Estimating causes of maternal death in data-sparse contexts

Monica Alexander
Statistical Sciences and Sociology
University of Toronto

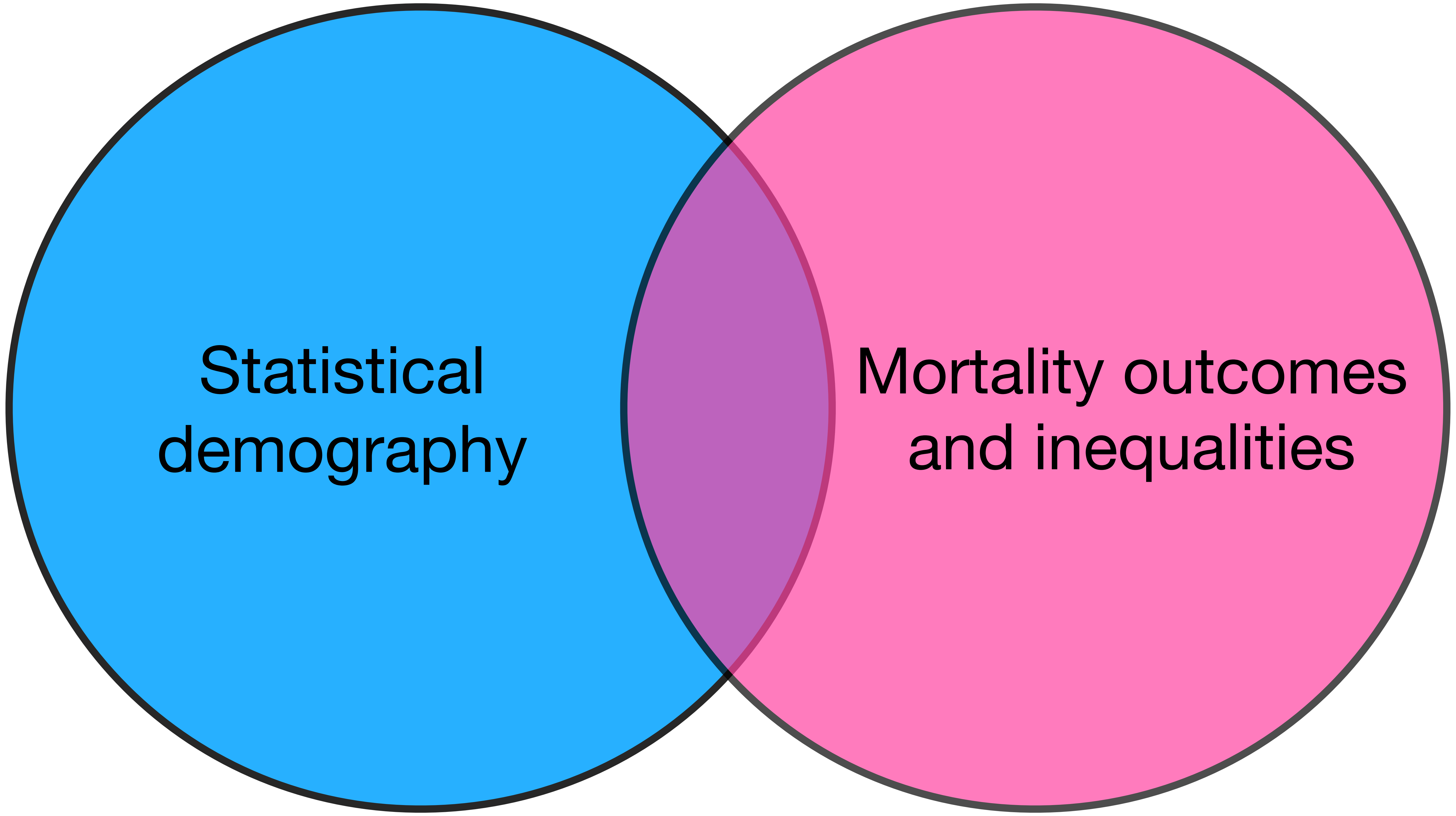
Introduction

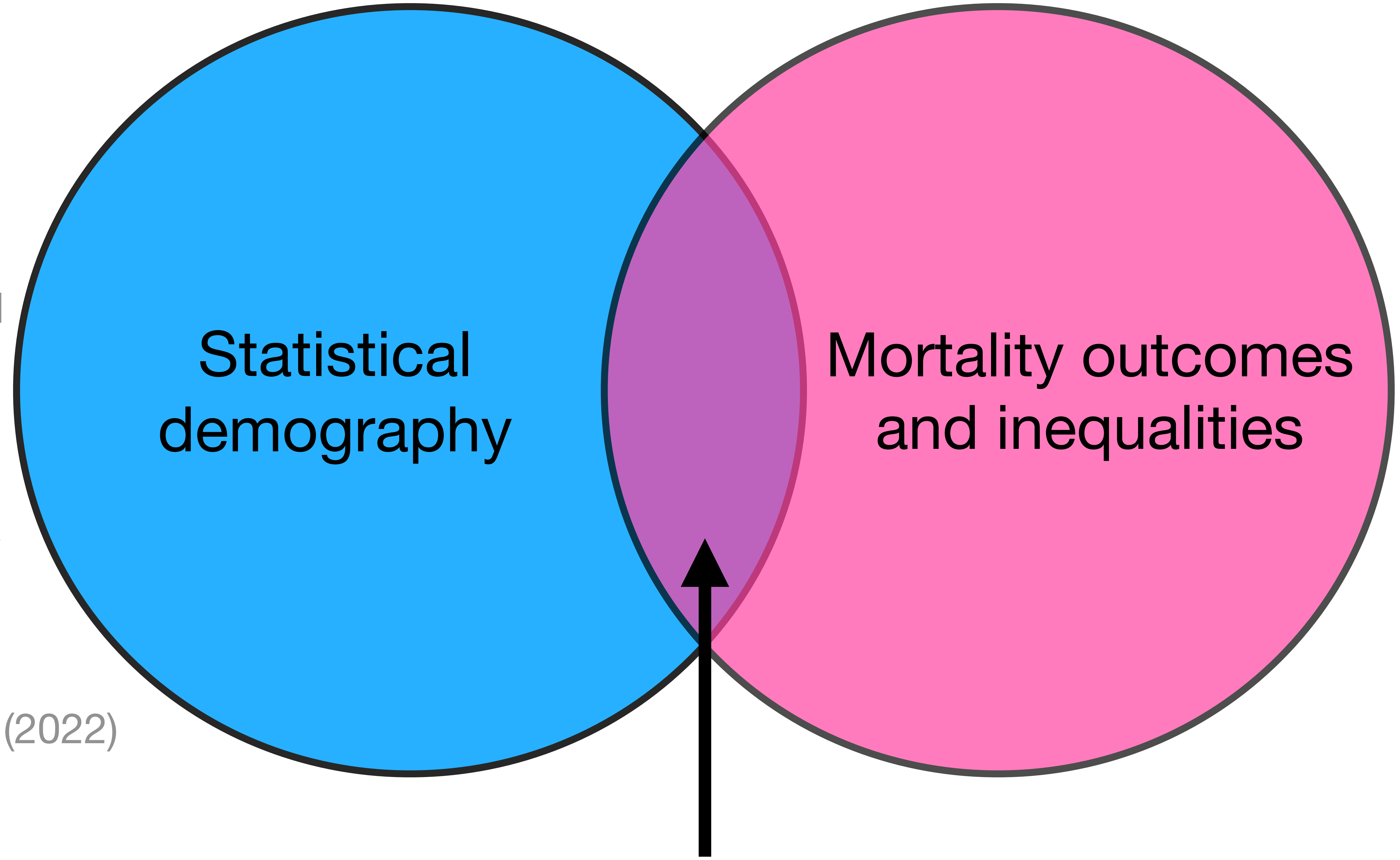
- Demographer, with a background in statistics
- Interested in demographic questions in contexts where populations/outcomes are hard to measure

Grew up in Hobart, Tasmania, Australia

Masters/PhD at UC Berkeley

Associate Prof at University of Toronto


Statistical demography
Mortality outcomes and inequalities



Kinship

Schulter, **Alexander** et al (2024) *JAMA*

Migration

Alexander et al (2020) *Population Research and Policy Review*

Populations

Alexander and Alkema (2022) *Demography*

Drug-related mortality

Kiang, Basu, Chen and **Alexander** (2019) *JAMA NO*

Perinatal outcomes

Alexander and Root (2022) *Demography*

Racial/ethnic disparities

Alexander, Barbieri, and Kiang (2018) *Epidemiology*

Small-area mortality

Alexander, Zagheni, and Barbieri (2017) *Demography*

Intergenerational mortality

Moon, Schluter, and **Alexander** (2024+)

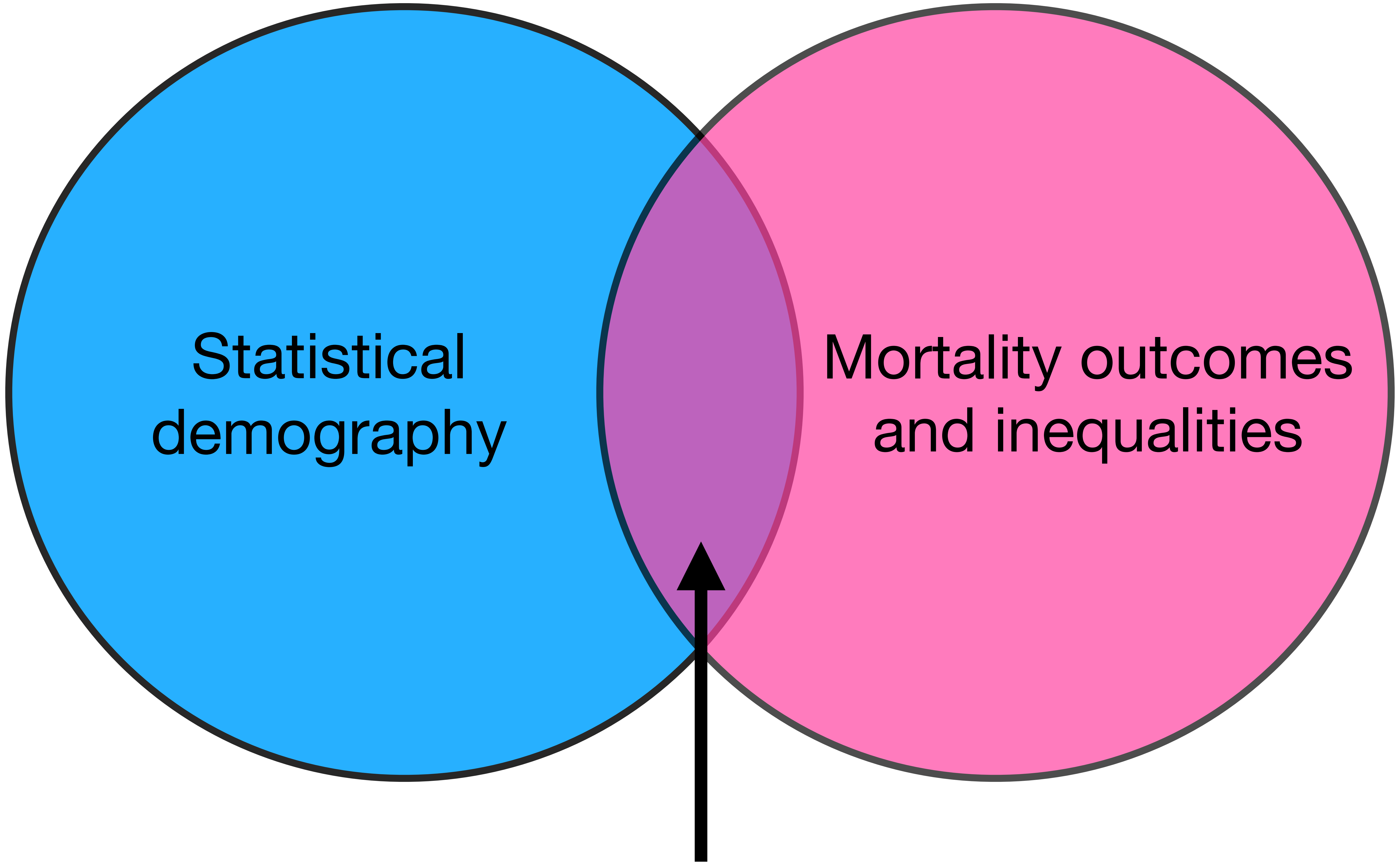
Maternal and child mortality

Chong, Pejchinovska, and **Alexander** (2024) *Statistics in Medicine*

Kinship

Migration

Fertility



Drug-related mortality

Perinatal outcomes

Racial/ethnic disparities

Small-area mortality

Intergenerational mortality

Maternal and child mortality

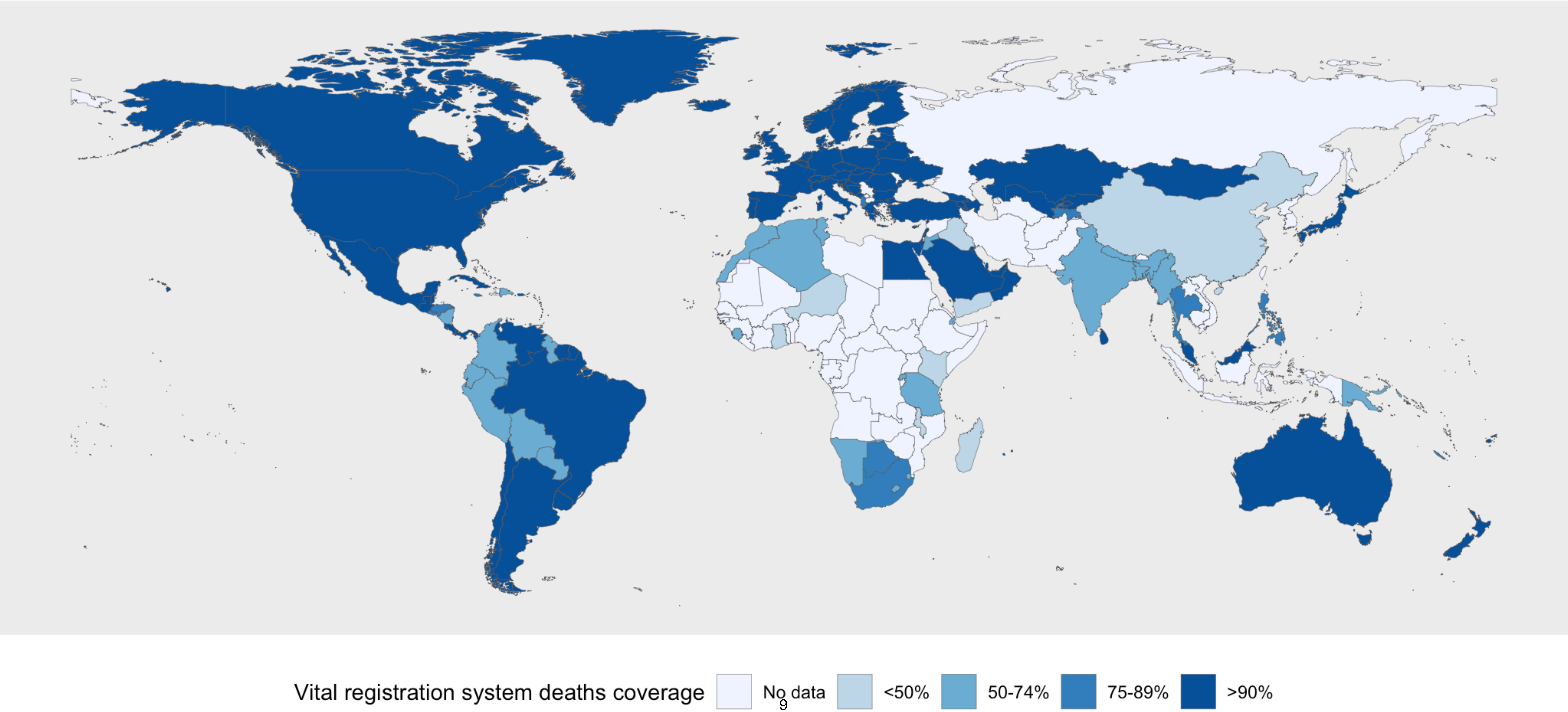
Global health estimation work

- Work closely with UNICEF, UNHCR, WHO, to improve methods of estimation of outcomes in the global context
  - Child mortality
    Alexander and Alkema (2018) *Demographic Research*
    Hug, **Alexander** et al (2019) *Lancet Global Health*
  - Stillbirths
    Chong and **Alexander** (2024) *JRSS:Series C*
  - Maternal mortality
    Chong, Pejchinovska, and **Alexander** (2024) *Statistics in Medicine*
- Member of the Technical Advisory Group to the UN Interagency Group of Child Mortality Estimation (UN-IGME)
- Work related to Sustainable Development Goals, direct policy impact

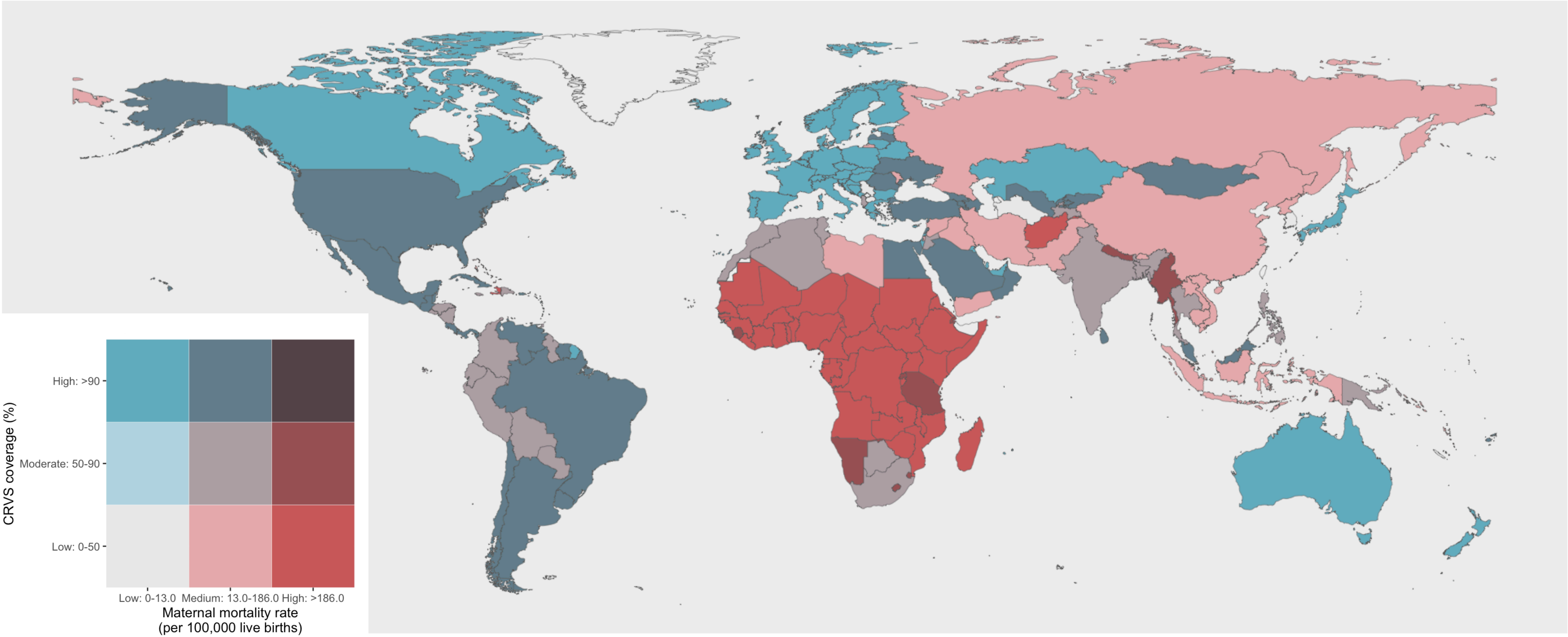
Estimating maternal causes of death in all countries worldwide

Substantial variation in maternal mortality

Substantial variation in data availability



The dual burden at the global scale



Background

- Maternal mortality makes up the **United Nations Sustainable Development Goal** 3.1: Reduce the global maternal mortality ratio to less than 70 per deaths100,000 live births

- While maternal mortality is declining in general, but there have been recent slowdowns, and large inequalities still exist

- Knowing the underlying causes of maternal death crucial to better allocating resources

- In this project, we consider seven main causes: abortion; embolism, hemorrhage, hypertension, sepsis, other direct causes, indirect causes

SUSTAINABLE DEVELOPMENT GOALS

Background

- Much existing literature focuses on estimating total maternal deaths (e.g. Alkema et al 2016; Hoyert 2024)
- Many studies focus on a single cause of death (e.g. Matia 2016; Marshall et al 2017)
- Existing cause-of-death work often relies on unadjusted data, which doesn't account for potential issues in data quality (e.g. Blanco et al 2022; Musarandega et al 2021)
- Existing statistical approaches have limitations: no adjustment for data quality, don't allow for particular data types to be included (Say et al 2014; IHME 2019)

Goals and contribution

Estimate main causes of maternal death for all countries and regions of the world for period 2009-2020

- We collected evidence from a systematic review on causes of maternal death
- We then developed a Bayesian hierarchical multinomial model to combine evidence from different sources

First to account for data quality issues and underreporting, and to include subnational studies, single-cause studies

Details

- Joint work with Michael Chong, Marija Pejchinovska (Statistics, UofT), and the Department of Sexual and Reproductive Health and Research, World Health Organization

- Methodology published in *Statistics in Medicine* (doi: https://doi.org/10.1002/sim.10199)

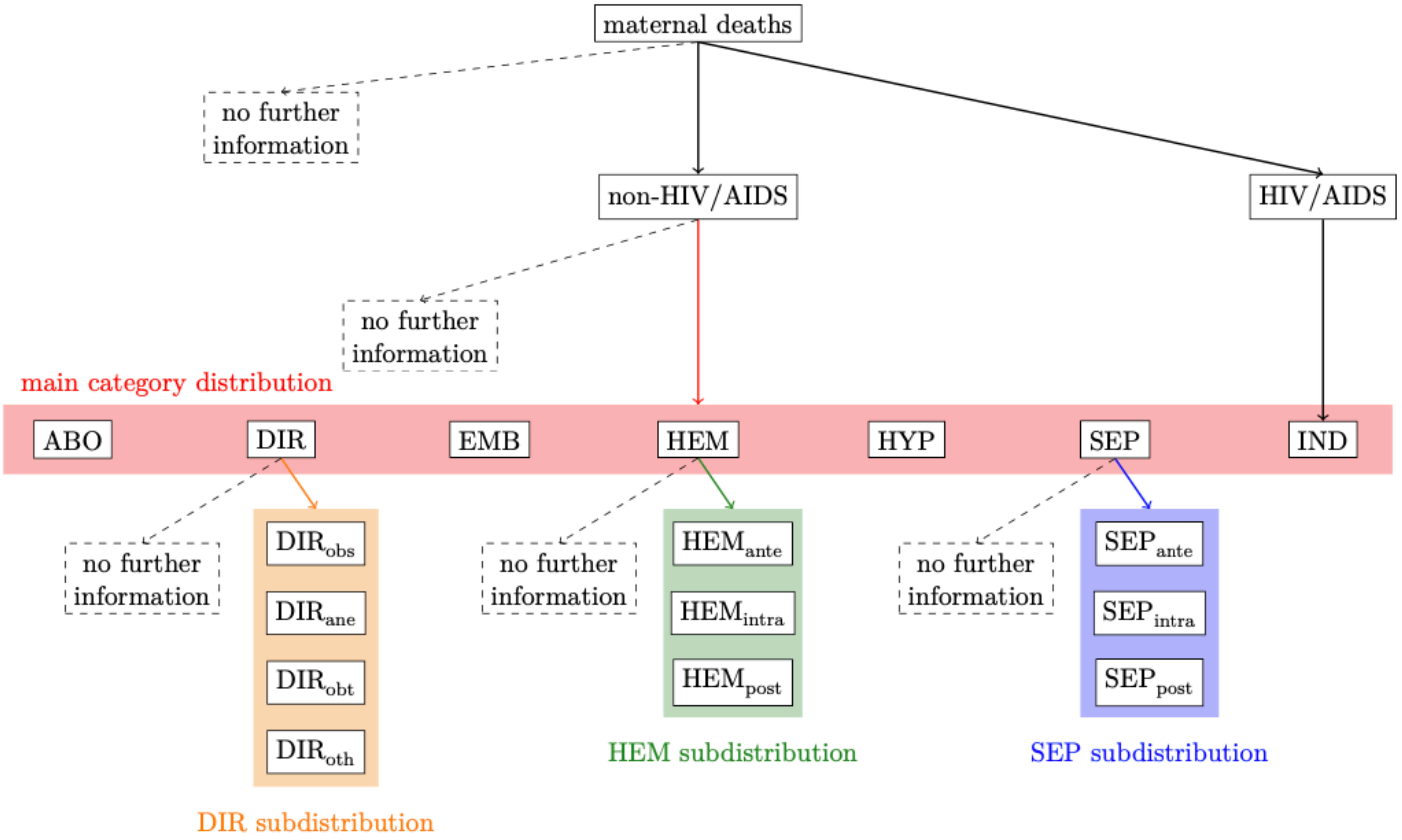
- Findings: revise and resubmit, *Lancet Global Health*

Data

Causes of death groupings

Seven main causes groupings·

- Abortion (ABO)
- Embolism (EMB)
- Hypertension (HYP)
- Hemorrhage (HEM)
- Sepsis (SEP)
- Other direct causes (DIR)
- Indirect causes (IND)



Data types

1. Civil Registration and Vital Statistics (CRVS) systems (varying quality)
2. 'Grey' literature (high-quality data from confidential enquiries and surveillance systems)
3. Studies (results from large scale literature review)
   - Large variation in geographic coverage

Data availability by region

SDG Region	Number of countries	Number of observed country-years	Number of observed country-years by data sources			
			CRVS	Grey Literature	Studies ADM1 or higher	Studies Below ADM1
Central and Southern Asia	12	122	31	16	2	73
Europe and Northern America	36	260	252	8	0	0
Northern Africa and Western Asia	18	91	81	6	0	4
Oceania excl. Australia and New Zealand	3	7	4	1	0	2
Sub-Saharan Africa	28	151	18	20	15	98
Latin America and the Caribbean	31	218	207	10	0	1
Australia and New Zealand	2	26	16	10	0	0
Eastern and South-Eastern Asia	12	75	46	9	2	18

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Modeling approach

Modeling goals

- Share information about cause of death distributions across geographic space
- Allow for different levels of measurement error based on data system
- Allow for missing observations in some causes
- Account for subnational data sources

Notation

- Observations $i \in 1,2,\ldots,N$
- Causes $j \in 1,2,\ldots 7$ corresponding to the 7 main cause-of-death categories: {ABO, EMB, HEM, SEP, DIR, IND, HYP}
- $\mathbf{y_i} = \left(y_{i,1}, \ldots, y_{i,7}\right)$ is the observed maternal deaths by cause
- Total number of observed and classifiable maternal deaths for the i^{th} observation is $d_i = \sum_j y_{i,j}$

Model for observed proportions

- Deaths in each observation are modeled using a multinomial distribution with proportions $\phi_{\mathbf{i}} = \left(\phi_{i,1}, \ldots, \phi_{i,7}\right)$:

$$\mathbf{y_i} \,|\, \boldsymbol{\phi}_i \sim \text{Multinomial}\left(d_i, \boldsymbol{\phi}_i\right)$$

- The log-ratios of the each of the proportions relative to $j = 7$ (HYP) are modeled hierarchically:

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \delta_{i,j}$$

Model for observed proportions

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \delta_{i,j}$$

Pooling information across geography

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \boxed{\alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j}} + \delta_{i,j}$$

Hierarchical region intercepts

$$\beta_{r,j} \sim N(0, \sigma_\beta^2)$$

Baseline country level is partially informed by other countries in the same region

Correlation across causes of death

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \boxed{\gamma_{c[i],j}} + \delta_{i,j}$$

Country-specific effects

Allow for the possibility of correlation across causes: that some causes are more likely to occur together

$$\left(\gamma_{c,1}, \ldots, \gamma_{c,6}\right) \sim \mathrm{MVN}(\mathbf{0}, \Sigma)$$

Accounting for different data quality by source

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \boxed{\delta_{i,j}}$$

Data quality adjustment

Allows for some data sources to be more reliable than others

Accounting for different data quality by source

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \boxed{\delta_{i,j}}$$

Data quality adjustment

For Grey literature: $\delta_{i,j} = 0$

Accounting for different data quality by source

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \boxed{\delta_{i,j}}$$

Data quality adjustment

For Grey literature: $\delta_{i,j} = 0$

For studies: $\delta_{i,j} \sim N\left(0, \sigma^2_{\delta,j}\right)$

Uncertainty varies by study type

Accounting for different data quality by source

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \boxed{\delta_{i,j}}$$

Data quality adjustment

For Grey literature: $\delta_{i,j} = 0$

For studies: $\delta_{i,j} \sim N\left(0, \sigma^2_{\delta,j}\right)$

For CRVS: $\delta_{i,j} \sim N\left(0, \sigma^2_{\delta,i,j}\right)$

Uncertainty depends on quality of CRVS

Accounting for different data quality by source

$$\log\left(\frac{\phi_{i,j}}{\phi_{i,7}}\right) = \alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \boxed{\delta_{i,j}}$$

Data quality adjustment

For CRVS: $\delta_{i,j} \sim N\left(0, \sigma^2_{\delta,i,j}\right)$

with $\sigma^2_{\delta,i,j} = (1 - \boxed{u_i})\sigma^2_{\delta,j}$

Variance is scaled by 'data quality index' u_i

Data Quality Index

u_i = (measure of quality of cause of death reporting) × (coverage of CRVS)

What happens when causes are not observed?

- In most cases, we **do not** observe maternal deaths from every cause category of interest
- Rather than treat unobserved causes as zero, we treat them as **missing**
- In the model, observations with missing causes are treated as coming from a multinomial distribution with a reduced set of categories
  - e.g. if one cause is not observed: multinomial with six categories
- We still recover information about the relative proportions of the non-missing categories, while estimates of missing categories is left mostly uninformed

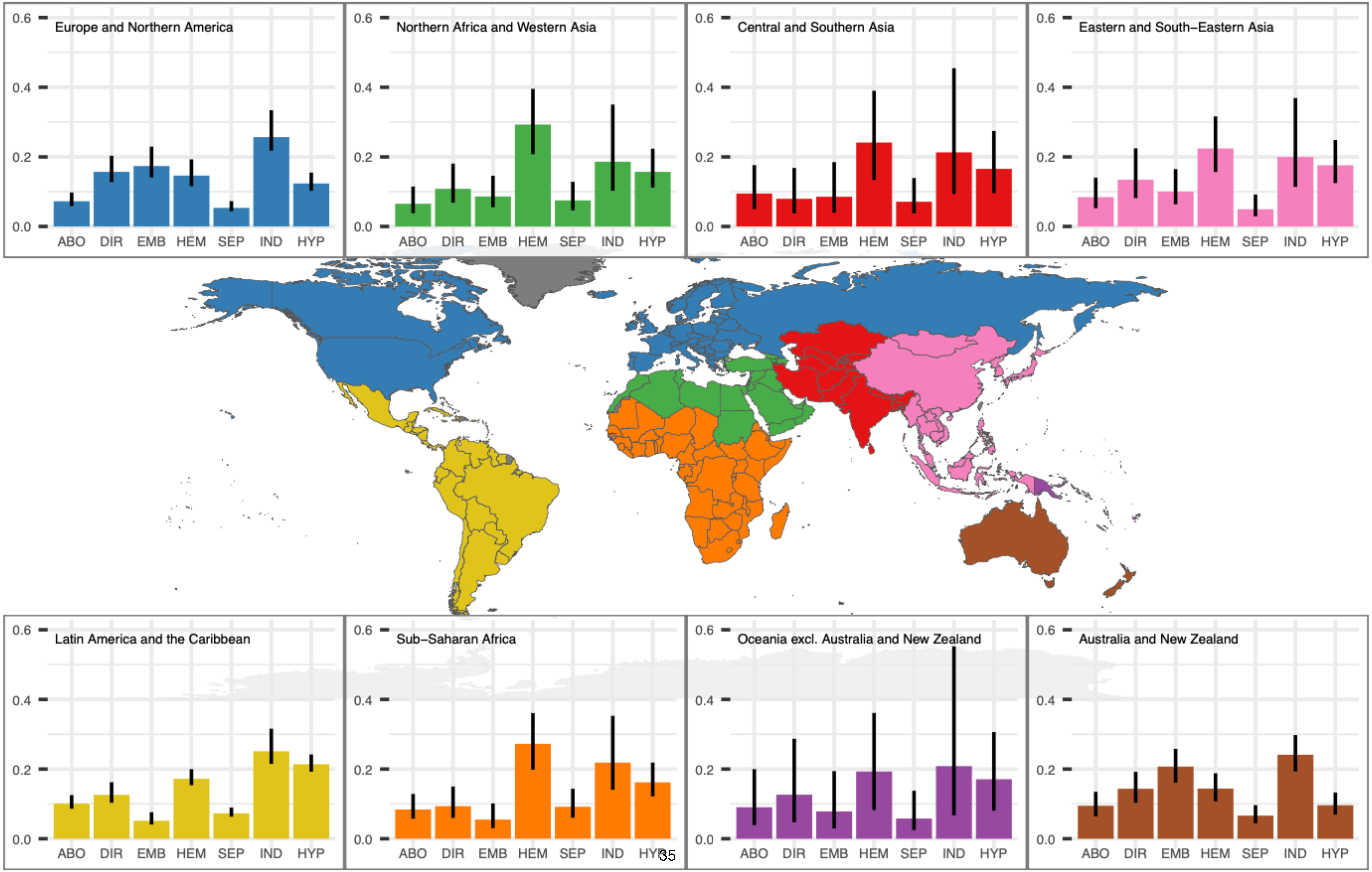
Adjusting for unobserved deaths

- In many cases, a large fraction of the deaths are unrecorded or unclassified
- We want to account for uncertainty we have about the unobserved deaths
- The final estimates are a weighted average of what we observed and predictions about what we don't observe

$$\log\left(\frac{\phi^*_{c,j}}{\phi^*_{c,7}}\right) = w_c\left(\text{estimate from observed deaths}\right) + (1 - w_c)\left(\text{prediction about unobserved deaths}\right)$$

- Weights w_c are calculated based on the proportion of maternal deaths that are observed

Results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Australia and New Zealand
0.0
0.2
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0.6
ABO
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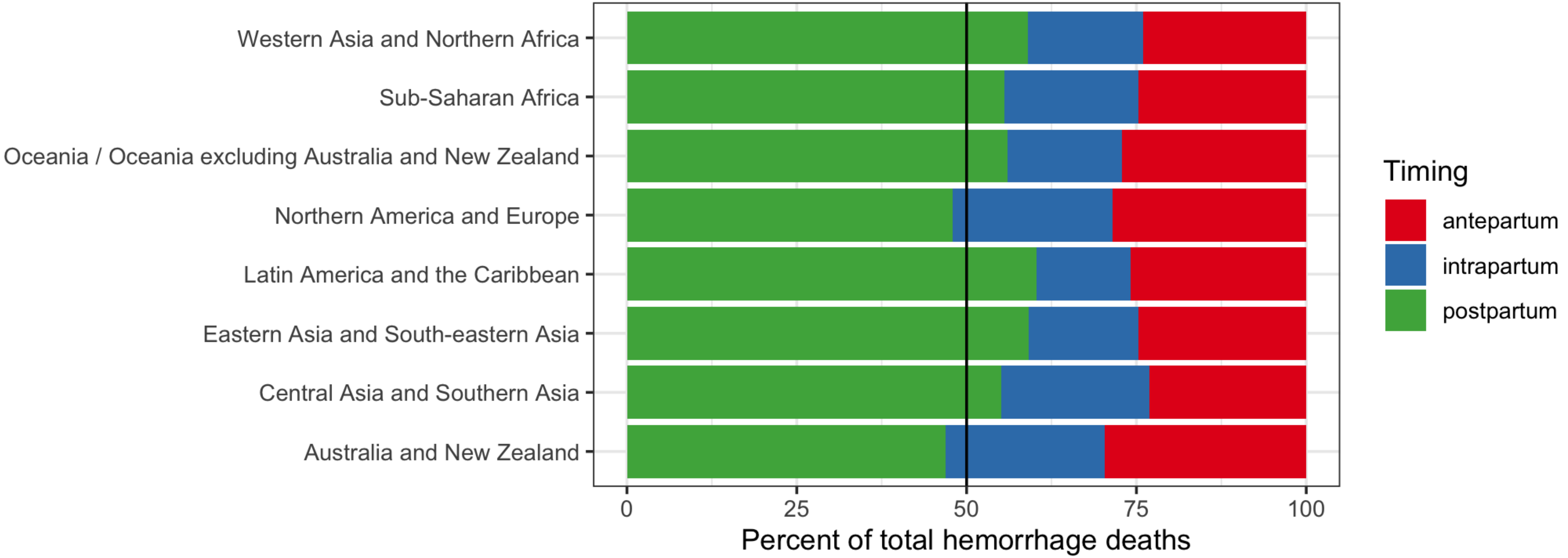
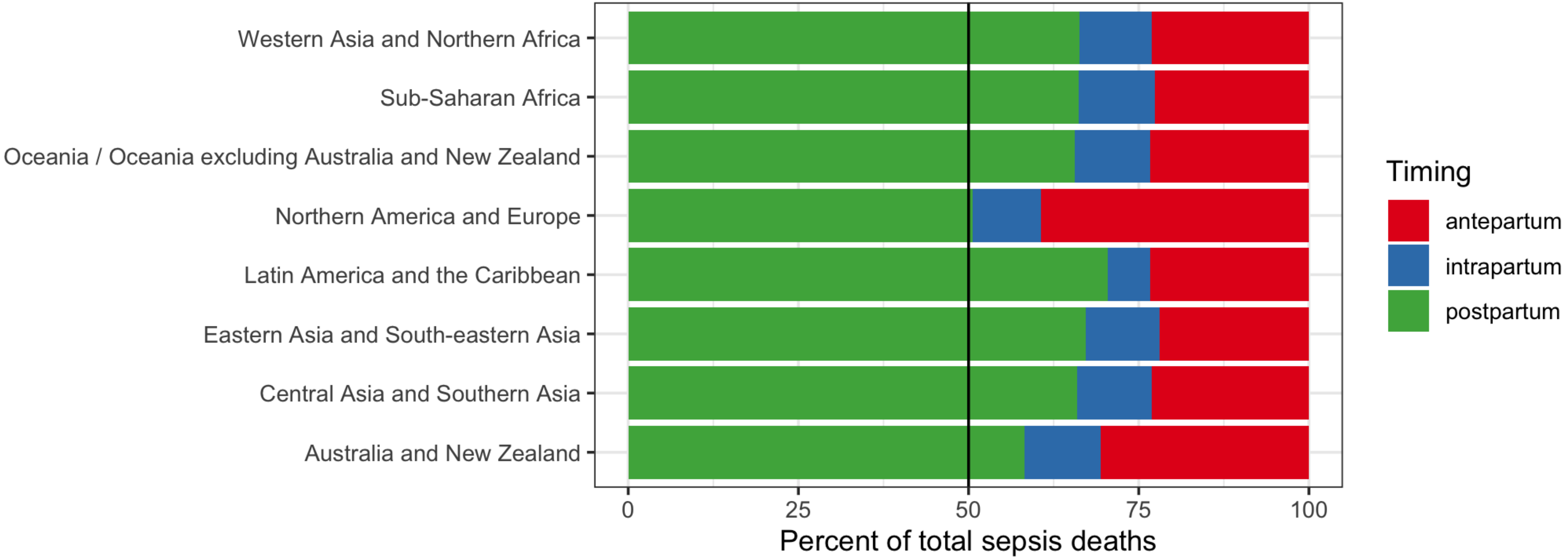
HYP

Timing of hemorrhage deaths



Timing of sepsis deaths



Maternal suicide

SDG Region	Number of reporting countries	Average proportion of total maternal deaths due to suicide
Australia and New Zealand	2	0.26
Central Asia and Southern Asia	2	0.03
Eastern Asia and South-eastern Asia	1	0.21
Latin America and the Caribbean	1	0.09
Northern America and Europe	3	0.06
Sub-Saharan Africa	1	0
Western Asia and Northern Africa	1	0.04

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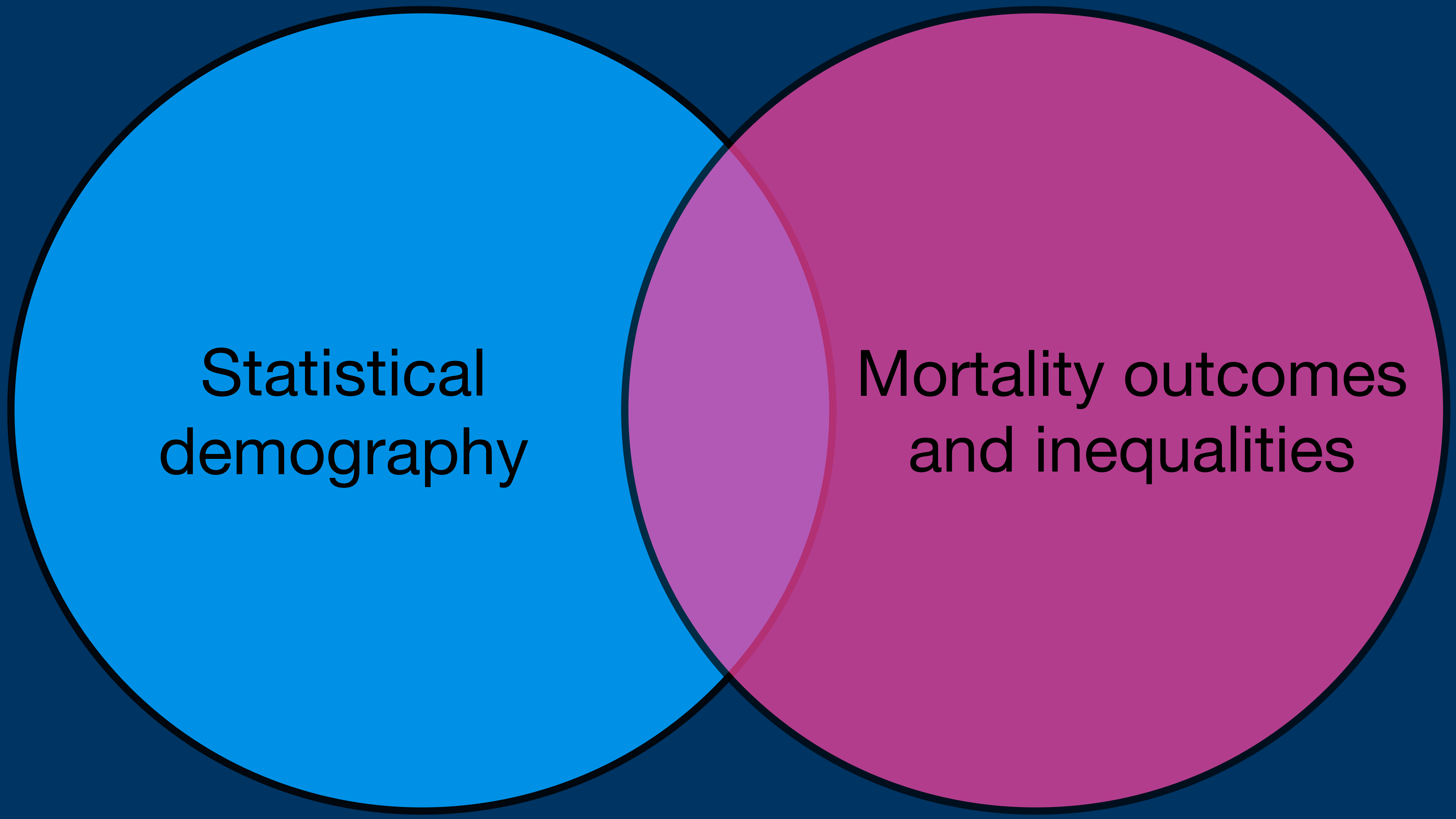
Key findings

- Globally, largest share of maternal deaths due to hemorrhage (27% [22-32%]), followed by indirect deaths (23% [18-30%])
- Huge variation across regions of the world
  - Hemorrhage disproportionately affects those in LMICs (29% in W Asia/N Africa, 14.5% in N America and Europe)
  - Type of indirect deaths vary substantially
- Most hemorrhage and sepsis deaths occurred in the postpartum period

Implications

- Persistent inequalities in access to and the quality of necessary healthcare
- Improved commitment to postpartum care
- Integration of obstetric and non-obstetric care
- Better reporting of suicide and later maternal deaths to understand the medium and long-term impacts of pregnancy and childbirth
- In the end, no model beats good-quality data

Future research agenda



Global health estimation

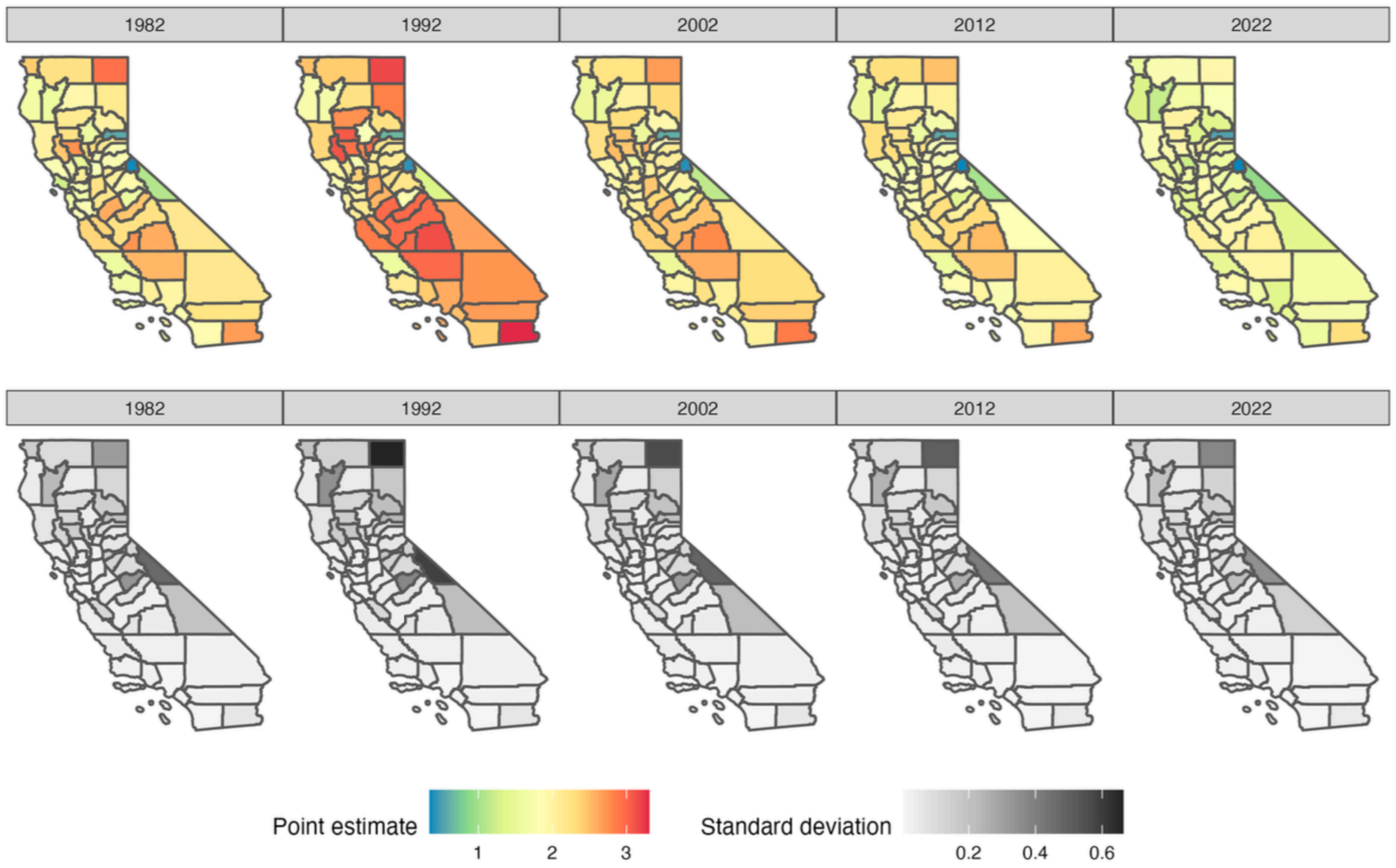
- Improving modeling:
    - weighting scheme to better account for non-representativeness
    - cause misclassification
- Incorporation/understanding of more data: high-quality data from surveillance sites, verbal autopsies
- Capacity building in national statistical offices

World Health Organization

IGME

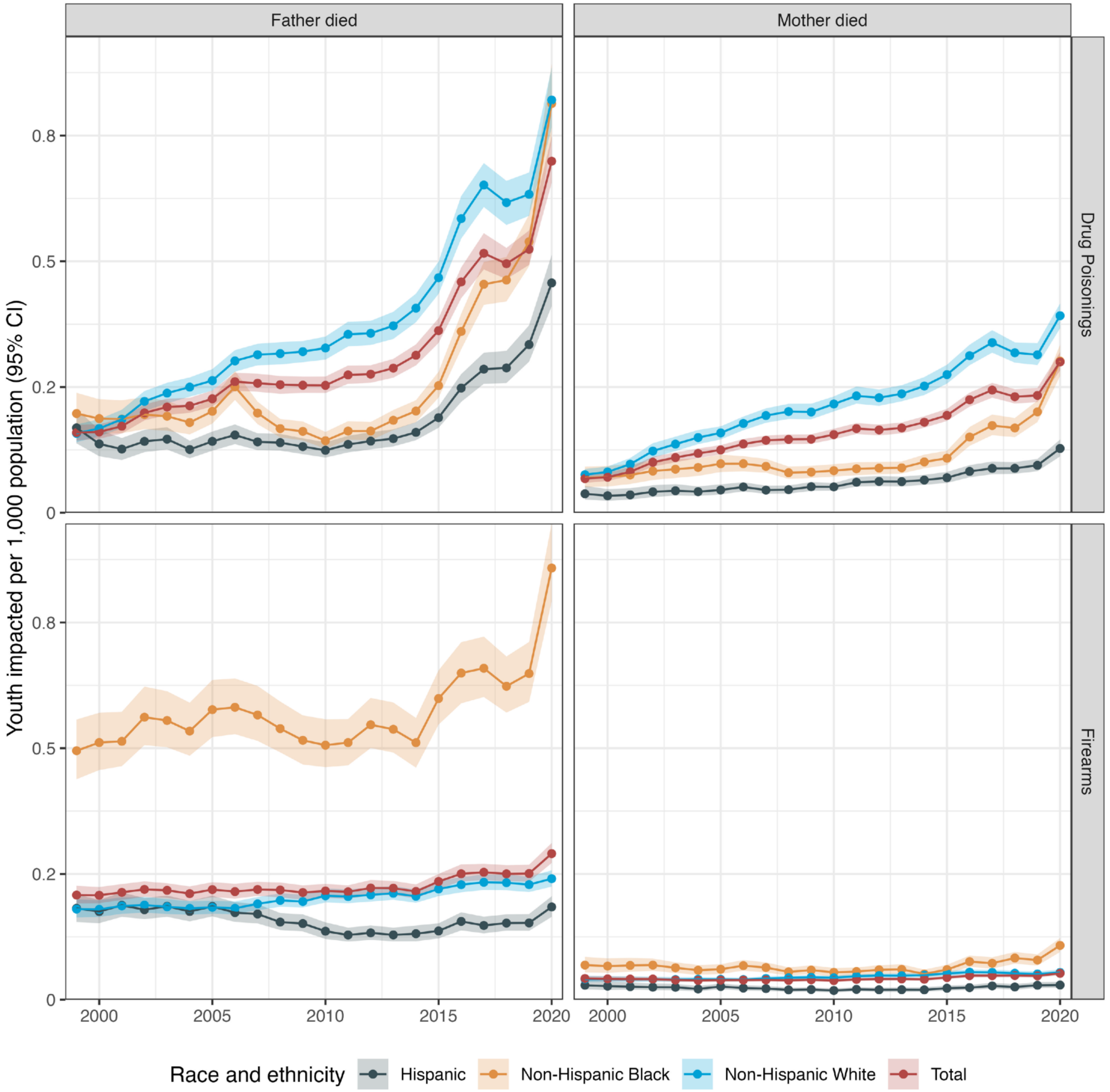
Statistical and formal demography

- Small area estimation
- Methods for studying kinship
- Formal demography of perinatal outcomes



Mortality outcomes and inequalities

- Link between child and parents health and mortality
- Multiple causes of death in the context of the drug epidemic
- Maternal health and mortality in the context of the drug epidemic



Thanks!

monica.alexander@utoronto.ca

monicaalexander.com

@monjalexander

MJAlexander

UNIVERSITY OF TORONTO

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Extra

Multinomial likelihood and missing values

- In an ideal situation where counts for all categories are recorded:

$$\frac{\phi_{i,j}}{\phi_{i,7}} = \eta_{i,j} = \exp\left(\alpha_j + \beta_{r[c[i]],j} + \gamma_{c[i],j} + \delta_{i,j}\right)$$

- and the corresponding multinomial likelihood for all N observations is

$$L_M = \prod_{i=1}^{N}\prod_{j=1}^{7}\phi_{i,j}^{y_{i,j}} = \prod_{i=1}^{N}\prod_{j=1}^{7}\left(\frac{\eta_{i,j}}{\sum_{k=1}^{7}\eta_{i,k}}\right)^{y_{i,j}}$$

Multinomial likelihood and missing values

- In many cases we do not observe death counts in all categories, and we would like to treat the missing values as unknown. In such cases we treat the observation as a multinomial observation with a reduced number of categories.

- For example if the first category is missing for observation *i* then the likelihood contribution becomes

$$\prod_{j=2}^{7} \breve{\phi}_{i,j}^{y_{i,j}} = \prod_{j=2}^{7} \left(\frac{\eta_{i,j}}{\sum_{k=2}^{7} \eta_{i,k}} \right)^{y_{i,j}}$$

- where $\breve{\phi}_{i,j}$ are the original probabilities rescaled to 1

Multinomial likelihood and missing values

- Under this setup, the model can still recover information about the relative proportions of the non-missing categories, while estimates of missing categories is left mostly uninformed
- Practically, we implement the multinomial model using an equivalent Poisson likelihood (Ghosh et al 2006).
- The Poisson implementation speeds up computation, and easily allows for arbitrary combinations of missing values, and means we don’t have to rescale probabilities

Adjusting for unobserved deaths

- In many cases, a large fraction of the deaths are unrecorded or unclassified
- We want to account for uncertainty we have about the unobserved deaths
- We apply a weighting scheme, with weights

$$w_c := \max_{i:c[i]=c} \frac{d_i}{\grave{d}_{ct[i]}}$$

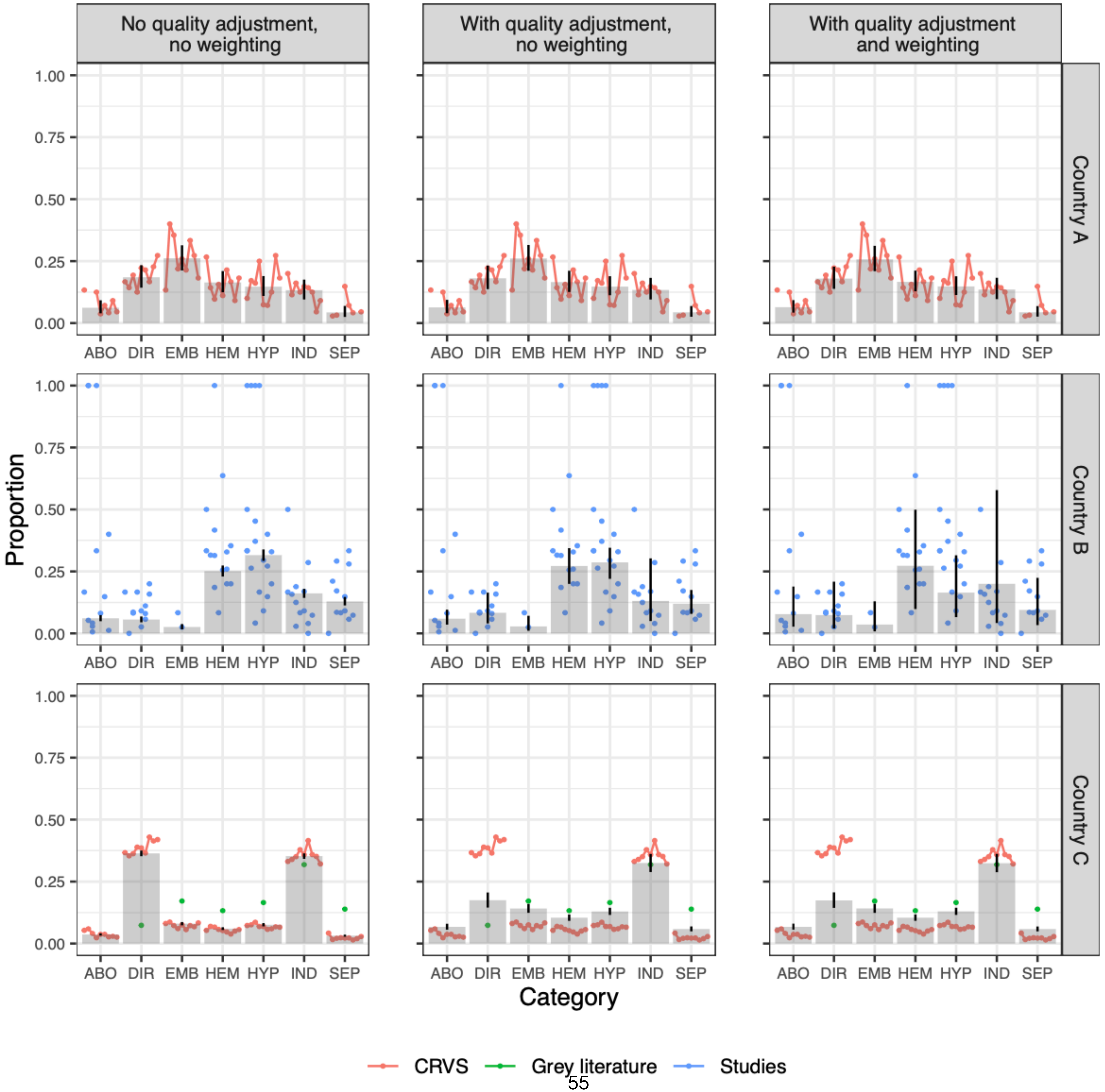
- where $\grave{d}_{ct[i]}$ is the WHO estimate of the total number of maternal deaths in that country-year.

Adjusting for unobserved deaths

The true proportions are then

$$\log\left(\frac{\phi^*_{c,j}}{\phi^*_{c,7}}\right) = \alpha_j + \beta_{r[c],j} + \underbrace{\boxed{w_c \cdot \gamma_{c,j}}}_{\text{Observed part}} + \underbrace{\boxed{\left(1 - w_c\right) \cdot \tilde{\gamma}_{c,j}}}_{\text{‘Unobserved part’}}$$

$\tilde{\gamma}_c$ are ‘new’ predictive draws based on the country-specific effect distribution


No quality adjustment, no weighting
With quality adjustment, no weighting
With quality adjustment and weighting
Country A
Country B
Country C
Proportion
Category
ABO DIR EMB HEM HYP IND SEP
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0.75
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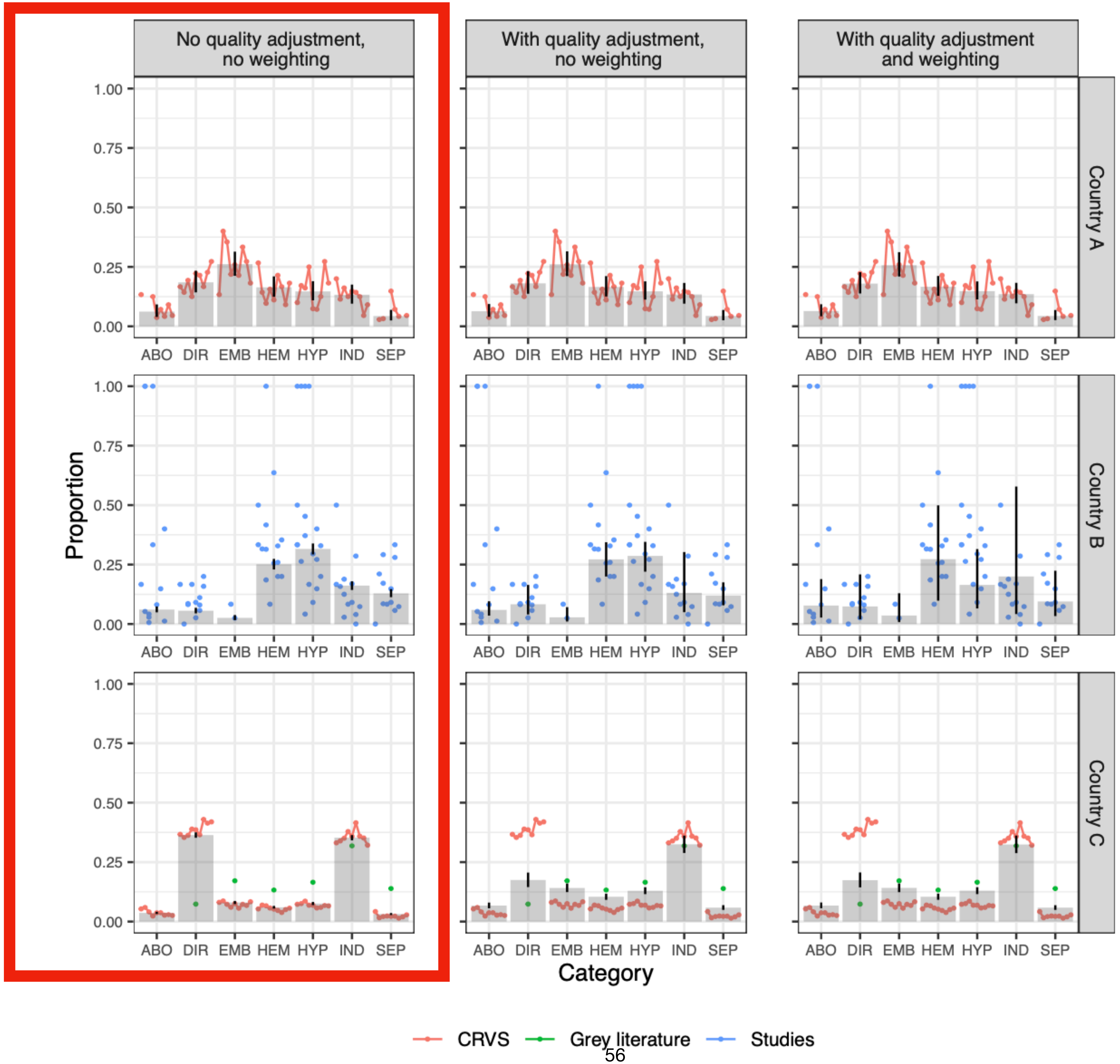
0.25
0.00
CRVS
Grey literature
Studies



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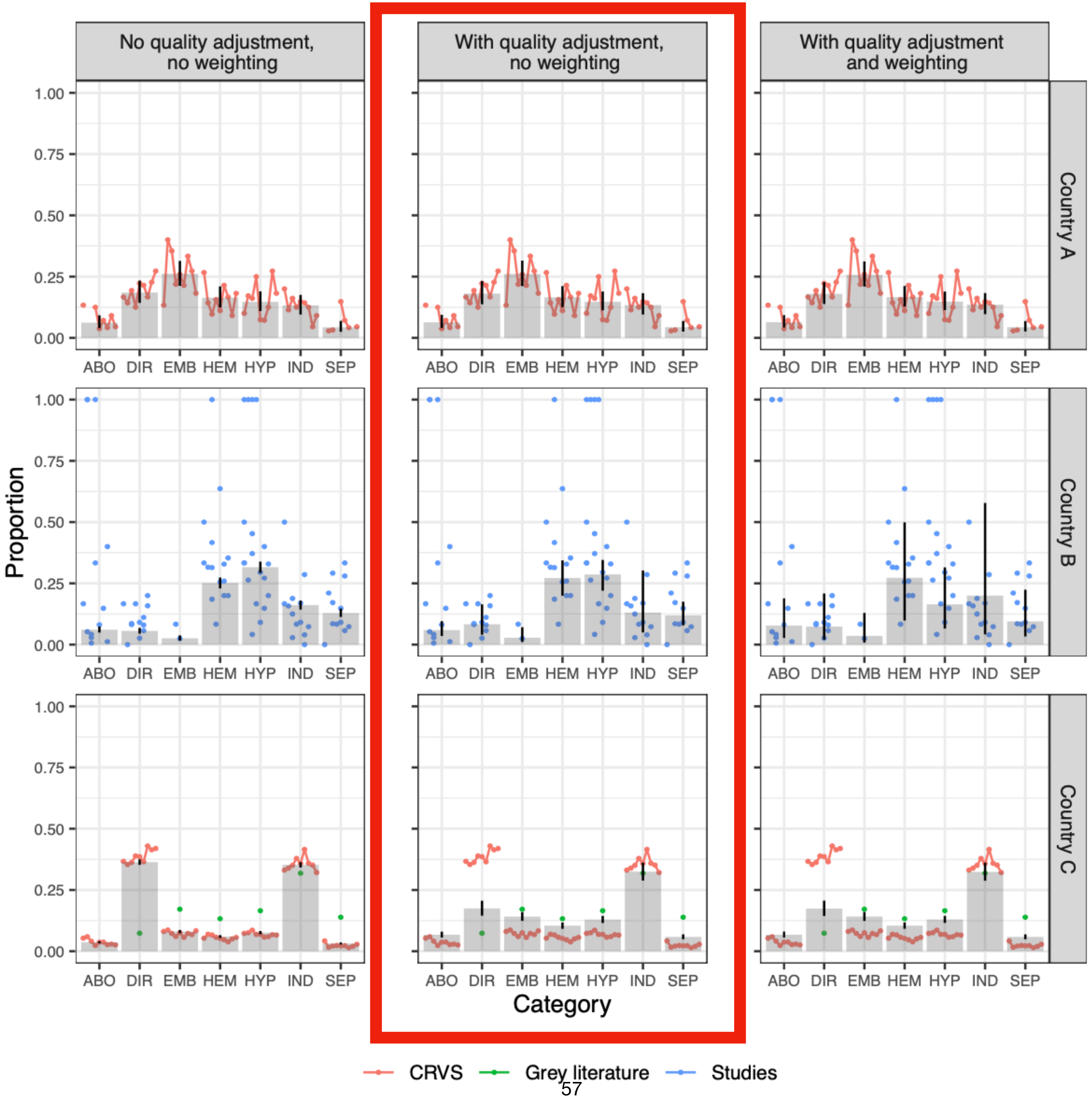

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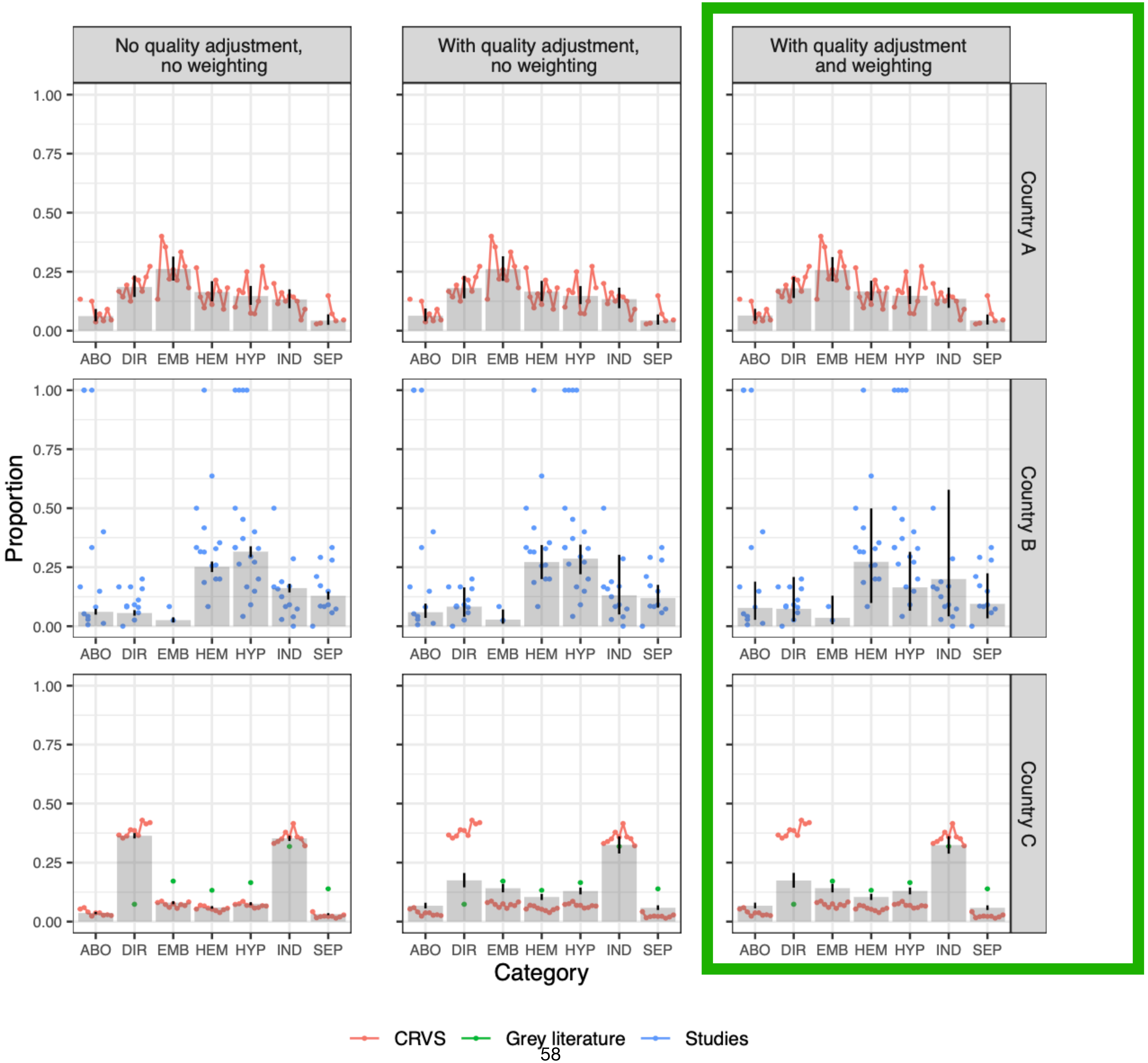

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Category
CRVS
Grey literature
Studies

Closing the data and methods gaps across countries

- We have a large gambit of possible models to choose from when studying causes of death
- But often options are limited when there’s not much data
- Even if we believe certain latent processes are at play, difficult to discriminate based on data we have
- Huge opportunities to share data, knowledge, and expertise, in the development of models, implementation of models, and policy and intervention design

Late maternal deaths

SDG Region	Number of reporting countries	Average ratio of late maternal to maternal deaths up to 42 days
Australia and New Zealand	2	0.03
Central Asia and Southern Asia	7	0.01
Eastern Asia and South-eastern Asia	8	0.03
Latin America and the Caribbean	30	0.06
Northern America and Europe	38	0.05
Sub-Saharan Africa	4	0.01
Western Asia and Northern Africa	20	0.07

Late maternal deaths

SDG Region	Number of reporting countries	Average ratio of late maternal to maternal deaths up to 42 days
Australia and New Zealand	2	0.03
Central Asia and Southern Asia	7	0.01
Eastern Asia and South-eastern Asia	8	0.03
Latin America and the Caribbean	30	0.06
Northern America and Europe	36	0.05
Sub-Saharan Africa	4	0.01
Western Asia and Northern Africa	20	0.07

Other direct deaths