Impact of Delayed Effects on Human Old-Age Mortality[1]

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Joint work with Alberto Palloni (UWisc-Madison)
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HMD-Satellite meeting

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[1] Verhulst,A., Beltrán-Sánchez,H., Palloni, A. (2019), *Dem Res 40(41)*

Objective

1. **Overview of importance of considering mechanisms and pathways derived from theories of Developmental Origins of Health and Disease (DOHaD) as part of population-based studies**

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1. **Overview of importance of considering mechanisms and pathways derived from theories of Developmental Origins of Health and Disease (DOHaD) as part of population-based studies**
2. **Delayed effects, including those from DOHaD, can help us better understand current and future health conditions of older populations in low- to middle-income countries (e.g., Latin America)**

In today's talk:

1. **Importance of changes in cohort composition by early childhood experiences with delayed effects: genetics, epigenetics, biological development, microbiome**

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1. **Importance of changes in cohort composition by early childhood experiences with delayed effects: genetics, epigenetics, biological development, microbiome**
2. **Present some evidence of the link between early child conditions and mortality at older ages in Latin American countries**

Theoretical background

1. **Developmental origins of health and disease (DOHaD)**
2. **Epigenetic mechanisms**
3. **The role of the microbiome**

Theoretical background: DOHaD

1. **Fetal programming or the 'thrifty' phenotype**
   - The timing ("critical windows" and "sensitive periods"), duration and severity of nutritional deprivation will determine its ultimate effects.
2. **Predictive adaptive responses (PARs)**
   - adaptive mechanism that evolves to cope with environmental oscillations
   - when early predictions and actual postnatal conditions are discordant there will be higher risks of adult diseases
3. **Disease, inflammation and hormonal imbalance**
   - linkages between exposure and contraction of early life infections and the development of adult chronic conditions
4. **Child nutritional status**
   - association between indicators of early nutritional status (height; weight by height) and adult diseases and mortality

Developmental Origins of Health & Disease (DOHaD)

Fetal programming or the 'thrifty' phenotype

Predictive adaptive responses (PARs)

Disease, inflammation and hormonal imbalance

Child nutritional status

common theme of these theories:

- **presence of perturbations of the development process of a phenotype**
- **After prolonged latency periods, the perturbations lead to irreversible changes**
- **These changes manifest themselves as increased susceptibility to adult chronic illness**

Reconciling DOHaD with Demography

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Reconciling DOHaD with Demography

1. **Delayed effects is equivalent to perturbing adult mortality patterns with a particular class of time-/age-varying frailty**
2. **Delayed effects are more likely to be observed in populations that experienced a mortality decline associated with medical innovations that reduced the load and lethality of infectious and parasitic diseases.**

Palloni, A. and Beltrán-Sánchez, H. Demographic Consequences of Barker Frailty. In Schoen, R. editor, Dynamic Demographic Analysis. Springer. Ch 8, pp. 147-176.
Palloni, A. and Beltrán-Sánchez, H. 2017. Discrete Barker Frailty and Warped Mortality Dynamics at Older Ages. *Demography* 54(2):655–671.

When will delayed effects be observed?

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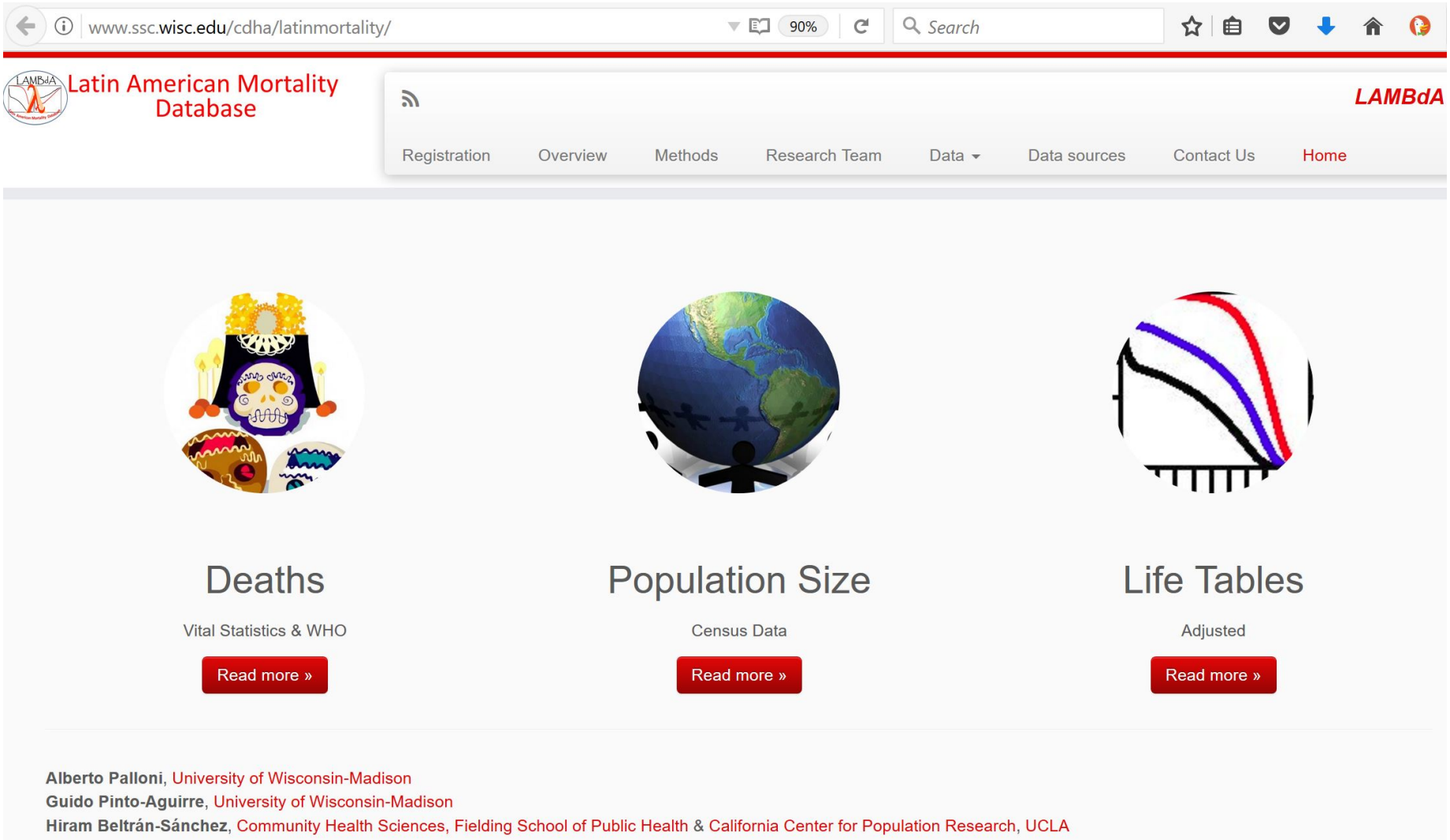
1. cohort members who experience early insults survive beyond some critical age $Y_1 \Longrightarrow$ damage begins to unfold;
2. a delayed effect must be significant: it should implicate higher than average risks for a broad range of illnesses and conditions with higher than average fatality rates;
3. mortality levels and patterns are influenced by a secular decline partially sustained by large improvements in infant and child survival;
4. the rate of survival gains during childhood is larger than that during adulthood,
5. the beneficial mortality (morbidity)-related effects of medical improvements adopted between the time of onset of adverse early experiences and the time at which a birth cohort attains the critical age Y_1 fail to offset delayed effects in the form of excess mortality risks due to some chronic illnesses.

Predictions in the presence of demographic changes

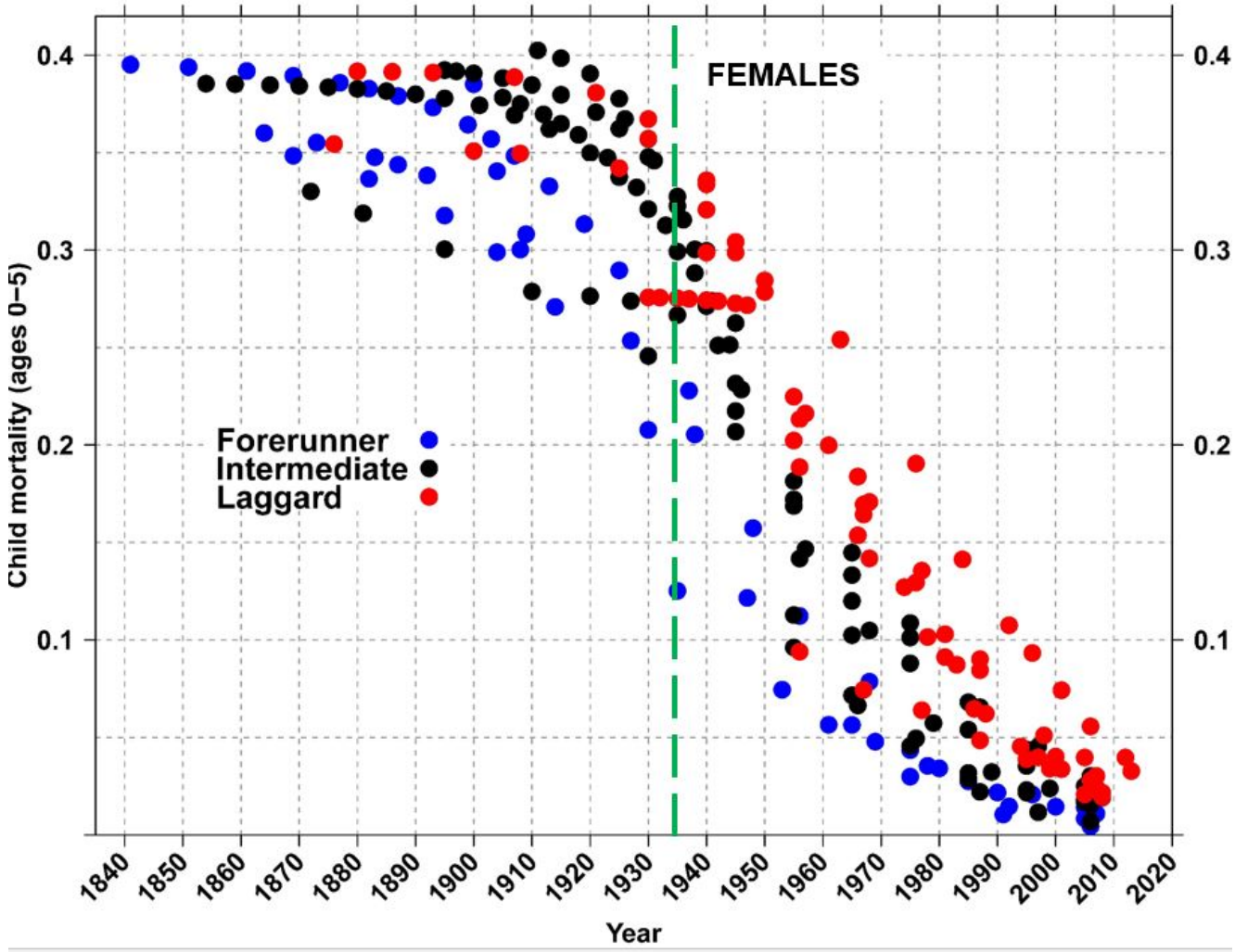
- **Predicition: a secular mortality decline → influx of surviving individuals susceptible to express delayed effects after some critical age.**
  1. **the observed rate of decline of adult mortality levels of successive cohorts will decelerate**
- **Formal empirical test:**
  - **Fit a log-log model to adult mortality rates as a function of early-life mortality**
  - **The log-log equation produces proportional changes in mortality rates.**
  - **Use Keyfitz's entropy to estimate gains in cohort life expectancy at older ages given their childhood mortality experience**

Data: Latin American Mortality Database–LAMBdA

www.ssc.wisc.edu/cdha/latinmortality

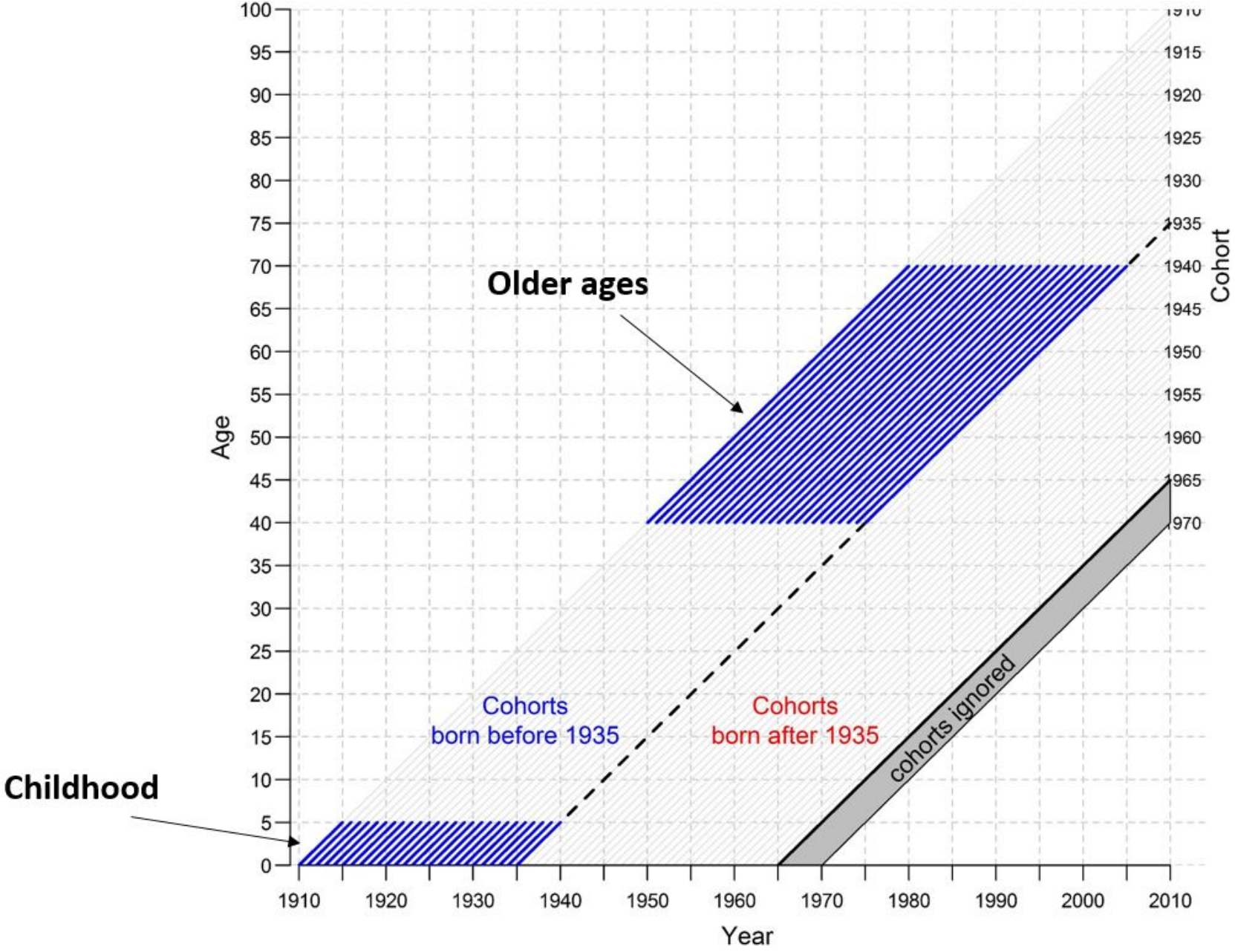


Trends in Child Mortality in Latin America: LAMBdA



Forerunner: Argentina, Costa Rica, Cuba and Uruguay
Intermediate: Brazil, Chile, Colombia, Dominican Republic, Mexico, Panama and Venezuela
Laggard: Bolivia, Ecuador, El Salvador, Guatemala, Nicaragua, Peru, Honduras and Paraguay.

Data: Latin American Mortality Database–LAMBdA



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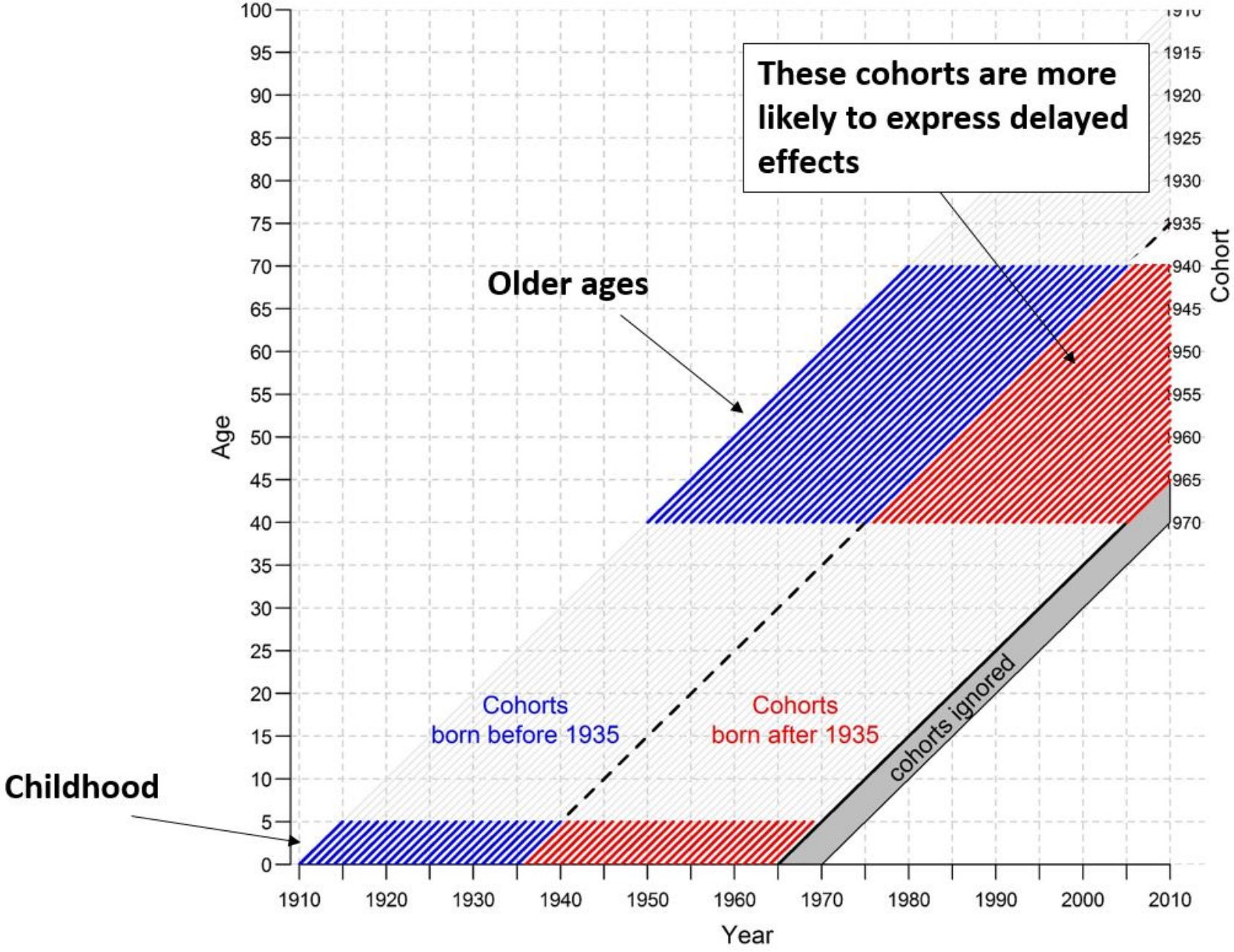

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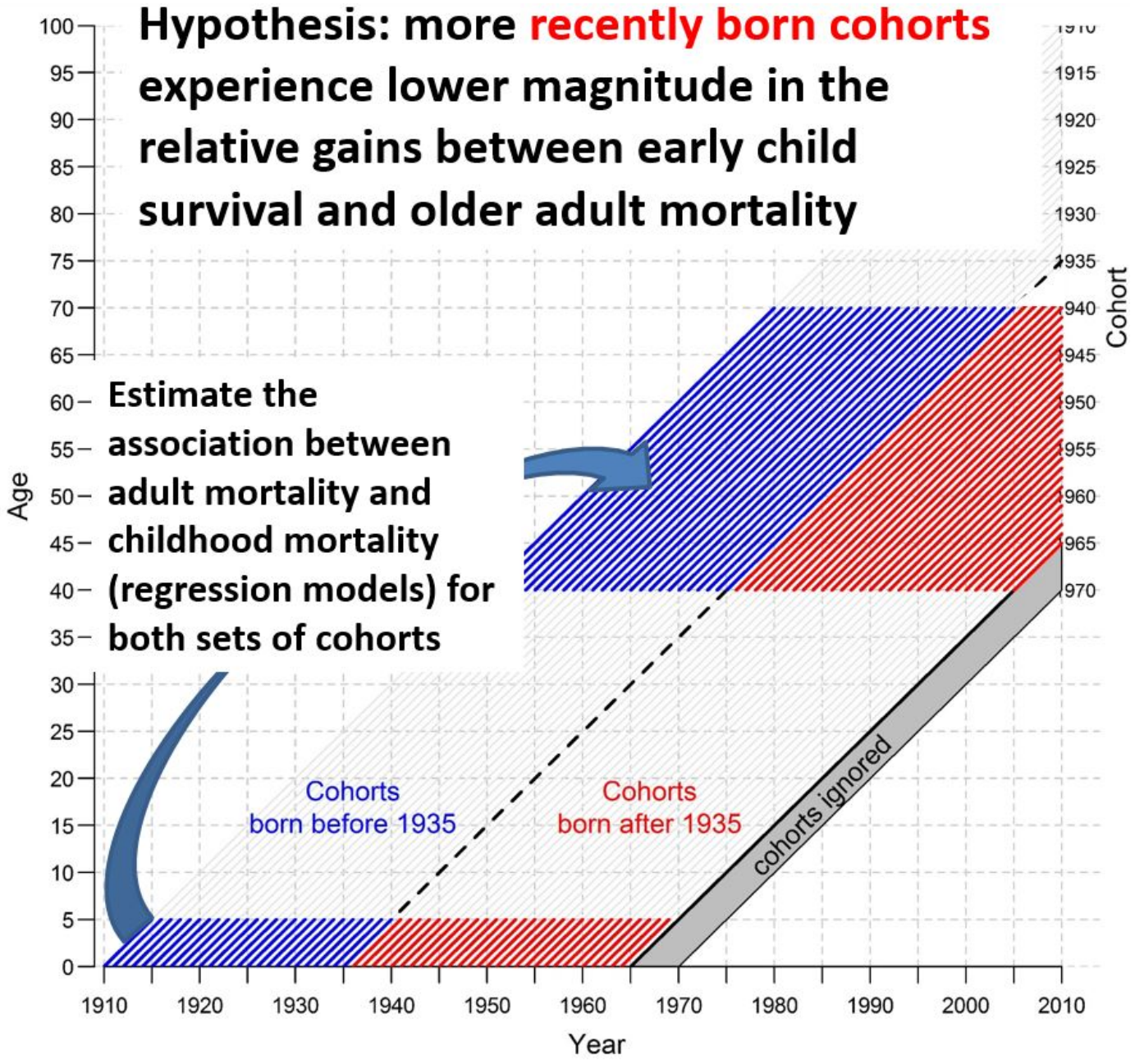

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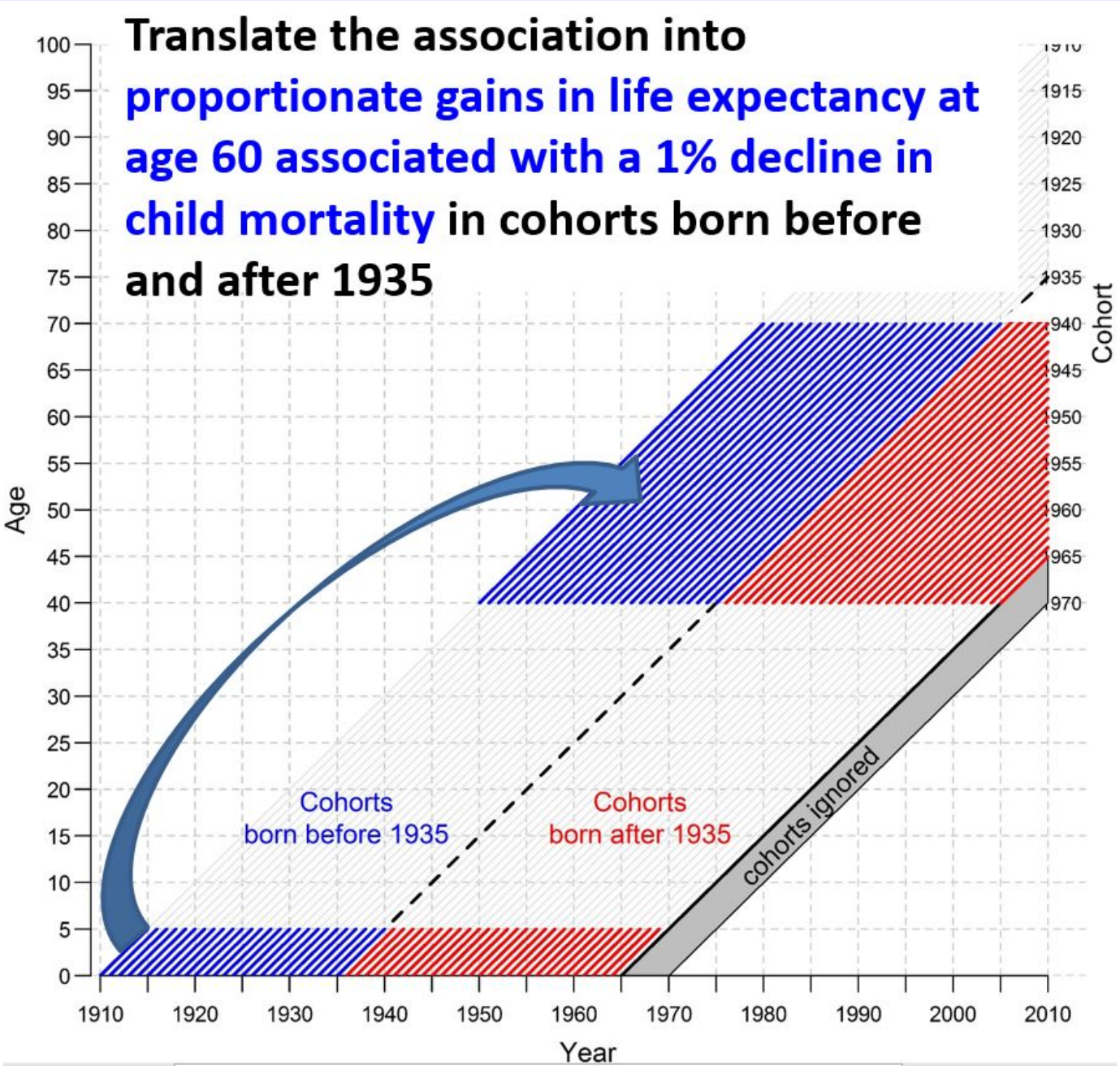

Results

Proportionate gains in life expectancy at age 60 for MALES associated with a 1% decline in child mortality

	Born before 1935 (older cohort)	Born after 1935 (younger cohort)	Ratio: younger/older
Brazil	2.02	1.43	
Dominican Rep.	1.41	1.34	
El Salvador	1.21	1.11	
Guatemala	1.90	1.31	
Peru	2.00	1.36	

PERU:
Born before 1935: a 1% decline in child mortality leads to gains in life expectancy at age 60 about twice as large

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Younger cohorts experienced lower gains in life expectancy at age 60 than older cohorts given an identical 1% decline in child mortality

Results

Proportionate gains in life expectancy at age 60 for MALES associated with a 1% decline in child mortality

	Born before 1935 (older cohort)	Born after 1935 (younger cohort)	Ratio: younger/older
Brazil	2.02	1.43	0.71
Dominican Rep.	1.41	1.34	0.95
El Salvador	1.21	1.11	0.91
Guatemala	1.90	1.31	0.69
Peru	2.00	1.36	0.68

PERU: the ratio 1.36/2.00= 0.68, indicates that the younger cohorts experience gains in life expectancy at age 60 about 68% of the gains in the older cohorts

Conclusion:

- **In a mortality regime with declining mortality, delayed effects will compound the decelerating force that naturally arises when only standard frailty prevails.**

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- **In a mortality regime with declining mortality, delayed effects will compound the decelerating force that naturally arises when only standard frailty prevails.**

As mortality declines:

delayed effects lead to additional excess mortality among those exposed to adverse early life conditions and attain adult ages

Conclusion:

- **Standard frailty always leads to deceleration of mortality rates at older ages BUT delayed effects unleashes forces that work in the opposite direction and promote increases in the "rate of aging".**

Conclusion:

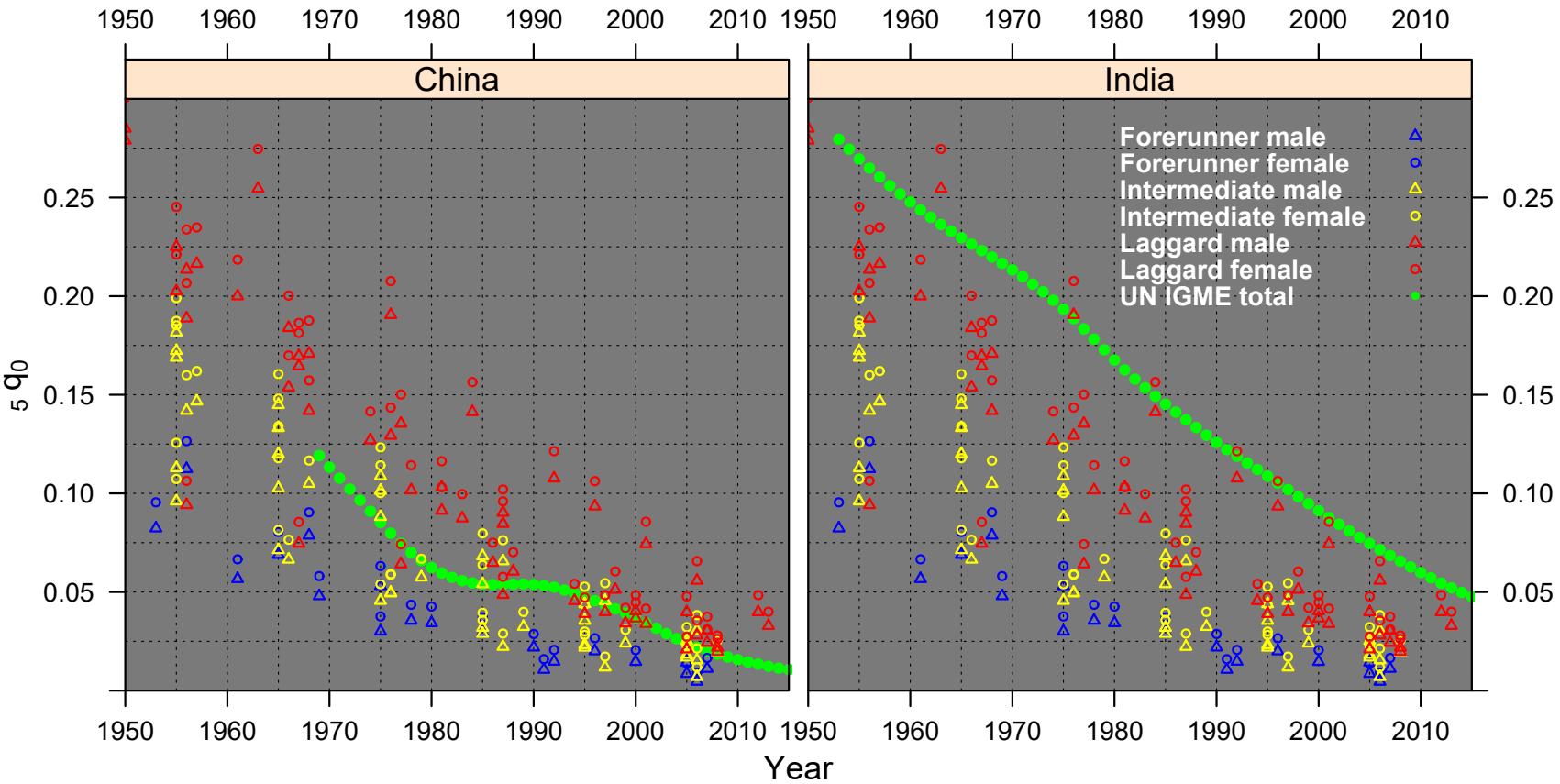
- **The impact of delayed effects on adult life expectancies is more likely to be observed in countries that experienced mortality declines that were at least partially sustained by massive improvements in infant and child survival.**

Conclusion:

- **Delayed effects have the potential to slow down improvements in old age mortality in Latin America and in other low- an middle-income countries (i.e., lower than expected longevity)**

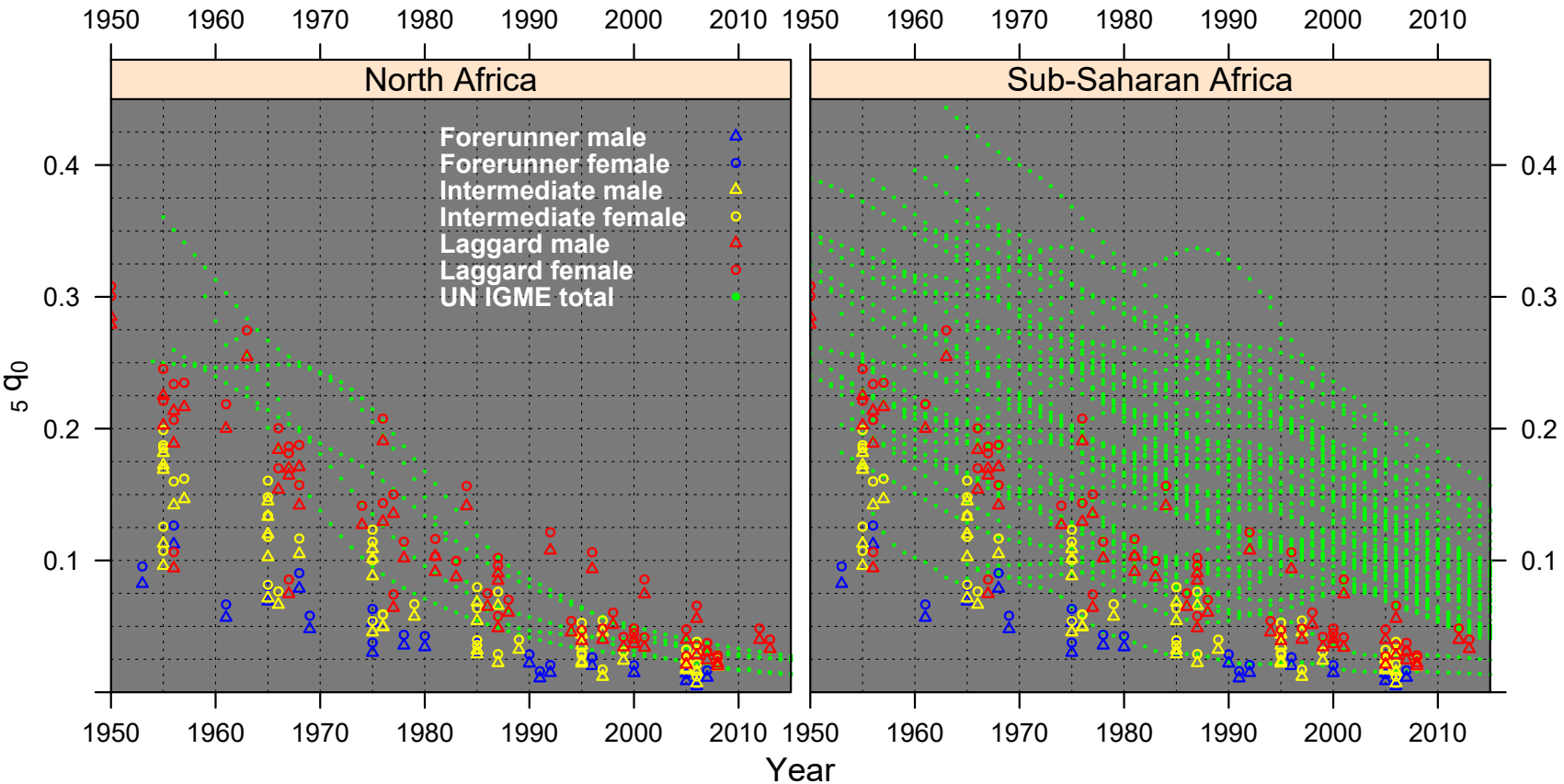
Conclusion:

Trends in Child Mortality in LAMBdA, China, India



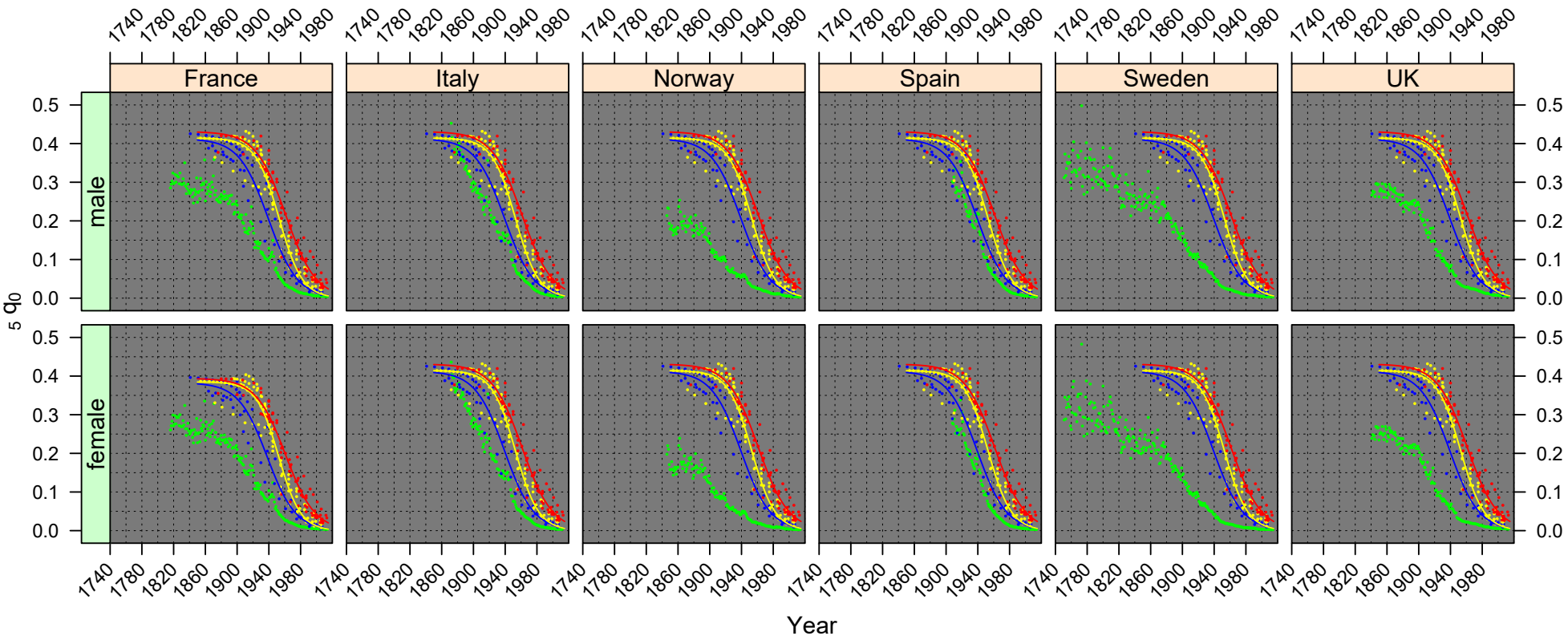
Conclusion:

Trends in Child Mortality in LAMBdA, North Africa, Sub-Saharan Africa



Conclusion:

Trends in Child Mortality in LAMBdA, and some European countries



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Thank you!

1. Those who experience early insults survive beyond some critical age $Y_1 \Longrightarrow$ damage begins to unfold;
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Back to conditions.

- Let Z be the critical age and assume it has a well-defined density $f_Z(z)\ \forall\ i \in$ DE, where DE=delayed effects.
- Excess mortality $= \lambda_{DE}$ for $Z \geqslant 40$.

The expected value of the force of mortality at $y \geqslant 40$

$$\bar{\mu}(y,t) \simeq k(t)\mu_s(y)[P^1_{DE}(y,t)\Phi_Z(y)(\lambda_{DE}-1)+1]$$

where:

- $\Phi_Z(y) =$ the distribution function of critical ages z evaluated at age y
- $P^1_{DE}(y,t)$ is the fraction of all survivors to age y who carry DE *and* whose critical ages satisfy $z \leqslant y$.

$$P^1_{DE}(y,t) \simeq \left[1+\exp(-k(t)(1-\lambda_{DE})\Lambda_S(\check{y},y))\left(\frac{1-\Phi_Z(y)}{\Phi_Z(y)}\right)+\frac{(1-g)/g}{\Phi_Z(y)}\right]^{-1}$$

with $\Lambda_S(\check{y},y)=\int_{\check{y}}^{y}\mu_s(v)dv$ and $40 \leqslant \check{y} \leqslant y$ is the (conditional) mean of the critical ages z among those with DE who survive to age y. Back to formulation.