Basic Instincts? Female Fertility and Genes

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What?

1. How does genetic endowment affect women's fertility behavior?

2. Can we go beyond the nature *v* nurture dichotomy?
   - In particular, what is the role of **gene-environment interactions** $[G \times E]$?

3. For the first time (in the economic literature), we analyze the impact of G and E and their interaction on a series of fertility (and fertility related) processes

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1. age at menarche (AAM)
2. age at first sex (A1S)
3. age at first birth (A1B)
4. completed fertility (CF)
5. teen fertility (TF)
6. childlessness (CLN)
7. age at menopause (not analyzed yet)

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(c) For each process we will provide evidence looking at:

i. Genetic **heritability** across birth cohorts
ii. **Genetic correlations**
iii. Outcome **differences by genetic endowment**
iv. **Regression** results

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2. Many of the changes are relevant to **economic theories** of family formation and dissolution, female labor supply, child care, child investment, parent-child interactions, human capital formation, etc.
    - (see Literature below)
3. Fertility outcomes may have a **genetic basis**
    - Importance of genetics on fertility seems to have increased over time (Tropf et al. 2015; Barban et al. 2017)

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4. So what? This is the first piece in this area, so we need to deepen our understanding of the impacts of G and E and $G \times E$. This in turn could then be embedded in **new** economic models of human fertility

Background (1)

1. Fertility has dramatically declined over the last 200 years:
   a. either the Crude Birth Rate (CBR), defined as the number of births per thousand (population) per annum
   b. or the Cohort Fertility Rate (CFR), defined as the average number of children born to women in a given cohort

2. **First births** have been delayed (although **age at first sex** has declined)

3. Age at menarche has gone down and age at menopause has increased (so the time span over which women are fertile has expanded)

Background (2)

Crude Birth Rate (Guinnane 2011 JEL, Figure 1)

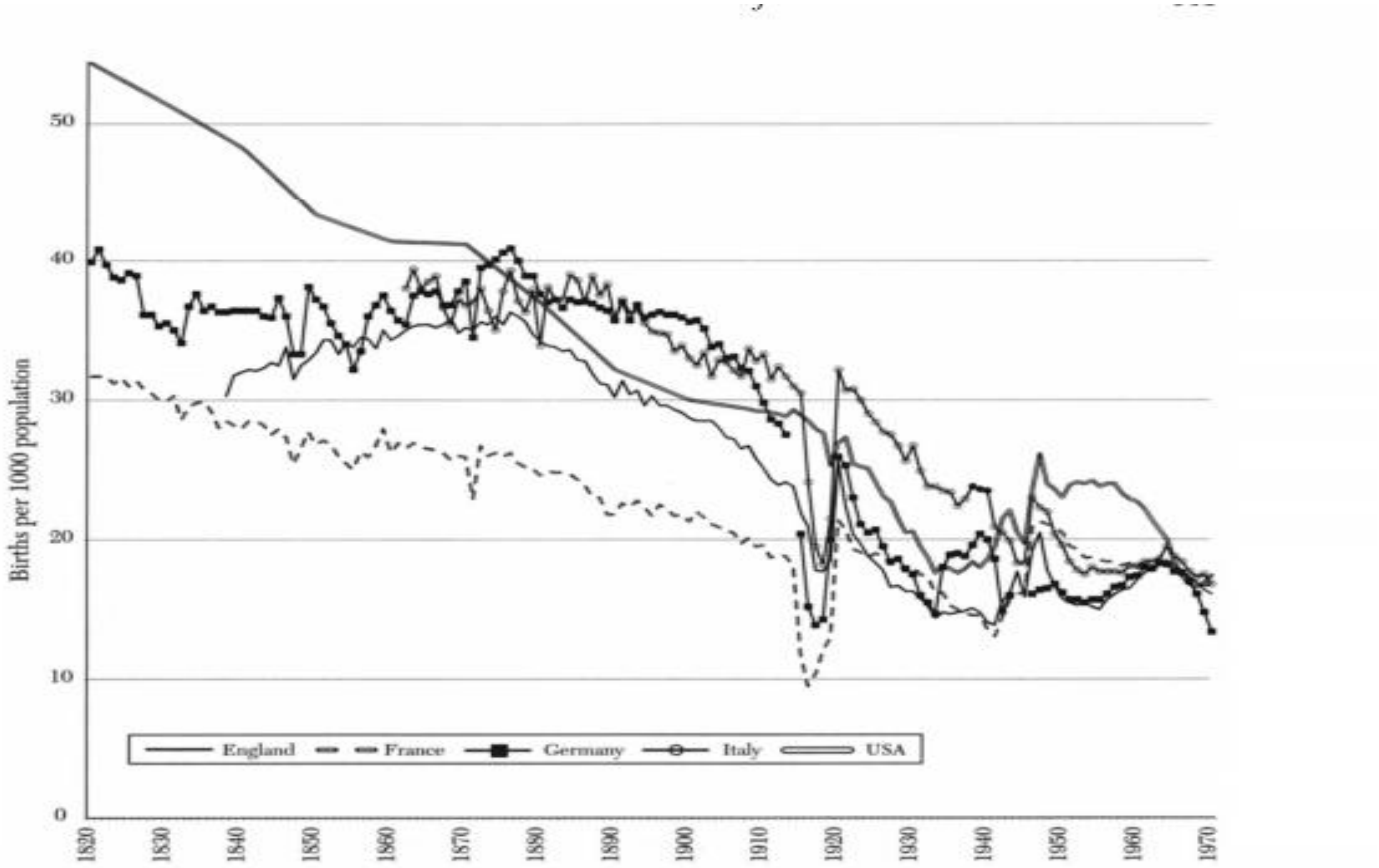


Figure 1. Crude Birth Rates, Selected Countries, 1820–1970

Note: For the United States, values before 1909 are linear interpolations between decennial census years.
Source: Crude birth rates as reported in Mitchell (1980).

Background (3)

Cohort Fertility Rate (Guinnane 2011 JEL, Figure 3)

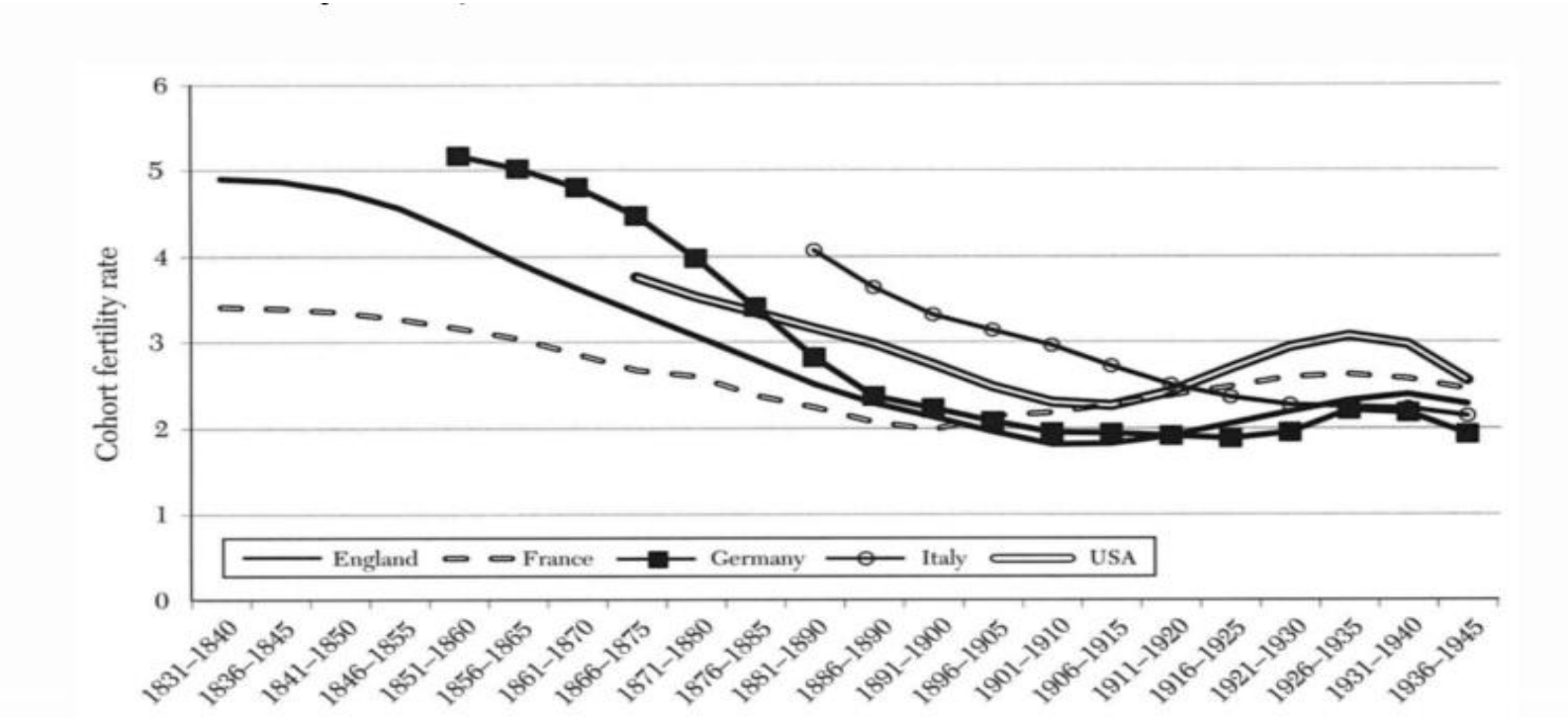


Figure 3. Cohort Fertility Rates, 1831–1945

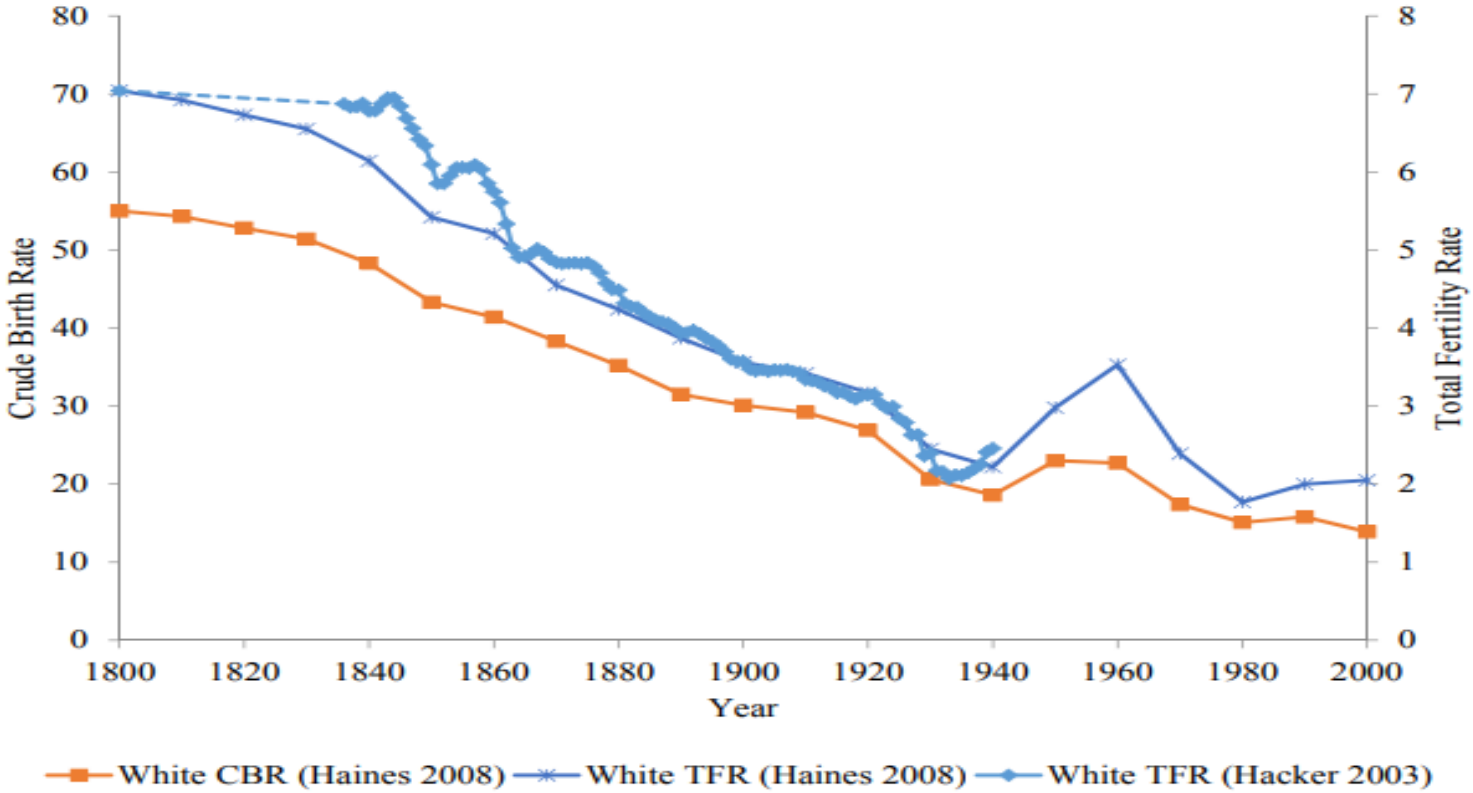
Notes: The cohort fertility rate is the mean number of children born to women belonging to the birth cohorts on the horizontal axis. The overlapping years are in the source. The precise birth cohorts vary slightly across countries.

Sources: Festy (1979): for England, p. 262; for France, pp. 266–67; for Italy, p. 283; for the United States, p. 290; and for Germany, p. 222. Marschalck (1984), table 3.6, for Germany for the years 1901–1945.

Background (4)

Crude Birth Rate and Total Fertility Rate (Bailey and Hershbein 2018)

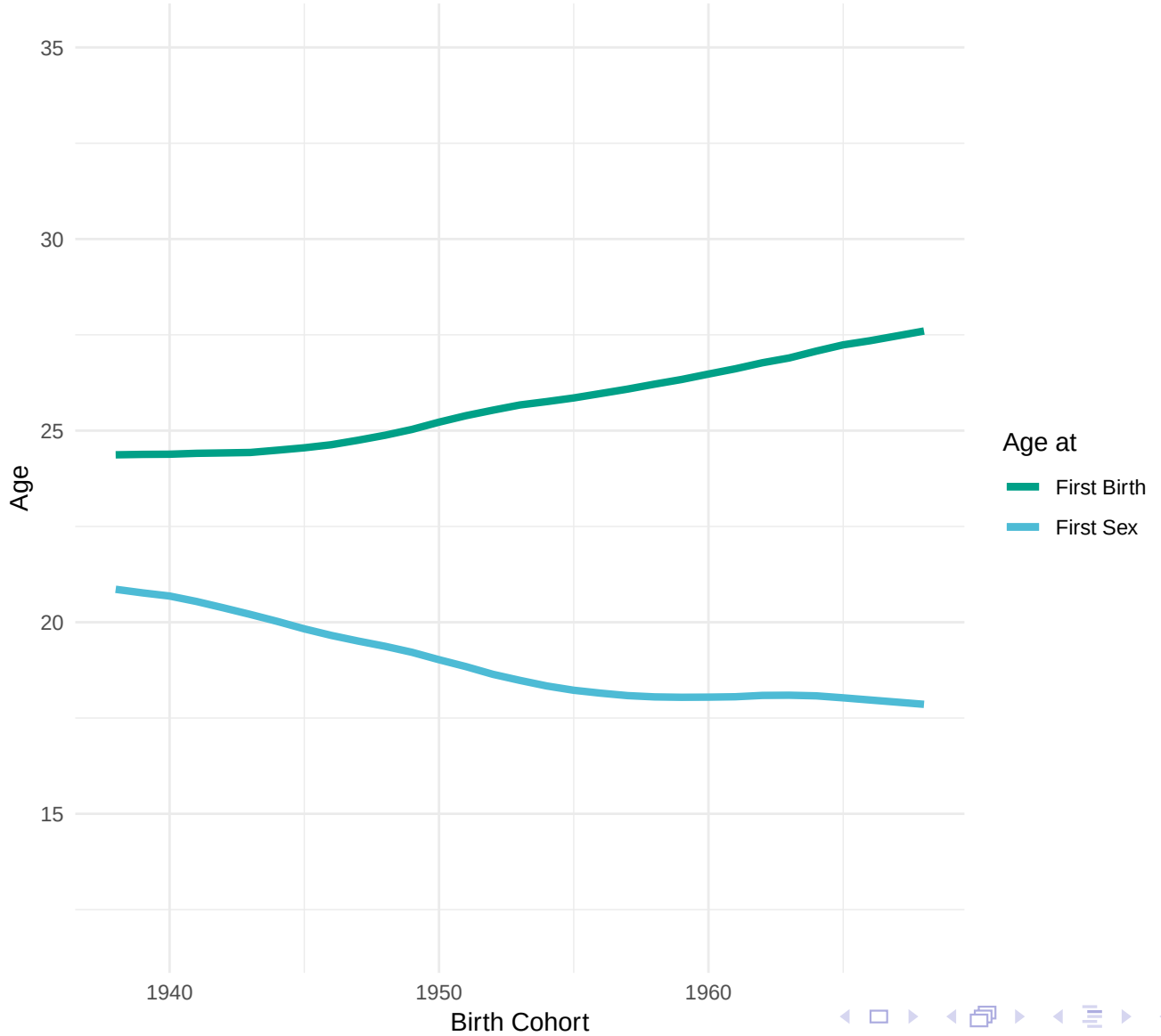
Figure 1. U.S. Crude Birth Rate (CBR) and Total Fertility Rate (TFR), 1800-2000



Notes: The CBR is plotted on the left vertical axis and is measured as the number of births per 1,000 whites in the population. The TFR is plotted on the right vertical axis and measures the cumulative number of births a woman would be expected to have over her lifetime if she experienced the current period's age-specific birth rates. Sources: Haines (2008) and Hacker (2003).

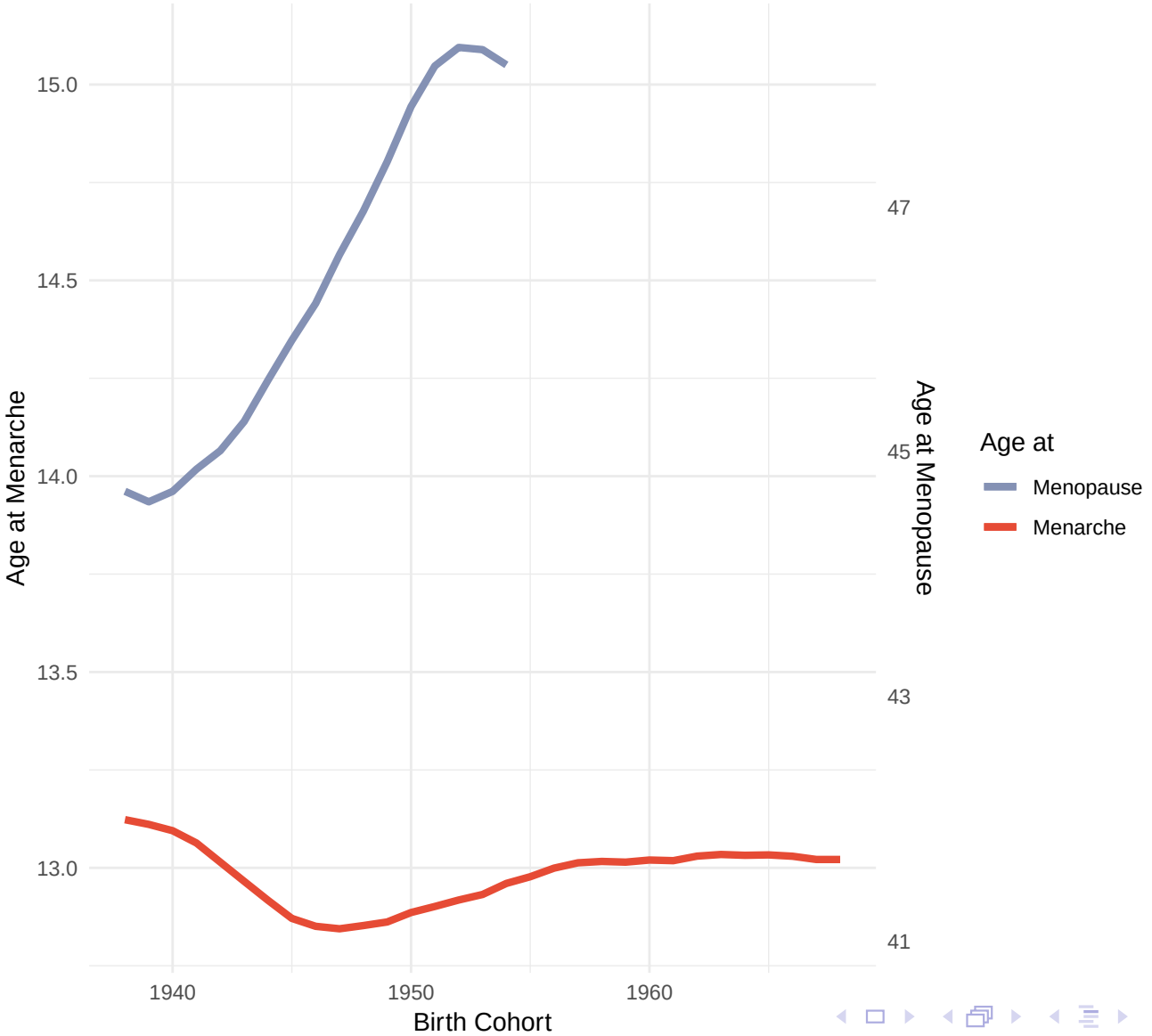
Background (4)

Mean Ages at First Sex and First Birth (Source: UKB)



Background (4)

Mean Ages at Menarche and Menopause (Source: UKB)



Literature (1)

1. **Malthusian models** (Guinnane 2011):
   - regulation of births reflects regulation of **marriage**
   - marital fertility (total number of children) depends only on age at marriage and the proportions who marry
   - positive relation between fertility rates and levels of per capita income

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   - positive relation between fertility rates and levels of per capita income

   - break away by growth theory (Barro and Becker 1989; Galor and Weil 2000): set aside marriage and model fertility without concern of its underlying determinants, and show that **fertility** depends
     - ⇀ positively on the world's long-term real interest rate, the degree of altruism, and the growth of child-survival probabilities; and
     - ↽ negatively on the rate of technical progress and the growth rate of social security

Literature (2)

2. **Becker's model** of the demand for children (1960, 1973/74, 1976, 1981)

- analyze demand for children using tools of consumer choice
- one key implication: standard *substitution* effect, i.e., wealthier couples have higher opportunity costs of time, and time is a major cost of child-rearing
- in a slightly different version: possible trade-off between number of children and their quality (Quantity/Quality model) [Becker and Lewis 1973]
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None of such models [in 1. and 2. above] embeds any **biological** (**genetic**) consideration seriously

Literature (3)

3. **Structural empirical models** of fertility
   - First generation: Wolpin (1984); Moffitt (1984); Hotz and Miller (1988)
   - More recent: Francesconi (2002), Adda, Dustmann, and Stevens (2017), Eckstein, Keane, and Osnat (2019)
4. **Design-based models** of fertility
   - Twinning experiment (many papers; see Rosenzweig and Wolpin 2000 for a critique)
   - Angrist and Evans (1998) (sex sameness)
5. Other models emphasize the importance of **technology**, e.g., condoms or the contraceptive pill (Goldin and Katz 2002; Guinnane 2011)

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Again biological/genetic considerations are tangential, not integral to the analysis in 3.–5.

Literature (4)

6. $G \times E$ in social sciences (very recent)
   - Most studies on **E=Educational attainment** (Barcellos et al., 2018; Barth et al., 2018; Wedow et al., 2018; Harden, Domingue, et al. 2019)
     - Outcomes: Health (obesity, smoking) or labor market (wealth)
     - G=PGS for education
   - New studies on childhood conditions **E=SES in early life** (Beirut et al., 2018; Ronda et al. 2019; Breinholt and Conley, 2019)
     - Outcomes: health (smoking), human capital (cognitive skills, cognitively stimulating activities, education) or labor market (income)
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Our paper:

1. Outcomes: fertility outcomes
2. G=PGS for different fertility traits (Barban et al., 2017)
3. E=different measures relevant for fertility processes (ongoing)

Data (1)

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- Large, population-based prospective study initiated by the UK National Health Service (NHS) (Sudlow et al. 2015)
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- Sample of 502,537 individuals who agreed to participate (response rate of 5.5%), 273,402 women
- Sample is not nationally representative, but estimates have internal validity and are based on large samples (high statistical power)

Data (2)

Study participants went through an assessment that comprised:

- a self-completed touch-screen questionnaire; a computer-assisted interview; physical and functional measures; and collection of blood, urine, and saliva;
- physical measures (e.g., anthropometrics, blood pressure, etc.) were gathered by trained nurses or healthcare practitioners
- although UKB does not have parental SES measures, it has precise geographic detail (at birth and at interview) which we use to construct our measures of environment

Every participant was genotyped

Data (3)

1. **"Interim Data Release, May 2015 (UKB v1 release)"** 152,249 individuals
2. **"Genotyping and Imputation Data Release, May 2017 (UKB v2 release)"** Genotyping and imputation data for all 500,000 participants in UK Biobank
3. **"Genotyping and Imputation Data Release, March 2018 (UKB v3 release)"** Genotyping and imputation data for all 500,000 participants in UK Biobank (More genetic variants, including sex chromosomes)
4. **"Exome sequencing data for 50,000 participants, March 2019"** (Sequencing all of the protein-coding regions of genes in a genome)

Genes – SNPs

Human genome

- 3 billion genetic addresses
- In each address we observe a base nucleotide-pair:
  - ⋆ Adenine-thymine pair (A or T)
  - ⋆ Guanine-cytosine pair (G or C)
- The nucleotide-pair is fixed in 99% of such addresses

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SNPs

- → The remaining 1% are called single-nucleotide polymorphisms (SNPs)
- → People are typically interested in the association between variation in SNPs and observable outcomes
- → Genotyping measures between 0.5 and 2.5 million SNPs

Polygenic Scores (PGSs)

- For outcome Y_i and observed set of SNPs ($\{\text{SNP}_{j=1}^{M}\}$), a GWAS estimates M ($M \sim 10$ million) regressions as:

$$Y_i = X_i'\Psi + \vartheta_j \text{SNP}_{ij} + \epsilon_{ij}$$

- where X_i is a vector of observable controls and ϵ_{ij} are *iid* shocks
- Using data from the UKB v1 release, PGSs are then constructed using transformed coefficients $\widetilde{\vartheta}_j$ that account for correlation across SNPs:

$$\text{PGS}_i^Y = \sum_j \widetilde{\vartheta}_j \text{SNP}_{ij}$$

Our PGSs

We calculate polygenic scores on the **UKB v3 data release** excluding respondents who were genotyped in the UKB v1 release.

- Use only individuals of European ancestry
- Weights come from published GWASs (publicly available) based on multiple cohorts and UKB "Interim Data Release (v1)"
  - AAM (Day et al. 2017, *Nature Genetics*)
  - A1B (Barban et al. 2016, *Nature Genetics*)
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- Plan: Compute new PGSs for CF, TF, CLN, and age at menopause

UKB Sample

- Cohorts 1938–1969
- Analysis only on the **UKB v3 data release**, excluding respondents who were genotyped in the UKB v1 release
- Size (N) varies depending on the outcome

Our Current Measures of E

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For now, we have 3 measures of E (motivated by related literatures):

1. **Childhood unemployment rate**: for AAM [e.g., Aurino et al. 2019]
2. **Childhood food consumption**: for AAM
3. **Contraceptive pill availability**: for A1S, A1B, CF, TF, CLN [e.g., Goldin and Katz 2002]

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Plan: construct additional outcome-specific measures of E (e.g., based on female educational attainment, LFP rates, fraction of women in managerial/professional occupations at different point of UKB women's life cycle), possibly construct a new factor

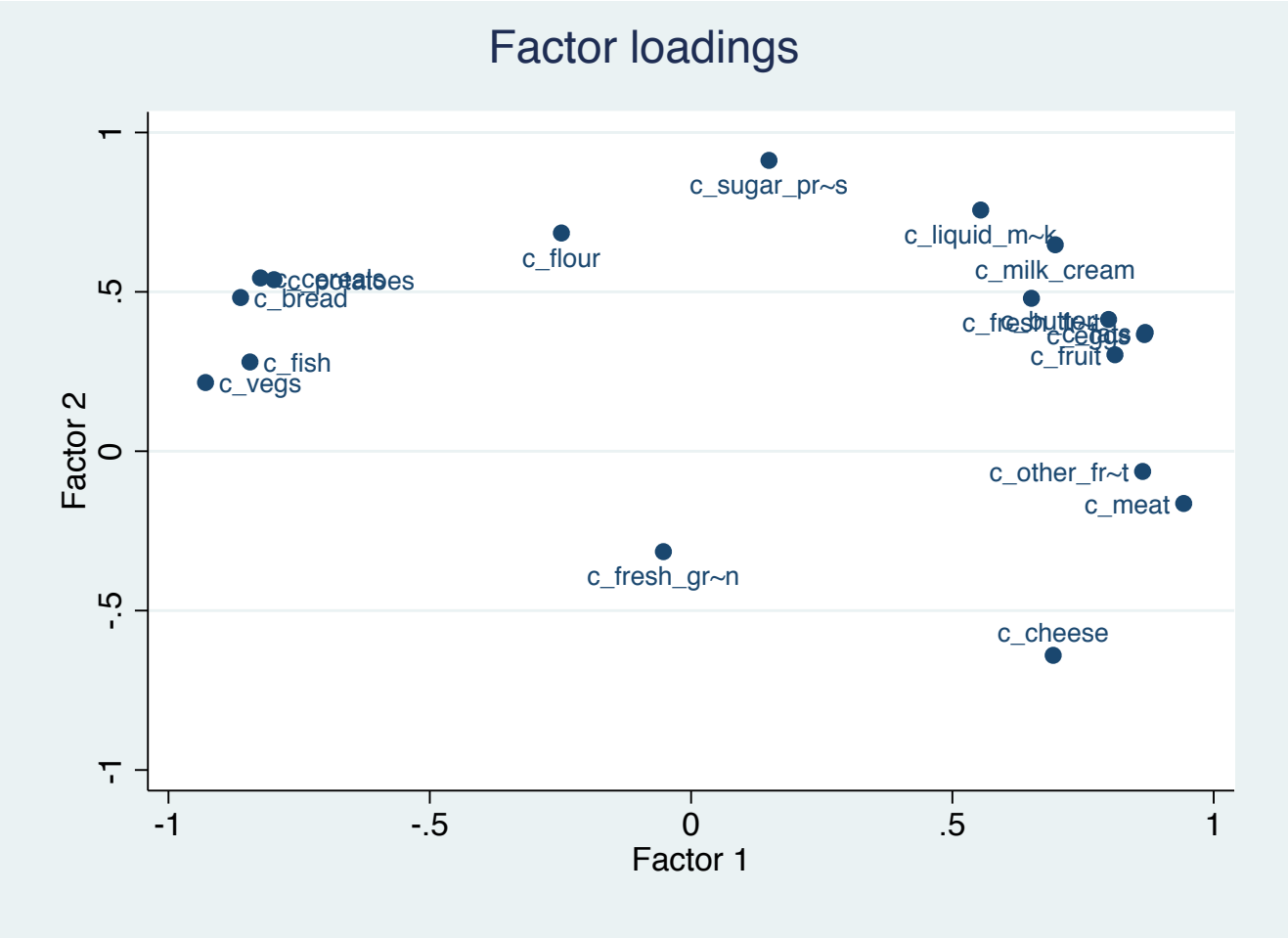
E (AAM): Unemployment rate

- We digitalize data from:
  - British Labour Statistics - Historical Abstracts 1886-1968 Great Britain unemployment rate relative to the period 1948-1968, pp.330-332, tab 169
- Construct a measure of average unemployment rate in the first 10 years of life of each individual in the UKB

E (AAM): Food Consumption (1)

- We digitalized data from:
  a. Domestic Food Consumption and Expenditure Reports for 1950–1984
  b. Studies in Urban Household Diets, 1944–1949
  c. The Urban Working-Class Household Diet, 1940–1949
  d. British Labour Statistics – Historical Abstracts 1886-1968, p.392, tabs. 189 and 191 for total weekly household total expenditure 1953–1954 and 1962–1968
- We then calculate a factor from 18 food consumption items
- We average the factor in the first 10 years of life of each individual in the UKB (as a proxy of nutrition in childhood)

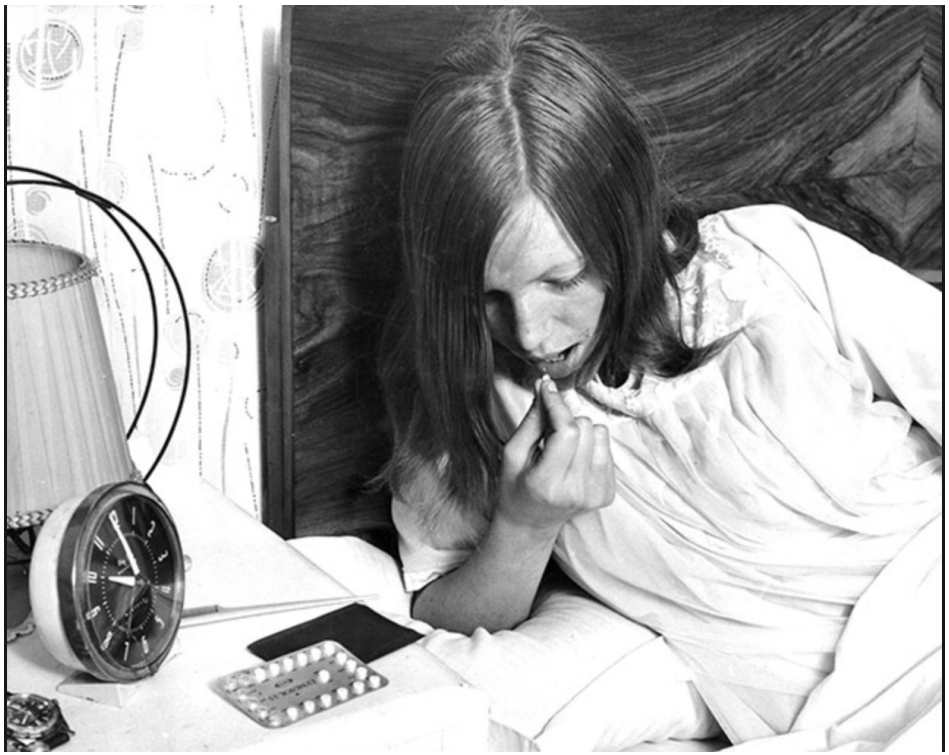
E (AAM): Food consumption



$\therefore$ Higher factor for more **protein-based** diet

E (other outcomes): Contraceptive Pill (1)

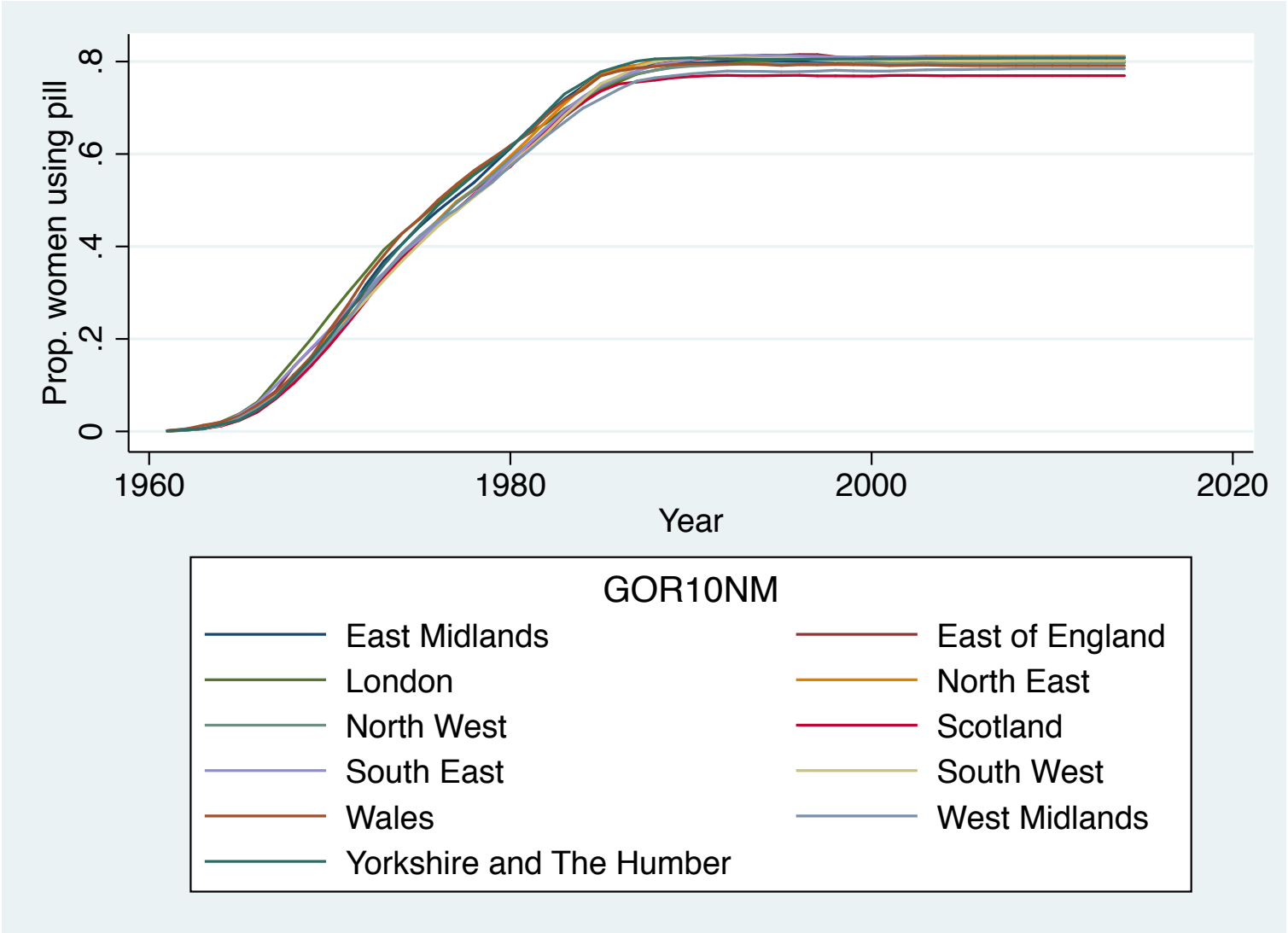
- 1961: oral contraception introduced in the UK, but made available only to married women
- 1967: pill is extended to everyone in England and Wales
- 1968: pill is introduced in Scotland (available to everyone)
- 1969: pill is introduced in Northern Ireland (available to everyone)



E (other outcomes): Contraceptive Pill (2)

- Data from UKB v1
- Calculate the proportion of women who use the pill for the first time *and* do not have children, by year and region
- Link this variable to UKB v3 respondents (excluding respondents from UKB v1) when they were 18 years old
- For Teen Fertility, the variable is linked to when respondents were 13 years of age
- Results are robust to changes of the timing (18 or 13, or 18–30, or 13–19)

E(other outcomes): Contraceptive Pill (3)



Empirical Specification with Simple $G \times E$

$$Y_{ir} = \beta_0 + \beta_1 G_{ir}^Y + \beta_2 E_{ir}^Y + \beta_3 \left(G_{ir}^Y \times E_{ir}^Y \right) + X_{ir}' \Gamma + \delta_r + e_{ir} \qquad (1)$$

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$$Y_{ir} = \beta_0 + \beta_1 G_{ir}^{Y} + \beta_2 E_{ir}^{Y} + \beta_3 \left(G_{ir}^{Y} \times E_{ir}^{Y} \right) + X_{ir}' \Gamma + \delta_r + e_{ir} \qquad (1)$$

- Y_{ir}: outcome for individual i, born in region r
- G_{ir}^{Y}: PGS related to outcome Y for individual i, born in region r
- E_{ir}^{Y}: environment to which individual i is exposed in region r (varies by Y)
- X_{ir}: vector of controls (besides year of birth FE):
  - WWII indicator (=1 if 1939–1945, =0 otherwise); [ongoing: severe bombings; rationing during/after WWII]
  - first 10 population stratification PCs;
  - early-life controls: self-reported birthweight, maternal smoking during pregnancy (0/1), breastfed (0/1)
- δ_r: region FE
- SE clustered at (region $\times$ year of birth)
- Notice: control for $\mathrm{PGS}^{education}$ *and* $\mathrm{PGS}^{risky\ behav}$ (Linnér et al. 2019) in all outcomes

Roadmap for Results

i. Genetic **heritability** across birth cohorts

ii. **Genetic correlations**

iii. Outcome **differences by** G

iv. **Regression** results

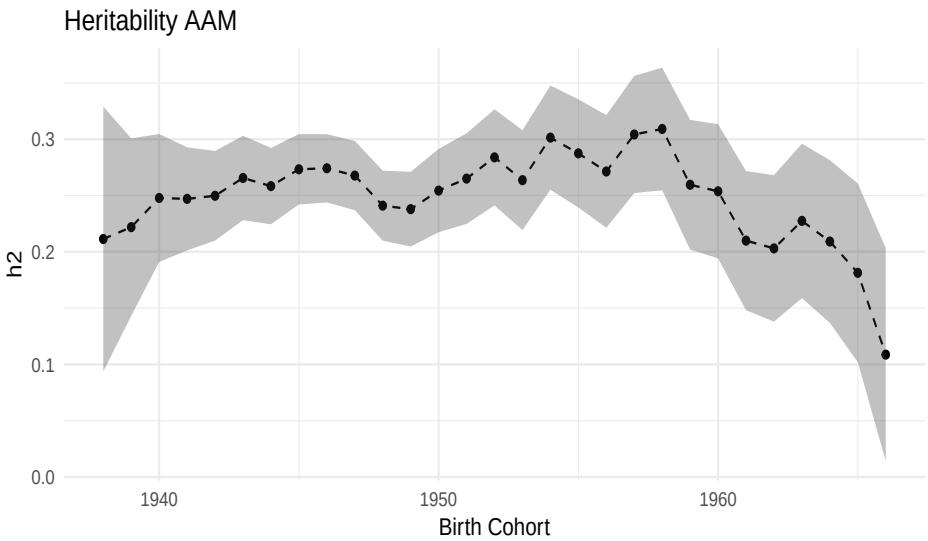
i. Heritability (1)

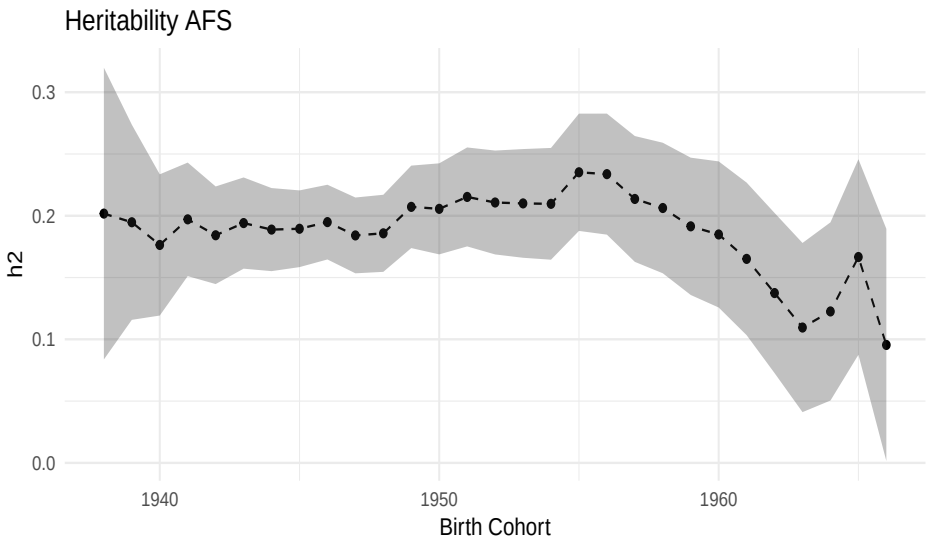
Proportion of phenotypic variance in a trait attributable to the additive genetic variation generated by all causal variants (h^2_{SNP}) (Yang et al. 2017)

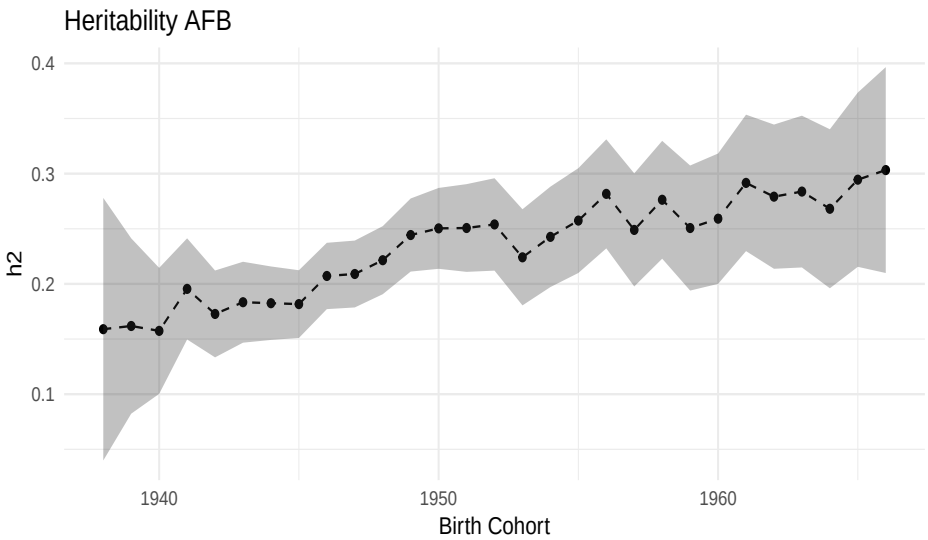
- Obtained from linear mixed models (with random effects)
- Relatives have been dropped from the estimating sample (otherwise the environment component would not be independent)
- Selected only independent SNPs (approx. 250,000 of the 800,000 genotyped)
- Most of the literature uses twins: e.g., h^2(AAM) $\sim$ 0.8 (Anderson et al. 2007); h^2(A1B) $\sim$ 0.25–0.35 (Tropf et al. 2015); h^2(CF) $\sim$ 0.1–0.3 (Kohler et al. 1999)

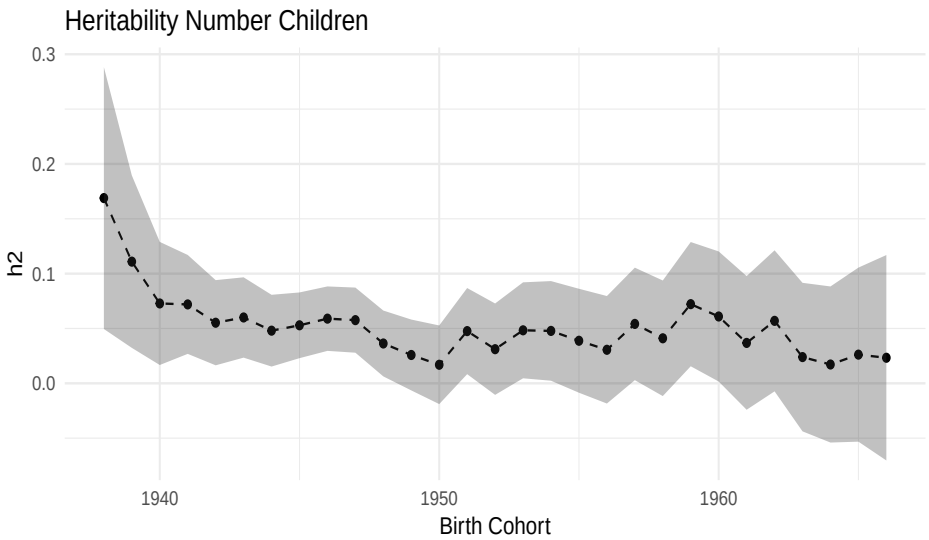
- Show estimates by birth cohort, computed as a 5-year moving average (only AAM, A1S, A1B, and CF)

Heritability (2)









Heritability (3)

1. Substantial **reduction** in h^2_{SNP} by birth cohort in AAM, A1S, and CF
2. fairly steady **increase** in h^2_{SNP} by birth cohort in A1B

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What does this evidence suggest?

Heritability (3)

1. Substantial **reduction** in h^2_{SNP} by birth cohort in AAM, A1S, and CF
2. fairly steady **increase** in h^2_{SNP} by birth cohort in A1B

What does this evidence suggest?

In all Ys, factors **other than genes** may have played an **important** role and:

(a) an increasingly greater role in explaining changes in AAM (albeit these changes seem to be negligible at the mean in the sample), A1S and CF;

(b) a smaller role in explaining A1B (in spite of greater role of female education, female labor market participation, technological advances such as the contraceptive pill, institutional reforms, and social norms)

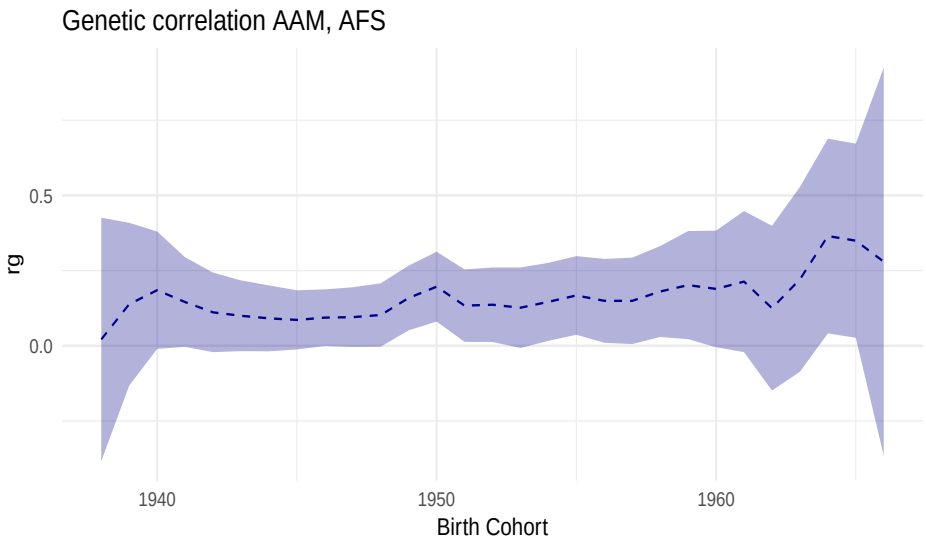
ii. Genetic Correlation (1)

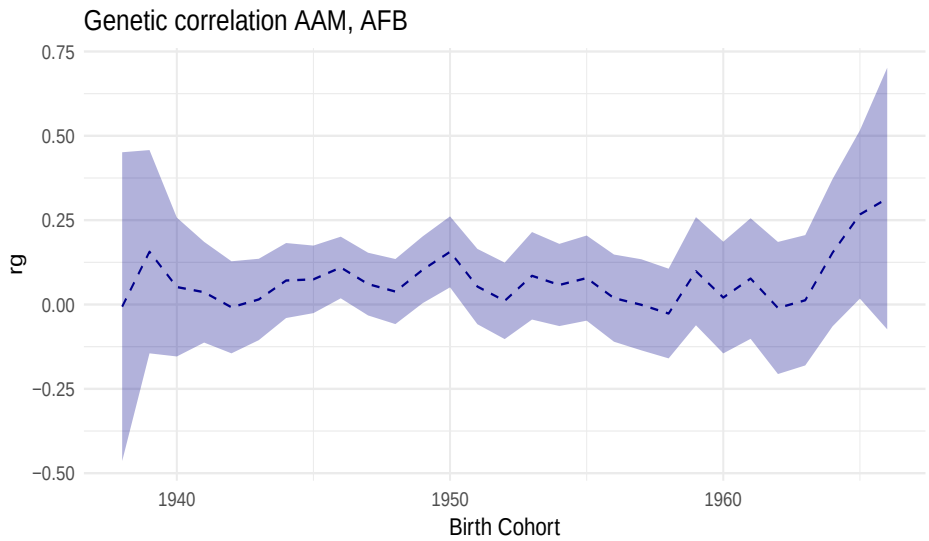
Genetic correlation (or genetic overlap) is the proportion of variance that two traits share due to genetic causes, r_g

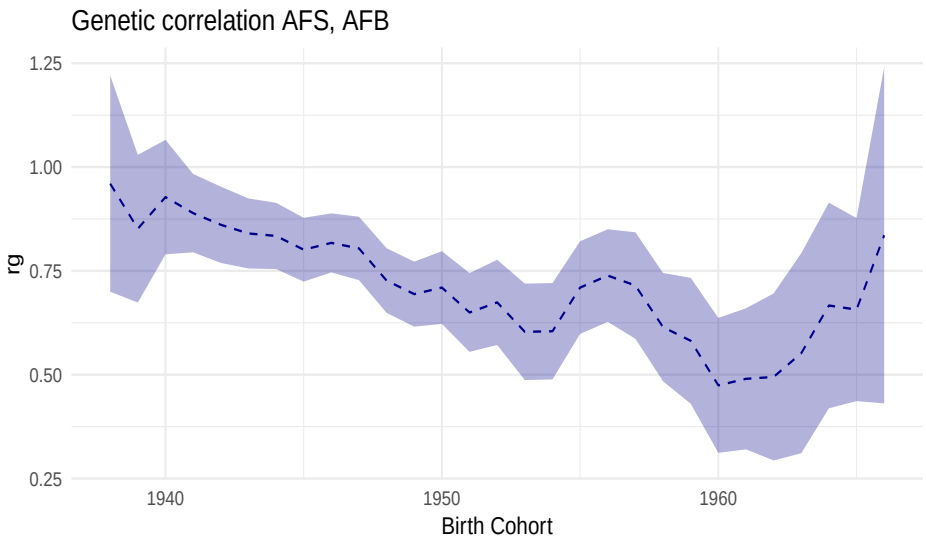
- Not the same as heritability, as it is about the overlap between the two sets of genetic influences
- Two traits could be highly heritable but not be genetically correlated, or have small heritabilities and be highly correlated

- Show estimates by birth cohort, computed as a 5-year moving average (only AAM, A1S, and A1B)

Genetic Correlation (2)







Genetic Correlation (3)

1. Fairly **small** correlations between AAM and A1S and between AAM and A1B (although both have slightly increased among those born in the 1960s)
2. Extremely **high** correlation between A1S and A1B for older cohorts, but this has decreased from around 1 for women born in the early 1940s to 0.5–0.6 for those born in the early 1960s (increase later)

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What does this evidence suggest?

(a) We can use G^{AAM} in explaining A1S and A1B; and

(b) We can use G^{A1S} in explaining A1B, although this may be less useful for early cohorts in the sample (and for late cohorts, to a lesser extent)

iii. Outcome Differences by G (1)

Next, we show (selected) results from linear predictions of the sort:

$$Y_{ir} = \alpha_0 + \alpha_1 G_{ir}^Y + \alpha_2 t + \left(\alpha_3 G_{ir}^Y \times t\right) + X_{ir}' \Upsilon + \delta_r + u_{ir}$$

where t is a linear year-of-birth trend; and

- when outcome is A1S, we also control for AAM and PGS(AAM)
- when outcome is A1B/CF/TF/CLN, we also control for AAM, PGS(AAM), A1S and PGS(A1S)

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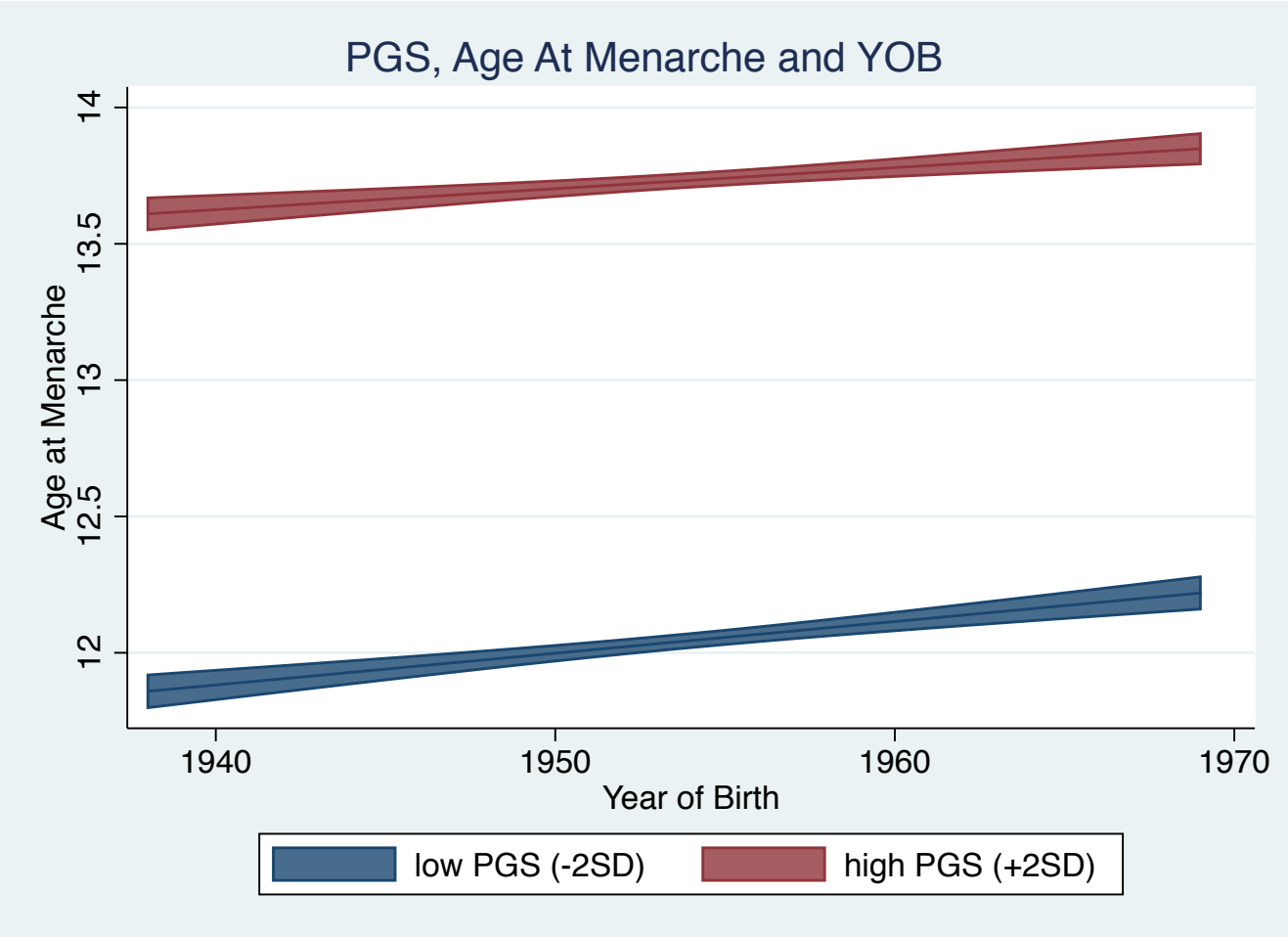
Looking at high- (top 5%) v low-G (bottom 5%), this analysis tells us that:

(a) if difference in Y is large, then G is likely to play an important role (besides incremental R^2); and

(b) if difference in Y changes over time, then the impact of G on outcomes changes too, providing indirect evidence of the importance of $G \times E$

Outcome Differences by G (2)

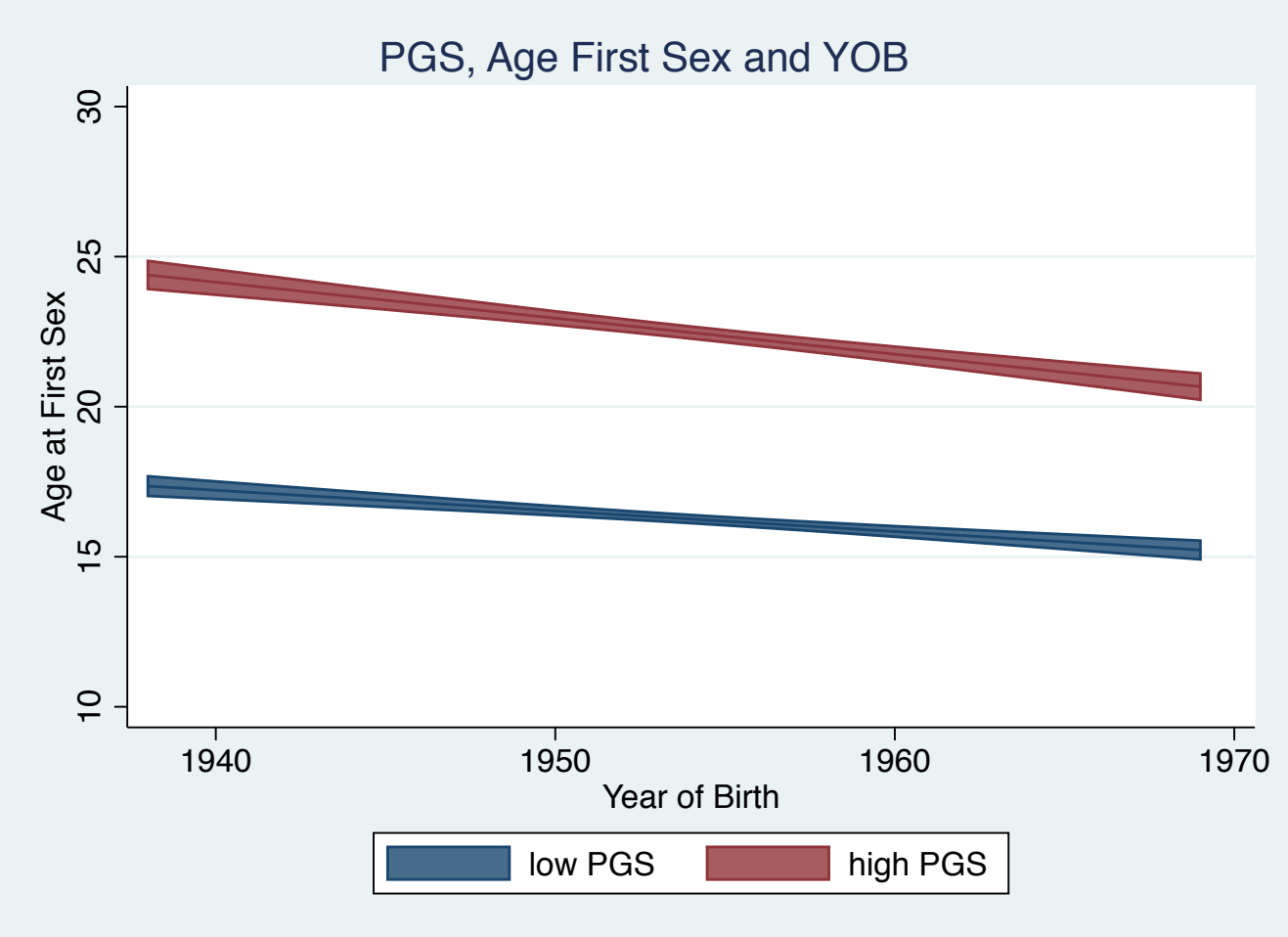
Age at Menarche



Note: Higher $\mathrm{PGS}^{\mathrm{AAM}} \Rightarrow$ Higher AAM (expect $\beta_1 > 0$ in (1)). Notice AAM *increases slightly* across birth cohorts when we let it be driven by G only.

Outcome Differences by G (3)

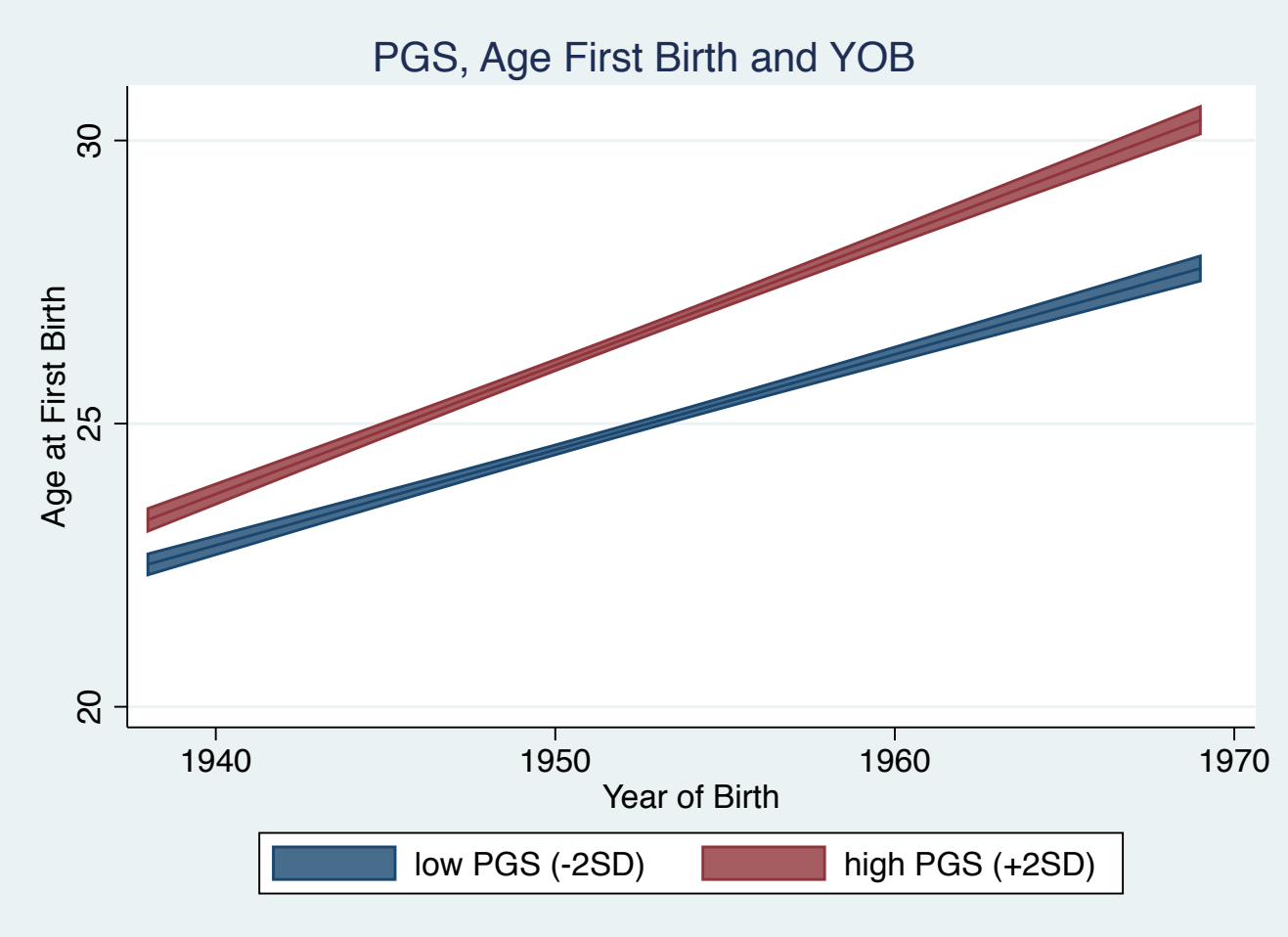
Age at First Sex



Note: Higher $\mathrm{PGS}^{\mathrm{A1S}} \Rightarrow$ Higher A1S (expect $\beta_1 > 0$ in (1)).

Outcome Differences by G (4)

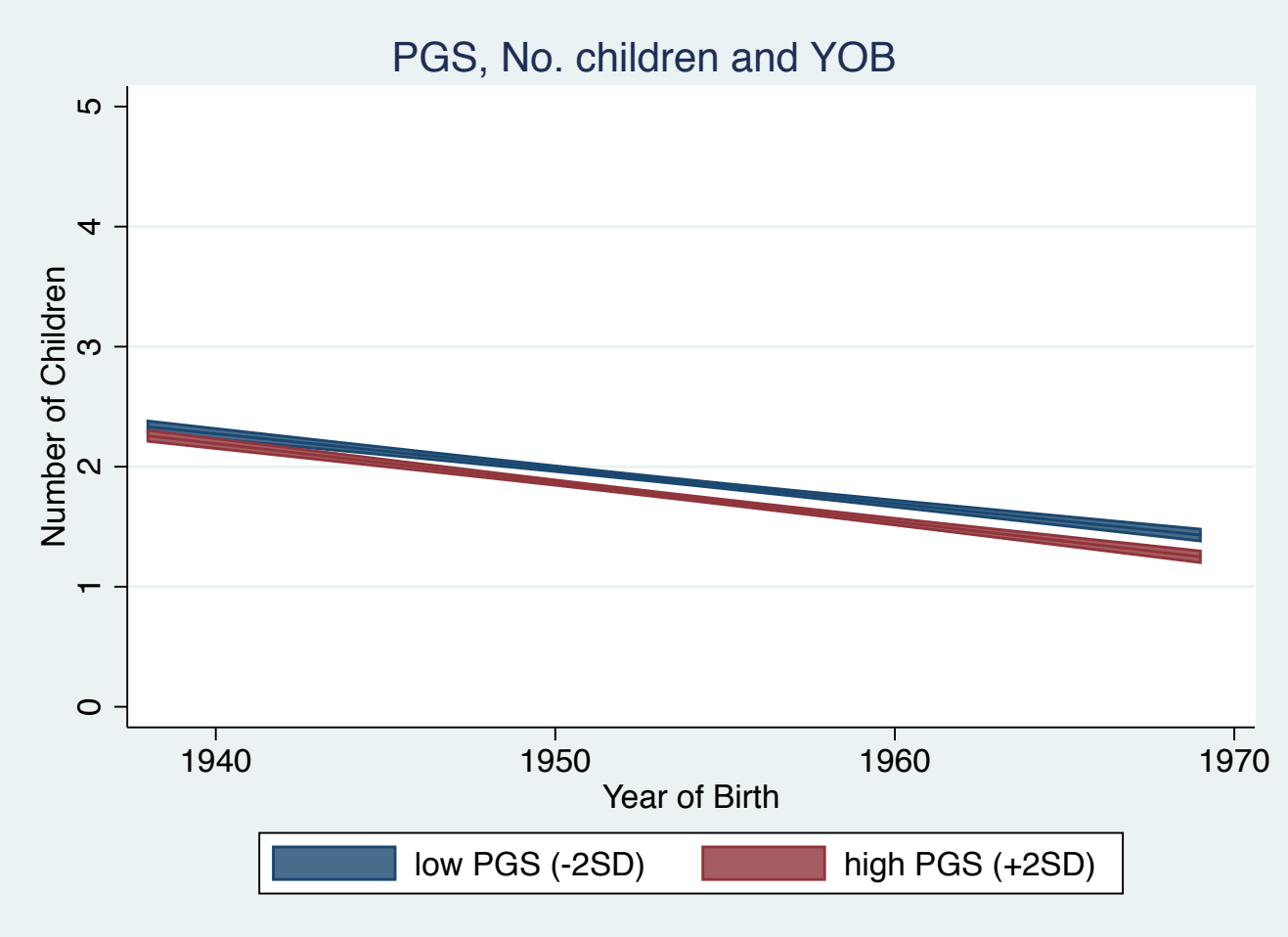
Age at First Birth



Note: Higher $\mathrm{PGS}^{\mathrm{A1B}} \Rightarrow$ Higher A1B (expect $\beta_1 > 0$ in (1)).

Outcome Differences by G (5)

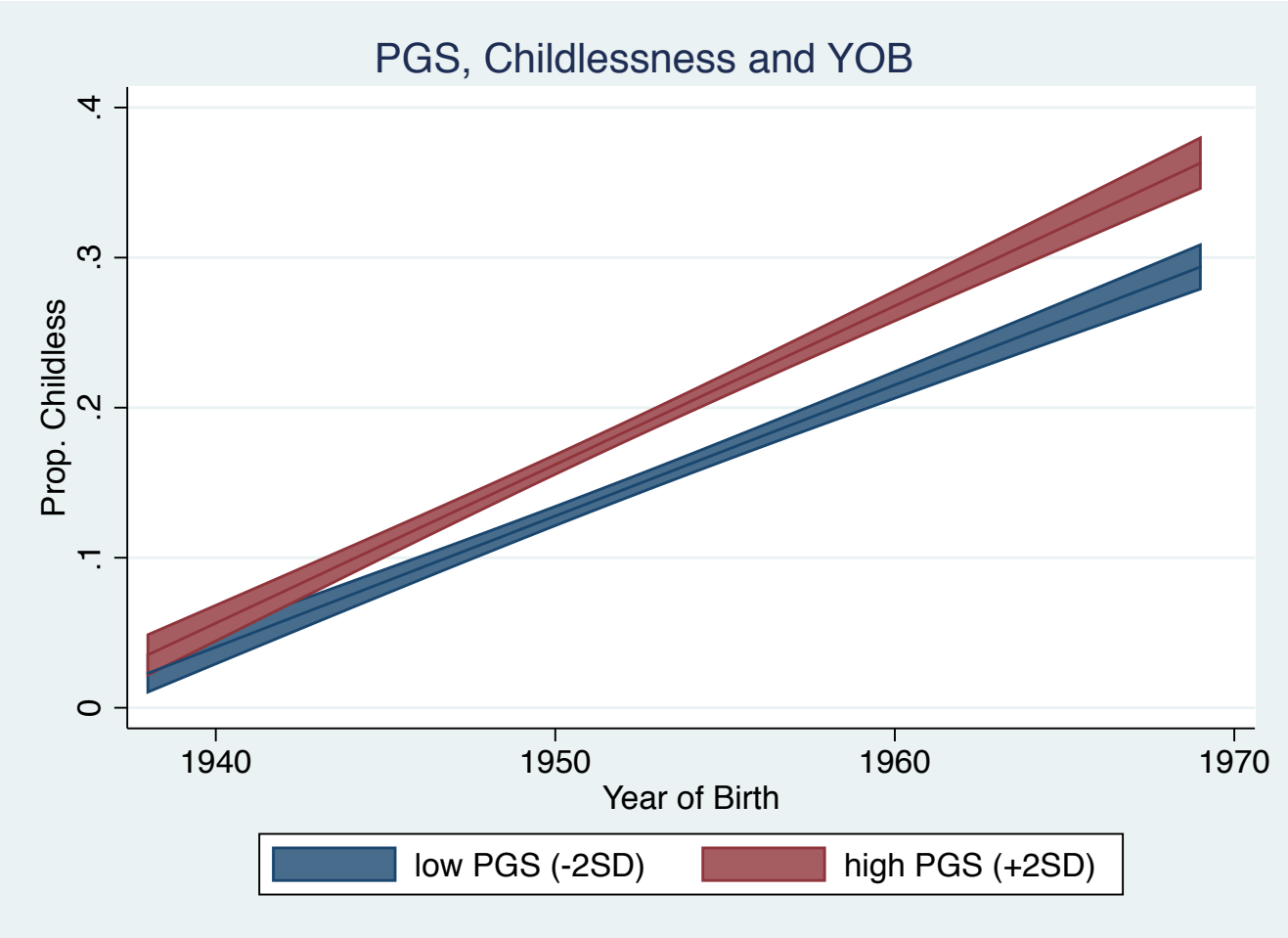
Completed Fertility



Note: Higher $\mathrm{PGS}^{\mathrm{CF}} \Rightarrow$ lower CF (expect $\beta_1 < 0$ in (1)).

Outcome Differences by G (6)

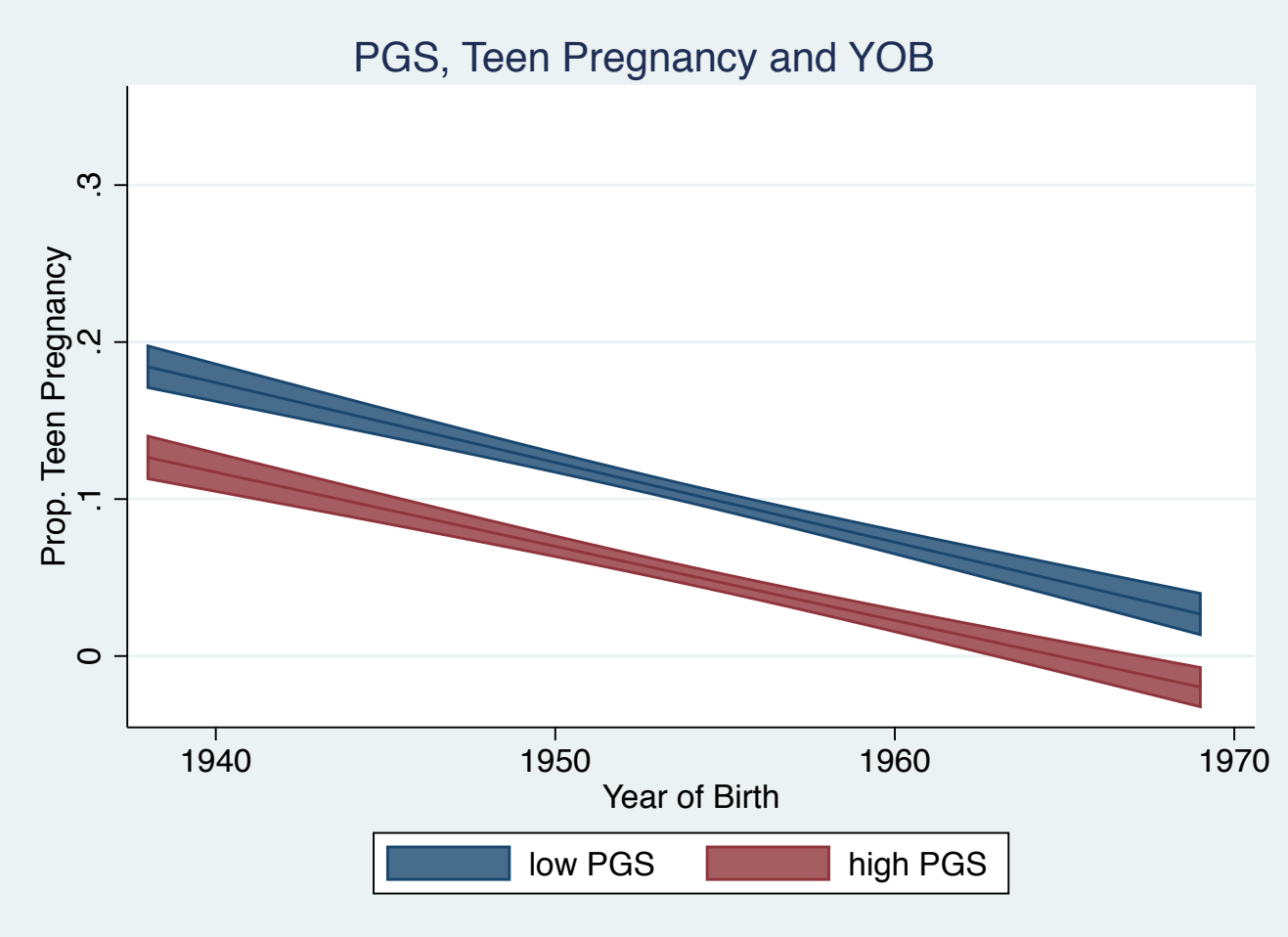
Childlessness



Note: Higher $\mathrm{PGS}^{\mathrm{CLN}} \Rightarrow$ Higher CLN (expect $\beta_1 > 0$ in (1)).

Outcome Differences by G (7)

Teenage Fertility



Note: Higher $\mathrm{PGS}^{\mathrm{TF}} \Rightarrow$ lower TF (expect $\beta_1 < 0$ in (1)).

Outcome Differences by G (9)

1. Differences between high- and low-G are **large**: AAM (almost 2 years), A1S (5–7 years), and TF (6 percentage points), but **constant** across birth cohorts
2. Differences are **large** and **increasing**: A1B (from less than 1 year to almost 3 years), CLN (from 0 to 7 percentage points)
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3. Differences are significant (although fairly small) for CF, but increasing over time

What does this evidence suggest?

(a) G **matters** for all fertility processes/decisions

(b) $Y-G$ relationship does not seem to be linear in a number of cases: G might interact with something else (e.g. E) in a meaningful way

iv. Regressions Results (1)

Age at Menarche

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Age at Menarche

	E: unempl. rate		E: nutrition	
	(1)	(2)	(1)	(2)
Mean of dep. var.	12.96	12.95	12.94	12.94
G	0.450***	0.479***	0.411***	0.419***
E	0.163***	0.195***	–0.117***	–0.122***
$G \times E$	–0.019	–0.030	0.005	0.013
N	93,783	56,553	136,076	75,270
R^2	0.054	0.058	0.055	0.059
Increm. R^2 (for G^{AAM})	0.051	0.053	0.051	0.054

Note: (1) without early life controls; (2) with early life controls. Each regression includes first 10 principal components of the genetic matrix, region FE, WWII dummy. SE clustered at birth cohort.
$\uparrow$ 1 SD in $G \Rightarrow \uparrow$ AAM by $\sim$ 0.5 years; $\uparrow$ 1ppt in UR $\Rightarrow \uparrow$ AAM by $\sim$ 0.2 years; $\uparrow$ 1 SD in nutrition factor $\Rightarrow \downarrow$ AAM by $\sim$ 0.12 years

Regressions Results (2)

Age at First Sex

	(1)	(2)
Mean of dep. var.	19.00	18.92
G	1.620***	1.677***
E (pill exposure)	–0.027***	–0.025***
$G \times E$	–0.0033***	–0.0038**
AAM	0.070***	0.072***
G^{AAM}	0.056***	0.058***
N	132,633	73,303
R^2	0.103	0.107
Increm. R^2 (for G^{A1S})	0.027	0.028

Note: (1) without early life controls; (2) with early life controls. All other controls included as in previous table. SE clustered at region$\times$ birth cohort.
$\uparrow$ 1 SD in G $\Rightarrow\uparrow$ A1S by $\sim$ 1.6 years; $\uparrow$ 1ppt in pill exposure $\Rightarrow\downarrow$ A1S by $\sim$ 0.03 years.

Regressions Results (3)

Age at First Birth

	(1)	(2)
Mean of dep. var.	25.41	25.73
G	0.302***	0.295***
E (pill exposure)	0.053***	0.054***
$G \times E$	0.0048***	0.0043**
AAM	0.015*	0.008
G^{AAM}	0.054***	0.033
A1S	0.634***	0.603***
G^{A1S}	0.062*	0.129***
N	93,319	50,573
R^2	0.233	0.234
Increm. R^2 (for G^{A1B})	0.007	0.007

Note: (1) without early life controls; (2) with early life controls. SE and all other controls included as in previous table.
$\uparrow$ 1 SD in $G \Rightarrow \uparrow$ A1B by $\sim$ 0.3 years; $\uparrow$ 1ppt in pill exposure $\Rightarrow \uparrow$ A1B by $\sim$ 0.05 years.

Regressions Results (4)

Completed Fertility

	(1)	(2)
Mean of dep. var.	1.86	1.83
G	–0.026***	–0.024***
E (pill exposure)	–0.008***	–0.008***
$G \times E$	–0.0004***	–0.0003
AAM	0.017***	0.016***
G^{AAM}	0.005	0.007
A1S	–0.056***	–0.054***
G^{A1S}	0.010	0.013
N	132,596	73,281
R^2	0.062	0.059
Increm. R^2 (for G^{CF})	0.001	0.001

Note: (1) without early life controls; (2) with early life controls. SE and all other controls included as in previous table.

$\uparrow$ 1 SD in $G \Rightarrow \downarrow$ CF by $\sim$ 0.025; $\uparrow$ 1ppt in pill exposure $\Rightarrow \downarrow$ CF by $\sim$ 0.01.

Regressions Results (5)

Teenage Fertility

	(1)	(2)
Mean of dep. var.	0.095	0.086
G	–0.016***	–0.015***
E (pill exposure)	–0.002***	–0.002***
$G \times E$	0.0001**	0.0001*
AAM	–0.001**	–0.001
G^{AAM}	–0.004***	–0.001
A1S	–0.029***	–0.025***
G^{A1S}	–0.0003	–0.003
N	93,319	50,573
R^2	0.095	0.089
Increm. R^2 (for G^{TF})	0.002	0.002

Note: (1) without early life controls; (2) with early life controls. SE and all other controls included as in previous table.
$\uparrow$ 1 SD in $G \Rightarrow \downarrow$ TB by $\sim$ 1.5ppt; $\uparrow$ 1ppt in pill exposure $\Rightarrow \downarrow$ TB by $\sim$ 0.02ppt.

Regressions Results (6)

Childlessness

	(1)	(2)
Mean of dep. var.	0.164	0.176
G	0.005***	0.006***
E (pill exposure)	0.003***	0.003***
$G \times E$	0.0002***	0.0001**
AAM	–0.005***	–0.005***
G^{AAM}	–0.002	–0.002
A1S	0.019***	0.019***
G^{A1S}	0.001	–0.004
N	132,596	73,281
R^2	0.059	0.057
Increm. R^2 (for G^{CLN})	0.001	0.001

Note: (1) without early life controls; (2) with early life controls. SE and all other controls included as in previous table.
$\uparrow$ 1 SD in $G \Rightarrow \uparrow$ CLN by $\sim$ 0.5ppt; $\uparrow$ 1ppt in pill exposure $\Rightarrow \uparrow$ CLN by $\sim$ 0.03ppt.

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3. In particular, being born in an area with a higher proportion of women using the pill leads to:
   a. **reduction** in A1S; and this is reinforced by $G \times E$
   b. **increase** in A1B; and this is reinforced by $G \times E$
   c. **reduction** in CF; and this is reinforced by $G \times E$
   d. **reduction** in TF; and this is attenuated by $G \times E$
   e. **increase** in CLN; and this is reinforced by $G \times E$

Robustness to Changes in E Measure & Extra

These are changes that affect A1S, A1B, CF, TF, and CLN (not AAM):

1. Use a pill exposure measure at the district level (370 LADs): **same results**
2. Use a pill exposure measure computed over an age interval rather than at 18 or 13 (e.g., over the ages 18–30 or 13-19): **same results**
3. Construct a pill exposure measure restricted only to young cohorts in 1961 (when pill was introduced) or 1967/68 (when it was extended to everyone), e.g., people born 1938–1943 or 1944–1950: **same results**

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Extra: We plan to re-analyze (1) with family FEs (using siblings and possibly cousins)

$G \times E$ by Cohort (1)

To understand the role played by $G \times E$ better, we run a new set of regressions:

$$\begin{aligned} Y_{ir} &= \phi_0 + \phi_1 G_{ir}^Y + \phi_2 E_{ir}^Y + \left(\phi_3 G_{ir}^Y \times E_{ir}^Y\right) \\ &\quad + \phi_4 t + \left(\phi_5 G_{ir}^Y \times E_{ir}^Y \times t\right) + X_{ir}'\Lambda + \delta_r + \varepsilon_{ir} \end{aligned} \tag{2}$$

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- This will help us see how the impact of $G \times E$ possibly changes over time,
- and whether this variation reinforces or attenuates the observed secular change in Y

$G \times E$ by Cohort (2)

Caveat: From this exercise we expect that the impact of $G \times E$ be understated (and underpowered), because:

a. the impact of G is likely to be stable over birth cohorts (since time span is short); and

b. $G \times E$ picks up the same time (cohort) variation as E (for pill diffusion varies in the same way over time across regions, for all outcomes except for AAM)

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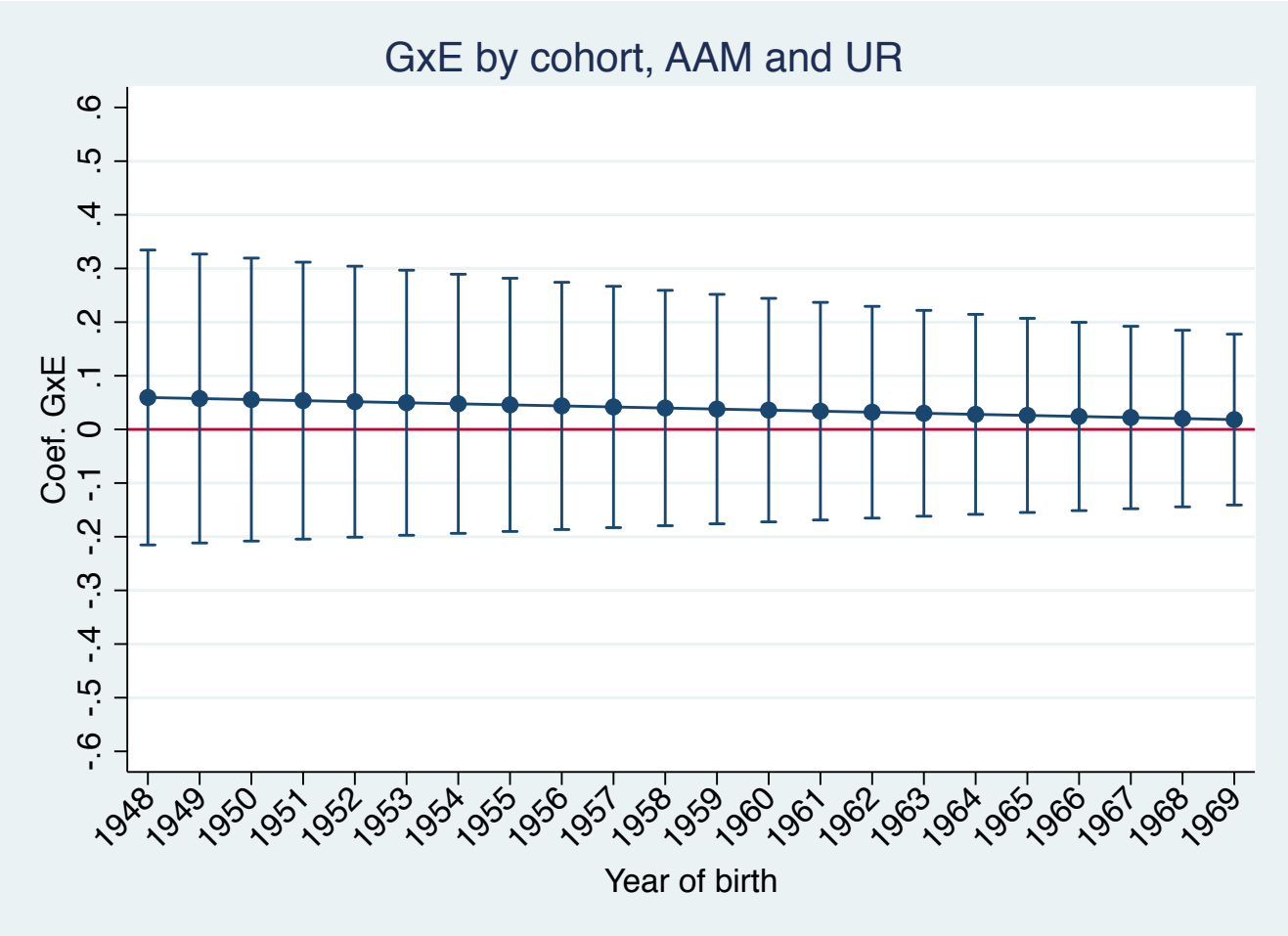
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Below, we show figures displaying the average marginal effect of $G \times E$ in (2) (with 95% CI)

$G \times E$ by Cohort (3)

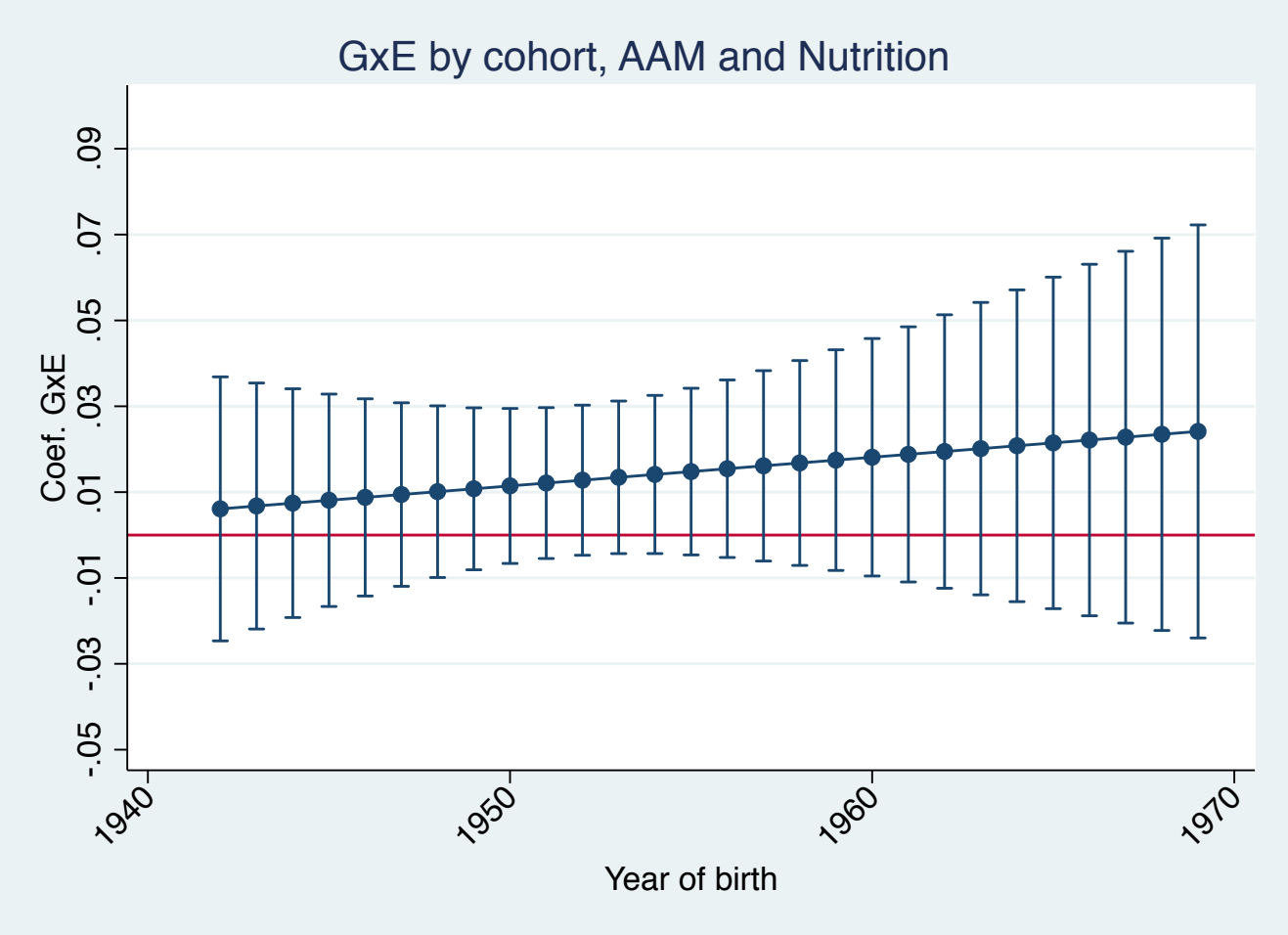
Age at Menarche – E: Unemployment Rate



Note: As in (1) $G \times E$ does not show a big role across cohorts. Remember also that AAM does not vary substantially in our sample over time.

$G \times E$ by Cohort (4)

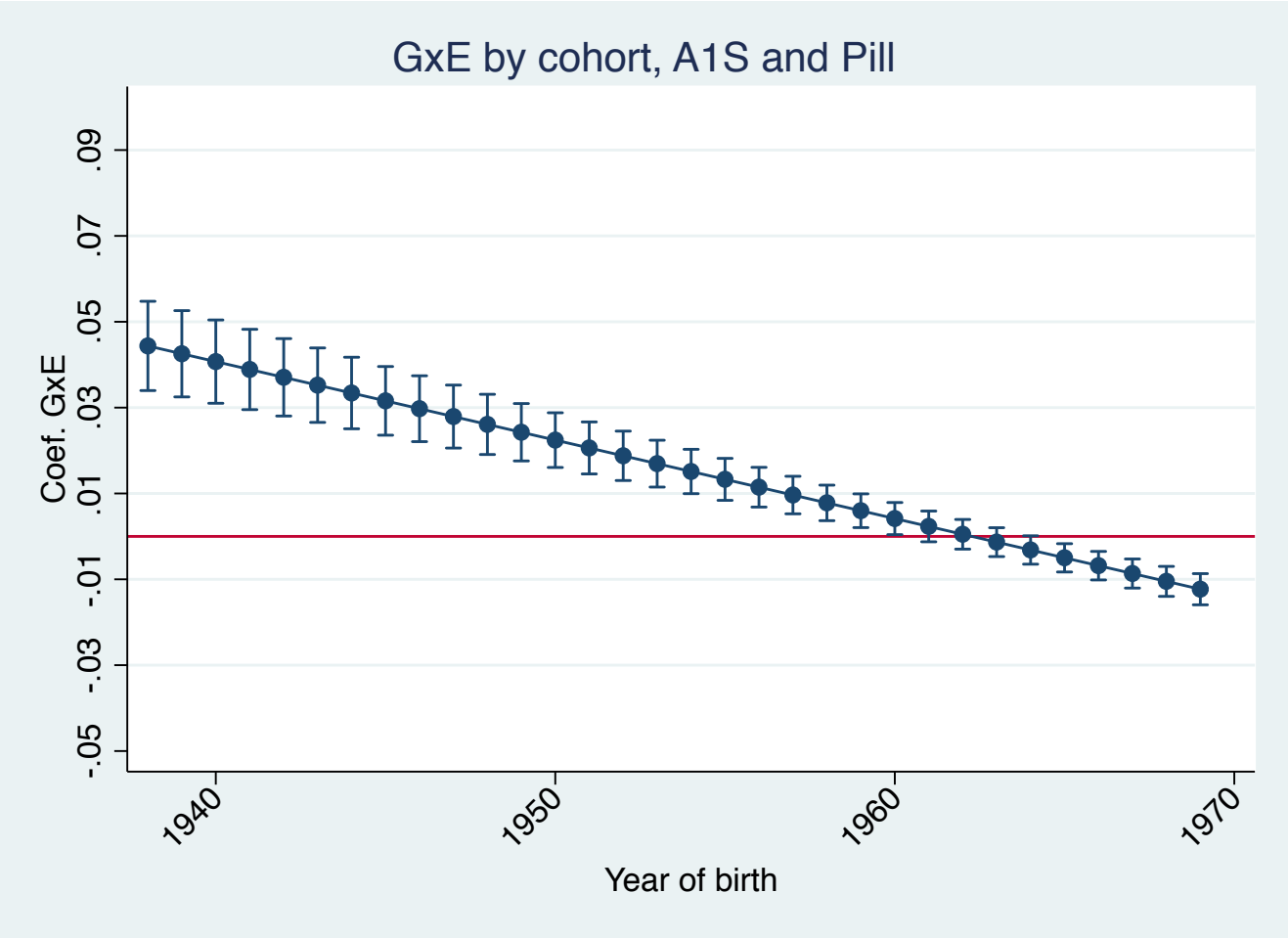
Age at Menarche – E: Food Consumption



Note: Same as in previous figure.

$G \times E$ by Cohort (5)

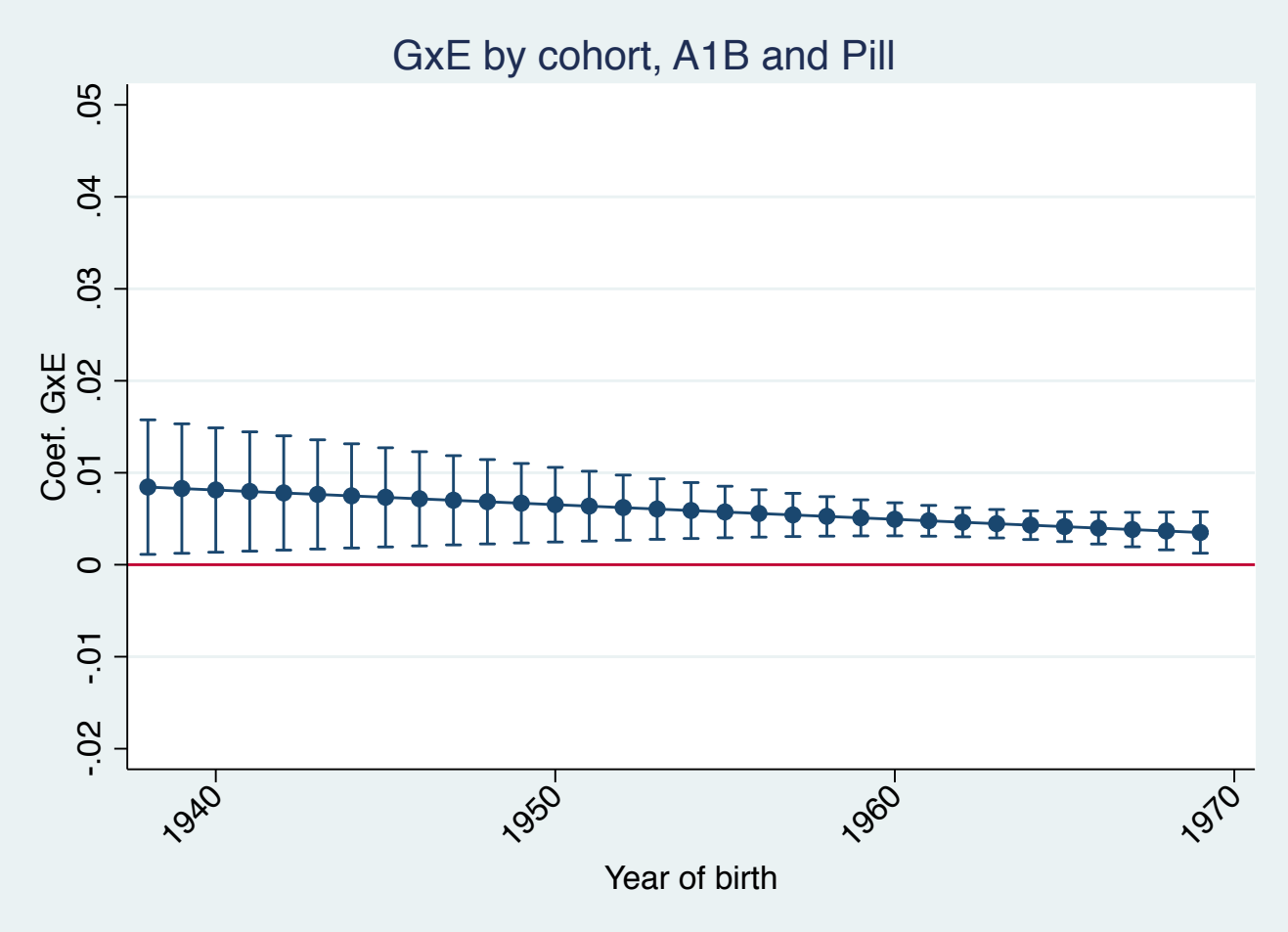
Age at First Sex



Note: Recall, E (high pill diffusion) reduces A1S and $G \times E$ reinforces this reduction. This reinforcement emerges only for **more recent** birth cohorts, while there is attenuation for older cohorts.

$G \times E$ by Cohort (6)

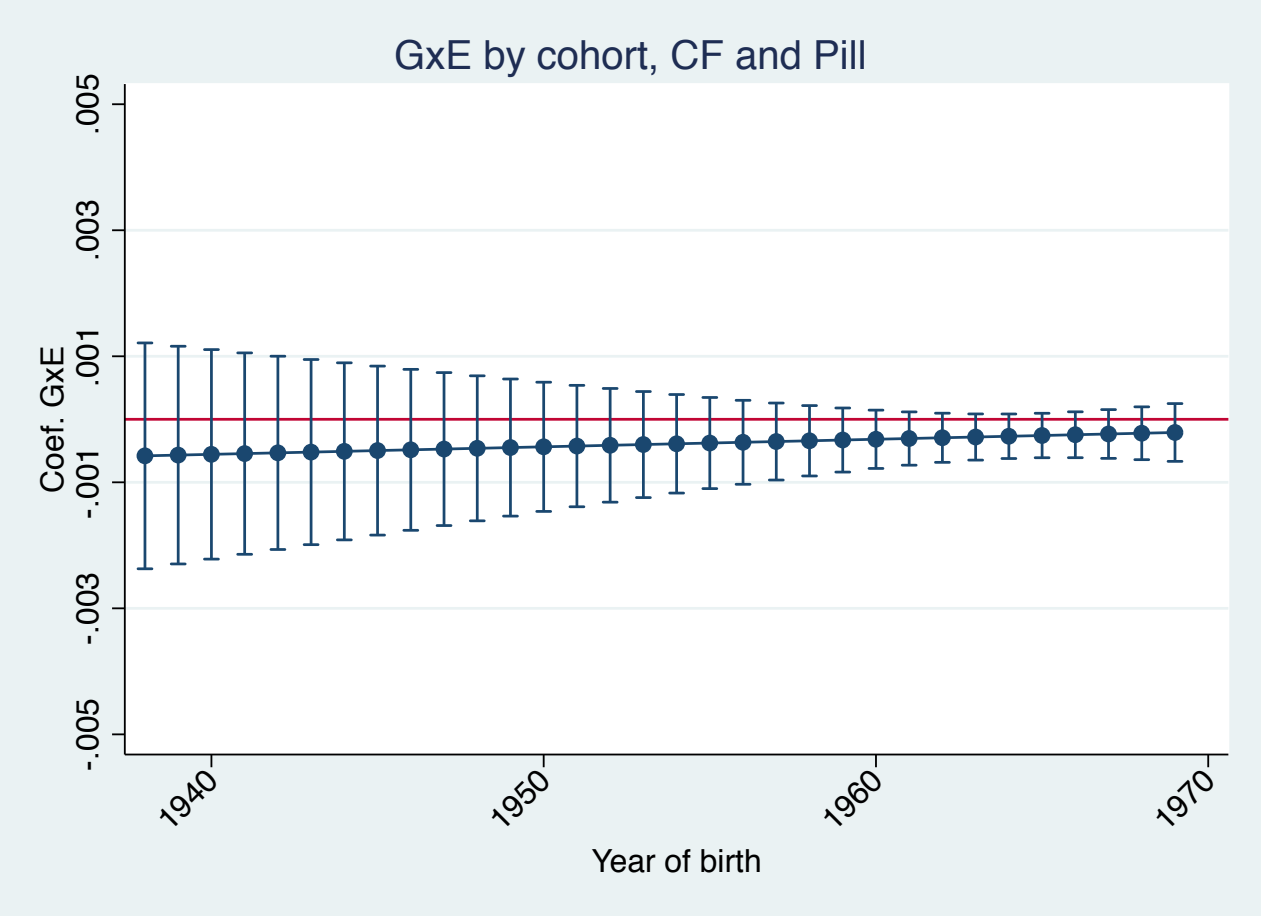
Age at First Birth



Note: Recall, E (high pill diffusion) increases A1B and $G \times E$ reinforces this increase. This reinforcement holds true across **all** birth cohorts.

$G \times E$ by Cohort (7)

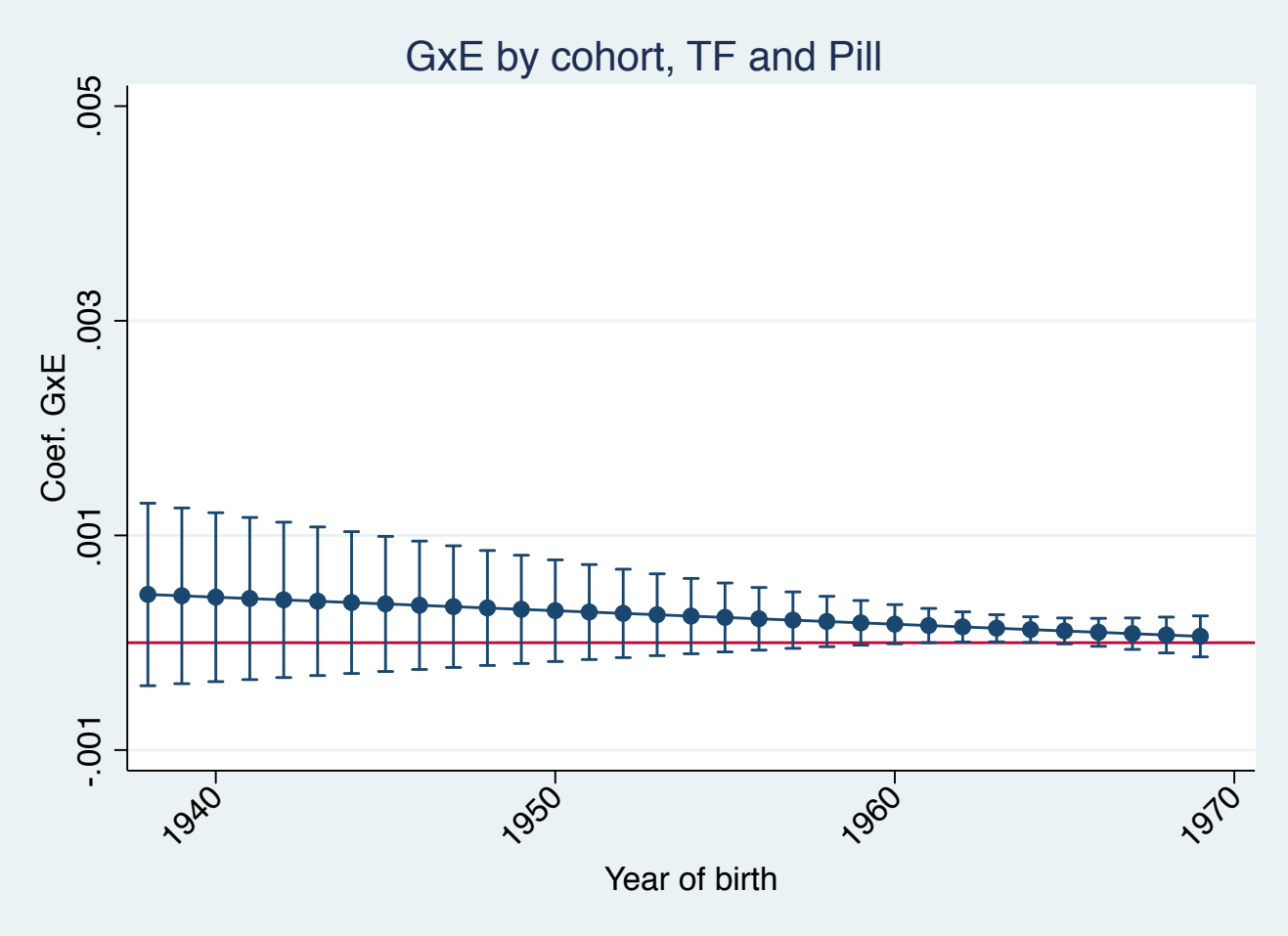
Completed Fertility



Note: Recall, E (high pill diffusion) reduces CF and $G \times E$ reinforces this reduction. This seems to be constant (albeit not significant) across cohorts.

$G \times E$ by Cohort (8)

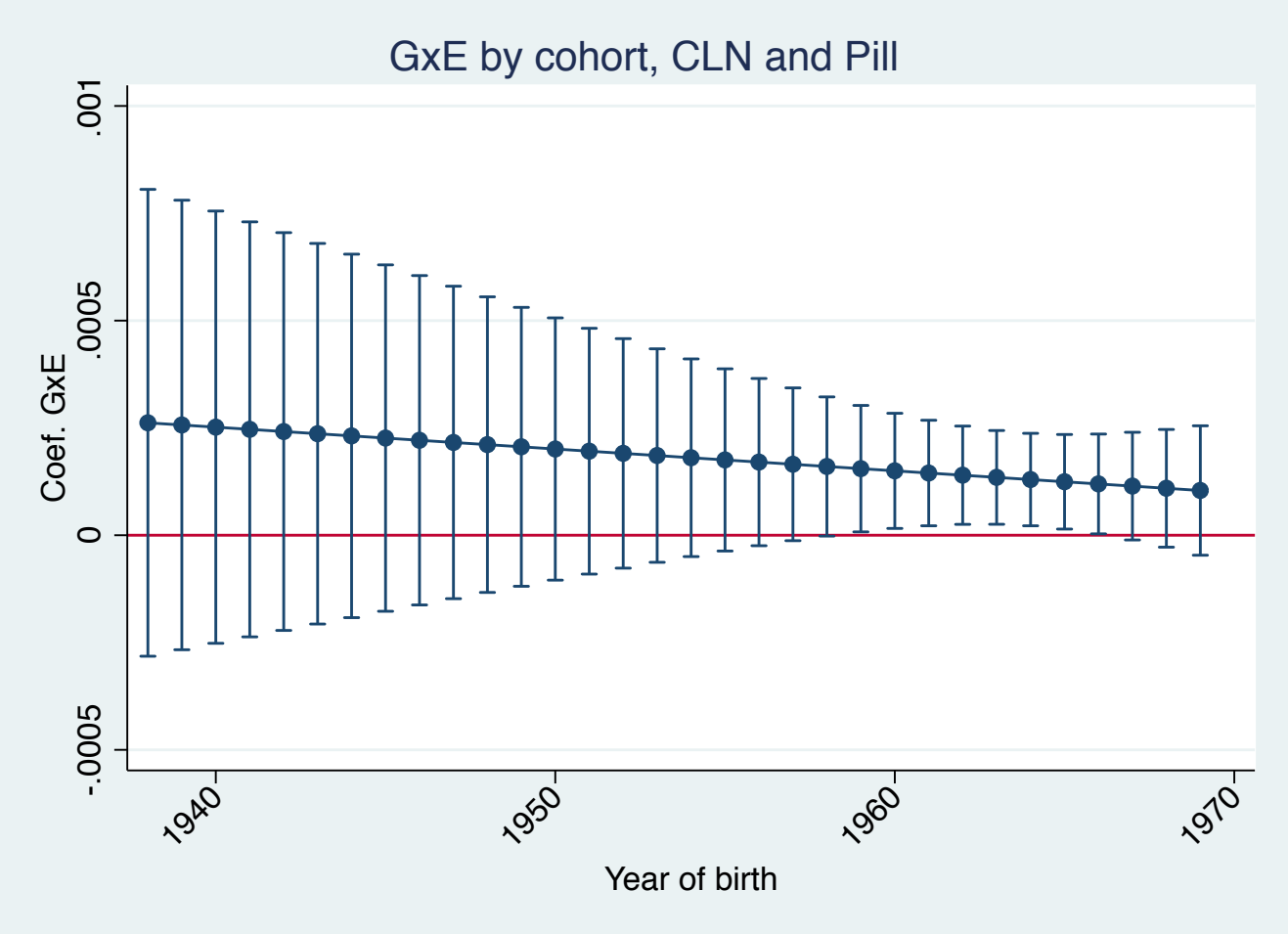
Teenage Fertility



Note: Recall, E (high pill diffusion) reduces TF and $G \times E$ attenuates this reduction. This attenuation holds true across **all** birth cohorts (albeit not significant).

$G \times E$ by Cohort (9)

Childlessness



Note: Recall, E (high pill diffusion) increases CLN and $G \times E$ reinforces this increase. This holds true across **all** birth cohorts (albeit not significant).

Summary of $G \times E$ by Cohort Results

1. The **reinforcement** of the impact of E that $G \times E$ has on **A1B**, **CF**, and **CLN** is
   - ⋆ the same across all cohorts

2. The **reinforcement** of the impact of E that $G \times E$ has on **A1S**
   - ⋆ emerges only for the most recent cohorts (those born after 1960), when social norms about sexual initiation are likely to be more liberal,
   - ⋆ while the impact is **attenuated** for earlier cohorts (i.e., $G \times E$ attenuates the impact of E). Keep in mind there is no (variation in) pill exposure among such cohorts.

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Genetic influences on fertility may be more important when social norms and economic conditions allow a broad range of life-course alternatives (Kohler et al. 1999):

- ⋆ Consistent with Becker (1981): fertility-relevant aspects of the utility function are subject to genetic influences (childbearing motivation);
- ⋆ relevant also to the literature on the evolution of preferences, e.g., Robson and Samuelson (2011)

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3. but also they **interact with the environment** ($G \times E$) in a meaningful way (reinforcing or attenuating its impact on outcomes), which helps us understand the secular changes in fertility
4. So what? This is the first piece in this area for economists: we need to deepen our understanding of the impacts of G, E, and $G \times E$. This could then be embedded in **new** economic models of human fertility

The End

THANK YOU

Appendix: Genetic Background (1)

Human genome

- 3 billion genetic addresses
- In each address we observe a base nucleotide-pair:
  - ⋆ Adenine-thymine pair (A or T)
  - ⋆ Guanine-cytosine pair (G or C)
- The nucleotide-pair is fixed in 99% of such addresses

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- The nucleotide-pair is fixed in 99% of such addresses

SNPs

- → The remaining 1% are called single-nucleotide polymorphisms (SNPs)
- → People are typically interested in the association between variation in SNPs and observable outcomes
- → Genotyping measures between 0.5 and 2.5 million SNPs

Appendix: Genetic Background (2)

- Traditional (*pre*-genotyping) approach was to examine candidate genes
  - ⋆ selected from prior knowledge/research
- Unfortunately the candidate genes approach suffers from a severe replication problems
  - → weak effects combined with small sample sizes
  - → studies are underpowered and results prone to the 'winner's curse'
- Editorial Statement at *Behavior Genetics*:
  - ⋆ "Many of the published findings of the last decade are wrong or misleading and have not contributed to real advances in knowledge" (Hewitt,2012)

Appendix: Genetic Background (3)

Alternative to candidate gene approach is the genome-wide association study (**GWAS**)

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Alternative to candidate gene approach is the genome-wide association study (**GWAS**)

- scans entire genome for SNPs associated with a particular phenotype
- controls for multiple hypothesis testing
- derives polygenic scores (PGSs): a weighted average of many SNPs

Appendix: Genetic Background (3)

Alternative to candidate gene approach is the genome-wide association study (**GWAS**)

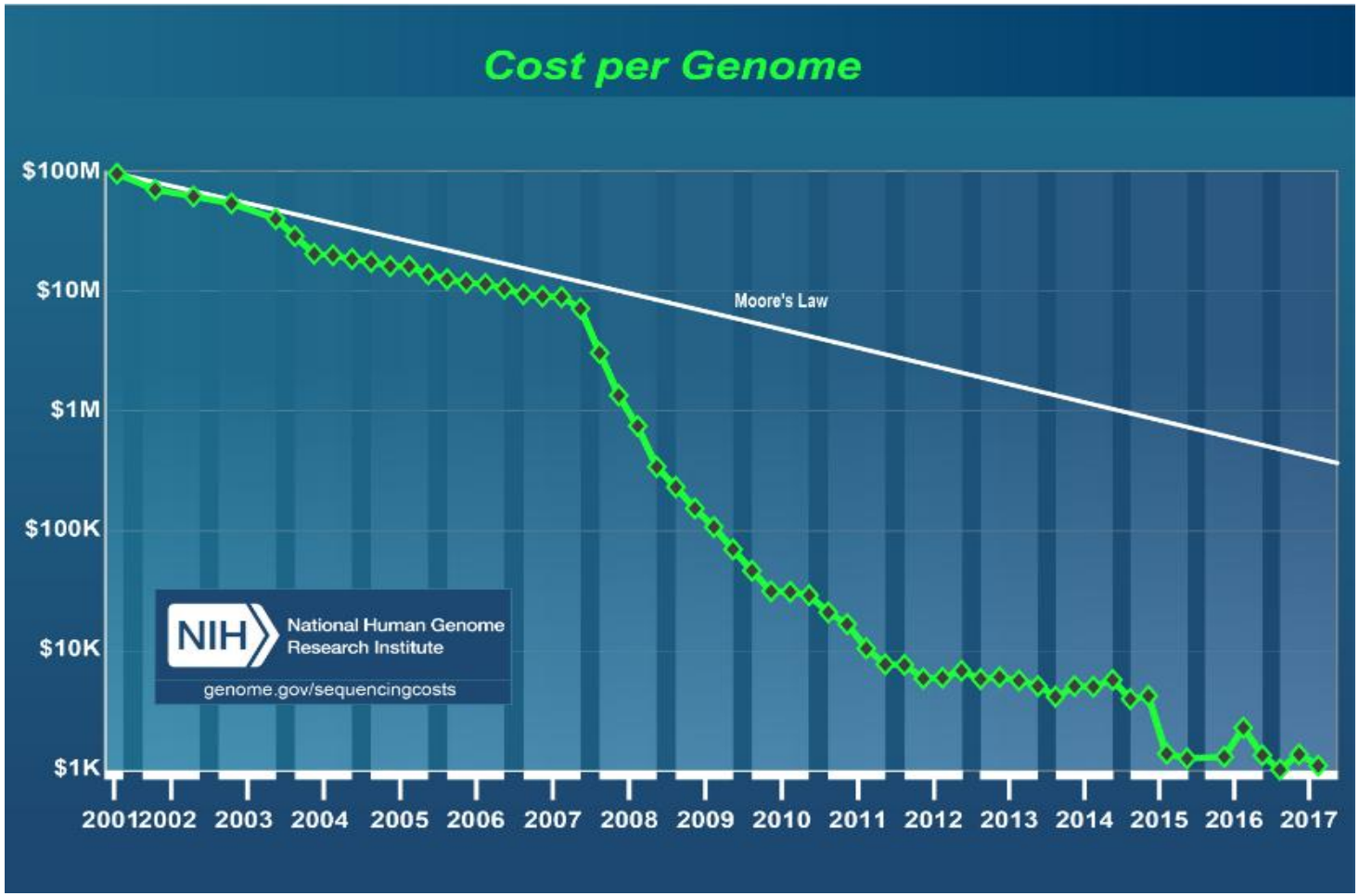
- → scans entire genome for SNPs associated with a particular phenotype
- → controls for multiple hypothesis testing
- → derives polygenic scores (PGSs): a weighted average of many SNPs

GWAS is now possible (and appealing) due to

- ⋆ exponentially decreasing costs of genotyping
- ⋆ large sample sizes (100 thousand - 1 million +)

Appendix: Genetic Background (4)

Sequencing Costs Over Time



Appendix: Genetic Background (5)

Polygenic (Risk) Scores

Advantages of using PGSs:

- high explanatory power
- out of sample reliability

Appendix: Genetic Background (5)

Polygenic (Risk) Scores

Advantages of using PGSs:

- high explanatory power
- out of sample reliability

Disadvantages of using PGSs:

- ⋆ hard to understand mechanisms (what is being captured?)
- ⋆ hard to use as IVs or structural parameters (many moving parts)
- ⋆ may be problematic for some analysis (e.g., $G \times E$) if different loci have different interaction signs

Appendix: Genetic Background (6)

Polygenic (Risk) Scores

Formally, for a particular outcome of interest (y_i) and observed set of SNPs ($\{\text{SNP}_{ij}\}_{j=1}^{N}$), a GWAS estimates N regressions of the form:

$$y_i = X_i'\gamma + B_j\text{SNP}_{ij} + \epsilon_{ij},$$

where X_i is a vector of observable controls (e.g., sex, age, and the first several principal components of the genetic data) and ϵ_{ij} are i.i.d. shocks

Appendix: Genetic Background (6)

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Polygenic scores (PGS) are constructed using transformed coefficients ($\widetilde{B}_j$) that account for correlation across SNPs:

$$\text{PGS}_i^y = \sum_j \widetilde{B}_j\text{SNP}_{ij}$$

Appendix: Genetic Background (7)

Over-fitting

To avoid over-fitting, it is important that the sample used for estimating the weights $\widetilde{B}_j$ does not include individuals from the prediction sample

Appendix: Genetic Background (8)

Linkage Disequilibrium

Linkage disequilibrium structure (i.e., the correlation structure) of the genotypic data

- There might be a non-random association of alleles at different loci in any given population

Appendix: Genetic Background (8)

Linkage Disequilibrium

Linkage disequilibrium structure (i.e., the correlation structure) of the genotypic data

- There might be a non-random association of alleles at different loci in any given population

Linkage disequilibrium might be driven by:

- Selection
- Genetic drift - change in allele frequency across generations
- Genetic linkage - close markers are more likely to be inherited together
- Population stratification - differences in ancestry
- Assortative mating

Appendix: Genetic Background (9)

Genotype Imputation

- Genotype imputation is the process of predicting genotypes that are not directly assayed in a sample of individuals
- A reference panel of haplotypes at a dense set of SNPs is used to impute genotypes into a study sample of individuals that have been genotyped at a subset of the SNPs
- Genotype imputation is used to boost the number of SNPs that can be tested for association

