Genome-Wide Association Studies

Part 4: gene-environment correlations and assortative mating

International Statistical Genetics Workshop – 2026

Abdel Abdellaoui
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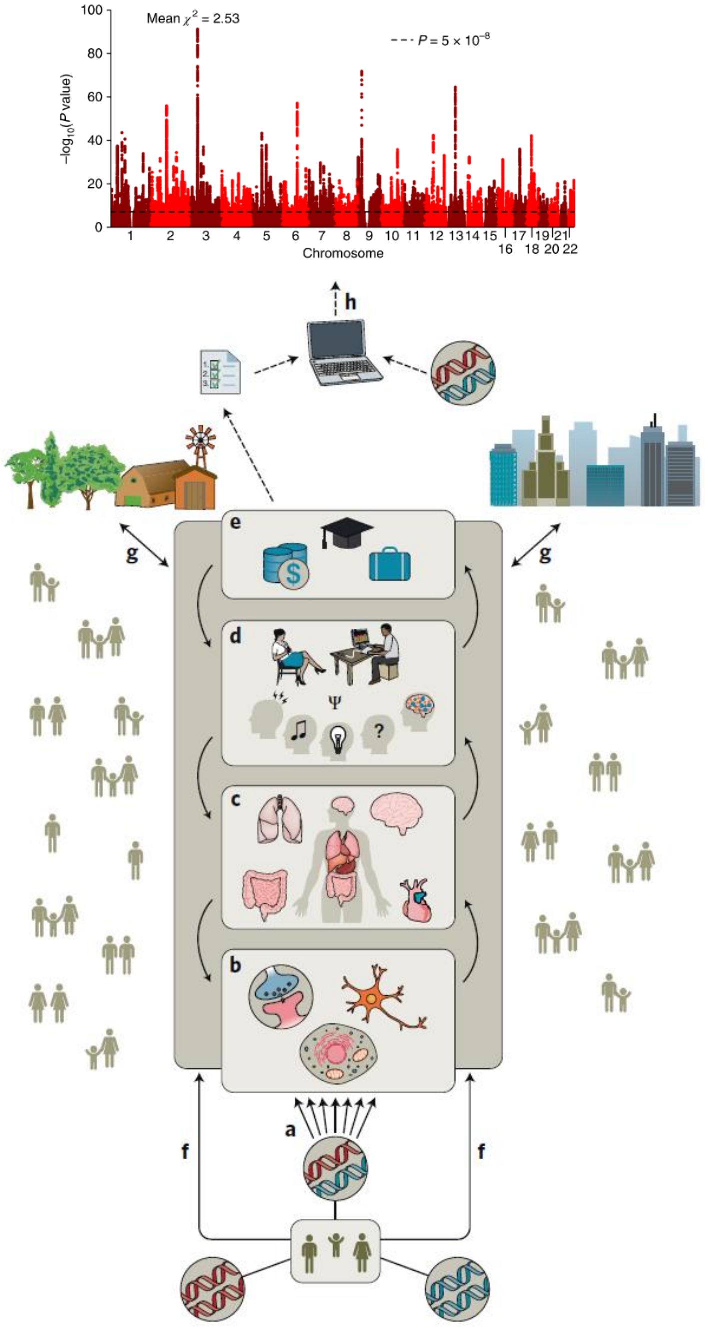

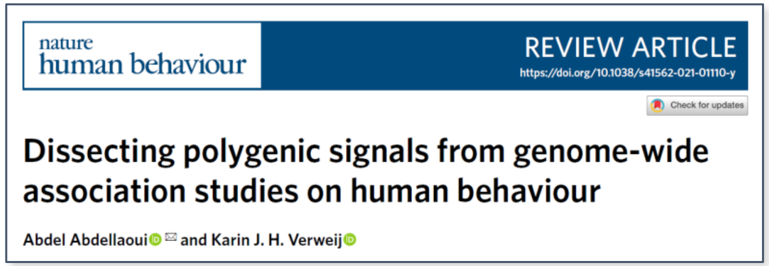
nature human behaviour

REVIEW ARTICLE

https://doi.org/10.1038/s41562-021-01110-y

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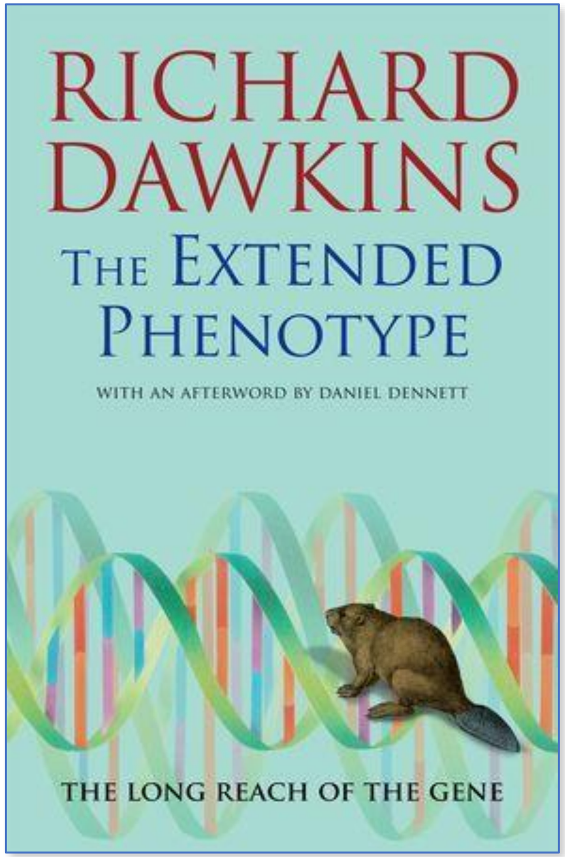
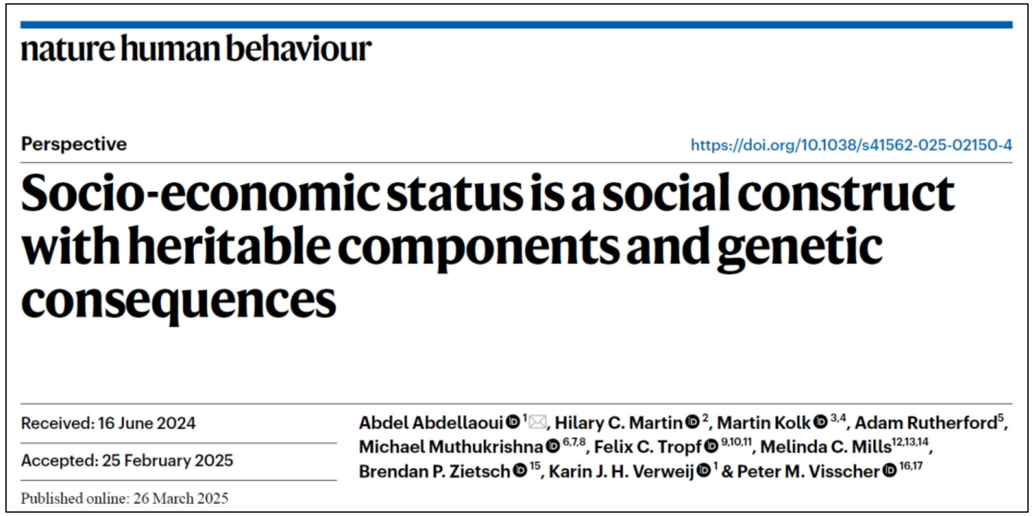
Dissecting polygenic signals from genome-wide association studies on human behaviour

Abdel Abdellaoui ✉ and Karin J. H. Verweij



"Phenotype" should include all effects that a gene has on its environment, both **inside** and **outside** the body of the individual organism.



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Perspective

https://doi.org/10.1038/s41562-025-02150-4

Socio-economic status is a social construct with heritable components and genetic consequences

Received: 16 June 2024

Accepted: 25 February 2025

Abdel Abdellaoui [1] ✉, Hilary C. Martin [2], Martin Kolk [3,4], Adam Rutherford[5], Michael Muthukrishna [6,7,8], Felix C. Tropf [9,10,11], Melinda C. Mills[12,13,14], Brendan P. Zietsch [15], Karin J. H. Verweij [1] & Peter M. Visscher [16,17]

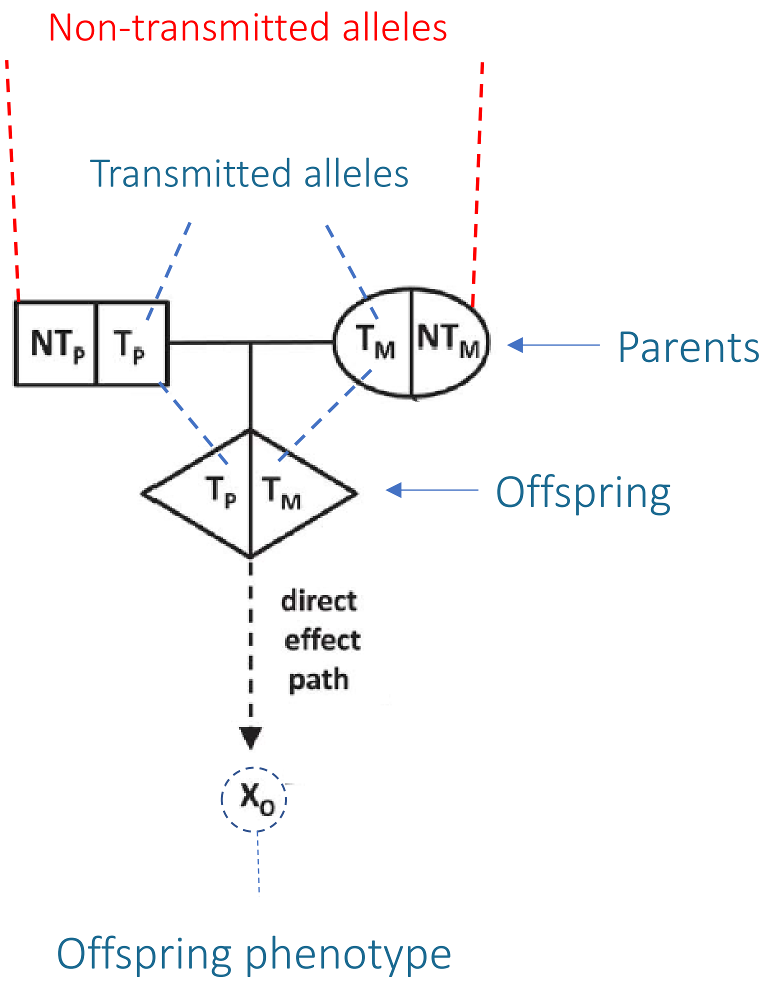
gene-environment correlations in families

Science **359**, 424–428 (2018)

HUMAN GENOMICS

The nature of nurture: Effects of parental genotypes

Augustine Kong,[1,2,3]* Gudmar Thorleifsson,[1] Michael L. Frigge,[1] Bjarni J. Vilhjalmsson,[4,5] Alexander I. Young,[1,2,6] Thorgeir E. Thorgeirsson,[1] Stefania Benonisdottir,[1] Asmundur Oddsson,[1] Bjarni V. Halldorsson,[1] Gisli Masson,[1] Daniel F. Gudbjartsson,[1,3] Agnar Helgason,[1,7] Gyda Bjornsdottir,[1] Unnur Thorsteinsdottir,[1,8] Kari Stefansson[1,8]*



Non-transmitted alleles

Transmitted alleles

Parents

Offspring

Offspring phenotype

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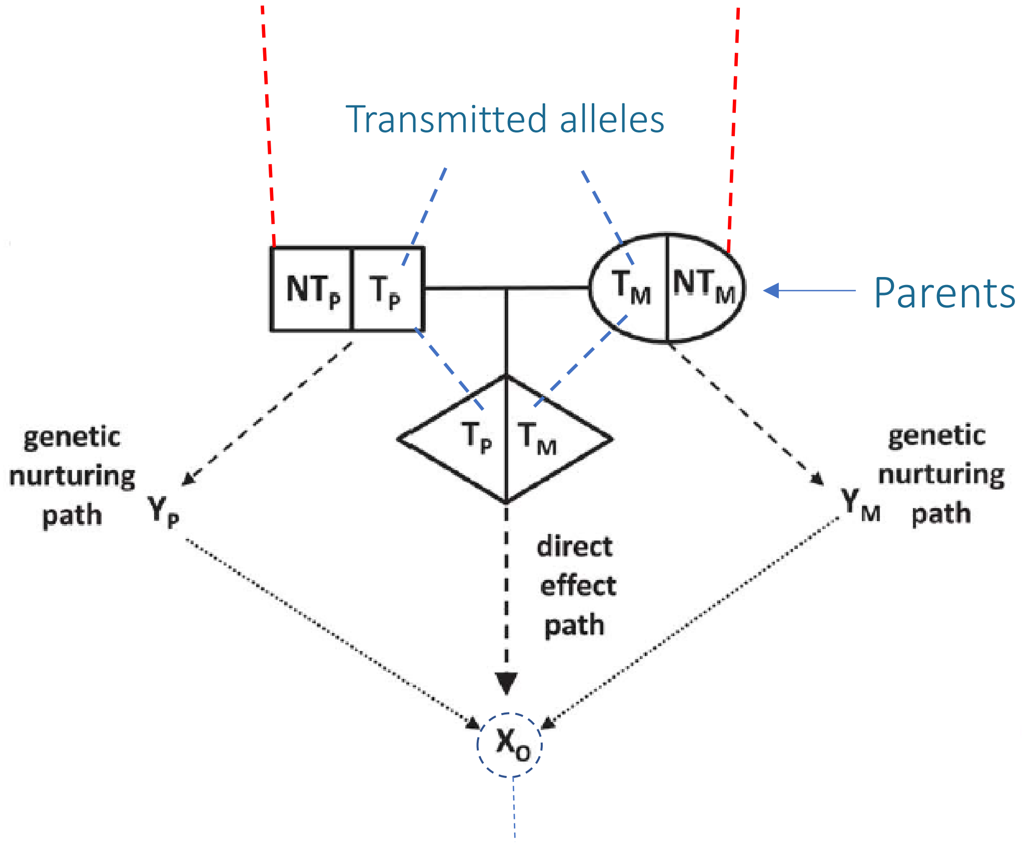

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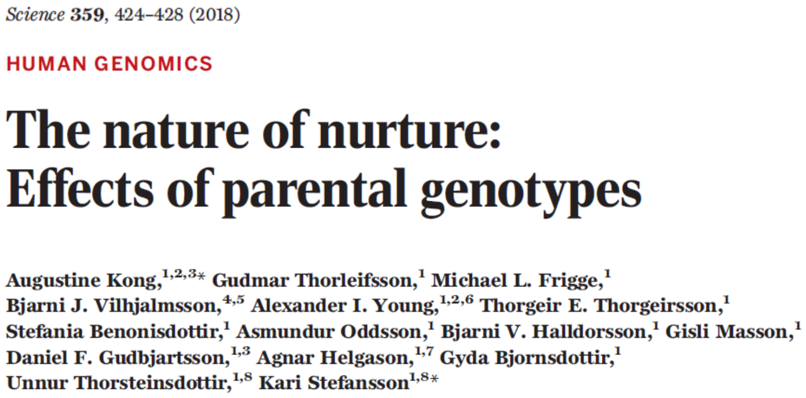

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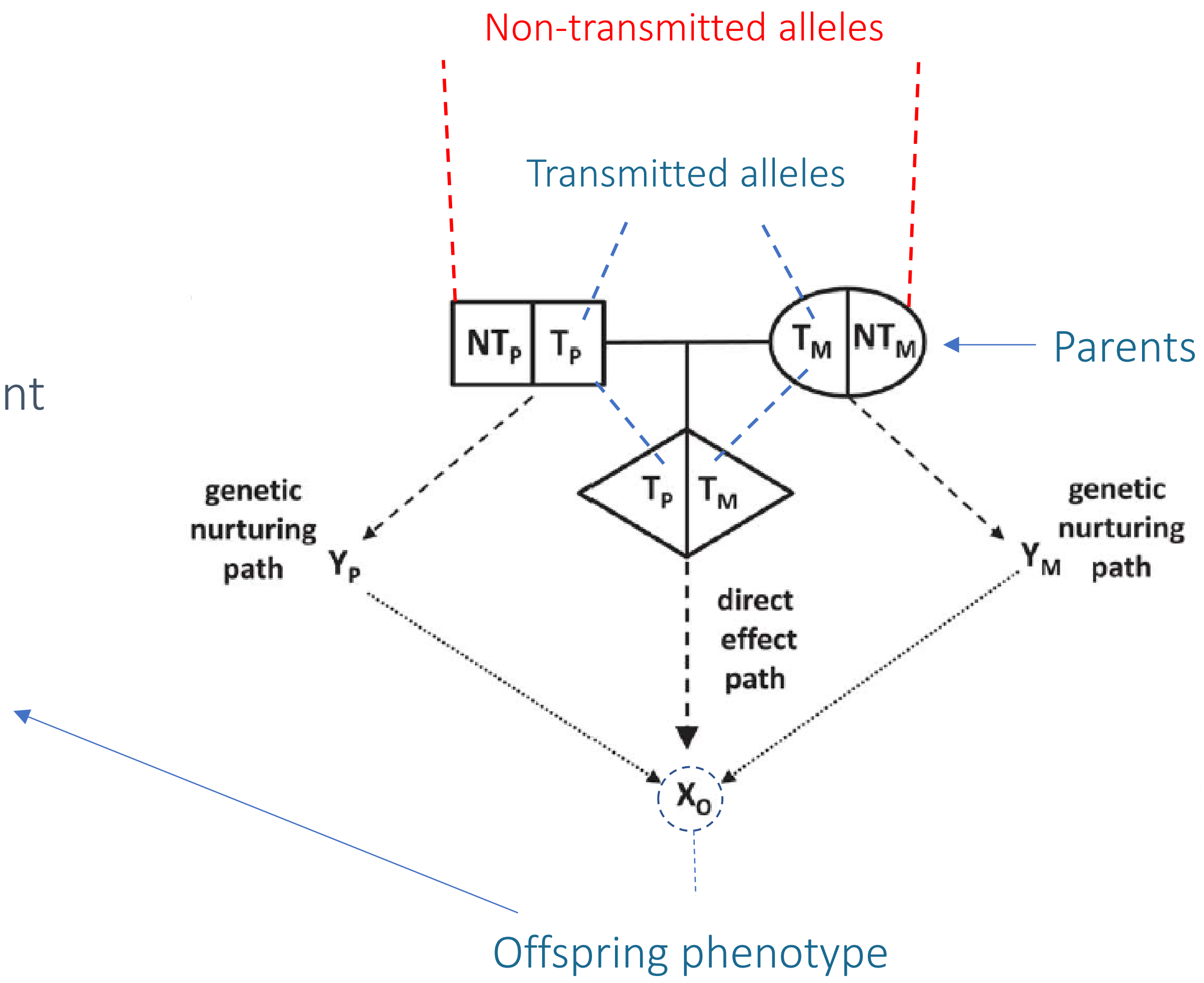
Non-transmitted educational attainment alleles are associated with:

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



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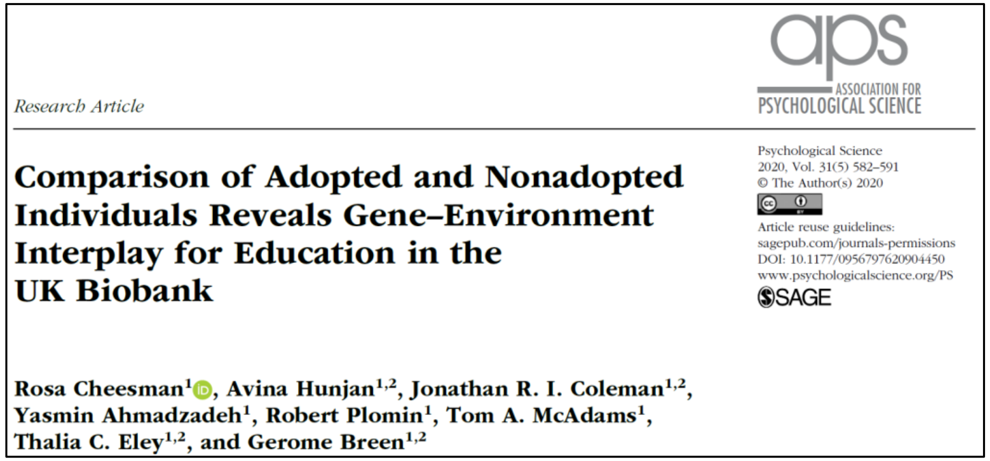

Research Article

ASSOCIATION FOR
PSYCHOLOGICAL SCIENCE

Psychological Science
2020, Vol. 31(5) 582–591

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DOI: 10.1177/0956797620904450
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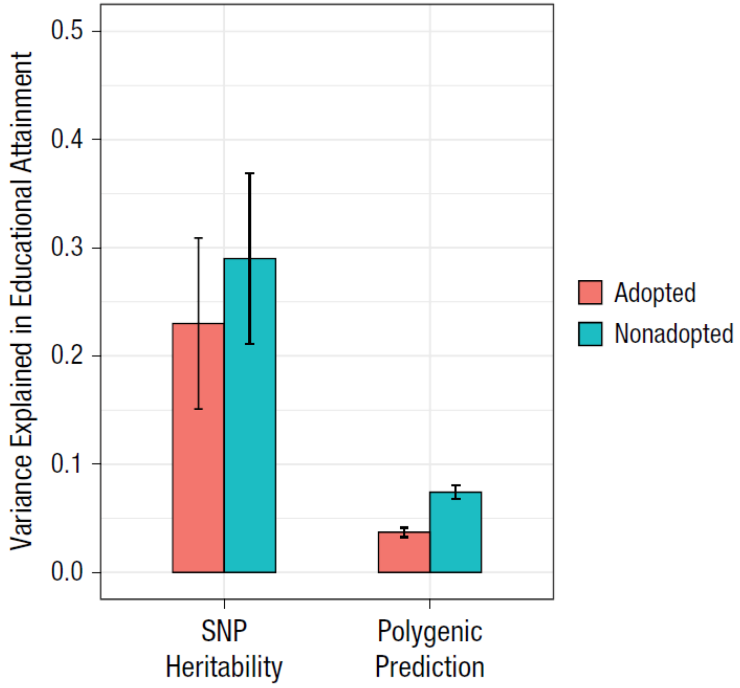
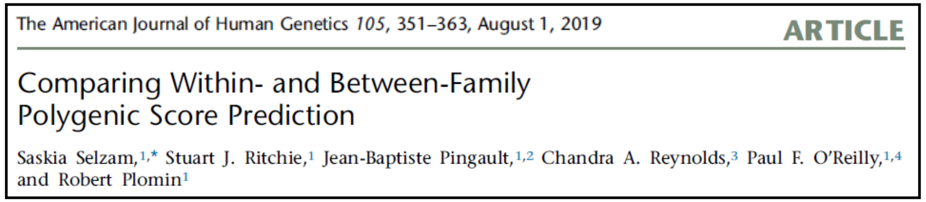
SAGE

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

Rosa Cheesman[1], Avina Hunjan[1,2], Jonathan R. I. Coleman[1,2], Yasmin Ahmadzadeh[1], Robert Plomin[1], Tom A. McAdams[1], Thalia C. Eley[1,2], and Gerome Breen[1,2]



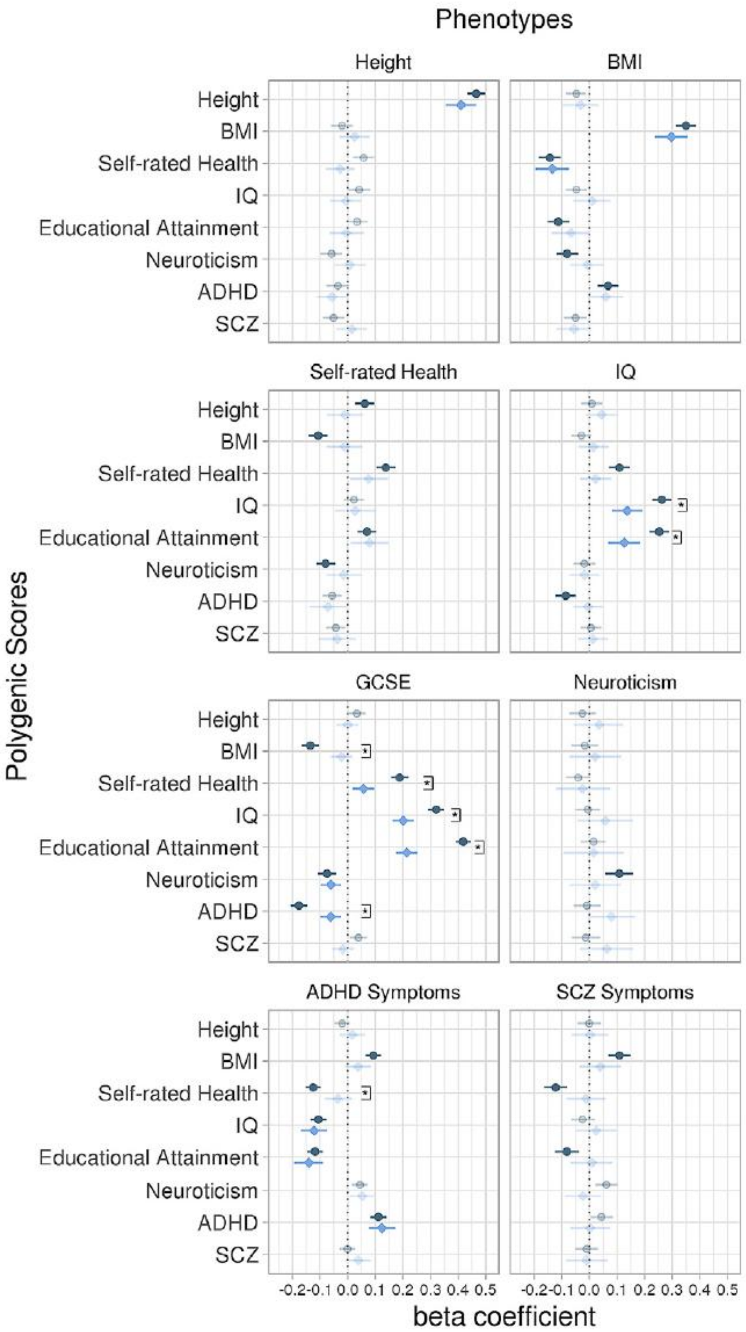
Predictive power of polygenic scores of cognitive traits (intelligence & education) was 60% greater between families than within families.



The American Journal of Human Genetics *105*, 351–363, August 1, 2019 **ARTICLE**

Comparing Within- and Between-Family Polygenic Score Prediction

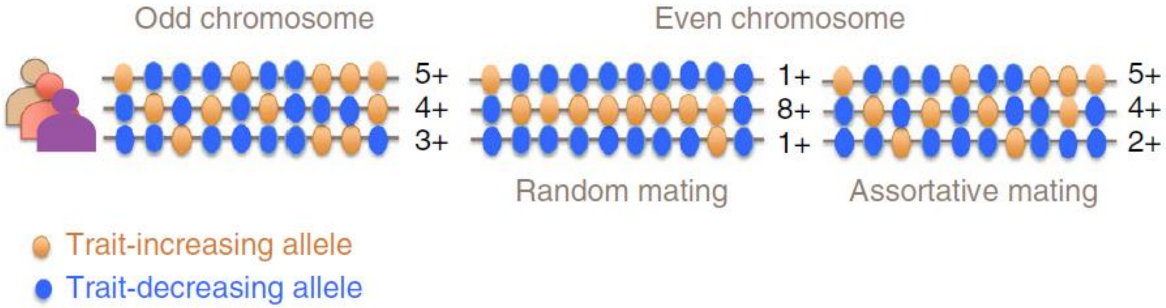
Saskia Selzam,[1,*] Stuart J. Ritchie,[1] Jean-Baptiste Pingault,[1,2] Chandra A. Reynolds,[3] Paul F. O'Reilly,[1,4] and Robert Plomin[1]

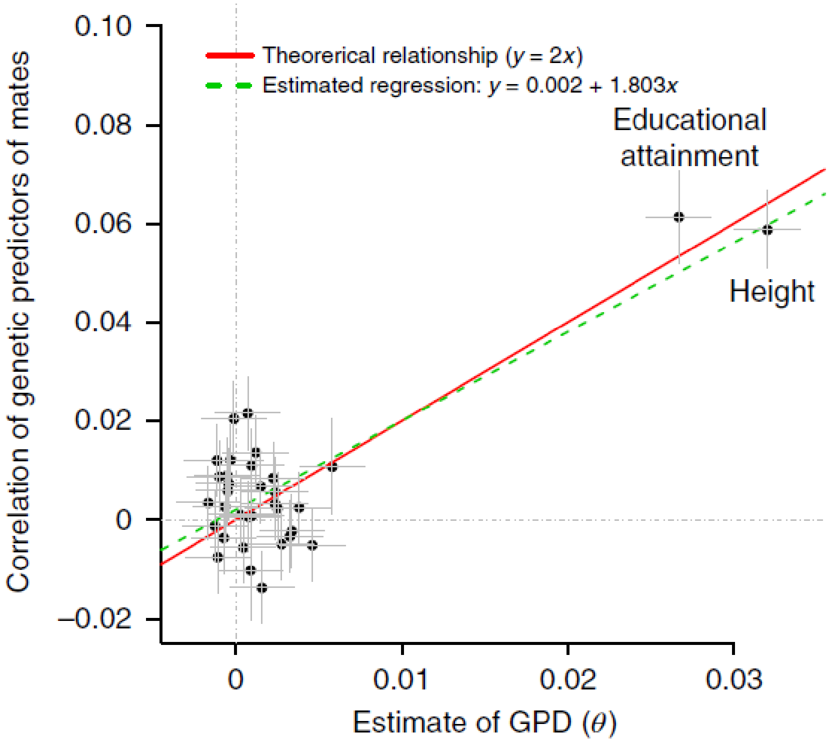


assortative mating

Assortative mating:

- **increases** genetic differences **between** families and **decreases** them **within** families
- **inflates** genetic effect estimates in GWASs






nature human behaviour

LETTERS

https://doi.org/10.1038/s41562-018-0476-3

Imprint of assortative mating on the human genome

Loic Yengo[1*], Matthew R. Robinson[1,2], Matthew C. Keller[3], Kathryn E. Kemper[1], Yuanhao Yang[1], Maciej Trzaskowski[1], Jacob Gratten[1,4], Patrick Turley[5,6], David Cesarini[7,8,9], Daniel J. Benjamin[7,10,11], Naomi R. Wray[1,12], Michael E. Goddard[13,14], Jian Yang[1,12] and Peter M. Visscher[1,12*]

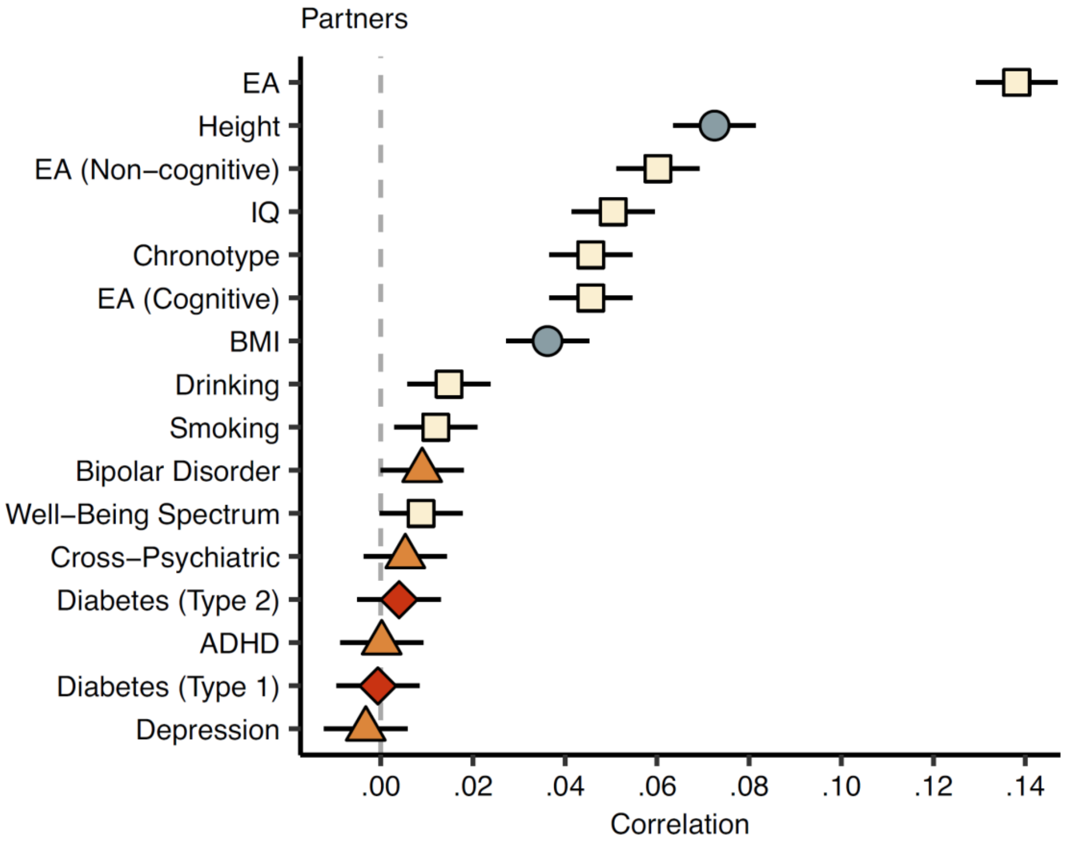
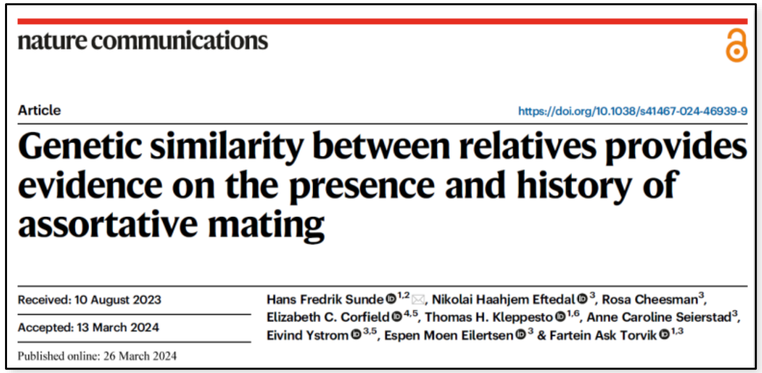


Fig. 3 | Correlations between family members. Polygenic index correlations (with 95% CIs) for various traits between various family members:



nature communications

Article

https://doi.org/10.1038/s41467-024-46939-9

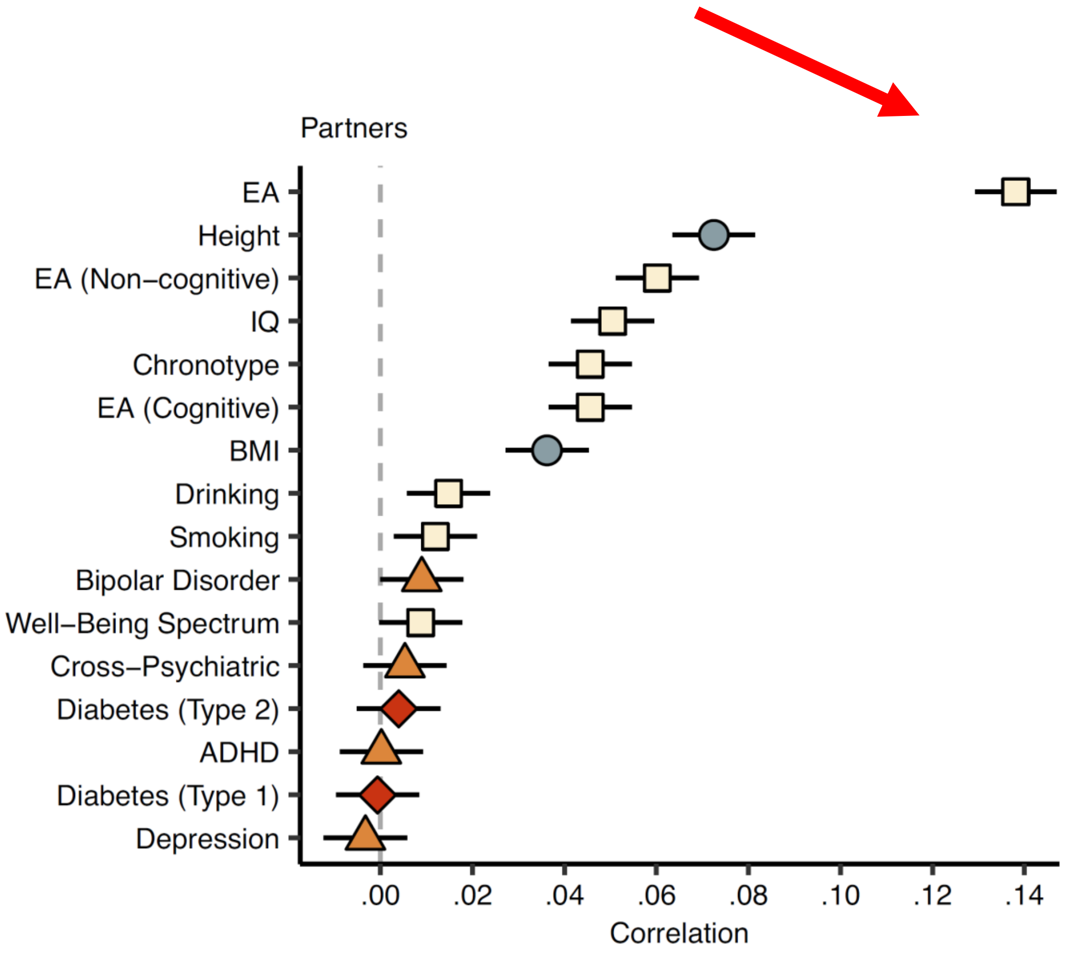
Genetic similarity between relatives provides evidence on the presence and history of assortative mating

Received: 10 August 2023

Accepted: 13 March 2024

Published online: 26 March 2024

Hans Fredrik Sunde[1,2], Nikolai Haahjem Eftedal[3], Rosa Cheesman[3], Elizabeth C. Corfield[4,5], Thomas H. Kleppesto[1,6], Anne Caroline Seierstad[3], Eivind Ystrom[3,5], Espen Moen Eilertsen[3] & Fartein Ask Torvik[1,3]



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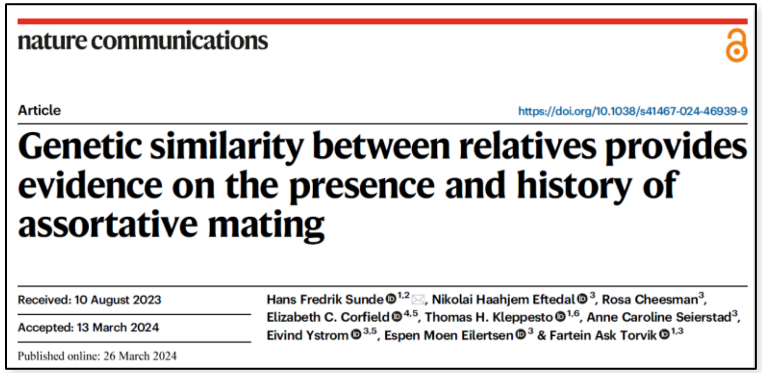
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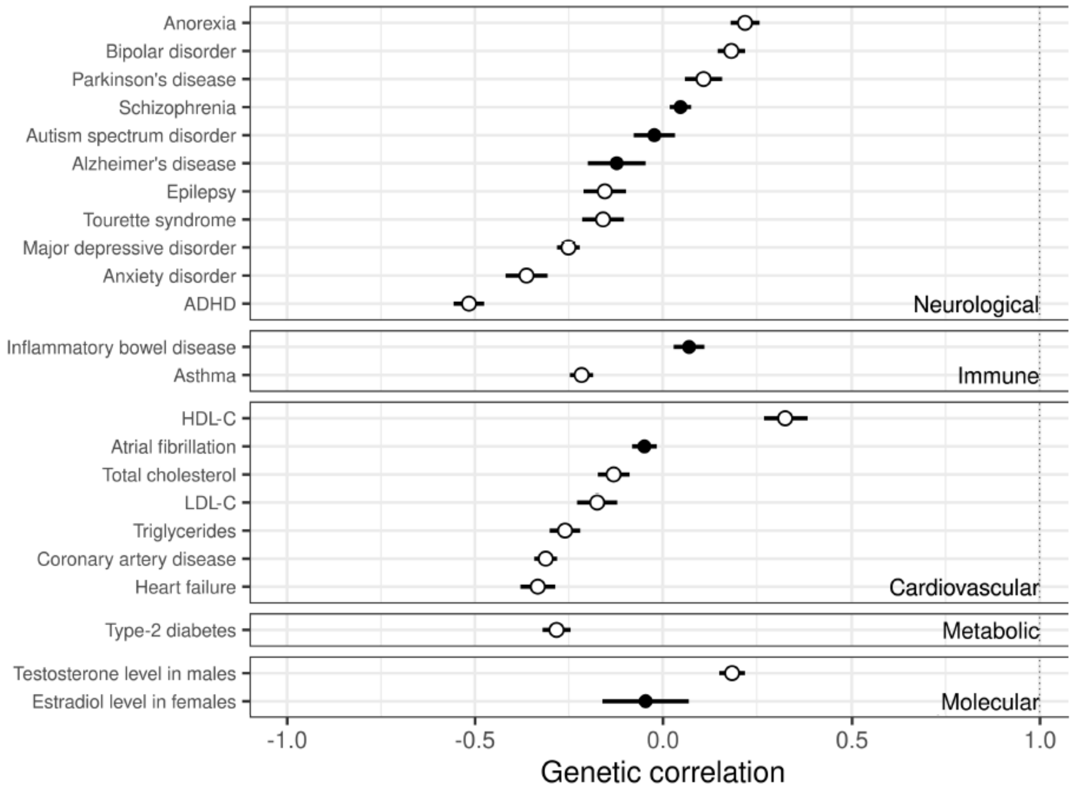

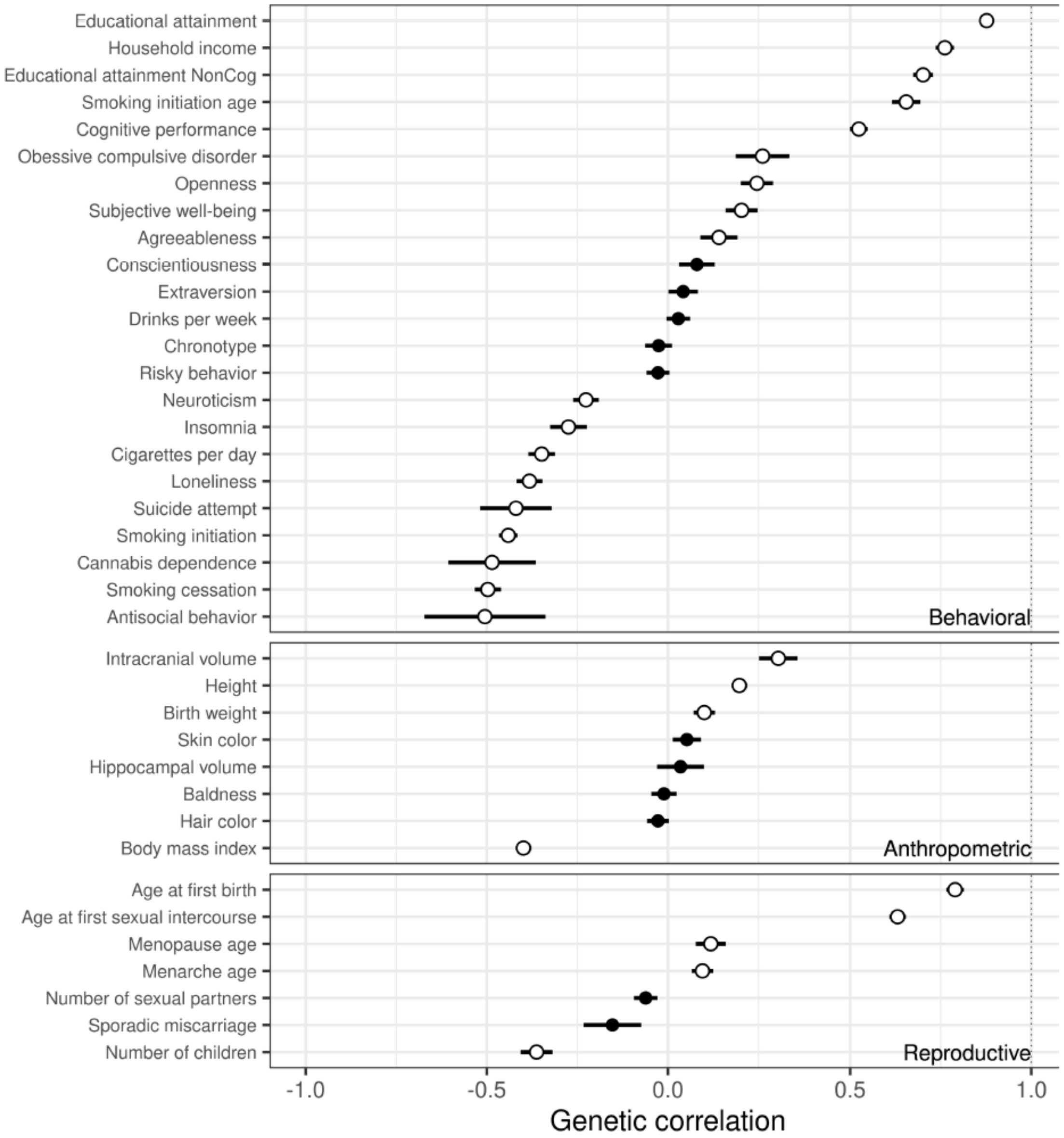

Genetic basis of partner choice

Qinwen Zheng, Sjoerd van Alten, Torkild Hovde Lyngstad, Edoardo Ciscato, Zhongxuan Sun, Jiacheng Miao, Yuchang Wu, Stephen Dorn, Boyan Zheng, Alexandra Havdahl, Elizabeth C. Corfield, Michel Nivard, Titus J. Galama, Patrick Turley, Pierre-André Chiappori, Jason M. Fletcher, Qiongshi Lu

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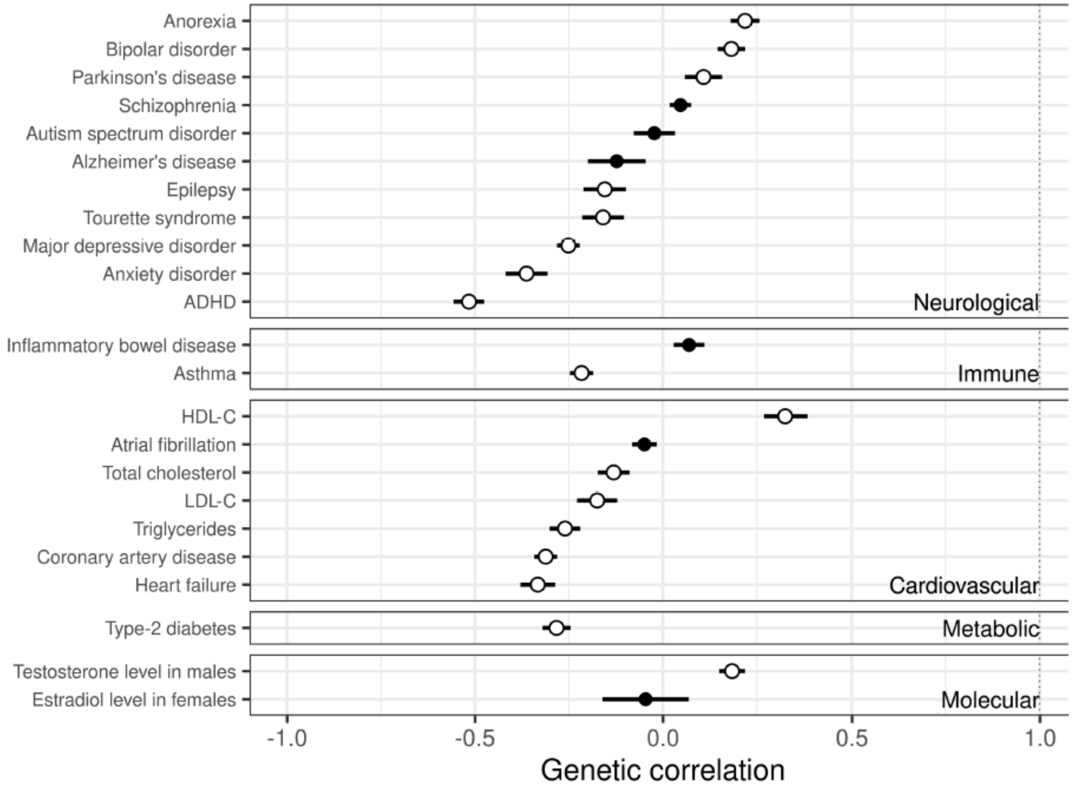

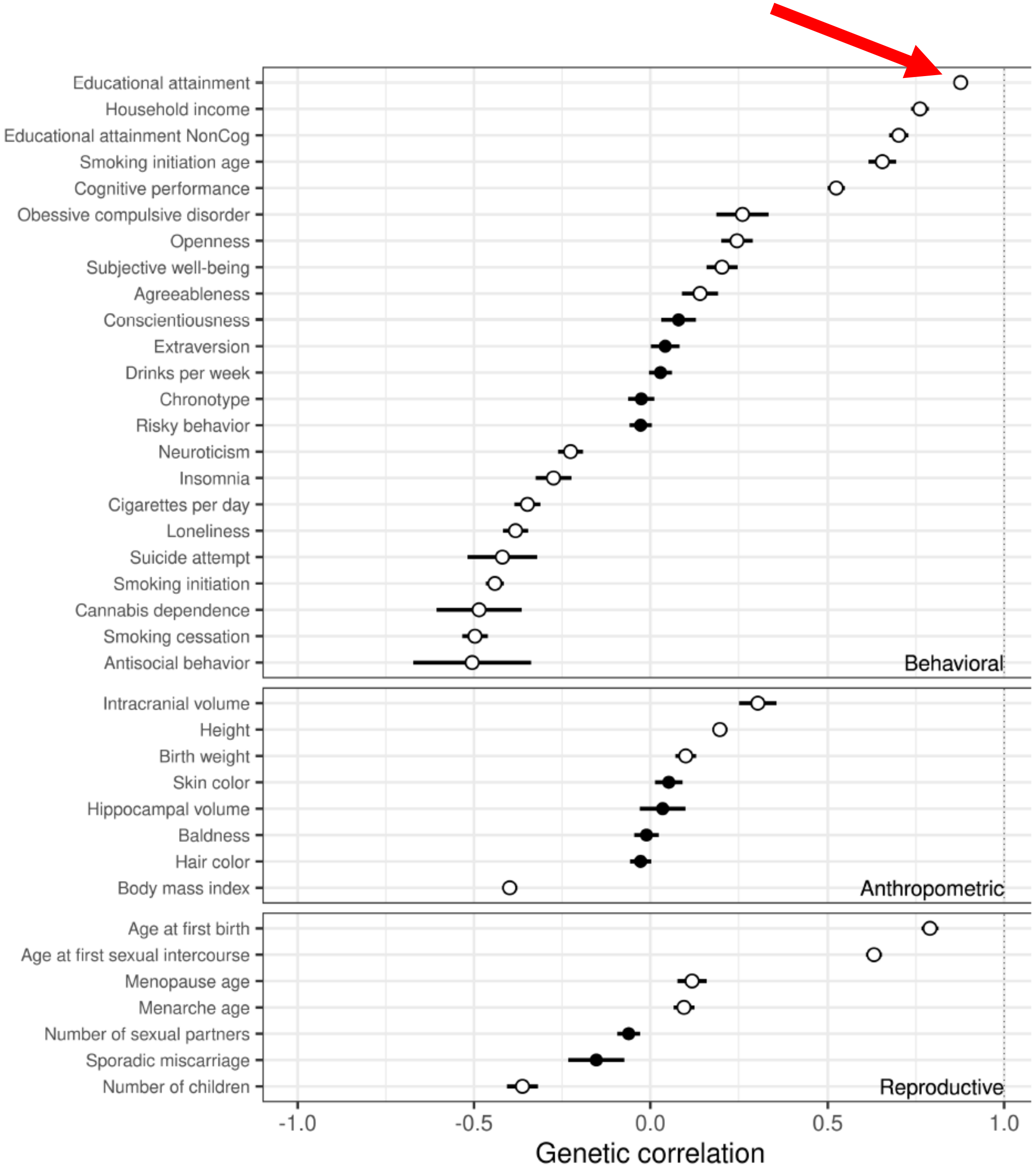

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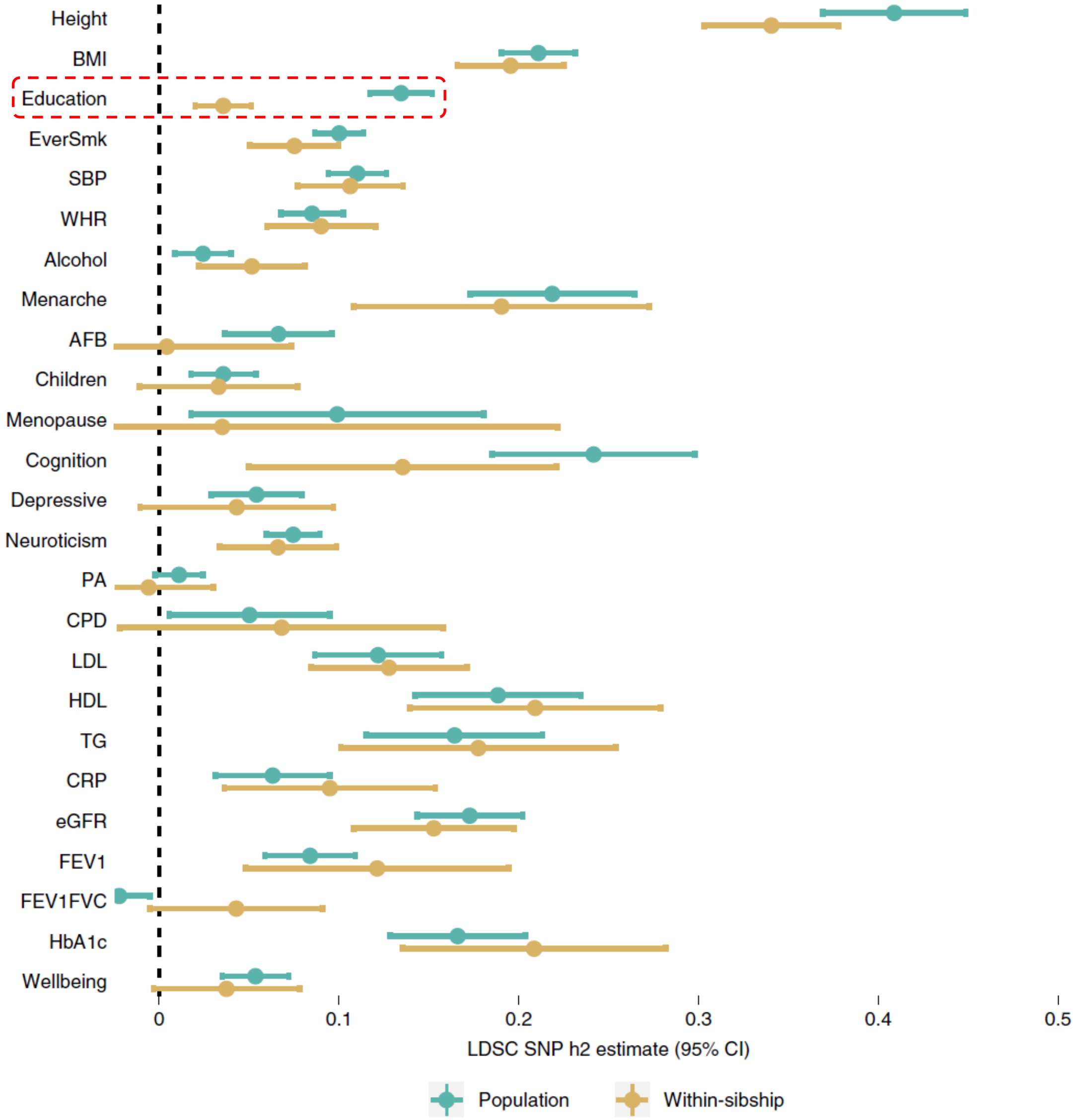
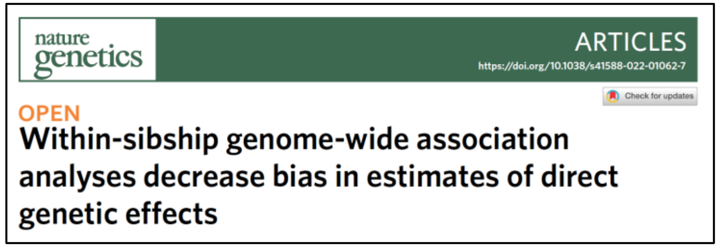
within-family GWAS





ARTICLES
https://doi.org/10.1038/s41588-022-01062-7

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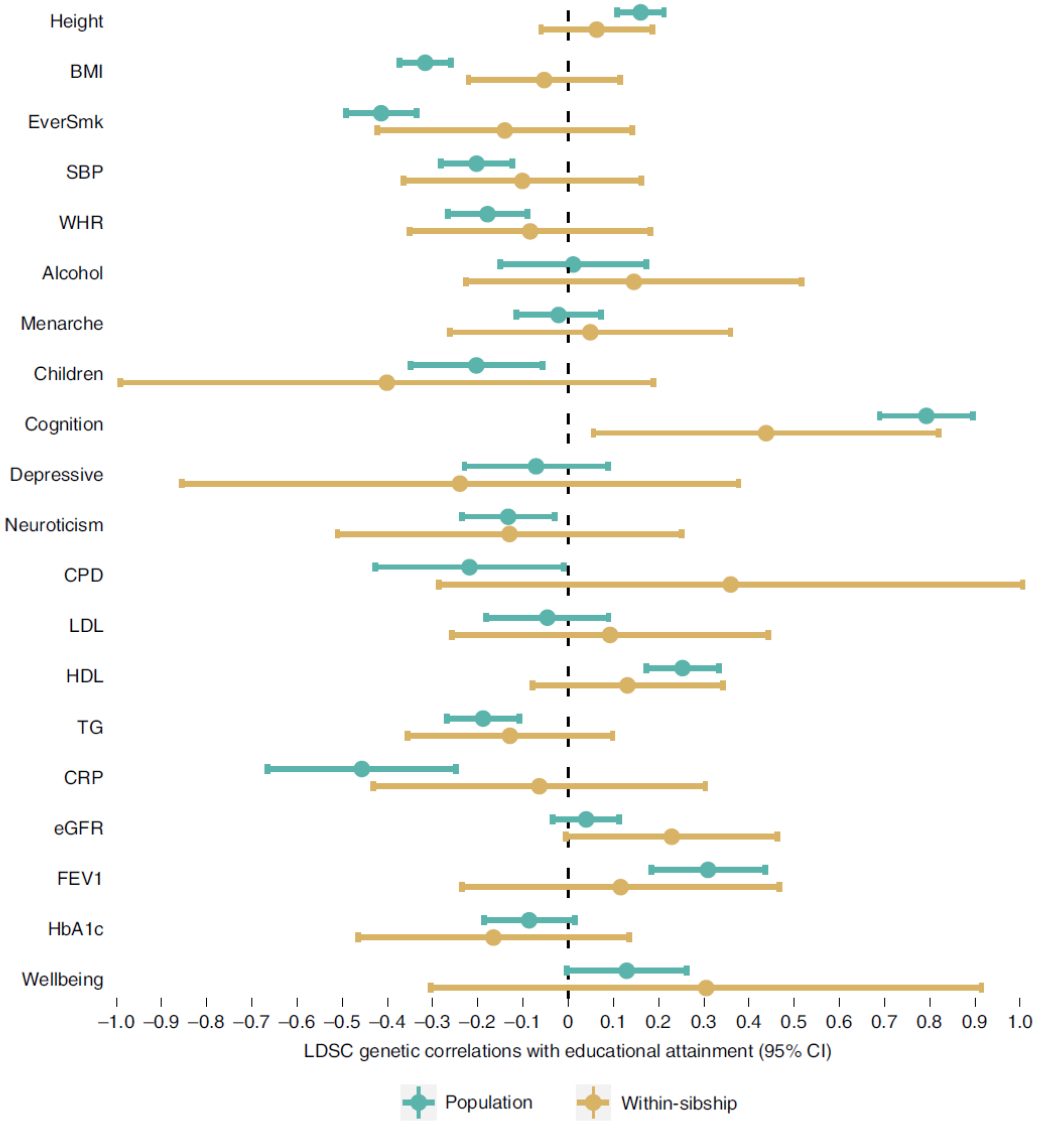
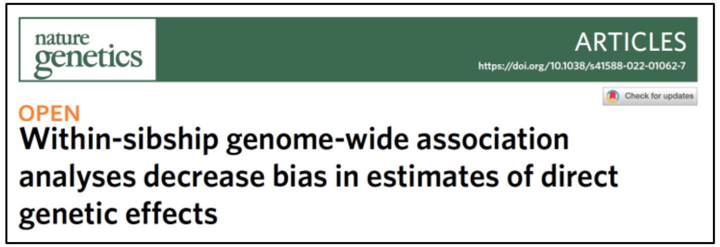
Within-sibship genome-wide association analyses decrease bias in estimates of direct genetic effects

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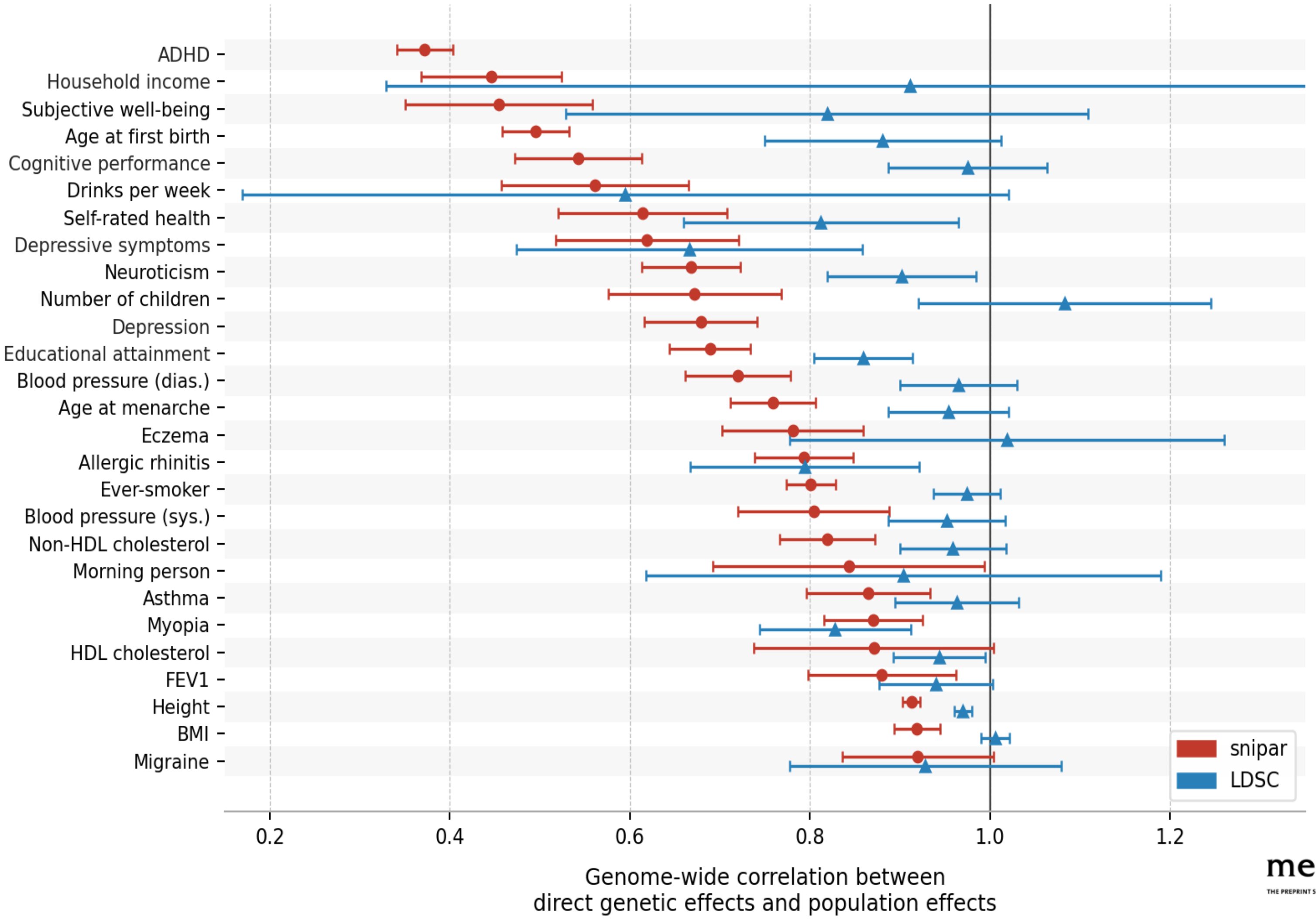

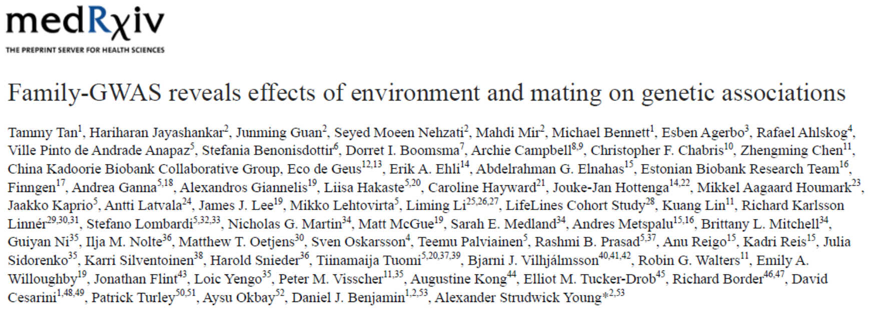

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Family-GWAS reveals effects of environment and mating on genetic associations

Tammy Tan[1], Hariharan Jayashankar[2], Junming Guan[2], Seyed Moeen Nehzati[2], Mahdi Mir[2], Michael Bennett[1], Esben Agerbo[3], Rafael Ahlskog[4], Ville Pinto de Andrade Anapaz[5], Stefania Benonisdottir[6], Dorret I. Boomsma[7], Archie Campbell[8,9], Christopher F. Chabris[10], Zhengming Chen[11], China Kadoorie Biobank Collaborative Group, Eco de Geus[12,13], Erik A. Ehli[14], Abdelrahman G. Elnahas[15], Estonian Biobank Research Team[16], Finngen[17], Andrea Ganna[5,18], Alexandros Giannelis[19], Liisa Hakaste[5,20], Caroline Hayward[21], Jouke-Jan Hottenga[14,22], Mikkel Aagaard Houmark[23], Jaakko Kaprio[5], Antti Latvala[24], James J. Lee[19], Mikko Lehtovirta[5], Liming Li[25,26,27], LifeLines Cohort Study[28], Kuang Lin[11], Richard Karlsson Linnér[29,30,31], Stefano Lombardi[5,32,33], Nicholas G. Martin[34], Matt McGue[19], Sarah E. Medland[34], Andres Metspalu[15,16], Brittany L. Mitchell[34], Guiyan Ni[35], Ilja M. Nolte[36], Matthew T. Oetjens[30], Sven Oskarsson[4], Teemu Palviainen[5], Rashmi B. Prasad[5,37], Anu Reigo[15], Kadri Reis[15], Julia Sidorenko[35], Karri Silventoinen[38], Harold Snieder[36], Tiinamaija Tuomi[5,20,37,39], Bjarni J. Vilhjálmsson[40,41,42], Robin G. Walters[11], Emily A. Willoughby[19], Jonathan Flint[43], Loic Yengo[35], Peter M. Visscher[11,35], Augustine Kong[44], Elliot M. Tucker-Drob[45], Richard Border[46,47], David Cesarini[1,48,49], Patrick Turley[50,51], Aysu Okbay[52], Daniel J. Benjamin[1,2,53], Alexander Strudwick Young*[2,53]

Standard GWAS

requires: unrelated individuals

$$y_i = \beta_l\, g_{il} + x_i'\alpha + \varepsilon_i$$

β_l population effect

g_{il} focal individual's genotype

$x_i'\alpha$ covariates (age, sex, PCs)

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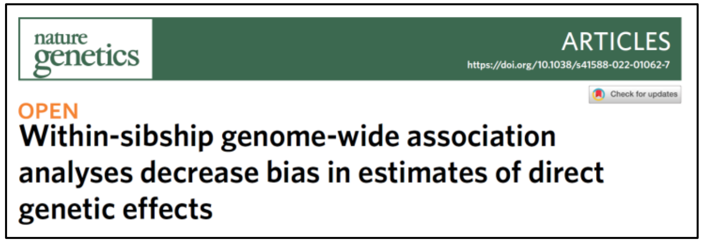
β conflates direct effects
with gene-environment correlation
(rGE), assortative mating (AM), and
population stratification



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Sib-GWAS

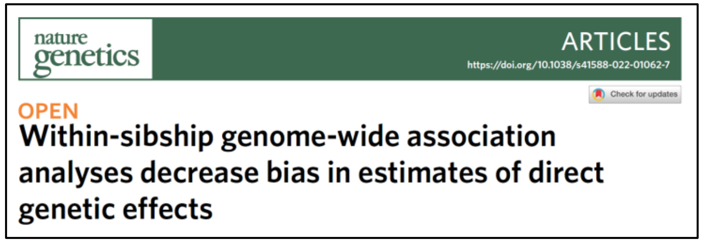
requires: sibling pairs

$$y_i = \beta_l G^{C}_{il} + G^{F}_{f(i)l} + x_i'\alpha + \varepsilon_i$$

β_l direct genetic effect

$G^{C}_{il} = G_{il} - G^{F}_{f(i)l}$ (within-family deviation)

$G^{F}_{f(i)l}$ = mean sibling genotype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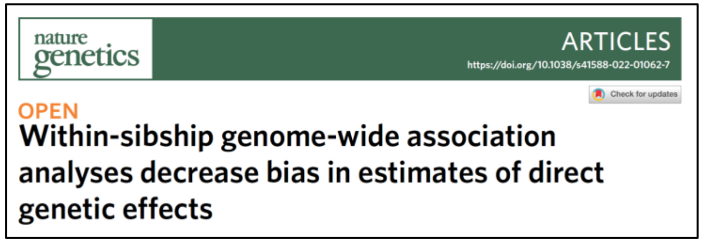
$G^{F}_{f(i)l}$ = mean sibling genotype

Including the family genetic background as a covariate isolates the random within-family variation due to Mendelian segregation, which captures more of the direct effect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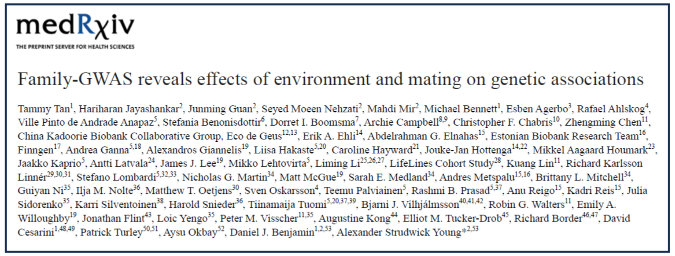
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Family-based GWAS (FGWAS)

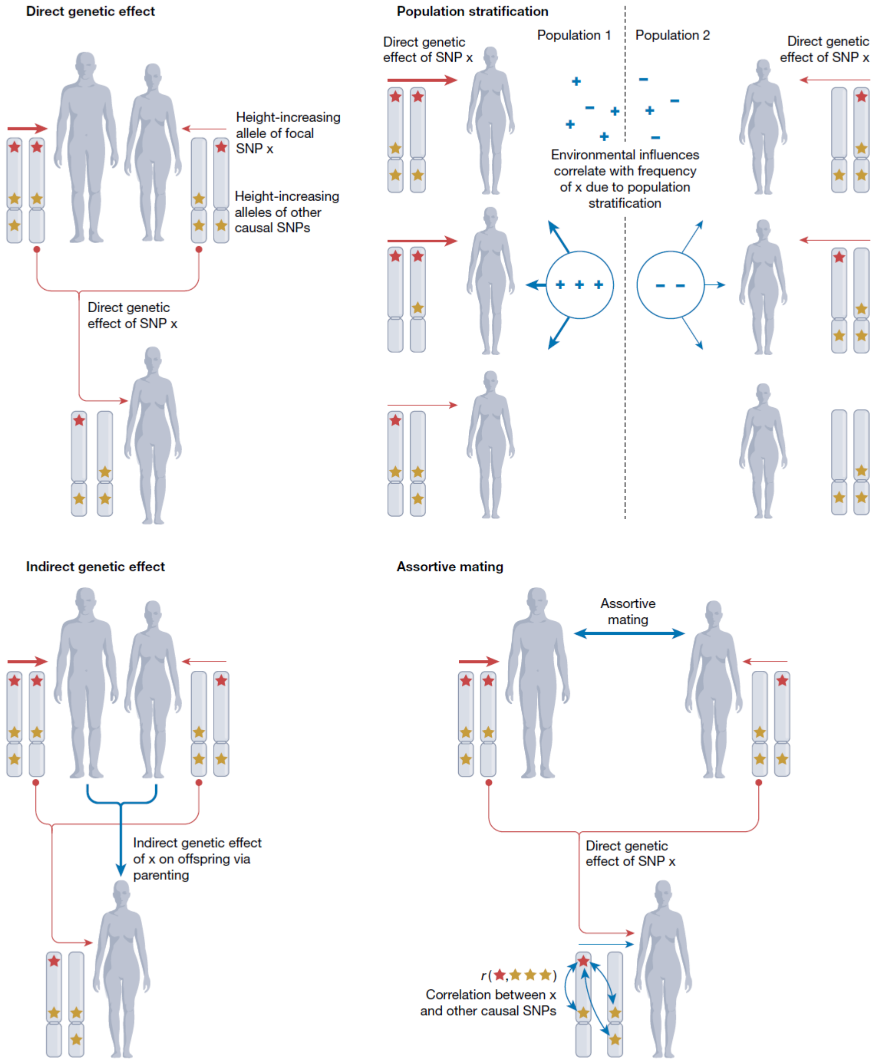
requires: trios/sib pairs
(parental G can be imputed)

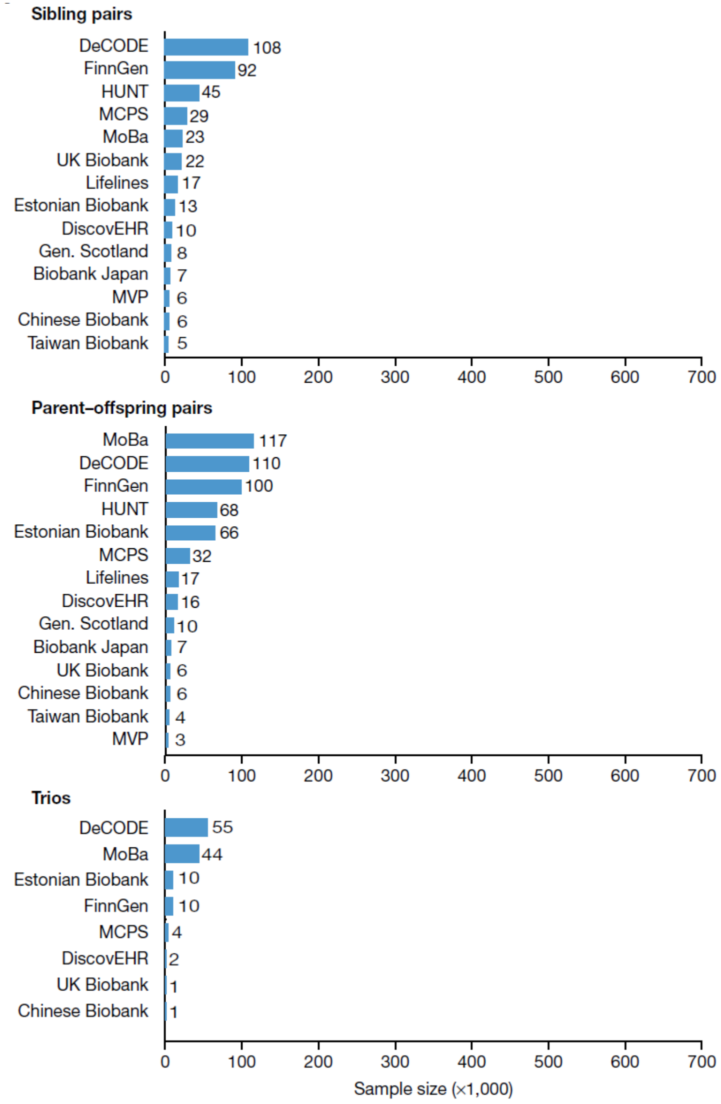
$$y_i = \beta_l\, g_{il} + g_{p(i)l} + g_{m(i)l} + x_i'\alpha + \varepsilon_i$$

β_l direct genetic effect

$g_{p(i)l}$ paternal genotype (non-transmitted)

$g_{m(i)l}$ maternal genotype (non-transmitted)






Perspective Nature | Vol 634 | 24 October 2024

The importance of family-based sampling for biobanks

https://doi.org/10.1038/s41586-024-07721-5

Received: 6 April 2023

Accepted: 13 June 2024

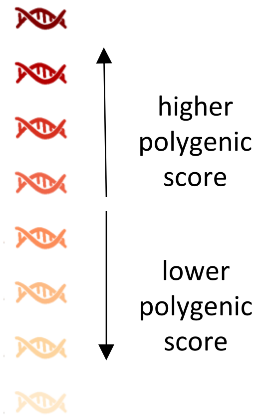
Published online: 23 October 2024

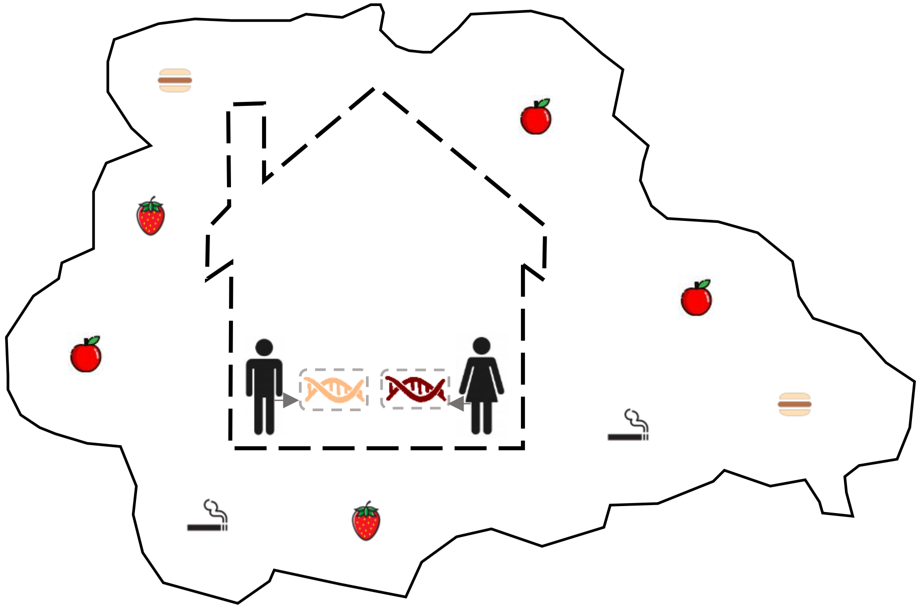
Neil M. Davies[1,2,3]✉, Gibran Hemani[4,5], Jenae M. Neiderhiser[6], Hilary C. Martin[7], Melinda C. Mills[8,9,10], Peter M. Visscher[11,12], Loïc Yengo[11], Alexander Strudwick Young[13,14] & Matthew C. Keller[15,16]✉

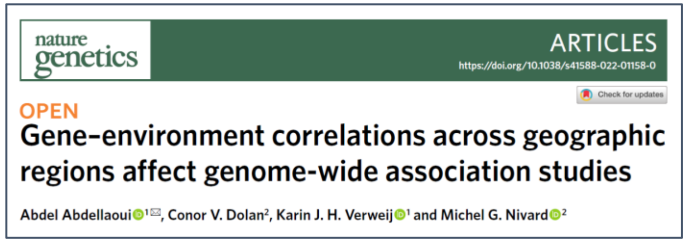
gene-environment correlations across geographic regions

🍓 🍎 = healthy environmental influences

🚬 🍔 = unhealthy environmental influences







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

Abdel Abdellaoui[1]✉, Conor V. Dolan[2], Karin J. H. Verweij[1] and Michel G. Nivard[2]

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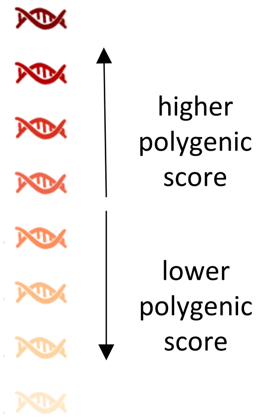
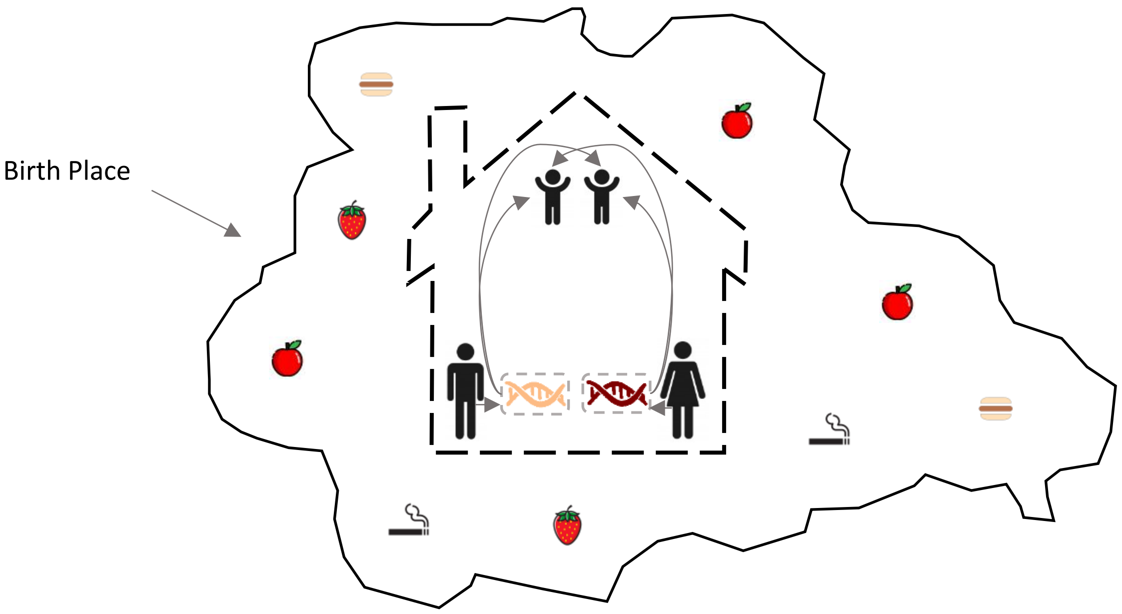
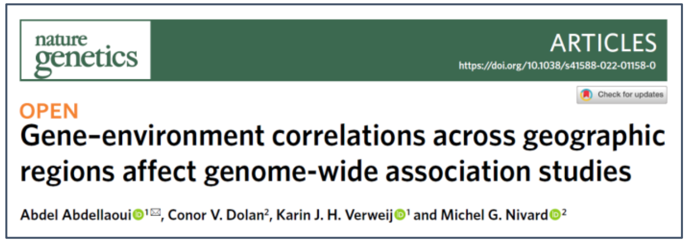

higher polygenic score

lower polygenic score

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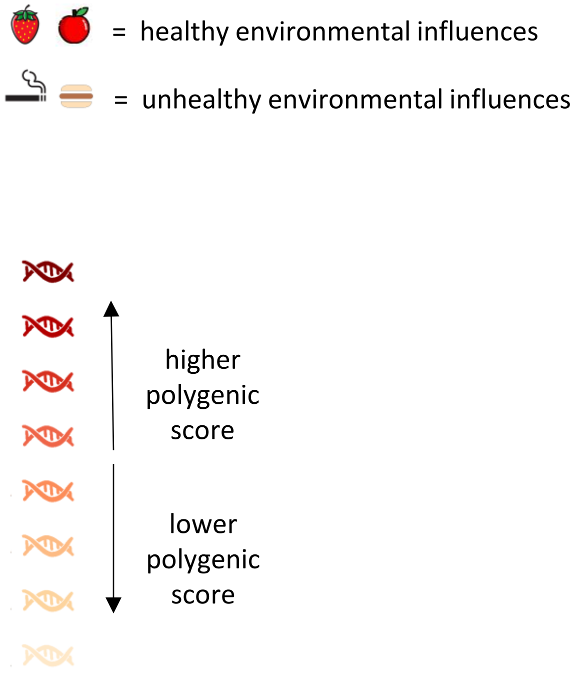

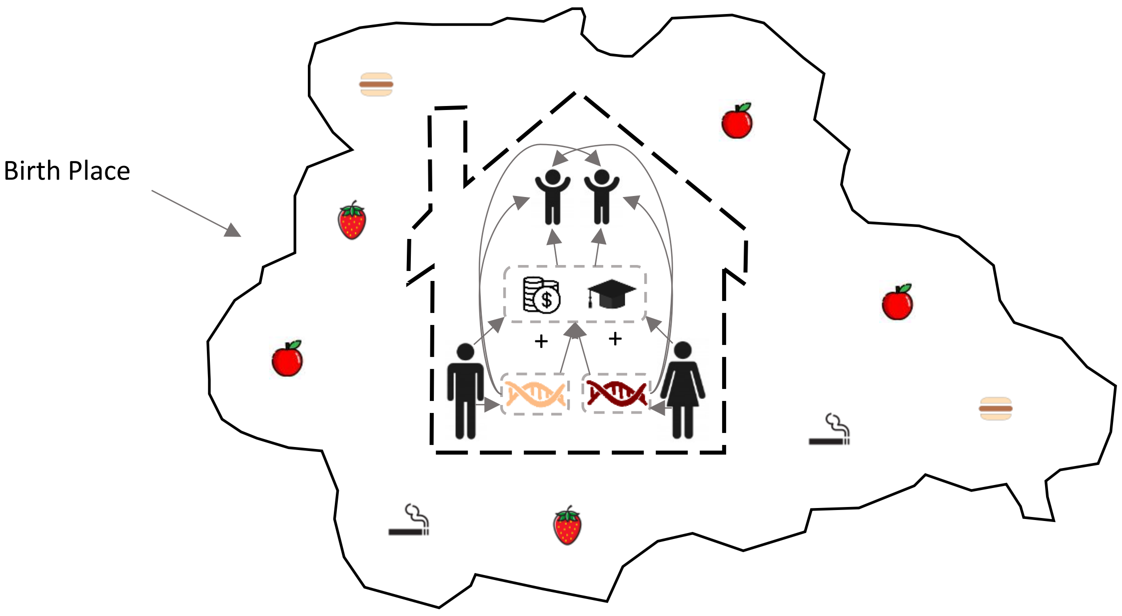

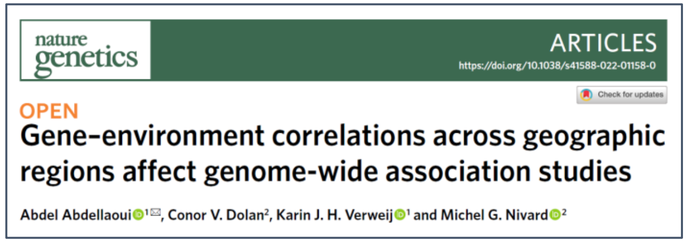
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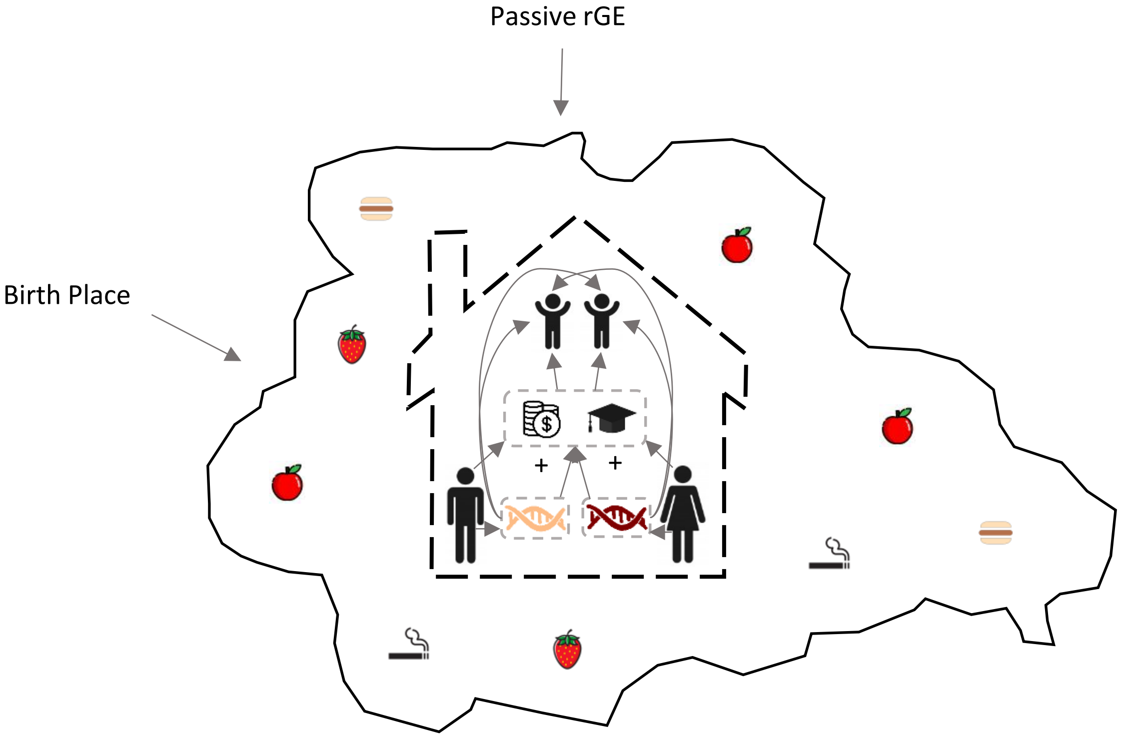

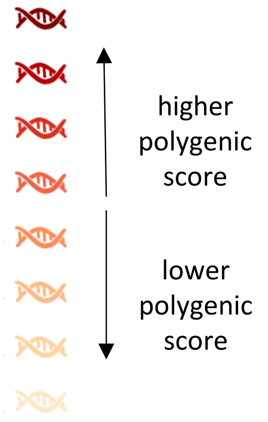

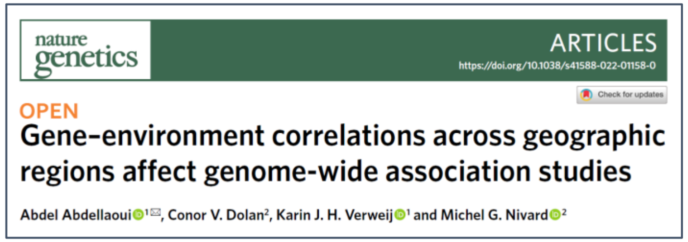
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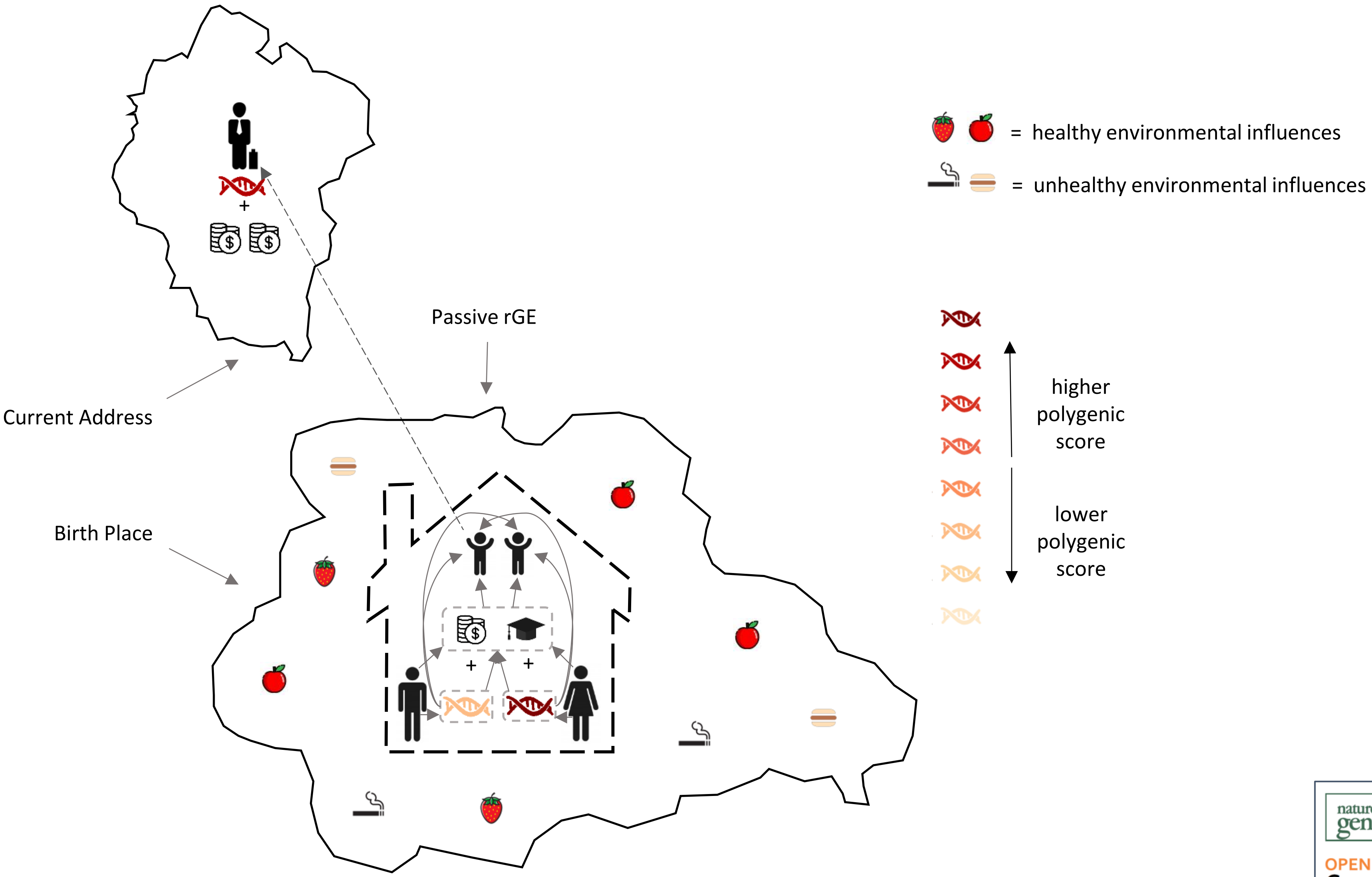

Passive rGE

Current Address

Birth Place

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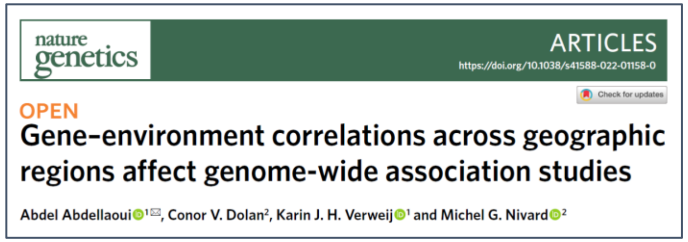
higher polygenic score

lower polygenic score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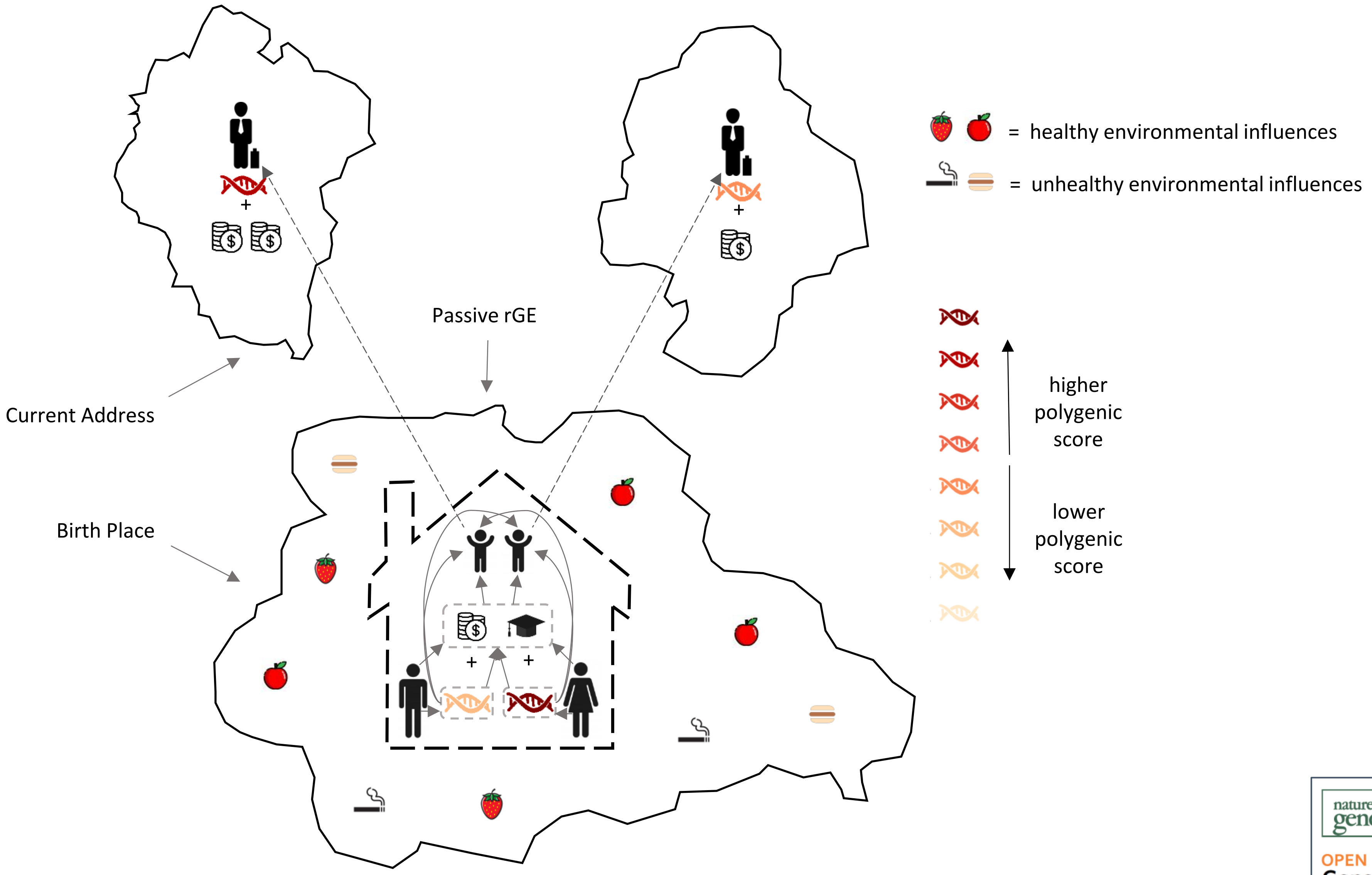

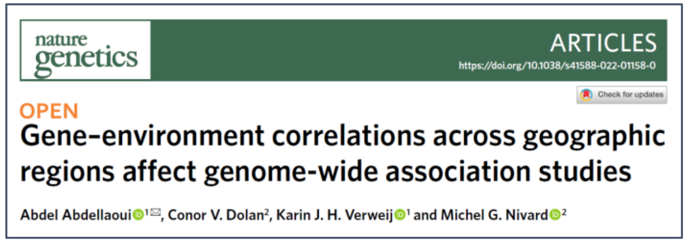
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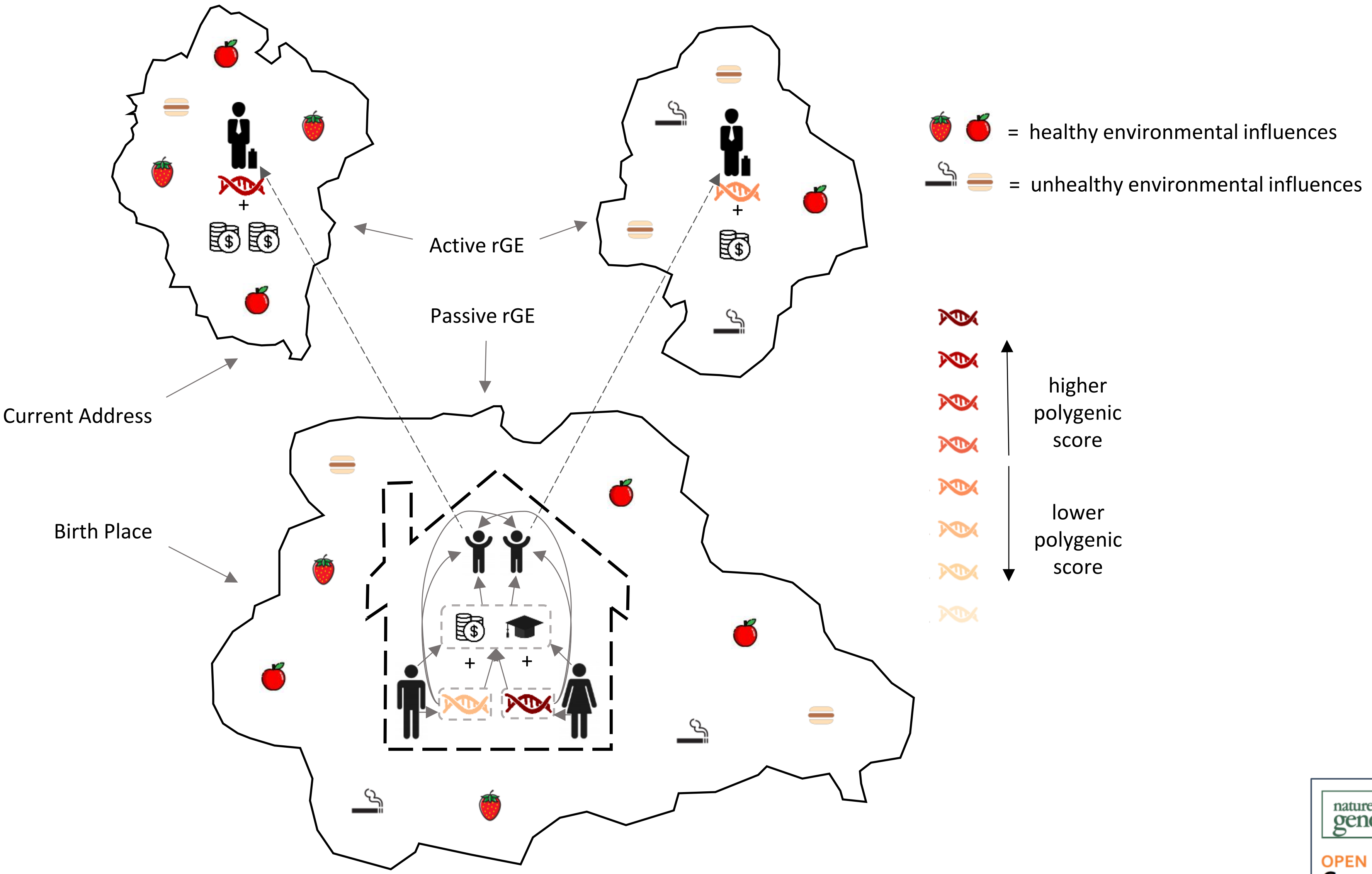

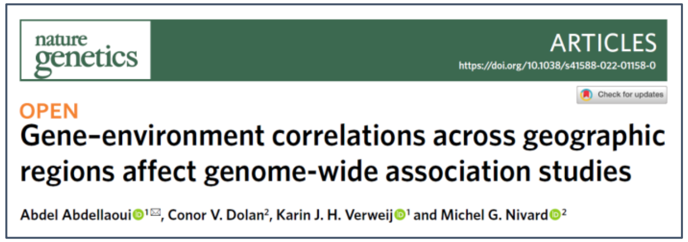

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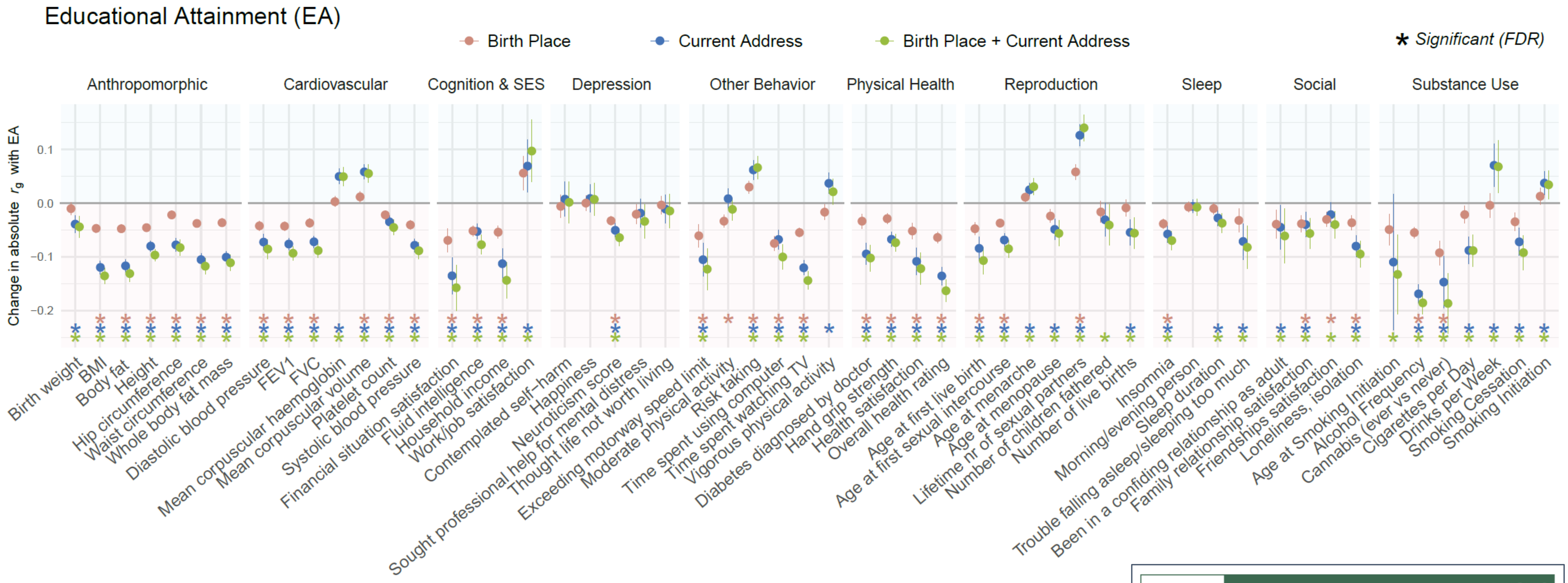
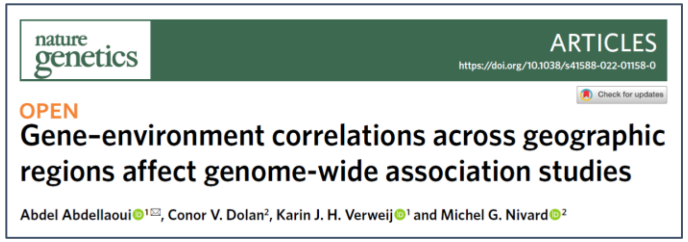
within-region GWAS

Genetic correlation with educational attainment decreases after including geographic region as covariate





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Now go have fun running a GWAS and good luck interpreting that mess of an output!