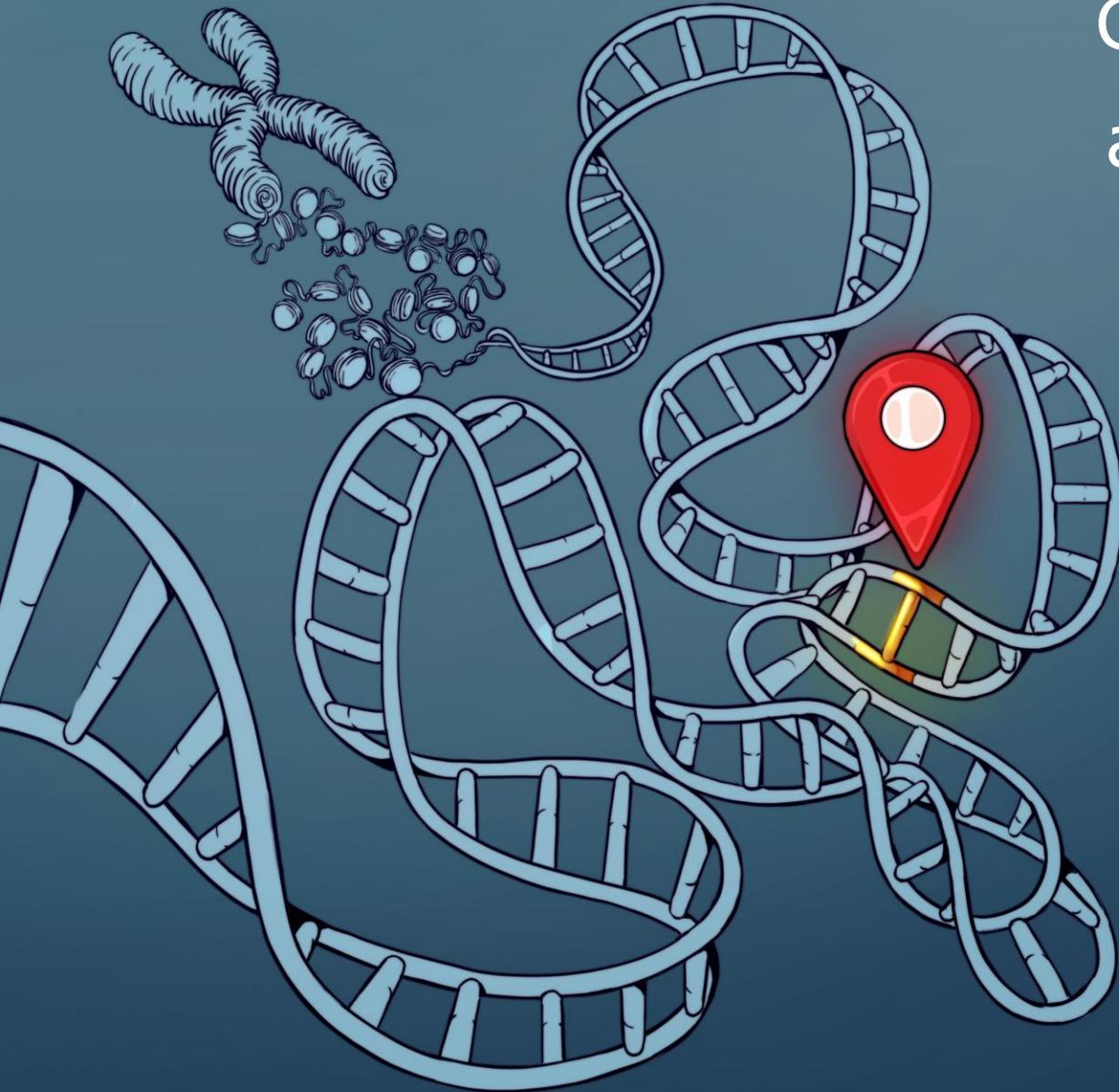


Gene-environment correlations across families and geographic regions affect GWASs

Abdel Abdellaoui

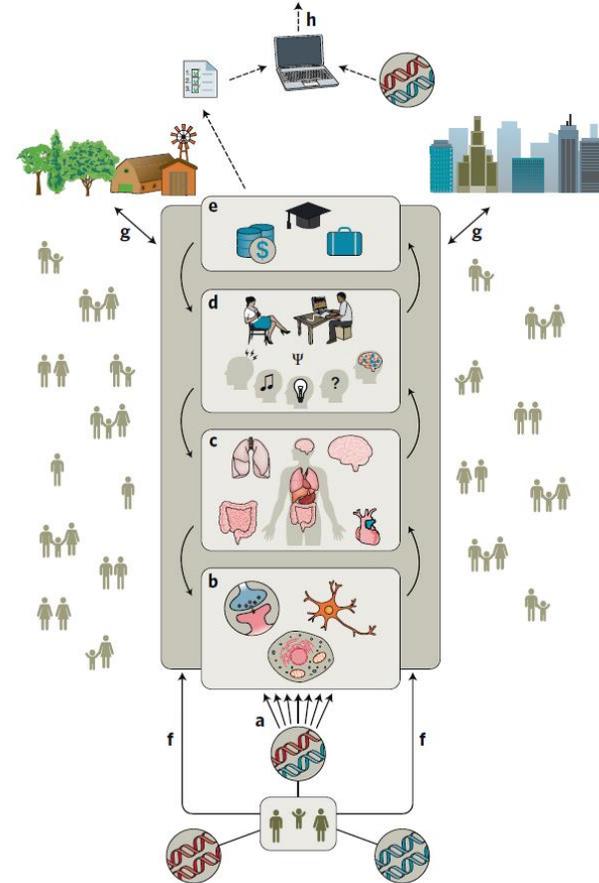
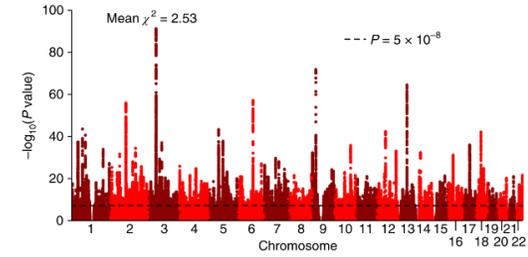


 *dr_appie*

a.abdellaoui@amsterdamumc.nl

Key points

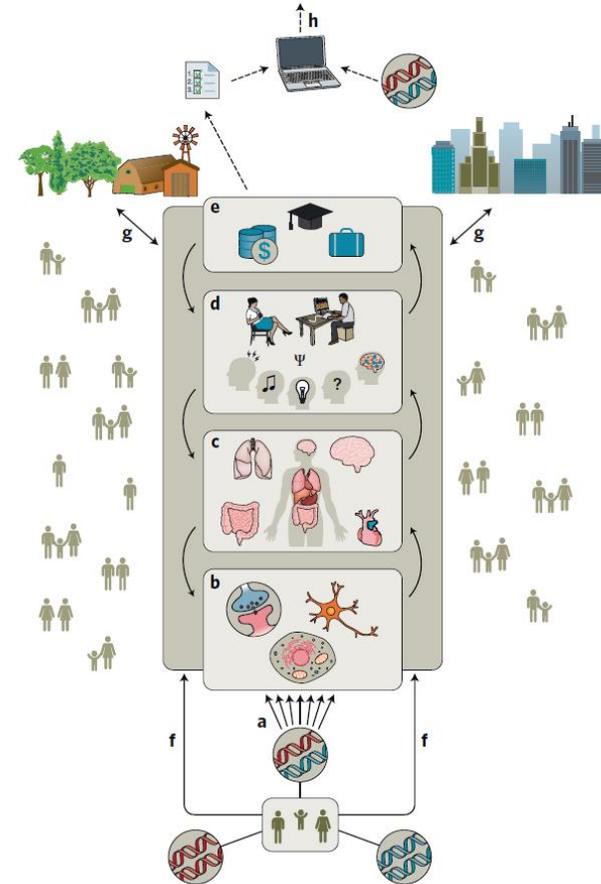
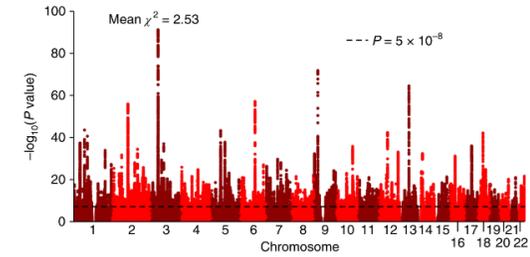
Society makes genetic effects stronger.



Key points

Society makes genetic effects stronger.

We reward certain genetic propensities with a better environment, and “punish” the lack of those propensities with a worse environment.



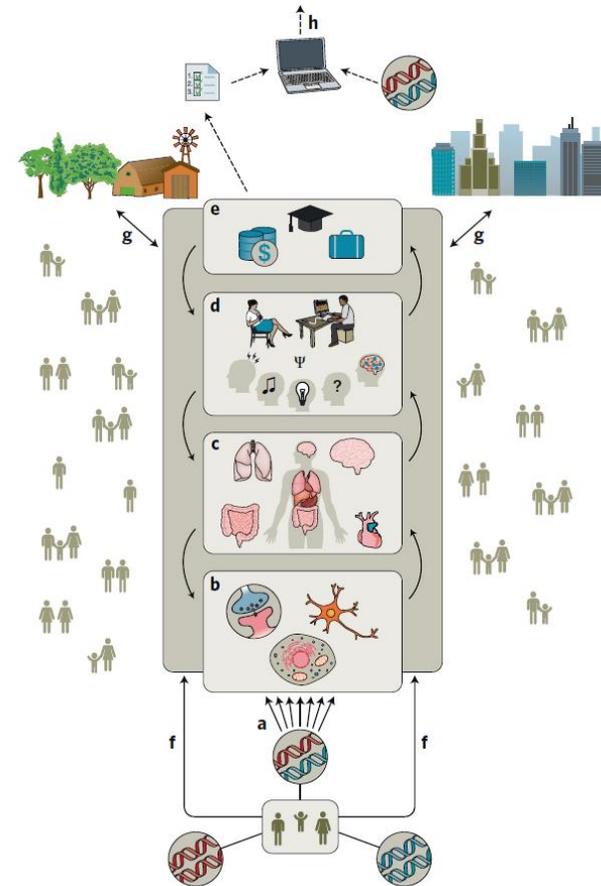
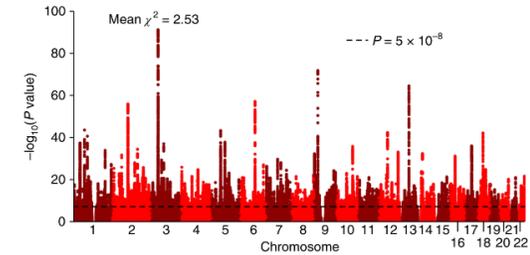
Key points

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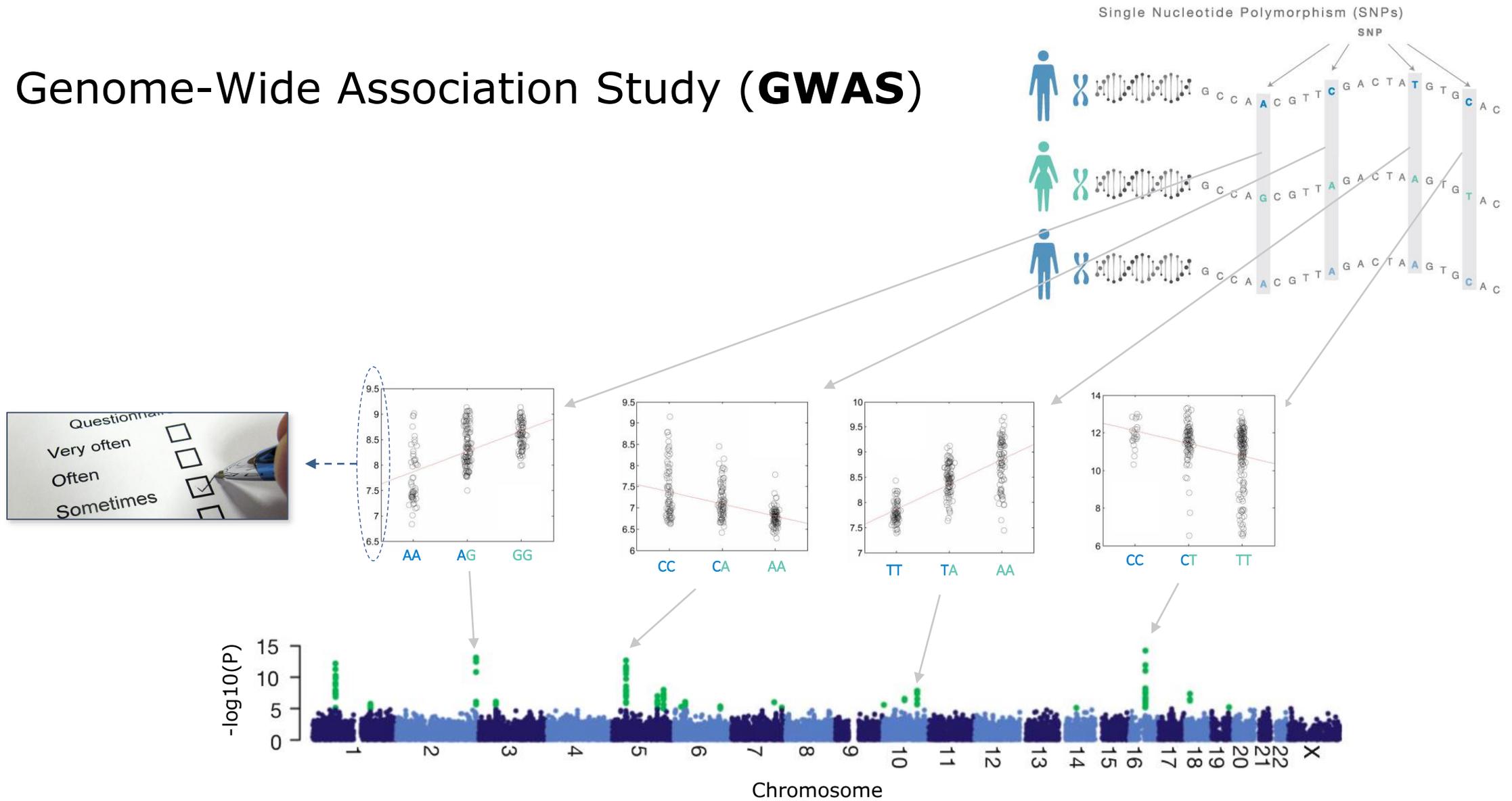
We reward certain genetic propensities with a better environment, and “punish” the lack of those propensities with a worse environment.

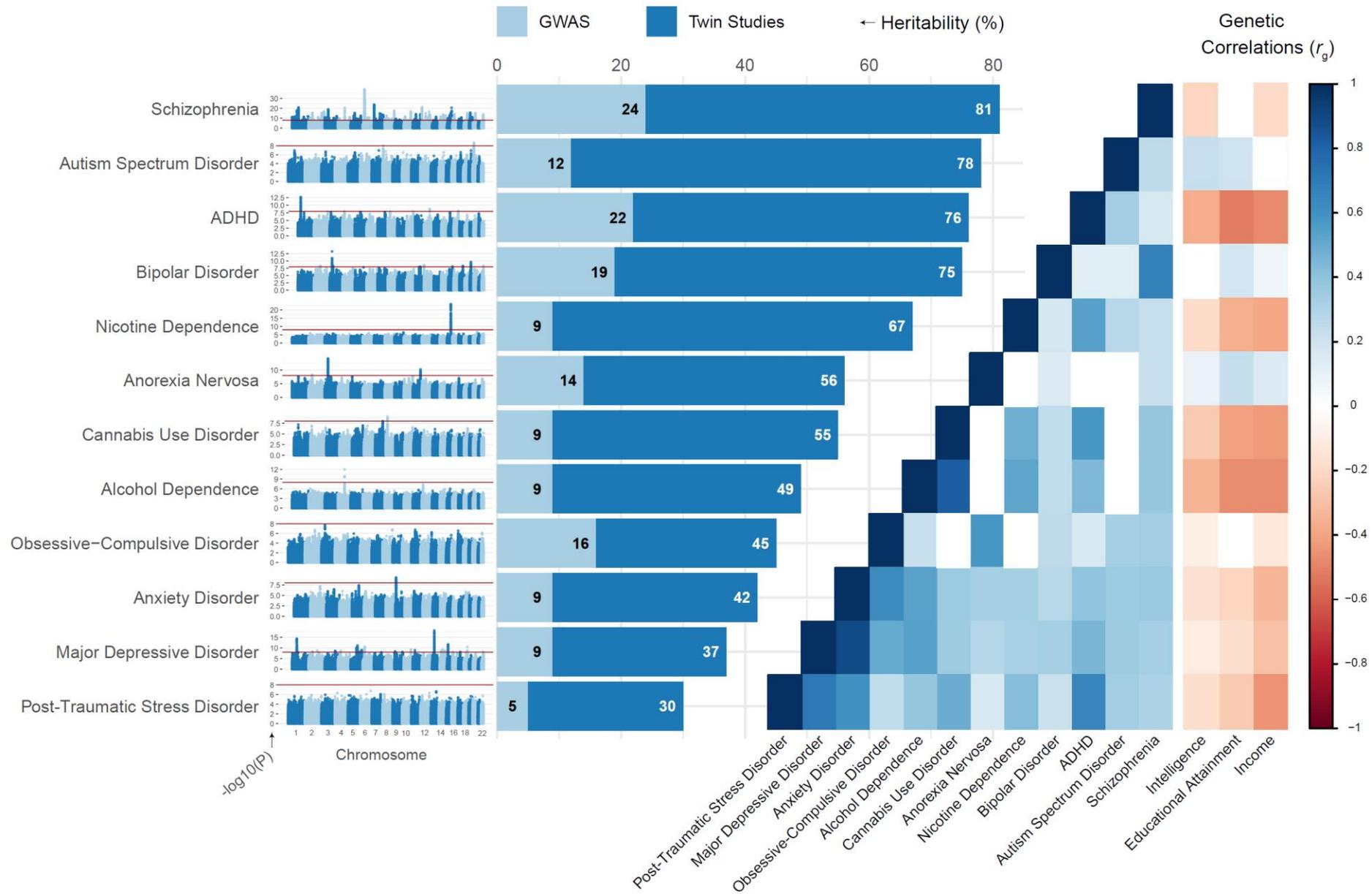
This makes society more unequal.

This makes studying genetics more difficult.

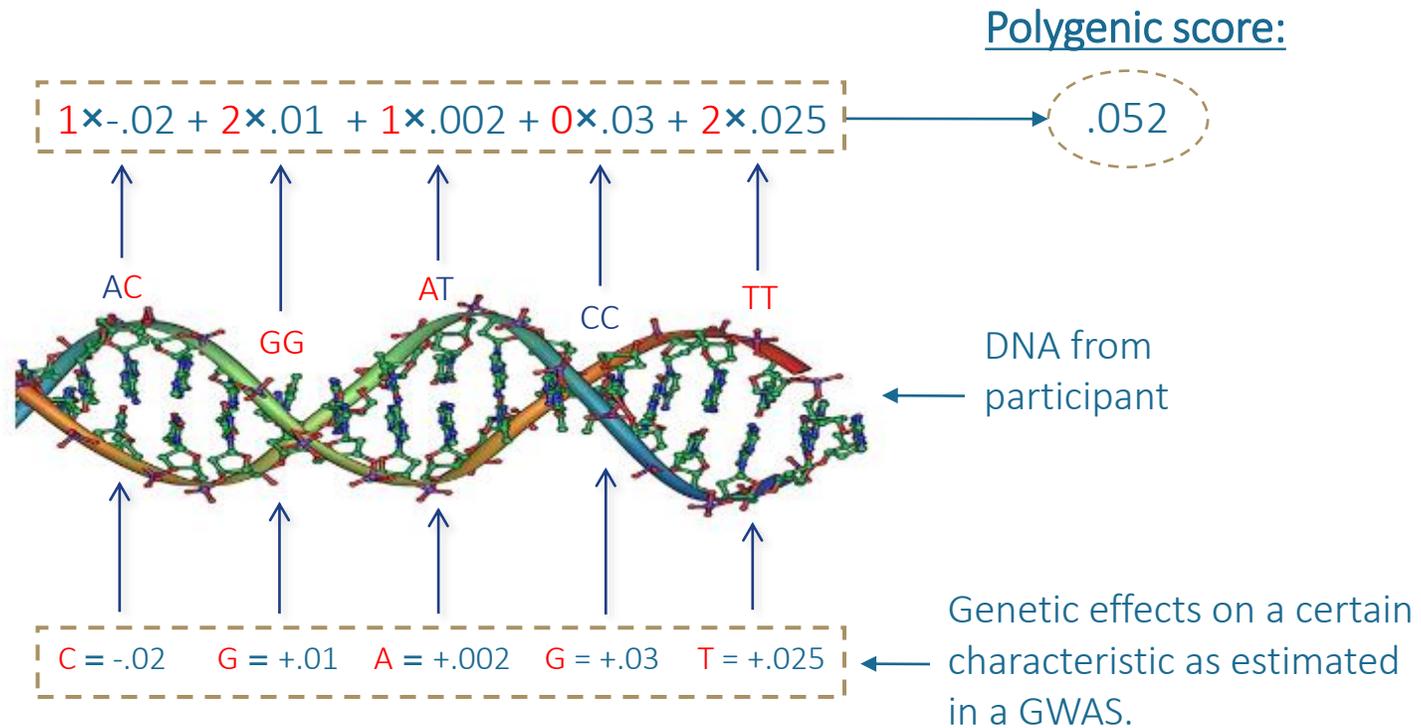


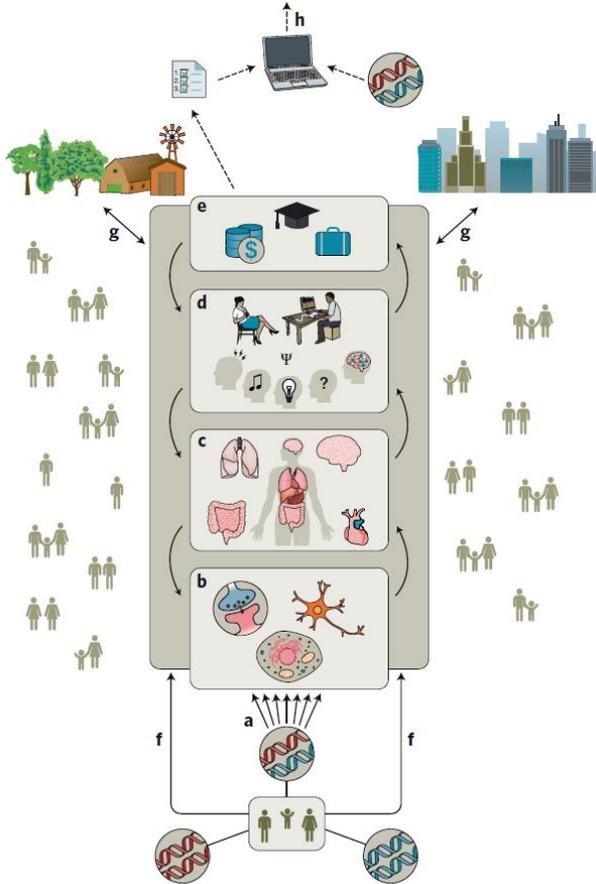
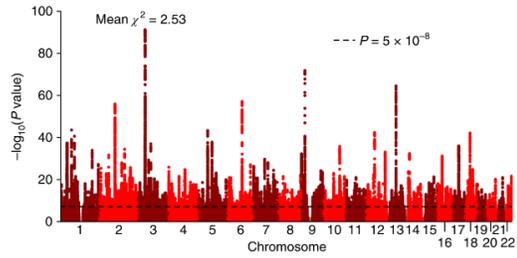
Genome-Wide Association Study (**GWAS**)





Polygenic Score = measure of genetic predisposition for complex trait or disease





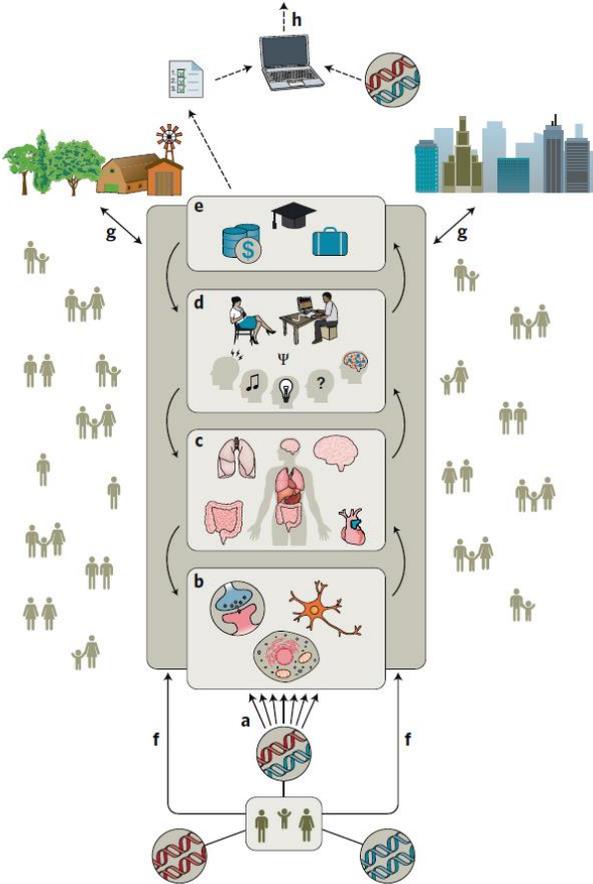
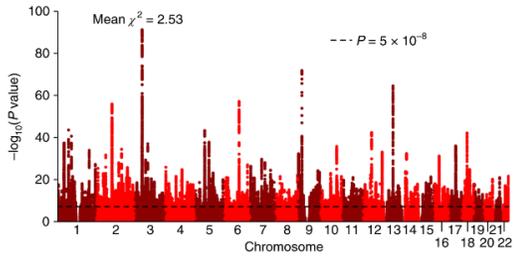
REVIEW ARTICLE
<https://doi.org/10.1038/s41562-021-01110-y>

Check for updates

Dissecting polygenic signals from genome-wide association studies on human behaviour

Abdel Abdellaoui and Karin J. H. Verweij

“When the nature of the predictive ability of polygenic scores for behavioural traits is not fully understood, applying them in either scientific research or the clinic can lead to incorrect interpretations and conclusions.”



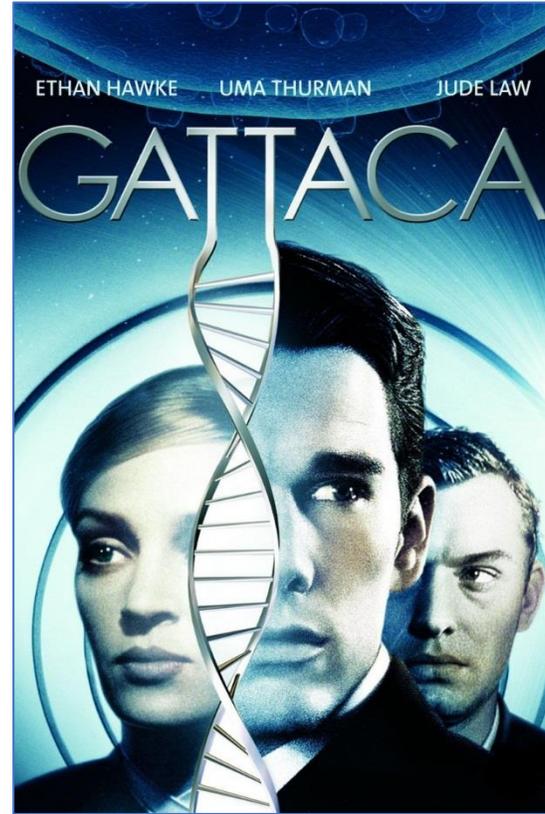
nature
human behaviour

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Dissecting polygenic signals from genome-wide association studies on human behaviour

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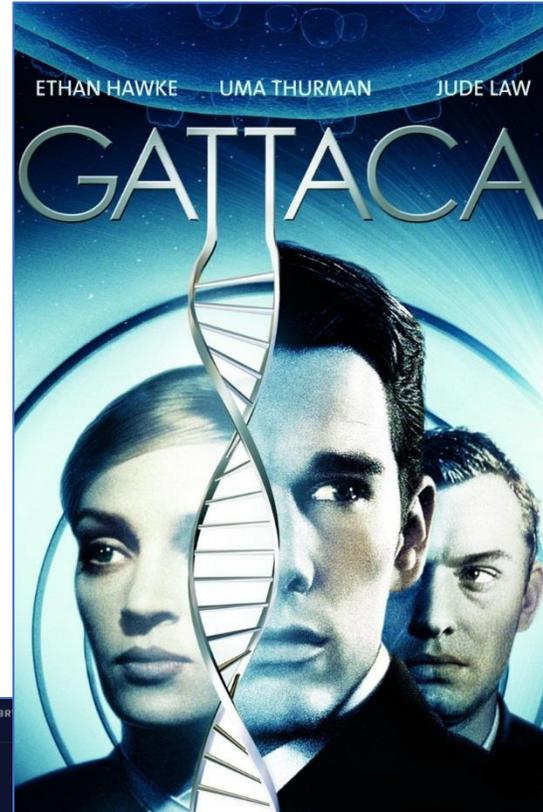
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BIOTECHNOLOGY

The world's first Gattaca baby tests are finally here

The DNA test claims to let prospective parents weed out IVF embryos with a high risk of disease or low intelligence.

By Antonio Regalado November 8, 2019



nature

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EDITORIAL | 21 March 2022 | Correction 28 March 2022

The alarming rise of complex genetic testing in human embryo selection

Companies are marketing polygenic risk scores as part of IVF well ahead of a full understanding of the potential benefits – or dangers.

[Twitter](#) [Facebook](#) [Email](#)

Embryo report card

	GRADE
diabetes	
diabetes	F
size	A

ORCHID COUPLE REPORT EMBR

Identify your healthiest embryo

Mitigate your family's genetic predispositions with advanced genetic screening for your embryos

WIRED

Genetic Screening Now Lets Parents Pick the Healthiest Embryos

AT 18 MONTHS old, Aurea Yenmai Smigrodzki is inquisitive like any other toddler. She likes peanut butter, the beach, and mobile phones—or any toys that look like phones. She likes to copy her mum and dad, Thuy and Rafal, when they are using theirs. Aurea doesn't know it yet, but her birth was very special: She is the world's first PGT-P baby, meaning she is statistically less likely than the rest of us to develop a genetic disease or disorder throughout her life.

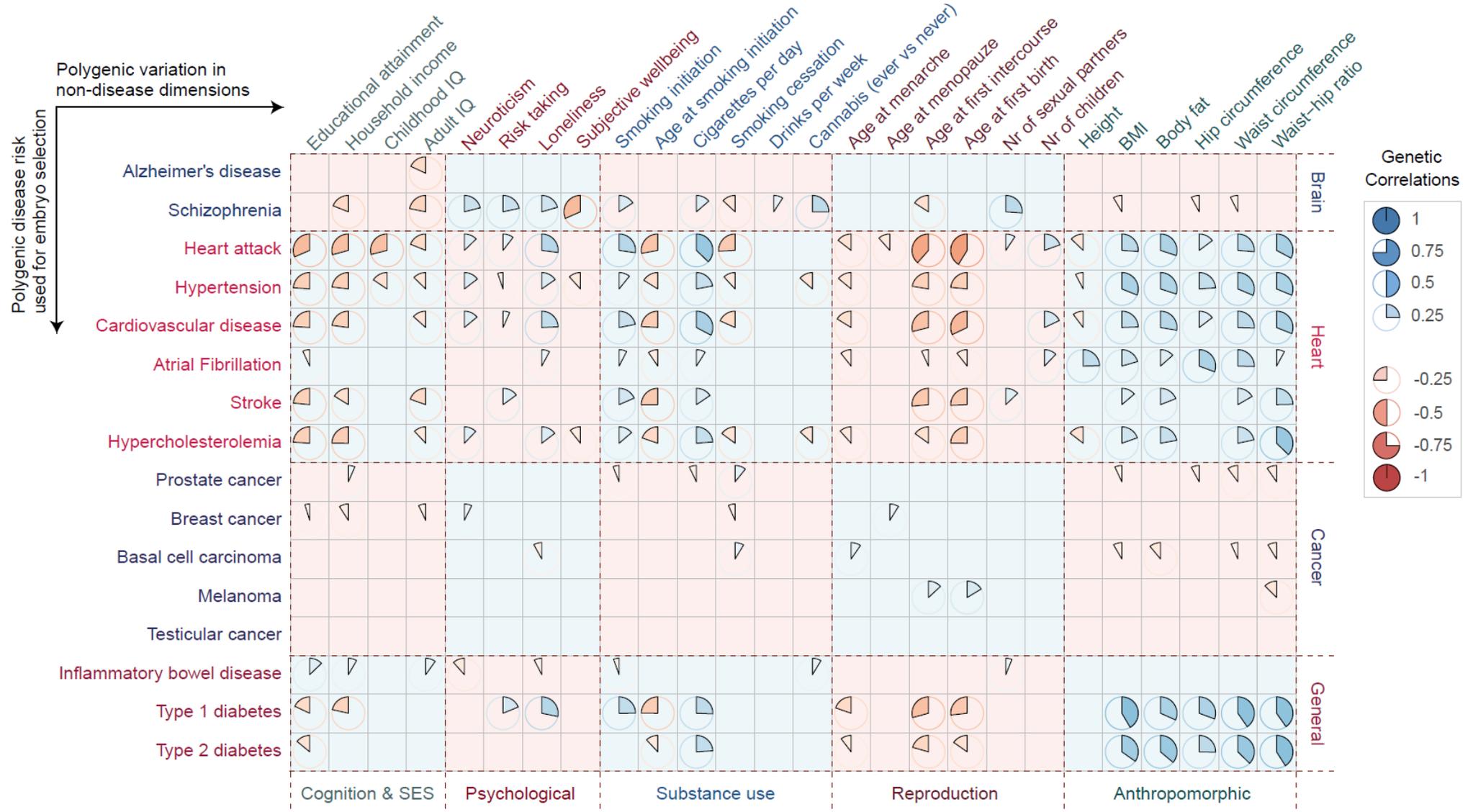


4.2 Does Genomic Prediction screen purely cosmetic traits?

No, we only provide risk scores for polygenic traits related to diseases, not for purely cosmetic traits such as hair color and eye color. Our goal is to provide improved health to IVF families.

4.3 Does Genomic Prediction Clinical Laboratory screen embryos for increased intelligence i.e. high IQ?

No.

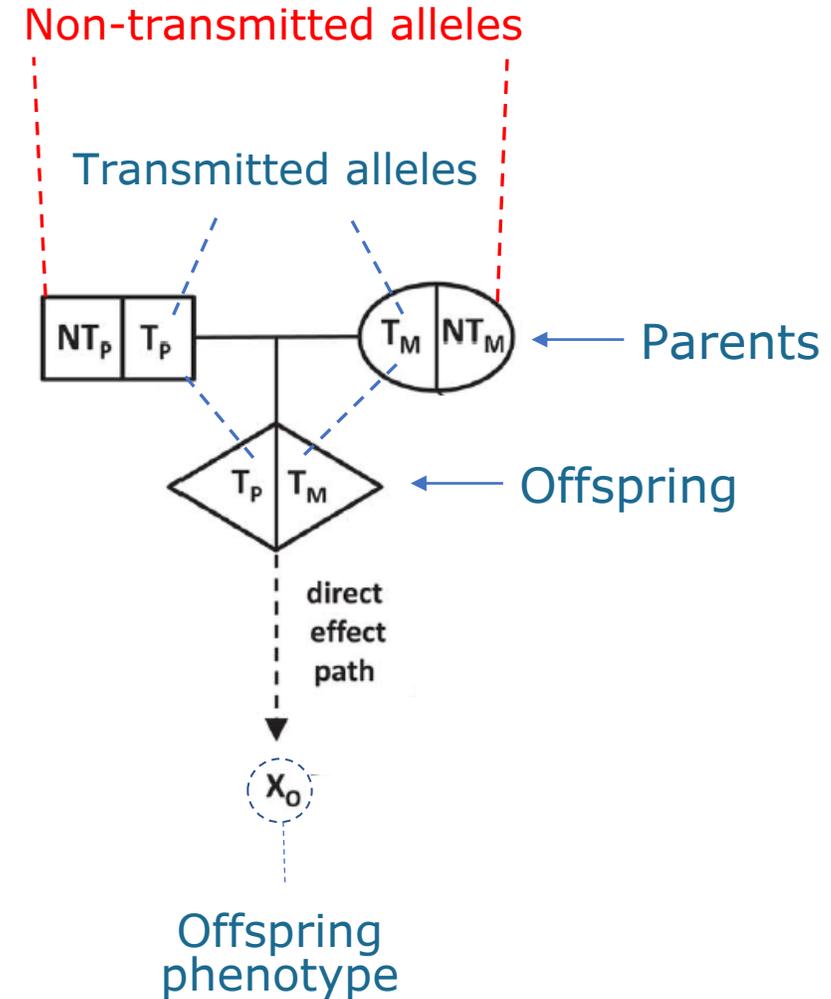


Unpublished results

Gene-Environment Correlations - Families

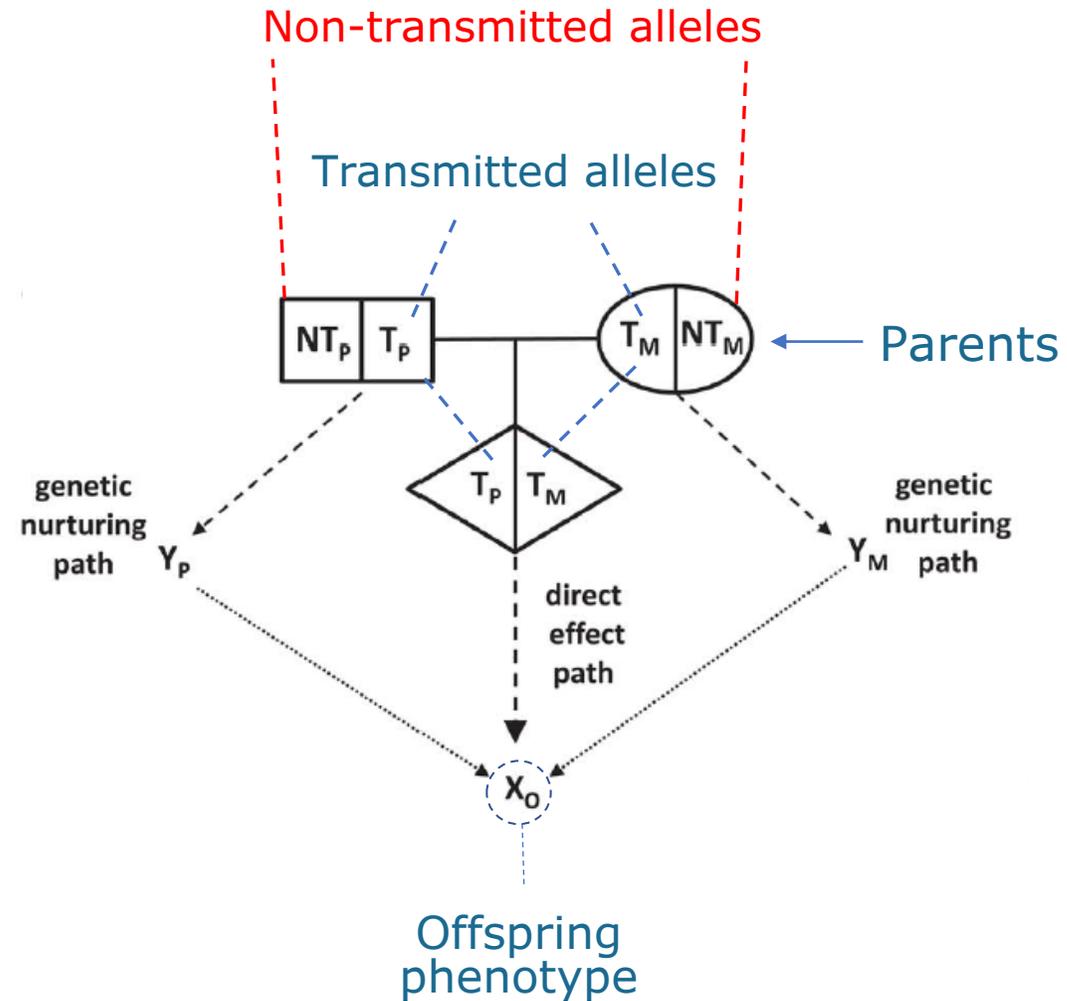
The nature of nurture: Effects of parental genotypes

Augustine Kong,^{1,2,3*} Gudmar Thorleifsson,¹ Michael L. Frigge,¹
Bjarni J. Vilhjalmsón,^{4,5} Alexander I. Young,^{1,2,6} Thorgeir E. Thorgeirsson,¹
Stefania Benonisdóttir,¹ Asmundur Oddsson,¹ Bjarni V. Halldorsson,¹ Gisli Masson,¹
Daniel F. Gudbjartsson,^{1,3} Agnar Helgason,^{1,7} Gyda Bjornsdóttir,¹
Unnur Thorsteinsdóttir,^{1,8} Kari Stefansson^{1,8*}



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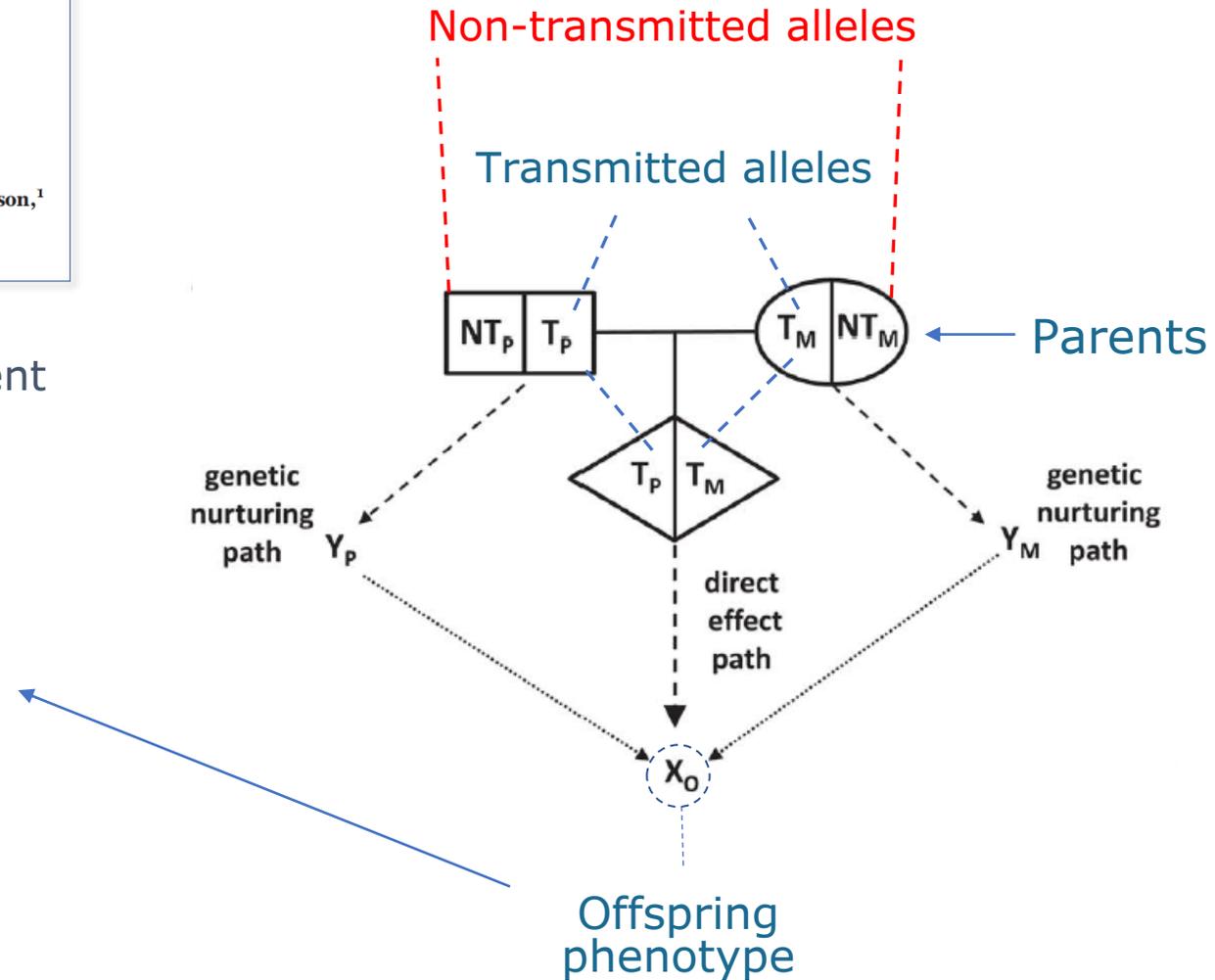


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Non-transmitted educational attainment alleles are associated with:

- Educational attainment
- Age at first child
- High-density lipoprotein (HDL)
- BMI
- Fasting glucose level
- Height
- Cigarettes per day
- Overall health



Research Article



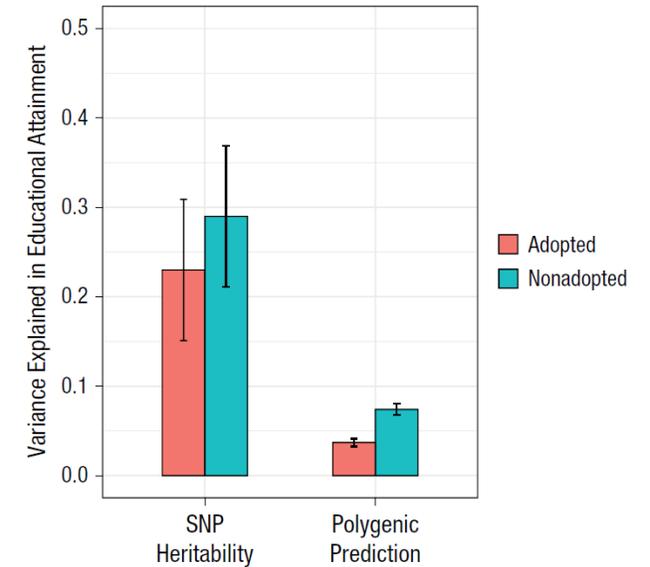
Comparison of Adopted and Nonadopted Individuals Reveals Gene–Environment Interplay for Education in the UK Biobank

Rosa Cheesman¹ , Avina Hunjan^{1,2}, Jonathan R. I. Coleman^{1,2}, Yasmin Ahmadzadeh¹, Robert Plomin¹, Tom A. McAdams¹, Thalia C. Eley^{1,2}, and Gerome Breen^{1,2}

Psychological Science
2020, Vol. 31(5) 582–591
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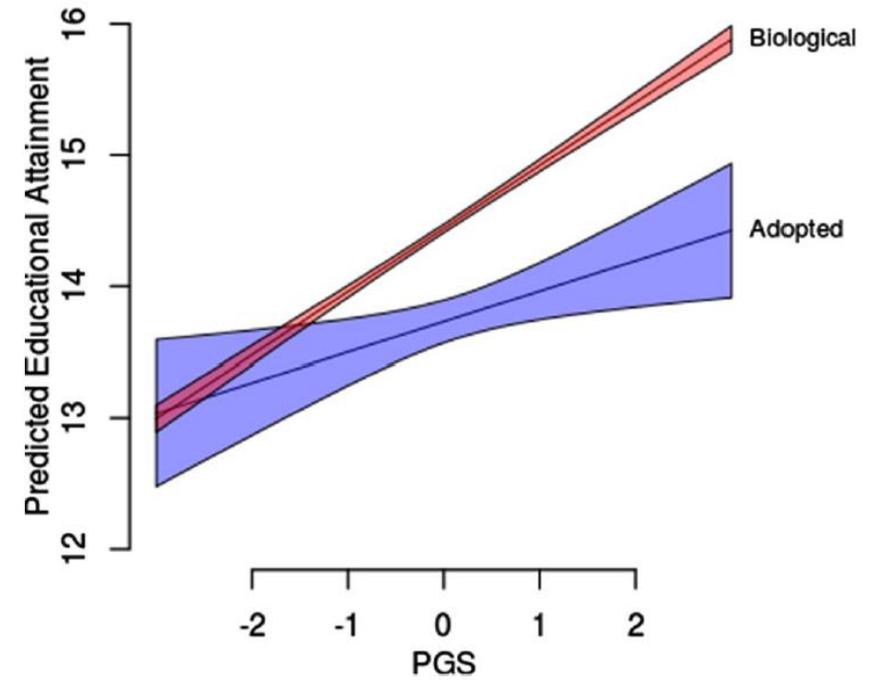
Behavior Genetics
<https://doi.org/10.1007/s10519-020-10000-4>

ORIGINAL RESEARCH



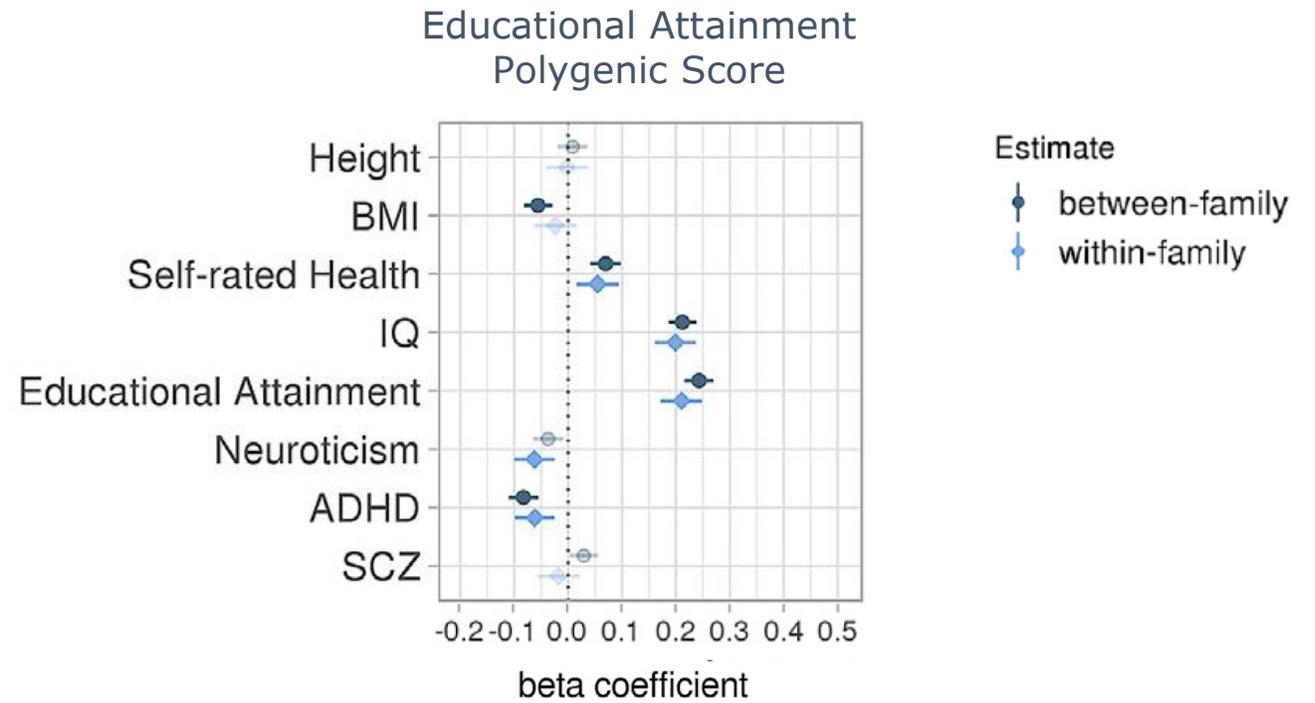
Separating Measured Genetic and Environmental Effects: Evidence Linking Parental Genotype and Adopted Child Outcomes

Benjamin W. Domingue¹ · Jason Fletcher²

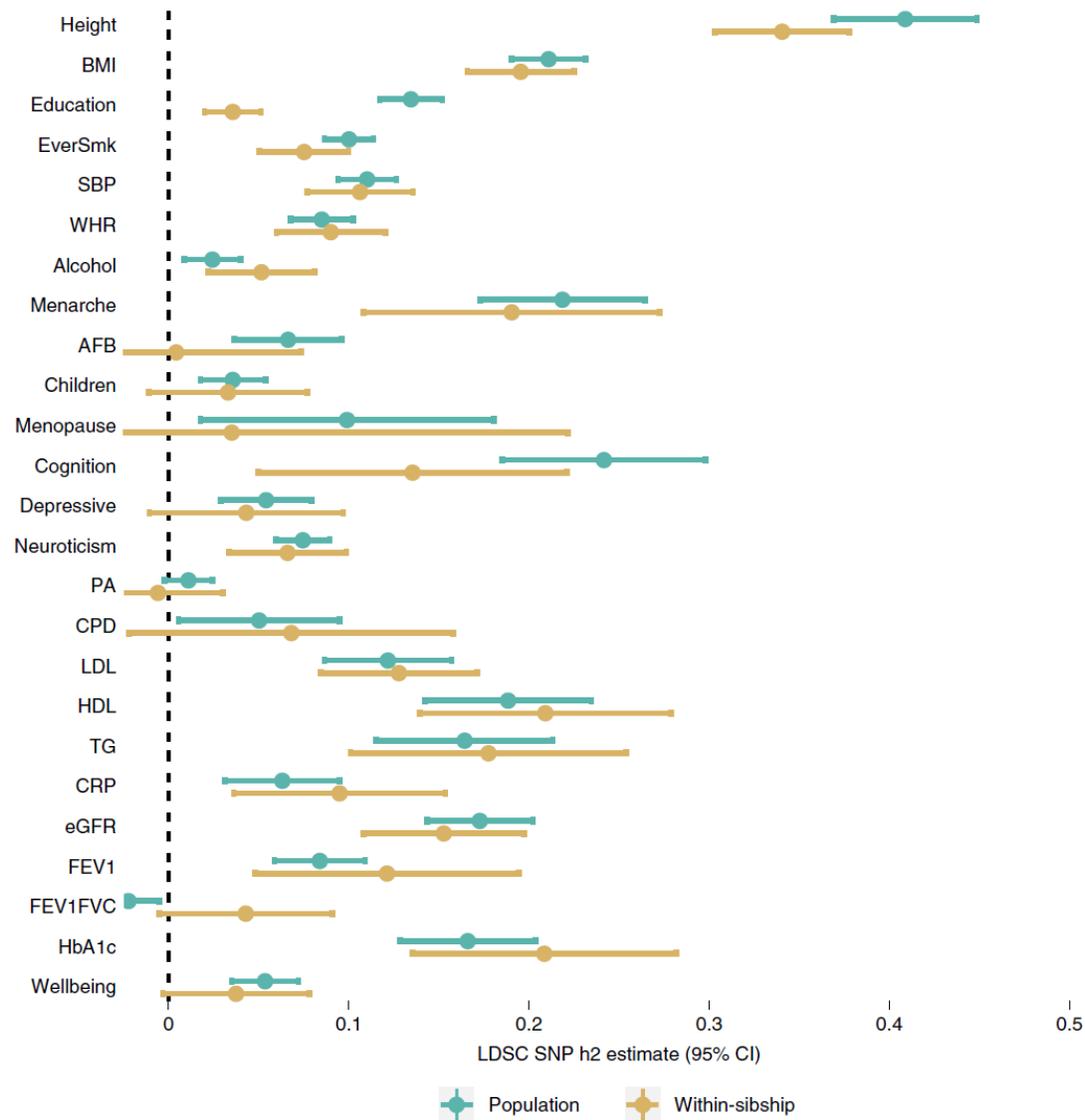


Comparing Within- and Between-Family Polygenic Score Prediction

Saskia Selzam,^{1,*} Stuart J. Ritchie,¹ Jean-Baptiste Pingault,^{1,2} Chandra A. Reynolds,³ Paul F. O'Reilly,^{1,4} and Robert Plomin¹

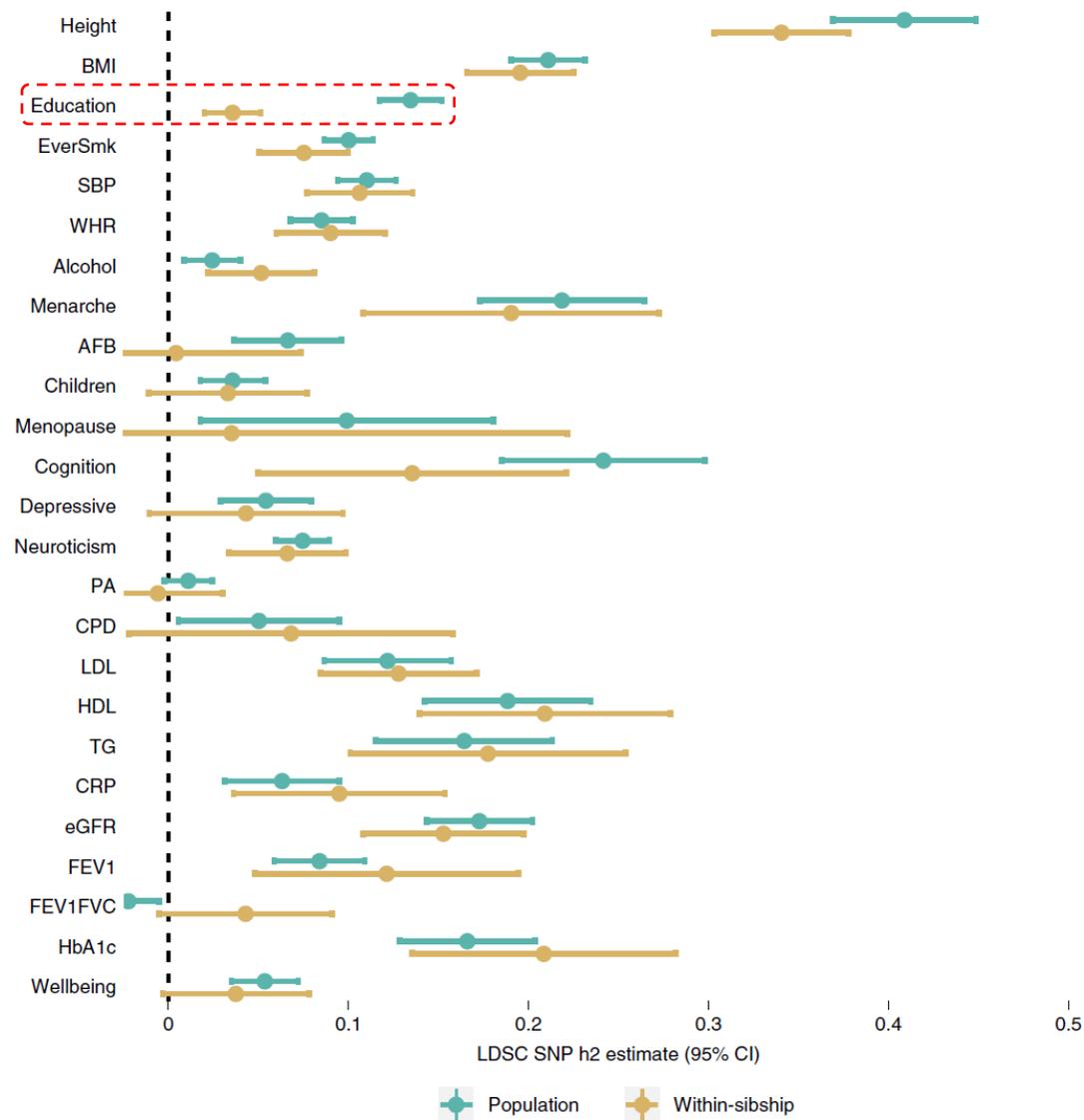


OPEN
Within-sibship genome-wide association analyses decrease bias in estimates of direct genetic effects

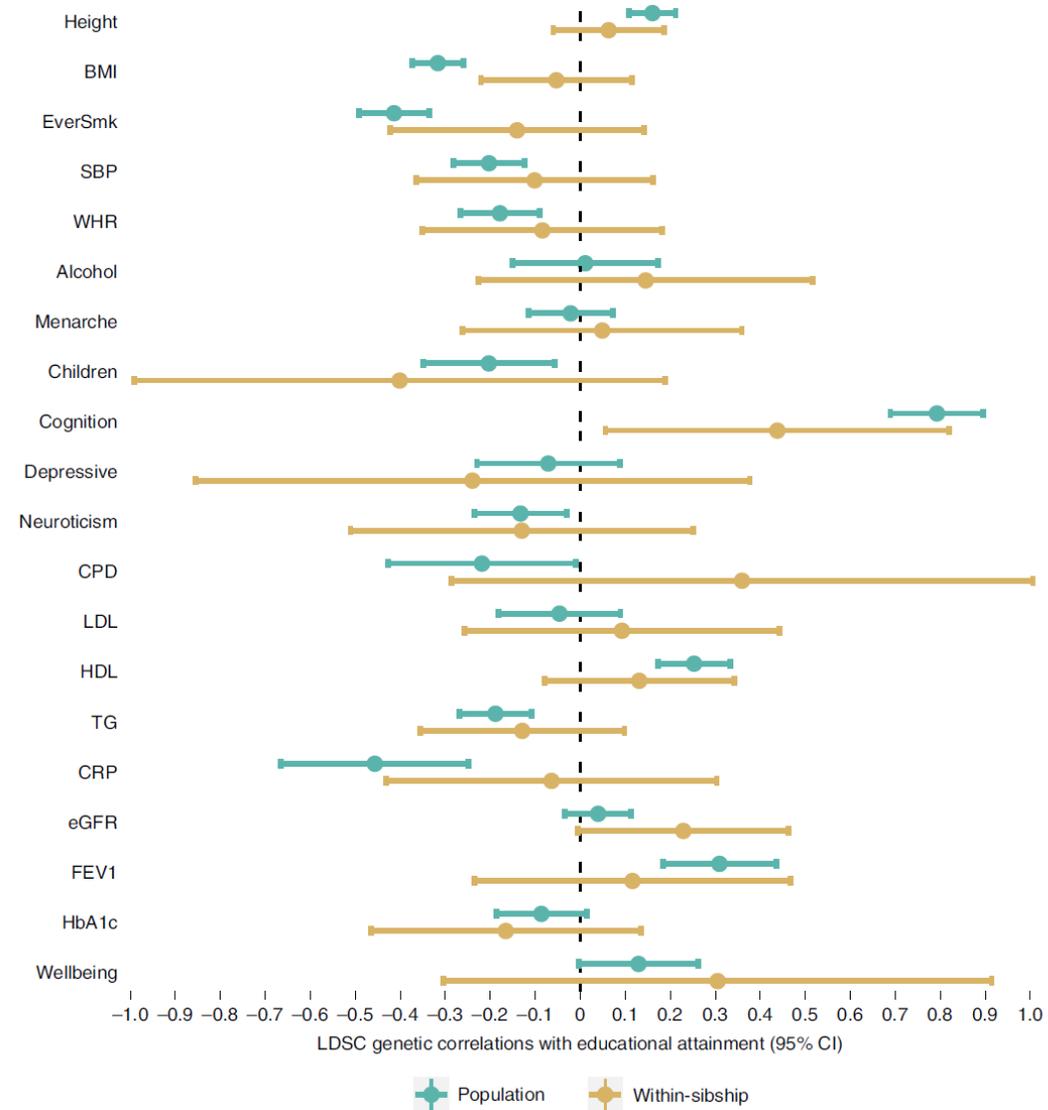


OPEN

Within-sibship genome-wide association analyses decrease bias in estimates of direct genetic effects



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Within-sibship genome-wide association analyses decrease bias in estimates of direct genetic effects

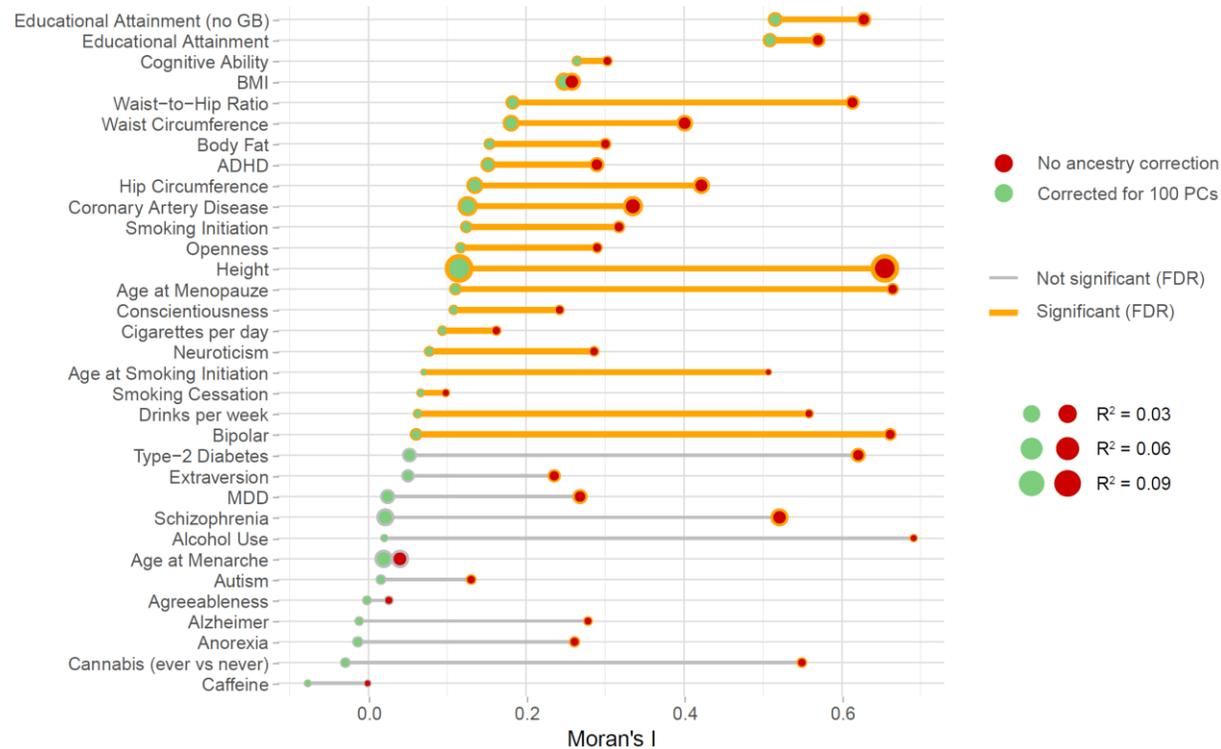


Gene-Environment Correlations - Geographic

Geography & Polygenic Scores

Genetic correlates of social stratification in Great Britain

Abdel Abdellaoui^{1*}, David Hugh-Jones², Loic Yengo³, Kathryn E. Kemper³, Michel G. Nivard⁴, Laura Veul¹, Yan Holtz³, Brendan P. Zietsch⁵, Timothy M. Frayling⁶, Naomi R. Wray^{3,7}, Jian Yang^{3,7}, Karin J. H. Verweij¹ and Peter M. Visscher^{3,7*}

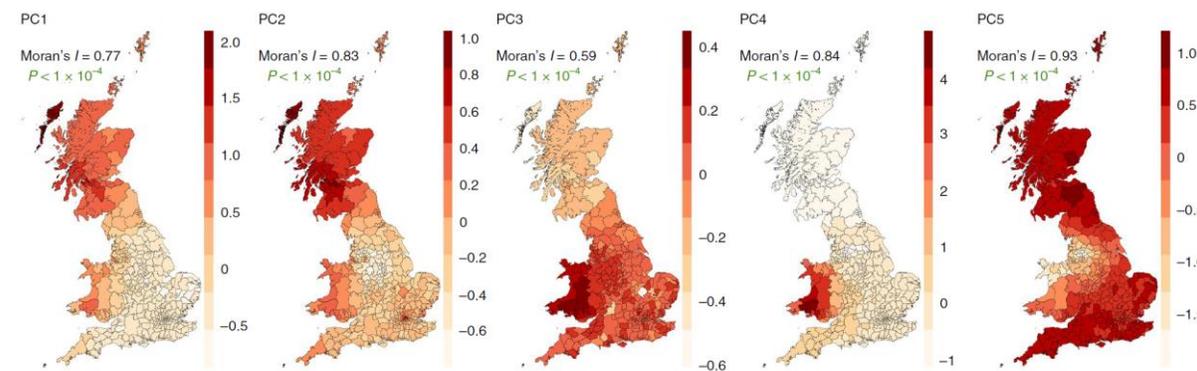
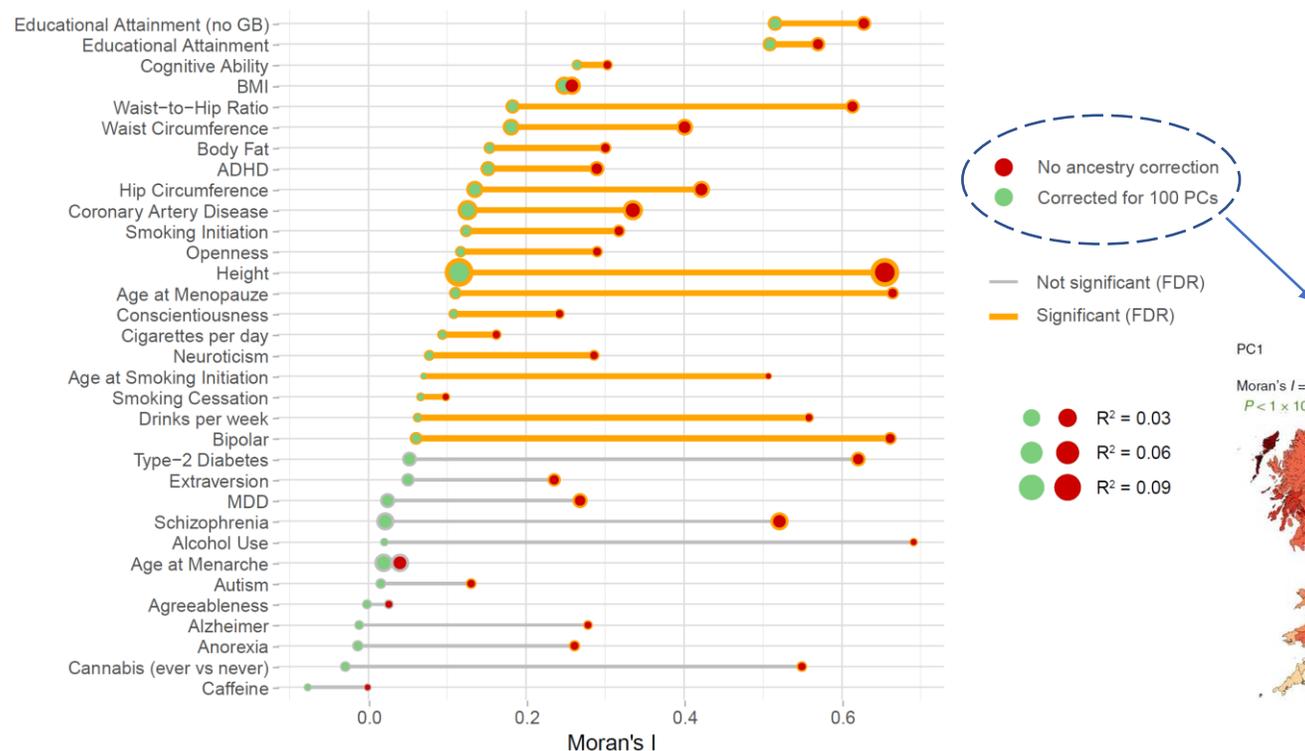


Moran's I = measure for geographic clustering

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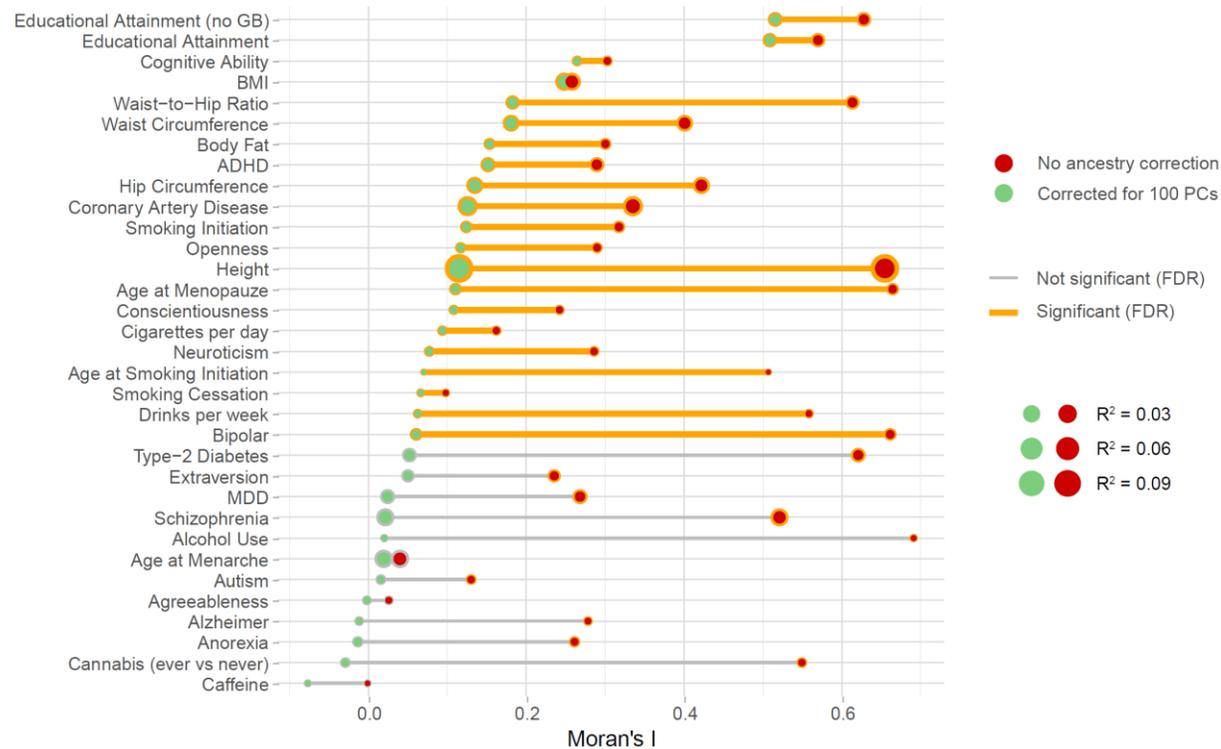


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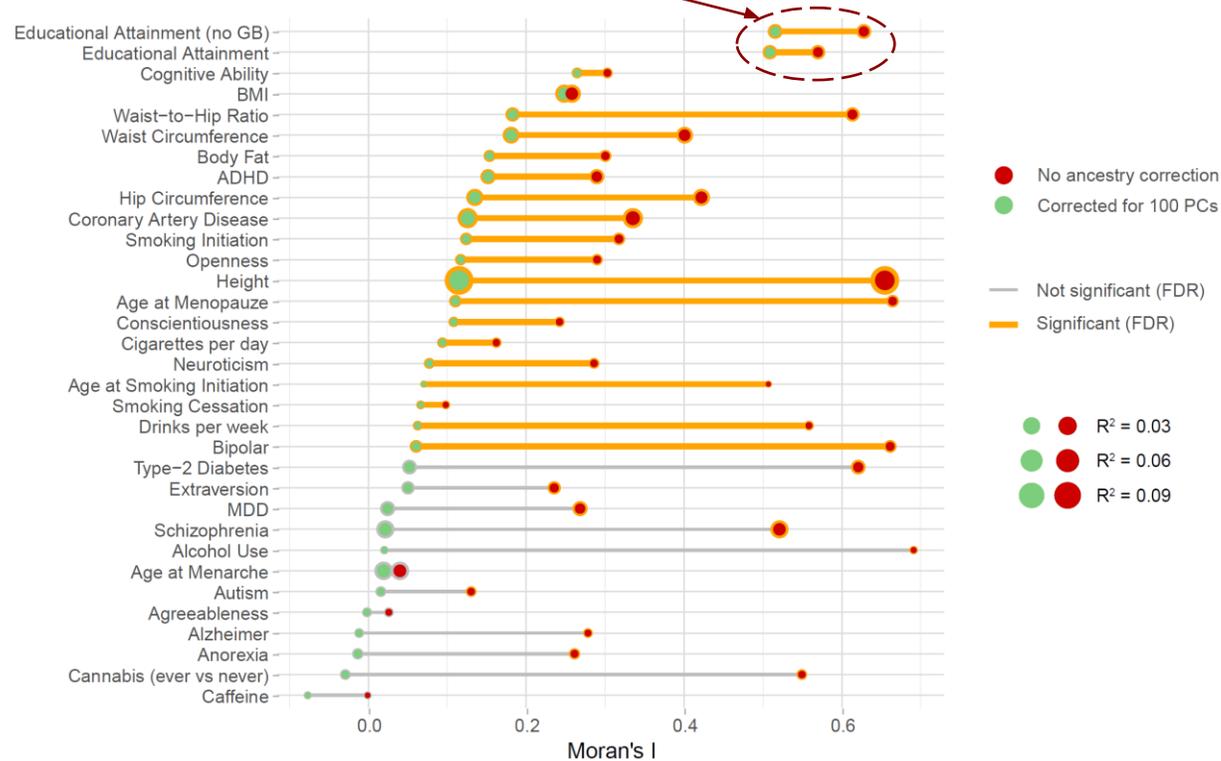
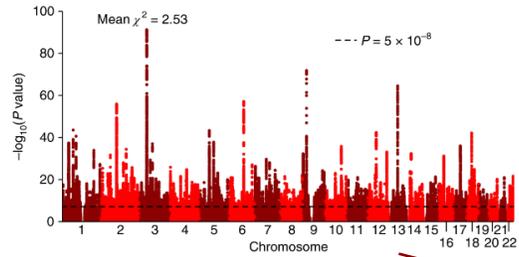


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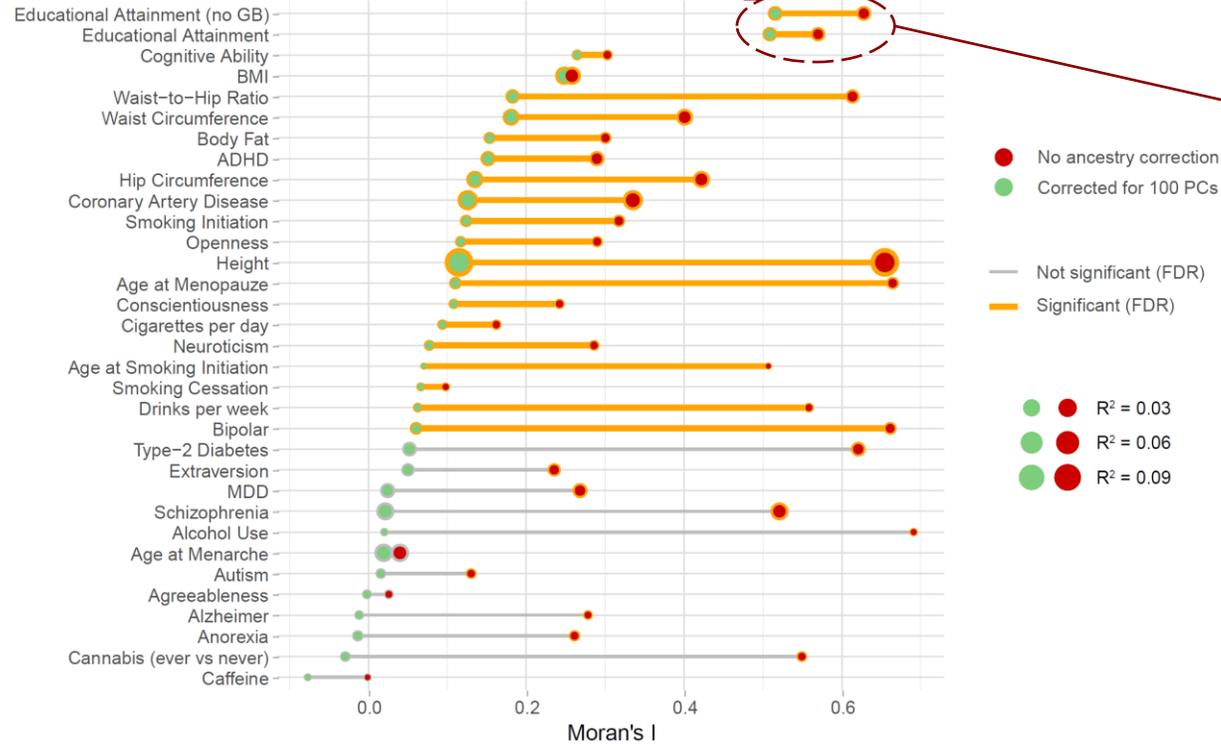
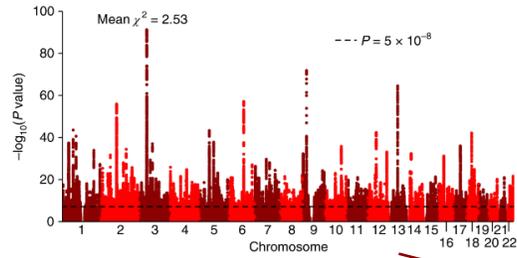


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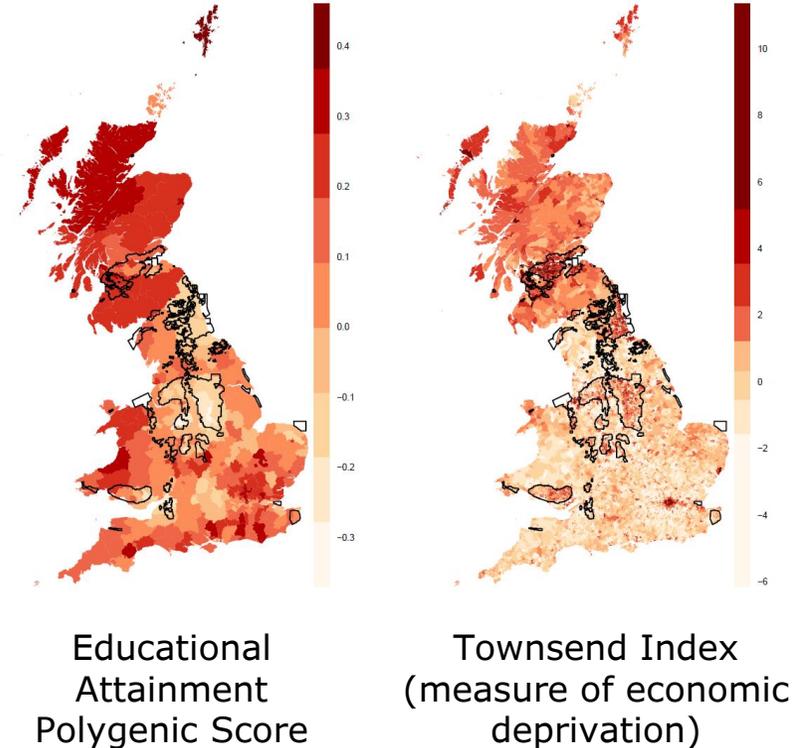
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Geography & Polygenic Scores



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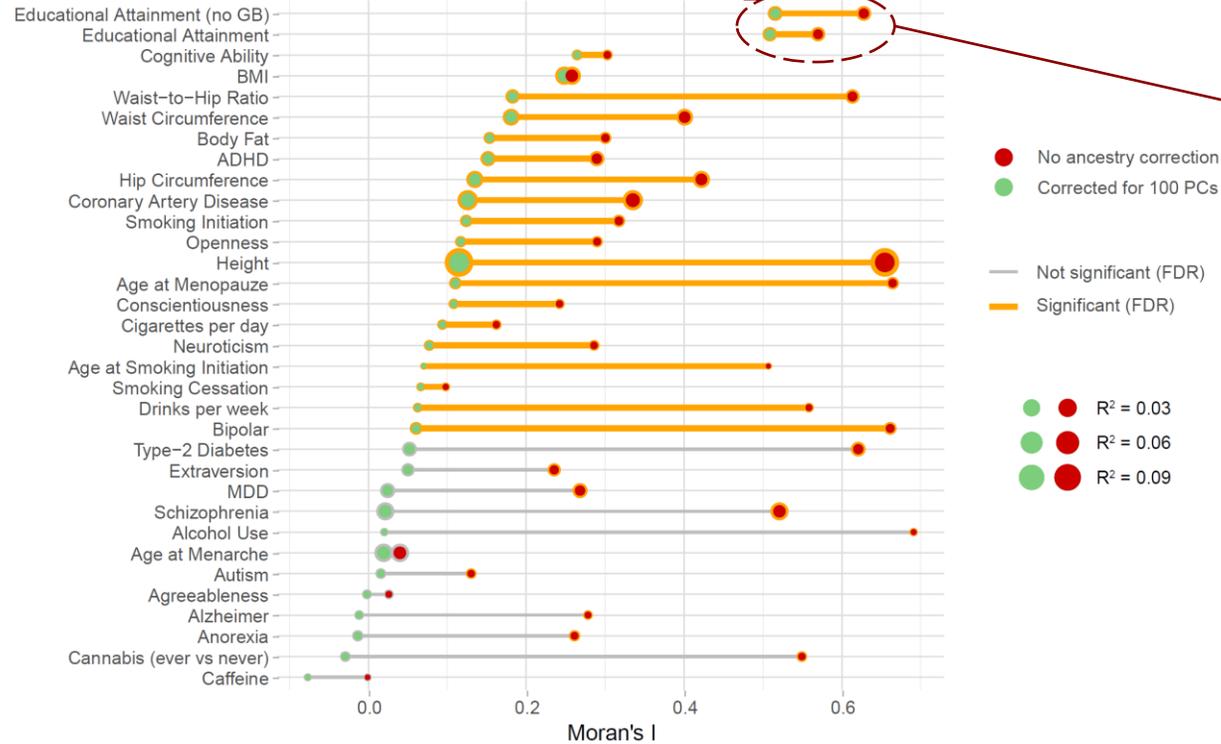
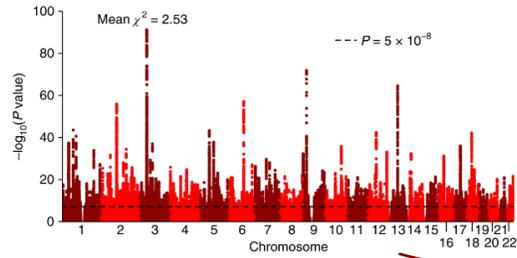


black lines = coal regions

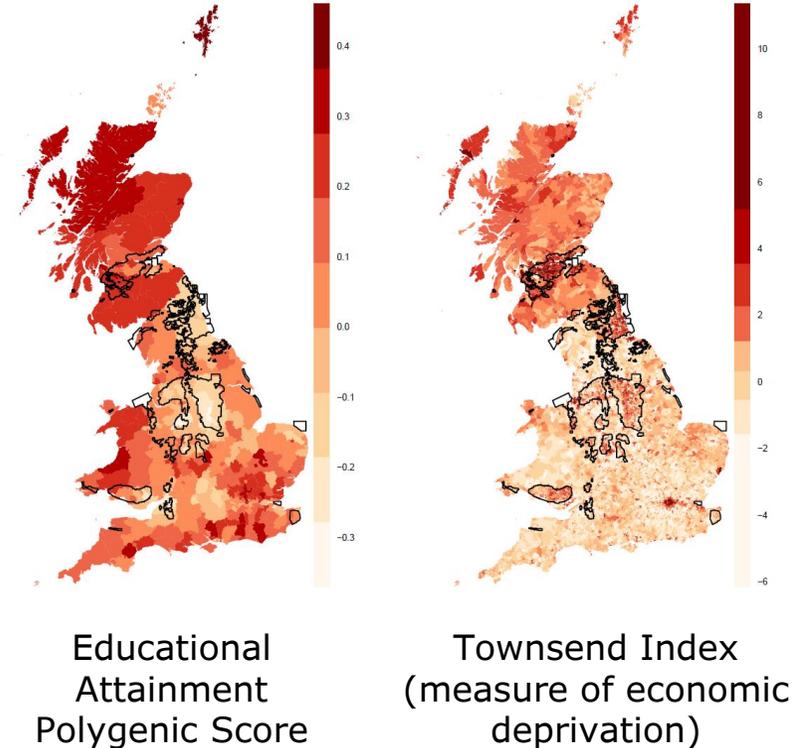
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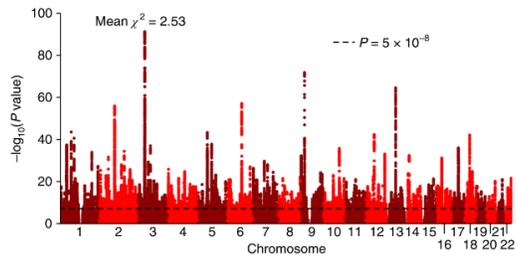
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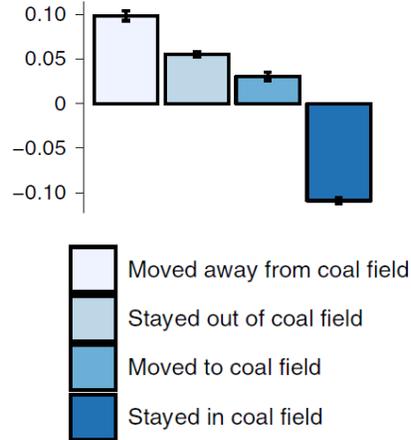


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Migration & SES

Educational
Attainment
Polygenic Score



ARTICLES

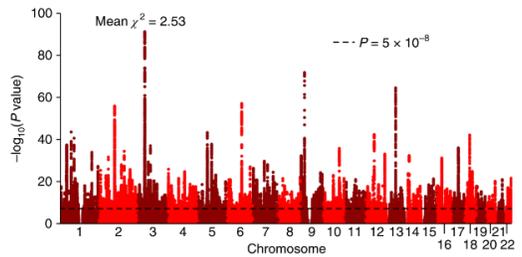
<https://doi.org/10.1038/s41562-019-0757-5>

nature
human behaviour

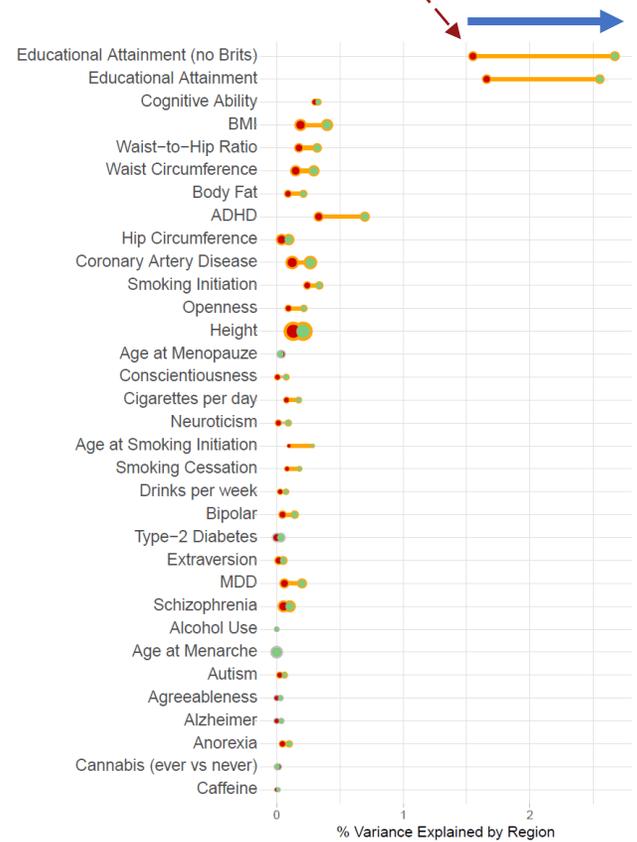
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Migration & SES



← Polygenic Scores

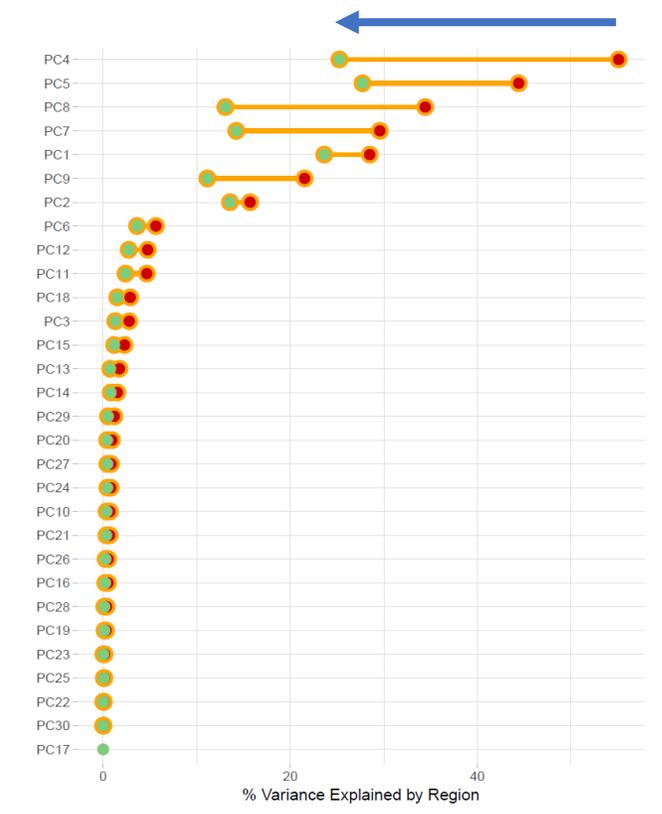
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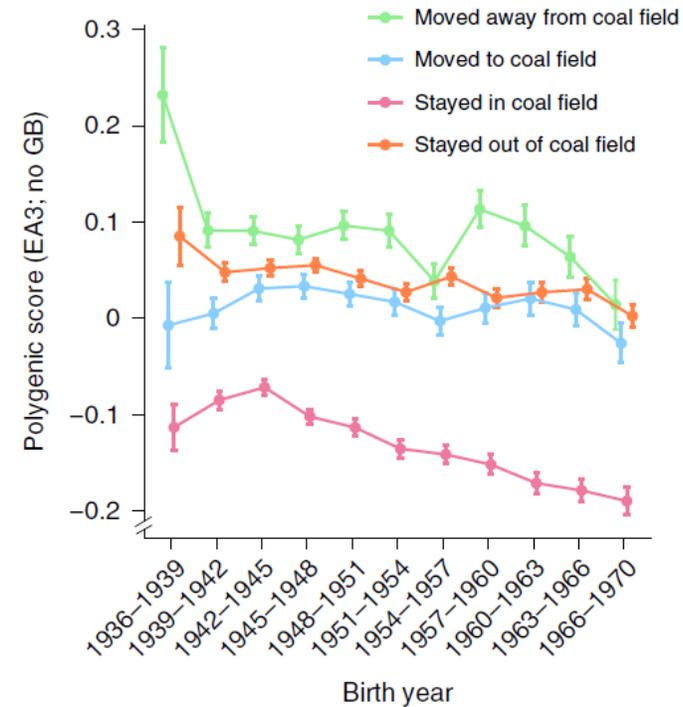
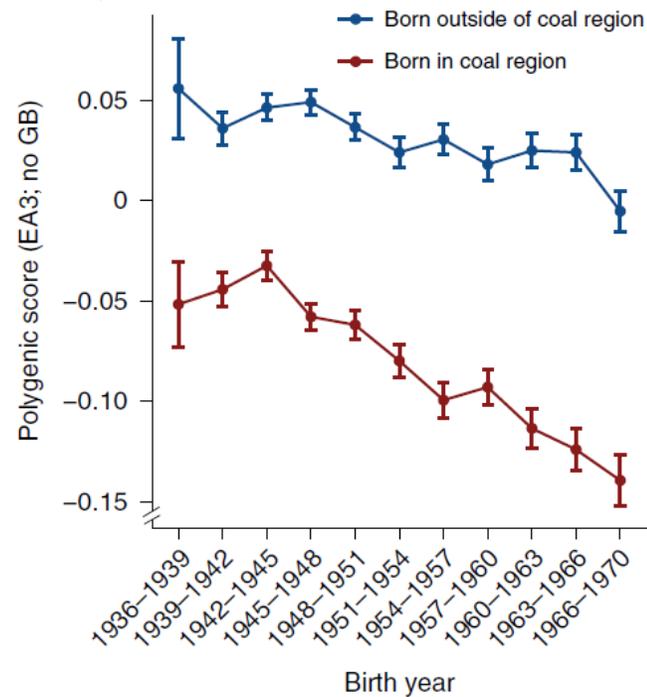
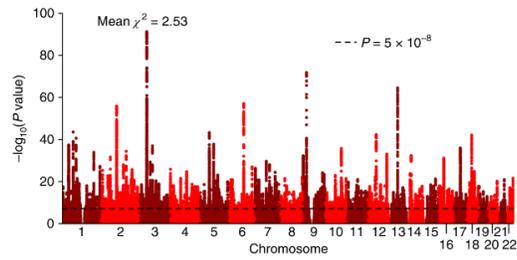


- Birthplace
- Current Address
- Not significant (FDR)
- Significant (FDR)

Migration & SES

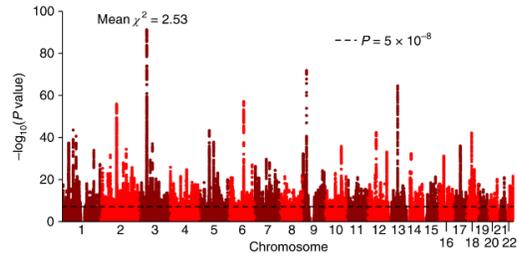
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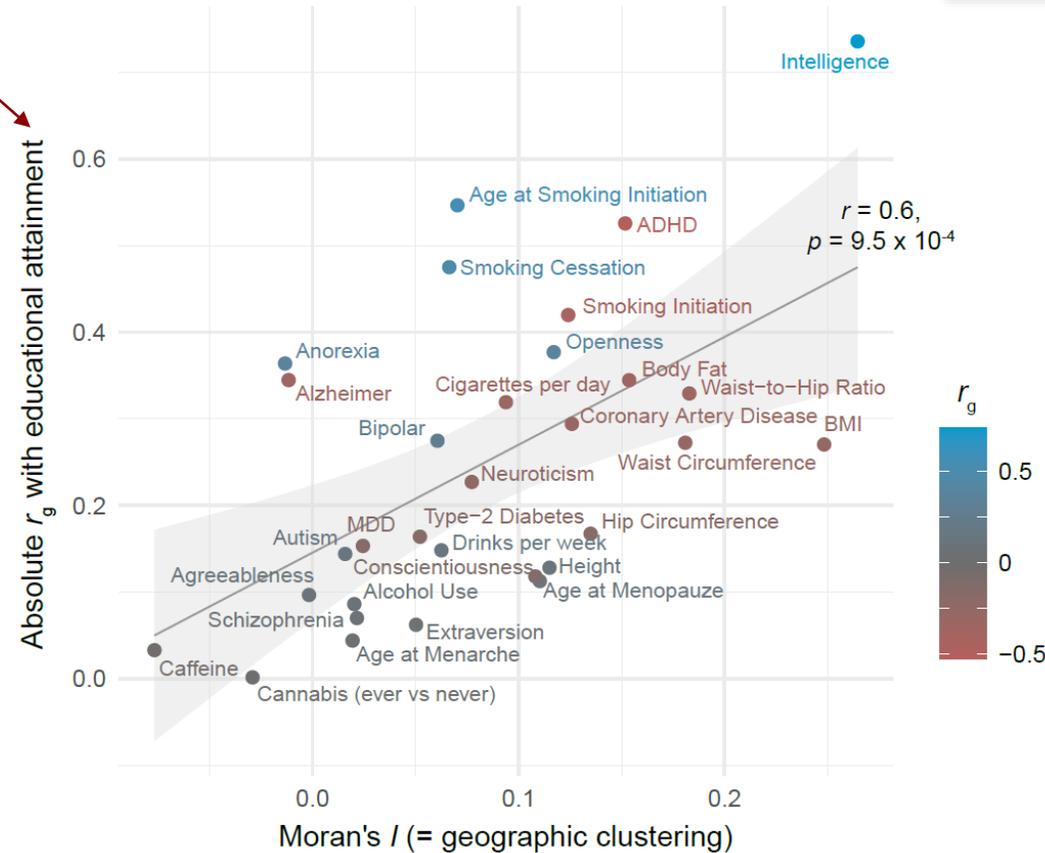


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Sharing more genetic effects with EA = stronger geographic clustering

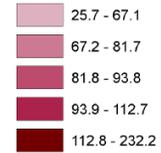


Obesity and the environment

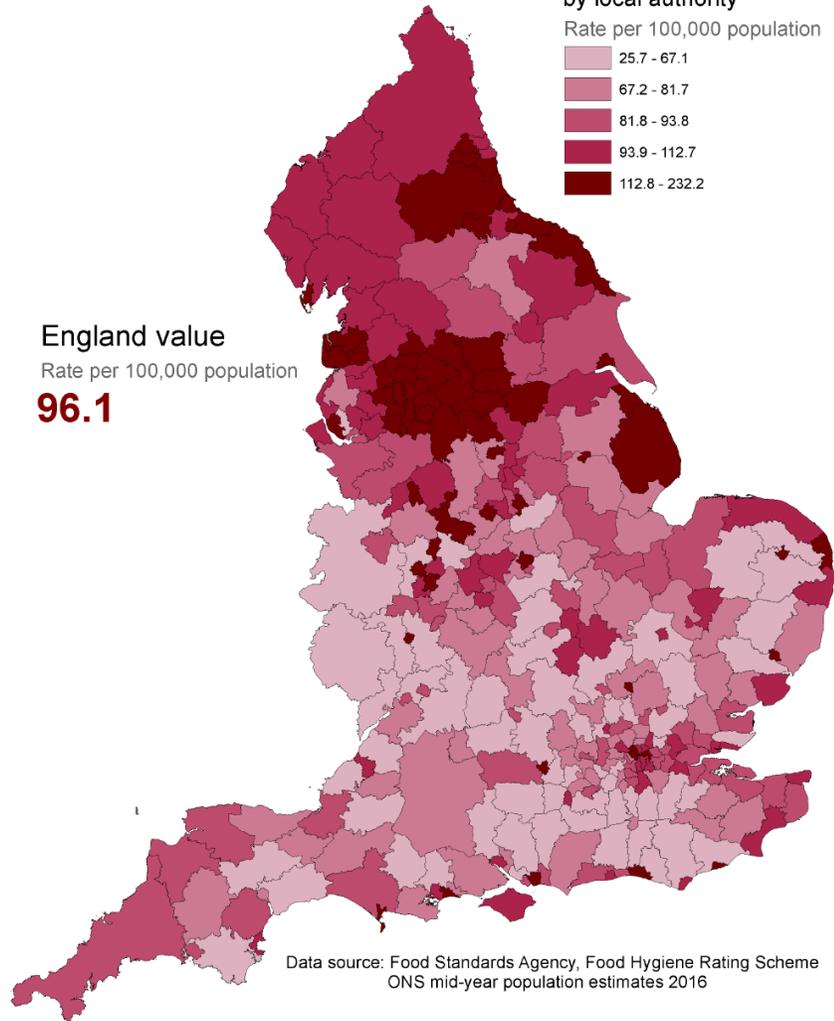
Density of fast food outlets at 31/12/2017

Fast food outlets by local authority

Rate per 100,000 population

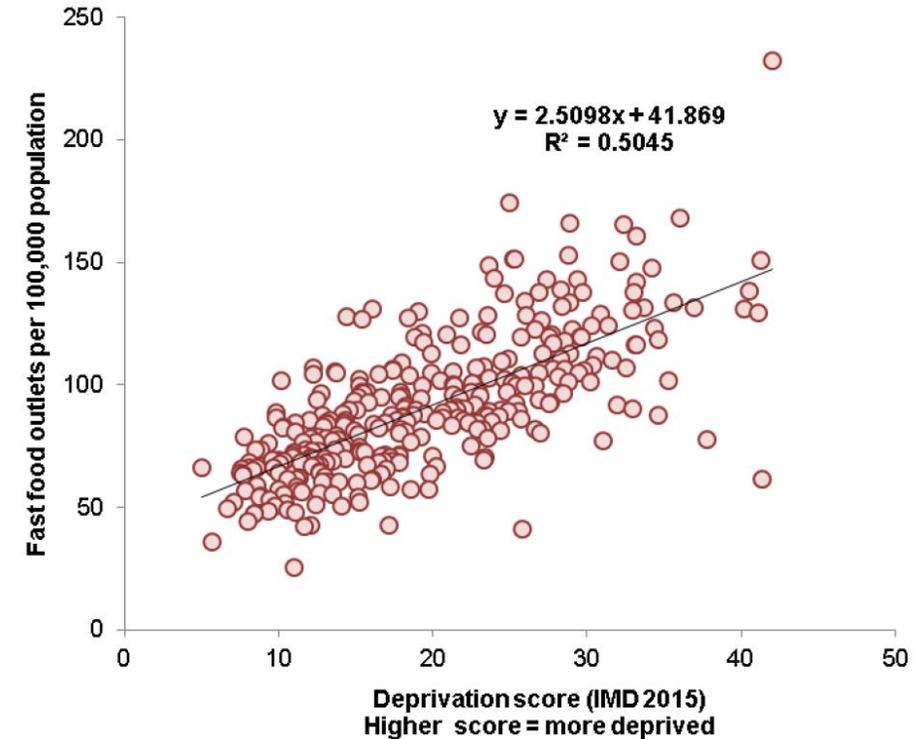


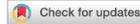
England value
Rate per 100,000 population
96.1



Data source: Food Standards Agency, Food Hygiene Rating Scheme
ONS mid-year population estimates 2016

Relationship between density of fast food outlets and deprivation by local authority*





OPEN

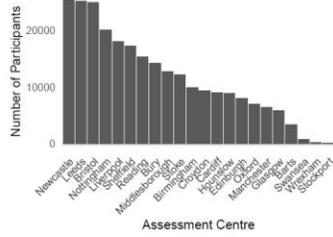
Gene-environment correlations across geographic regions affect genome-wide association studies

Abdel Abdellaoui¹, Conor V. Dolan², Karin J. H. Verweij¹ and Michel G. Nivard²

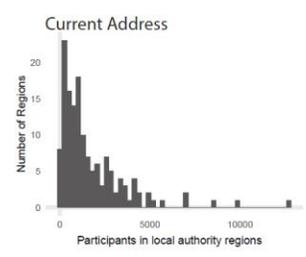
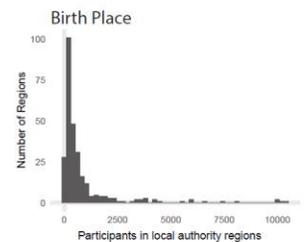
The paper consists of two parts:

- **Part 1:** detecting gene-environment correlations using polygenic scores in up to 43,516 siblings
 - **Part 2:** controlling for gene-environment correlations in GWASs in up to 254,387 participants

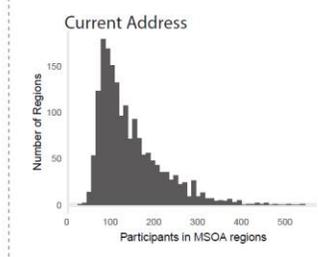
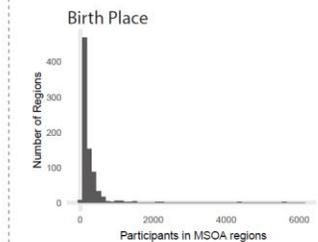
UK Biobank Assessment Centres



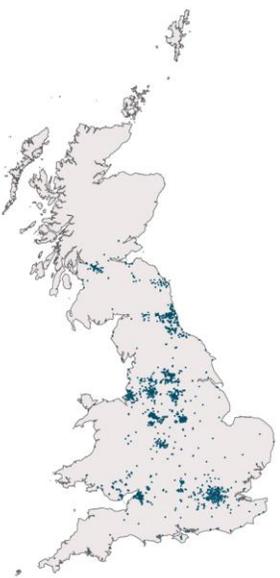
Local Authority



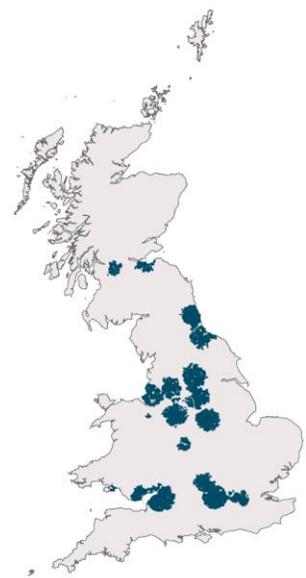
MSOA



N = ~255k →

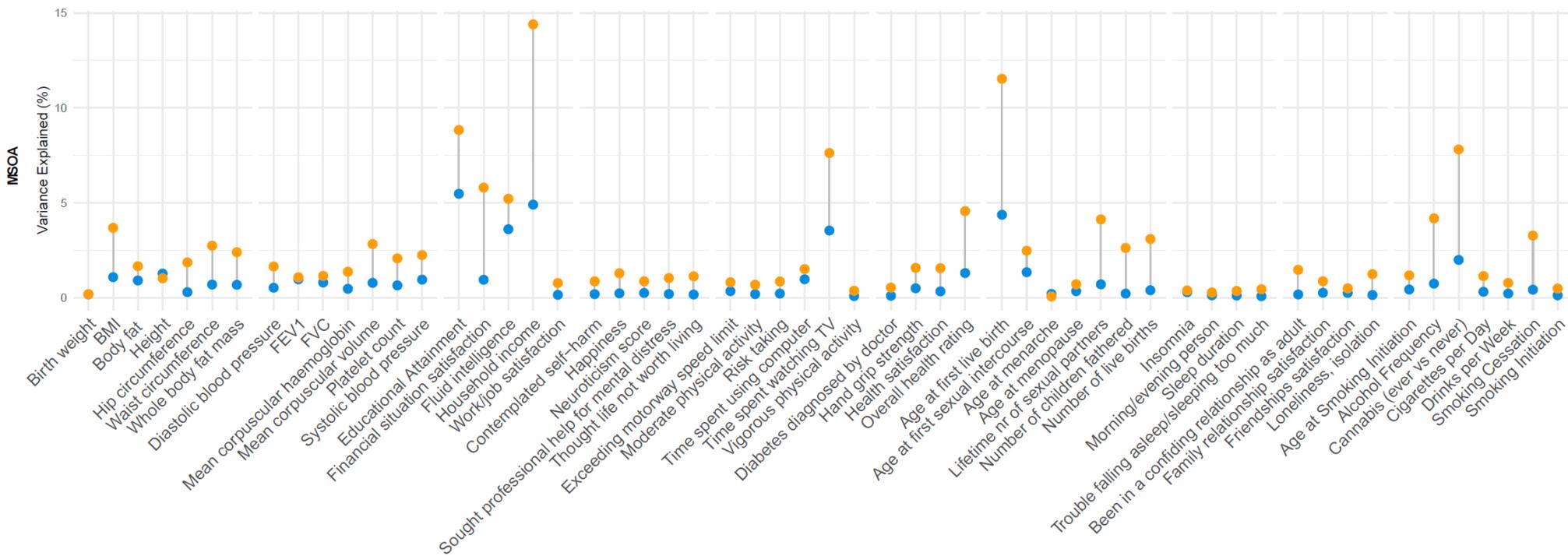
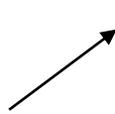
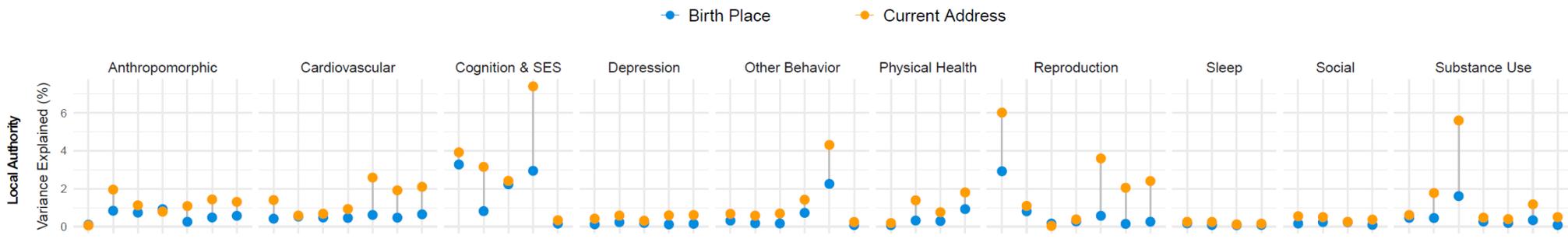


Birth Place



Current Address

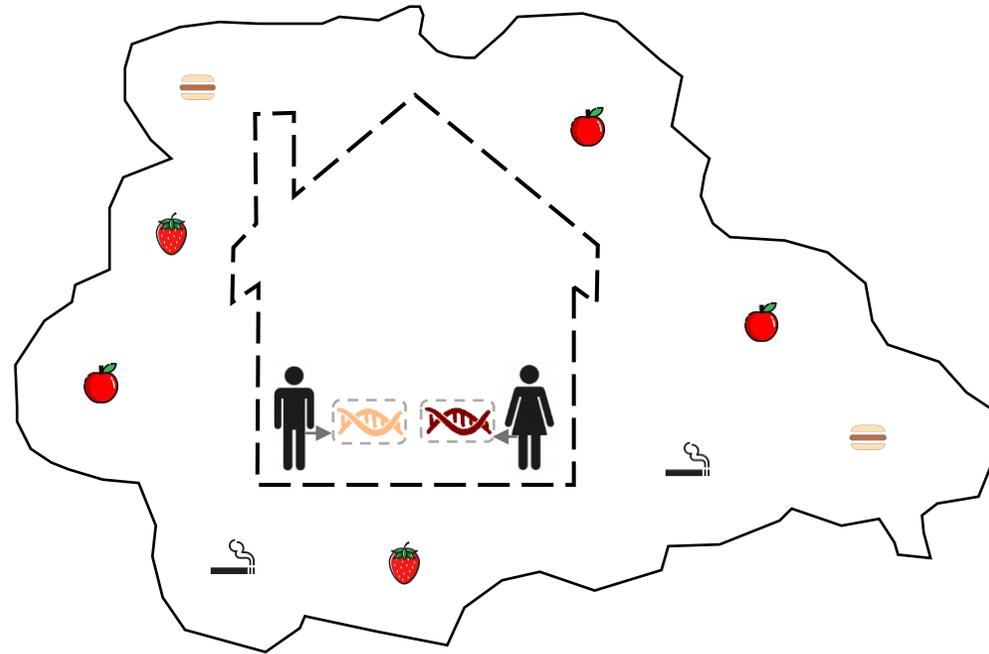
Variance explained by region:

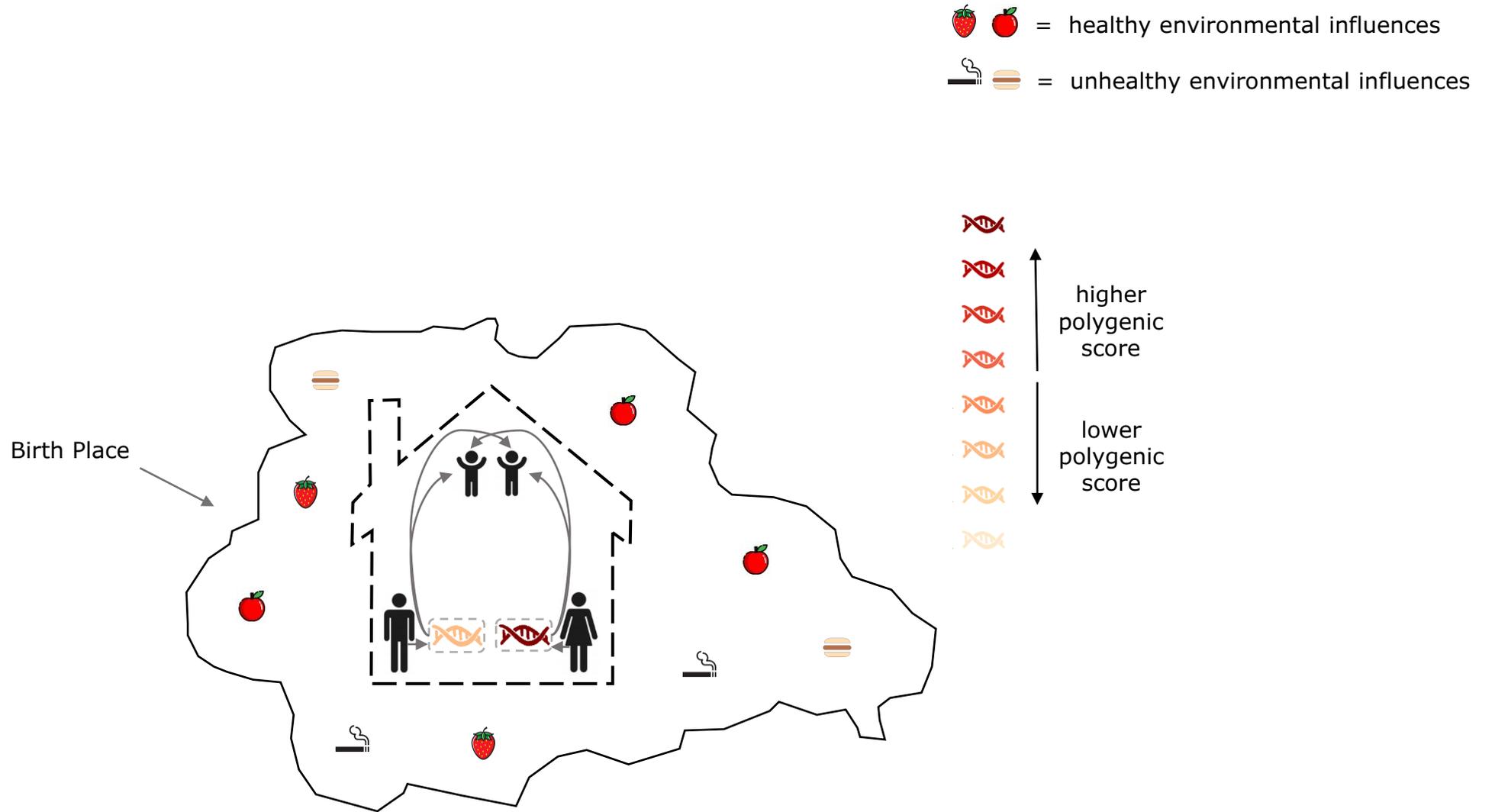


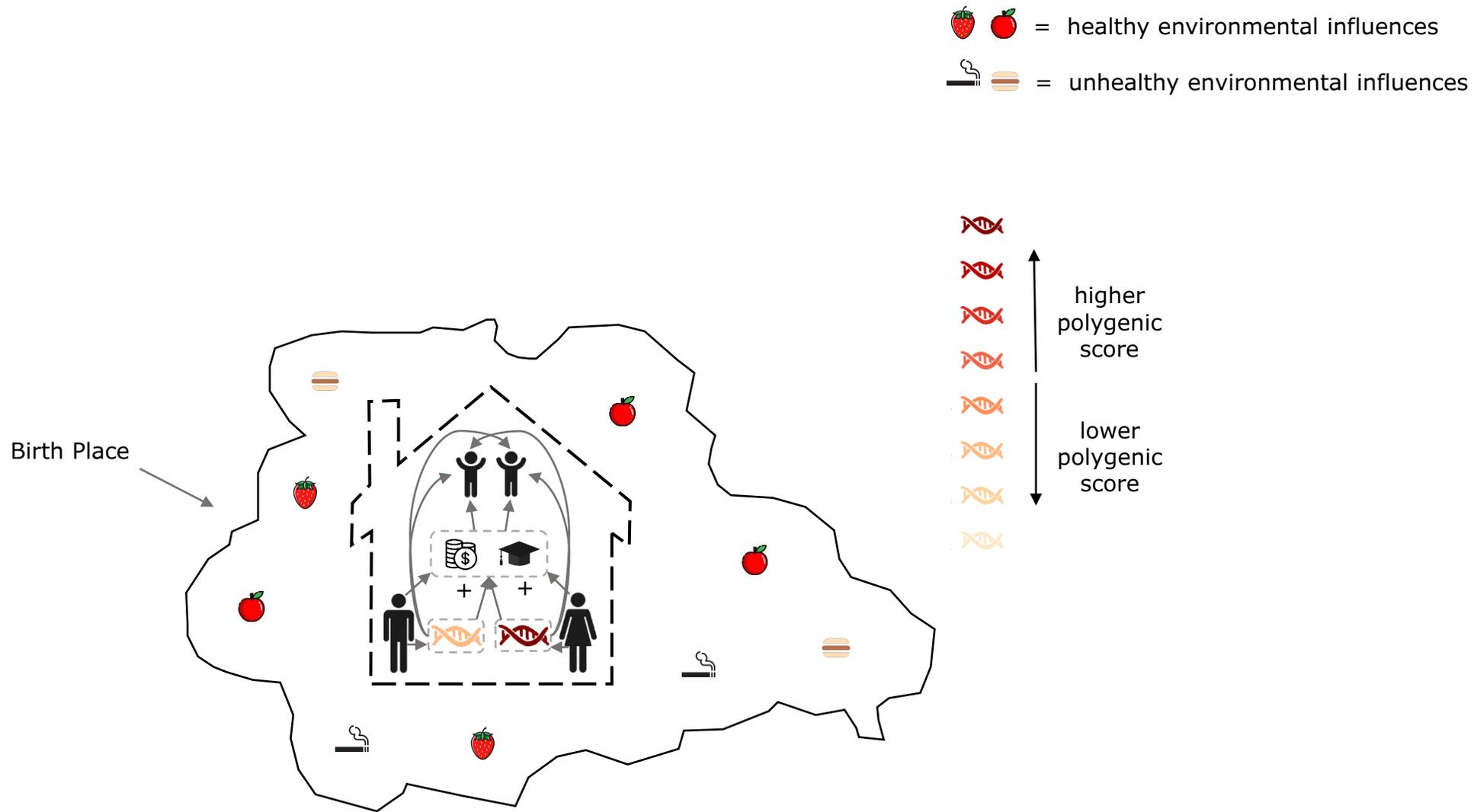
Polygenic Scores in Siblings

🍓 🍎 = healthy environmental influences
🚬 🍔 = unhealthy environmental influences

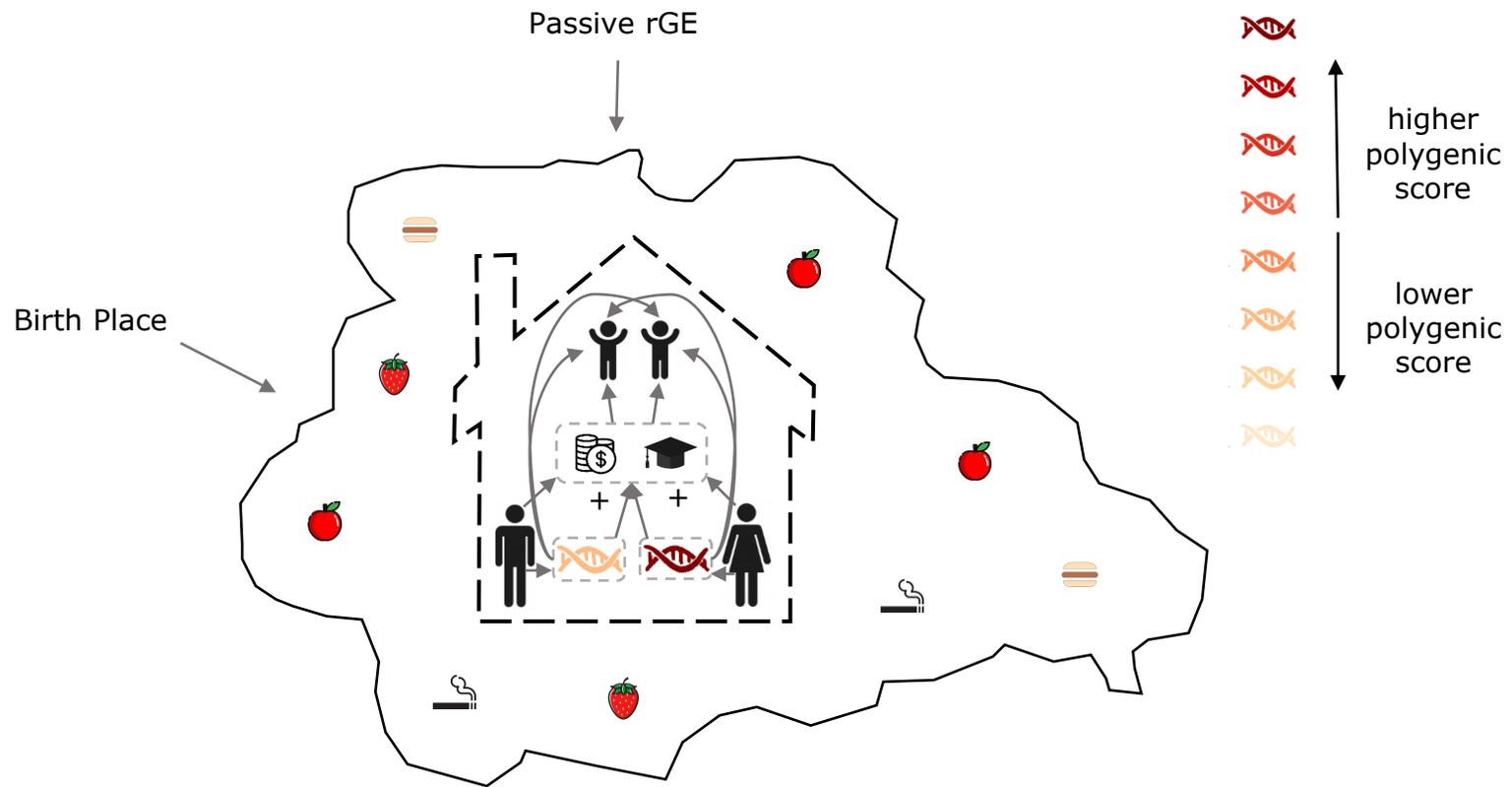
🧬
🧬
🧬
🧬
🧬
🧬
🧬
🧬
↑ higher polygenic score
↓ lower polygenic score

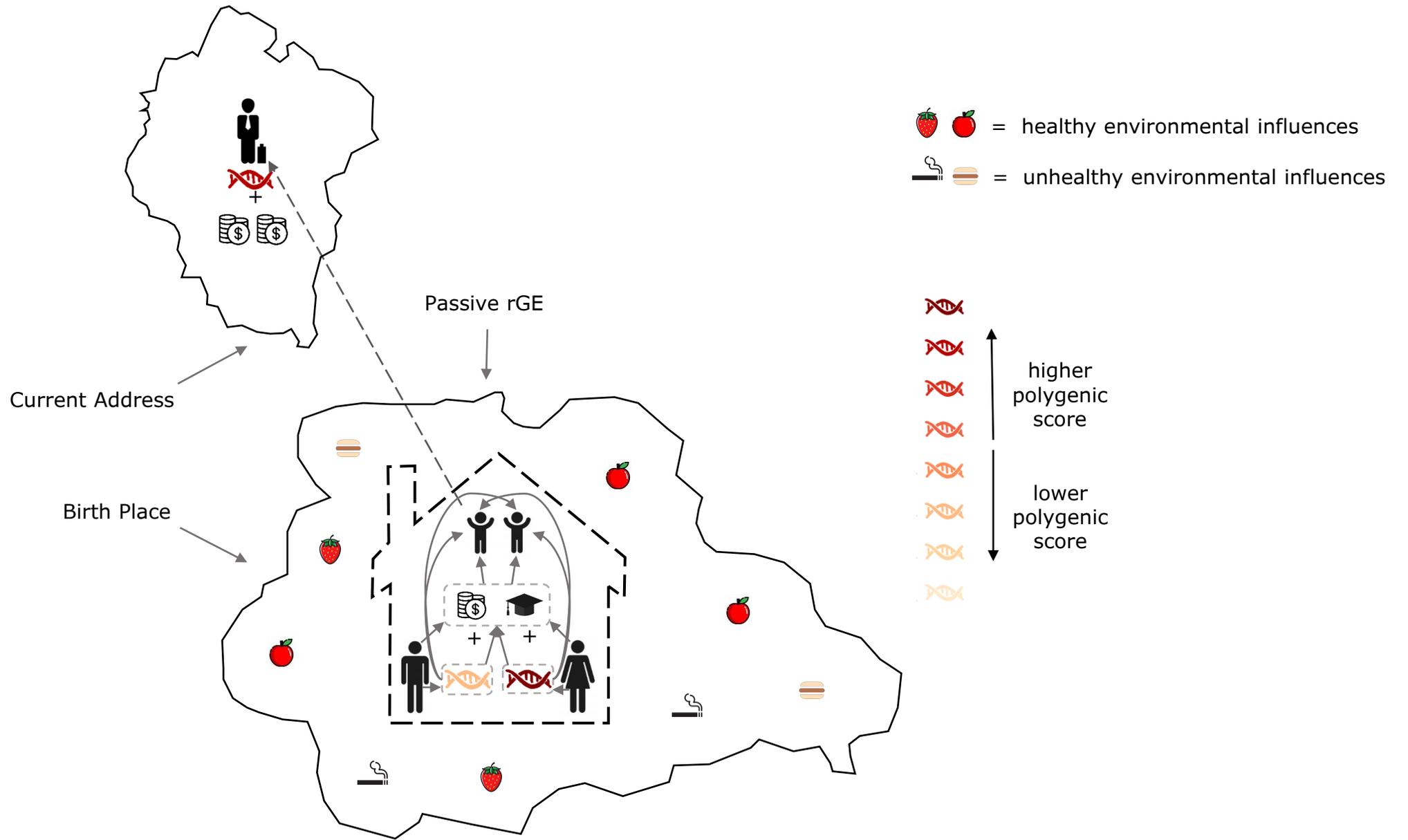


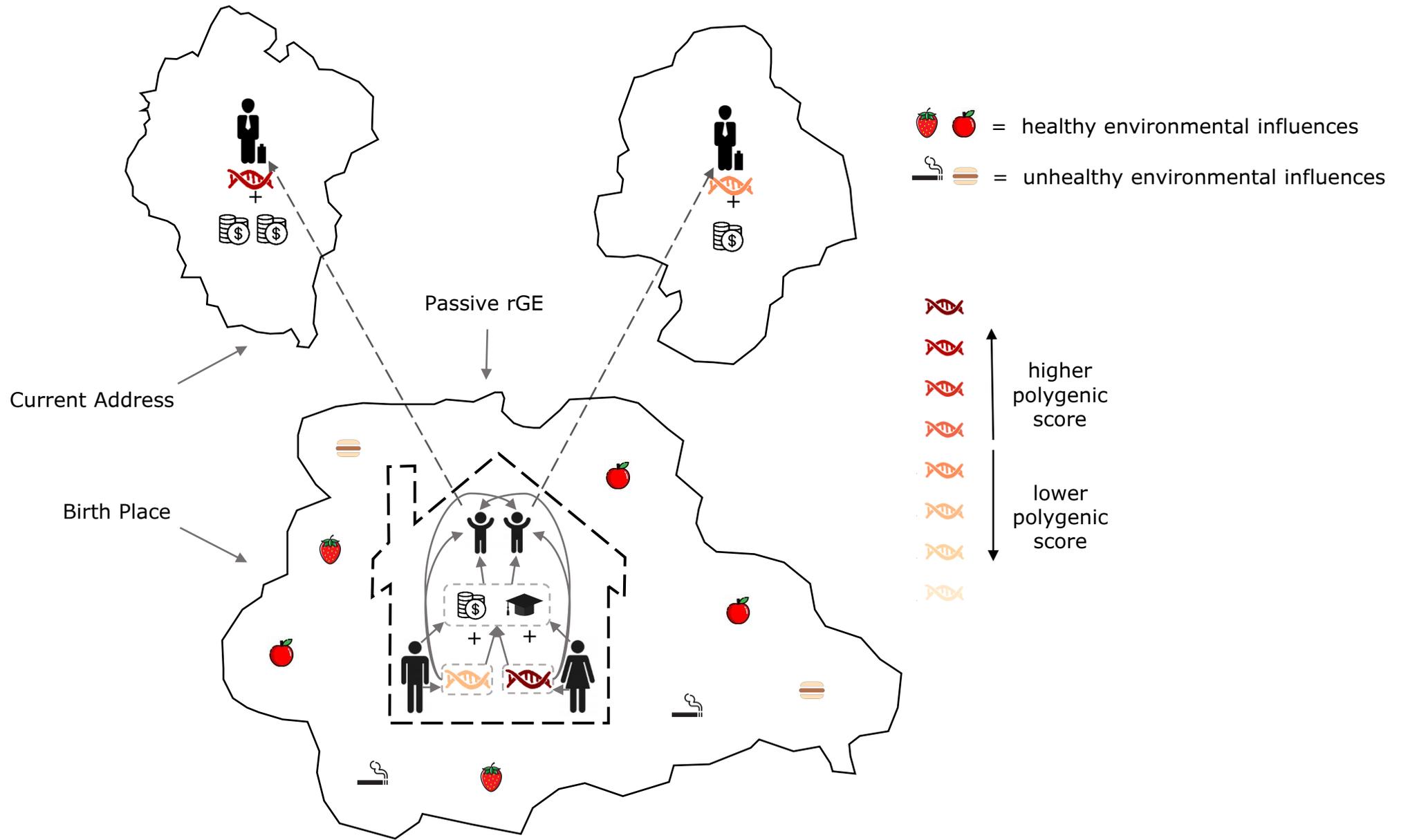


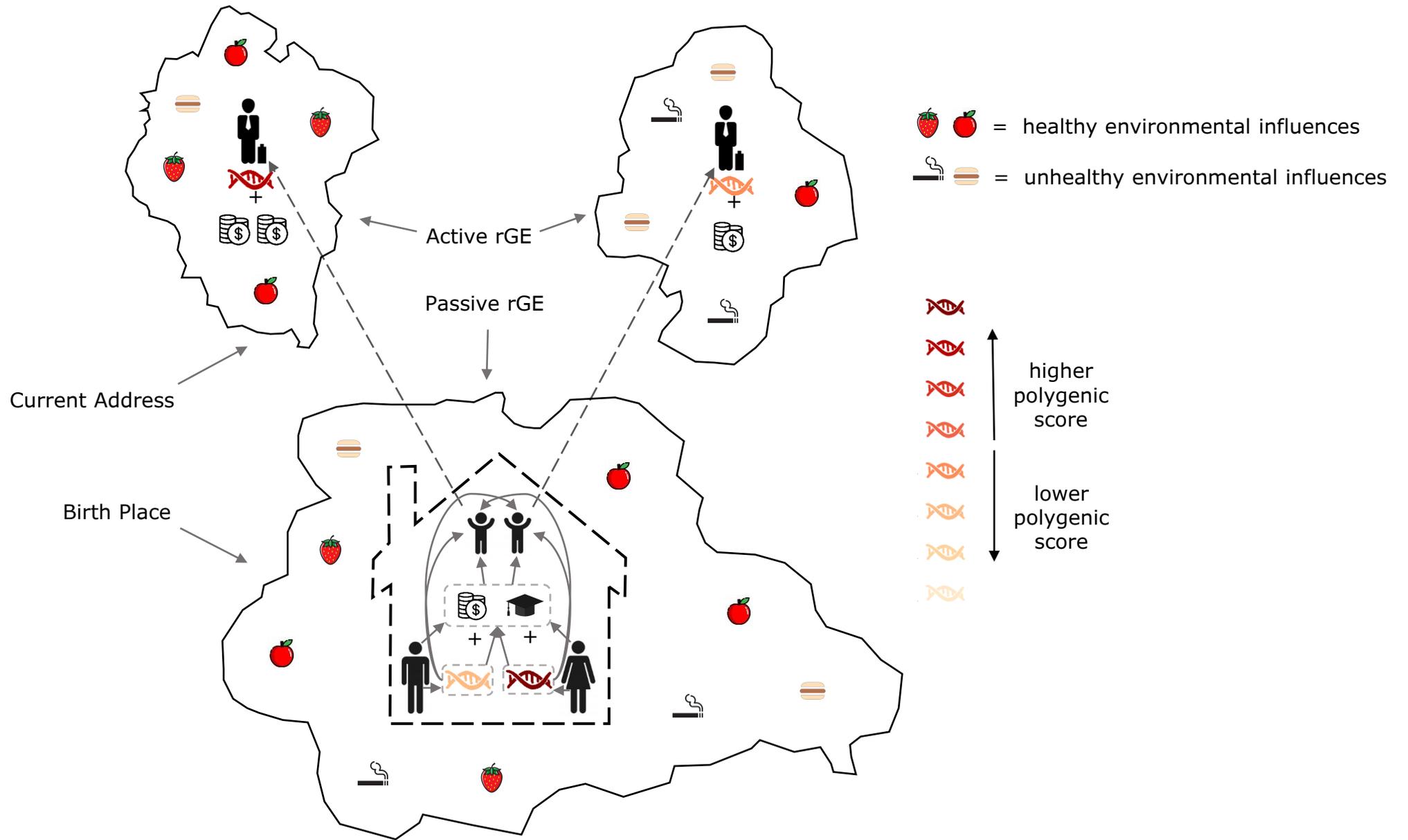


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Comparing Within- and Between-Family Polygenic Score Prediction

Saskia Selzam,^{1,*} Stuart J. Ritchie,¹ Jean-Baptiste Pingault,^{1,2} Chandra A. Reynolds,³ Paul F. O'Reilly,^{1,4}
and Robert Plomin¹

$$Y_{ij} = \alpha_0 + \beta PRS_{ij} + \gamma_j + \varepsilon_{ij},$$

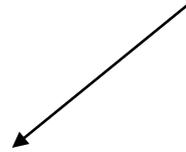
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Within-family
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$$Y_{ij} = \alpha_0 + \beta_W (PRS_{ij} - \overline{PRS}_j) + \beta_B \overline{PRS}_j + \gamma_j + \varepsilon_{ij}$$

Between-
family effect

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Between-family effect

In children (N ~2,300 pairs), predictive power of polygenic scores of cognitive traits (intelligence & education) was 60% greater between families than within families.

$$Y_{ij} = \alpha_0 + \beta PRS_{ij} + \gamma_j + \varepsilon_{ij},$$

Within-family
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$$Y_{ij} = \alpha_0 + \beta_W (PRS_{ij} - \overline{PRS}_j) + \beta_B \overline{PRS}_j + \gamma_j + \varepsilon_{ij}$$

Between-
family effect

We looked at adult siblings
(N ~26k pairs) in UK Biobank.

PRS = Educational
Attainment Polygenic Score
(based on GWAS excluding
all British)

$$Y_{ij} = \alpha_0 + \beta PRS_{ij} + \gamma_j + \varepsilon_{ij},$$



Within-family
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$$Y_{ij} = \alpha_0 + \beta_W (PRS_{ij} - \overline{PRS}_j) + \beta_B \overline{PRS}_j + \gamma_j + \varepsilon_{ij}$$

Between-
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Are there any additional gene-
environment correlations at the
regional level not captured by family?

$$Y_{ij} = \alpha_0 + \beta PRS_{ij} + \gamma_j + \varepsilon_{ij},$$



Within-family
effect

*Decreases when adding
between-family effect*



$$Y_{ij} = \alpha_0 + \beta_W (PRS_{ij} - \overline{PRS}_j) + \beta_B \overline{PRS}_j + \gamma_j + \varepsilon_{ij}$$



Between-
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Within-family
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$$Y_{ijk} = \alpha_0 + \beta_W (PRS_{ijk} - \overline{PRS}_j - \overline{PRS}_k) + \beta_{BF} (\overline{PRS}_j - \overline{PRS}_k) + \beta_{BR} (\overline{PRS}_k) + \gamma_j + \gamma_k + \varepsilon_{ijk}$$

Between-
family effect

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?

Within-family effect

$$Y_{ij} = \alpha_0 + \beta_W (PRS_{ij} - \overline{PRS}_j) + \beta_B \overline{PRS}_j + \gamma_j + \varepsilon_{ij}$$

Between-family effect

?

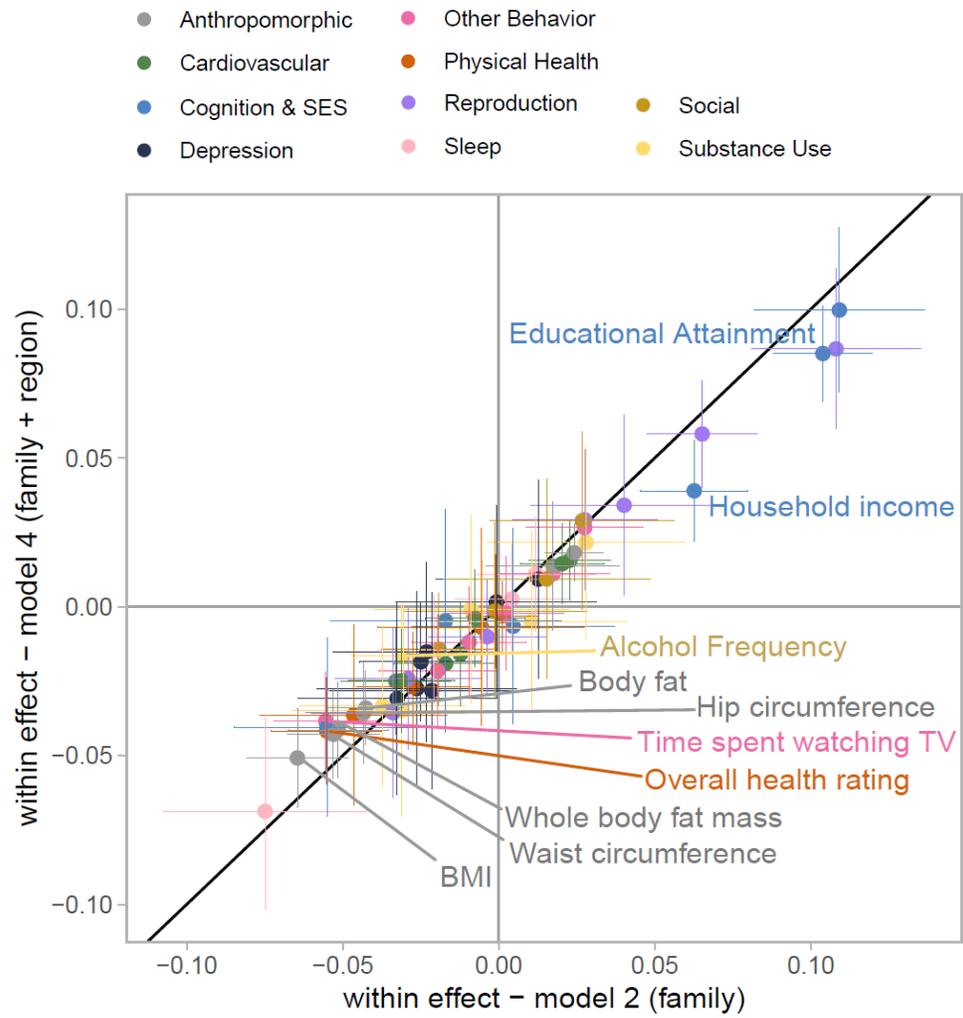
Within-family effect

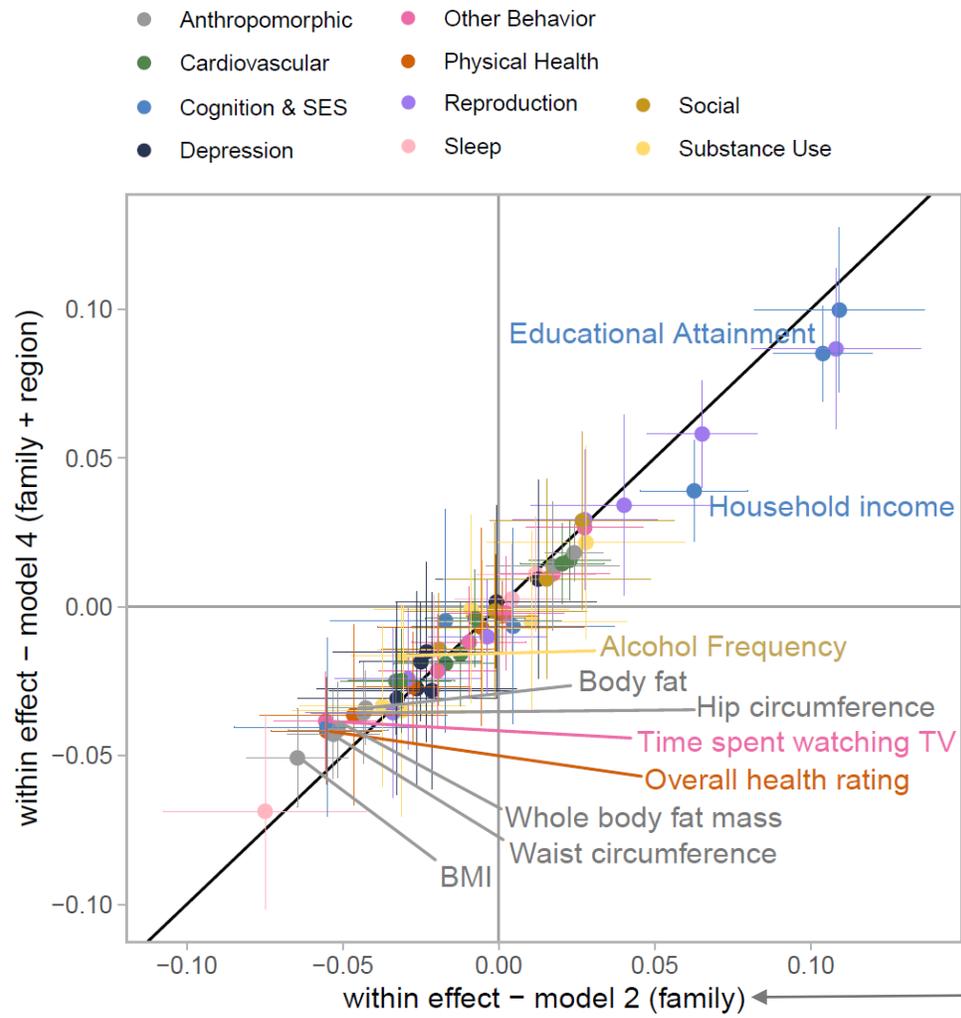
Between-region effect

Are there any additional gene-environment correlations at the regional level not captured by family? →

$$Y_{ijk} = \alpha_0 + \beta_W (PRS_{ijk} - \overline{PRS}_j - \overline{PRS}_k) + \beta_{BF} (\overline{PRS}_j - \overline{PRS}_k) + \beta_{BR} (\overline{PRS}_k) + \gamma_j + \gamma_k + \varepsilon_{ijk}$$

Between-family effect



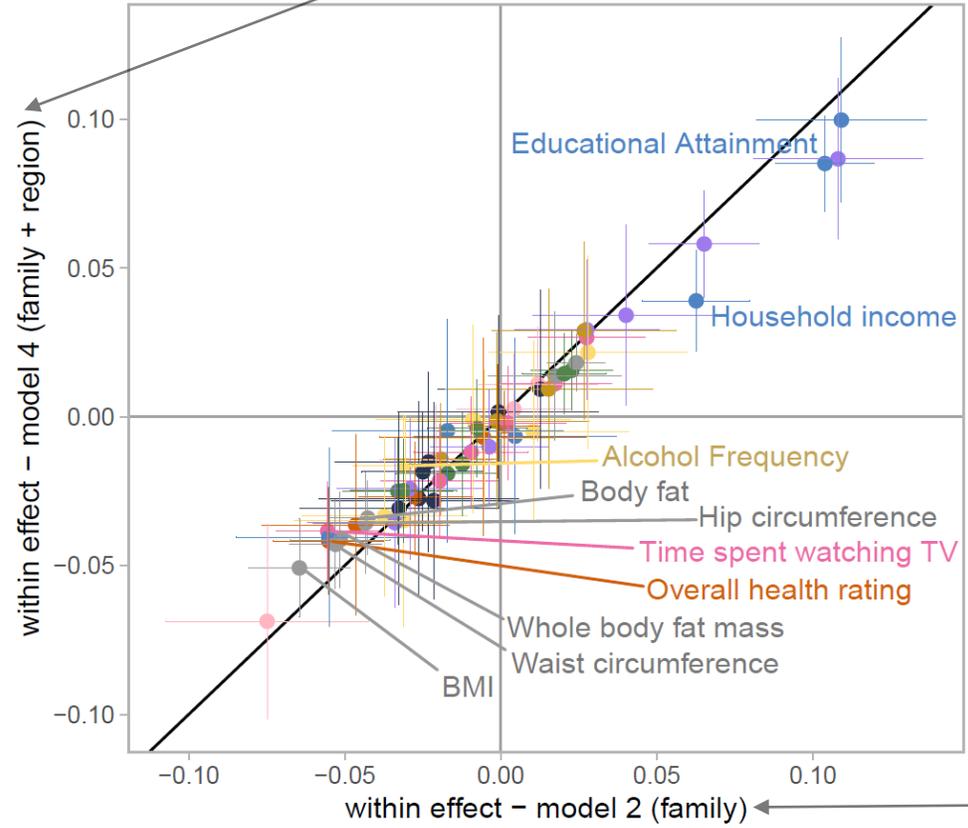


$$Y_{ij} = \alpha_0 + \underbrace{\beta_W (PRS_{ij} - \overline{PRS}_j)}_{\text{Within-family effect}} + \underbrace{\beta_B \overline{PRS}_j}_{\text{Between-family effect}} + \gamma_j + \varepsilon_{ij}$$

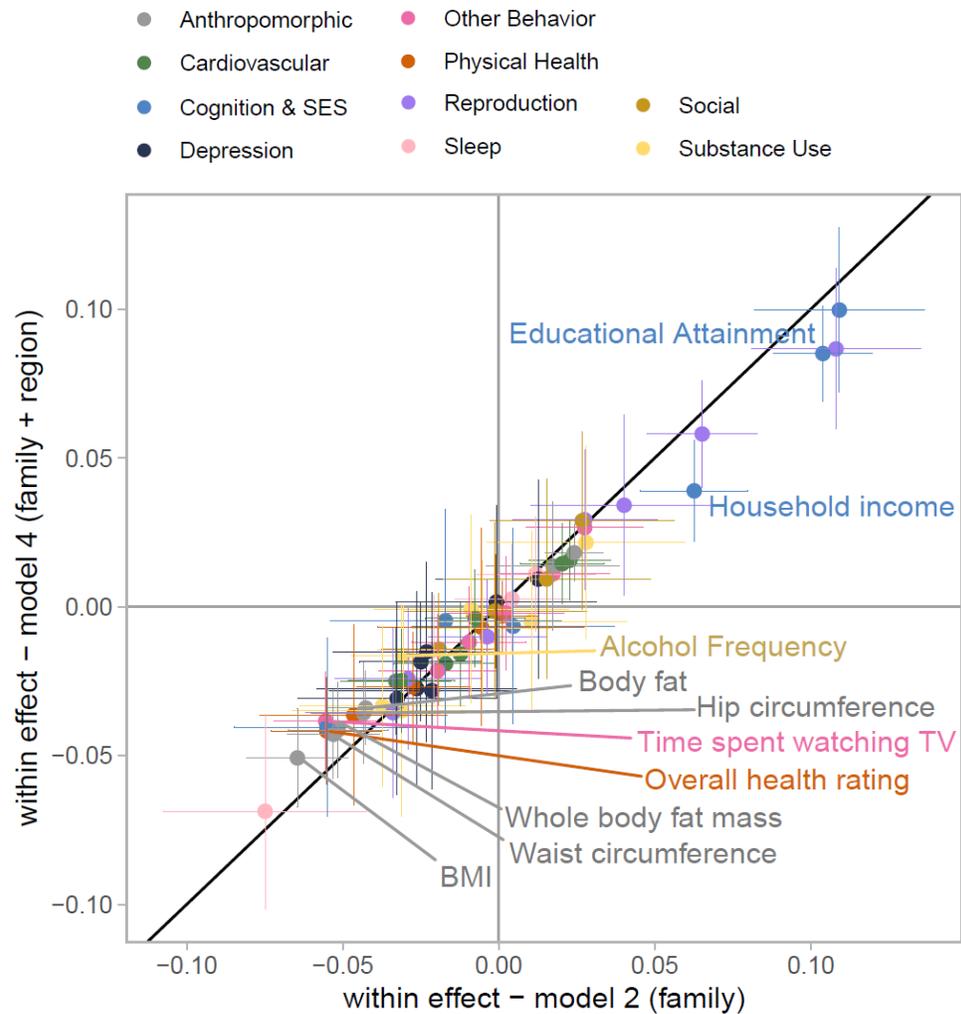
- Anthropomorphic
- Cardiovascular
- Cognition & SES
- Depression
- Other Behavior
- Physical Health
- Reproduction
- Sleep
- Social
- Substance Use

$$Y_{ijk} = \alpha_0 + \underbrace{\beta_W (PRS_{ijk} - \overline{PRS}_j - \overline{PRS}_k)}_{\text{Within-family effect}} + \underbrace{\beta_{BF} (\overline{PRS}_j - \overline{PRS}_k) + \beta_{BR} (\overline{PRS}_k)}_{\text{Between-family effect}} + \gamma_j + \gamma_k + \varepsilon_{ijk}$$

Between-region effect



$$Y_{ij} = \underbrace{\alpha_0 + \beta_W (PRS_{ij} - \overline{PRS}_j)}_{\text{Within-family effect}} + \underbrace{\beta_B \overline{PRS}_j + \gamma_j + \varepsilon_{ij}}_{\text{Between-family effect}}$$



Adding geography significantly decreased within-family effect for 10 traits. The most significant 5:

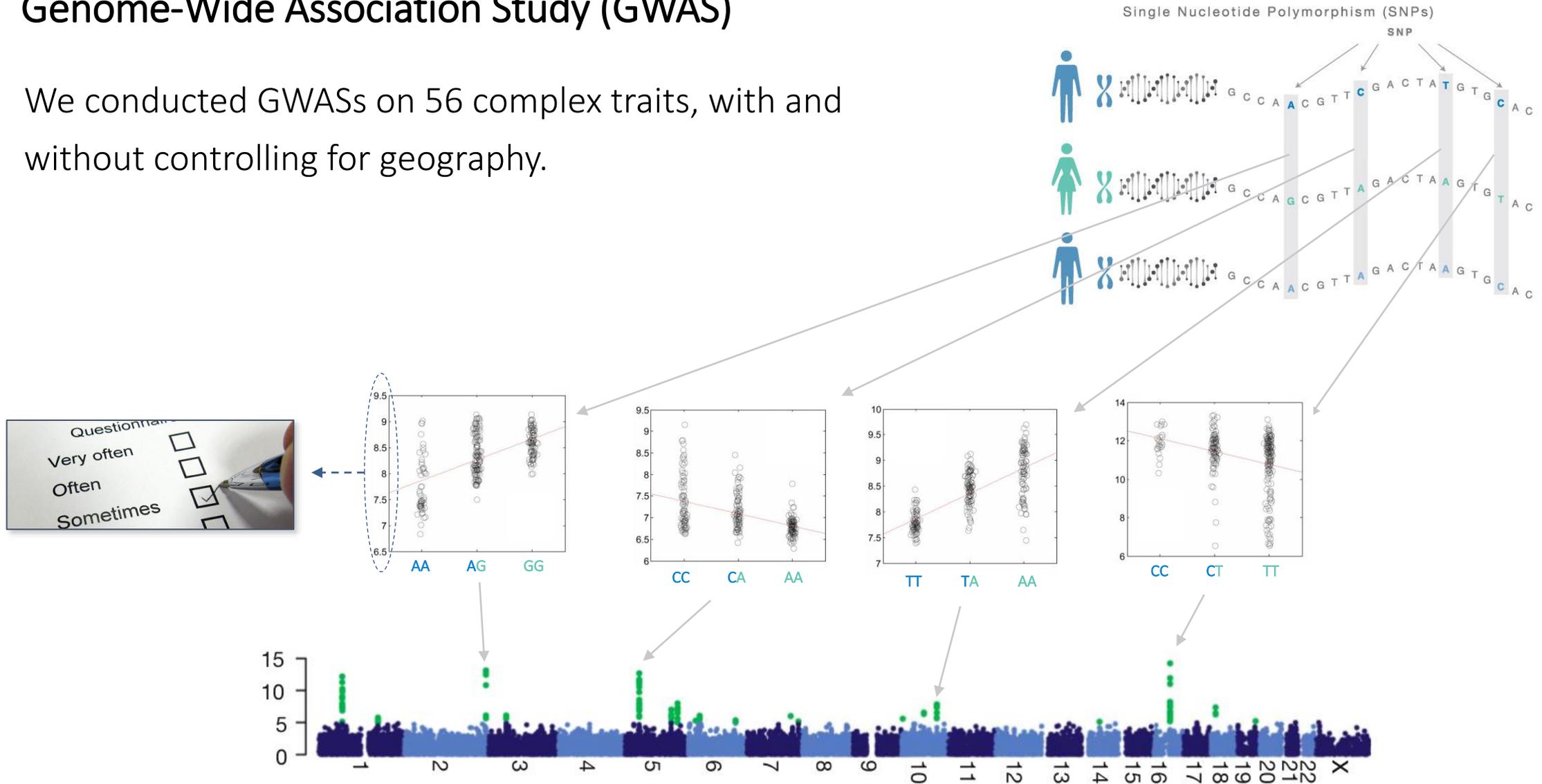
- BMI ($p = 1 \times 10^{-5}$)
- Waist circumference ($p = 1 \times 10^{-4}$)
- Household income ($p = 1 \times 10^{-4}$)
- Time spent watching TV ($p = 3 \times 10^{-4}$)
- Whole body fat mass ($p = 6 \times 10^{-4}$)

These are traits that are more subject to change after siblings migrated out of the parental residence.

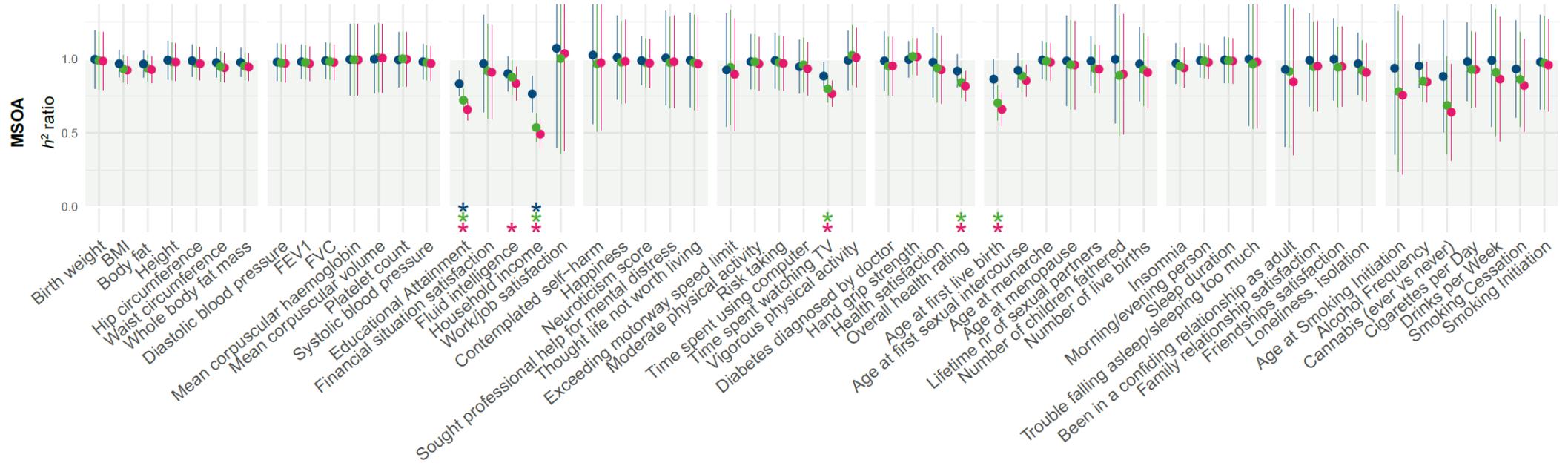
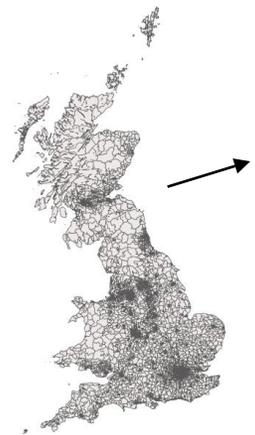
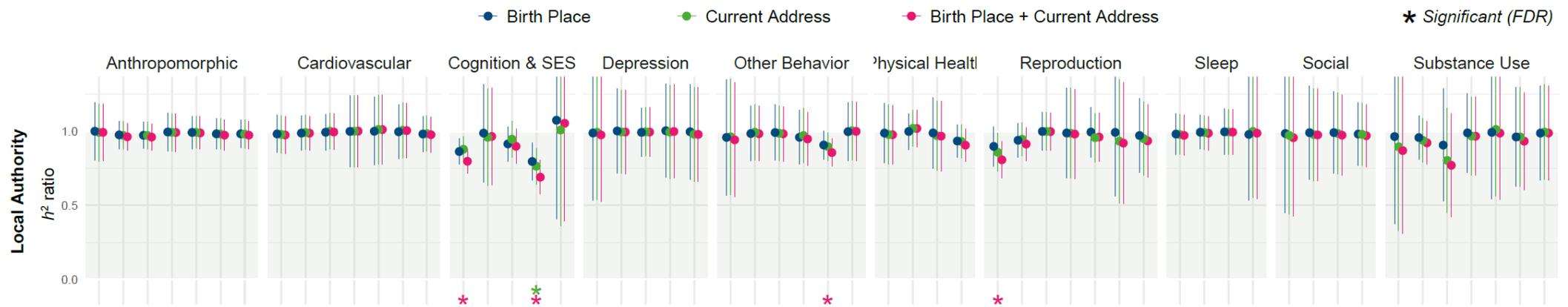
GWASs Controlled for Geography

Genome-Wide Association Study (GWAS)

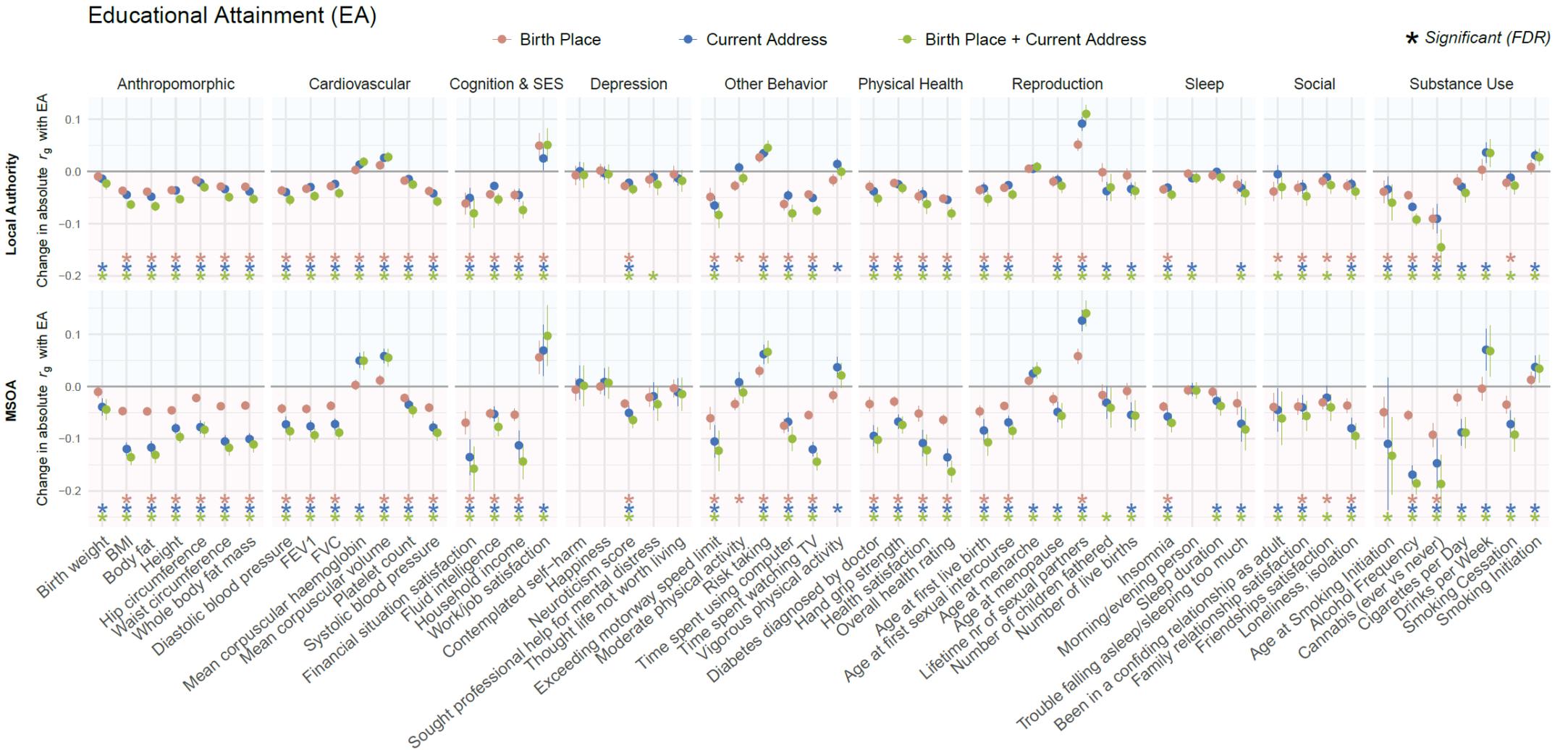
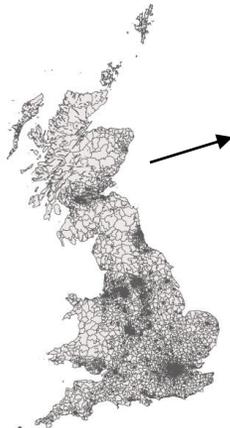
- We conducted GWASs on 56 complex traits, with and without controlling for geography.



Changes in SNP-based heritability



Changes in genetic correlation with SES - Educational Attainment



Changes in genetic correlation with SES - Household Income

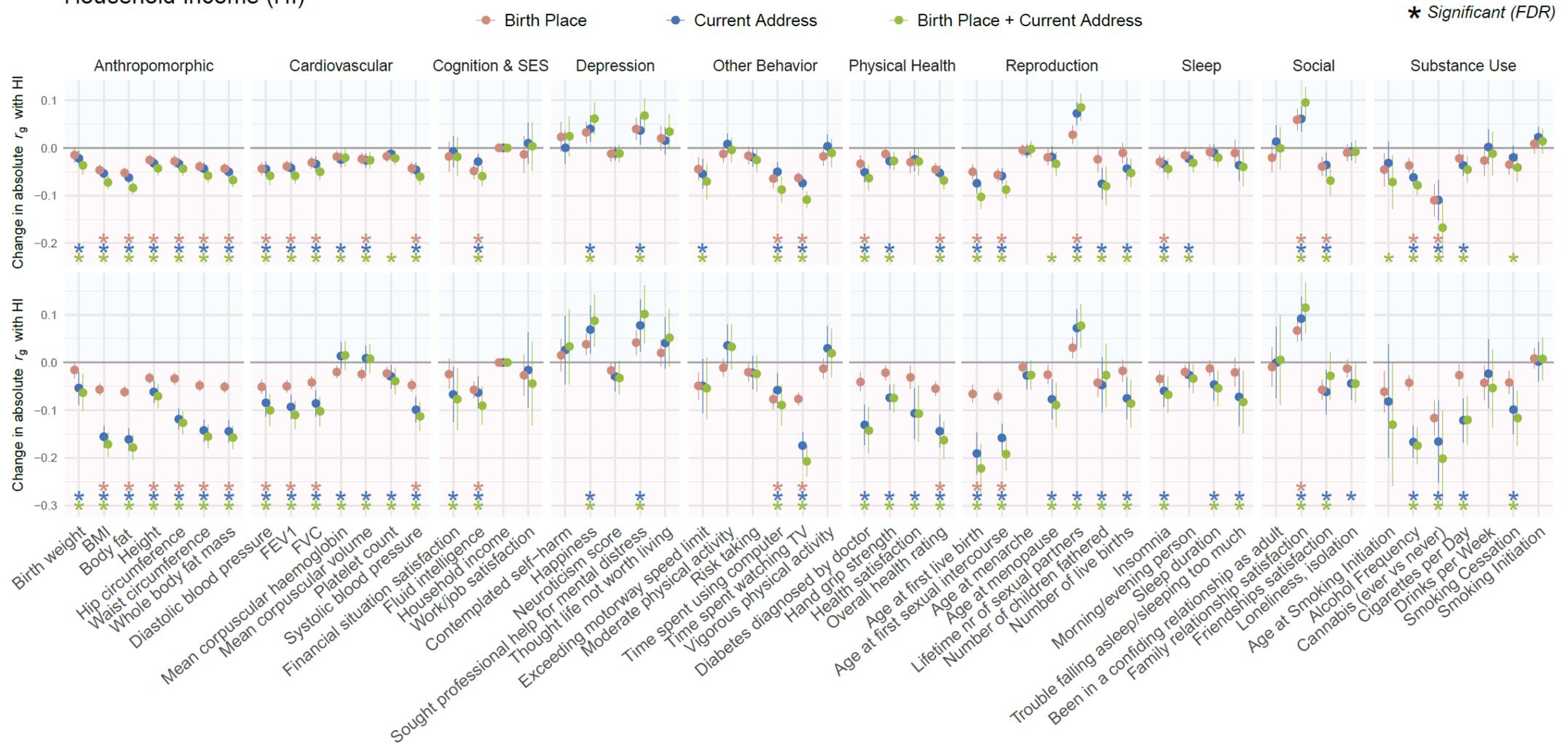


Local Authority



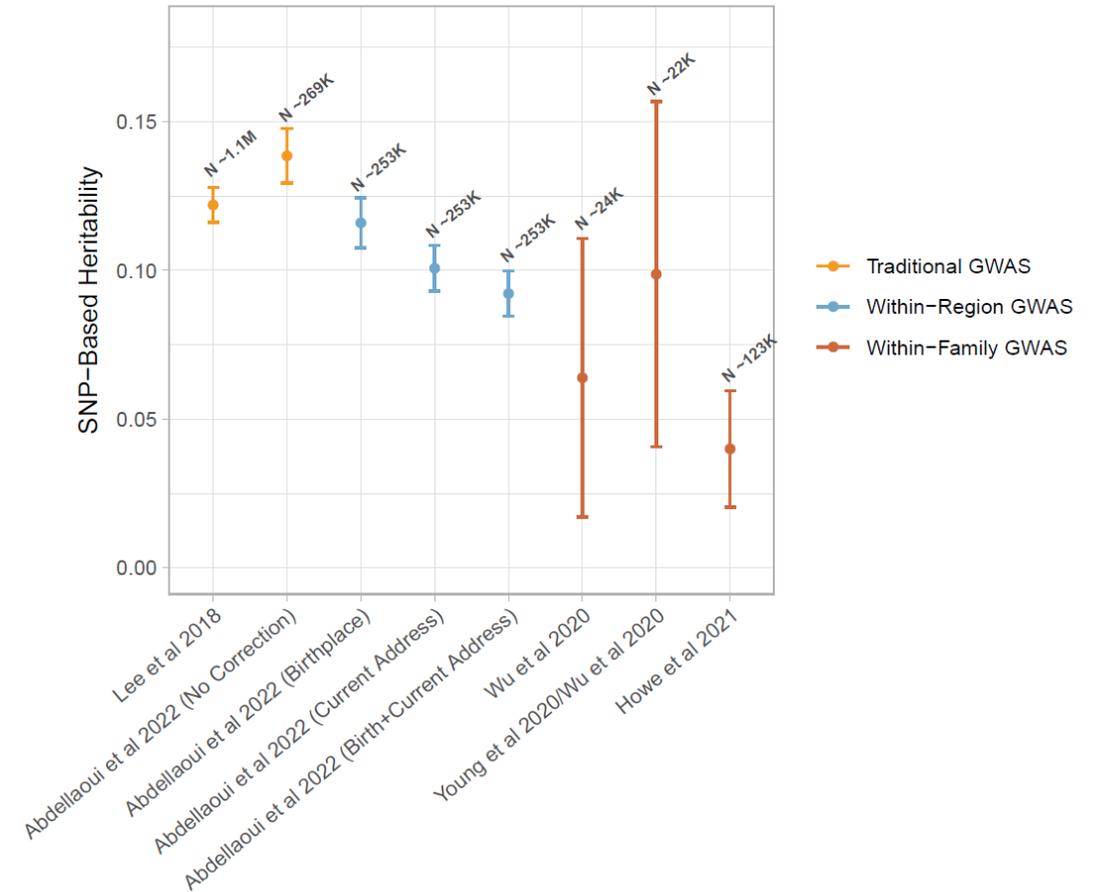
MSOA

Household Income (HI)



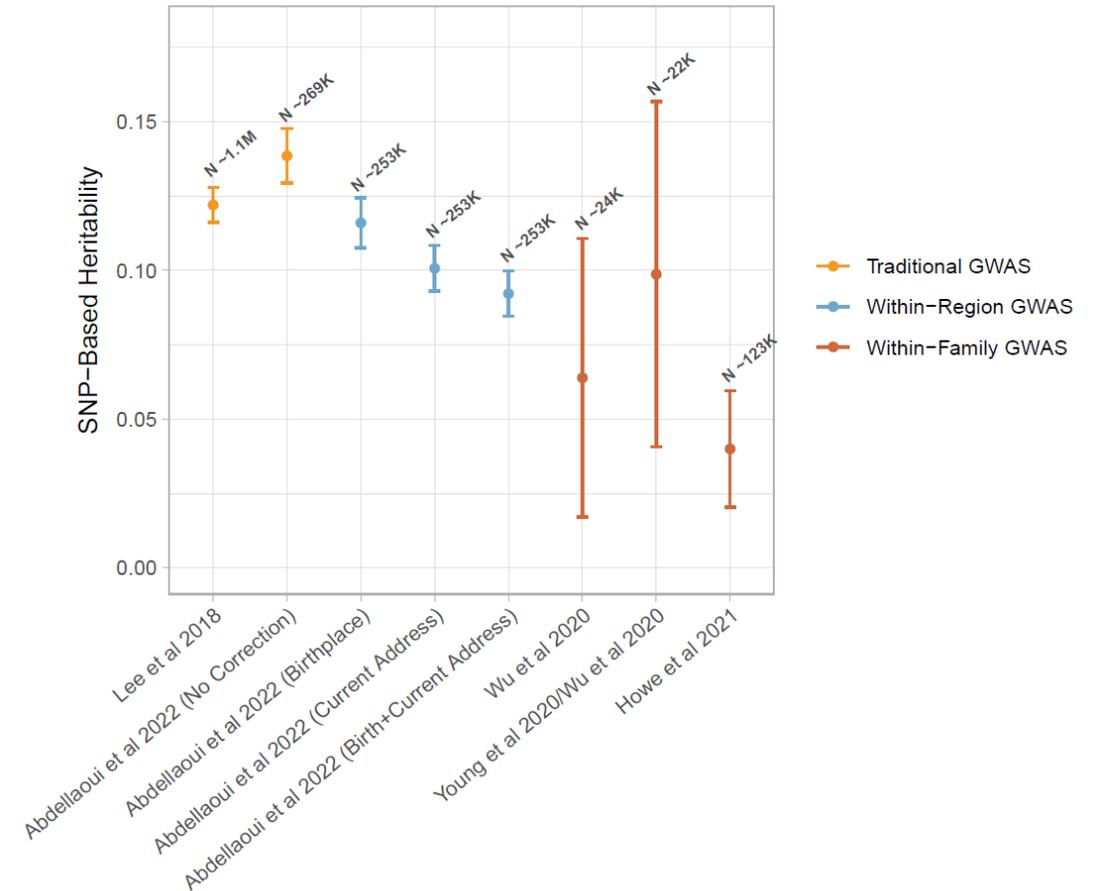
Summary

- Controlling for geographic region decreases the heritability for SES (education/income)



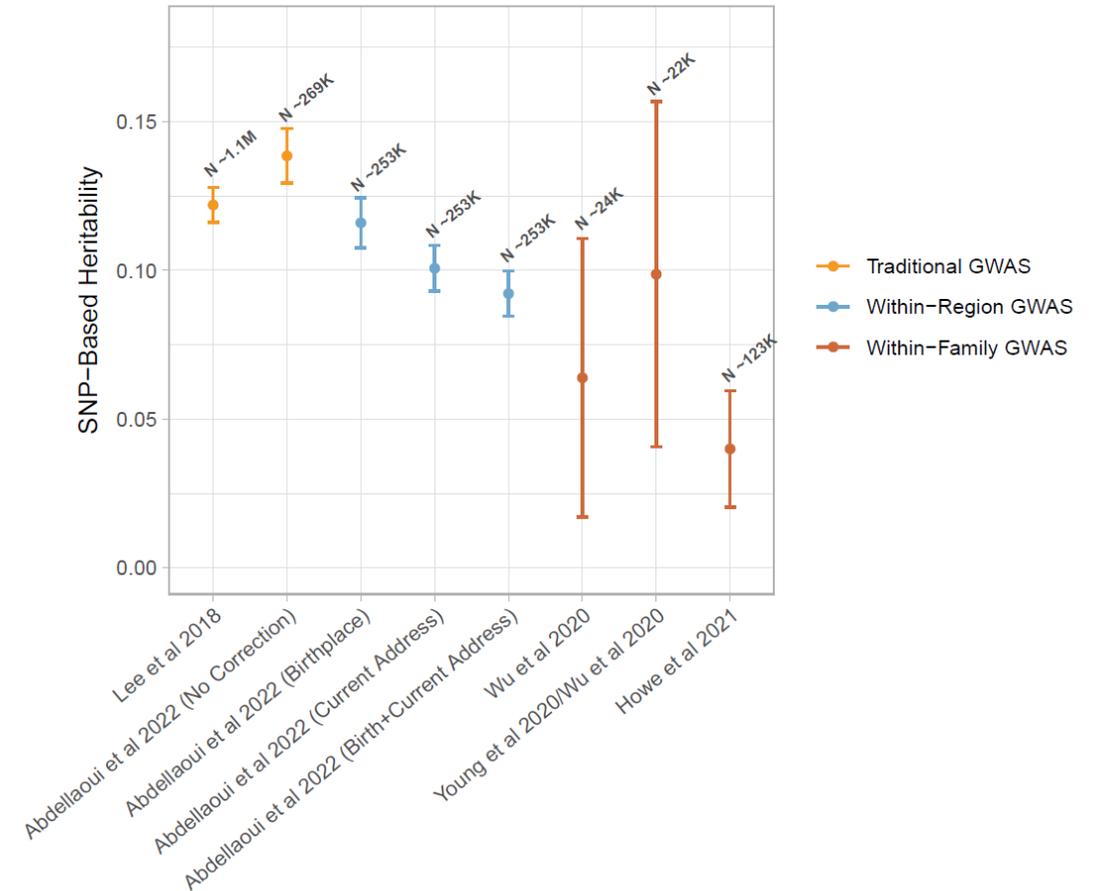
Summary

- Controlling for geographic region decreases the heritability for SES (education/income)
- Controlling for region reduces genetic correlations with SES (EA/income), most significantly for BMI, sedentary behavior, and substance use



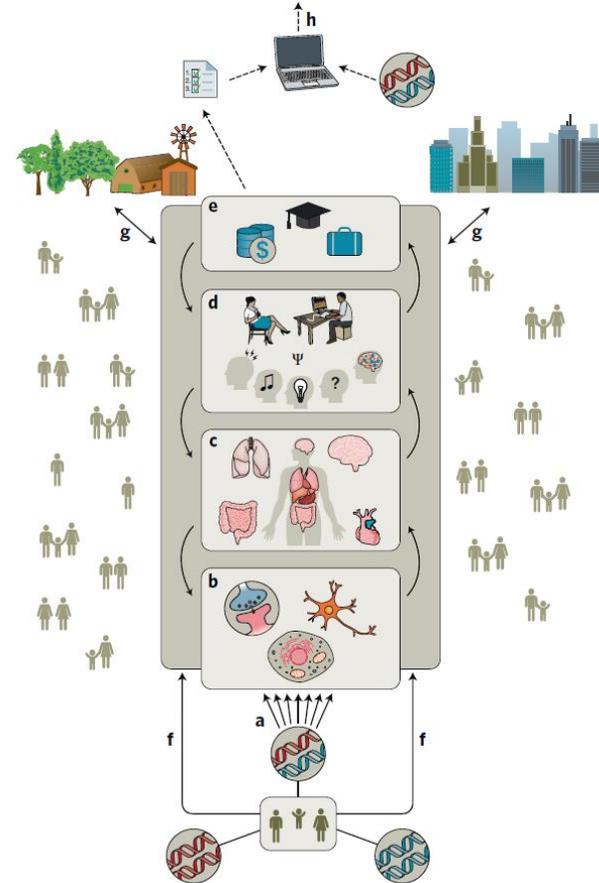
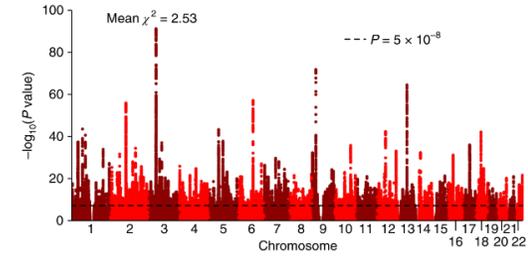
Summary

- Controlling for geographic region decreases the heritability for SES (education/income)
- Controlling for region reduces genetic correlations with SES (EA/income), most significantly for BMI, sedentary behavior, and substance use
- Our findings can be explained driven by both passive and active gene-environment correlations



Key points

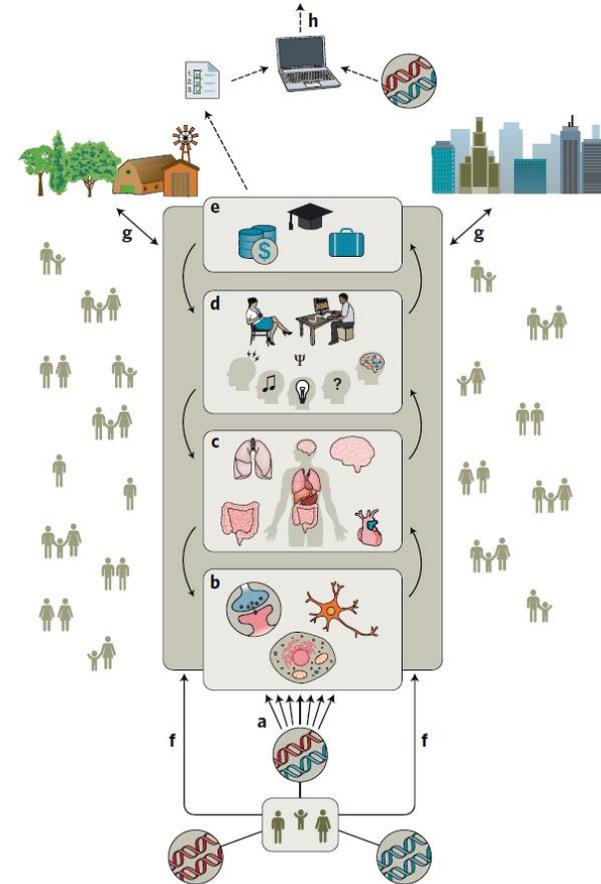
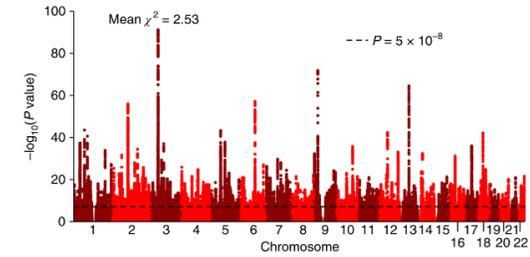
Society makes genetic effects stronger.



Key points

Society makes genetic effects stronger.

We reward certain genetic propensities with a better environment, and “punish” the lack of those propensities with a worse environment.



Key points

Society makes genetic effects stronger.

We reward certain genetic propensities with a better environment, and “punish” the lack of those propensities with a worse environment.

This makes society more unequal.

This makes studying genetics more difficult.

