Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Understanding the exceptional pre-vaccination Era East Asian COVID-19 outcomes☆

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ABSTRACT

During the first year of the pandemic, East Asian countries have reported fewer infections, hospitalizations, and deaths from COVID-19 disease than most countries in Europe and the Americas. Our goal in this paper is to generate and evaluate hypothesis that may explain this striking fact. We consider five possible explanations: (1) population age structure (younger people tend to have less severe COVID-19 disease upon infection than older people); (2) the early adoption of lockdown strategies to control disease spread; (3) genetic differences between East Asian population and European and American populations that confer protection against COVID-19 disease; (4) seasonal and climactic contributors to COVID-19 spread; and (5) immunological differences between East Asian countries and the rest of the world. The evidence suggests that the first four hypotheses are unlikely to be important in explaining East Asian COVID-19 exceptionalism. Lockdowns, in particular, fail as an explanation because East Asian countries experienced similarly good infection outcomes despite vast differences in lockdown policies adopted by different countries to control the COVID-19 epidemic. The evidence to date is consistent with our fifth hypothesis – pre-existing immunity unique to East Asia – but there are still essential parts of this story left for scientists to check.

1. Introduction

The worldwide COVID-19[1] pandemic has had dramatically different impacts on different countries. While in some countries, large numbers of people quickly contracted COVID-19, other countries escaped the worst ravages of the epidemic. Perhaps most striking is that large cross-national regions have fared similarly, despite vastly different policy responses to control disease spread.

For East Asian countries, Fig. 1 displays cumulative confirmed covid deaths per million people compared to Africa, Europe, North

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[1] Throughout the paper, we intentionally do not include the "19" suffix in referencing COVID-19-19, the infection caused by the SARS-CoV-2 virus. It is unnecessary since the term "COVID-19" was not in common use prior to the 2020 COVID-19 epidemic.

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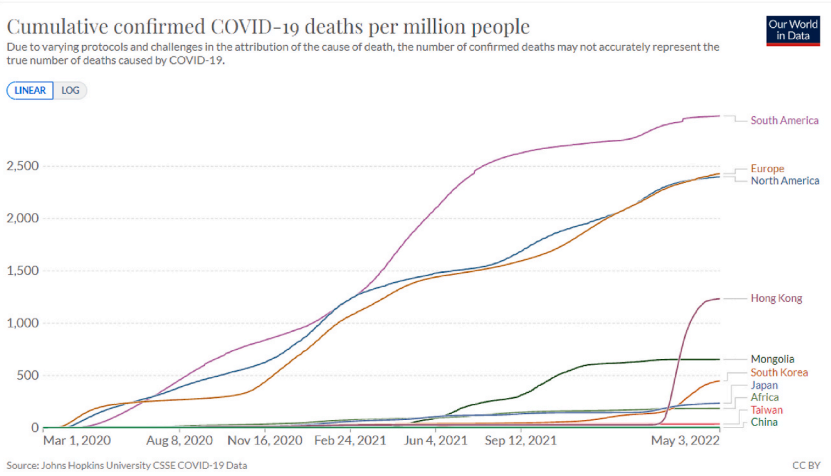

Fig. 1. Cumulative reported covid deaths by continent/select Asian countries.

America, and South America. Asia's performance stands out relative to Europe and the Americas, with relatively few deaths in 2020 before the dissemination of COVID-19 vaccines.[2] While Europe and the Americas experienced the highest per-capita COVID-19 mortality in 2020, East Asia emerged relatively unscathed.[3]

While official case and death counts summarize the epidemic's extent, interpreting such numbers is complicated since many different medical, economic, and social processes and facts contribute to these outcomes. Our goal in this paper is to generate and evaluate hypothesis that may explain these striking facts. We consider five non-mutually exclusive explanations for East Asian COVID-19 exceptionalism in 2020:

- The differential mortality risk conditional on infection faced by the young and the old and the age distribution of East Asian populations;
- The adoption of lockdowns and other non-pharmaceutical interventions aimed at restricting human contact and interactions to slow disease spread;
- The protection against COVID-19 infection and severe outcomes conferred by unidentified genetic differences between East Asian and non-Asian populations;
- The effect of seasonality and climate on the spread of the SARS-CoV-2 virus as a factor in East Asian exceptional outcomes;
- The protection conferred by immunological differences between East Asian and non-Asian populations.

We offer the paper in the spirit of a preliminary assessment of the relative importance of these explanations rather than a definitive and detailed decomposition. Our focus is on outcomes that predate the widespread availability of COVID-19 vaccines that effectively protect the vaccinated against hospitalization and death. Our tentative conclusion is that, of the explanations we consider, only immunological differences are likely important in explaining the divergent East Asia numbers, but the mechanisms underlying this explanation remain to be elucidated.

2. Age and COVID-19 mortality

A crucial fact about COVID-19 infection is that there is a substantial age gradient in mortality risk. People over 70 face a sharply greater infection fatality risk than younger people (Axfors and Ioannidis, 2022). We focus on age as the critical covariate because it is the single most important risk factor predicting mortality after COVID-19 infection (SAGE, 2020). While anyone can get infected, there is a thousand-fold difference in COVID-19 mortality risk between the oldest and youngest age groups (Kulldorff, 2020).

The best estimates of covid infection fatality come from seroprevalence studies, which measure the fraction of a population with specific SARS-CoV-2 antibodies – providing evidence of past infection. Seroprevalence studies provide better evidence on the total number of people who have been infected than do case reports or positive reverse transcriptase-polymerase chain reaction (RT-PCR) test counts. The latter both miss infected people who are not identified by the public health authorities or do not volunteer for RT- PCR

[2] Statistics provided by African public health agencies also suggest relatively low rates of mortality per capita from covid in 2020 relative to countries in Europe or the Americas. Scientists have raised concern that there may be undercounting of covid incidence and mortality in many African countries (Ioannidis, 2021b). Though we believe this is a vitally important issue to resolve, we leave it for future work to address.

[3] One important caveat is that the counting of COVID-19 deaths is inconsistent across countries, with overcounting more likely in richer countries with more comprehensive capture of COVID-19 cases counting a COVID-19 death even when COVID-19 was an incidental cause, and undercounting less likely in poorer countries with less comprehensive capture of COVID-19 infections by public health authorities (Ioannidis, 2021b).

testing (Cevik et al., 2020). According to a comprehensive meta-analysis of seroprevalence studies published in the *Bulletin of the World Health Organization*, worldwide, for people under the age of 70, the infection survival ratio is 99.95%. In contrast, for people 70 and over, it is 95% (Ioannidis, 2021a).

Table 1 summarizes infection fatality rate (IFR) by continent, based on country-level IFRs reported by Ioannidis (2021a). These numbers reflect the lethality of the version of the virus circulating in 2020.[4] Since seroprevalence studies have not been conducted in every country, the estimates reflect the countries where studies have been reported. The table shows sharp differences across continents, with Europe and the Americas experiencing higher infection fatality rates than East Asia and South Asia.

Countries and regions with an older population – all else equal – will have a higher COVID-19 mortality rate. Appendix Table 1 presents the median age and proportion of the population above 65 for select countries in East Asia and elsewhere. It is striking that Japan, which has one of the oldest populations globally and would hence be expected to have a high COVID-19 mortality rate, has experienced much lower mortality during the epidemic than younger countries in Europe and the Americas. Similarly, countries with younger populations, such as Brazil, which we would expect to fare well in the epidemic, have experienced a high mortality rate. Thus, the population age structure is insufficient to explain why East Asian countries have done well. In some cases where populations are older, it deepens the puzzle of their relatively good performance during the epidemic.

3. Lockdown and non-pharmaceutical interventions

Throughout the pandemic, a popular explanation for the relative success of the East Asian countries with COVID-19 centers on lockdown policies aimed at controlling the spread of the SARS-CoV-2 virus. The idea is mechanically simple – a policy that inhibits interactions among humans will necessarily reduce the transmission of a virus that requires the proximity of infected and uninfected individuals. Lockdowns and non-pharmaceutical interventions (NPIs), however, are not all the same. Some lockdown policies are draconian, such as the forced quarantines, stay-at-home orders, and mandated school and business closures adopted by many countries. Others involve simple public health advice to stay home when sick, and of course, there is a wide range of policies between those extremes. We adopt a macro-level approach: we use a summary measure of lockdown stringency and voluntary cell phone tracking data to assess whether a country has limited its interactions among humans.

The Oxford stringency index is a statistic summarizing, on a scale from zero to 100, the adoption of 18 different lockdown policies, including shelter in place orders, border restrictions, quarantines, and school closures (Oxford COVID-19 Government Response Tracker, 2021).[5] Different countries adopted and relaxed lockdown policies at various times as the epidemic progressed. Fig. 2 shows how this index evolved from January 2020 to February 2021. According to this scoring system, China adopted the most stringent lockdowns, but New Zealand and Vietnam adopted even stricter policies early in the epidemic than even China. By contrast, Japan, South Korea, and Taiwan have consistently imposed limited lockdown measures, milder than most European and American countries.

Understanding the formal imposition of lockdown policies is essential. More important still is compliance with these policies – did lockdown actually lead to fewer interactions between people in contexts where the disease might spread? Fig. 3 plots variation in cell phone mobility data in retail and recreation contexts from February 2020 to January 2021 for six countries: Japan, South Korea, Taiwan, Thailand, Vietnam, and (for comparison) Australia (Google, 2021). Chinese mobility data are unfortunately not available. The figure is oriented with zero on the y-axis representing no mobility difference relative to a pre-COVID-19 baseline taken from January 2020.

We focus on three conclusions that the graph makes obvious. First, the advent of the epidemic in East Asia in February and March 2020 led to sharp declines in individual mobility in all of these countries except Taiwan through June 2020. They remained only marginally below the pre-COVID-19 mobility baseline in the months after that. Second, there is considerable variation across countries in the extent of mobility reductions throughout the epidemic. Third, by contrast with mobility reductions seen in Europe and the Americas (not pictured), the East Asian contraction of mobility was shallow. For instance, mobility in the locked-down UK was 60% below its mobility baseline in retail in February 2021. By then, the US and the rest of Europe had rebounded to about 20% below the pre-COVID-19 baseline.

These data presented here show a *prima facie* lack of correlation between COVID-19 results and lockdown policy. Across continents, though most countries in Europe and the Americas locked down more heavily than most East Asian countries (except China), the former experienced worse COVID-19 outcomes than the latter. There were sharp differences in the adoption of lockdowns across countries and over time within East Asia itself, yet no first-order differences in COVID-19 outcomes.

Disentangling correlation and causation is scientifically challenging and is the focus of many studies. The primary difficulty is constructing a plausible counterfactual scenario about what would have happened had formal lockdown policies not been implemented. Whatever the method employed, since there are only a limited number of randomized trials measuring the efficacy of non-pharmaceutical interventions, identifying causal effects is statistically challenging (Hirt et al., 2022).

[4] In using the Oxford stringency index, we acknowledge the discretionary dimensions of its scoring system as well as the difficulties entailed in creating a single harmonized measure of policies that differ in both their rigor of enforcement and their regional or subregional application. The index nonetheless captures the timing and relative movements of specific policy changes for cross-country comparison, which illustrates the widespread international variation in lockdowns and related NPI measures.

[5] We call specific attention to a deficit of robust causal inference strategies in the existing literature on lockdown efficacy and we highlight the need for further empirical testing of counterfactual scenarios derived from observed natural experiments, as distinct from theoretical modeling, which often conflate their own assumptions as evidence of causality.

Table 1
2020 infection fatality rate (IFR) for different regions of the world.

	Studies from	IFR	IFR for age <70
Europe	15 different Western or Central European countries	0.39%	0.06%
South Asia	India, Pakistan	0.07%	0.04%
South America	Brazil, Chile	0.20%	0.09%
North America	US and Canada	0.44%	0.10%
East Asia	Japan, Korea	0.06%	0.01%

Source: Authors calculations based on Ioannidis (2021)

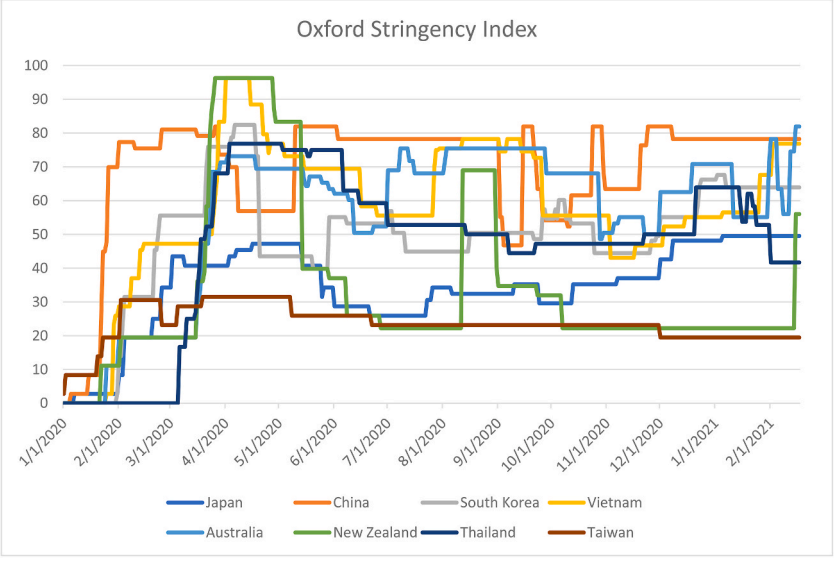

Fig. 2. Oxford lockdown stringency index on lockdown policy in East Asia.

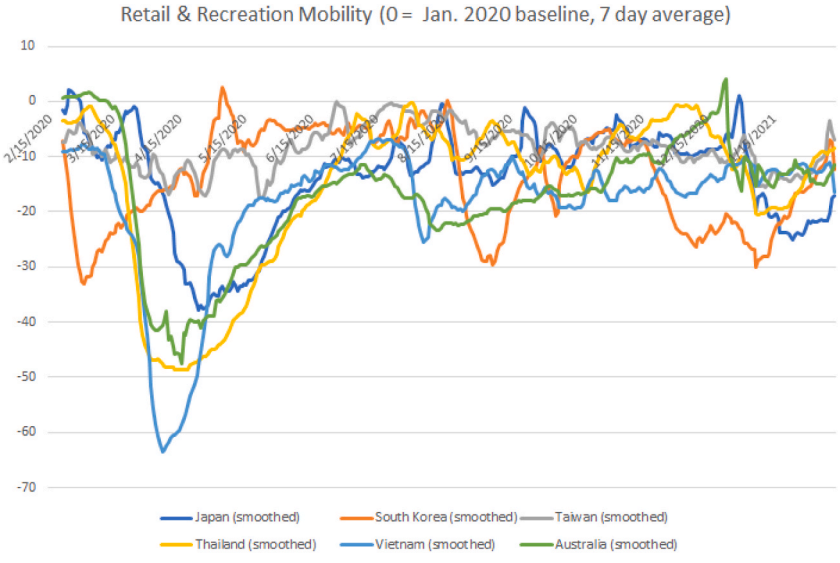

Fig. 3. Google cell phone mobility data during the COVID-19 epidemic in East Asia.

The research conducted on this topic broadly takes one of two distinct approaches. One set of studies constructs a counterfactual scenario based on a compartment or agent-based model of disease spread, comparing the model predictions about COVID-19 incidence or mortality in the presence or absence of a policy against observed data, with differences in outcomes attributed to policy differences.

A second approach compares the actual COVID-19 outcomes of countries or subnational regions that adopted different policies, attempting to adjust statistically for salient differences between observational units (Bendavid et al., 2021). The latter approach is preferable because the former often relies on forecasting models that have proved unreliable during the pandemic (Chen et al., 2021; Ioannidis et al., 2022).

A comprehensive meta-analysis of this literature found little evidence from the most credible studies that lockdowns and non-pharmaceutical interventions had a clinically meaningful effect on COVID-19-related mortality during the epidemic (Herby et al., 2022). The authors of the review downgrade papers that use modeling rather than real-world counterfactuals because of the impossibility of verifying the models' assumptions. The standards of empirical evidence in the social sciences view studies that employ real-world counterfactuals as more likely to produce causally-meaningful results.

The macro-level data on COVID-19 cases and associated mortality from East Asia similarly do not justify a conclusion that lockdowns are a primary reason why countries there had relatively low COVID-19 mortality in 2020.[6] While we cannot rule out by this analysis alone that lockdowns may have played some role in delaying the onset of infections, by the same token, we cannot rule out that lockdowns played no role whatsoever in the ultimate experience of East Asian countries with COVID-19.

4. Genetics

It is a theoretical possibility that East Asian populations have some specific genetic protection against severe reactions to SARS-CoV-2 infection. Some well-established genetic differences exist between Asian and non-Asian populations with medical consequences, such as a dominant mutation in the acetaldehyde dehydrogenase gene that causes Asian flush syndrome in some Asians after alcohol consumption (Higuchi et al., 2004). There are also differences in disease incidence thought to partially stem from epigenetic differences, such as high stomach cancer rates in Japan. (Padmanabhan et al., 2017). One simple test of this idea involves looking at COVID-19 outcomes for Asians in diaspora nations like the US, which have a large Asian population.

Table 2 shows, by ethnicity, the risk of becoming a COVID-19 case, being hospitalized for COVID-19, and dying with a COVID-19 diagnosis in the United States. The table, duplicating information provided by the US Centers for Disease Control (2021), presents these risks for each ethnicity as a multiple of the risk faced by non-Hispanic white Americans. CDC numbers show that Asians are about as likely to die from COVID-19 as whites in the US and less likely to die from COVID-19 than African Americans and Hispanics.[7] There is no evidence in these data that would lead us to conclude that genetic differences are important in explaining East Asian COVID-19 outcomes.

5. Climate and seasonal effects on the spread of COVID-19

Like other coronaviruses in common human circulation, there is a correlation between COVID-19 spread and the changing of the seasons. Broadly speaking, the highest case loads have come during the late fall and winter in the Northern Hemisphere. However, there are exceptions to this rule, with some areas like the American south experiencing substantial COVID-19 waves in the summer. Other factors, including humidity and other climactic contributors, are thought to play a role as well. A systematic analysis of worldwide COVID-19 case rates through 2020 found a correlation between latitude and country-level case rates, with lower case rates in countries nearer the equator (Chen et al., 2021).

However, the fact that seasonality and geography contribute to COVID-19 spread does not necessarily mean that they are primary explanations for the exceptional East Asian outcomes. The nations of East Asia vary wildly in their geography and climate. Yet, the region as a whole experienced much less heterogeneity in COVID-19 outcomes than might be inferred from seasonal and climatological differences. Even within Japan, in the spring of 2020, COVID-19 prevalence varied from 2.7% in Kobe in the southern part of the country (Doi et al., 2021) and 0.17% in Sapporo in the north (Suda et al., 2020).[8] A systematic review of the literature in 2020 concluded that: "Considering the existing scientific evidence, warm and wet climates seem to reduce the spread of COVID-19. However, these variables alone could not explain most of the variability in disease transmission" (Mecenas et al., 2020). Climate then may matter, but there must be other contributors that matter more.

6. Immunological explanations

If age, lockdown, and genetics are insufficient to explain relatively good COVID-19 outcomes experienced by East Asian countries, what can? Though the answer is still unknown, one prominent hypothesis – the presence of some protective immunity in East Asian populations that predates the official start of the epidemic in December 2019 in China – may prove to be the answer. We present two possible mechanisms here, both premised on the idea that these mechanisms are differentially more important in East Asia – for

[6] One important limitation of this finding is that it does not distinguish South Asian and East Asian origin populations in the US. We do not know any source that separately tracks covid incidence and mortality in the US for South Asian and East Asian populations. The figures we present are a weighted average of covid outcomes for the two populations, with a substantial majority of Asians in the United States of East Asian rather than South Asian origin. The latter represent about 19% of the populations of Asians in the United States (US Census, 2022). In 2020, covid incidence in India was higher than in most East Asian countries, but per capita covid mortality nevertheless low relative to countries in Europe and the Americas.

[7] While the Kobe study sampled a community population, the Sapporo study focused on patients with asymptomatic liver disease. This sampling difference may contribute to the difference in measured prevalence, though the direction of this bias is impossible to sign.

Table 2
Relative risk of COVID-19 infection, hospitalization, and death in the U.S.by ethnicity.

Rate ratios compared to white, non-Hispanic	American Indian or Alaska native, non-Hispanic	Asian, non-Hispanic	Black or African American, non-Hispanic	Hispanic or Latino
COVID-19 Cases	1.9x	0.7x	1.1x	1.3x
COVID-19 Hospitalization	3.7x	1.1x	2.9x	3.2x
COVID-19 Deaths	2.4x	1.0x	1.9x	2.3x

Source: CDC (2021).

reasons that are not fully understood – than they are elsewhere. We emphasize that our discussion here is meant to motivate hypotheses rather than provide definitive evidence.

There is considerable evidence in the biomedical literature that prior infection by other human coronaviruses (included among the common cold viruses) confers some protection against severe manifestations of COVID-19 disease (Sattar et al., 2020; Ng et al., 2020). There is also some evidence that patients who were previously infected with the original SARS virus in 2003 retain memory T-cells that are cross-reactive with the SARS-CoV-2 virus (Le Bert et al., 2020). One study finds that parents with young children, who are more likely to be exposed to other human coronaviruses frequently, are less likely to require hospitalization after SARS-CoV-2 infection, presumably due to cross-reactive immunity (Wood et al., 2020).

A recent study by Swadling et al. (2022) considered health care workers who were repeatedly exposed to the SARS-CoV-2 virus but never tested positive by PCR for the virus and never developed clinical symptoms of COVID-19. The authors posted that these workers who never seroconverted possessed "pre-existing memory T cells with cross-protective potential against SARS-CoV-2" as the potential mechanism. They compared the memory T-cell response against control samples drawn from before the pandemic. The authors identified a specific T-cell response against the replication-transcriptase complex (RTC), which is transcribed early in SARS-CoV-2 replication and occurs more frequently in the seronegative health care workers than in the control samples. This specific T-cell response halts RNA replication early and may be responsible for aborting the development of clinical symptoms in the health care workers despite exposure. (Swadling et al., 2022). The authors conclude that:

> "Individuals with potential exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) do not necessarily develop PCR or antibody positivity, suggesting that some individuals may clear subclinical infection before seroconversion."

While this is a promising hypothesis, it is not yet established that cross-reactive immunity is more common in East Asia than in Europe and the Americas.

A second immunological hypothesis to explain the East Asian COVID-19 outcomes posits the early spread of the SARS-CoV-2 virus throughout East Asia (Djaparidze and Lois, 2020). In this hypothesis, the virus mutated at some point to become both more infectious and more deadly before it spread outside. East Asia was protected by the immunity provided by infection by the less virulent viral strain, which spread before the mutation. In support of this hypothesis, there is increasing evidence that the virus spread in China several months before the official start date of the epidemic in December 2019 (Nsoesie et al., 2020; Hinshaw et al., 2021; Woodward, 2021). However, there is no direct evidence that we are aware that the earliest viral variants were less infectious or less deadly than the viral variant that spread throughout Europe and the Americas in February and March 2020, so this hypothesis is very speculative.

Pre-existing immunity could have been sufficient to suppress the early variants of covid below the herd immunity threshold, but not the later, more contagious Omicron variant. That would explain a few cases early on, followed by sharp spikes once Omicron arrived.

7. Conclusions

The relatively low COVID-19 prevalence in East Asia in 2020 is a genuine puzzle needing an explanation. Of the explanations we have considered, lockdowns, genetics, seasonality, and climate are less likely to solve the puzzle. The relatively older demographic composition of some East Asian countries deepens the mystery since COVID-19 is more likely to cause severe disease in older patients. On the other hand, a differential presence of pre-existing protection against SARS-CoV-2 infection – perhaps from prior human coronavirus or SARS 1 infection – is the most likely answer, but questions remain regarding the specific mechanism. Whatever the mechanism turns out to be, it will need to explain the rapid spread of COVID-19 through East Asia, including China, with the arrival of the Omicron variant in 2022.

There are other potential explanations of East Asian exceptionalism that we do not explicitly consider in this paper such as the culture of masking in East Asian countries. Some scientists and many public health agencies around the world have encouraged routine masking as a population measure to reduce the spread of the SARS-CoV-2 virus (World Health Organization, 2022). It's true that surveys show high mask compliance in some East Asian countries during the pandemic than in many other non-East Asian countries. An April 2020 YouGov survey showed substantially higher prevalence of masking in East Asian countries than in the rest of the world, though masking compliance was high in non-East Asian countries like India, the US, Italy, and Spain (Choubey, 2020). Nevertheless, this culture of masking has not protected East Asian populations from the spread of omicron covid in 2022. It's possible that masks were effective against earlier variants but less effective against omicron, though there is no physical reason to believe that to be the case. The randomized evidence on the effectiveness of mask wearing against the spread of respiratory viruses like influenza and indeed covid itself, does not provide a strong basis to conclude a high degree of protection provided by masking.

Since near the beginning of the pandemic, obesity has been identified as a risk factor for severe covid disease in individuals who are

infected (Sattar et al., 2020). Of course, the populations of East Asian countries are less likely to be obese than most the populations of countries in European and the Americas (World Health Organization, 2017). For instance, in 2017, the measured prevalence of obesity in Japan, China, Sweden, Italy, and the United States in 2017 were 4.3%, 6.2%, 20.6%, 19.9%, and 36.2% respectively. However, the interaction between covid disease and obesity is complicated. A March 2021 meta-analysis on the topic found that obese individuals were more likely to suffer severe disease than non-obese individuals on infection, but not more likely die from the infection (Zhang et al., 2021). The influence of body weight on covid incidence is perhaps even more complicated, as obese populations are more likely to be poor and were less able to comply with social distancing dictates during the pandemic. Though this explanation cannot be ruled out, we think it unlikely or sufficient to explain the exceptional outcomes of East Asian countries in 2020.

There are still other explanations that we did not consider. For instance, one hypothesis posits the better performance of health care systems where overcrowding of hospitals did not occur as a contributor to successful management of the epidemic. However, Japan and China both experienced low COVID-19 mortality in 2020, although Japan's high number of hospitals per capita meant that hospitals were unlikely to be overwhelmed (Yoshikawa et al., 1996), while Chinese hospitals in Wuhan were famously overwhelmed early in the epidemic. Another complication we do not address relates to differences between countries in how COVID-19 cases and deaths are defined. Some countries require stricter evidence, while others require looser proof to establish that patient has COVID-19 (Ioannidis, 2021b). Finally, there are unresolved concerns about the reliability of China's official COVID-19 statistics related to political factors affecting the reporting of the pandemic at its outset (He et al., 2020).

Though we do not provide a complete answer to this puzzle, the *prima facie* evidence that age, lockdowns, genetics, and seasonality are unlikely to be a key part of the story is an essential lesson for COVID-19 policy in East Asia and beyond.

CRediT authorship contribution statement

Jay Bhattacharya: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Phillip Magness:** Methodology, Investigation, Writing – original draft, Visualization. **Martin Kulldorff:** Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None of the authors has accepted any payment for his work on this paper or has a conflict of interest to report. We are grateful to Eran Bendavid and John Ioannidis for helpful comments and suggestions. All views expressed and errors are our own.

Data availability

Data will be made available on request.

Appendix

Table 1
Population Age Structure from Select Countries

	Median age (2017)	% over age 65 (2017)
Asia		
Japan	46.3	27.0%
Taiwan	39.6	13.9%
South Korea	40.8	13.9%
Vietnam	30.4	7.2%
Thailand	37.8	11.4%
China	37.0	10.6%
North America		
United States	37.6	15.4%
Canada	40.5	17.0%
South America		
Brazil	31.3	8.6%
Mexico	27.5	6.9%
Peru	27.5	7.2%
Argentina	30.8	11.2%
Europe		
France	41.2	19.7%
UK	40.2	18.5%
Germany	45.9	21.5%
Sweden	40.9	19.9%
Italy	45.9	23.0%
Africa		

(*continued on next page*)

Table 1 (*continued*)

	Median age (2017)	% over age 65 (2017)
Kenya	19.0	2.7%
Egypt	24.7	5.2%
Congo	18.9	3.0%
Mozambique	17.2	3.2%
South Africa	26.1	5.3%

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