

Assessing the Age Specificity of Infection Fatality Rates for COVID-19: Systematic Review, Meta-Analysis, and Public Policy Implications

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Structured Abstract

Objective: Determine age-specific infection fatality rates for COVID-19 to inform public health policies and communications that help protect vulnerable age groups.

Methods: Studies of COVID-19 prevalence were collected by conducting an online search of published articles, preprints, and government reports. A total of 120 studies were reviewed in depth and screened, of which 34 studies satisfied the inclusion criteria and were included in the meta-analysis. Age-specific IFRs were computed using the prevalence data in conjunction with reported fatalities four weeks after the midpoint date of the study, reflecting typical lags in fatalities and reporting. Meta-regression procedures in Stata were used to analyze IFR by age.

Results: Our analysis finds an exponential relationship between age and IFR for COVID-19. The estimated age-specific IFRs are very low for children and younger adults but increase progressively to 0.4% at age 55, 1.4% at age 65, 4.6% at age 75, and 15% at age 85. We find that differences in the age structure of the population and the age-specific prevalence of COVID-19 explain about 90% of the geographical variation in population IFR.

Discussion: These results indicate that COVID-19 is hazardous not only for the elderly but also for middle-aged adults, for whom the infection fatality rate is two orders of magnitude greater than the annualized risk of a fatal automobile accident and far more dangerous than seasonal influenza. Moreover, the overall IFR for COVID-19 should not be viewed as a fixed parameter but as intrinsically linked to the age-specific pattern of infections. Consequently, public health measures to mitigate infections in older adults could substantially decrease total deaths.

Introduction

Since the onset of the COVID-19 pandemic in winter 2020, it has been evident that the severity of the disease varies markedly across infected individuals.[1, 2] Some remain asymptomatic throughout the course of infection or experience only mild symptoms such as headache or ageusia, whereas others experience much more severe illness, hospitalization, or even death. Thus, official case reporting may tend to encompass a high fraction of severe cases but only a small fraction of asymptomatic or mildly symptomatic cases. Moreover, the availability of live virus tests has varied significantly across locations and over time, and the deployment of such tests may differ markedly across demographic groups.

Consequently, assessments of the *case fatality rate* (*CFR*), the ratio of deaths to reported cases, are fraught with pitfalls in gauging the severity of COVID-19. For example, early case reports from Wuhan noted a preponderance of older people among hospital admissions and a high CFR. Subsequent studies have documented that children and young adults tend to exhibit fewer and milder symptoms and a far lower CFR. Nonetheless, the link between age and severity of COVID-19 infections has remained unclear for the reasons noted above.

To provide more accurate assessments of the spread of COVID-19, researchers have conducted seroprevalence studies in numerous locations. Such studies analyze samples of serum to detect antibodies in those infected with SARS-CoV-2, the virus that causes COVID-19. Seroprevalence results can be used to estimate the *infection fatality rate* (*IFR*), the ratio of fatalities to total infections, thereby facilitating the identification of vulnerable segments of the population and informing key policy decisions aimed at mitigating the consequences of the pandemic.

For example, as shown in Table 1, the New York Department of Health conducted a large-scale seroprevalence study and estimated about 1.6 million SARS-CoV-2 infections among the 8 million residents of New York City.[3] However, only one-tenth of those infections were captured in reported COVID-19 cases, about one-fourth of which required hospitalization, and a substantial fraction of cases had fatal outcomes.[4] All told, COVID-19 fatalities in NYC represented a tenth of reported cases but only one-hundredth of all SARS-CoV-2 infections.

Nonetheless, divergences in study design and reporting have hampered comparisons of seroprevalence and IFRs across locations and demographic groups. For example, a number of studies have analyzed a representative sample of the general population, while other studies have made use of “convenience samples” of residual sera collected for other purposes (such as laboratory tests or blood donations). Some studies have simply reported results for raw prevalence (the fraction of seropositive results), whereas other studies have reported results adjusted for antibody test characteristics (sensitivity and specificity).

While the NYC data indicate an IFR of about 1%, seroprevalence estimates from other locations have yielded a wide array of IFR estimates, ranging from about 0.6% in Geneva to levels exceeding 2% in northern Italy. Such estimates have fueled intense controversy about the

severity of COVID-19 and the appropriate design of public health measures to contain it, which in turn hinges on whether the hazards of this disease are mostly limited to the elderly and infirm. Indeed, a recent meta-analysis noted the high degree of heterogeneity across aggregate estimates of IFR and concluded that research on age-stratified IFR is “*urgently needed to inform policymaking.*”[5]

This paper reports on a systematic review and meta-analysis of age-specific IFRs for COVID-19. We specifically consider the hypothesis that the observed variation in IFR across locations may primarily reflect the age specificity of COVID-19 infections and fatalities. Based on these findings, we are able to assess and contextualize the severity of COVID-19 and examine how age-specific prevalence affects the population IFR and the total incidence of fatalities.

Methodology

To perform the present meta-analysis, we collected published papers and preprints on the seroprevalence and/or infection fatality rate of COVID-19 that were publicly disseminated prior to 18 September 2020. As described in Supplementary Appendix B, we systematically performed online searches in MedRxiv, Medline, PubMed, Google Scholar, and EMBASE, and we identified other studies listed in reports by government institutions such as the U.K. Parliament Office.[6] Data was extracted from studies by three authors and verified prior to inclusion.

We restricted our meta-analysis to studies of advanced economies, based on current membership in the Organization for Economic Cooperation and Development (OECD), in light of the distinct challenges of health care provision and reporting of fatalities in developing economies.[7] We also excluded studies aimed at measuring prevalence in specific groups such as health care workers.

Our meta-analysis encompasses two distinct approaches for assessing the prevalence of COVID-19: (1) seroprevalence studies that test for antibodies produced in response to the virus, and (2) comprehensive tracing programs using extensive live-virus testing of everyone who has had contact with a potentially infected individual. Seroprevalence estimates are associated with uncertainty related to the sensitivity and specificity of the test method and the extent to which the sampling frame provides an accurate representation of prevalence in the general population; see Supplementary Appendix C. Prevalence measures from comprehensive tracing programs are associated with uncertainty about the extent of inclusion of infected individuals, especially those who are asymptomatic.

Sampling frame

To assess prevalence in the general population, a study should be specifically designed to utilize a random sample using standard survey procedures such as stratification and weighting by demographic characteristics. Other sampling frames may be useful for specific purposes such as

sentinel surveillance but not well-suited for assessing prevalence due to substantial risk of systemic bias. Consequently, our meta-analysis excludes the following types of studies:

- *Blood Donors.* Only a small fraction of blood donors are ages 60 and above—a fundamental limitation in assessing COVID-19 prevalence and IFRs for older age groups—and the social behavior of blood donors may be systematically different from their peers.[8, 9] These concerns can be directly investigated by comparing alternative seroprevalence surveys of the same geographical location. As of early June, Public Health England (PHE) reported seroprevalence of 8.5% based on specimens from blood donors, whereas the U.K. Office of National Statistics (ONS) reported markedly lower seroprevalence of 5.4% (CI: 4.3–6.5%) based on its monitoring of a representative sample of the English population.[10, 11]
- *Dialysis Centers.* Assessing seroprevalence of dialysis patients using residual sera collected at dialysis centers is crucial for gauging the infection risks faced by these individuals, of which a disproportionately high fraction tend to be underrepresented minorities. Nonetheless, the seroprevalence within this group may be markedly different from that of the general population. For example, a study of U.K. dialysis patients found seroprevalence of about 36%, several times higher than that obtained using a very large random sample of the English population.[12, 13] Similarly, a recent U.S. study found a seropositive rate of 34% for dialysis patients in New York state that was more than twice as high as the seroprevalence in a random sample of New York residents.[3, 14]
- *Hospitals and Urgent Care Clinics.* Estimates of seroprevalence among current medical patients are subject to substantial bias, as evident from a pair of studies conducted in Tokyo, Japan: One study found 41 positive cases among 1071 urgent care clinic patients, whereas the other study found only two confirmed positive results in a random sample of nearly 2000 Tokyo residents (seroprevalence estimates of 3.8% vs. 0.1%).[15, 16]
- *Active Recruitment.* Soliciting participants is particularly problematic in contexts of low prevalence, because seroprevalence can be markedly affected by a few individuals who volunteer due to concerns about prior exposure. For example, a Luxembourg study obtained positive antibody results for 35 out of 1,807 participants, but nearly half of those individuals (15 of 35) had previously had a positive live virus test, were residing in a household with someone who had a confirmed positive test, or had direct contact with someone else who had been infected.[17]

Our critical review has also underscored the pitfalls of seroprevalence studies based on “convenience samples” of residual sera collected for other purposes. For example, two studies assessed seroprevalence of Utah residents during spring 2020. The first study analyzed residual sera from two commercial laboratories and obtained a prevalence estimate of 2.2% (CI: 1.2–3.4%), whereas the second study collected specimens from a representative sample and obtained

a markedly lower prevalence estimate of 0.96% (CI: 0.4–1.8%).[18, 19] In light of these issues, our meta-analysis includes residual serum studies but we flag such studies as having an elevated risk of bias.

Comprehensive Tracing Programs

Our meta-analysis incorporates data on COVID-19 prevalence and fatalities in countries that have consistently maintained comprehensive tracing programs since the early stages of the pandemic. Such a program was only feasible in places where public health officials could conduct repeated tests of potentially infected individuals and trace those whom they had direct contact. We identify such countries using a threshold of 300 for the ratio of cumulative tests to reported cases as of 30 April 2020, based on comparisons of prevalence estimates and reported cases in Czech Republic, Korea, and Iceland; see Supplementary Appendices D and E.[20] Studies of Iceland and Korea found that estimated prevalence was moderately higher than the number of reported cases, especially for younger age groups; hence we make corresponding adjustments for other countries with comprehensive tracing programs, and we identify these estimates as subject to an elevated risk of bias.[21–23]

Measurement of fatalities

Accurately measuring total deaths is a substantial issue in assessing IFR due to time lags from onset of symptoms to death and from death to official reporting. Symptoms typically develop within 6 days after exposure but may develop as early as 2 days or as late as 14 days.[1, 24] More than 95% of symptomatic COVID patients have positive antibody (IgG) titres within 17–19 days of symptom onset, and those antibodies remain elevated over a sustained period.[25–28] The mean time interval from symptom onset to death is 15 days for ages 18–64 and 12 days for ages 65+, with interquartile ranges of 9–24 days and 7–19 days, respectively, while the mean interval from date of death to the reporting of that person’s death is about 7 days with an IQR of 2–19 days; thus, the upper bound of the 95% confidence interval between symptom onset and reporting of fatalities is about six weeks (41 days).[29]

Figure 1 illustrates these findings in a hypothetical scenario where the pandemic was curtailed two weeks prior to the date of the seroprevalence study. This figure shows the results of a simulation calibrated to reflect the estimated distribution for time lags between symptom onset, death, and inclusion in official fatality reports. The histogram shows the frequency of deaths and reported fatalities associated with the infections that occurred on the last day prior to full containment. Consistent with the confidence intervals noted above, 95% of cumulative fatalities are reported within roughly four weeks of the date of the seroprevalence study.

As shown in Table 2, the precise timing of the count of cumulative fatalities is relatively innocuous in locations where the outbreak had been contained for more than a month prior to the date of the seroprevalence study. By contrast, in instances where the outbreak had only recently

been contained, the death count continued rising markedly for several more weeks after the midpoint of the seroprevalence study.

Therefore, we construct age-specific IFRs using the seroprevalence data in conjunction with cumulative fatalities four weeks after the midpoint date of each study; see Supplementary Appendix F. We have also conducted sensitivity analysis using cumulative fatalities five weeks after the midpoint date, and we flag studies as having an elevated risk of bias if the change in cumulative fatalities between weeks 4 and 5 exceeds 10%.

By contrast, matching prevalence estimates with subsequent fatalities is not feasible if a seroprevalence study was conducted in the midst of an accelerating outbreak. Therefore, our meta-analysis excludes seroprevalence studies for which the change in cumulative fatalities from week 0 to week 4 exceeds 200%.

Metaregression procedure

To analyze IFR by age, we use meta-regression with random effects, using the *meta regress* procedure in *Stata* v16.[30, 31] We used a random-effects procedures to allow for residual heterogeneity between studies and across age groups by assuming that these divergences are drawn from a Gaussian distribution. Publication bias was assessed using Egger's regression and the trim-and-fill method. See Supplementary Appendix G for further details.

Results

After an initial screening of 1153 studies, we reviewed the full texts of 120 studies, of which 54 studies were excluded due to lack of age-specific data on COVID-19 prevalence or fatalities.[11, 15, 16, 28, 32-81] Seroprevalence estimates for two locations were excluded because the outbreak was still accelerating during the period when the specimens were being collected and from two other locations for which age-specific seroprevalence was not distinguishable from zero.[18, 82-84] Studies of non-representative samples were excluded as follows: 13 studies of blood donors; 5 studies of patients of hospitals, outpatient clinics, and dialysis centers; 4 studies with active recruitment of participants, and 6 narrow sample groups such as elementary schools.[10, 14, 16, 17, 82, 85-107] Supplementary Appendix H lists all excluded studies.

Consequently, our meta-analysis encompasses 34 studies, of which 28 are included in our metaregression and 6 are used for out-of-sample analysis. The metaregression studies can be categorized into three distinct groups:

- *Representative samples* from studies of England, France, Ireland, Italy, Netherlands, Portugal, Spain, Geneva (Switzerland), and four U.S. locations (Atlanta, Indiana, New York, and Salt Lake City).[3, 13, 19, 108-117]

- *Convenience samples* from studies of Belgium, Sweden, Ontario (Canada), and eight U.S. locations (Connecticut, Louisiana, Miami, Minneapolis, Missouri, Philadelphia, San Francisco, and Seattle).[18, 118-120]
- *Comprehensive tracing programs* for Australia, Iceland, Korea, Lithuania, and New Zealand.[121-125]

The metaregression includes results from the very large REACT-2 seroprevalence study of the English population.[13] Thus, to avoid pitfalls of nested or overlapping samples, two other somewhat smaller studies conducted by U.K. Biobank and the U.K. Office of National Statistics are not included in the metaregression but are instead used in out-of-sample analysis of the metaregression results.[11, 126] Similarly, the metaregression includes two large-scale studies involving representative samples from three French provinces and from Salt Lake City, and hence two other studies using convenience samples from laboratories in France and in Utah are used in the out-of-sample analysis along with two other small-scale studies.[18, 19, 127-129]

Data taken from included studies is shown in Supplementary Appendix I. Supplementary Appendix J assesses the risk of bias for each individual study. As indicated in Supplementary Appendix K, no publication bias was found using Egger's test ($p > 0.10$), and the trim-and-fill method produced the same estimate as the metaregression.

We obtain the following metaregression results:

$$\log_{10}(IFR) = \begin{matrix} -3.27 \\ (0.07) \end{matrix} + \begin{matrix} 0.0524 * age \\ (0.0013) \end{matrix}$$

where the standard error for each estimated coefficient is given in parentheses. These estimates are highly significant with t-statistics of -44.5 and 40.4, respectively, and p-values below 0.0001. The residual heterogeneity $\tau^2 = 0.071$ (p-value < 0.0001) and $I^2 = 97.0$, confirming that the random effects are essential for capturing unexplained variations across studies and age groups. The adjusted R^2 is 94.7%.

As noted above, the validity of this metaregression rests on the condition that the data are consistent with a Gaussian distribution. The validity of that assumption is evident in Figure 3: Nearly all of the observations fall within the 95% prediction interval of the metaregression, and the remainder are moderate outliers.

This specification of the metaregression also assumes that the intercept and slope parameters are stable across the entire age distribution. We have confirmed the validity of that assumption by estimating alternative specifications in which the parameters are allowed to differ between three distinct age categories (ages 0–34, 35–59, and 60+ years). The estimated parameters are similar across all three age categories, and the null hypothesis of parameter constancy is consistent with the metaregression data (see Supplementary Appendix L).

Figure 4 depicts the exponential relationship between age and the level of IFR in percent, and Figure 5 shows the corresponding forest plot. Evidently, the SARS-CoV-2 virus poses a

substantial mortality risk for middle-aged adults and even higher risks for elderly people: The IFR is very low for children and young adults but rises to 0.4% at age 55, 1.4% at age 65, 4.6% at age 75, 15% at age 85, and exceeds 25% for ages 90 and above. These metaregression predictions are well aligned with the out-of-sample IFRs; see Supplementary Appendix M.

As shown in Figure 6, the metaregression explains nearly 90% of the geographical variation in population IFR, which ranges from about 0.5% in Salt Lake City and Geneva to 1.5% in Australia and England and 2.7% in Italy. The metaregression explains this variation in terms of differences in the age structure of the population and age-specific prevalence of COVID-19.

Discussion

The IFR is central to our understanding of the public health impact of the COVID-19 pandemic and the appropriate policies for mitigating those consequences. In the absence of effective therapies or vaccines, such policies will primarily involve non-pharmaceutical interventions (NPIs). NPIs may include relatively mild measures (such as prohibitions on large gatherings) or more draconian restrictions such as shelter-in-place edicts, popularly known as “lockdowns.”

Unfortunately, public debate on these issues has been hampered by diverging assessments of the severity of COVID-19. For example, some early seroprevalence studies (using relatively small and non-representative samples, often in areas of low prevalence) yielded miniscule estimates of population IFR similar to those of seasonal influenza. Such estimates implied that strict NPIs would be completely irrational given the limited benefits and severe economic and social costs. With the dissemination of many more seroprevalence studies over recent months, a wide array of hypotheses have been mooted to explain the diverging implications for IFR, including regional variations in the quality of treatment or the extent of T-cell immunity to other betacoronaviruses.

By contrast, our critical review identifies the key characteristics of seroprevalence studies that can be used to provide reliable assessments of IFR. Indeed, once we focus on this group of studies (which includes nine national seroprevalence studies), our metaregression reveals a remarkably high degree of consistency in the implications for age-specific IFR. Moreover, our results indicate that most of the variation in population IFR across locations reflects differences in the extent to which vulnerable age groups were exposed to the virus.

One key implication of our findings is that the incidence of fatalities from a COVID-19 outbreak depends crucially on the age groups that are infected, which in turn reflects the age structure of that population and the extent to which public health measures limit the incidence of infections among vulnerable age groups. Indeed, even if an outbreak is mainly concentrated among younger people, it may be very difficult to prevent the virus from spreading among older adults.

To illustrate the benefits of age-stratified public health strategies for COVID-19, we have constructed a set of three scenarios for the U.S. trajectory of infections and fatalities (see Supplementary Appendix N). Each scenario assumes that U.S. prevalence rises to a plateau of

around 20% but with different patterns of age-specific prevalence. In particular, if prevalence becomes uniform across age groups, this analysis projects that total U.S. fatalities would exceed 500 thousand and that population IFR would converge to around 0.8%. By contrast, a scenario with relatively low incidence of new infections among vulnerable age groups would be associated with less than half as many deaths and a much lower population IFR of about 0.3%.

A further implication of our results is that the risks of infection to the middle aged cannot be neglected. This is important for pandemic management strategies that aim to avoid large influxes of patients to healthcare. Indeed, it is likely that an unmitigated outbreak among adults over 35 years old could have severe consequences on the healthcare system. Table 3 contextualizes this issue by comparing the age-specific IFRs from our meta-regression analysis to the annualized risks of fatal automobile accidents or other unintentional injuries in England and in the United States.[130, 131] For example, an English person aged 55–64 years who gets infected with SARS-CoV-2 faces a fatality risk that is more than 200 times higher than the annual risk of dying in a fatal car accident. These results also confirm that COVID-19 is far more deadly than seasonal flu, for which the population IFR is about 0.05% (see Supplementary Appendix O). Moreover, seasonal influenza outbreaks are limited by prior immunity, whereas that is not the case for SARS-CoV-2.

Our critical review highlights the benefits of assessing prevalence using large-scale studies of representative samples of the general population rather than convenience samples of blood donors or medical patients. Conducting such studies on an ongoing basis will enable public health officials to monitor changes in prevalence among vulnerable age groups and gauge the efficacy of public policy measures. Moreover, such studies enable researchers to assess the extent to which antibodies to SARS-CoV-2 may gradually diminish over time as well as the extent to which advances in treatment facilitate the reduction of age-specific IFRs.

Our critical review also underscores the importance of methodological issues in assessing IFR. For example, the raw prevalence results reported by a national study of Italy would imply a population IFR of about 2.3%, whereas test-adjusted prevalence implies a substantially higher IFR of 2.7%. Likewise, a few recent studies have excluded all deaths occurring in nursing homes and retirement communities and have obtained estimates of population IFR that are markedly lower than our estimates based on all confirmed COVID-19 fatalities, whereas assessments of IFR based on measures of excess mortality are broadly similar to our estimates.[110, 132-134] See Supplementary Appendix P for further discussion.

Our metaregression results are broadly consistent with the study of Verity et al. (2020), which was completed at a very early stage of the COVID-19 pandemic and characterized an exponential pattern of age-specific IFRs (see Supplementary Appendix Q).[135] Our results are also well-aligned with a more recent meta-analysis of population IFR; indeed, our age-specific analysis explains a very high proportion of the dispersion in population IFRs highlighted by that study.[5] In contrast, our findings are markedly different from those of an earlier review of

population IFR, mostly due to differences in selection criteria.[136] Finally, the exponential pattern of our age-specific IFR estimates is qualitatively similar to that of age-specific CFRs but the magnitudes are systematically different (see Supplementary Appendix R).

A potential concern about measuring IFR based on seroprevalence is that antibody titers may diminish over time, leading to underestimation of true prevalence and corresponding overestimation of IFR, especially for locations where the seroprevalence study was conducted several months after the outbreak had been contained. However, a key feature of our metaregression analysis is that we also utilize age-specific IFR data based on RT-PCR results (*not* seroprevalence) for five countries that have maintained comprehensive tracing programs since the onset of the pandemic, namely, Australia, Iceland, Korea, Lithuania, and New Zealand. As shown in figure 3, the age-specific IFRs for those five countries are well aligned with the metaregression predictions, indicating that these findings do not rely upon any specific method of gauging prevalence.

A substantial limitation of our work is that we have not considered factors apart from age that affect the IFR of COVID-19. For example, a recent U.K. study found that mortality outcomes are strongly linked to specific comorbidities such as diabetes and obesity but did not resolve the question of whether those links reflect differences in prevalence or causal effects on IFR.[137] See Supplementary Appendix S for additional evidence. Likewise, we have not considered the extent to which IFRs may vary with other demographic factors such as race and ethnicity or potential causal interactions between these factors.[32, 61] Further research on these issues is clearly warranted.

It should also be noted that our analysis has focused exclusively on the incidence of fatalities but has not captured the full spectrum of adverse health consequences of COVID-19, some of which may be severe and persistent. Further research is needed to assess age-stratified rates of hospitalization as well as longer-term sequelae attributable to SARS-CoV-2 infections. These factors are likely to be particularly important in quantifying risks to health care.

In summary, our meta-analysis demonstrates that COVID-19 is not only dangerous for the elderly and infirm but also for healthy middle-aged adults. The metaregression explains nearly 90% of the geographical variation in population IFR, indicating that the population IFR is intrinsically linked to the age-specific pattern of infections. Consequently, public health measures to protect vulnerable age groups could substantially reduce the incidence of mortality.

Declaration of Interests

The authors have no financial interests nor any other conflicts of interest related to this study. No funding was received for conducting this study. This study was preprinted at:

<https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v3>.

Table 1: COVID-19 Infections in New York City

	<u>Total as of July 15, 2020</u>	<u>Share of Infections</u>
NYC residents	8 million	NA
Estimated infections	1.6 million	100%
Symptomatic infections	1.1 million	65%
Reported cases	220 thousand	12%
Hospitalized patients	55 thousand	3%
Fatal outcomes	23 thousand	1%

Note: This table reports on the characteristics of COVID-19 infections in New York City (NYC). Infection prevalence was estimated by the New York Department of Health.[3] The ratio of symptomatic to total infections reflects a recent assessment by the U.S. Center for Disease Control and Prevention.[29] The number of cases, hospitalized patients, and fatal outcomes is reported by the NYC Department of Health.[4]

Table 2: Timing of reported fatalities for selected seroprevalence studies

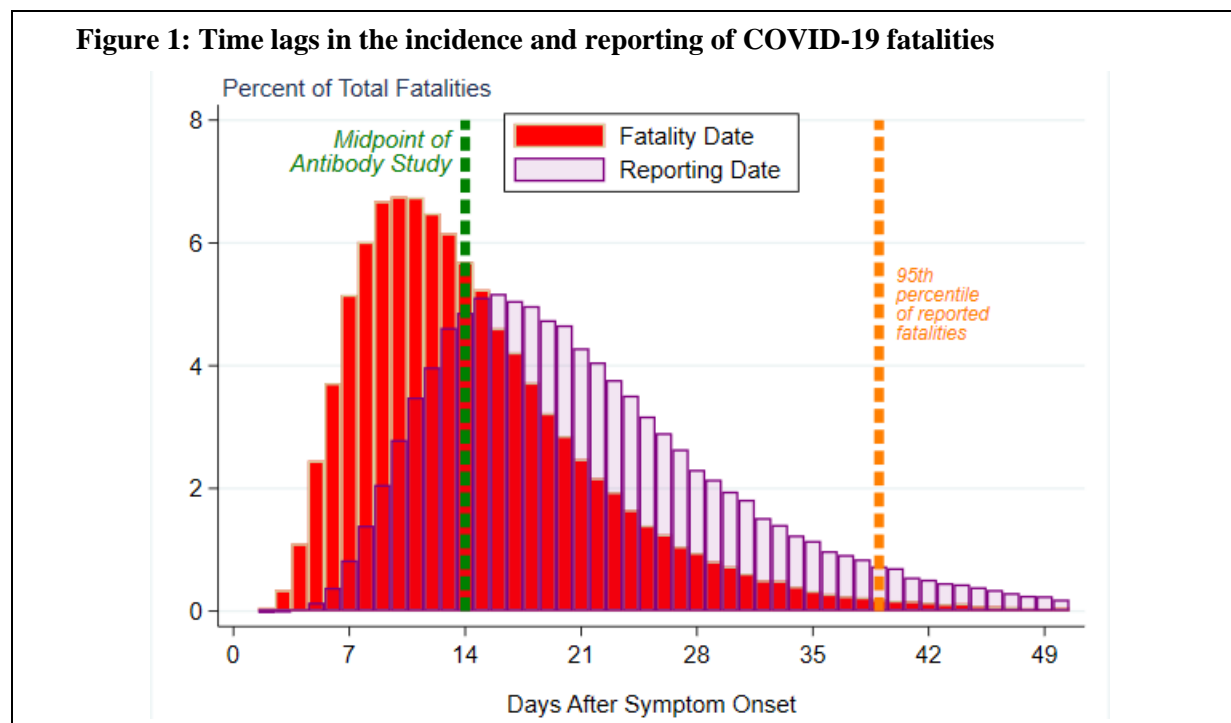
Location	Cumulative Fatalities			Change (%)	
	Study midpoint	4 weeks later	5 weeks later	Weeks 0 to 4	Weeks 4 to 5
Europe					
Belgium	6,262	8,843	9,150	41	3
Geneva, Switzerland	255	287	291	13	1
Spain	26,834	27,136	28,324	1	4
Sweden	2,586	3,831	3,940	48	3
USA					
Connecticut	2,257	3,637	3,686	61	1
Indiana	932	1,984	2,142	113	8
Louisiana	477	2,012	2,286	322	14
Miami	513	1,160	1,290	126	11
Minneapolis	393	964	1093	145	13
Missouri	218	562	661	158	18
New York	20,212	28,663	29,438	42	3
Philadelphia	456	1509	1754	231	16
San Francisco	265	424	449	60	6
Seattle	536	732	775	37	6
Utah	41	96	98	134	2

Note: This table shows data on confirmed COVID-19 deaths for 4 European locations and 11 U.S. locations where seroprevalence has been assessed.[18, 114, 119, 138-140] Sources of fatality data are given in Supplementary Appendix F. For each location, the second column shows cumulative fatalities from the onset of the pandemic until the midpoint date of that seroprevalence study, while the next two columns report cumulative deaths 4 and 5 weeks later, respectively. The last two columns show the percent change in cumulative fatalities over each specified time interval (weeks 0 to 4 and weeks 4 to 5, respectively).

Table 3: Age-specific fatality rates for COVID-19 infections vs. accidental deaths (%)

Age Group	COVID-19 IFR (95% CI)	<u>Automobile Fatalities</u>		<u>Other Accidental Fatalities</u>	
		England	USA	England	USA
0 to 34	0.004 (0.003–0.005)	0.002	0.015	0.004	0.032
35 to 44	0.068 (0.058–0.078)	0.002	0.012	0.017	0.043
45 to 54	0.23 (0.20–0.26)	0.002	0.013	0.019	0.043
55 to 64	0.75 (0.66–0.87)	0.003	0.013	0.014	0.043
65 to 74	2.5 (2.1–3.0)	0.003	0.013	0.020	0.040
75 to 84	8.5 (6.9–10.4)	0.005	0.017	0.069	0.094
85+	28.3 (21.8–36.6)	0.007	0.019	0.329	0.349

Note: This table compares IFRs for COVID-19 with the incidence of accidental deaths in England and in the USA. For each age group, the second column shows the metaregression estimate of the age-specific IFR with its 95% confidence interval enclosed in parentheses. The final four columns report the annual incidence of automobile fatalities and other accidental fatalities as a percent of the population of each age group in each country. The accidental fatality data for England as of 2019 is reported by the U.K. Office of National Statistics, while the corresponding U.S. data are reported as of 2018 by the U.S. National Center for Health Statistics.[130, 131]



Note: This figure illustrates time lags in the incidence and reporting of COVID-19 fatalities using the results of a simulation calibrated to reflect the estimated distribution for time lags between symptom onset, death, and inclusion in official fatality reports.[29] As indicated by the vertical green line, this simulation assumes that the seroprevalence study was conducted two weeks after the pandemic was curtailed. The histogram shows the frequency of deaths and reported fatalities associated with the infections that occurred on the last day prior to full containment. As indicated by the orange vertical line, 95% of cumulative fatalities are reported within about four weeks after the midpoint date of the seroprevalence study.

Figure 2: Study selection (PRISMA flow diagram)

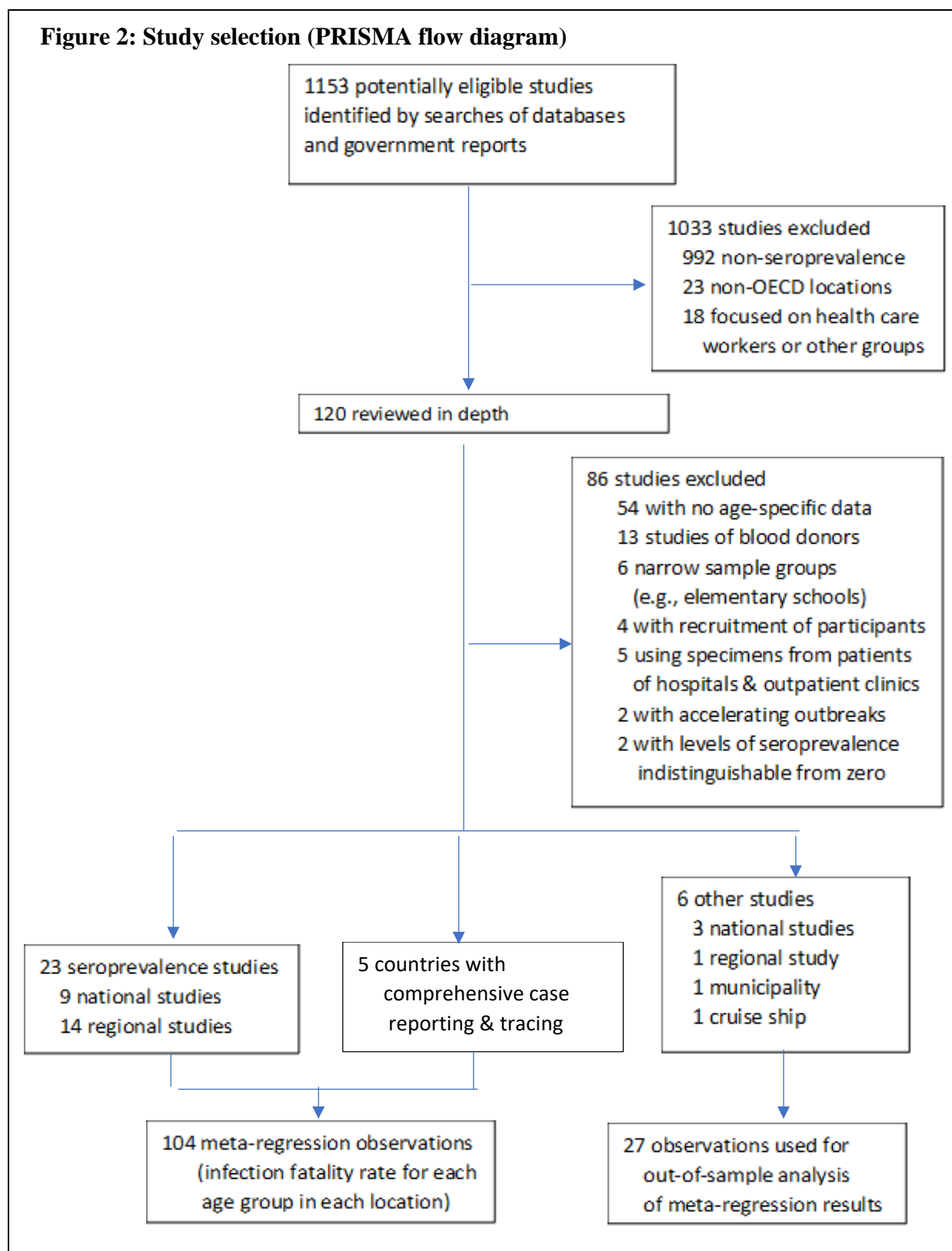
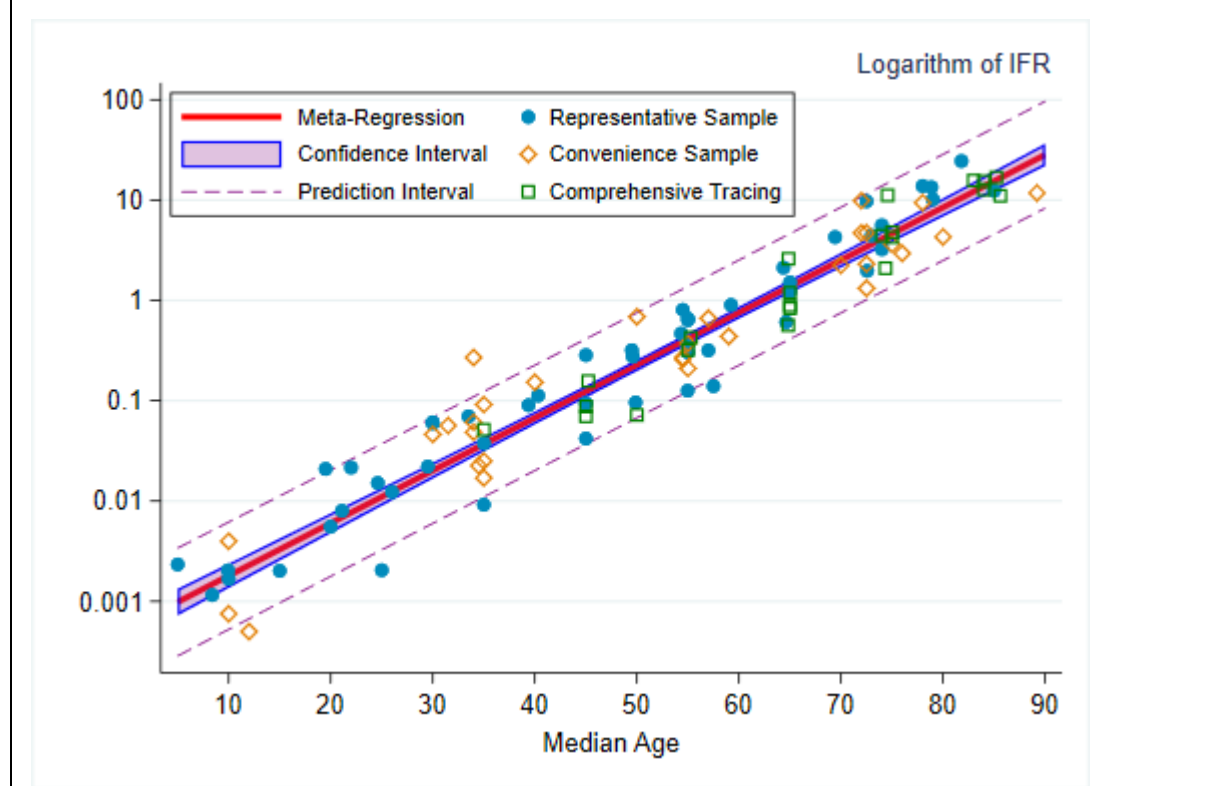
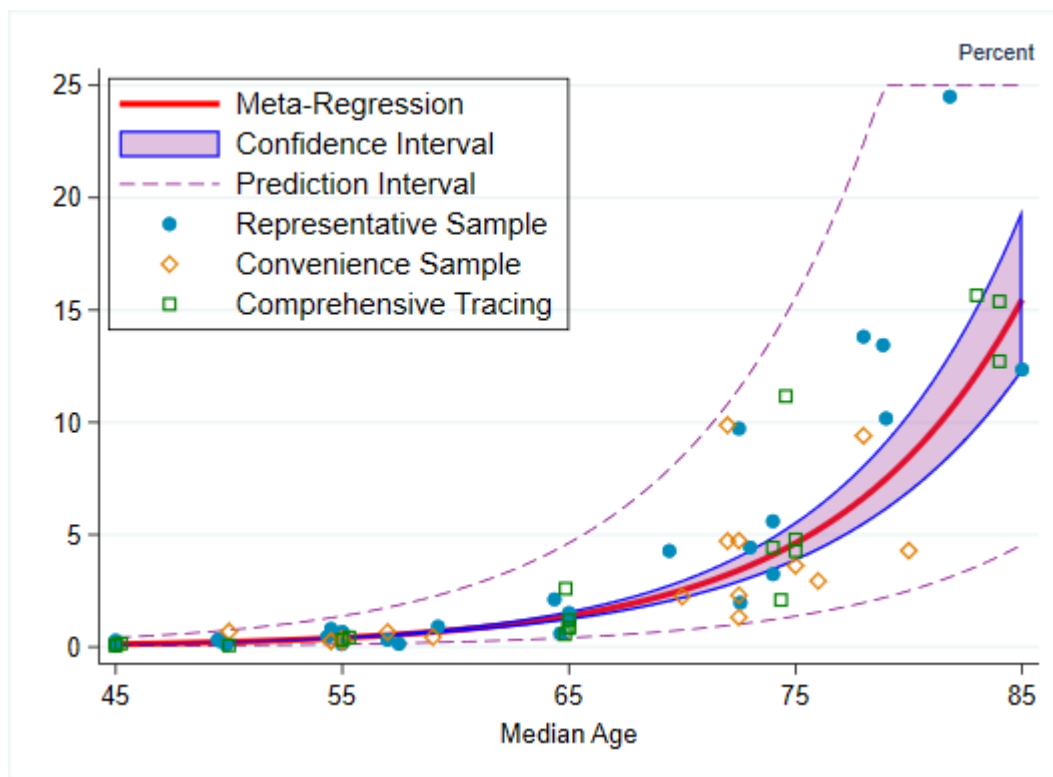


Figure 3: The log-linear relationship between IFR and age



Note: Our metaregression indicates that the infection fatality rate (IFR) increases exponentially with age, and hence this figure uses a base-10 logarithmic scale so that the relationship is evident across all ages from 5 to 95 years. Each marker denotes a specific metaregression observation, that is, the IFR for a particular age group in a particular location. The marker style reflects the type of observation: circles for observations from seroprevalence studies of representative samples, diamonds for seroprevalence studies of convenience samples, and squares for countries with comprehensive tracing programs. The red line denotes the metaregression estimate of IFR as a function of age, the shaded region depicts the 95% confidence interval for that estimate. The dashed lines denote the prediction interval (which includes random variations across studies and age groups), and almost all of the 108 metaregression observations lie within that interval.

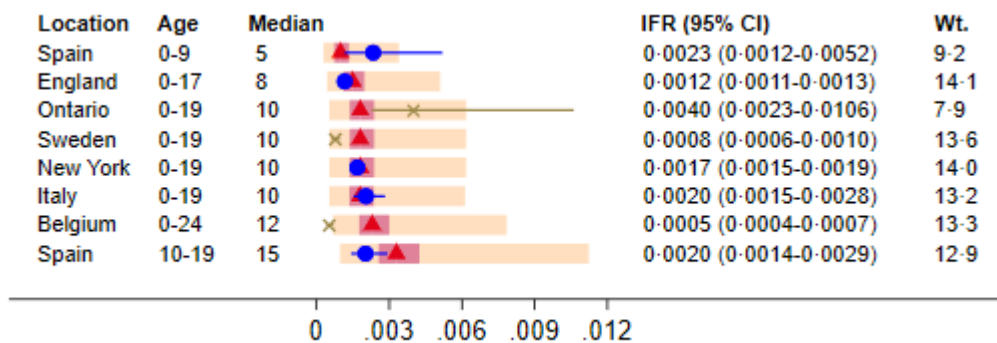
Figure 4: Benchmark analysis of the link between age and IFR



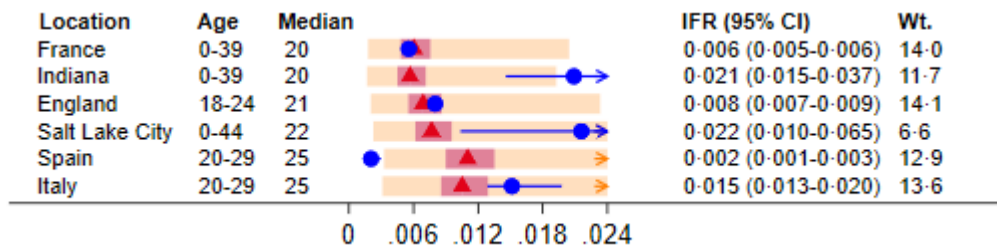
Note: This figure depicts the relationship between the infection fatality rate (IFR) and age, where IFR is shown in percentage terms. Each marker denotes a specific metaregression observation, that is, the IFR for a particular age group in a particular location. The marker style reflects the type of observation: circles for observations from seroprevalence studies of representative samples, diamonds for seroprevalence studies of convenience samples, and squares for countries with comprehensive tracing programs. The red line denotes the metaregression estimate of IFR as a function of age, the shaded region depicts the 95% confidence interval for that estimate. The dashed lines denote the prediction interval (which includes random variations across studies and age groups); almost all of the 104 metaregression observations lie within that interval.

Figure 5: Forest plot of metaregression data

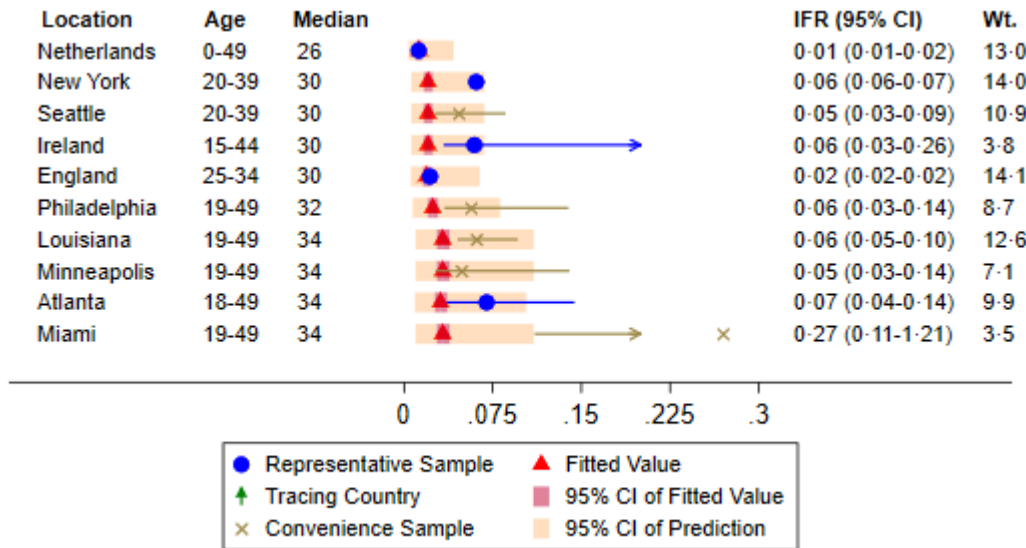
Cohorts with median age of 5-15 years



Cohorts with median age of 16-25 years

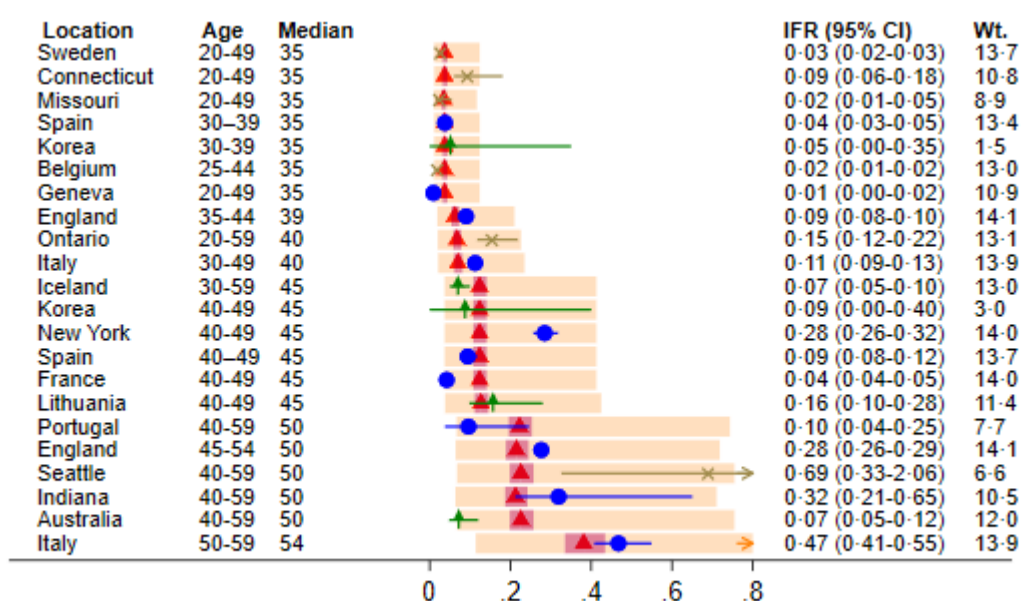


Cohorts with median age of 26-34 years

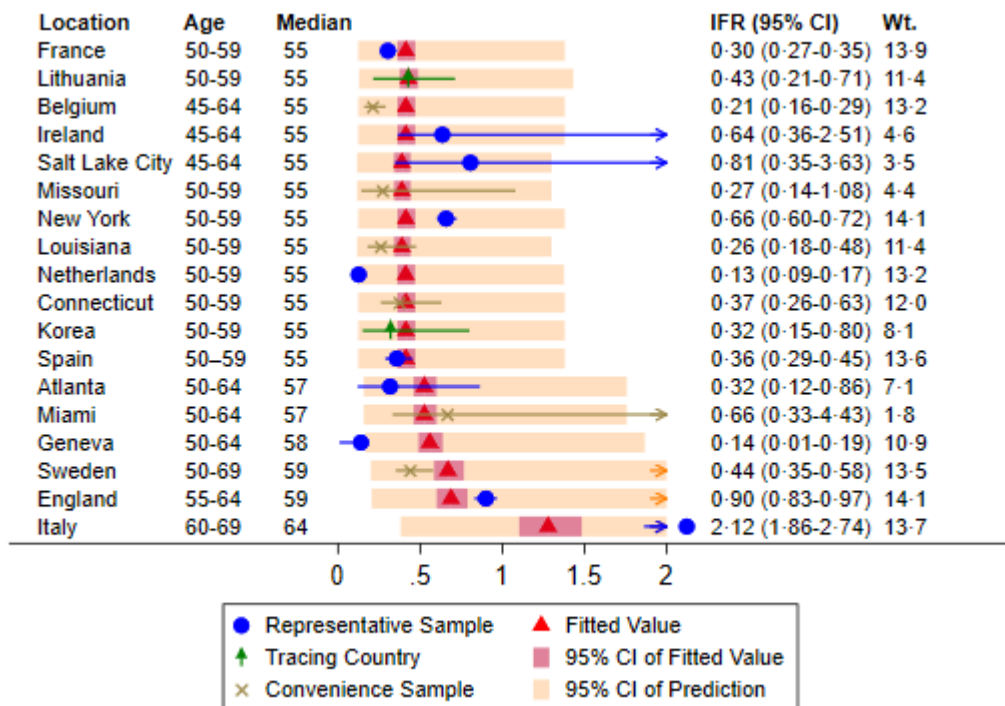


(Figure 5 continues on next page)

Cohorts with median age of 35-54 years

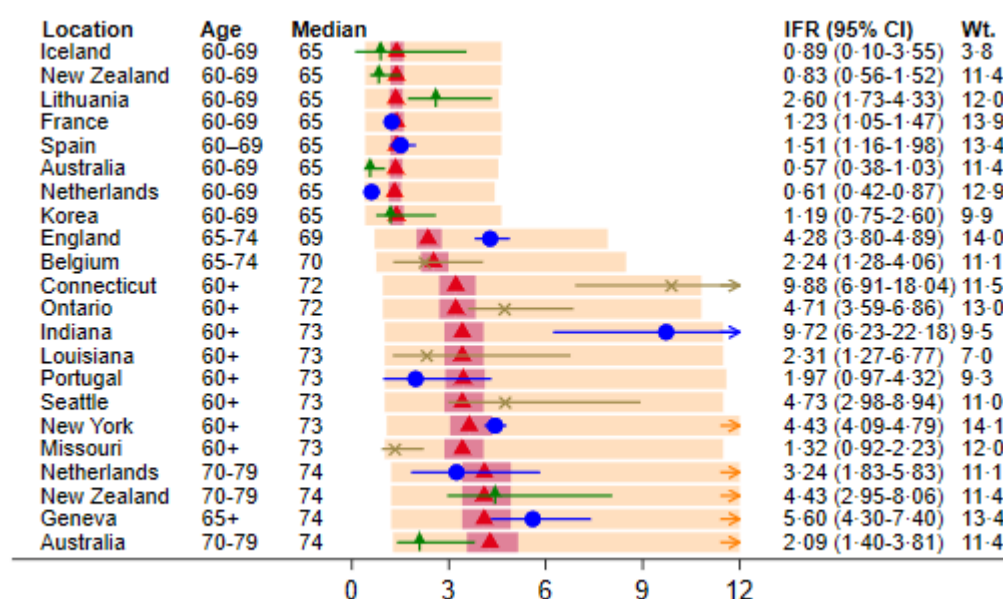


Cohorts with median age of 55-64 years



(Figure 5 continues on next page)

Cohorts with median age of 65-74 years



Cohorts with median age of 75 years and above

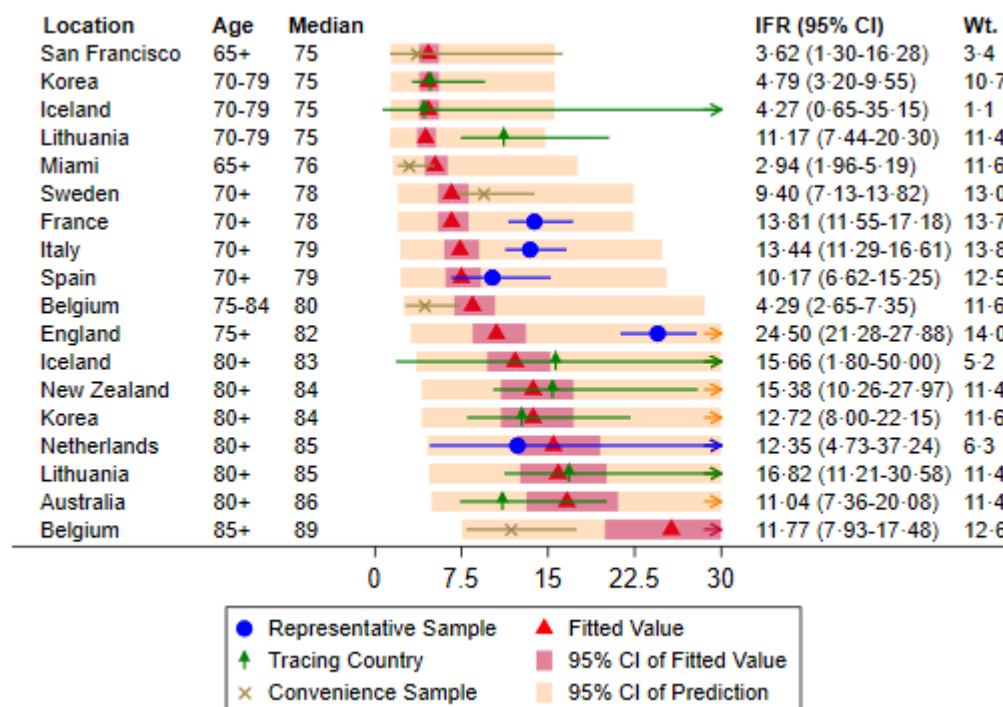
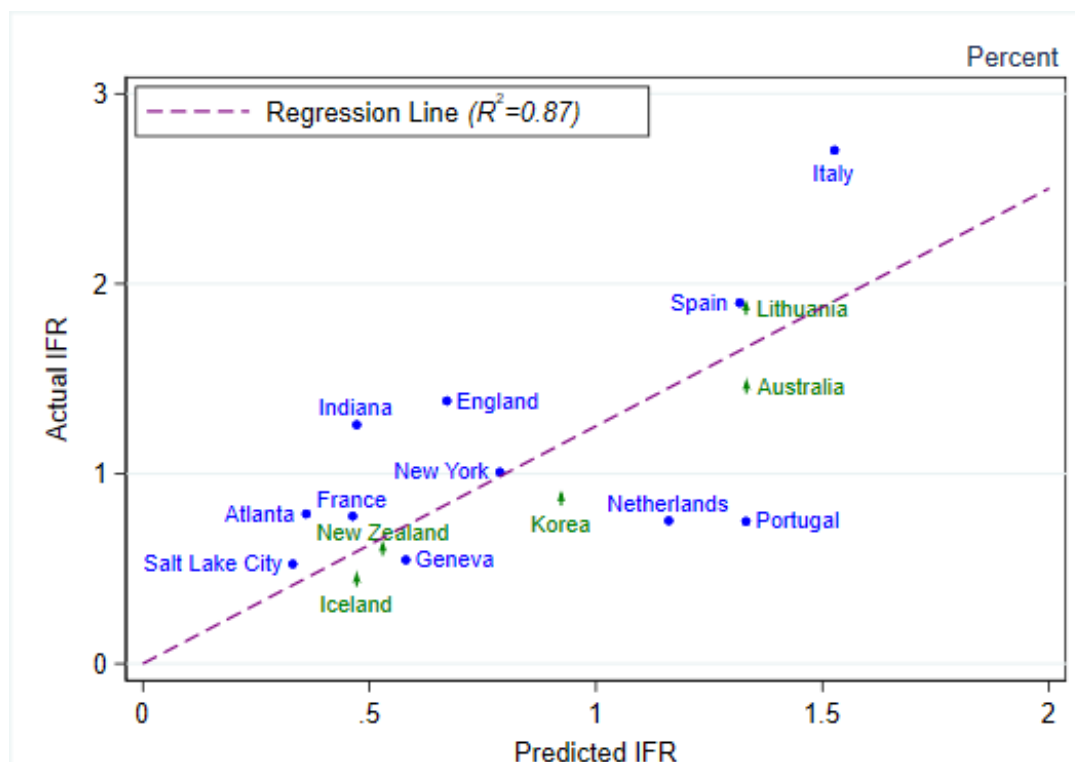


Figure 6: Variations in population IFR across geographical locations



Note: This figure depicts the extent to which the metaregression results account for variations in population IFR across geographical locations. The blue circles denote seroprevalence studies of representative samples, and the green diamonds denote countries with comprehensive tracing programs. For each observation, its position on the horizontal axis denotes its predicted IFR obtained by aggregating across the age-specific predictions of the metaregression, and its position on the vertical axis denotes the actual population IFR for that location. The dashed segments denote the estimated line obtained by fitting a regression to these 16 observations. The R^2 of this regression is 0.87, indicating that nearly 90% of the variation in population IFR can be explained by variations in age composition and age-specific prevalence of COVID-19.

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