THE ECONOMY, THE GHOST IN YOUR GENE AND THE ESCAPE FROM PREMATURE MORTALITY

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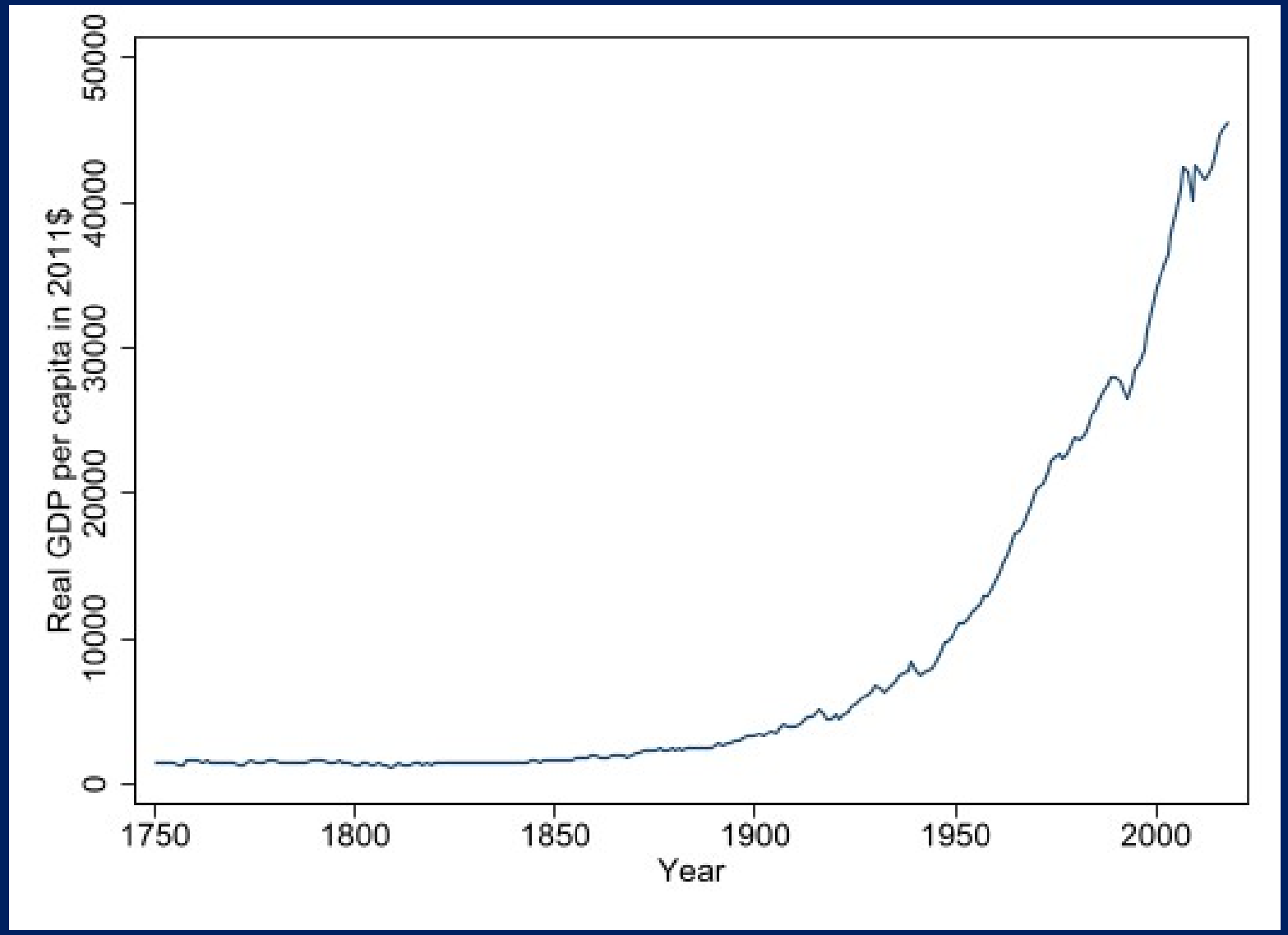
BIG ACHIEVEMENTS OVER TWO CENTURIES

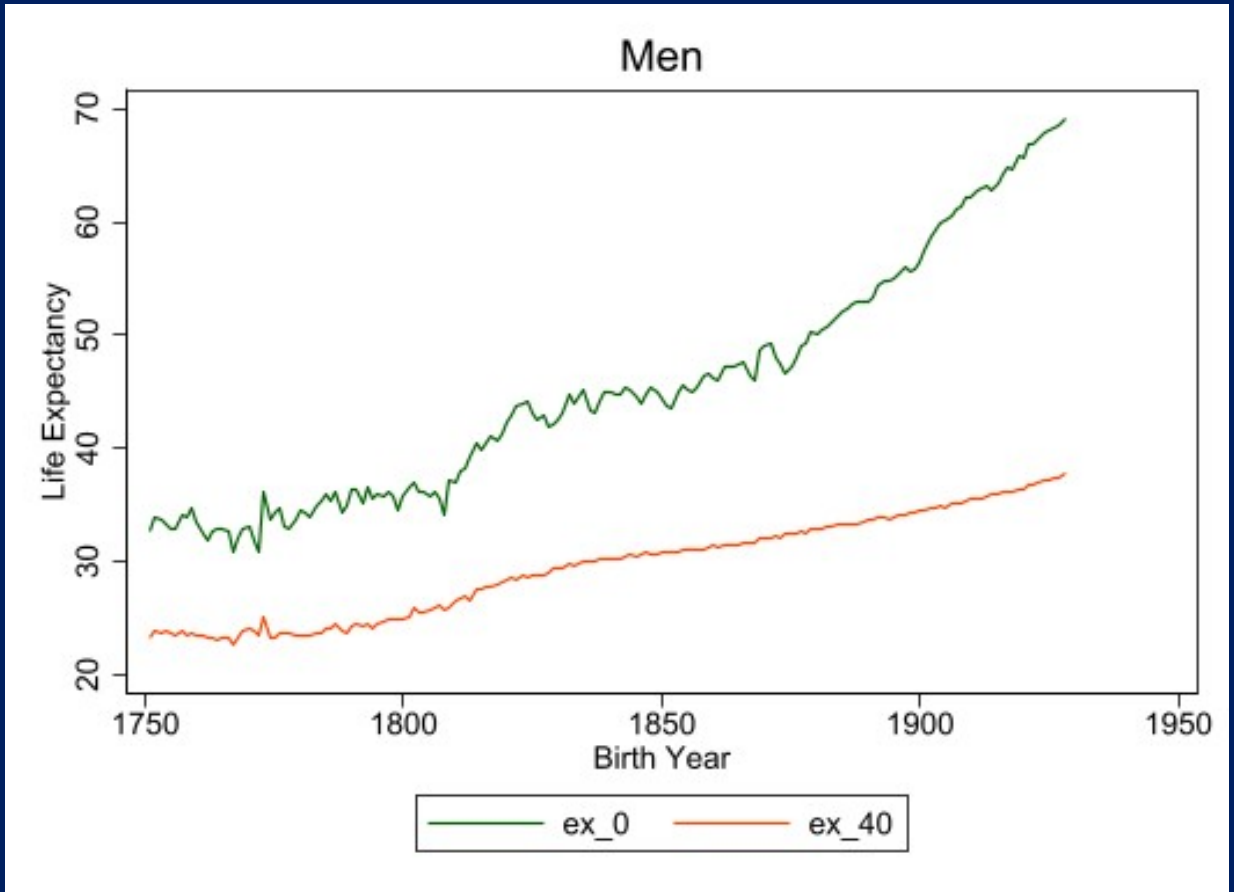
ECONOMIC GROWTH
RISING LIFE EXPECTANCY

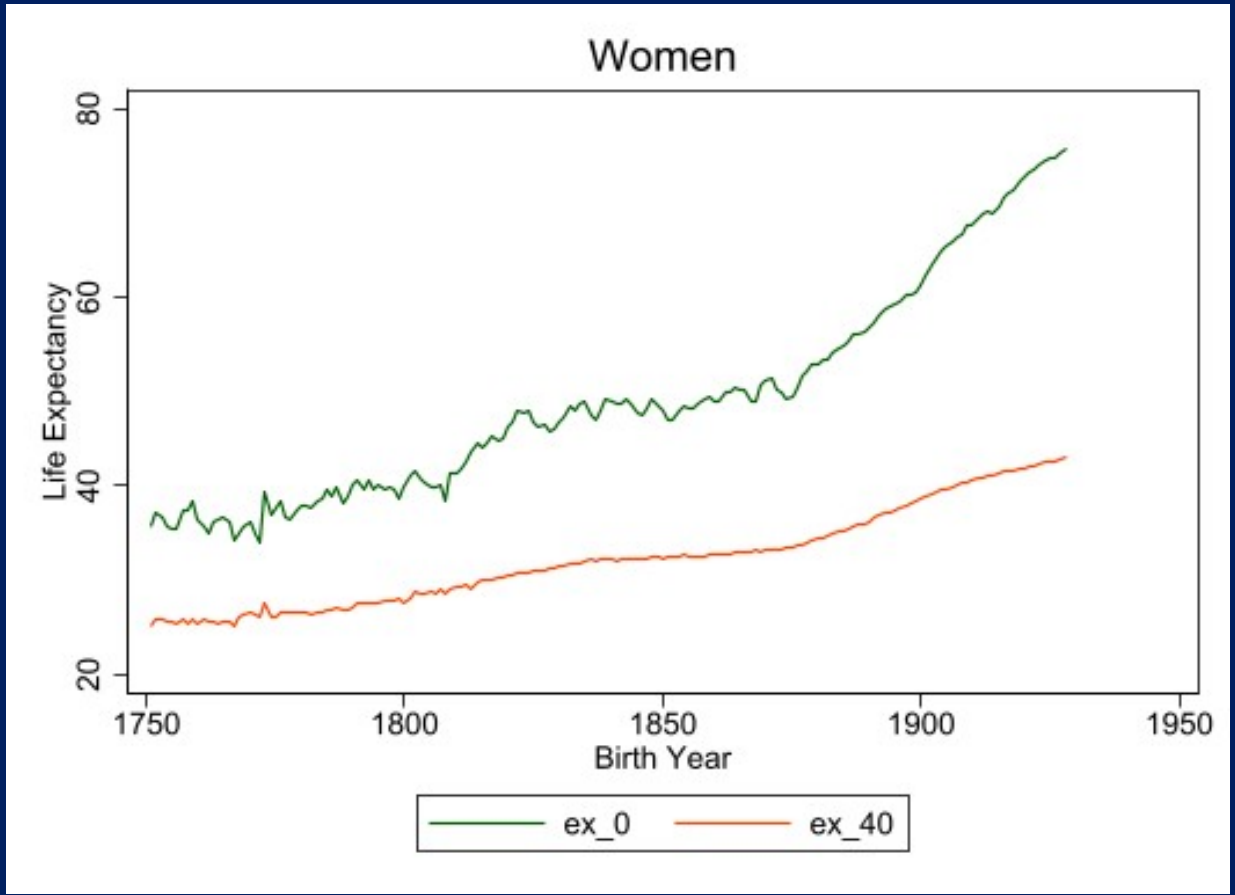
CONSIDER THE CASE OF SWEDEN



Source: Maddison Project Database 2020

EXPECTED YEARS OF LIFE AT AGE 0 AND 40 BY BIRTH COHORT, SWEDEN





Source: Human Mortality Database

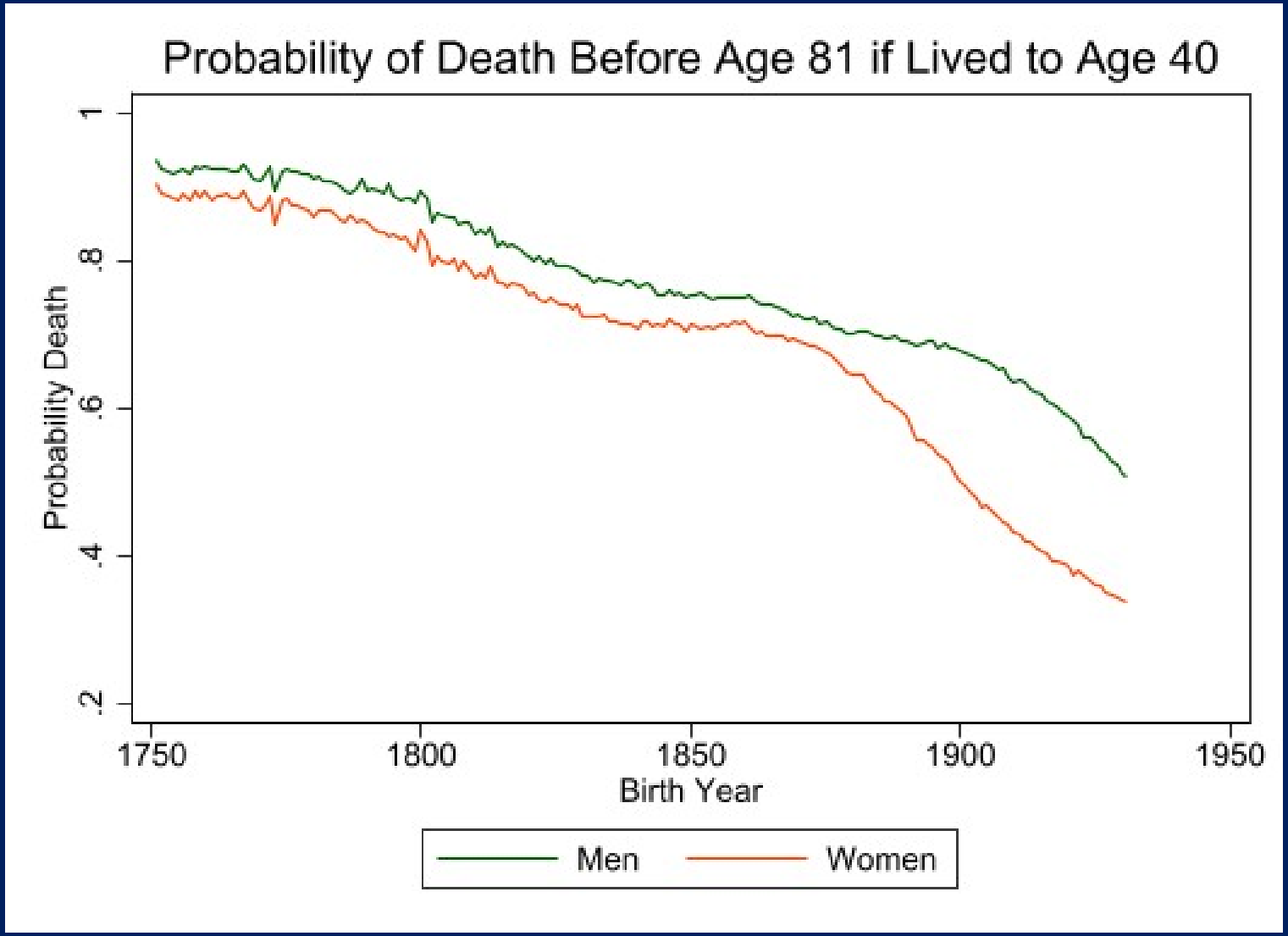
PROBABILITY OF DEATH BY AGE 80 AMONG 40 YEAR OLDS BY BIRTH COHORT, SWEDEN

Estimated break points:

Men's birth year:
1813
1867
1904

Women's birth year:
1808
1876
1903

Age 60 in
< 1875
1875-1929
1930-1963
1964+



Source: Human Mortality Database

HOW DOES THE ECONOMY'S LEVEL OF DEVELOPMENT AFFECT HEALTH?

- **Low productivity/income**
  - Crisis mortality before 1780s
  - Chronic malnutrition important after 1780s (Fogel)
    - Affects development before age 2, including fetal programming
    - Intergenerational effects through parental investments in child health

HOW DOES ECONOMY'S LEVEL OF DEVELOPMENT AFFECT HEALTH?

- **Low knowledge economy**
  - Cannot control infectious disease (Preston, Easterlin, Deaton)
    - High infant and before age 5 mortality
    - Survivors have organ damage and inflammation at older ages
    - Survivors do not learn as much in school (Bleakley)
    - Health as public good
      - Developed bond markets (Cutler and Miller)
  - Explanation for 1870-1960s mortality trends

A BOLD CLAIM

- We have underestimated the role of early economic growth in post-1870 improvements because we have ignored ancestral effects
- Past and present economic growth is in the epigenome
- Changes in gene function triggered by variance in food intake at critical ancestral ages
  - Direct biological effect

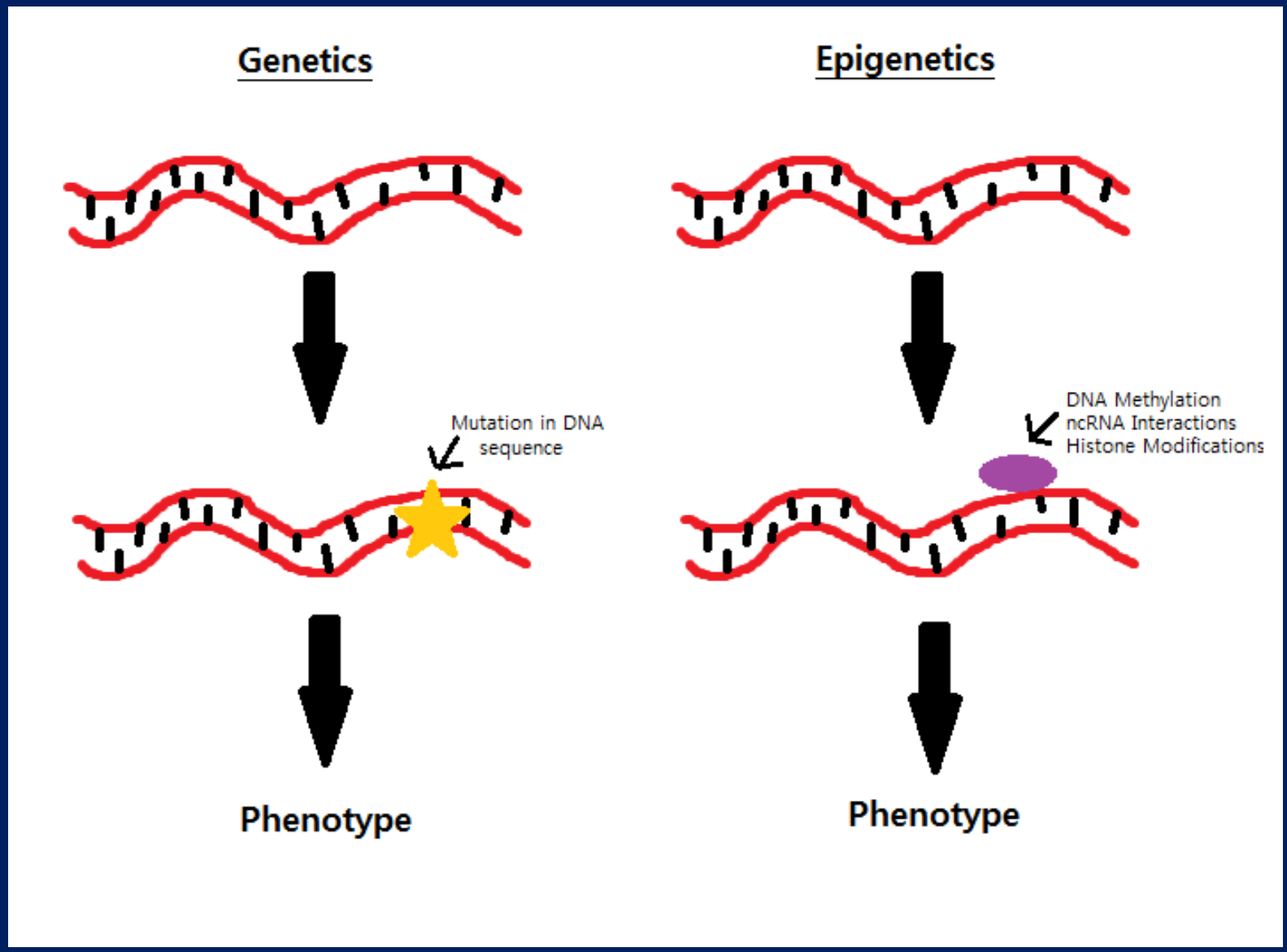
VARIANCE IN EARLY ECONOMIES

- Both lower levels income and higher variance
- Harvests more dependent on weather
- Food supply more dependent on local harvests
- Limited ability to preserve food
- Seasonality greater
- Less social and private insurance

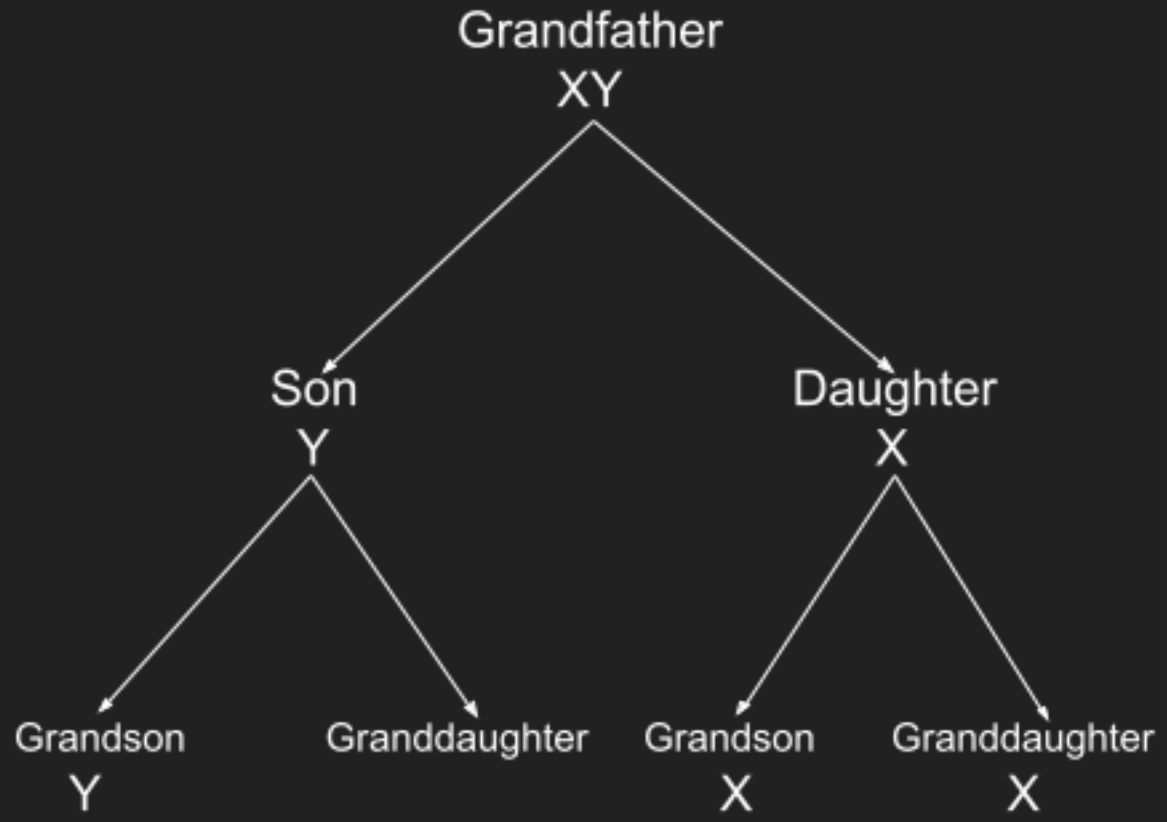
WHAT MIGHT HAPPEN IN A LOW INCOME AND HIGH VARIANCE ECONOMY?

- Feasts and famines trigger epigenetic change in gene function which is inherited (Bygren)
  - Outcome is chronic disease for later generations
  - Men particularly sensitive (Y chromosome)
- Persistence as long as bad conditions remain
  - Epigenetic marks not erased in early gestation
  - Epigenetic marks not reprogrammed in late gestation
  - In utero mortality selection

WHAT IS EPIGENETICS?



If Effect Passed Along Sex Chromosome



- Males pass down Y chromosome to sons and X chromosome to daughters.
- If Y Chromosome
  - Effect on sons and male-line grandsons only. (Only males carry Y chromosome.)
- If X Chromosome
  - Effect on daughters only and female-line grandchildren only.
- Is the Y chromosome more sensitive?
  - Non-recombining part might retain epigenetic marks more easily.

INSERTING EPIGENETICS INTO GROSSMAN'S PRODUCTION FUNCTION FOR HEALTH

Health (H) is a function of past health, the epigenome (P), and past investments (I).

$$H_t = f(H_{t-1}, P_t, I_{t-1})$$

The epigenome (P) depends on genetics (G), ancestral investments (I_A) and past investments (I_{t-1}).

$$P_t = g(G, I_A, I_{t-1})$$

TESTING THE EPIGENETICS HYPOTHESIS

- Intuition for testing the null hypothesis
- Challenge for testing the null
- Biological markers
- Sex-specific transmission in response to ancestral shock at sensitive age
  - Evidence transgenerational transmission requires 3 generations if post-natal shock and 4 if prenatal
  - Need to separate from socioeconomic inheritance, culture (how sex-specific?)

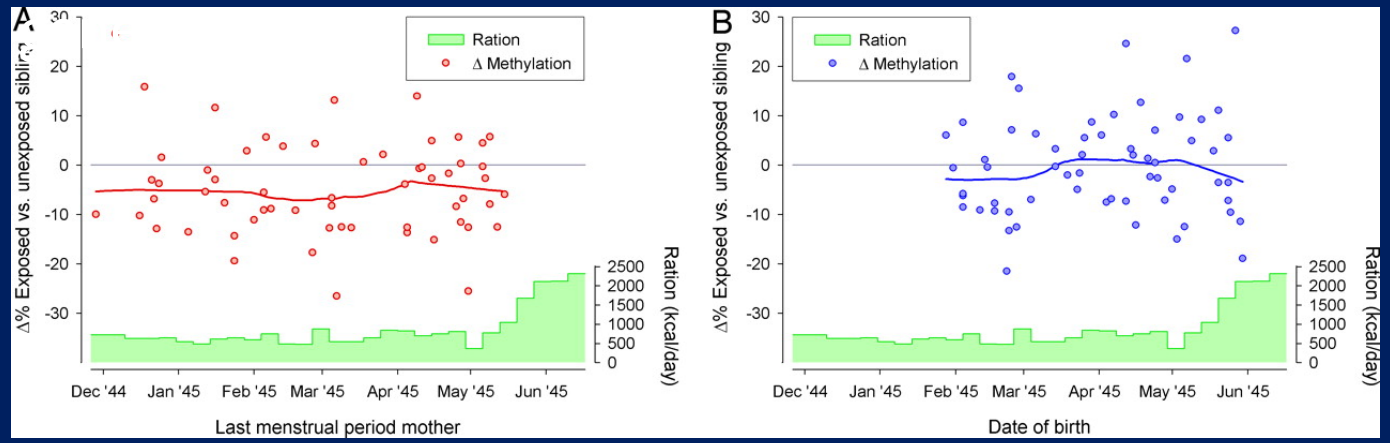
OF MICE AND MEN

- Evidence of epigenetic inheritance in some animals
  - 25 generations of worms and 4 of mice
  - Can reverse in mice with good prenatal nutrition
  - Epigenetic transmission species-specific
- Handful of circumstantial evidence studies about humans

DUTCH WWII HUNGER WINTER STUDIES

Adverse metabolic profile and higher risk schizophrenia after prenatal famine exposure

Differential DNA methylation after prenatal famine exposure at promoter and imprinted regions of

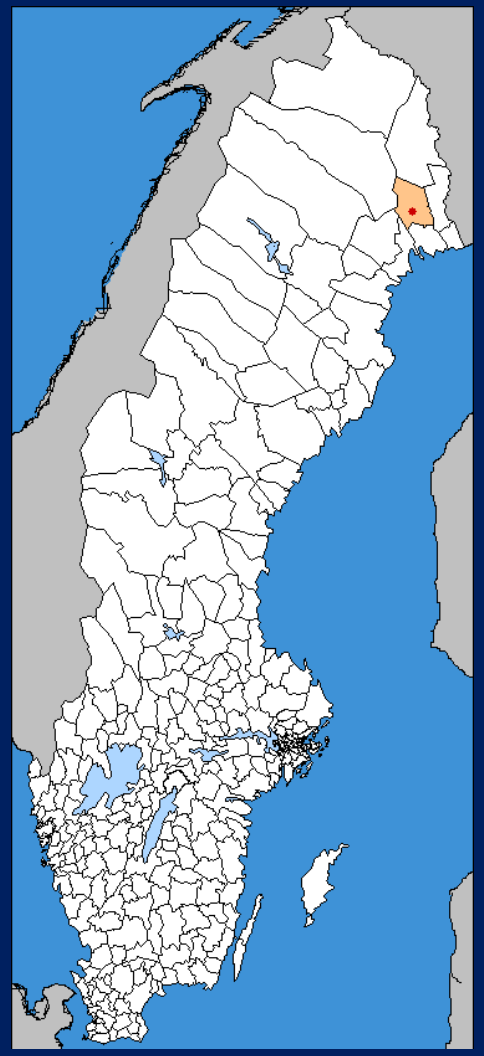


A: Periconceptional exposure, B: later exposure
Source: Heijmans et al. 2008

- Suggestive of epigenetic mechanism
- Start of pregnancy important
- Sex-specific methylation differences for some but not all genes
- What drives methylation?
  - Damage?
  - Plasticity? (match expected future environment)
  - Selection?
    - Stochastic DNA methylation and then differential survival on that DNA methylation

ÖVERKALIX STUDIES

- Bygren et al.
  - 1,818 grandchildren of 164 men and 139 women born 1890, 1905, or 1920
  - Good harvests during paternal grandfathers' (FF) pre-puberty slow growth period (ages 9-12) predict grandsons' mortality from cardiovascular disease and diabetes
  - Change from good to bad harvests during paternal grandmothers' (FM) pre-puberty slow growth period (ages 8-10) predicts granddaughters' mortality from cardiovascular disease
  - Ancestral year fixed effect



VÅGERÖ ET AL. : UPPSALA MULTIGENERATION STUDY

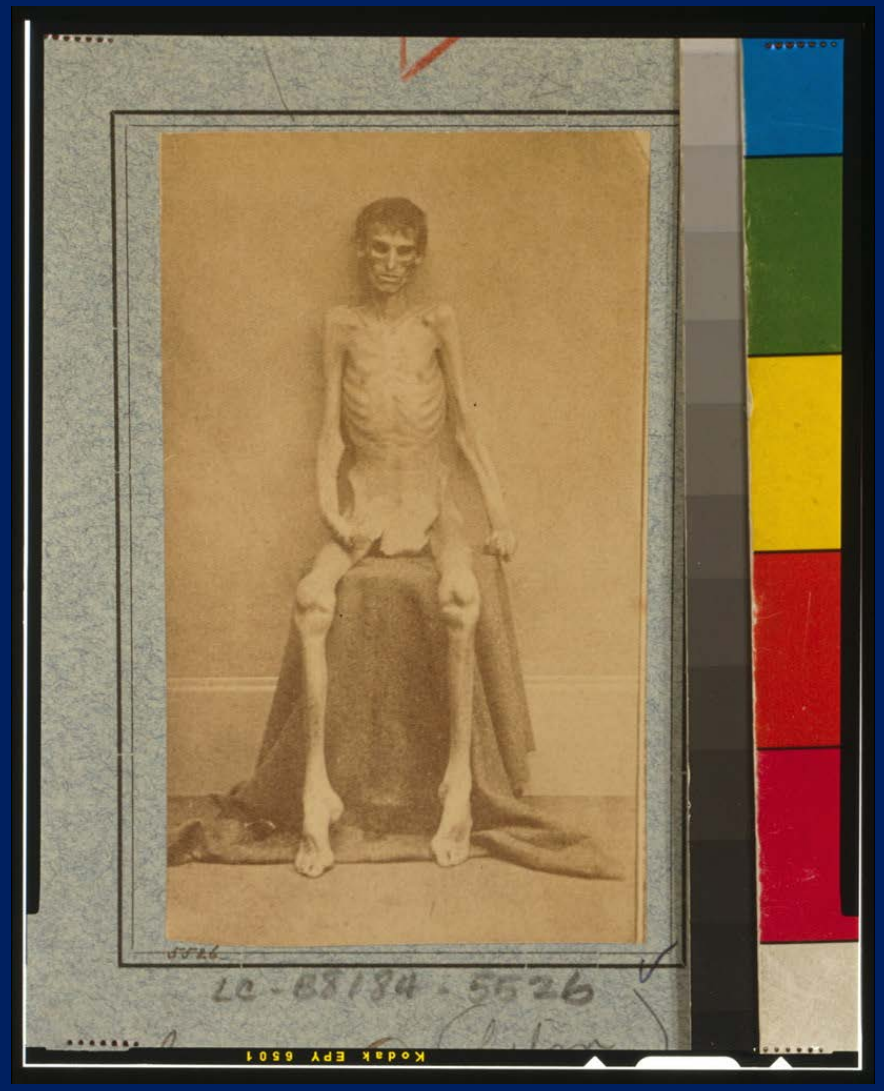
- Grandparents alive 1874-1910
- Good harvests during paternal grandfathers' (FF) pre-puberty slow growth period predict grandsons' mortality from cancer and cancer rates
- No effects of maternal grandmothers' (FM) pre-puberty slow growth period
- Grandchildren sample underpowered (incomplete life spans)

UNION ARMY VETERANS: COSTA

3 Groups

1. Non-POWs
2. Exchange Period Ex-POWs
   - Shorter captivity period, better conditions
3. Non-Exchange Period Ex-POWs
   - Longer captivity period, reduced to walking skeletons

- Slow growth period ages 19-24 (specific to historical populations)



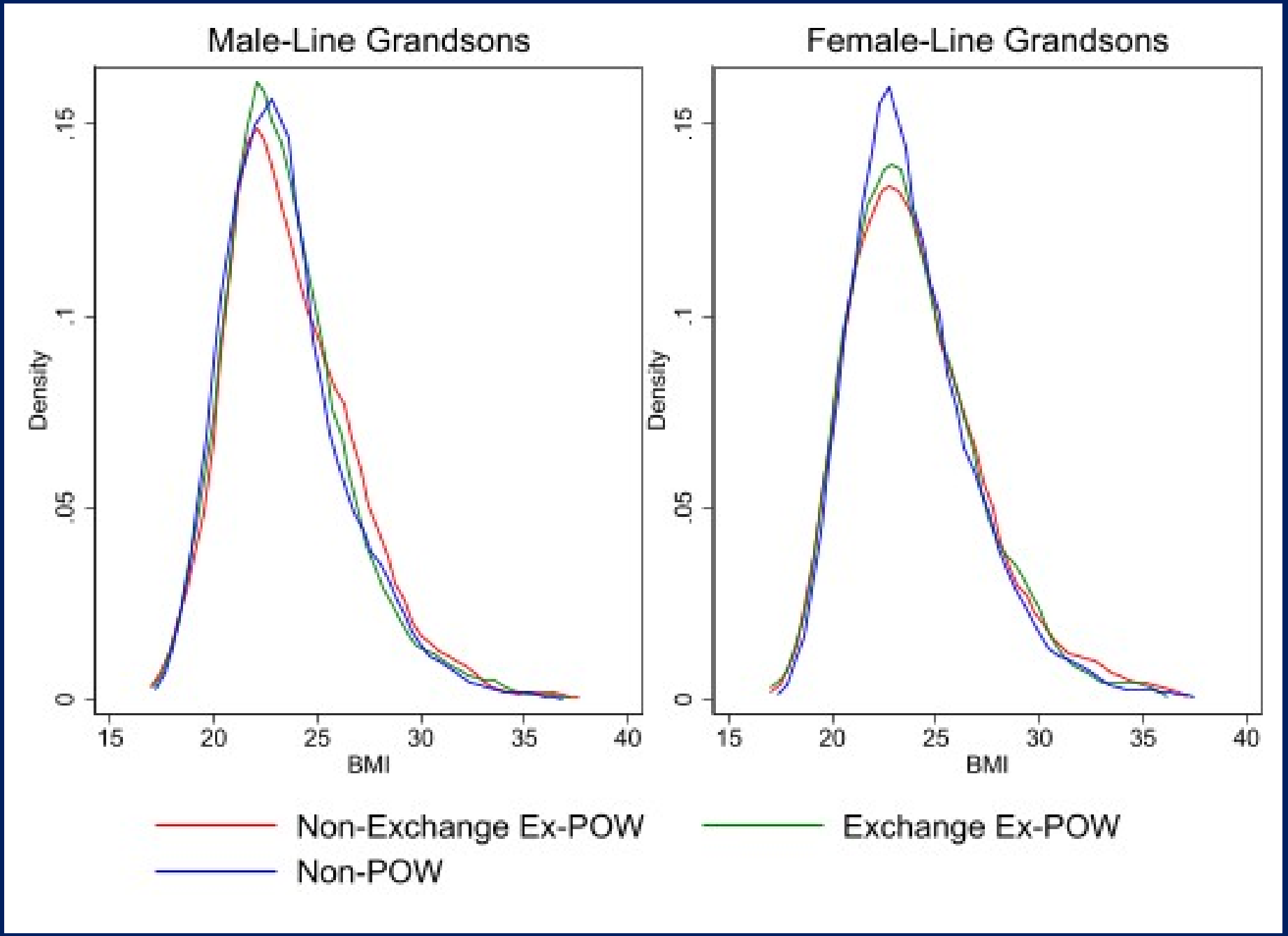
Male-line grandsons living to age 45 lose one year of life

Granchildren's Mean Years Lived by Ancestral Line and Grandfather's Ex-POW Status

	Male-line		Female-line	
Grandfather's Ex-POW status	Grand-sons	Grand-daughters	Grand-sons	Grand-daughters
Non-POW	73.79	79.64	73.13	79.53
Exchange Ex-POW	73.60	79.78	72.62	79.27
Non-exchange Ex-POW	72.74	79.41	73.34	79.40

Years lived are for grandchildren who lived to age 45 and who were descended from the child of a veteran born after the war.

Male-Line Grandsons of Non-Exchange Ex-POWs are Overweight

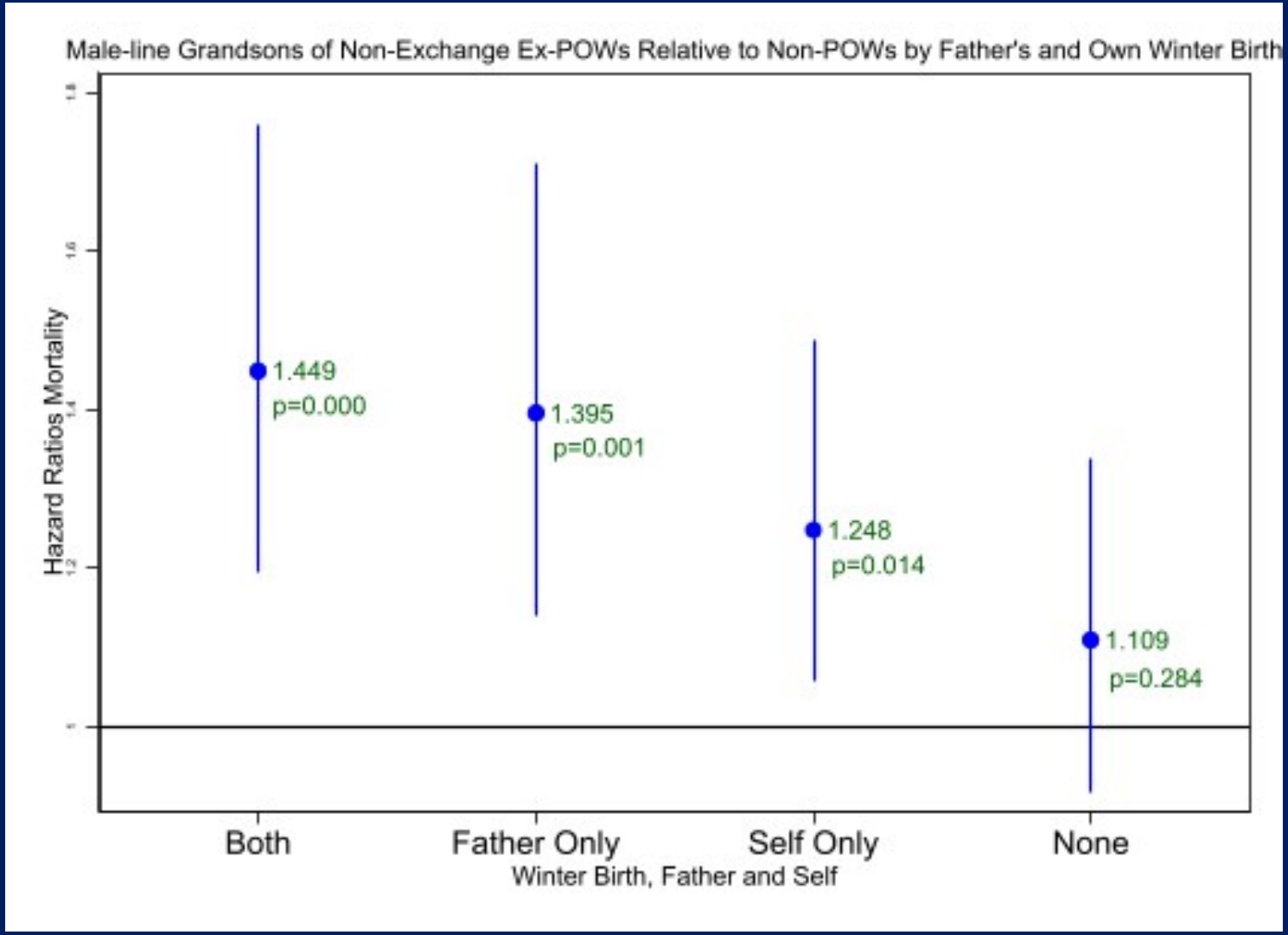


VETERANS EXPOSED DURING SLOW GROWTH PERIOD

Food prices highest and vitamin levels lowest in first half of the year

Dynamic process where interactions with intrauterine environment (proxied by quarter of birth)?

Selection in intrauterine environment?



1.5 times more likely to die at any age after 45 if paternal grandfather exposed and both father and self born in the first half of the year vs 1.11 if both born in the second half of the year

Both vs None statistically significantly different, p=0.033

SUMMARY OF HUMAN STUDIES

- Evidence of epigenetic transmission when
  - Starvation in utero
  - Overnutrition or swings in nutrition pre-puberty
  - Starvation in late growing years

OPEN QUESTIONS

- What type of exposure leads to epigenetic transmission?
  - Feasts
  - Famines
  - Swings between feasts and famines ✓
  - Implications for benefits of economic growth ✓
- What timing of exposure leads to epigenetic transmission?
  - Periconceptional
  - Slow growth periods ✓
- What sex-specificity of transmission? ✓
  - Can we explain male-female health differences?
- Can we reverse epigenetic transmission? ✓

OPEN QUESTIONS, CONTINUED

- How much does epigenetics matter at the population level? ✓
- Can epigenetics partially explain the escape from premature mortality? ✓

ANOTHER LOOK AT SWEDEN

- Harvest fluctuations
- Remote areas
- Good data

- Focus on harvest swings

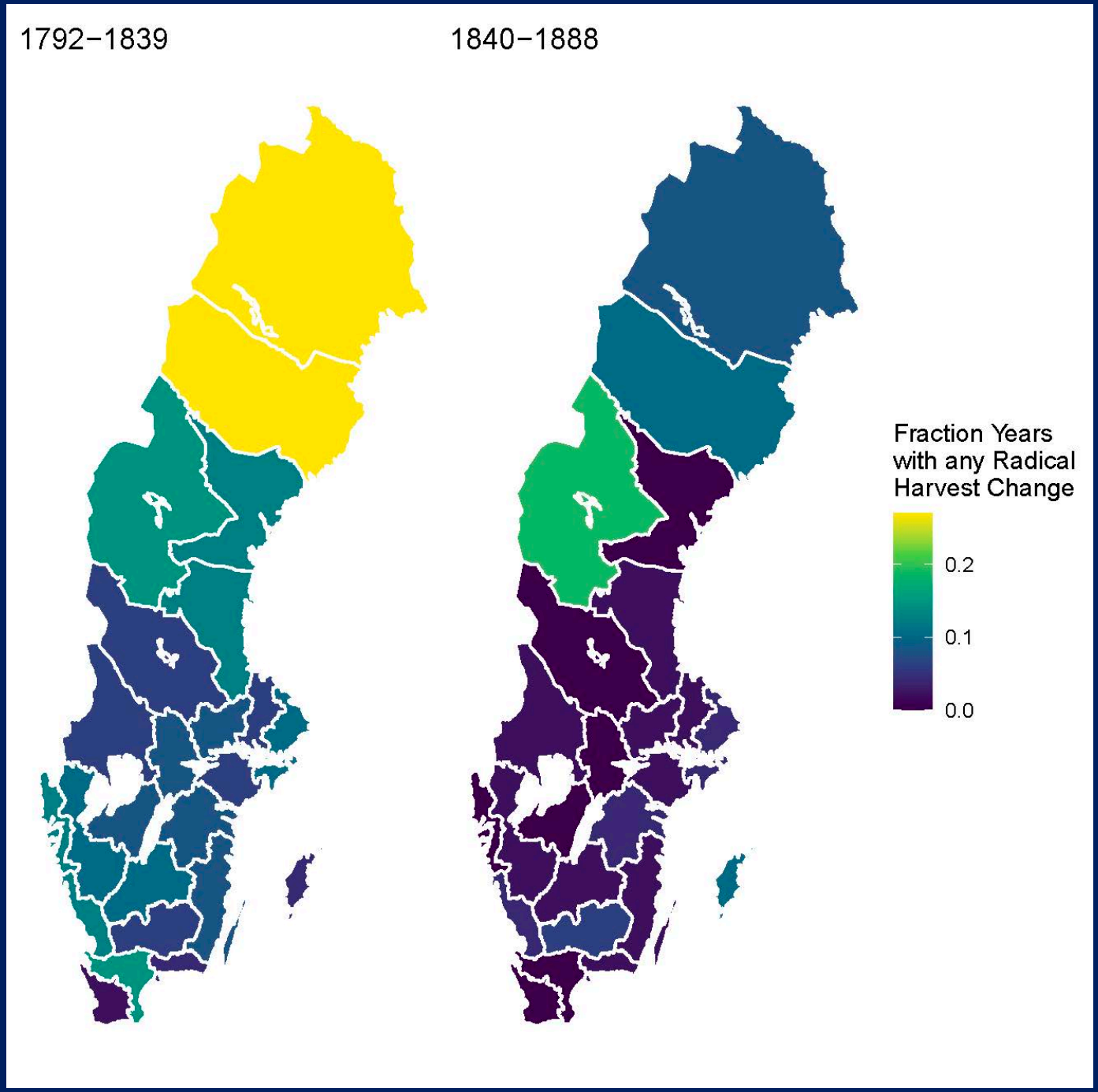
HARVESTS IN SWEDEN

- Create harvest data series by county (län)
  - Hellstenius, Statistics Sweden, Utterström, Hallberg et al.
  - Assess as good, normal, bad
  - Radical change = (good to bad) or (bad to good) harvest swing
  - Not balanced panel (more likely to have northern Sweden early on)

- More shocks and bigger shocks occur prior to 1820

Most harvest swings are before 1840

Caveat: looking at big swings only



BAD HARVESTS DON'T AFFECT LOG(CROP INDEX PRICE) AFTER 1840

	Before 1840		After 1840	
Bad Harvest	0.111***	0.068***	-0.001	-0.032*
	(0.014)	(0.014)	(0.016)	(0.018)
	[0.000]	[0.000]	[0.972]	[0.073]
Good Harvest	-0.077***	-0.035***	-0.062***	-0.031***
	(0.012)	(0.012)	(0.008)	(0.009)
	[0.000]	[0.005]	[0.000]	[0.000]
Neighbor has a Bad Harvest		0.089***		0.019
		(0.013)		(0.013)
		[0.000]		[0.138]
Good Harvest		-0.063***		-0.056***
		(0.012)		(0.009)
		[0.000]		[0.000]
Observations	1,409	1,409	1,756	1,756
Number of counties	25	25	25	25

Crop price index constructed using 1820 production weights and the Jöberg's price series for rye, barley, and oats.

BAD HARVESTS AFFECT MORTALITY PRIOR TO 1790 ONLY

Bad Harvests and Log(Crude Mortality Rate) in Parishes

	1749-1788	1789-1819	1820-1859
Bad harvest	0.054***	0.004	0.008
	(0.009)	(0.005)	(0.006)
	[0.000]	[0.444]	[0.144]
Observations	22,984	55,546	88,031
R-squared	0.152	0.116	0.138

Annual parish level crude mortality rates are from SHiPS (https://www.umu.se/en/centre-for-demographic-and-ageing-research/infrastructure-at-cedar/open-data/ships/)

FOCUS ON DESCENDANTS OF GRANDPARENTS BORN BEFORE 1820

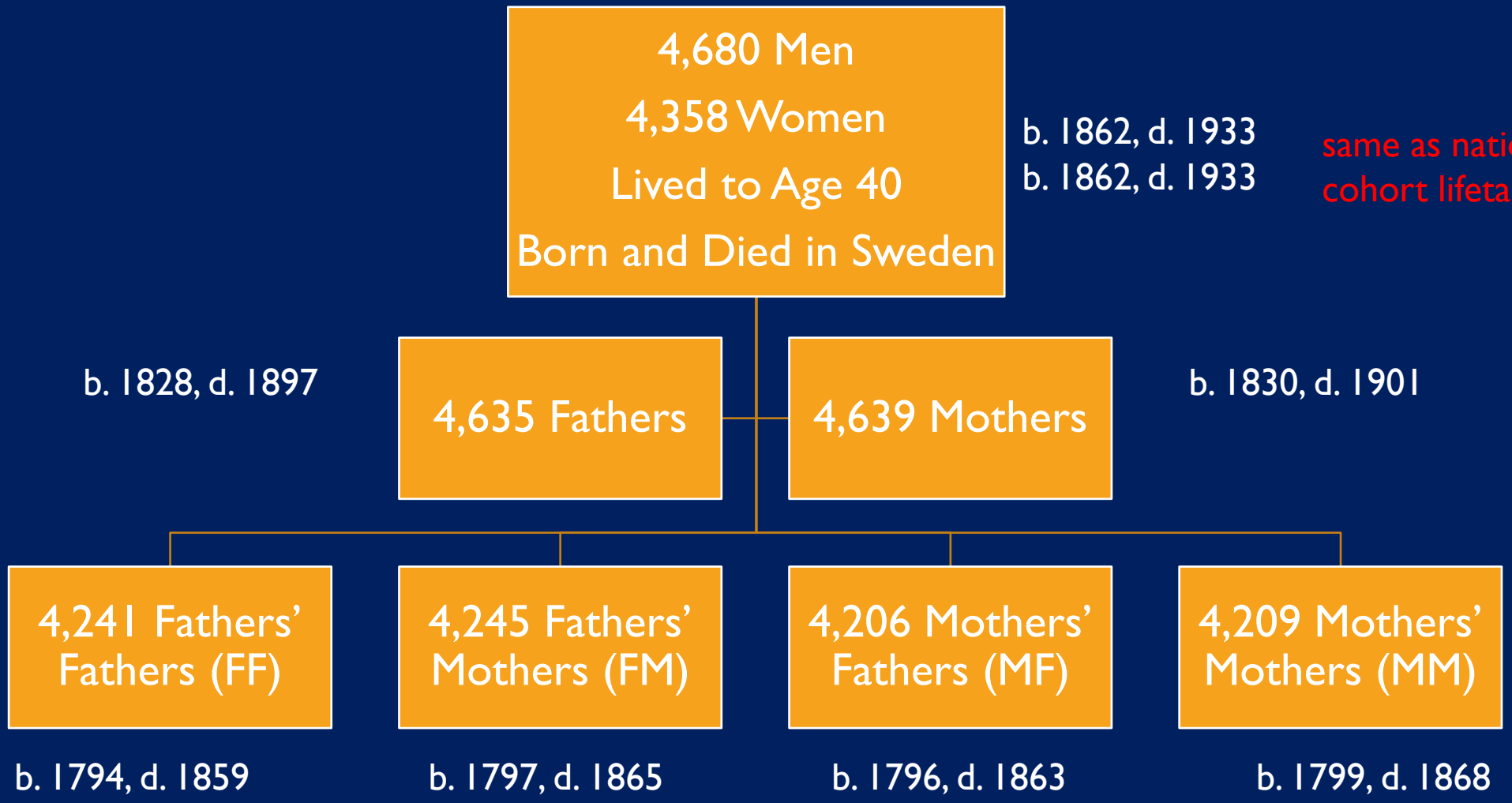
- Grandparents were in a Malthusian economy
- High transport costs
  - Roads impassible in spring
- Limited harvest storage possibilities
  - Stored grain destroyed by damp weather, vermin, fire
  - Parish storehouses (magasins) more common in central Sweden

DATA SOURCE

- Family Search
  - Everyone born in a Swedish county and their descendants
    - > 6.6 million people
    - All deceased
    - Birth place and less often death place

      Extensive place coding required
    - High child mortality
    - Most family histories incomplete
    - More records for those born late 1800s/early 1900s

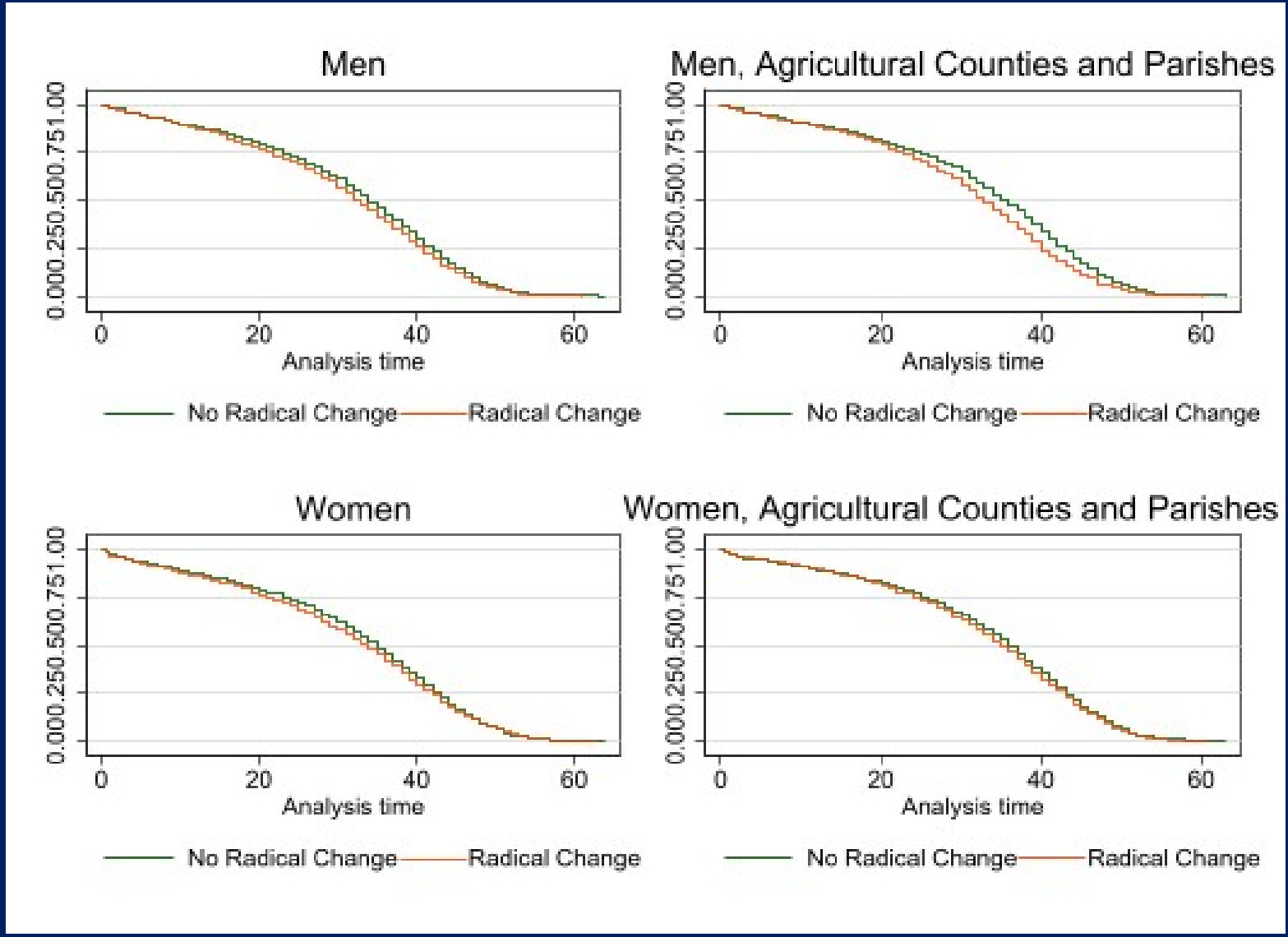
ANALYTICAL SAMPLE WITH MEDIAN BIRTH AND DEATH YEAR



All grandparents were born before 1820 and harvest information is available on all 4 grandparents at ages 0-20. Gotland, Norrbotten and Västerbotten are over-represented.

SURVIVORSHIP AND RADICAL CHANGE HARVEST QUALITY FF AT AGE 9-12

Restricted to those born and dying in paternal grandfather's birth county

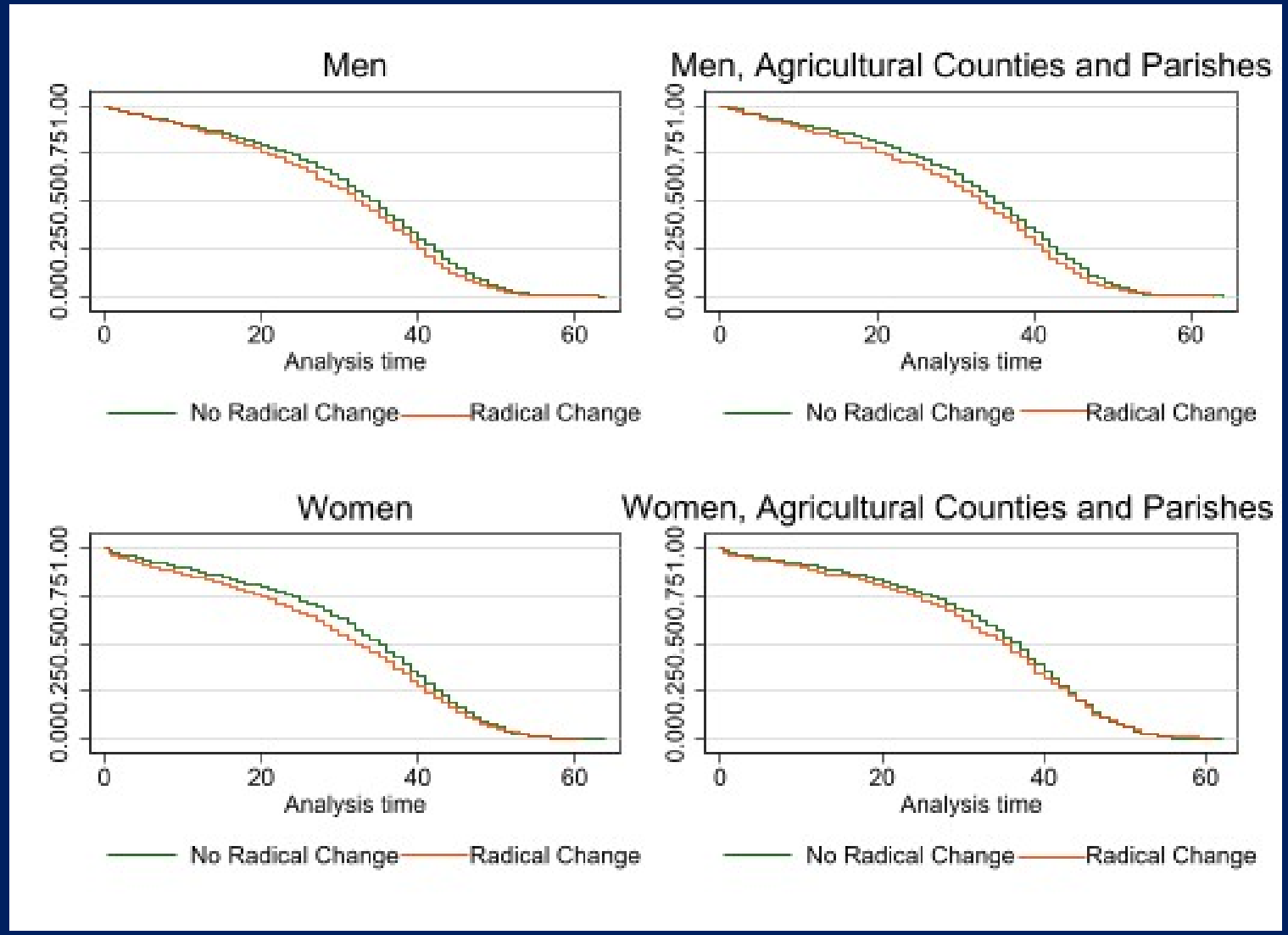


FF (father's father) or FM (father's mother) Agricultural Counties and Parishes
Exclude low agricultural and high manufacturing and mining value added counties in 1800: Stockholm, Blekinge, Goteborg och Bohus, Gavleborg, Orebro, Dalarna, Varmland, Vastmanland, Sodermanland

Keep parishes with open soil sown above 50% or more than 75% farmers or cottagers

SURVIVORSHIP AND RADICAL CHANGE HARVEST QUALITY FM AT AGE 9-12

Restricted to those born and dying in paternal grandmother's birth county



FF or FM Agricultural Counties and Parishes

Exclude low agricultural and high manufacturing and mining value added counties in 1800: Stockholm, Blekinge, Goteborg och Bohus, Gavleborg, Orebro, Dalarna, Varmland, Vastmanland, Sodermanland

Keep parishes with open soil sown above 50% or more than 75% farmers or cottagers

MAIN SPECIFICATION

Identification is from grandparents' harvest conditions in county of residence at critical ages

Basically a grandparents' (birth year x birth county) fixed effect

Each year of life (t) between age 40 and 80 for individual i is a single observation. Either live or die in that year.

Dependent variable is

$D_{i,t} = 1$ if died in year t, 0 otherwise

Linear probability models for each sex, clustered on i

Allows for fixed effects

Controls are for grandparents', own early life and contemporaneous conditions

MAIN SPECIFICATION

$$D_{i,t} = \beta_0 + \sum_G \sum_a \beta_{1,a,G} R_{a,G,i} + \beta_2 A_i + \beta_3 B_i + \beta_4 Q_i + \beta_5 \log(\text{IMR}_{i,t}) + \beta_6 C_i + \beta_7 C_{G,i}$$

$R_{a,G,i} = 1$ if radical change in harvest quality of grandparent (G) at age group a, 0 otherwise

Q_i = quarter of birth dummies

$B_i = 1$ if bad harvest in county at birth, 0 otherwise

$\text{IMR}_{i,t}$ = national infant mortality rate in year t

A_i = fixed effect for age

C_i = fixed effects own birth year, death county

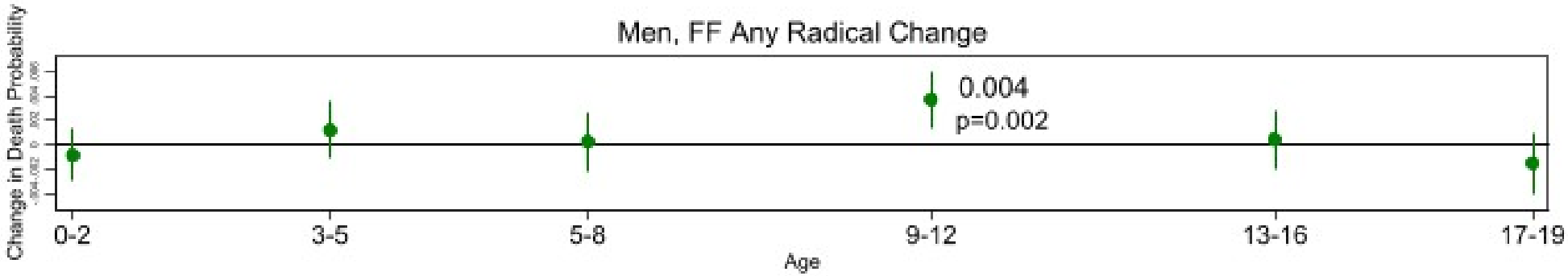
$C_{G,i}$ = fixed effects grandparental birth year, birth county

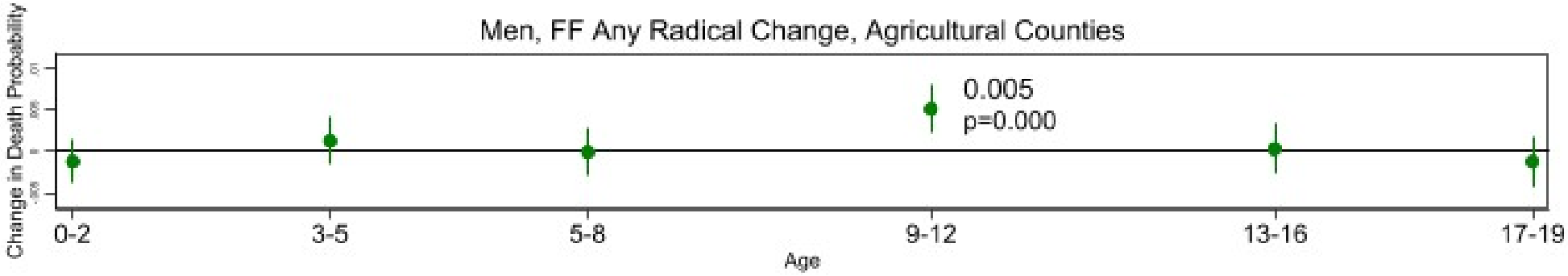
plus control for latitude and longitude of own birth place

VARIABLES

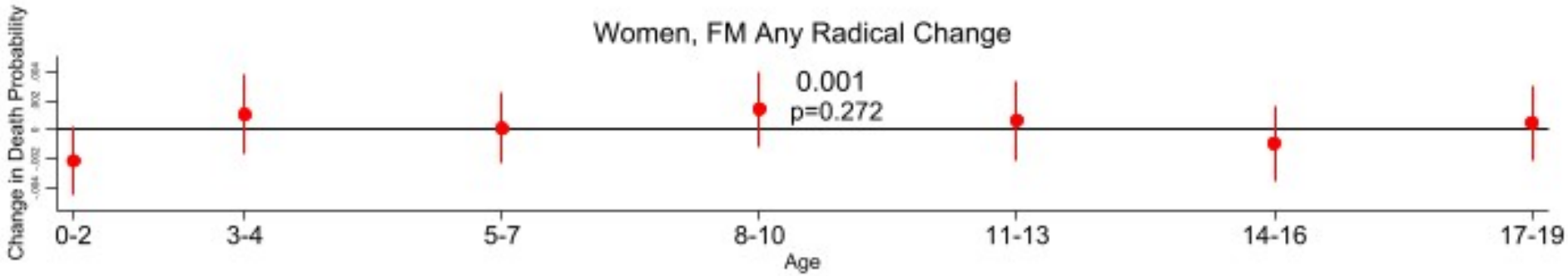
Factor Type	Variable	Mean Men	Mean Women
Ancestral	FF (father's father) any radical change in harvest quality at age 9-12	0.37	0.36
	FM (father's mother) any radical change in harvest quality at age 8-10	0.31	0.29
Early life	Bad harvest in utero	0.16	0.16
	Quarter of birth: 1st 2nd 3rd 4th	0.26 0.24 0.25 0.25	0.26 0.25 0.24 0.25
Contemporaneous	Log(national infant mortality rate) Average over each year lived age 40-80	-2.77 (6.3% IMR)	-2.78 (6.2% IMR)

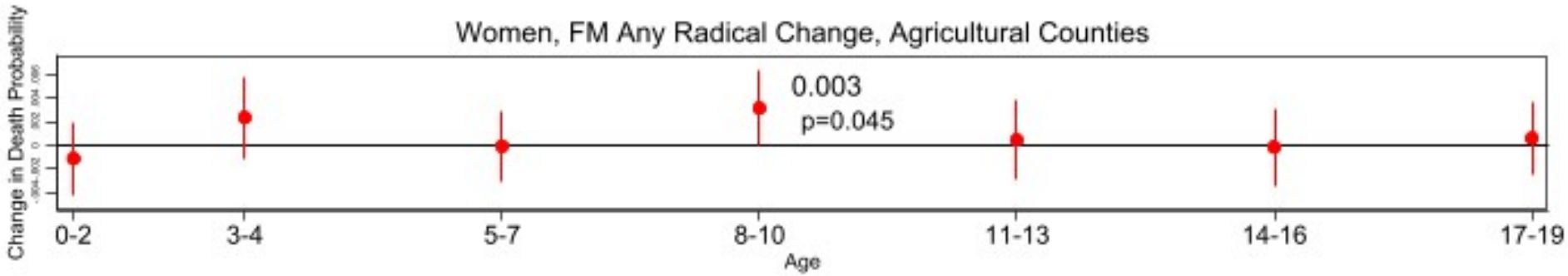
FATHER'S FATHER'S (FF) RADICAL CHANGE AT AGES 9-12 ASSOCIATED WITH MEN'S MORTALITY

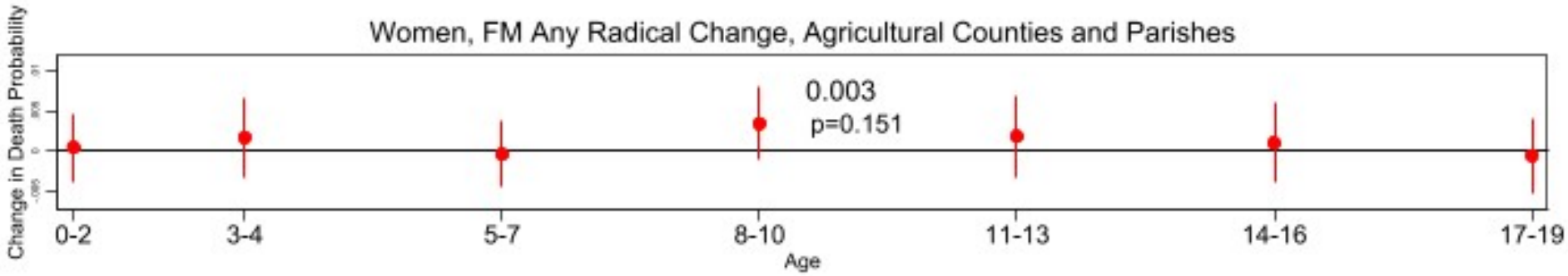




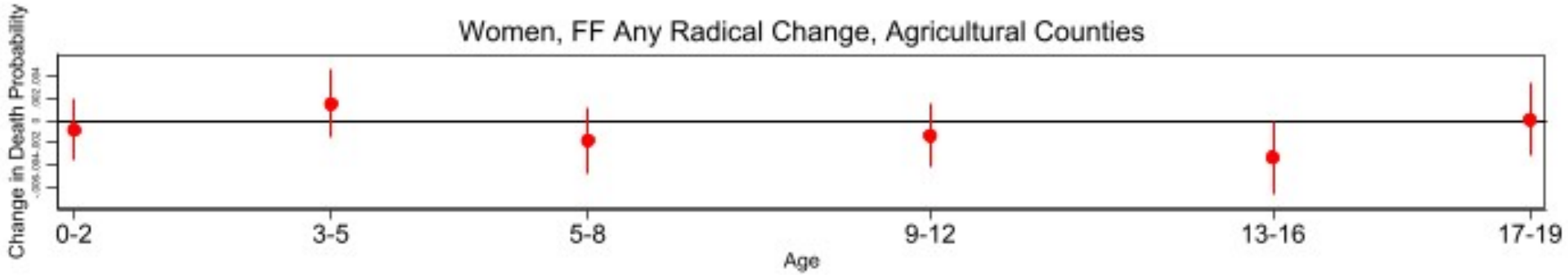
WEAK RELATIONSHIP WOMEN'S MORTALITY AND FATHER'S MOTHER'S (FM) RADICAL CHANGE AGE 8-10

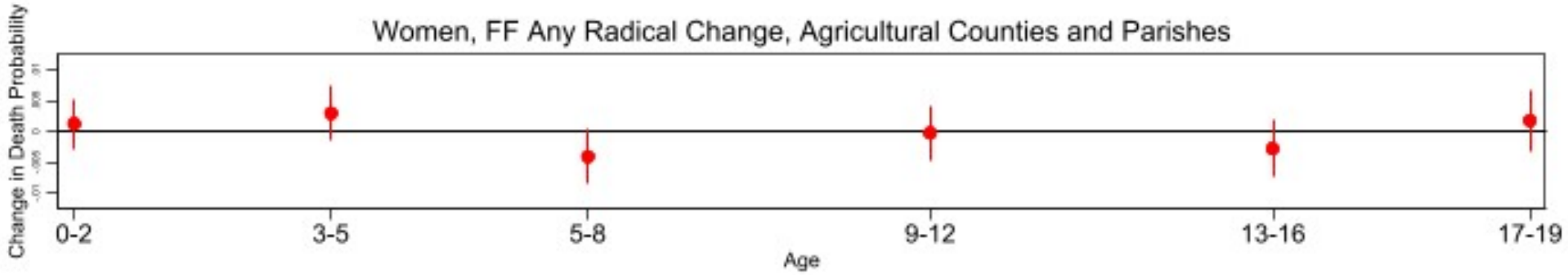




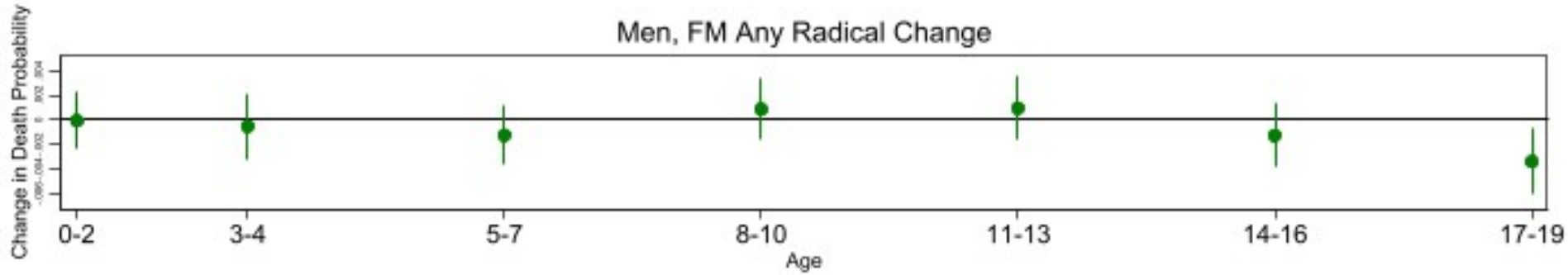


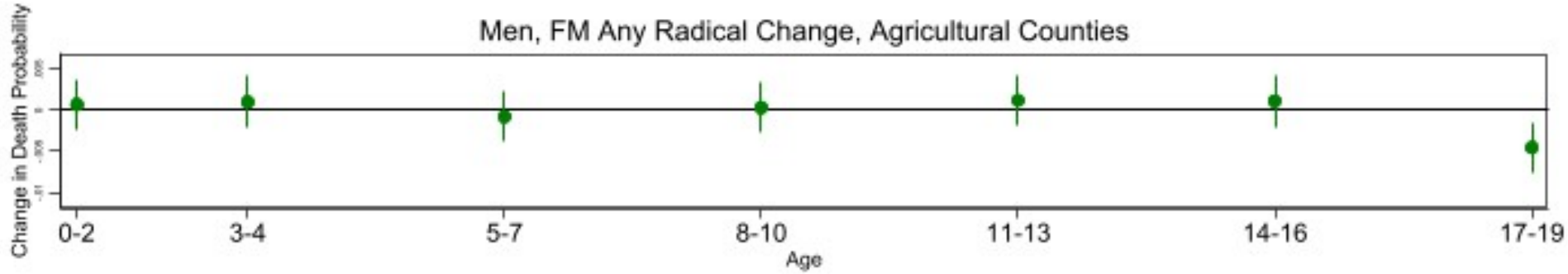
NO RELATIONSHIP FATHER'S FATHER'S (FF) RADICAL CHANGE AT AGES 9-12 AND WOMEN'S MORTALITY

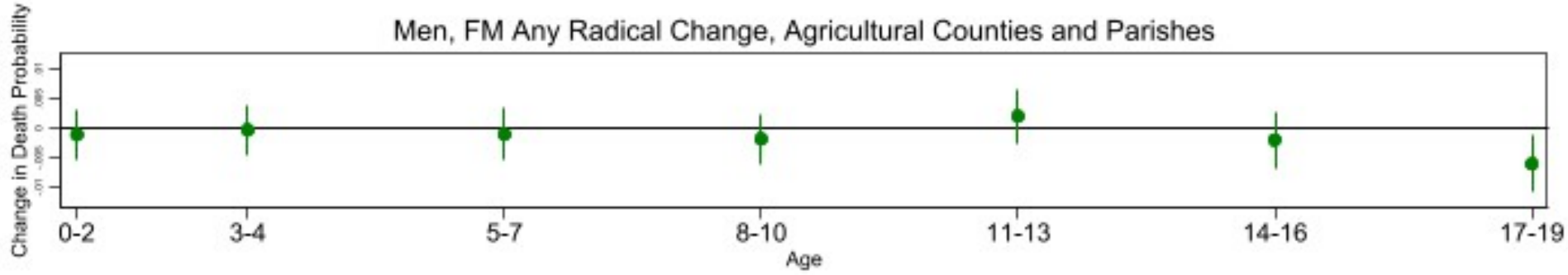




NO RELATIONSHIP FATHER'S MOTHER'S (FM) RADICAL CHANGE AT AGES 8-10 AND MEN'S MORTALITY







ROBUSTNESS

- Similar results if restrict sample to
  - Husbands and Wives (suggests not adult SES)
  - Cousins or Siblings (suggests not childhood factors)
- Reweight main regression so that FF counties representative of county populations in 1795
  - Coefficient falls to **0.003** (p=0.021) on FF radical change at ages 9-12

MAGNITUDE OF ANCESTRAL EFFECTS FOR MEN SIMILAR TO CONTEMPORANEOUS FACTORS

FF Population Weighted Results	Men	Women
FF radical change age 9-12 (men) FM radical change age 8-10 (women)	**0.003** P=0.021	0.002 P=0.264
Bad harvest in utero	0.002 P=0.124 Statistically significant **0.003** and **0.005** if restrict to agricultural counties and agricultural counties and parishes	0.001 P=0.557
Born 2nd quarter vs 4th quarter	0.001 P=0.695	0.001 P=0.334
Log(national infant mortality) in each year	**0.012** P=0.007	**0.017** P=0.001
½ std dev increase in log(national infant mortality rate)	**0.003**	**0.004**

FATHER'S FATHER (FF) RADICAL CHANGE IMPORTANT FOR MEN'S NATIONAL MORTALITY

- Consider 1862 cohort

31% of population experienced radical harvest swing

Did NOT experience bad harvest in utero

log(national infant morality rate) fell by 0.026 per year
Infant mortality rate fell from 9 to 3%

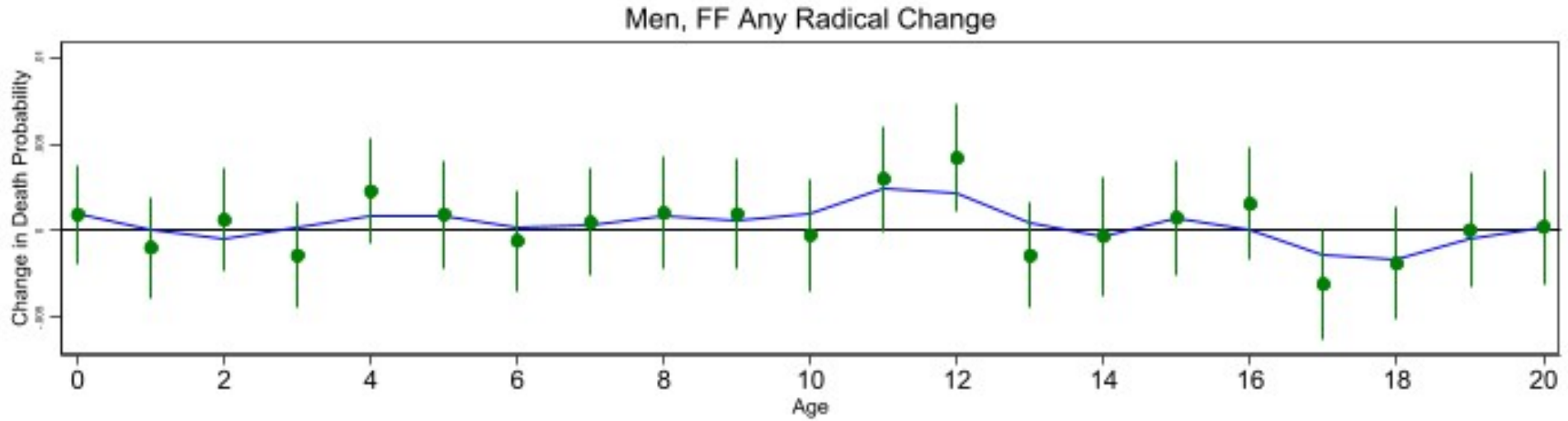
Explains 1.7% of deaths

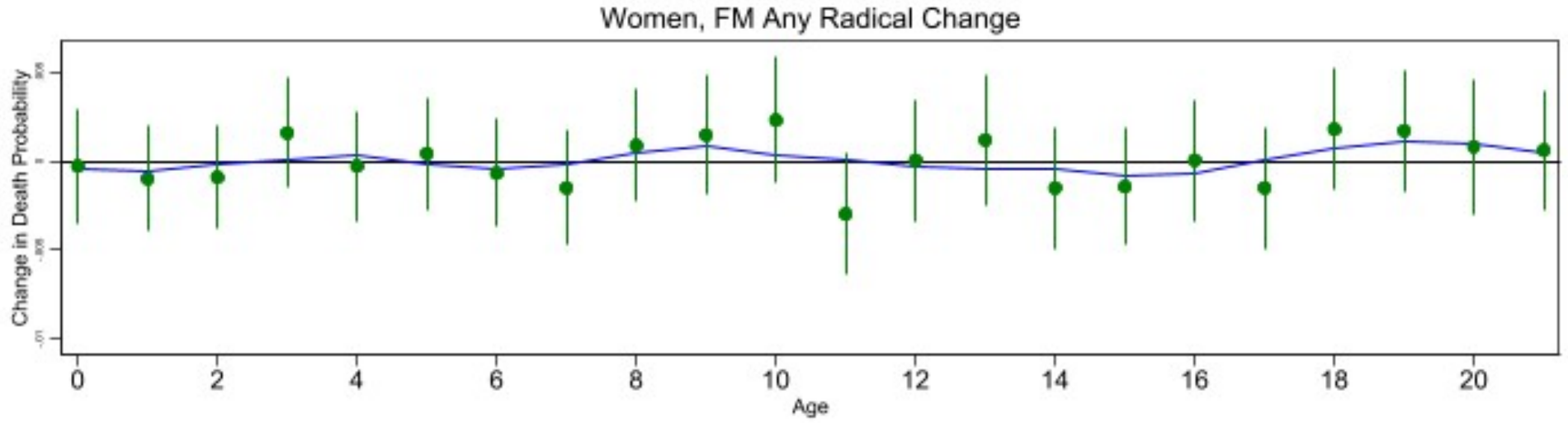
Explains 5.0% of deaths between ages 40-80

If could eliminate get death rate of 1882 male cohort and 1862 female cohort

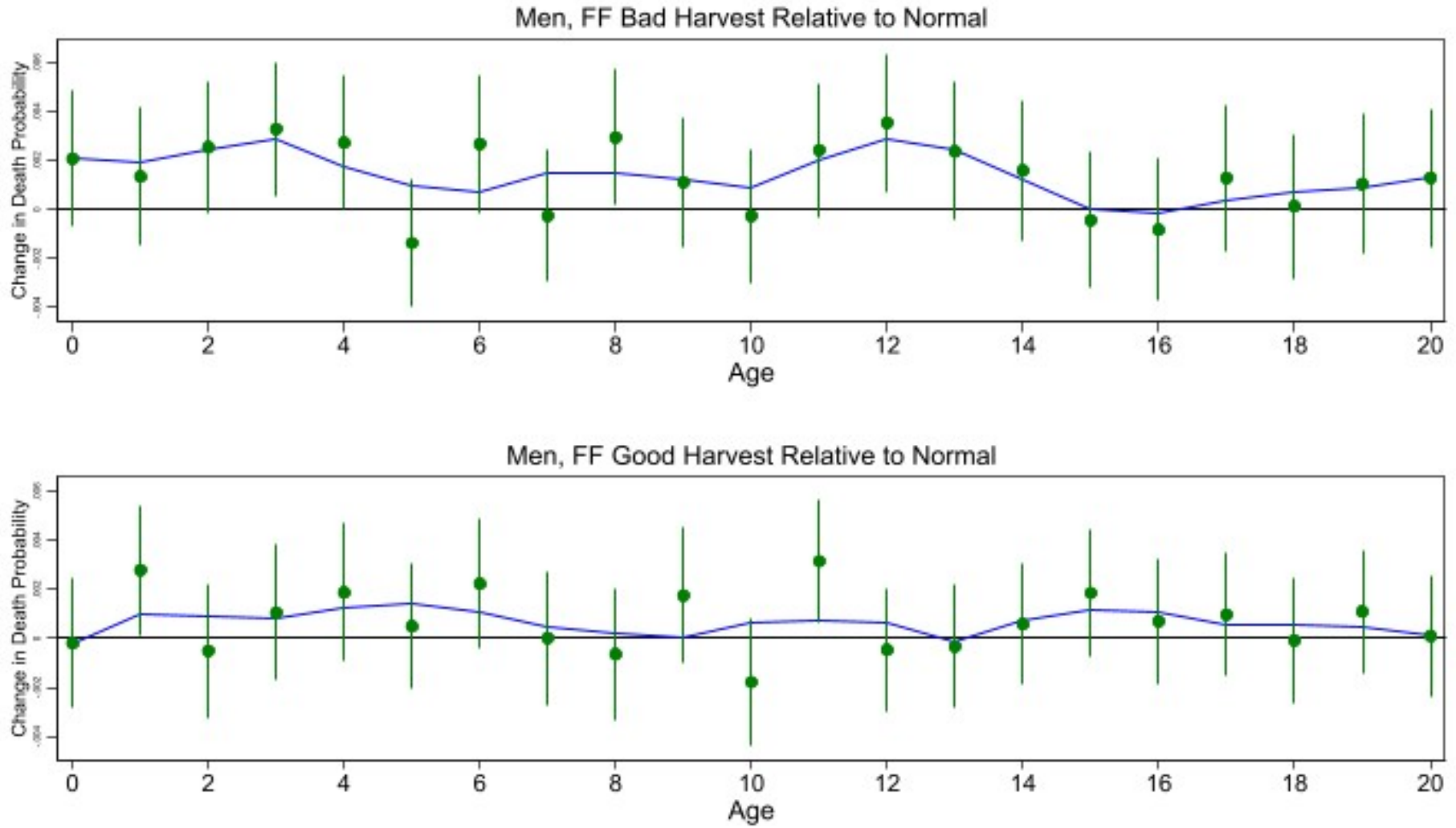
HARVEST SWINGS VS HARVEST TYPE?

CONSIDER FF AND FM RADICAL CHANGE IN EACH YEAR AND DEATH PROBABILITY (NO CONTROLS FOR OTHER GRANDPARENTS' HARVEST SWINGS)

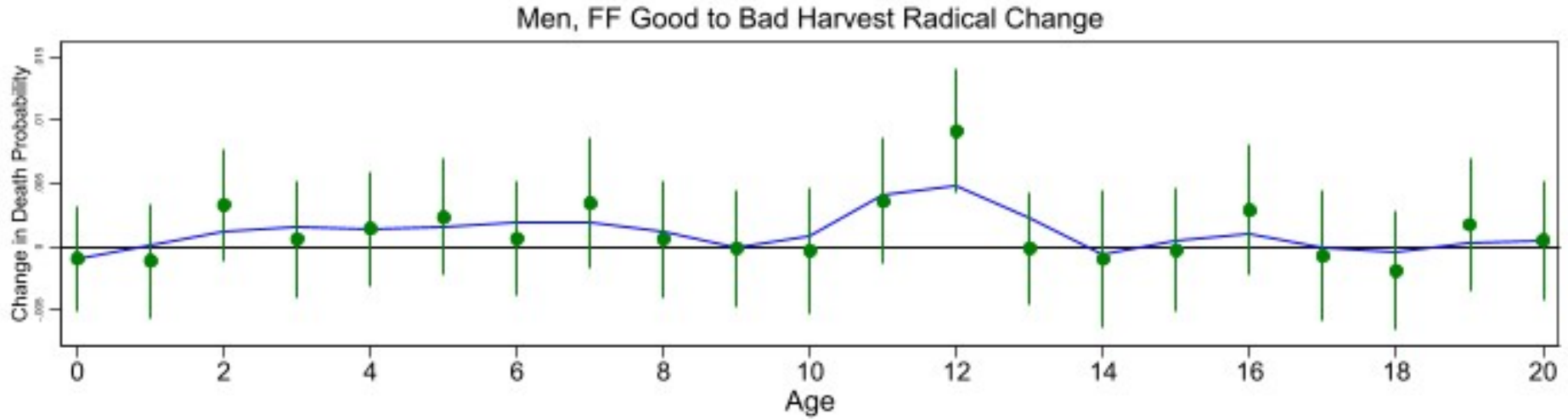


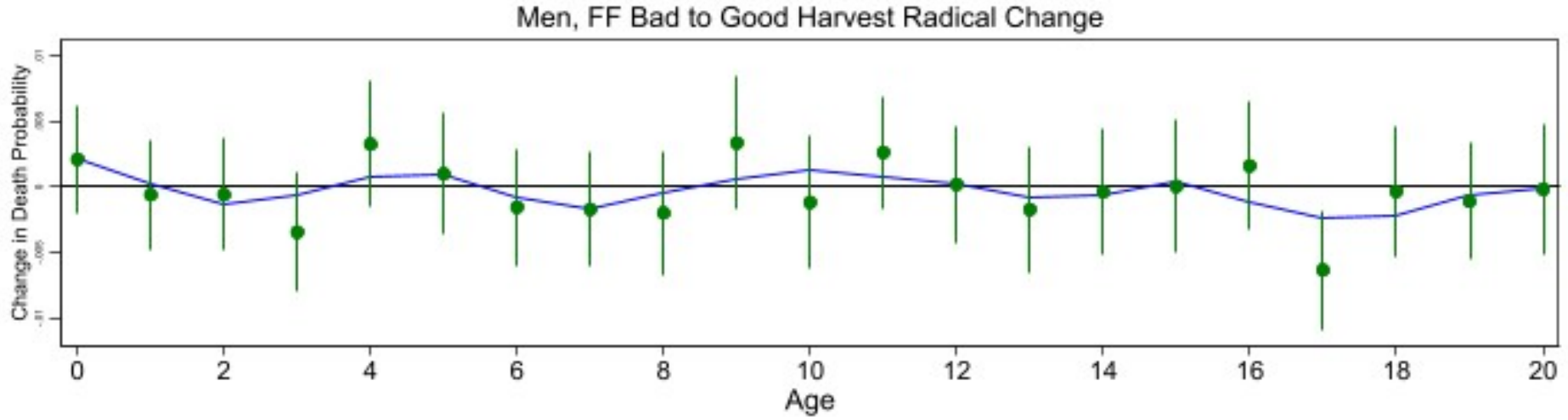


BAD AND GOOD HARVESTS ASSOCIATED WITH HIGHER MORTALITY AT FF AGES 9-12 SUGGESTING IT IS SWINGS



BOTH GOOD TO BAD AND BAD TO GOOD FF HARVEST SWING AT AGES 9-12 ASSOCIATED WITH MEN'S HIGHER MORTALITY





HOW REDUCE HARVEST SWINGS?

- Reduce likelihood of bad harvest
- 1700-80: Agricultural production and population grow at same pace
- 1780-1860: Agricultural production more than quadruples and Sweden becomes grain exporter
- Rye price convergence across areas after 1820

HOW REDUCE HARVEST SWINGS?

- Incentives and Institutions
  - Farmers keep more of production
  - Abolition of interior tolls in 1810
  - Export regulations eliminated 1828
  - Enclosures of 1803, 1807 and 1827 lead to crown tenants purchasing land and turning forest land into farm land
- Incentives from Growing Markets
  - Market access to mining areas and manufacturing towns
- Scientific Agriculture
  - "Enlightened" landlords and newly engaged commercial classes

ABILITY TO ADJUST TO DROUGHT IMPROVES OVER TIME

Dependent Variable: Dummy =1 if Bad Harvest	**1749-1839**	**1840-1870**	**Δ**
	Average Marginal Effects		
Below average spring temperature	0.177***	0.173***	-0.004
	(0.025)	(0.043)	(0.049)
	[0.000]	[0.000]	[0.930]
Below average summer precipitation	0.102***	-0.005	-0.107**
	(0.021)	(0.047)	(0.050)
	[0.000]	[0.916]	[0.033]

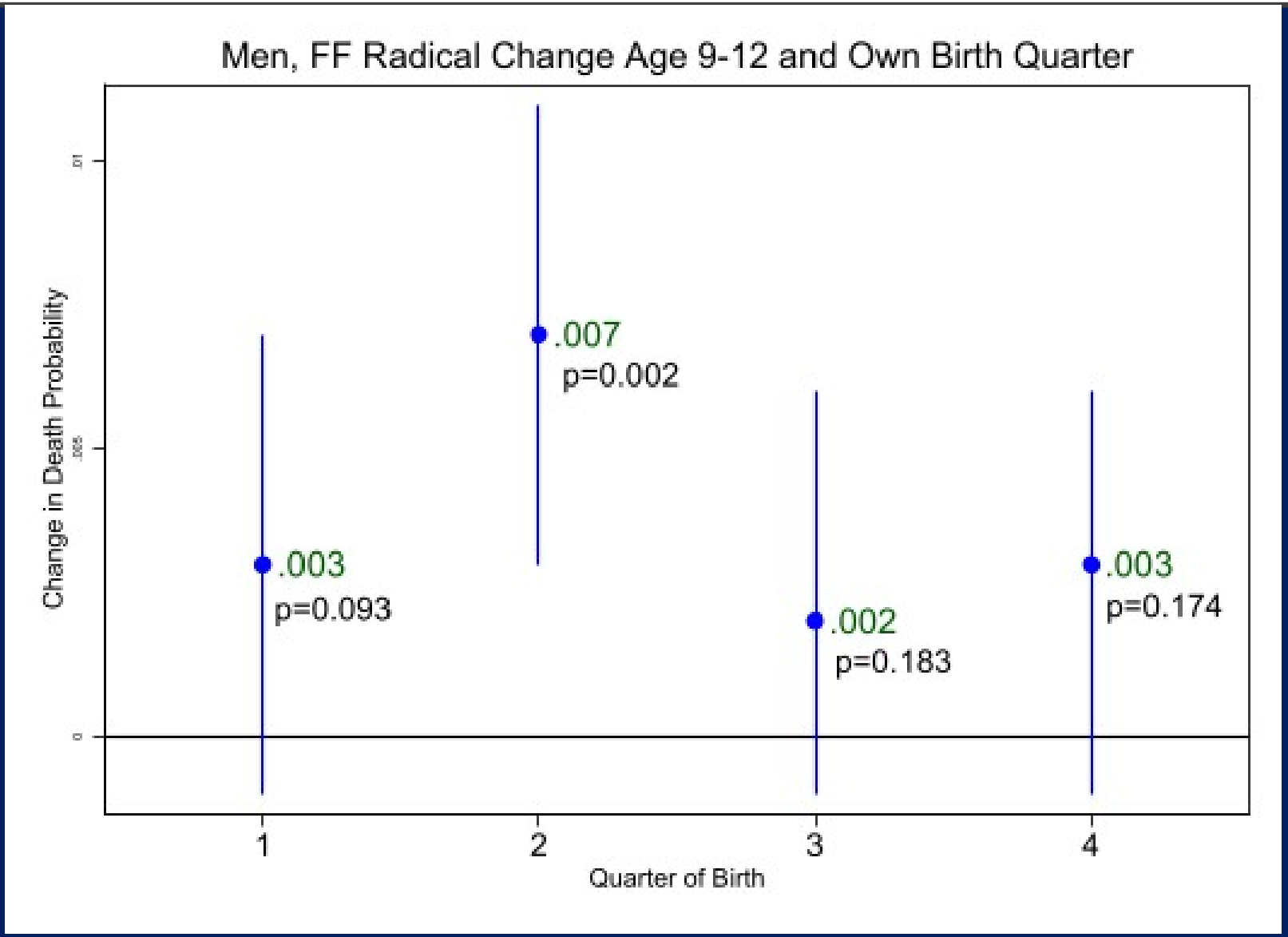
Thanks to Nippe Lagerlöf for providing the temperature and rainfall data. County smoothed temperature and precipitation were constructed using a Hodrick-Prescott filter on the logarithmic values. Below a logarithmic value of 0.15 is below average.

WHY ARE BAD LOCAL HARVESTS NO LONGER SO IMPORTANT?

- Trade: local shocks no longer systemic shocks
  - Decline in transport costs
    - Abolition tolls
    - Canal building
    - 1845 private railroads and 1855 state railroads
- Insurance
  - National poor law in 1847

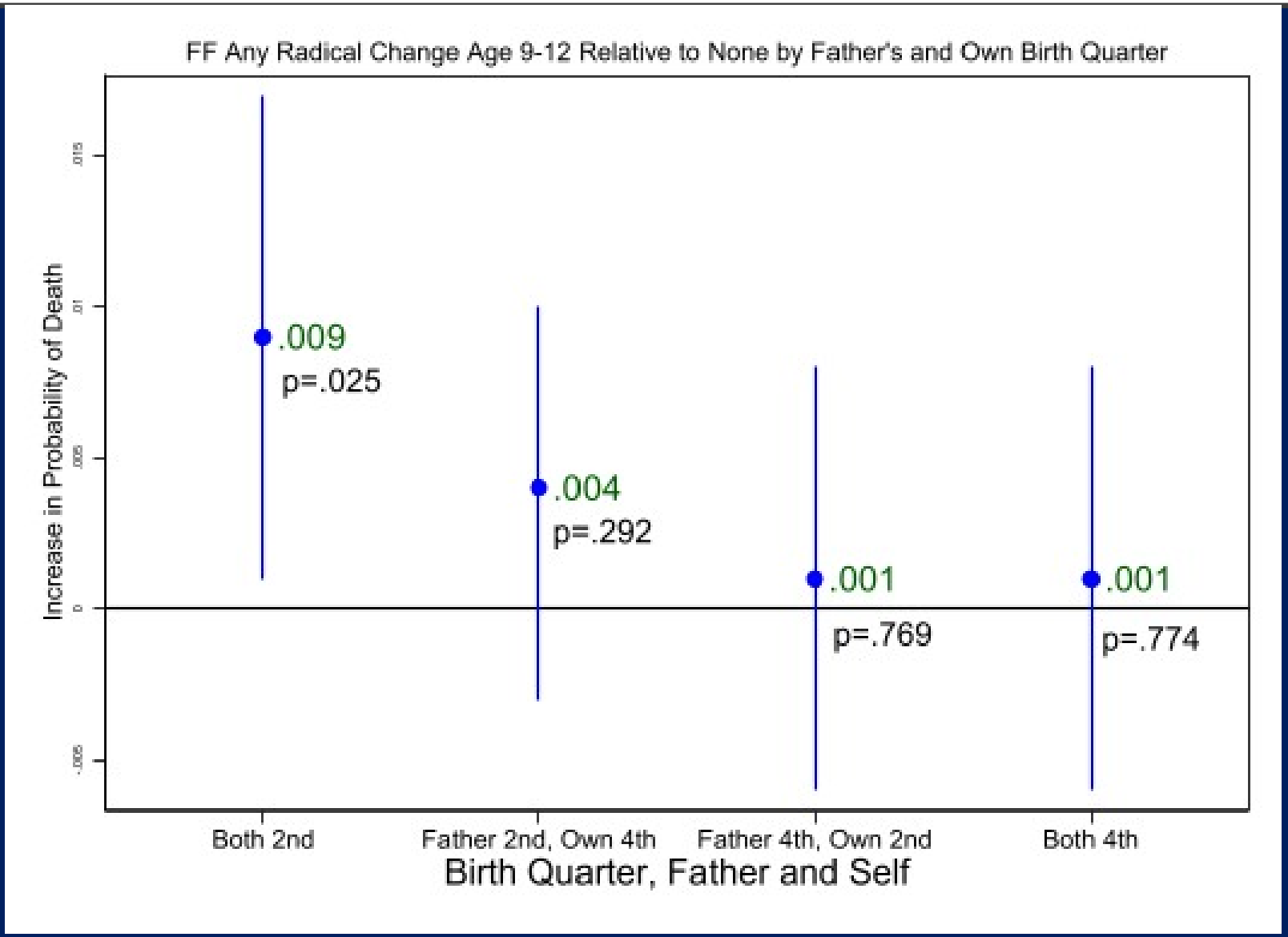
GIVEN ANCESTRAL INHERITANCE, HOW MITIGATE THE EFFECTS?

EFFECTS OF FATHER'S FATHER'S (FF) RADICAL CHANGE AT AGE 9-12 CONCENTRATED AMONG MEN BORN IN THE SECOND RELATIVE TO THE FOURTH QUARTER



Statistical significance of difference between 2nd quarter and
1st: 0.123
3rd: 0.059
4th: 0.072

IF BOTH FATHER AND SELF BORN IN FOURTH QUARTER THEN WORST OFF?



Differences are not statistically significant but are suggestive. Difference between both 2nd and both 4th is 0.008 (p=0.124)

HOW TO INTERPRET QUARTER OF BIRTH EFFECTS?

- Interaction uterine effects and epigenetic effects
- 2nd quarter harshest in terms of food supply
  - No epigenetic reprogramming male primordial germ cells in late gestation?
    - Room for policy interventions to mitigate ancestral shocks
  - Mortality selection via stillbirths?
    - Still get random adverse epigenetic profiles

SUMMARY RESULTS

- Epigenetic inheritance plays a role in the transmission of longevity
  - Shocks to men matter and male offspring are disproportionately affected
  - Male mortality greater than female mortality and different chronic diseases
- Dynamic process: contemporaneous effects interact with epigenetic effects
- Inheritance likely in early/developing economies
  - Variance in ancestral food supplies
  - Levels of contemporary food supply
- Malthusian economy left its inheritance in changed epigenome
- Economic growth important for escape premature mortality

IMPLICATIONS OF EPIGENETICS FOR HEALTH TODAY?

- Can we explain health in developing countries?
  - 1850-1899: 24 major famines in India
- As overall health improves concern becomes health inequality
  - Regional/local health inequality (e.g. Överkalix)
  - Family health inequalities

IMPLICATIONS OF EPIGENETICS FOR HEALTH TODAY?

- Medical innovations important for health today
  - Challenge of incentives for innovations and how deliver innovations
  - Behavioral challenge: better educated better able to use innovations
    - Heckman: grafts early childhood development of self-control onto Grossman health model
- Family transmission of poverty and risky behavior (Dunnedin Study)
  - Double-whammy of complementarity of epigenetic inheritance and behavior?

If they ask you anything you don't know, just just say it's due to epigenetics.

13-01-2017