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

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Challenges in Assessing the Severity of COVID-19

- A large fraction of cases are asymptomatic or only mildly symptomatic and may not be fully reflected in official case reports.
- Availability of live virus tests (RT-PCR) has varied over time, across geographical locations, and between demographic groups.
- Seroprevalence studies (antibody tests) have varied widely in sample design and reporting.
- Divergent results have fueled intense controversy about appropriate public health measures for addressing the pandemic.

Example: New York City, Spring 2020

	Number	Share of Infections
NYC Residents	8 million	NA
Total Infections *(estimated 4/28/20)*	1·6 million	100%
Symptomatic Infections	1·1 million	65%
Reported Cases	220 thousand	12%
Hospitalized patients	55 thousand	3%
Confirmed fatalities *(as of 5/22/20)*	17 thousand	1%

Sources: Rosenberg et al. (2020), NYC Dept. of Health (2020)

Our Approach

- **Systematic Review: sift data from seroprevalence studies and countries with comprehensive tracing programs.**
- **Metaregression: estimate infection fatality rate (IFR) as a log-linear function of age, where each observation is the prevalence for a specific age group in a specific geographical location.**
- **Out-of-Sample Analysis: compare metaregression predictions to other seroprevalence studies.**
- **Population IFR: use age-specific IFRs to assess and compare overall IFR across geographical locations.**

Systematic Review: Excluded Studies

- **Developing Countries**
  - **Differences in Health Care Systems**
  - **Limitations on Real-Time Fatality Reporting**
- **No Age-Specific Prevalence or Fatality Data**
- **Seroprevalence Indistinguishable from Zero**
- **Accelerating Outbreaks**

  (Deaths rise 500% or more over subsequent 4 weeks)
- **Non-Representative Samples**
  - **Active recruitment of participants**
  - **Patients from hospitals and urgent care clinics**
  - **Kidney dialysis patients**
  - **Blood donors**

Examples of Excluded Studies

Excluded Sample	Estimated Prevalence	Representative Sample	Estimated Prevalence
New York City Outpatient Clinics	44%	New York City *(NY Dept of Health)*	23%
Oise, France Elementary School	26%	Hauts-de-France *(Pasteur Institute)*	1.9%
Tokyo Outpatient Clinics	3.8%	Tokyo *(Japan Ministry of Health)*	0.1%

Note: Each of these excluded studies was included in the meta-analysis of Ioannidis (WHO Bulletin, Oct. 2020).

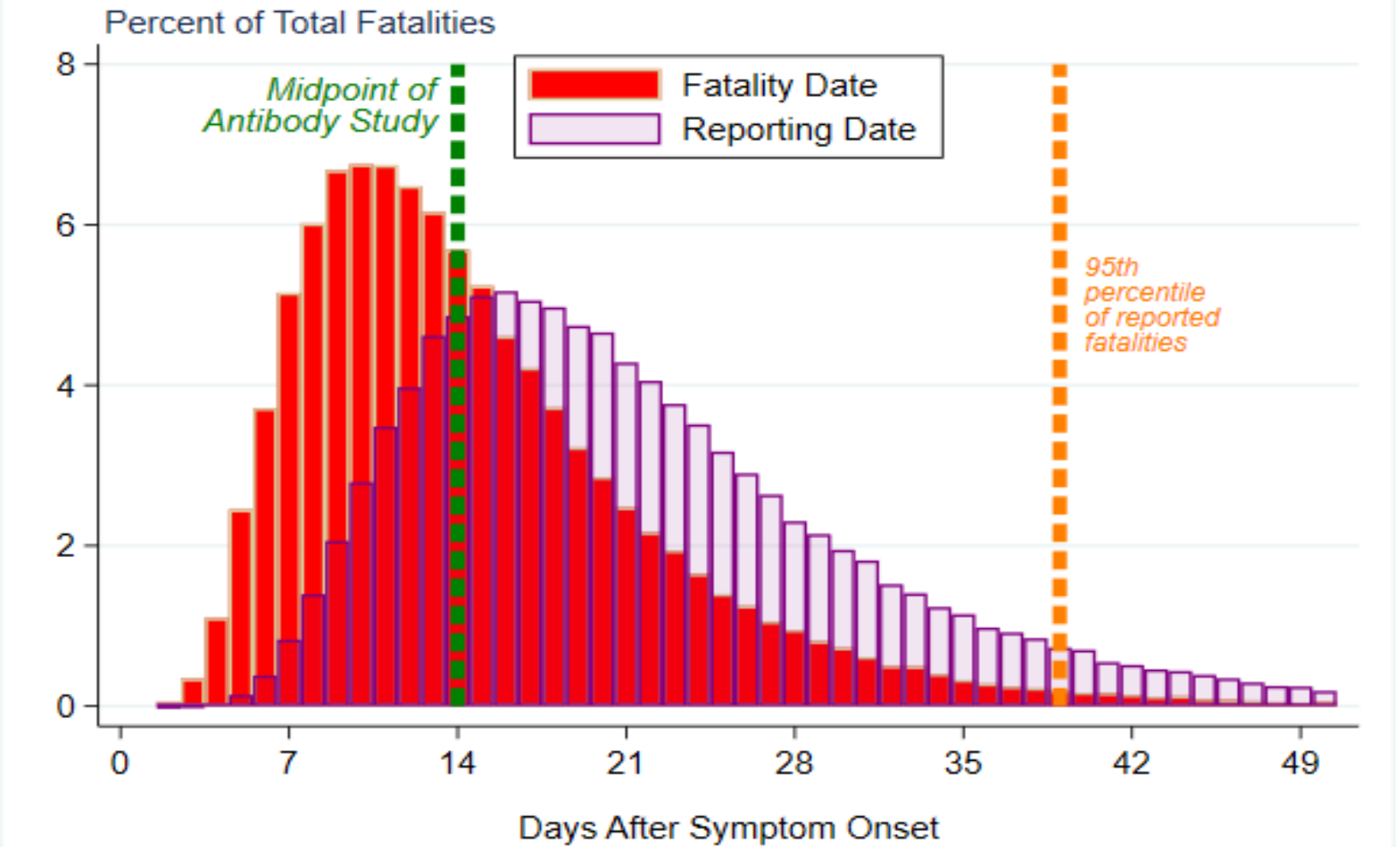
Systematic Review: Seroprevalence

- **Antibody Tests**
  - **Specificity: incidence of false positives**
  - **Sensitivity: incidence of false negatives**
- **Adjustment for Test Characteristics**
  - **Ideal: use Bayesian approach that reflects uncertainty about test characteristics; cf. Manski & Molinari (2020), Gelman & Carpenter (2020)**
  - **Practical: in the absence of detailed sampling info, we use the Gladen-Rogan formula:**

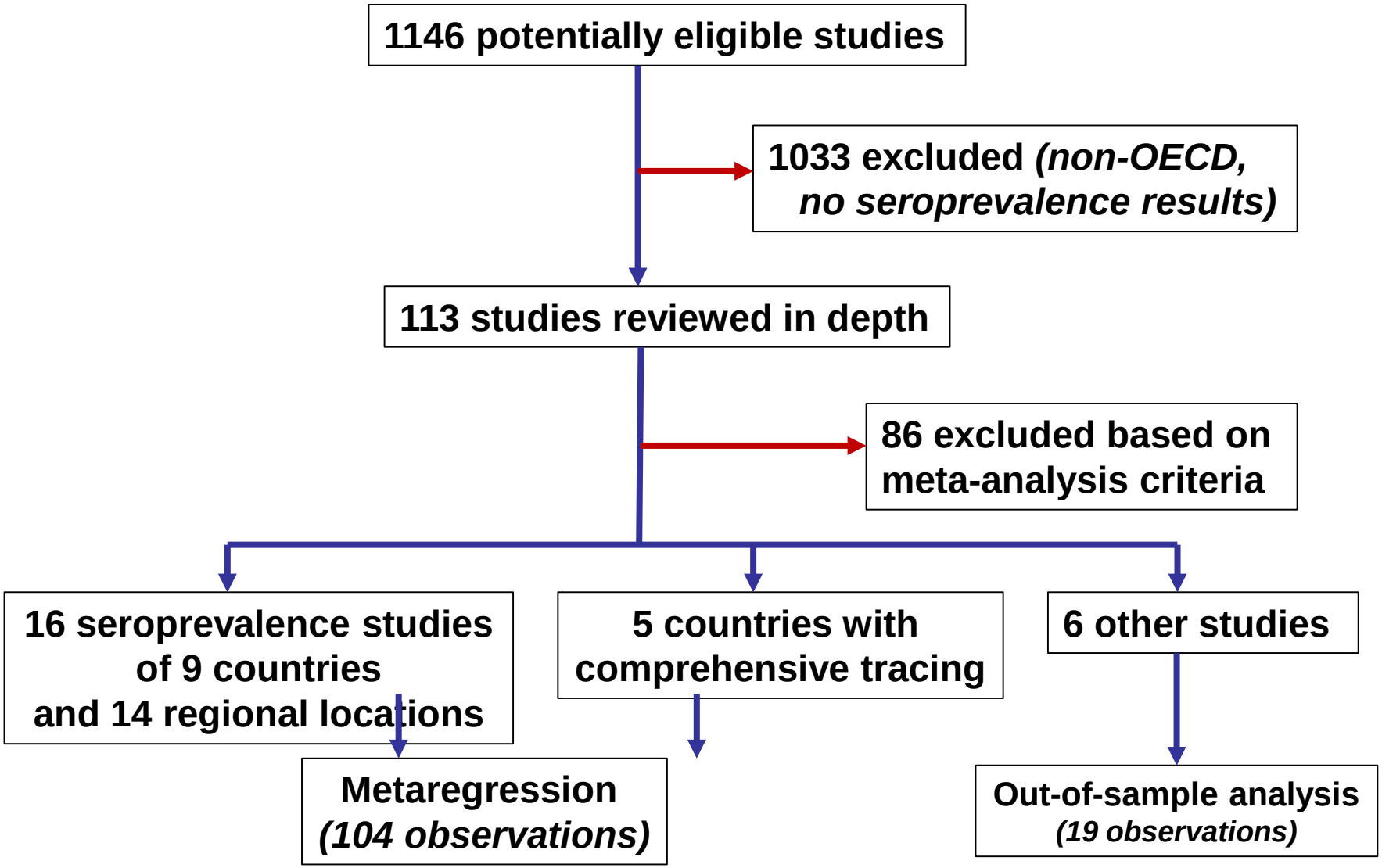
$$Prevalence = \frac{raw\ prevalence + specificity - 1}{sensitivity + specificity - 1}$$

  - **Robustness: our appendix compares G-R vs. Bayesian estimates of prevalence where feasible.**

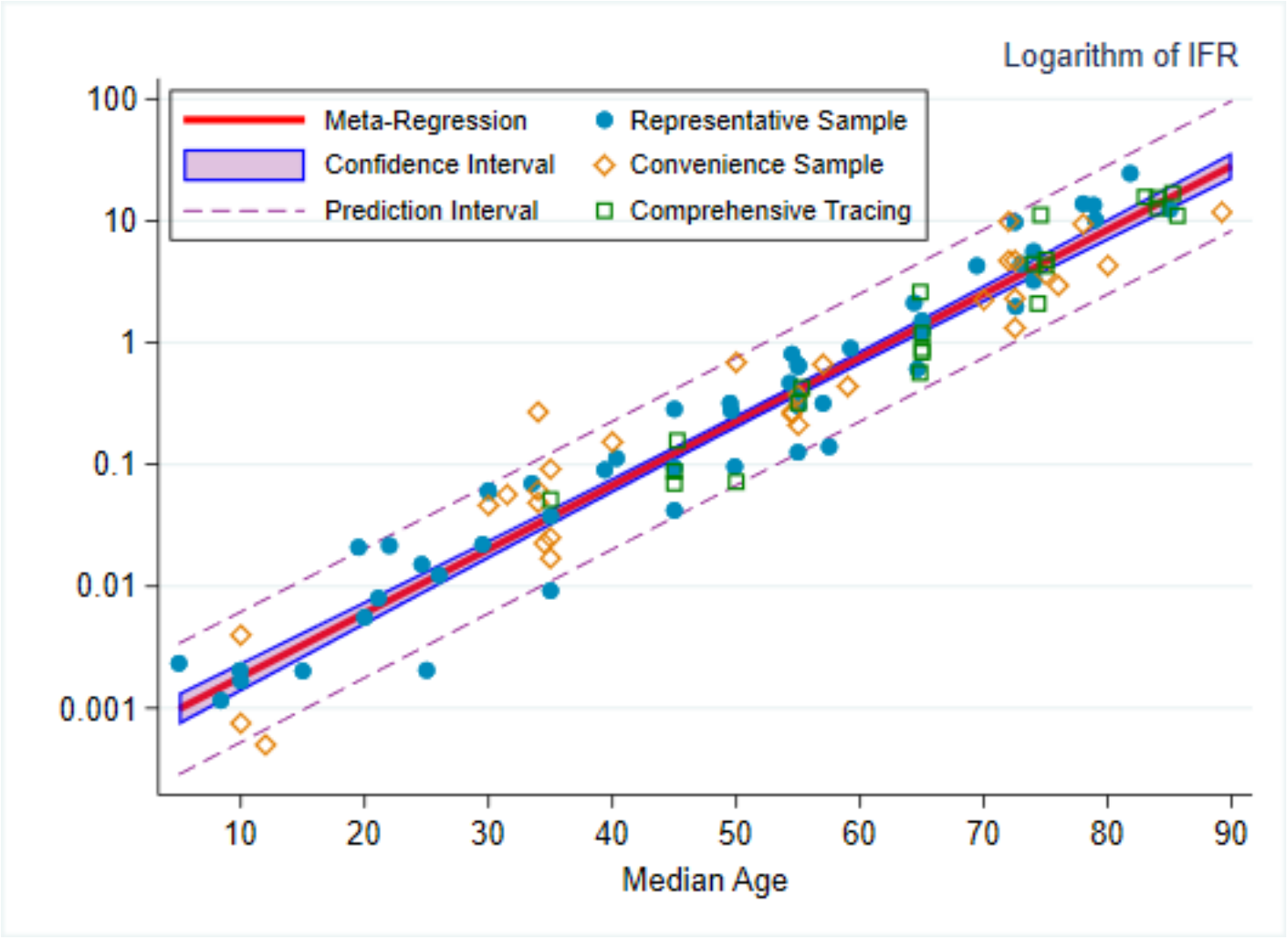
Time Lags in Incidence & Reporting of COVID-19 Fatalities



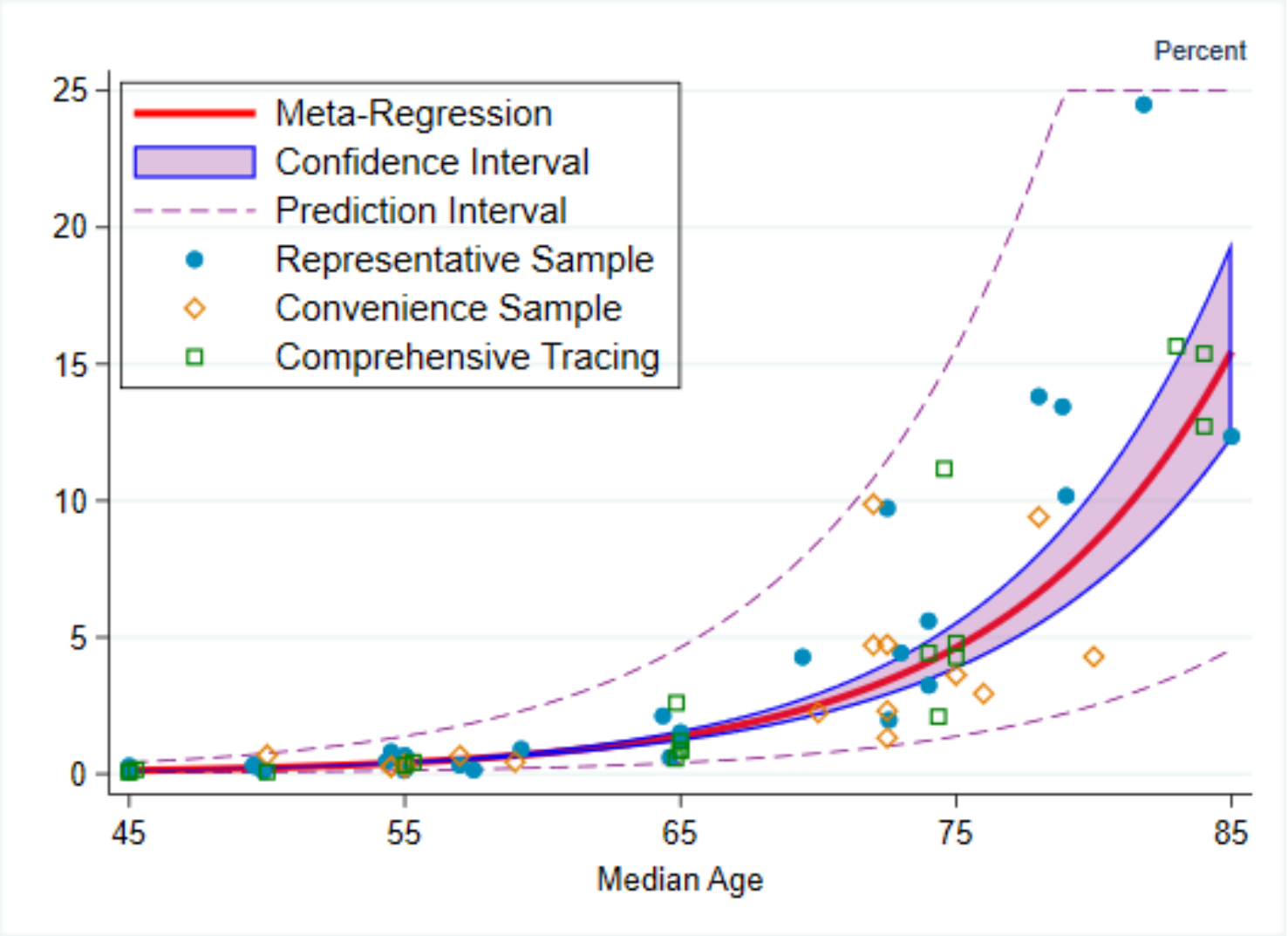
Meta-Analysis Flow Diagram



Metaregression Results



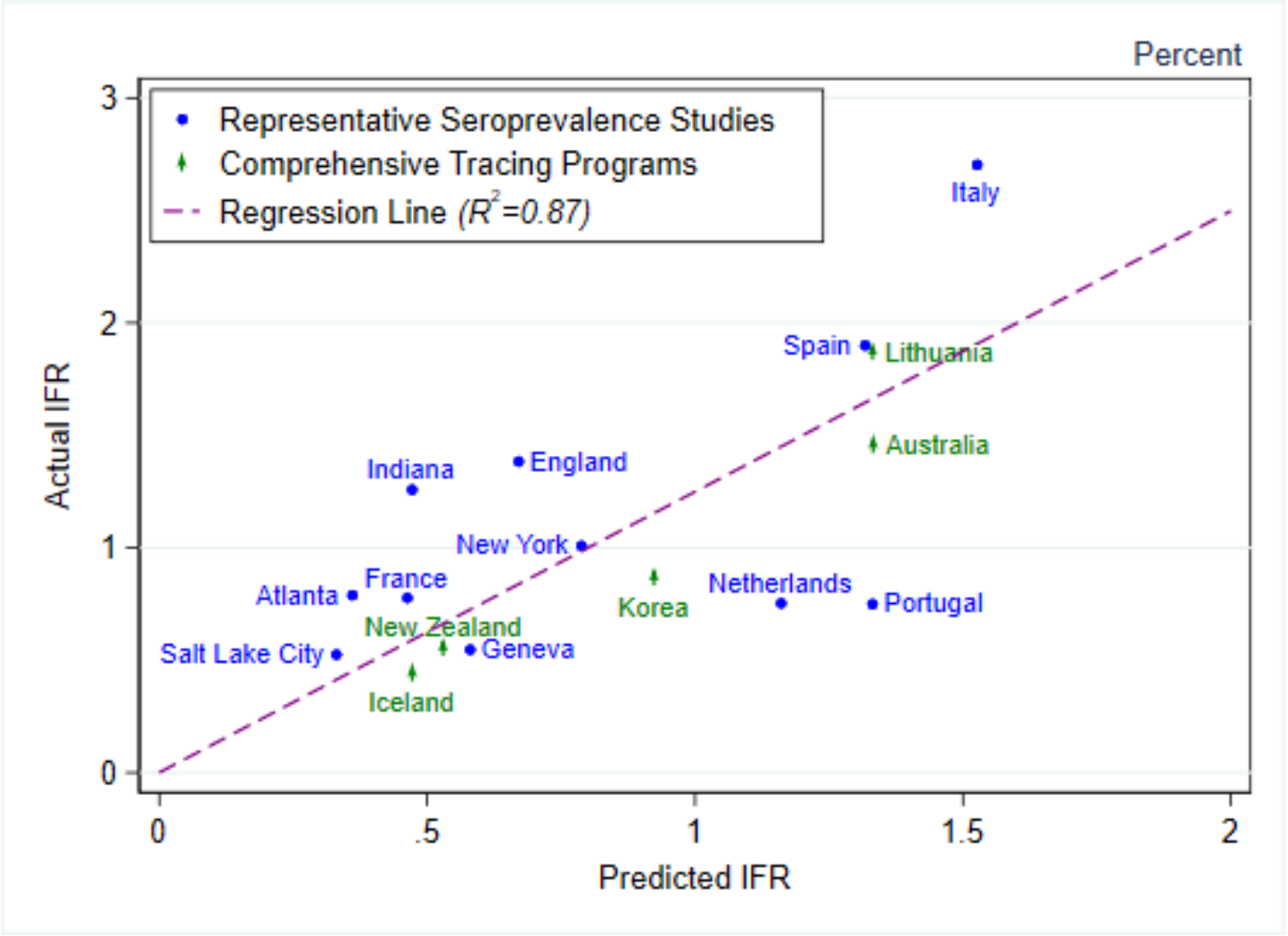
The Link between IFR and Age



Sensitivity Analysis

- **Stability across Age Categories**
  Age < 35, 35 ≤ Age ≤ 60, and Age > 60 years
- **Robustness to Exclusion of Top Age Groups**
- **Forest Plots**
- **Assessment of Publication Bias**
  - **Funnel chart**
  - **Egger's test**
  - **Trim-and-fill**
- **Out-of-Sample Analysis**
  - **Multiple seroprevalence studies of a location**
  - **Small-scale prevalence studies**
    (Diamond Princess, Castiglione d'Adda)

Geographical Variations in Population IFR



Age-Specific Risks in Context

Age Group	COVID-19 IFR (%)	U.S. Automobile Fatalities (%)
0 to 34	0.004	0.015
35 to 44	0.068	0.012
45 to 54	0.23	0.013
55 to 64	0.75	0.013
65 to 74	2.5	0.013
75 to 84	8.5	0.017
85+	28.3	0.019

Implications for Current U.S. Prevalence

Age Group	COVID-19 Deaths *(as of 11/12/20)*	Implied Prevalence
0 to 44	7,157	16%
45 to 64	43,064	11%
65 to 74	52,111	7%
75 to 84	64,391	5%
85+	74,618	4%
All Ages	241,340	13%

Sources: Center for Disease Control & Prevention, Johns Hopkins University, authors' calculations.

Directions for Further Research

- **Comorbidities: a recent study using a very large longitudinal sample (UK Biobank) found measures of comorbidity and frailty did *not* have significant effects on mortality risk, controlling for age & sex.**
- **Improving Treatments: mortality rates of Florida hospitalized patients during July-September were about 10 to 20% lower than in March-June.**
- **Non-Fatal Cases: COVID-19 may have severe and protracted adverse health consequences.**
- **Developing Countries: the pandemic has been devastating in Brazil (160K deaths), India (120K), Mexico (90K), and other locations. Analysis of prevalence and IFR is urgently needed.**

Conclusions

- **Severity: COVID-19 is much more dangerous than seasonal influenza.**
- **Vulnerability: COVID-19 is hazardous not only for the elderly but for middle-aged adults.**
- **Endogeneity: the population IFR of COVID-19 is *not* a fixed parameter but crucially depends on the age distribution of infections.**
- **Policy Implications: public health measures and communications should be aimed at insulating vulnerable age groups.**