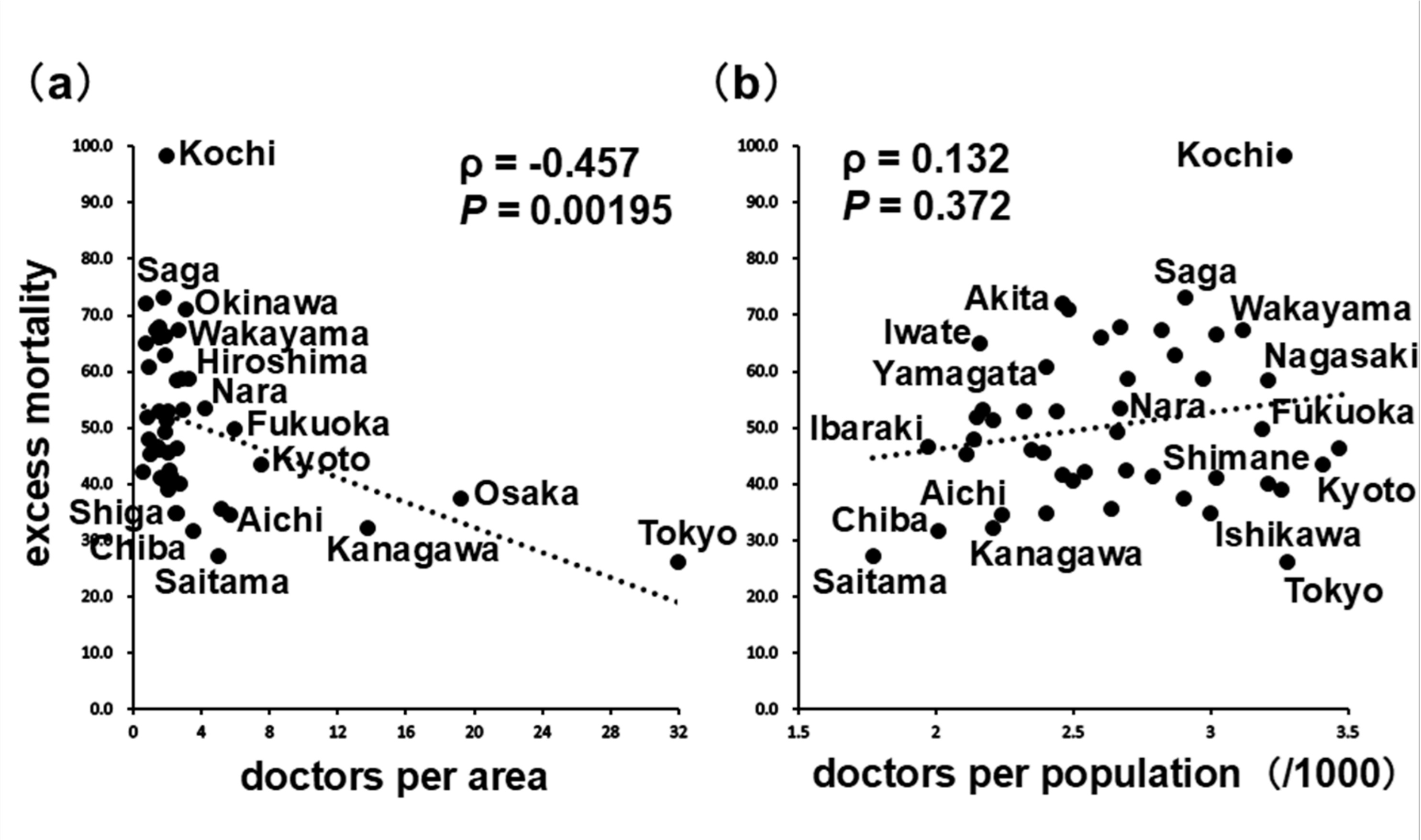

Figure 6

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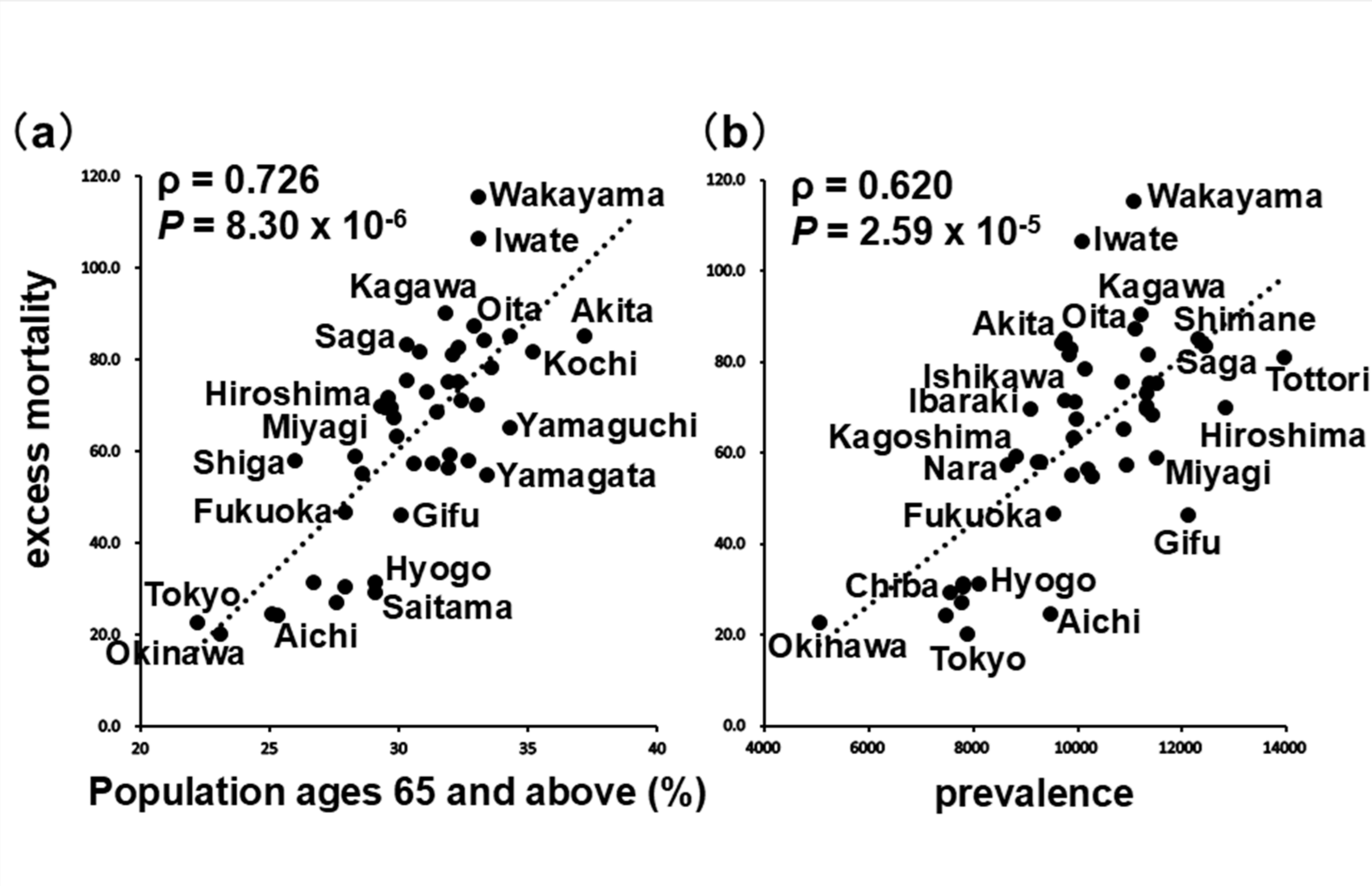

Figure 7

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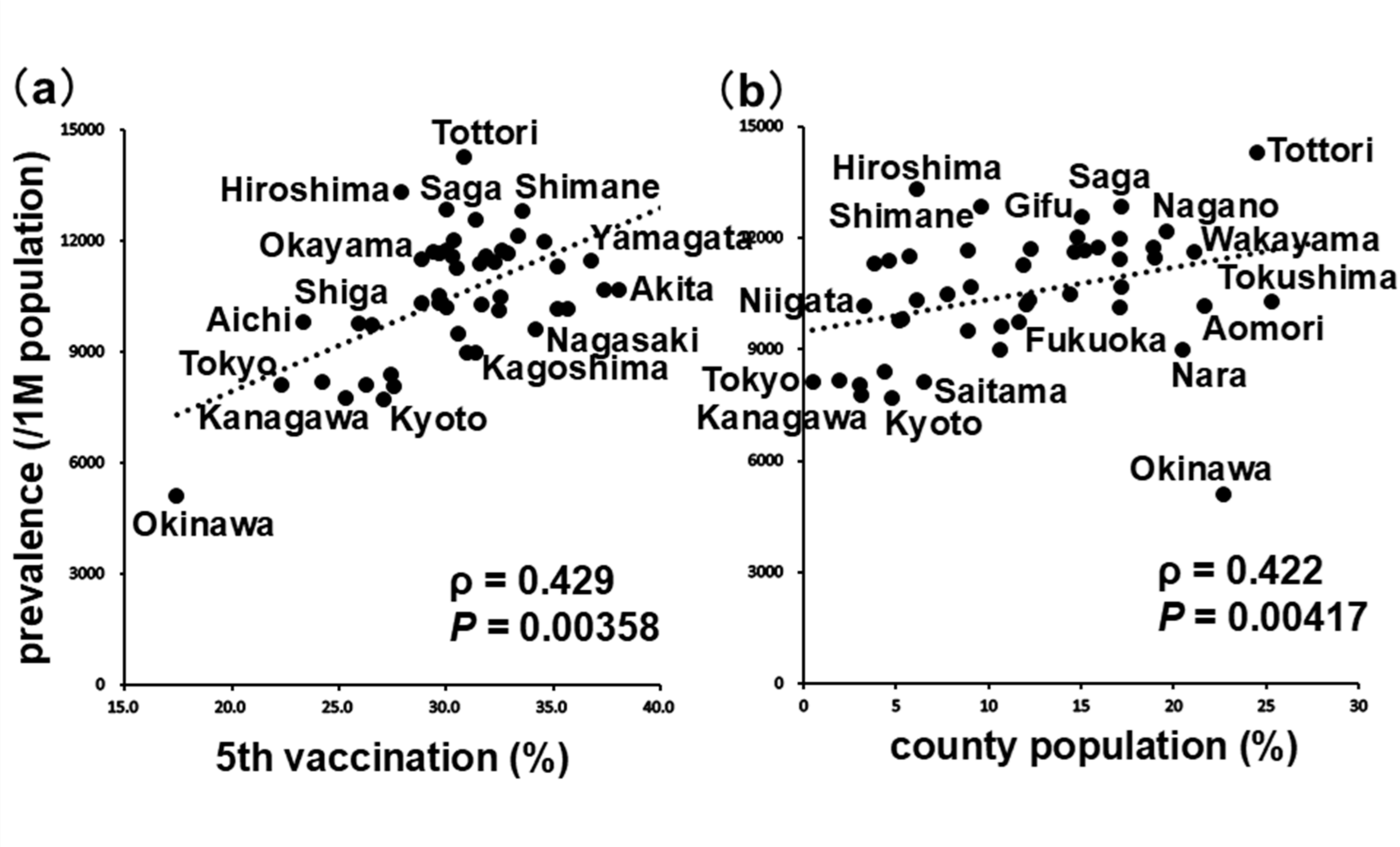

Figure 8

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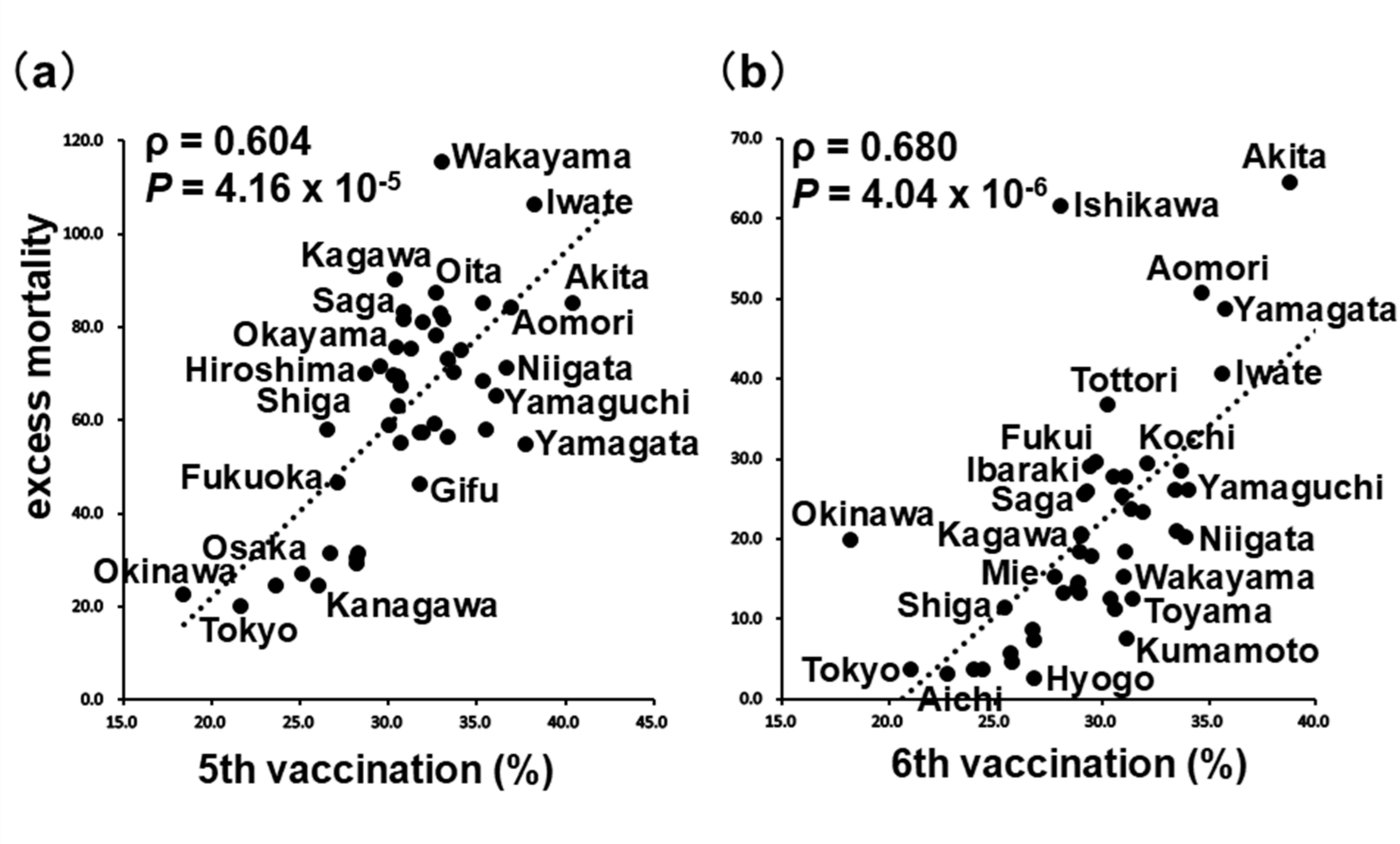

Figure 9

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