Polygenic Scores

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Outline

1. ***SNP Heritability***
2. Polygenic Scores
3. Predictive Power of Polygenic Scores
4. Constructing Polygenic Scores
5. Potential Uses and Limitations
6. Applications

Consider the additive model (ignoring confounds for simplicity):

$$\tilde{y}_i = A(\boldsymbol{x}_i) + \epsilon_i = \sum_{j=1}^{J} \beta_j x_{ij} + \epsilon_i.$$

Narrow heritability: $h_A^2 \equiv \frac{\text{Var}\left(A(\boldsymbol{x}_i)\right)}{\text{Var}(\tilde{y}_i)}$.

In genome-wide data, we only measure $K \ll J$ genetic variants, all SNPs.

Without loss of generality, index these as variants $j = 1,2, \ldots, K$.

Define:

$$A_{\text{SNP}}(\boldsymbol{x}_i) \equiv \sum_{j=1}^{K} b_j x_{ij} \,,$$

where $A_{\text{SNP}}(\boldsymbol{x}_i)$ is the best linear predictor using just the first *K* SNPs.

We can thus re-express the model:

$$\tilde{y}_i = A_{\text{SNP}}(\boldsymbol{x}_i) + \epsilon_{\text{SNP},i} = \sum_{j=1}^{K} b_j x_{ij} + \epsilon_{\text{SNP},i}.$$

SNP heritability : $h^2_{\text{SNP}} \equiv \dfrac{\text{Var}\left(A_{SNP}(\boldsymbol{x}_i)\right)}{\text{Var}(\tilde{y}_i)}$.

By definition, $h^2_{\text{SNP}} \leq h^2_A$.

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SNP heritability can be estimated from individual-level genome-wide data or with GWAS summary statistics.

It is an upper bound on the total predictive power of the SNPs identified by GWAS.

It is a lower bound on narrow heritability.

In the limit of sequencing data—with every genetic variant measured—SNP heritability will converge to narrow heritability.

Estimating SNP Heritability

Two main types of methods:

1. Molecular-level data
   - E.g., GREML (Yang et al., 2010), LDAK (Speed et al. 2010)
2. Summary-statistic-level data
   - E.g., Linkage-disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015), SumHer (Speed and Balding 2019)

Some shared assumptions, some distinct.

Some Estimated SNP Heritabilities
(in European-descent populations)

Phenotype	Paper	GWAS *N*	h^2_{SNP}
Height	Wood et al. (2014)	253,288	50%
BMI	Locke et al. (2015)	339,224	21%
EA	Rietveld et al. (2013)	101,069	22%
EA	Okbay et al. (2016a)	394,769	22%
SWB	Okbay et al. (2016b)	298,420	9%*
Age at first birth	Barban et al. (2016)	238,064	15%

* From Rietveld et al. (2013, *PNAS*).

SNP vs. Narrow Heritability

Estimates of h^2_{SNP} tends to be one-half to one-third as large as estimates of h^2_A. Why?

- h^2_{SNP} does not include the effects of all SNPs.
  - In particular, it misses the effects of rare variants (those with MAF < 0.01), which are not well tagged by SNPs measured in genome-wide data.
- h^2_A may be overestimated.
  - As we've seen, estimates of h^2_A from twin studies are biased upward.
  - This is a result of model misspecification by assuming away non-additive effects
- On the other hand, h^2_{SNP} may be biased upward
  - Assortative mating and indirect parental effects

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2. **Polygenic Scores**
3. Predictive Power of Polygenic Scores
4. Constructing Polygenic Scores
5. Potential Uses and Limitations
6. Applications

Start with additive model using measured SNPs:

$$\tilde{y}_i = A_{\text{SNP},i}(\boldsymbol{x}_i) + \epsilon_{i,\text{SNP}} = \sum_{j=1}^{K} b_j x_{ij} + \epsilon_{i,\text{SNP}}.$$

True polygenic score : $A_{\text{SNP},i} \equiv \sum_{j=1}^{K} x_{ij} b_j$.

Variance explained by the true polygenic score is the SNP heritability, h^2_{SNP}.

Polygenic score (PGS) : Linear predictor of y_i using *estimated* coefficients (Meuwissen et al., 2001; Purcell et al., 2009):

$$\hat{A}_{\text{SNP},i} \equiv \sum_{j=1}^{K} x_{ij} \hat{b}_j \, .$$

PGS = True PGS + error

If $\widehat{\boldsymbol{b}}$ is an unbiased estimate of $\boldsymbol{b}$, then $\widehat{\boldsymbol{b}} = \boldsymbol{b} + \boldsymbol{u}$, where $\boldsymbol{u}$ is mean-zero estimation error uncorrelated with $\boldsymbol{\beta}$.

$$\hat{A}_{SNP,i} = \sum_{j=1}^{K} x_{ij}\hat{b}_j = \sum_{j=1}^{K} x_{ij}\left(b_j + u_j\right) = A_{SNP,i} + U_i,$$

where $U_i \equiv \sum_{j=1}^{K} x_{ij}u_j$ is mean-zero measurement error.

Therefore,

$$E\left(\hat{A}_i \middle| A_i\right) = A_i.$$

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Predictive Power of the PGS

If we regress $\tilde{y}_i$ on $\hat{A}_{SNP,i}$, we get an OLS coefficient of

$$\alpha = \frac{Cov\left(\hat{A}_{SNP,i}, \tilde{y}_i\right)}{Var\left(\hat{A}_{SNP,i}\right)}$$

$$= \frac{Cov\left(A_{SNP,i} + U_i, A_{SNP,i} + \epsilon_{i,\mathrm{SNP}}\right)}{Var\left(A_{SNP,i} + U_i\right)}$$

$$= \frac{Var\left(A_{SNP,i}\right)}{Var\left(A_{SNP,i}\right) + Var(U_i)}$$

Predictive Power of the PGS

And predictive power is

$$E(R^2) = \frac{a^2 Var\left(\hat{A}_{SNP,i}\right)}{\mathrm{Var}(\tilde{y}_i)}$$

$$= \frac{Var\left(A_{SNP,i}\right)^2 / \mathrm{Var}(\tilde{y}_i)}{Var\left(A_{SNP,i}\right) + Var(U_i)}$$

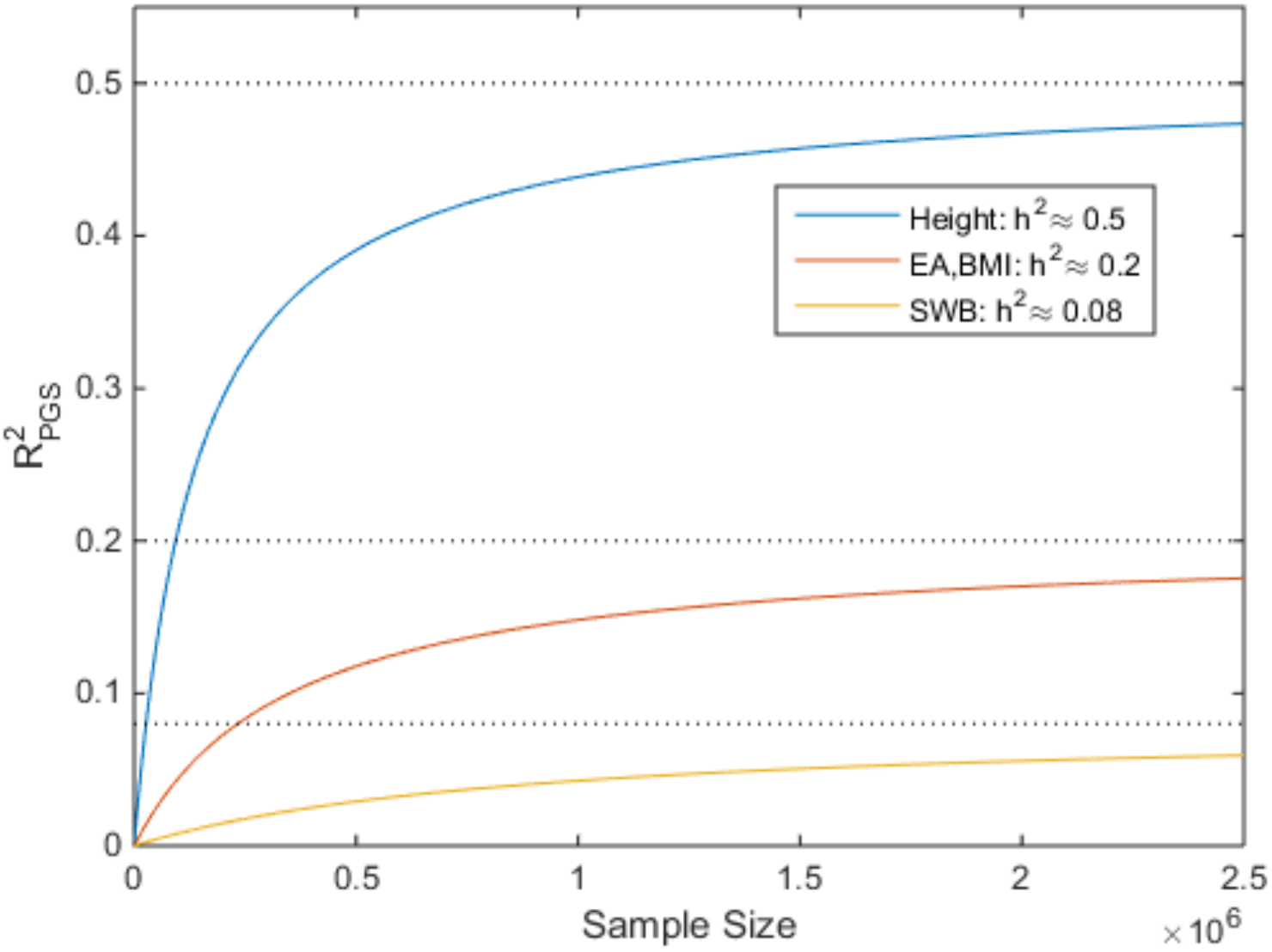
$$= \frac{\left[Var\left(A_{SNP,i}\right)/\mathrm{Var}(\tilde{y}_i)\right]^2}{Var\left(A_{SNP,i}\right)/\mathrm{Var}(\tilde{y}_i) + Var(U_i)/\mathrm{Var}(\tilde{y}_i)}$$

$$= \frac{(h^2_{SNP})^2}{h^2_{SNP} + M_e/N}$$

This is sometimes called the Daetwyler formula (Daetwyler et al. 2008)

- M_e is the effective number of SNPs in the PGS
- M_e is between 50k-70k in genome-wide data (Wray et al. 2013)

Theoretical Projection for R^2_{PGS}



Predictive Power and Heterogeneity

What if we are predicting into a cohort where the genetic architecture isn't the same? (Mostafavi et al. 2019)

Let $A^{\star}_{SNP,i}$ be the additive genetic factor for phenotype $\tilde{y}^{\star}_{i}$ in the prediction cohort

- So $A^{\star}_{SNP,i} \neq A_{SNP,i} \rightarrow h^{2\star}_{SNP} \equiv Var\left(A^{\star}_{SNP,i}\right)/Var(\tilde{y}^{\star}_{i}) \neq h^{2}_{SNP}$
- Define the genetic correlation to be $\mathrm{r_g} \equiv Corr\left(A^{\star}_{SNP,i}, A_{SNP,i}\right)$

In this setting, we have

$$E(R^2) = \frac{r_g^2 h^2_{SNP} h^{2\star}_{SNP}}{h^2_{SNP} + M_e/N}$$

(De Vlaming et al. 2016)

Note that this formula will hold even if $\tilde{y}^{\star}_{i}$ is a different phenotype

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Measurement Error Correction for Effect of PGS

- Typical application runs a regression of some outcome w_i on the PGS $\hat{A}_{\text{SNP},i}$.
- Effect sizes normally reported in units of SD of the PGS.
  - But interpretation of these units isn't always clear.
  - Scaling of the PGS puts true PGS on wrong scale
  - Attenuation bias varies by GWAS for PGS→PGSs not comparable
- More meaningful to report effect sizes from regression of w_i on the *true* PGS $A_{\text{SNP},i}$.
  - Can adjust estimates to obtain this quantity

Measurement Error Correction for Effect of PGS

- Recall that

$$E(R^2) = \frac{r_g h_{SNP}^2 h_{SNP}^{2\star}}{h_{SNP}^2 + M_e/N}$$

- The term, M_e/N, is the term that is a result of measurement error which leads to attenuation bias
- If we know h_{SNP}^2, M_e, and N, we can get the value of R^2 without attenuation by multiplying by

$$\frac{h_{SNP}^2 + M_e/N}{h_{SNP}^2}$$

- Similar principles can be used to correct beta estimates in simple and multi-variate regressions

- Major advantage of PGS over specific genetic variants: can have much greater predictive power, especially if J is large.

Some R^2_{PGS} from Published GWAS
(in European-descent populations)

Phenotype	Paper	GWAS *N*	h^2_{SNP}	R^2_{PGS}
Height	Wood et al. (2014)	253,288	50%	14%
BMI	Locke et al. (2015)	339,224	21%	7%
EA	Rietveld et al. (2013)	101,069	22%	2%
EA	Okbay et al. (2016a)	394,769	22%	7%
SWB	Okbay et al. (2016b)	298,420	9%*	1%
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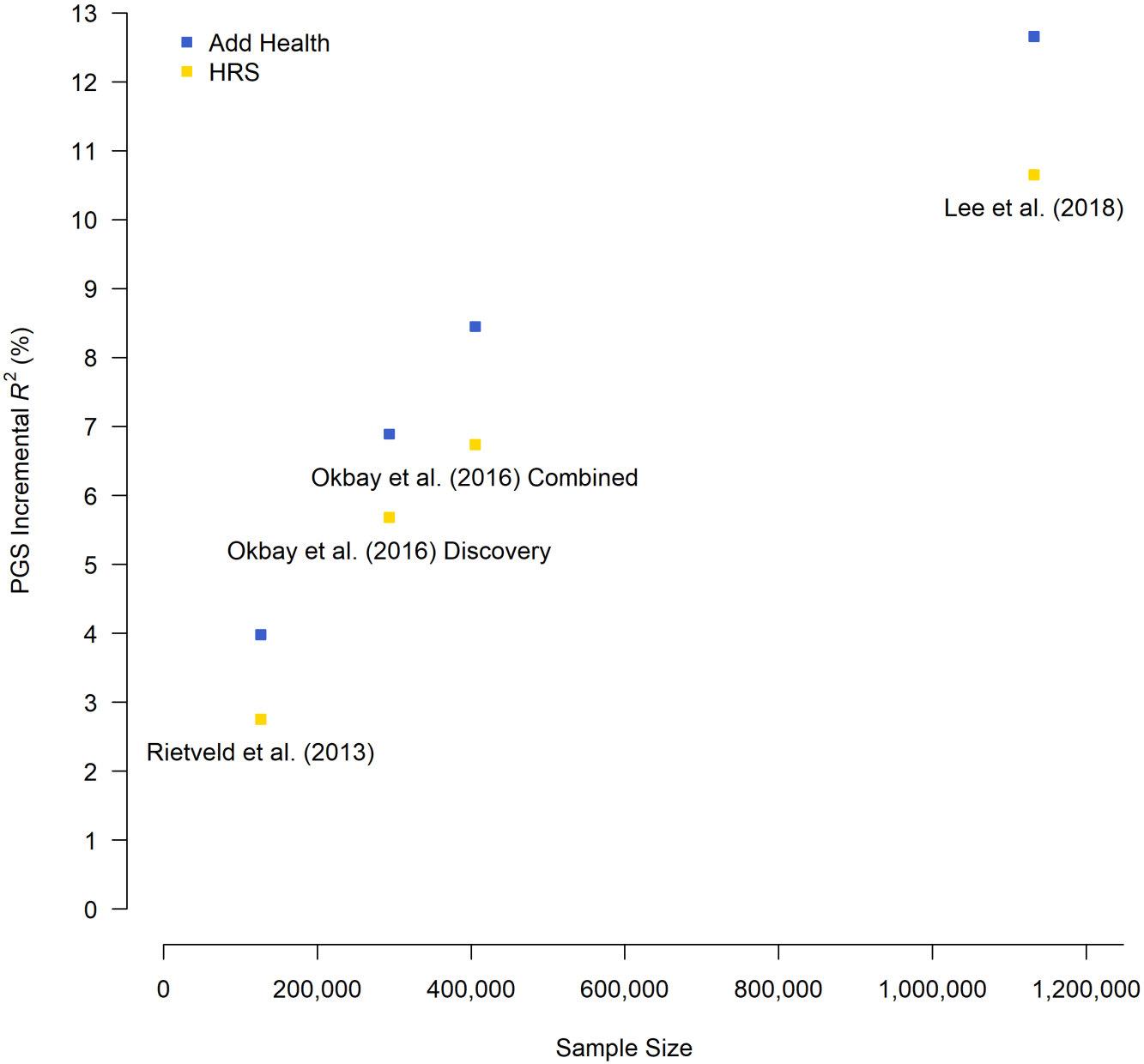

Source: Lee et al. (2018).

- Major advantage of PGS over specific genetic variants: can have much greater predictive power, especially if J is large.

- Can estimate $\{\hat{b}_j\}$ in large-*N* GWAS, but then construct PGS in other samples that have measured the J genetic variants.
  - Can be well-powered to study PGS in much smaller samples.
    - E.g., if $R^2_{\text{PGS}} = 0.07$, then 80% to detect its effect in a sample of size ~110 individuals. If $R^2_{\text{PGS}} = 0.09$, then ~85 individuals.
  - Can study PGS in datasets containing high quality measures of outcomes, mediators, and covariates.

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Constructing PGSs

Problem: GWAS results give us $\hat{b}_j^{GWAS}$, not $\hat{b}_j$.

Why is this a problem?

If we construct $\sum_{j=1}^{K} x_{ij} \hat{b}_j^{GWAS}$, we will overweight ("double count") SNPs with high LD scores.

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Three solutions:

1. Pruning: Include only a single SNP from each LD block, the most strongly associated SNP. (Purcell et al., 2009)
   - Reduces R^2_{PGS} because it makes K smaller.
2. Conditional-joint analysis (COJO): Infer $\hat{b}_j$'s from $\hat{b}_j^{GWAS}$'s and LD estimates from a reference panel. (Yang et al., 2012)
   - Key idea: For LD matrix $\boldsymbol{D}$, $\widehat{\boldsymbol{b}}^{GWAS} = \boldsymbol{D}\widehat{\boldsymbol{b}}$. Hence we can calculate $\widehat{\boldsymbol{b}} = \boldsymbol{D}^{-1}\widehat{\boldsymbol{b}}^{GWAS}$.
3. Bayesian approaches accounting for LD
   - LDpred (Vilhjálmsson 2015) or PRS-CS (Ge et al. 2019)

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Bayesian/Shrinkage Approaches

Uses as weights

$$E\left(\boldsymbol{b} \mid \widehat{\boldsymbol{b}}^{GWAS}, \boldsymbol{D}\right)$$

By Bayes' Rule

$$f\left(\boldsymbol{b} \mid \widehat{\boldsymbol{b}}^{GWAS}, \boldsymbol{D}\right) = \frac{f\left(\widehat{\boldsymbol{b}}^{GWAS} \mid \boldsymbol{b}, \boldsymbol{D}\right) f\left(\boldsymbol{b} \mid \boldsymbol{D}\right)}{f\left(\widehat{\boldsymbol{b}}^{GWAS} \mid \boldsymbol{D}\right)}$$

Shrinkage depends on the prior.

Bayesian/Shrinkage Approaches

Potential prior distributions

1. LDpred: Gaussian or Spike-and-Slab

$$\left(b_j \mid \boldsymbol{D}\right) = b_j \sim \begin{cases} 0 & \text{with probability } \pi \\ N(0, \tau^2) & \text{with probability } 1-\pi \end{cases}$$

2. PRS-CS: "Continuous shrinkage"

$$\left(b_j \mid \boldsymbol{D}\right) = b_j \sim N\left(0, \phi\psi_j\right)$$
$$\psi_j \sim \text{Gamma}\left(a, \delta_j\right)$$
$$\delta_j \sim \text{Gamma}(b, 1)$$

   - Parameters a and b determine how aggressively to shrink small estimates and how much you don't shrink large ones
   - Complicated prior, but much simpler computationally

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Some Uses of PGSs

- Identify correlates of genetic factors
  - Educational attainment PGS predicts early speech acquisition and is mediated by cognitive ability (Belsky et al., 2016).
  - Educational attainment PGS predicts school achievement (e.g., Ward et al., 2014) and the quality of mid-life financial decision making (Barth, Papageorge, and Thom, 2016).
  - Educational attainment PGS substitutes for SES in preventing high school dropout, but complements SES in facilitating college attendance (Papageorge and Thom, 2016).
  - Twin studies could address these questions, but PGSs enable addressing them in other samples and with different assumptions.
- Identify causal effects of genetic factors
  - PGS is randomly assigned conditional on parents.
  - Sibling data and family fixed effects → causal effect of PGS.

- Study treatment effect heterogeneity by genotype
  - Increase of compulsory schooling age in U.K. reduces BMI only among those with a high-BMI PGS (Barcellos, Carvalho, and Turley 2016).
  - Swedish comprehensive schooling reform increased completion of compulsory schooling among those with low-EA PGS, and completion of higher degrees among those with high-EA PGS (Beauchamp, Okbay, Oskarsson, and Thom, 2016).
- Use as control variable
  - To control for confounding genetic factors.
  - To increase statistical power for estimating the effect of a randomized treatment.
    - Rietveld et al. (2013) calculate: if incremental R^2_{PGS} is 15%, then power increase is equivalent to 17% increase in sample size.
    - Especially useful when treatment is expensive (e.g., providing free preschool).
  - As long as genetic variants are measured, could construct and control for many PGSs.
- Use for balance tests of randomization
  - PGSs should be identically distributed in treatment and control groups (Davies et al. 2016, Barcellos, Carvalho, and Turley 2016).
- Identify at-risk individuals
  - Still speculative, but especially useful at young ages before accurate testing is possible (e.g., dyslexia).

Limitation #1

- *Mechanisms* affecting behavior are poorly understood.
  - Hard to specify what is captured by PGS.
  - Use as structural parameter or IV is difficult to justify.
- Often a tradeoff: Including many genetic variants…
  - Increases predictive power.
  - But requires including many genetic variants with unknown function.
- Will learn more as PGSs are studied.
- Potential for functionally-partitioned PGS in future.

Limitation #2

- Current polygenic scores far less predictive in non-European-descent samples.
- For example, for the EA2 score in HRS:
  - $R^2 \approx 7\%$ for European-ancestry individuals.
  - $R^2 \approx 1\%$ for African-ancestry individuals.
  - $R^2 \approx 1\%$ for self-classified Hispanics.
- Optimal $\hat{\beta}_j$'s may differ for many reasons, including:
  - Different true β_j's.
  - Different correlations between measured x_{ij}'s and unmeasured x_{ik}'s that are proxied for.
- With larger non-European samples or improved methods, will be able to estimate appropriate $\hat{\beta}_j$'s.

Limitation #3

- Communication is difficult
  - All the critiques of interpreting heritability correspond to polygenic scores
  - What does it mean for a person to have a high polygenic score?
- Even the word “score” may carry value judgments to lay-people
  - If I have a “higher score,” does that make me a better person?

Limitation #4

- Two sources of population stratification
- In the discovery phase
  - Leads to bias in the GWAS estimates, so the polygenic score may give more weight to SNPs that just correspond to ancestry
- In the prediction phase
  - If the prediction sample is stratified, this can lead to bias in our PGS-based analyses even if SNP-weights are unbiased
- Interaction of bias in both phases
  - The combination of these two interact so group differences are strongly exaggerated

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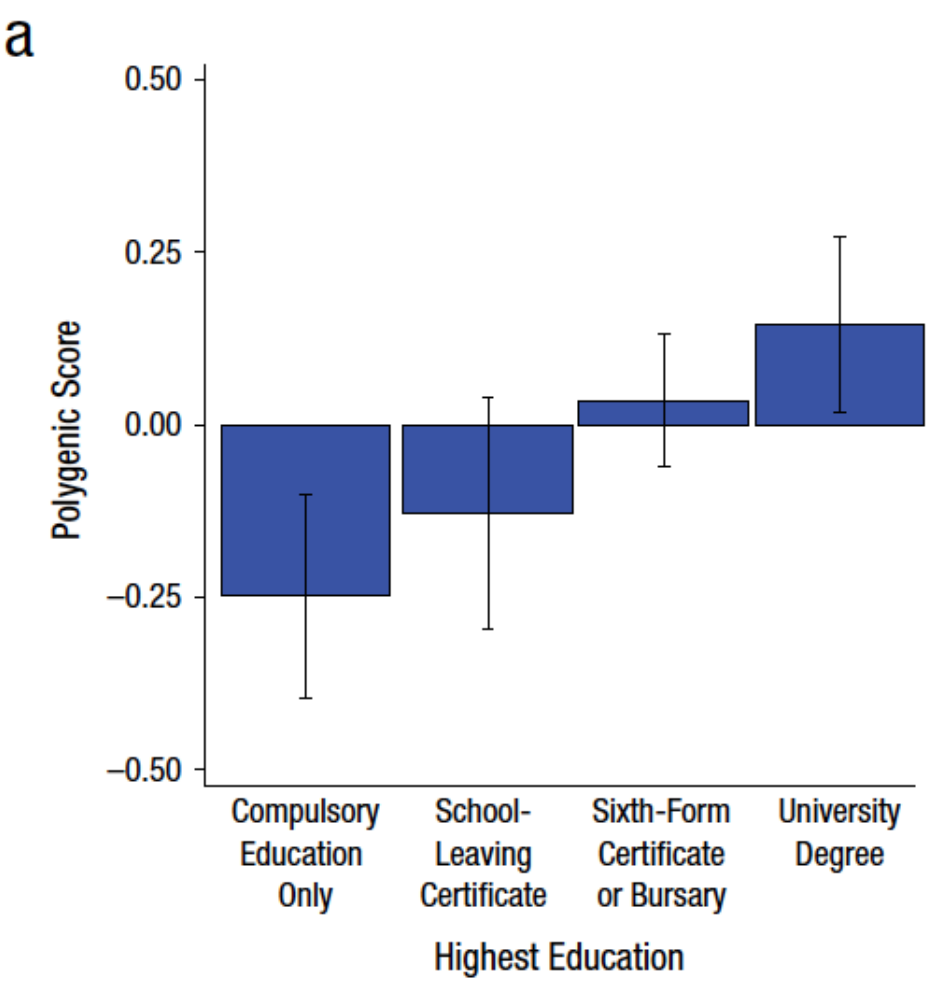
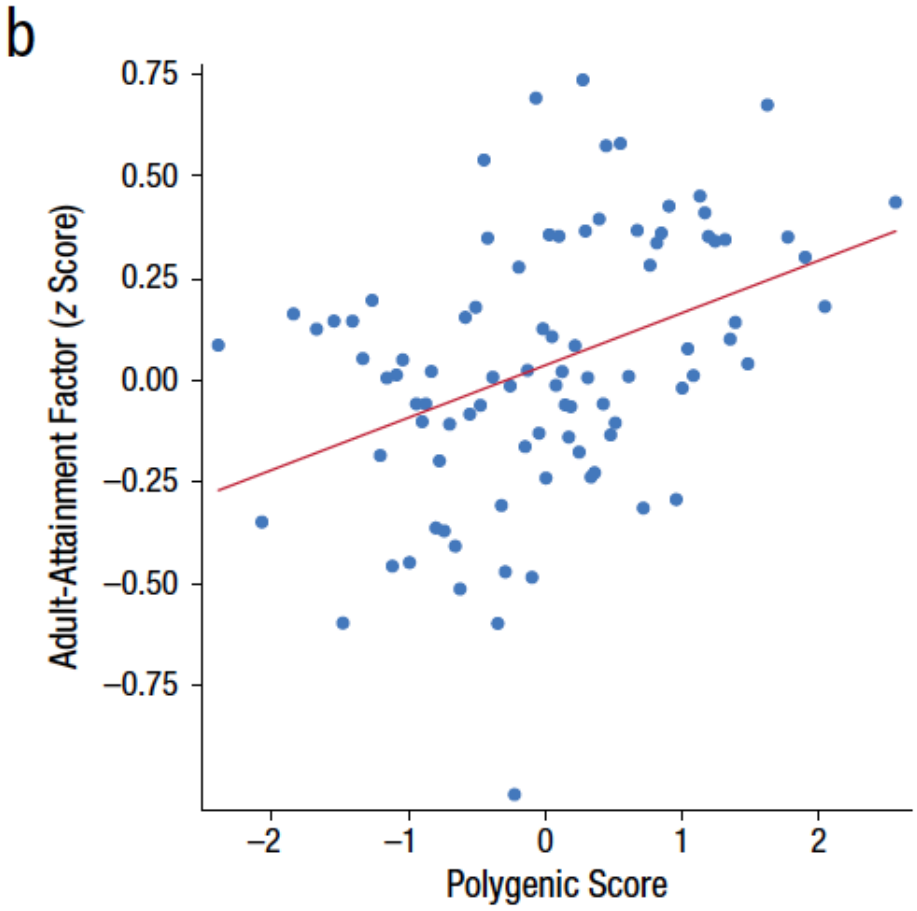
Example: Belsky et al. (2016)

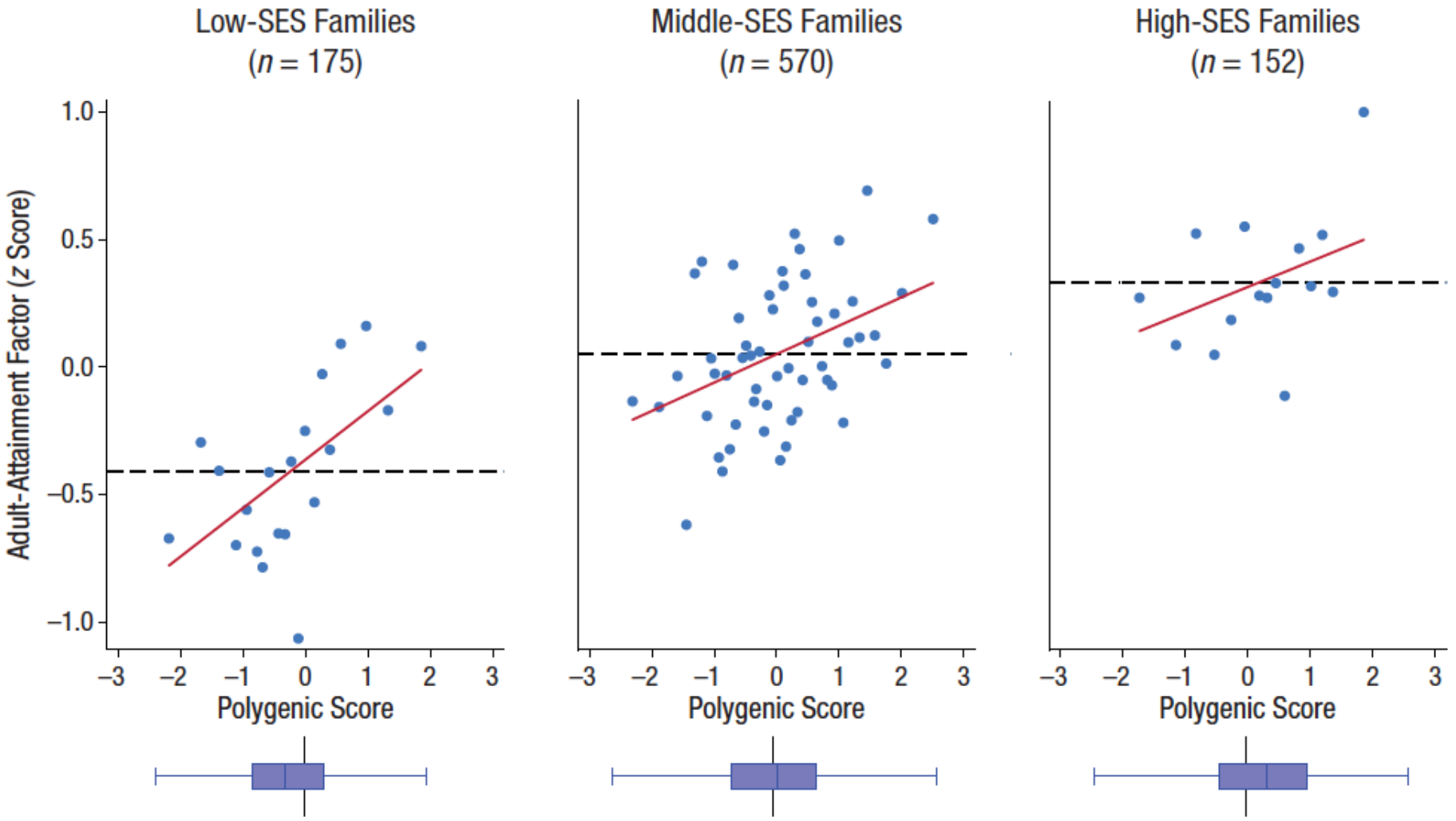
- How does the additive genetic component of EA relate to life-course development?
- Used longitudinal Dunedin Study (*N* ≈ 1,000).
  - Born 1972-1973 in Dunedin, New Zealand.
  - Rich data from ages 3 through 38.
- Constructed PGS for EA based on EA1 (Rietveld et al, 2013), $R^2_{\text{PGS}} \approx 2.3\%$.
- "Adult attainment factor": Constructed from factor analysis of occupation, income, wealth, financial situation, and credit score.

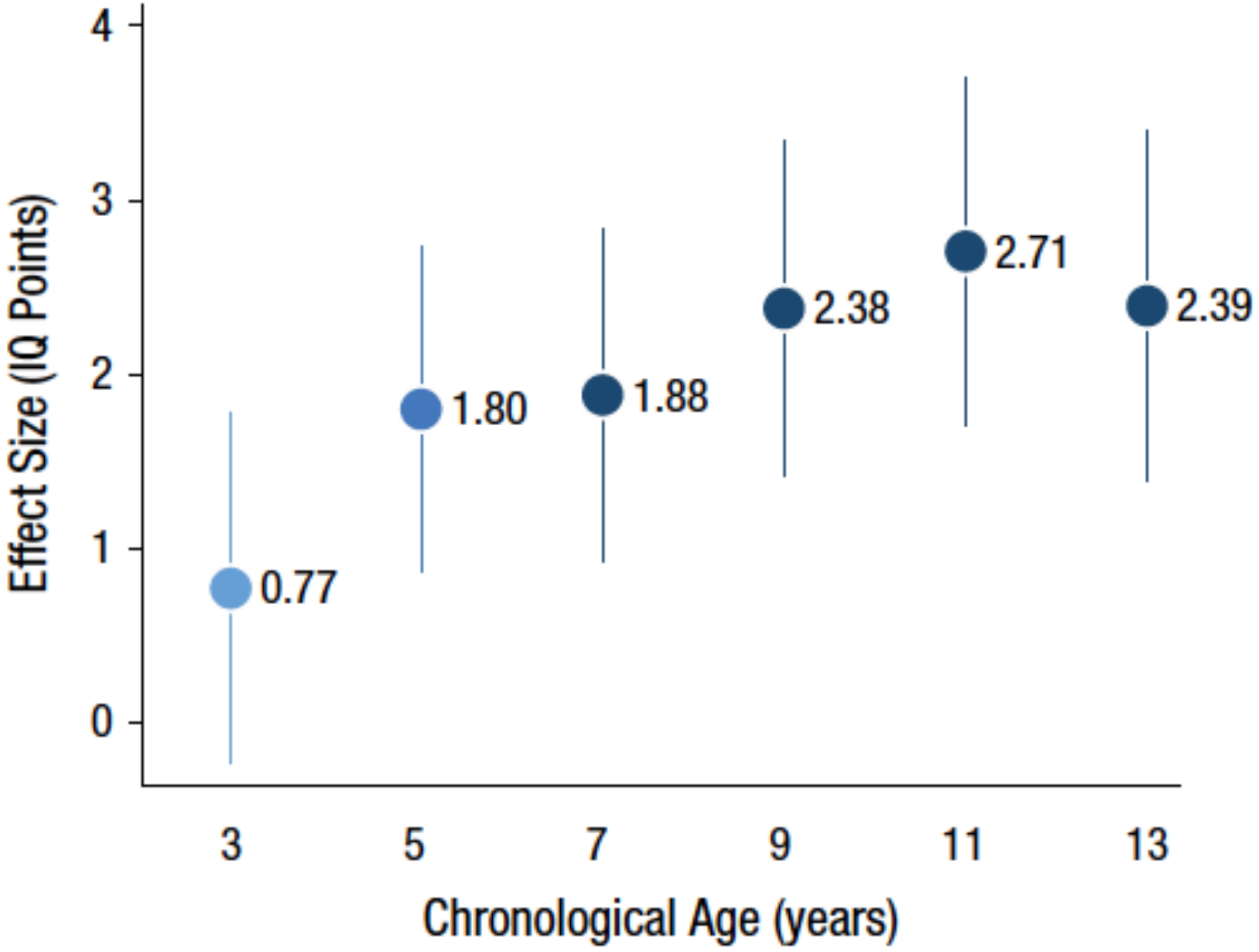


$r = 0.15$ ($p < 0.001$)



$r = 0.13$ ($p < 0.001$)
Controlling for EA: $r = 0.07$ ($p = 0.035$)


Low-SES Families
(n = 175)
Middle-SES Families
(n = 570)
High-SES Families
(n = 152)
Adult-Attainment Factor (z Score)
1.0
0.5
0.0
−0.5
−1.0
−3
−2
−1
0
1
2
3
Polygenic Score



Note: Effect of 1 SD increase in PGS.

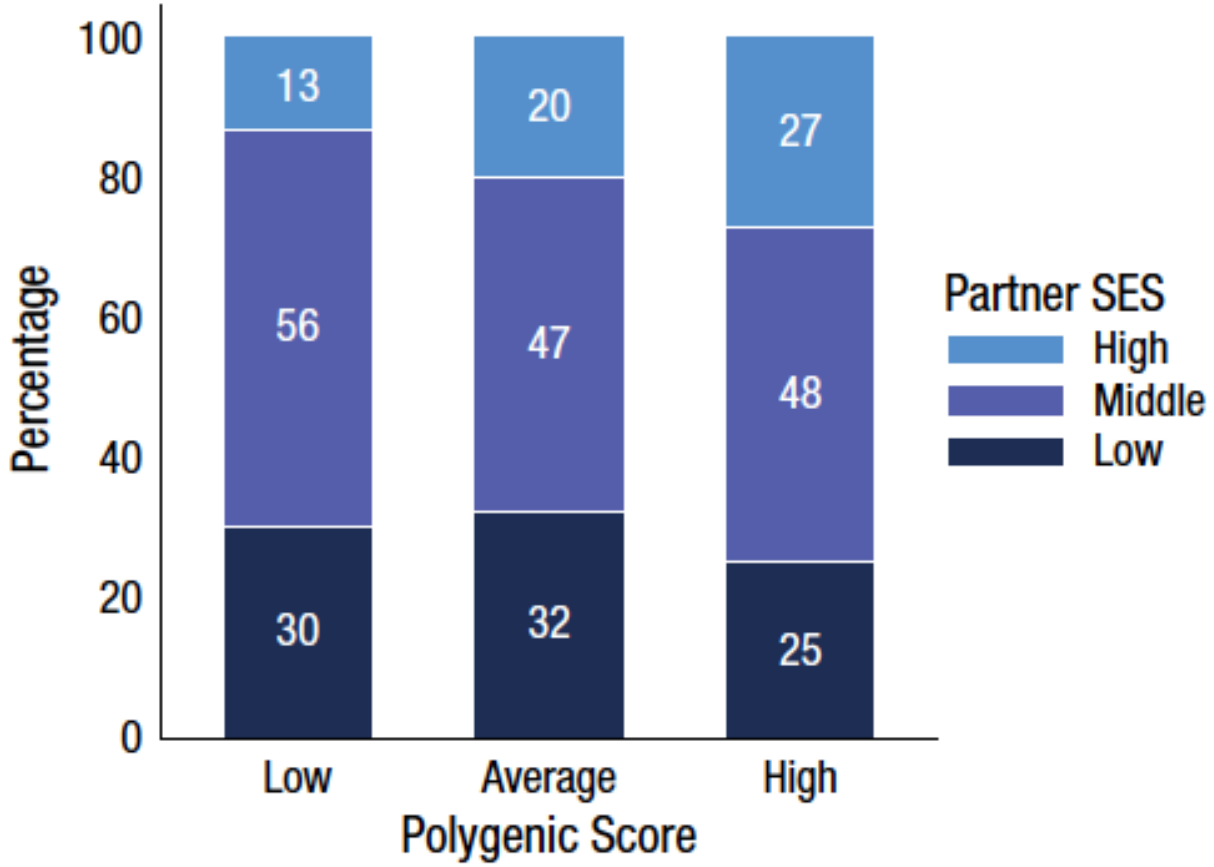


Fig. 5. Association between polygenic score and partner's socioeconomic status (SES). The graph shows the percentages (inside bars) of members who had low-, middle-, and high-SES partners, separately for Dunedin Study members with low polygenic scores (≥ 1 *SD* below the mean; $n = 119$), average polygenic scores (within 1 *SD* of the mean; $n = 504$), and high polygenic scores (≥ 1 *SD* above the mean; $n = 136$). Partners' SES was defined according to whether they had completed a university degree and whether their income was above the national sex-specific median: High-SES partners had a university education and an above-median income, middle-SES partners met only one of these criteria, and low-SES partners met neither criterion.