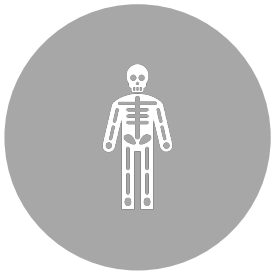
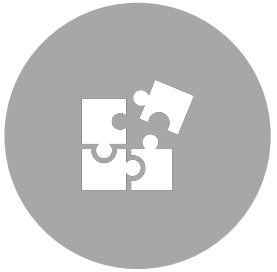
Quantitative genetics



AETIOLOGY OF TRAIT(S) OF INTEREST

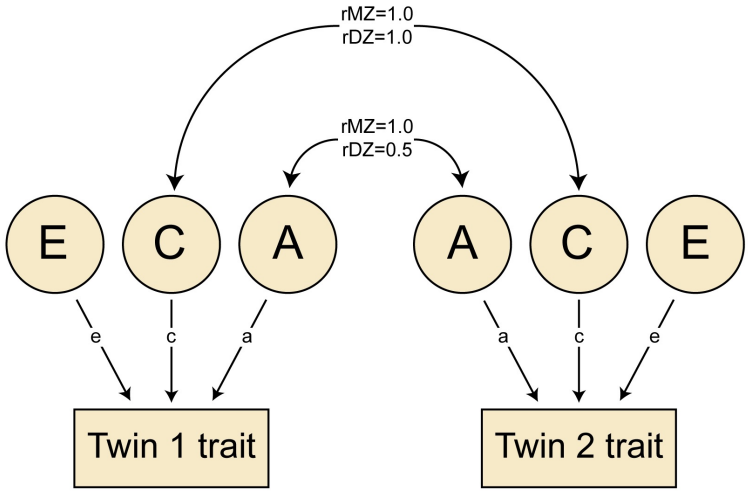
GENETIC CONTINUITY AND CHANGE



COVARIANCE BETWEEN TRAITS

MECHANISMS BY WHICH GENETIC FACTORS INFLUENCE BEHAVIOR

Twin method


rMZ=1.0
rDZ=1.0
rMZ=1.0
rDZ=0.5
E
C
A
A
C
E
e
c
a
a
c
e
Twin 1 trait
Twin 2 trait

What are the **origins** of individual differences in complex human traits and disorders?

Twin studies:

Estimate how much genetic (and environmental) factors contribute to variance/risk in a measured trait or disorder

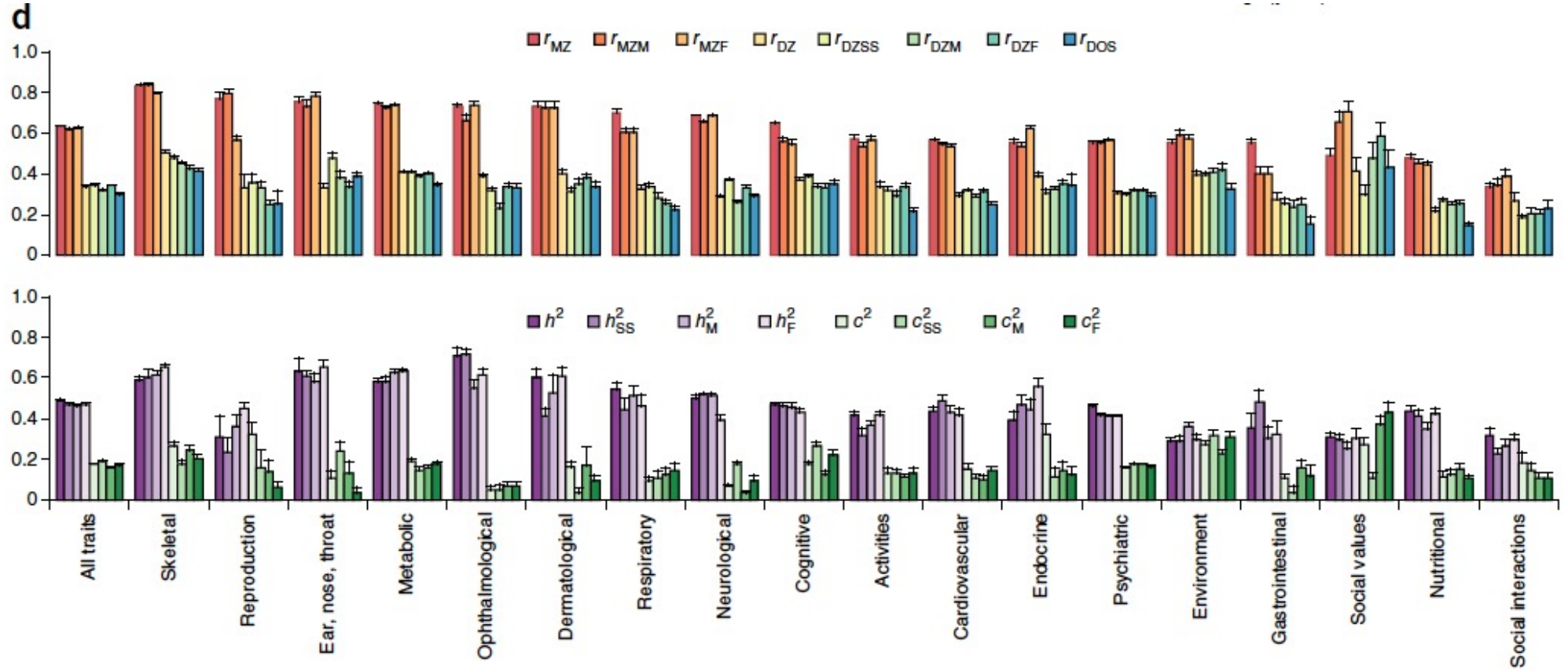
"Heritability"

The proportion of variance in a trait that can be attributed to genetic differences *between individuals*

Meta-analysis of the heritability of human traits based on fifty years of twin studies

Tinca J C Polderman[1,10], Beben Benyamin[2,10], Christiaan A de Leeuw[1,3], Patrick F Sullivan[4–6], Arjen van Bochoven[7], Peter M Visscher[2,8,11] & Danielle Posthuma[1,9,11]

nature genetics



Common misconceptions about heritability

- Heritability does **not** describe an individual
  - It is a population statistic based on the variance that describes populations, not individuals!

- Heritability is **not** determinism.
  - Just because something is highly heritable **does not** mean it will happen

- Heritability **describes** what **is** in a current population at a current time, **not what could be**
  - BMI is heritable, but you can lose weight!
  - The effects of your genes can change over time, age, and the environment ….

Negligible effects of the shared environment

- A remarkably consistent finding in quantitative genetic studies of behavioural traits

  It suggests that once we take genetics into account, you are no more similar to your brother or sister than a random person off the street!

- It also suggests that shared factors like your parenting, your neighbourhood, your school, and your SES all have little effect on many life outcomes – contrary to many, many studies

- Can this be right?

Negligible effects of the shared environment

The twin model does not measure the occurrence of the *shared environment* it measures the *effects of the shared environment* on the twins

- Example
  - Imagine a twin-pair in which the parents get divorced
  - This is what we might think of as a shared environment
  - **But if one twin gets depressed following the divorce and the other stays healthy, this would show up as a non-shared environmental influence**

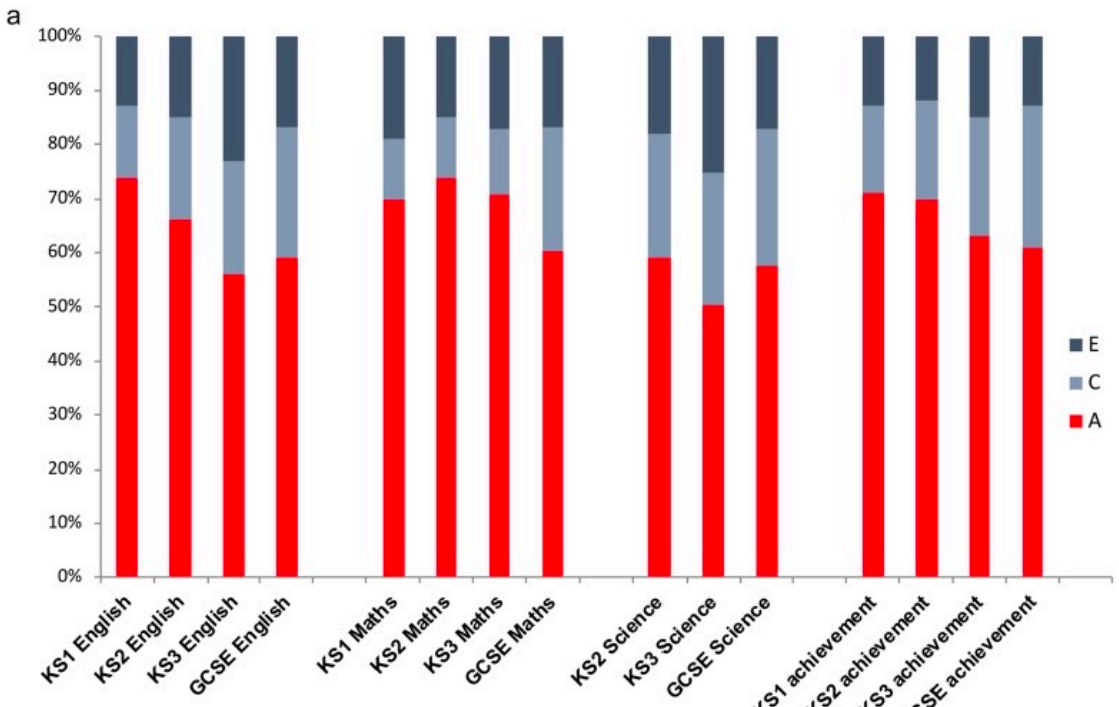
- This might also explain the consistently high non-shared environmental influences

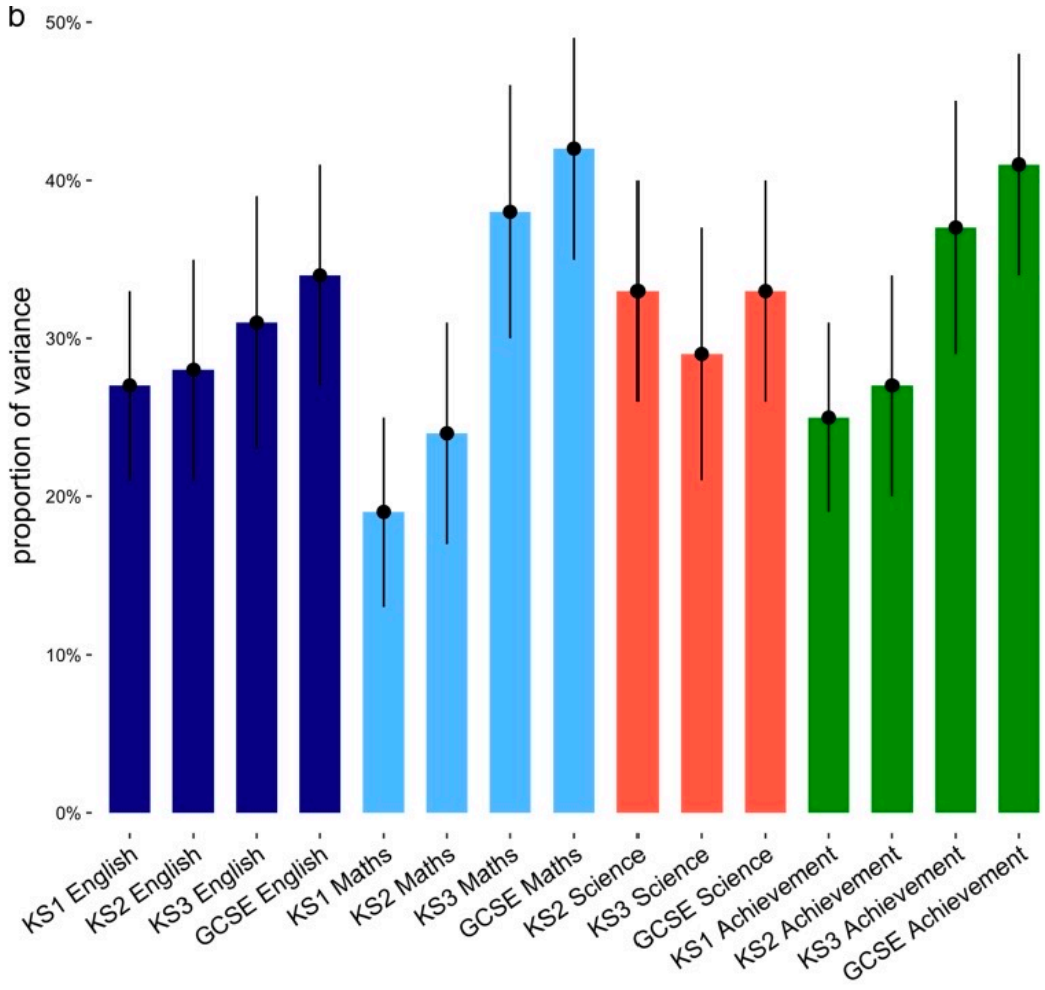
Beyond heritability

- Twin studies can be used to understand the **aetioligy** of complex traits. We can estimate the relative contribution of:
  - Genes (h^2/A^2)
  - Shared environment (C^2)
  - Non-shared environment (E^2)

- **BUT** twin studies can do far more than this
- We can also use them to understand phenomena includi
  - Comorbidity
  - Heterogeneity
  - Specificity
  - …

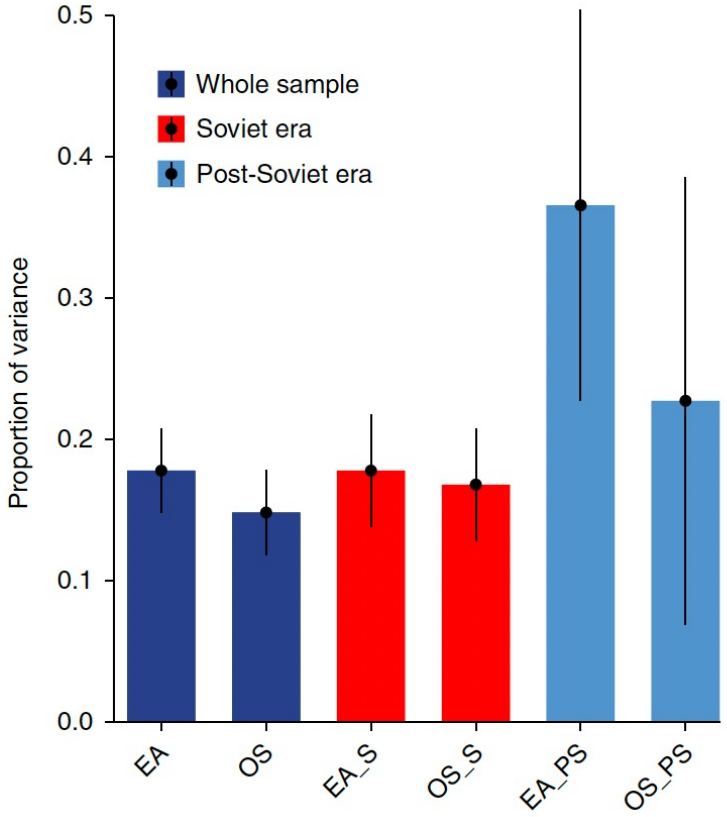
Heritability of school achievement

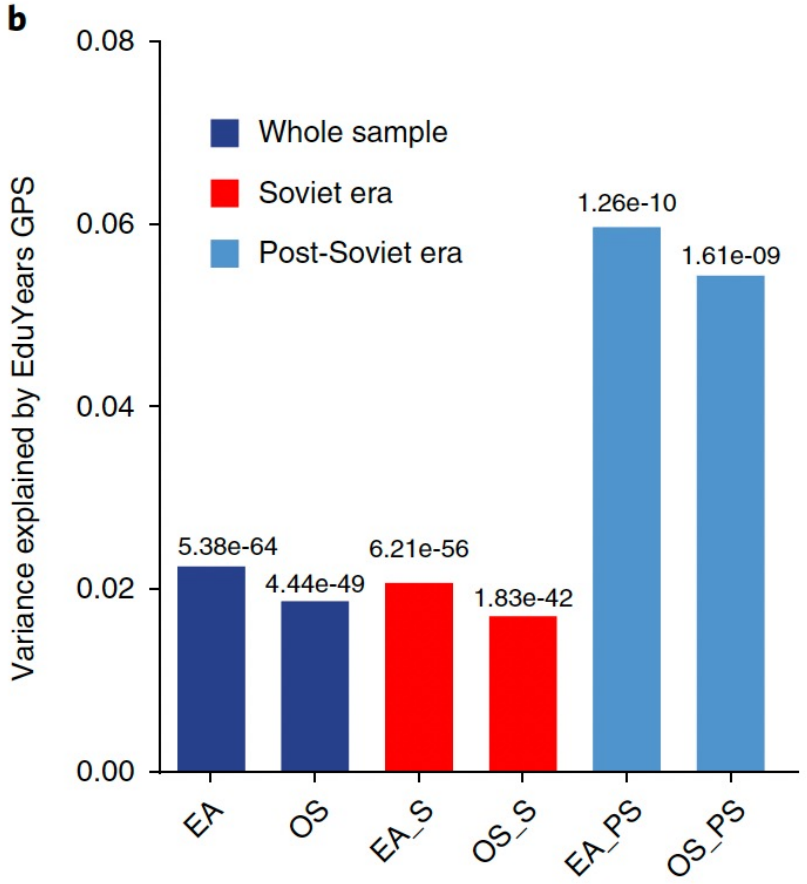




Rimfeld, Malanchini et al. 2018, *npj Science of Learning*

Heritability can change with major changes in environment

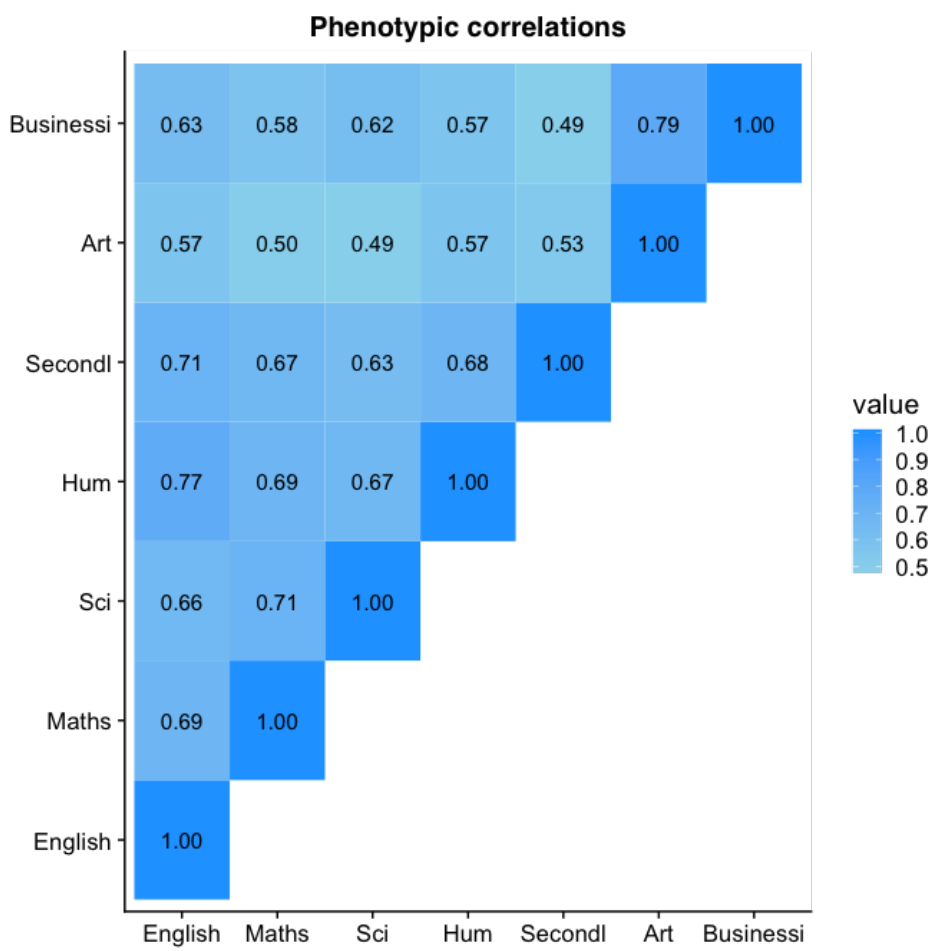


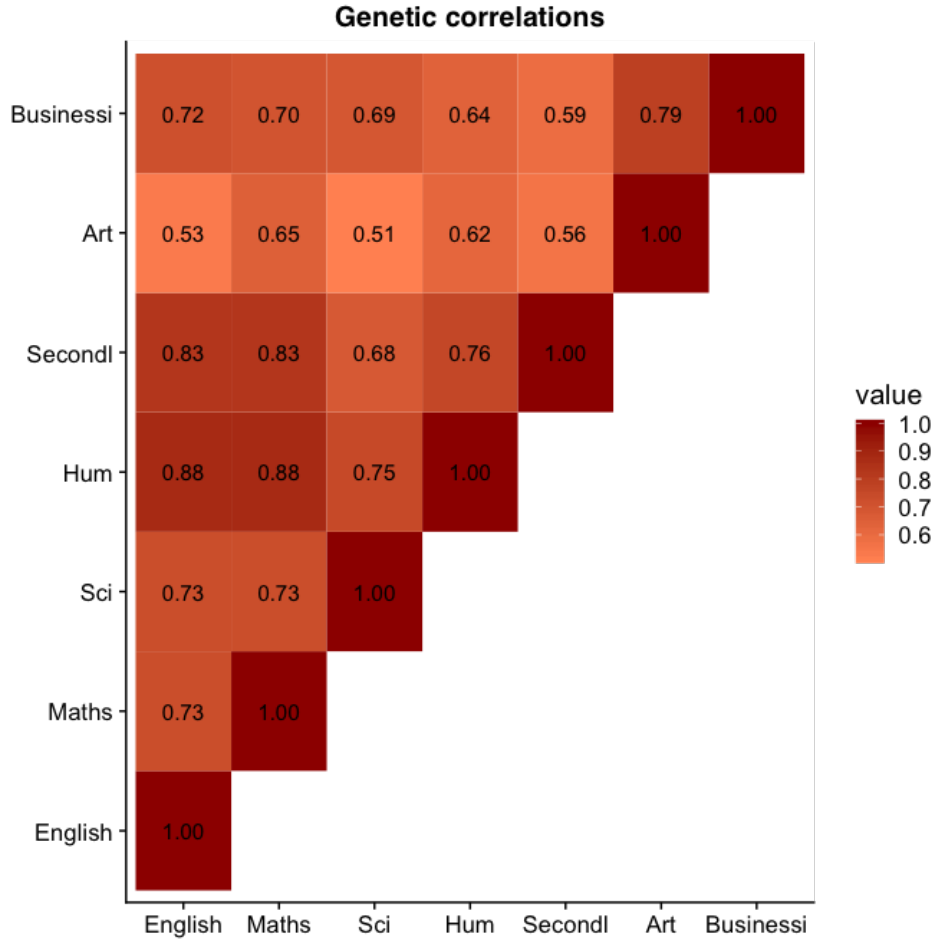


Rimfeld et al. (2018),
Nature Human Behaviour

UNIVERSITY OF TARTU
1632
estonian genome center

Shared aetiology?

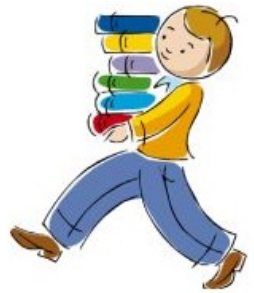




Rimfeld, Malanchini et al. 2018; *npj Science of Learning*

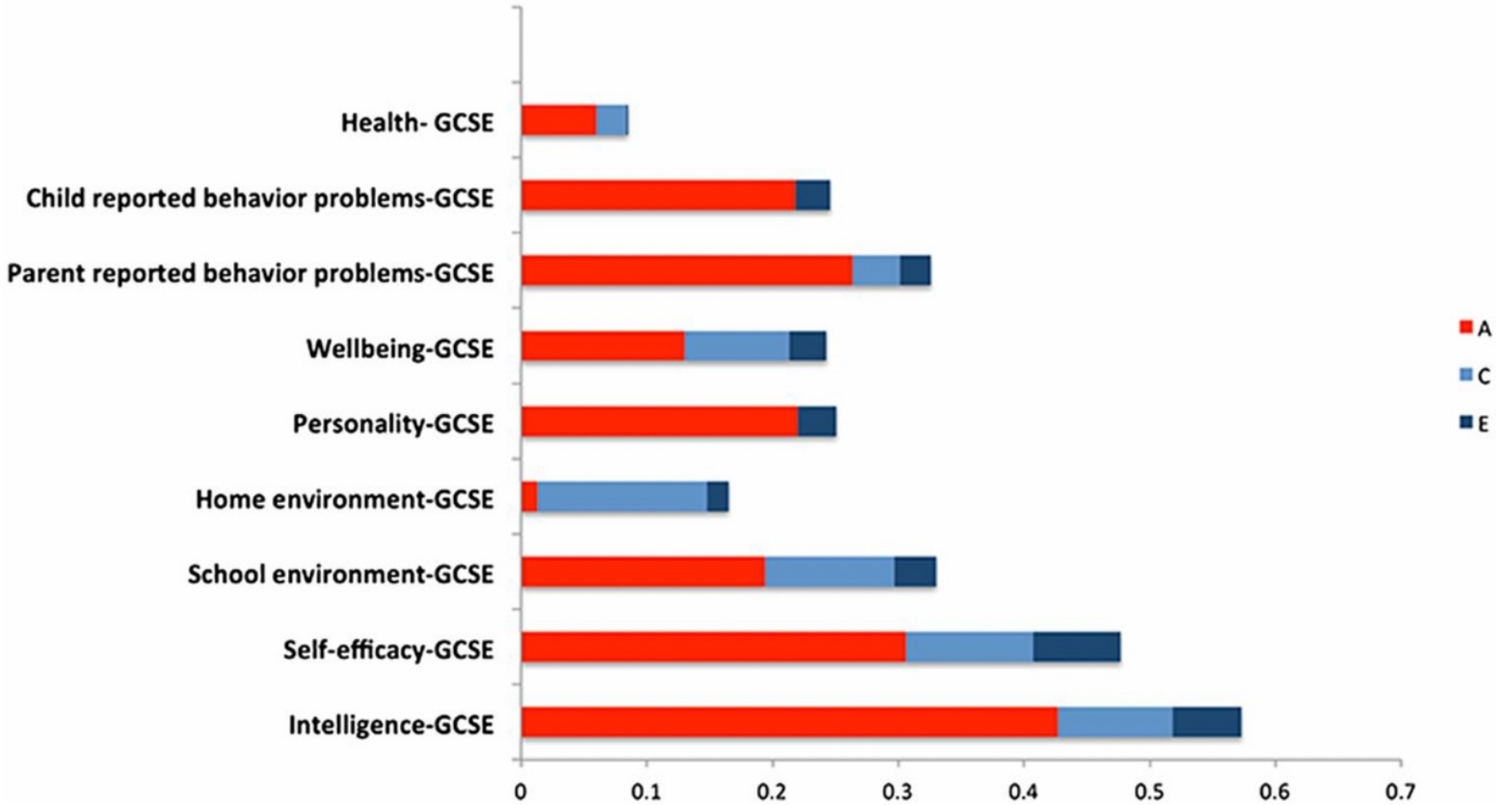
Correlates of academic achievement

- What drives the high heritability of educational achievement?
- Intelligence one of the best predictors of academic achievement
- Range of cognitive and non-cognitive predictors



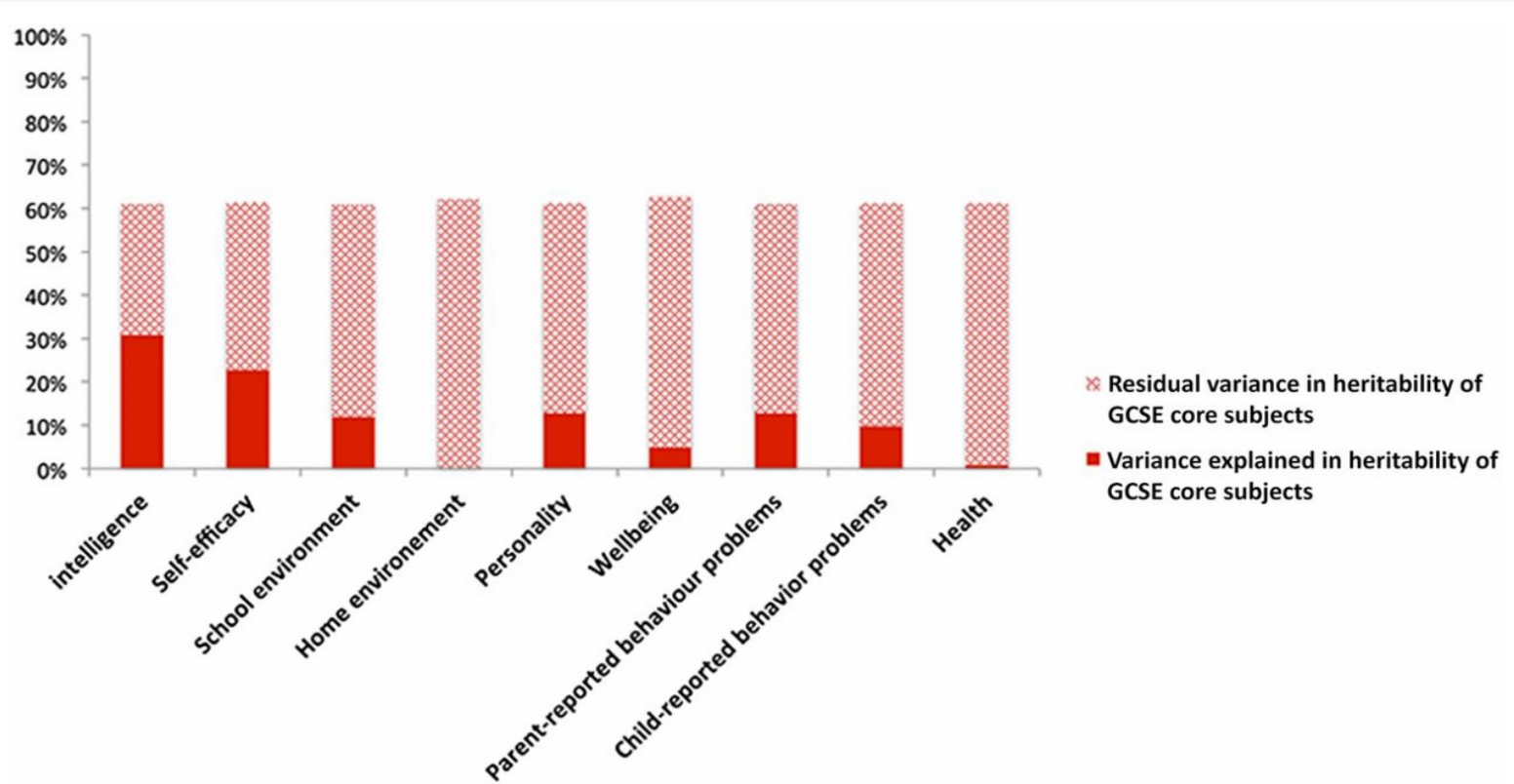
Deary, Strand, Smith & Fernandes, 2007; Deary, Johnson & Houlihan, 2009; Haworth et al., 2010; Kovas et al., 2013; Krapohl, Rimfeld et al 2014

Correlates of educational achievement



Krapoh

Bivariate estimates of the extent to which the heritability of GCSE can be explained by the nine predictors



Krapohl, Rimfeld et al. 2014, *PNAS*

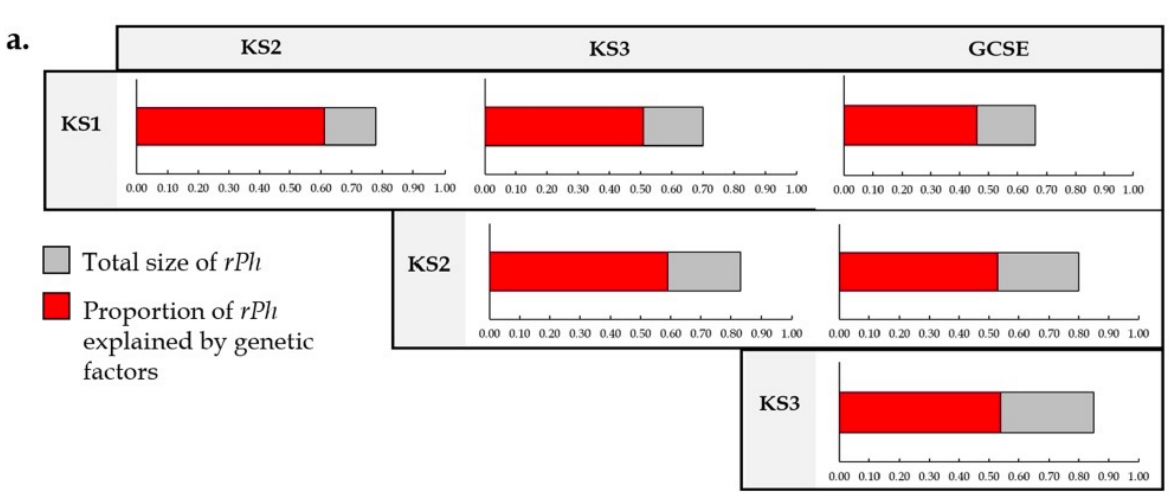
Educational achievement is a package of genetically influenced traits

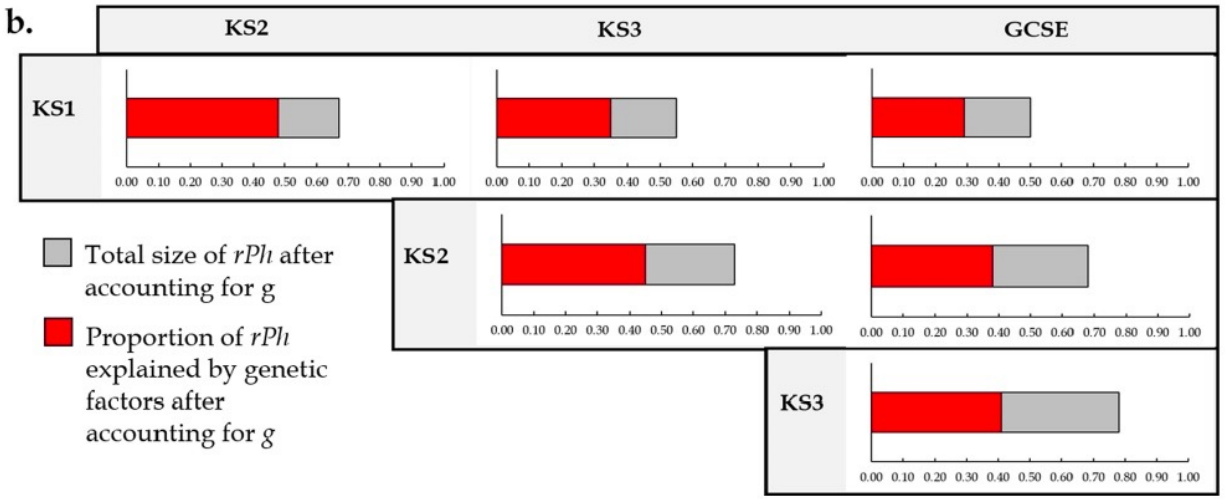
- Intelligence accounts for more heritability in GCSE results than any other domains
- All other domains collectively explain as much heritability in GCSE as intelligence
- All domains together explain 75% of the heritability of GCSE

Krapohl, Rimfeld et al. 2014, *PNAS*

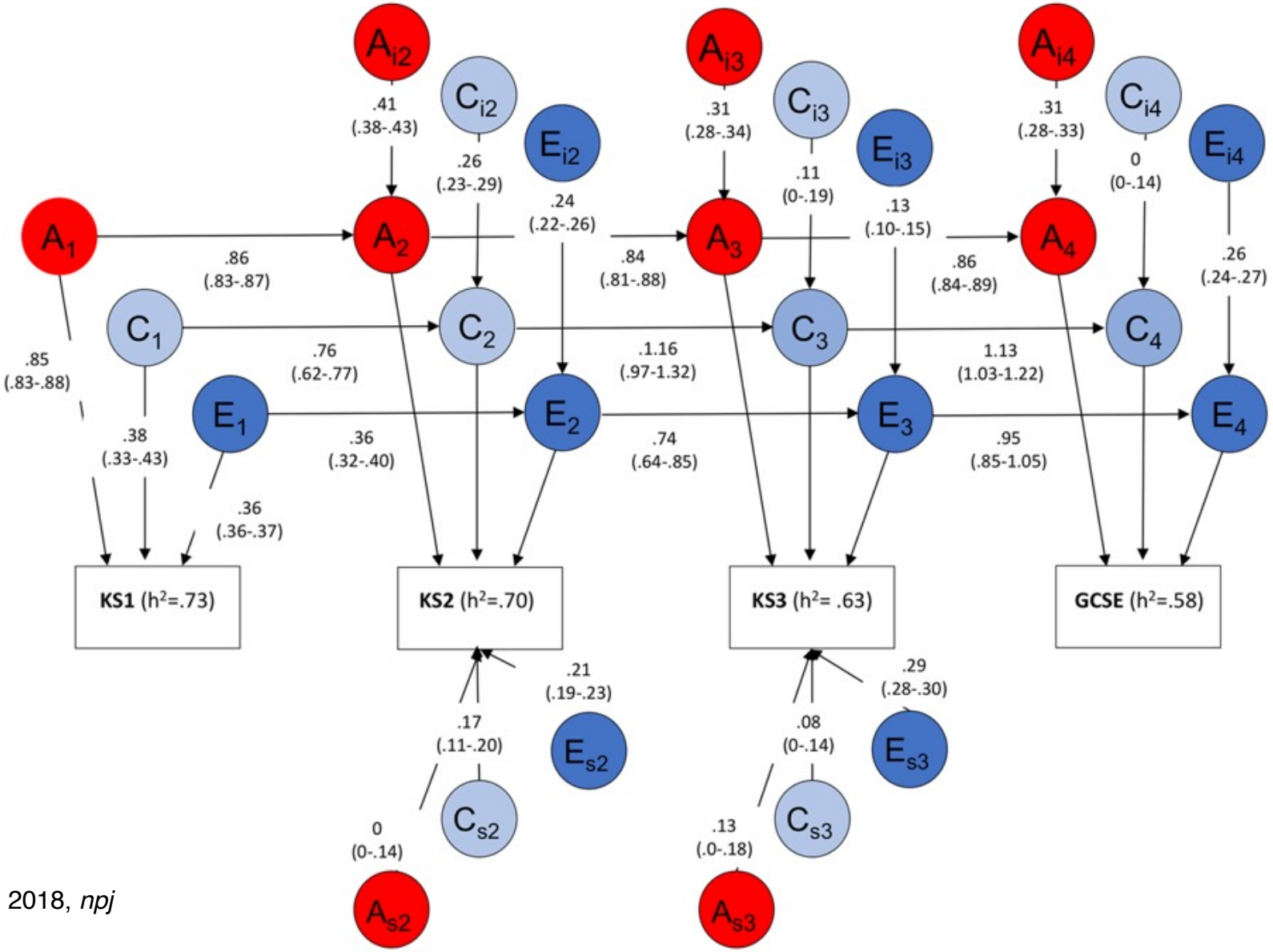
Stability of educational achievement

Controlling for *g*





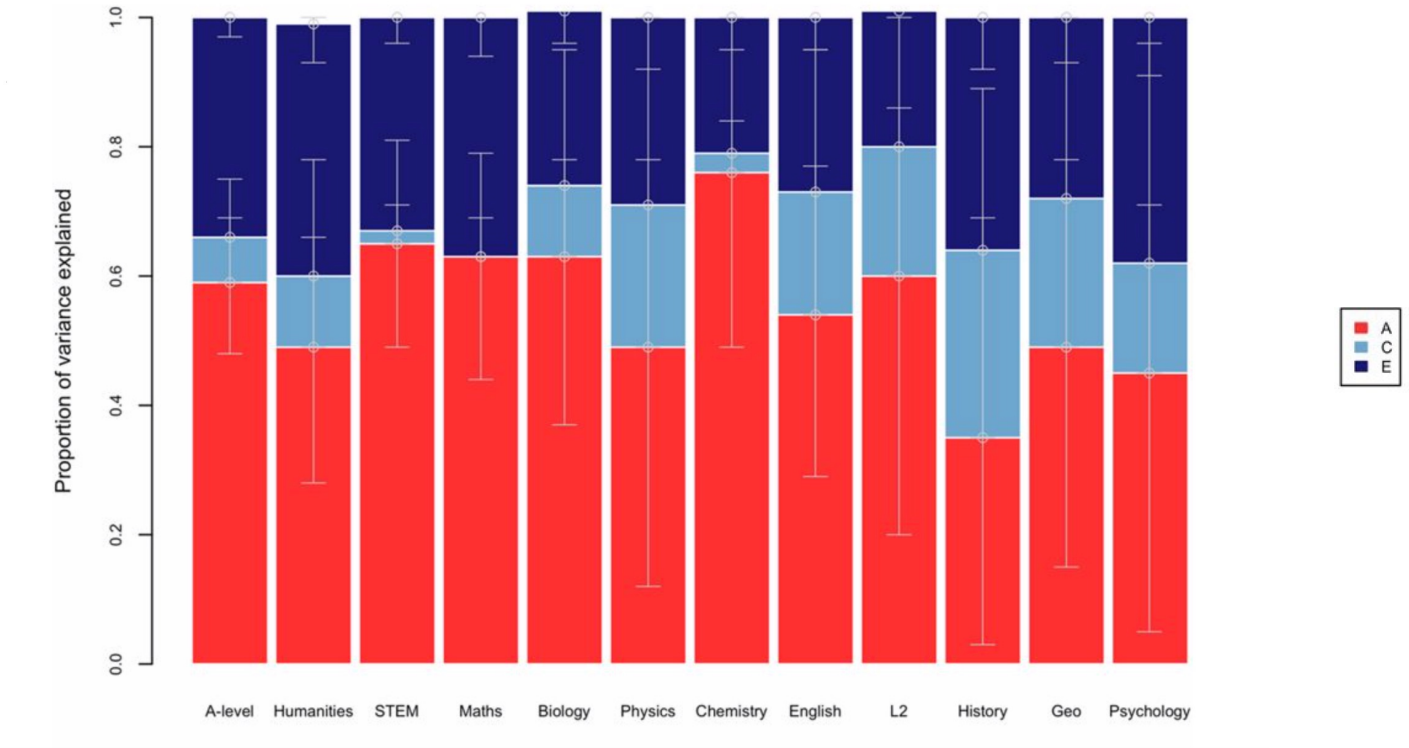
Rimfeld, Malanchini et al. 2018, *npj Science of Learning*



Rimfeld, Malanchini et al. 2018, *npj Science of Learning*

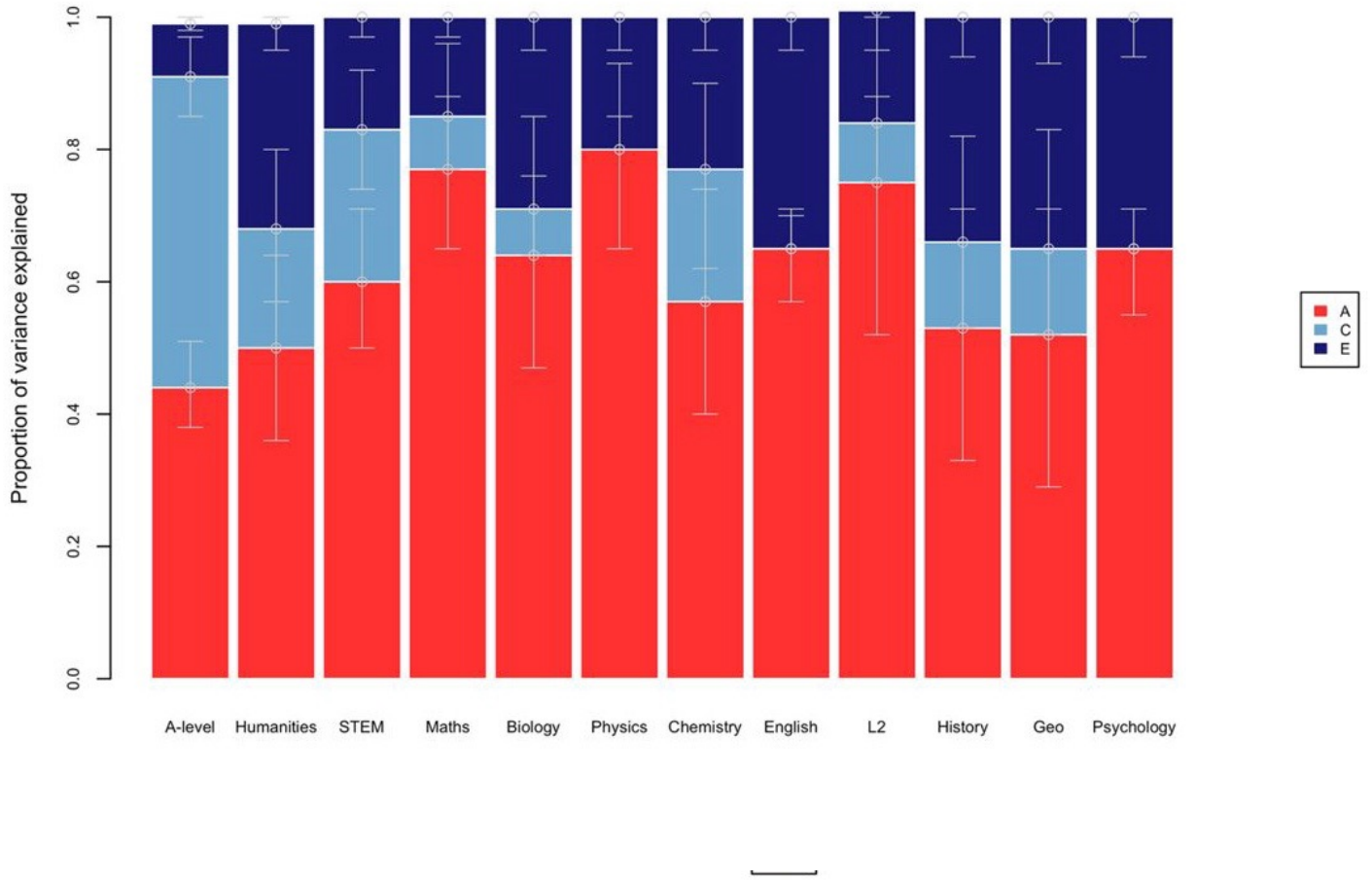
A-level achievement

From: Genetics affects choice of academic subjects as well as achievement



Rimfeld et al. 2016;
Scientific Reports

Appetite as well as aptitude



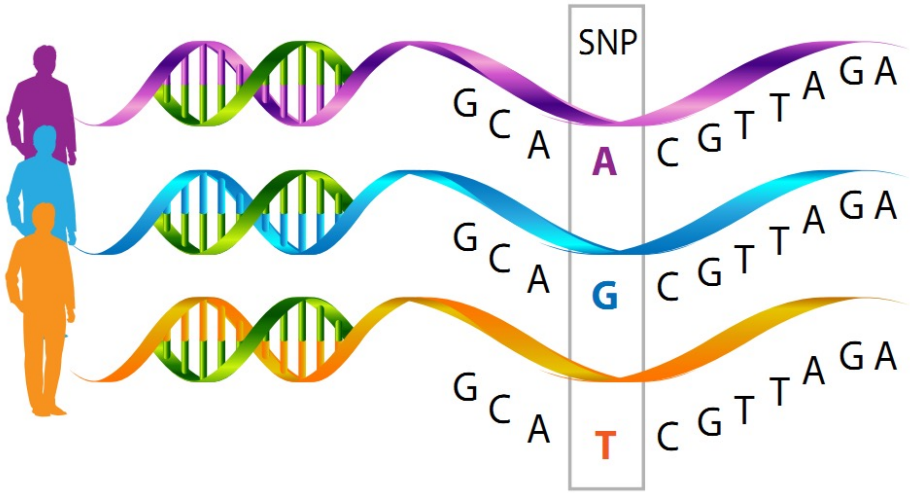
Rimfeld et al. 2018;
NPJ Science of Learning

Triangulate

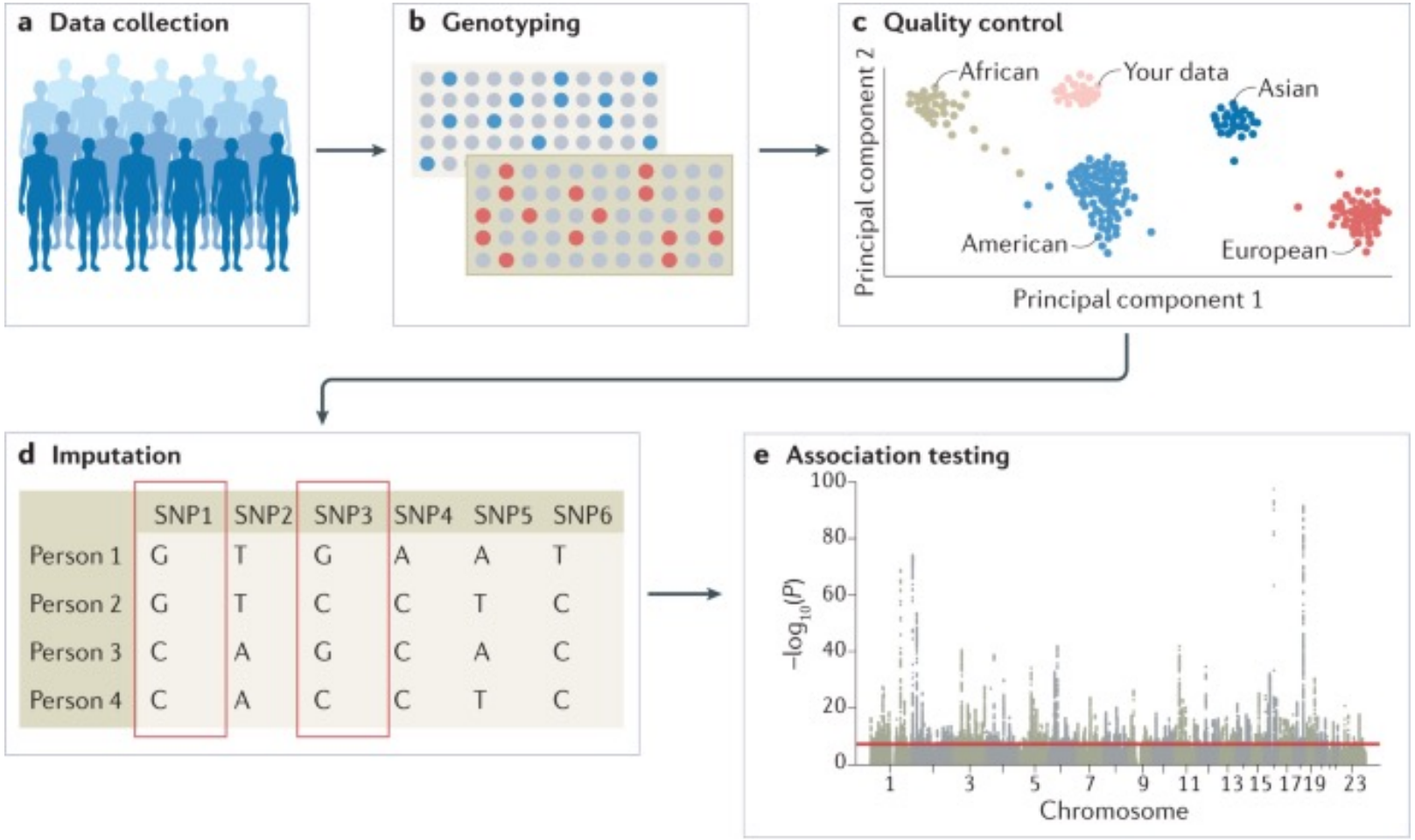
- Every method has strength and limitations
- Adoption studies
- DNA based methods

What is a GWAS?

- **<u>GW</u> = Genome-wide**
  - Comprehensive coverage of the genome
  - (millions of **SNPSs**)
  - “data driven” and “hypothesis free”
- **<u>AS</u> = Association study**
  - Does a SNP co-occur with a given phenotype?
  - Just like doing hundreds of thousands of candidate gene studies simultaneously (but with an atheoretical, data-driven approach)



Genome-wide association study



Uffelmann, Nat Rev Gen, 2021

What have we learnt from GWAS?

1) Human complex traits are extremely **polygenic**

2) There are **no SNPs of large effect** size

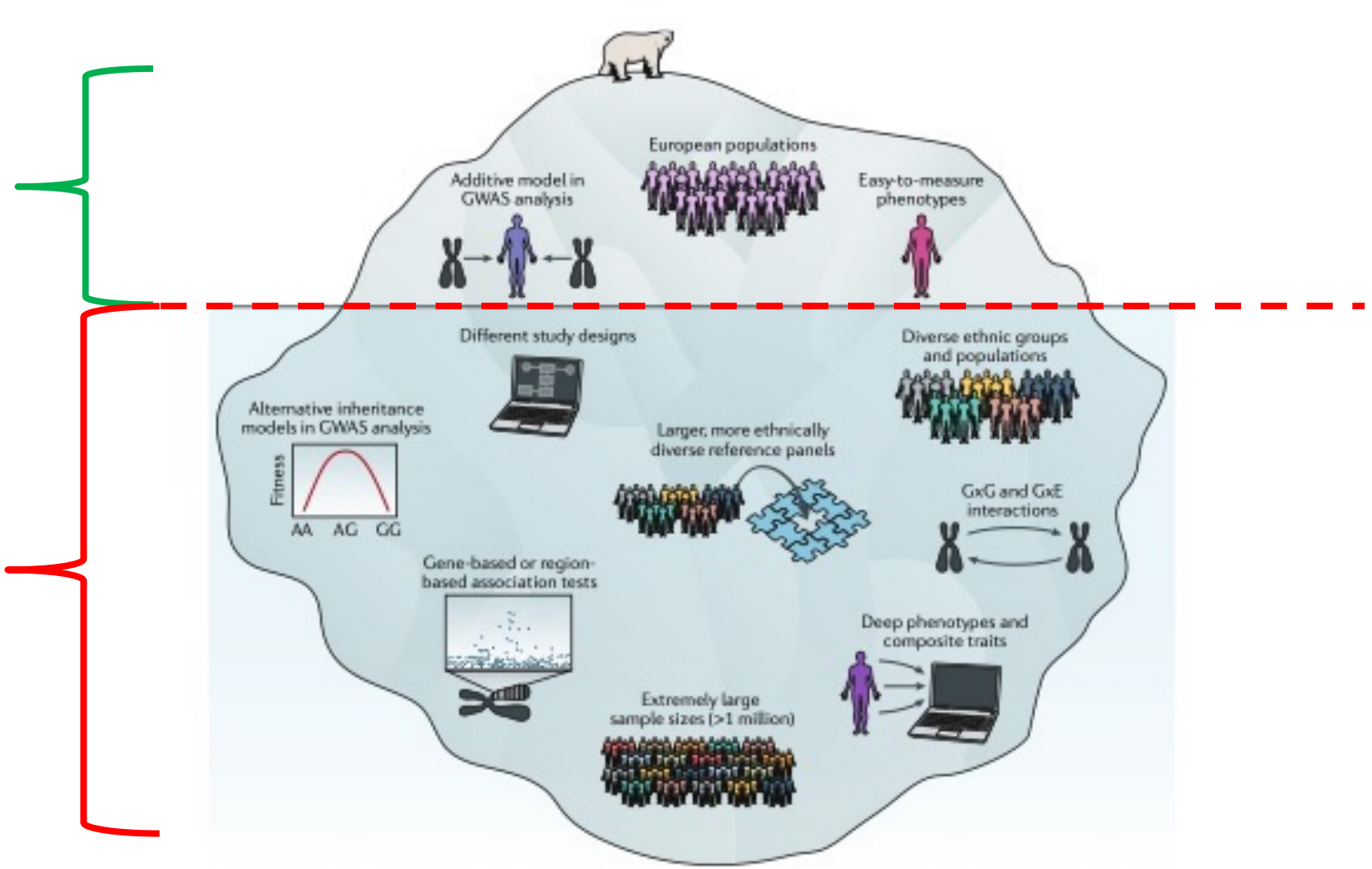
3) Genome-wide significant hits **do not account** for most of heritability

Visscher et al. (2017) *Am. J. Hum. Genet.;* Visscher et al. (2012) *Am. J. Hum. Genet.*

GWAs performed to date represent only the tip of the iceberg

Discoveries made to date

What we cannot yet consider in GWAS but we should aim to



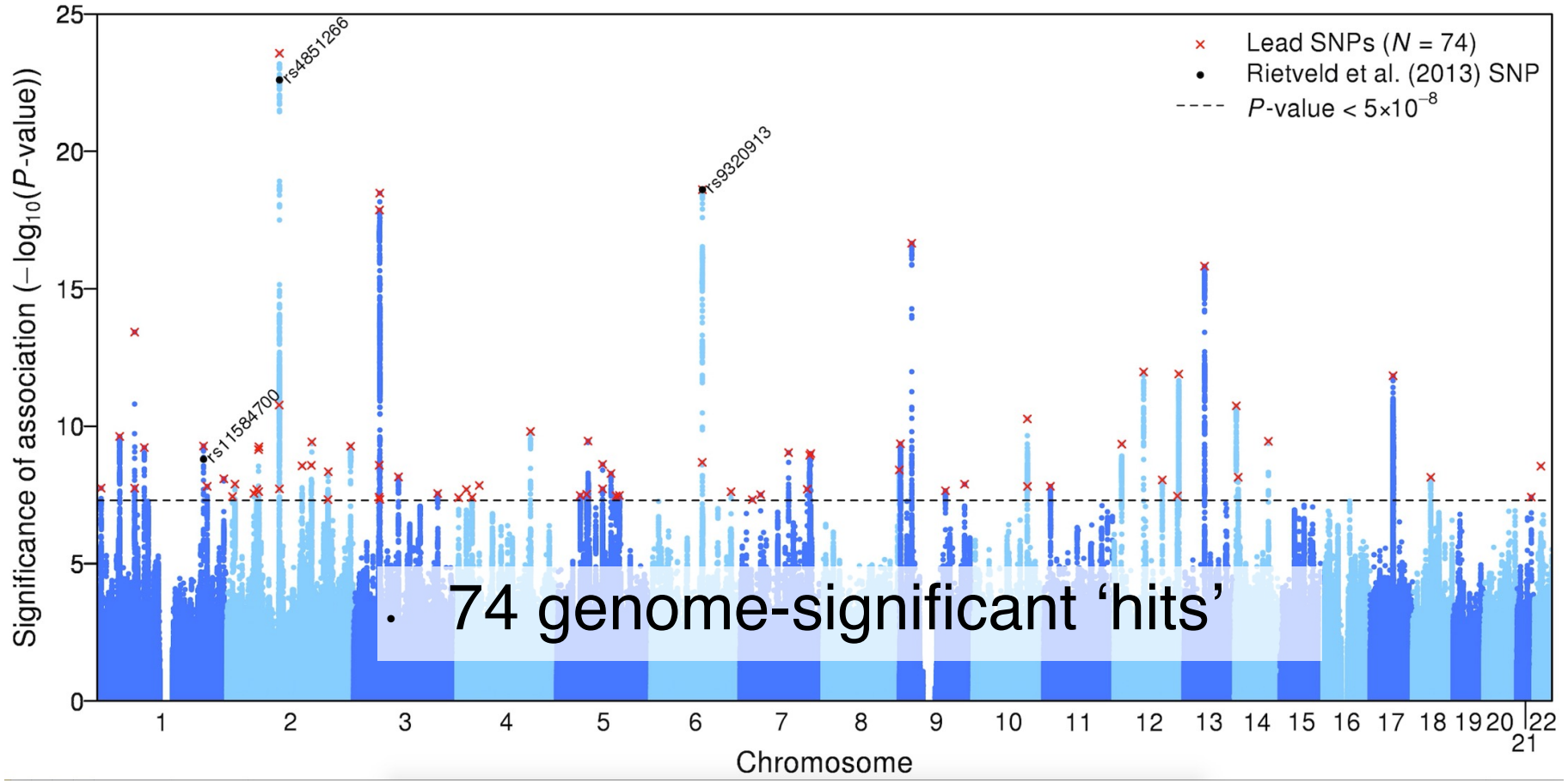
Tam et al. (2019)

NATURE | LETTER

Genome-wide association study identifies 74 loci associated with educational attainment

Aysu Okbay, Jonathan P. Beauchamp, Mark Alan Fontana, James J. Lee, Tune H. Pers, Cornelius A. Rietveld, Patrick Turley, Guo-Bo Chen, Valur Emilsson, S. Fleur W. Meddens, Sven Oskarsson, Joseph K. Pickrell, Kevin Thom, Pascal Timshel, Ronald de Vlaming, Abdel Abdellaoui, Tarunveer S. Ahluwalia, Jonas Bacelis, Clemens Baumbach, Gyda Bjornsdottir, Johannes H. Brandsma, Maria Pina Concas, Jaime Derringer, Nicholas A. Furlotte, Tessel E. Galesloot + *et al.*

2016 GWA of years of education (EA2) (N = 300,000)



- 74 genome-significant ‘hits’

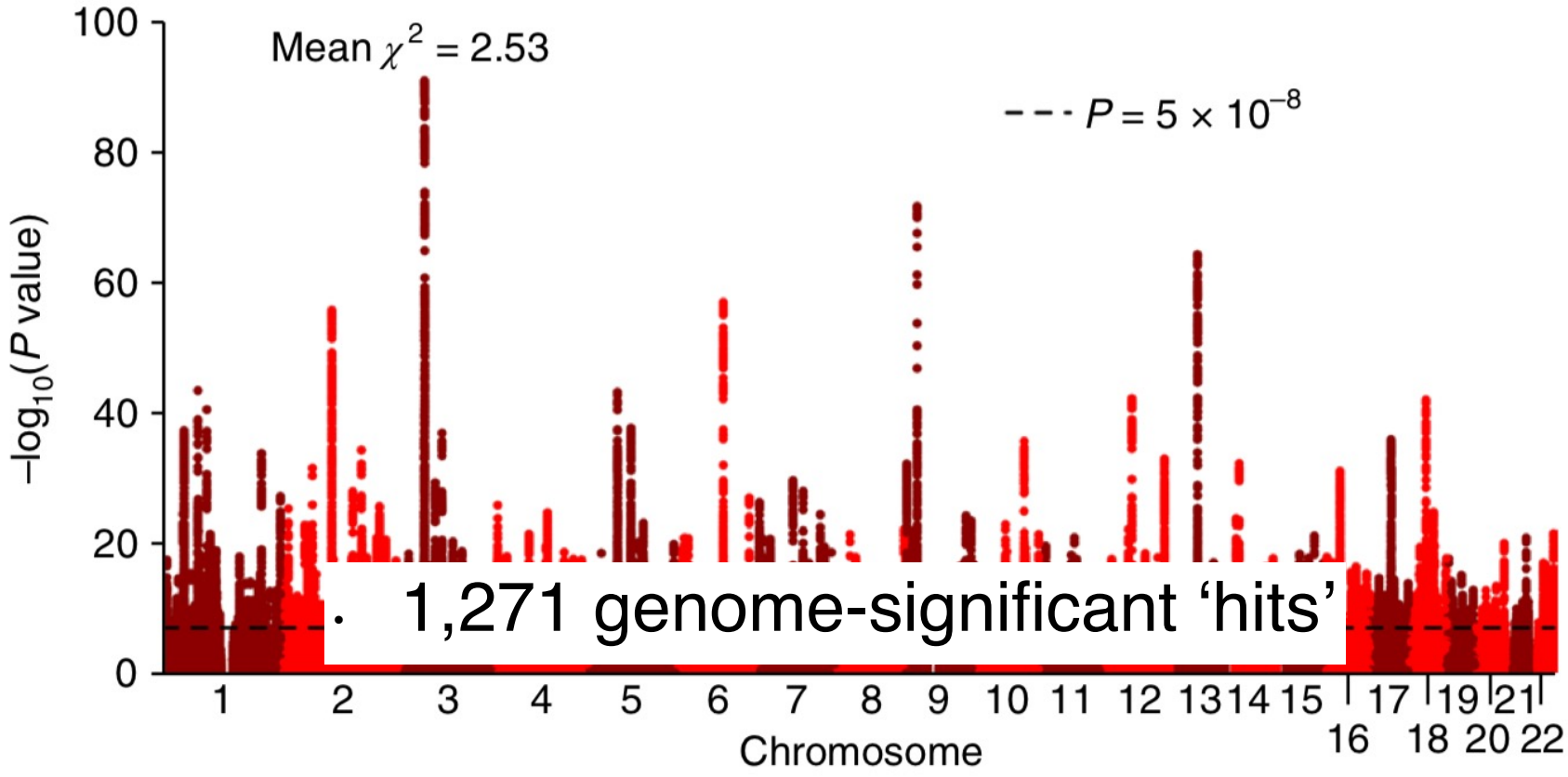
Okbay et al. 2016

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-018-0147-3

Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals

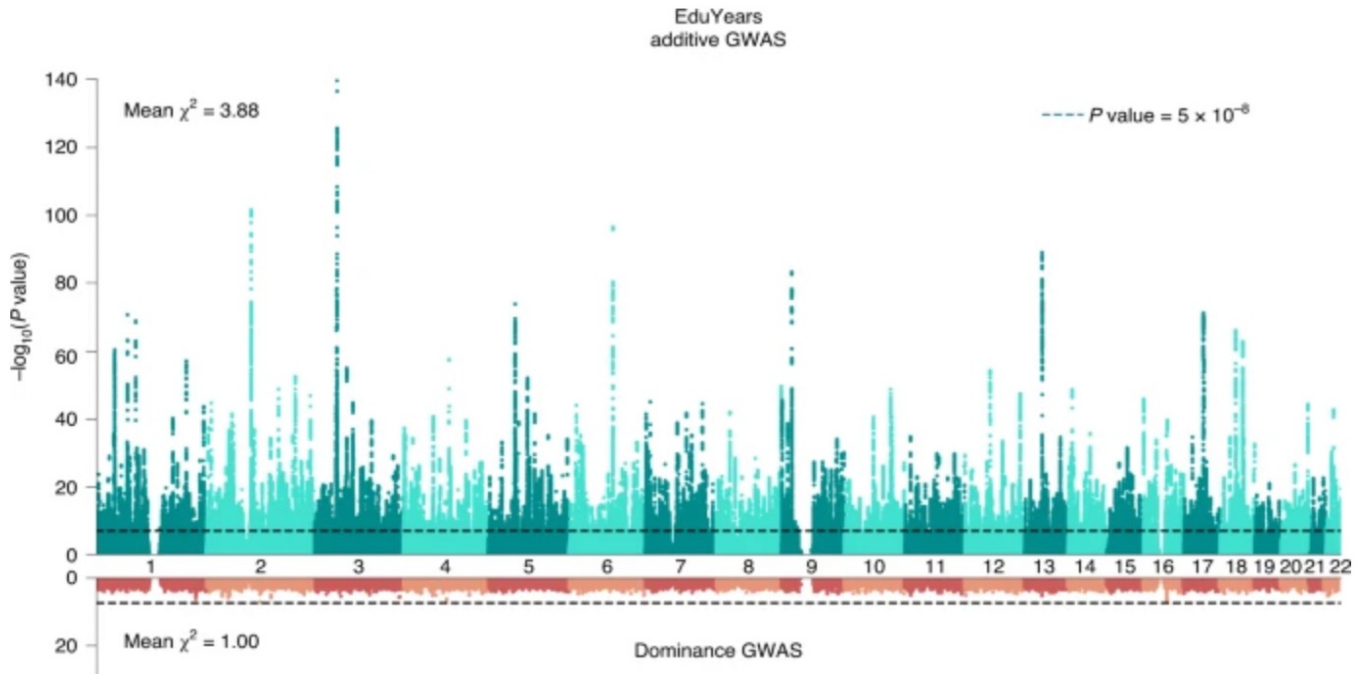


Lee et al. 2018

Article | Open Access | Published: 31 March 2022

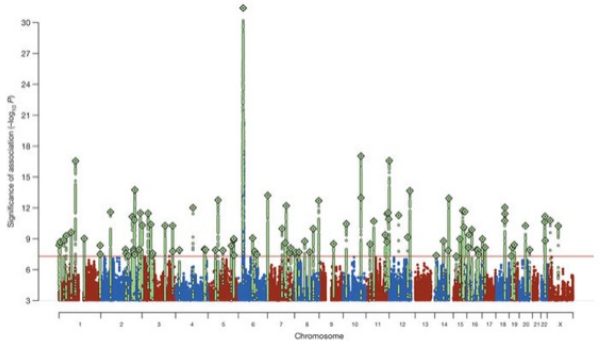
Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals

Fig. 1: Manhattan plots for the additive and dominance GWASs.



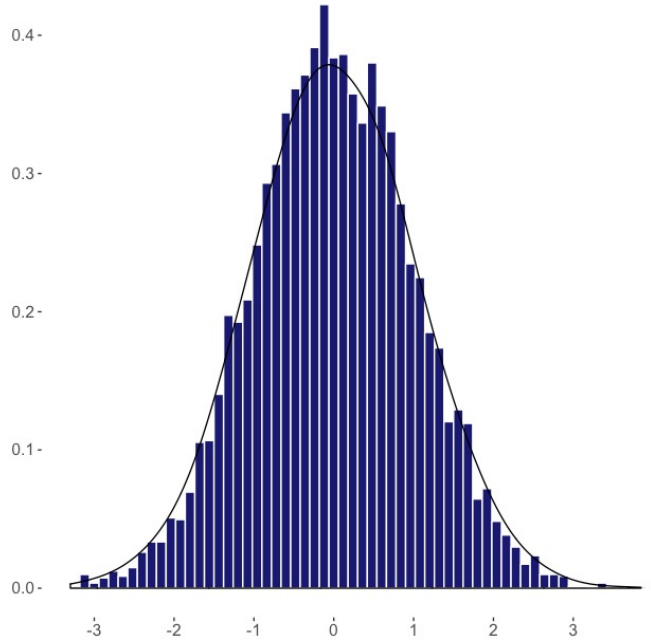
The top graph (green) shows the additive GWAS (N = 3,037,499 individuals), and the bottom graph (red) shows the dominance GWAS (N = 2,574,253 individuals). The P value and mean χ^2 values are based on inflation-adjusted two-sided Z tests. The x axis is chromosomal position, and the y axis is the significance on a $-\log_{10}$ scale. The dashed line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$).

Genome-wide polygenic scores (GPS)



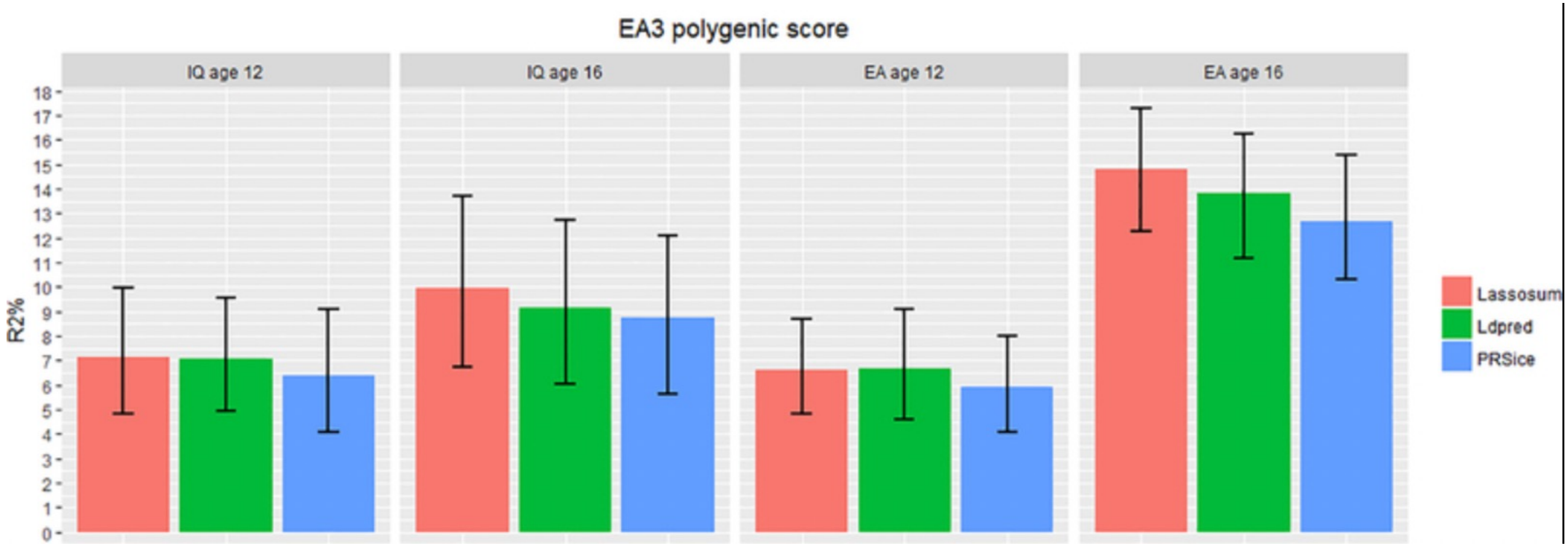
Independent sample

$$GPS_i = \sum_{j=1}^{k} \hat{\beta}_j SNP_j$$



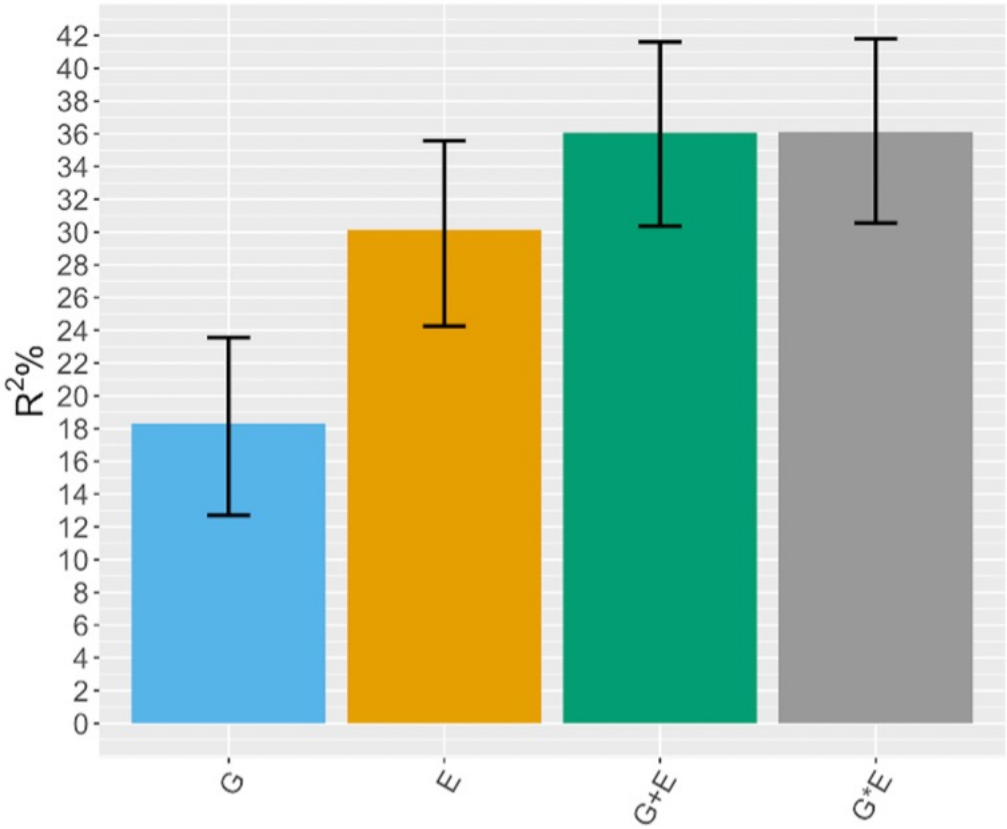
GPS distribution

Predicting educational achievement from DNA



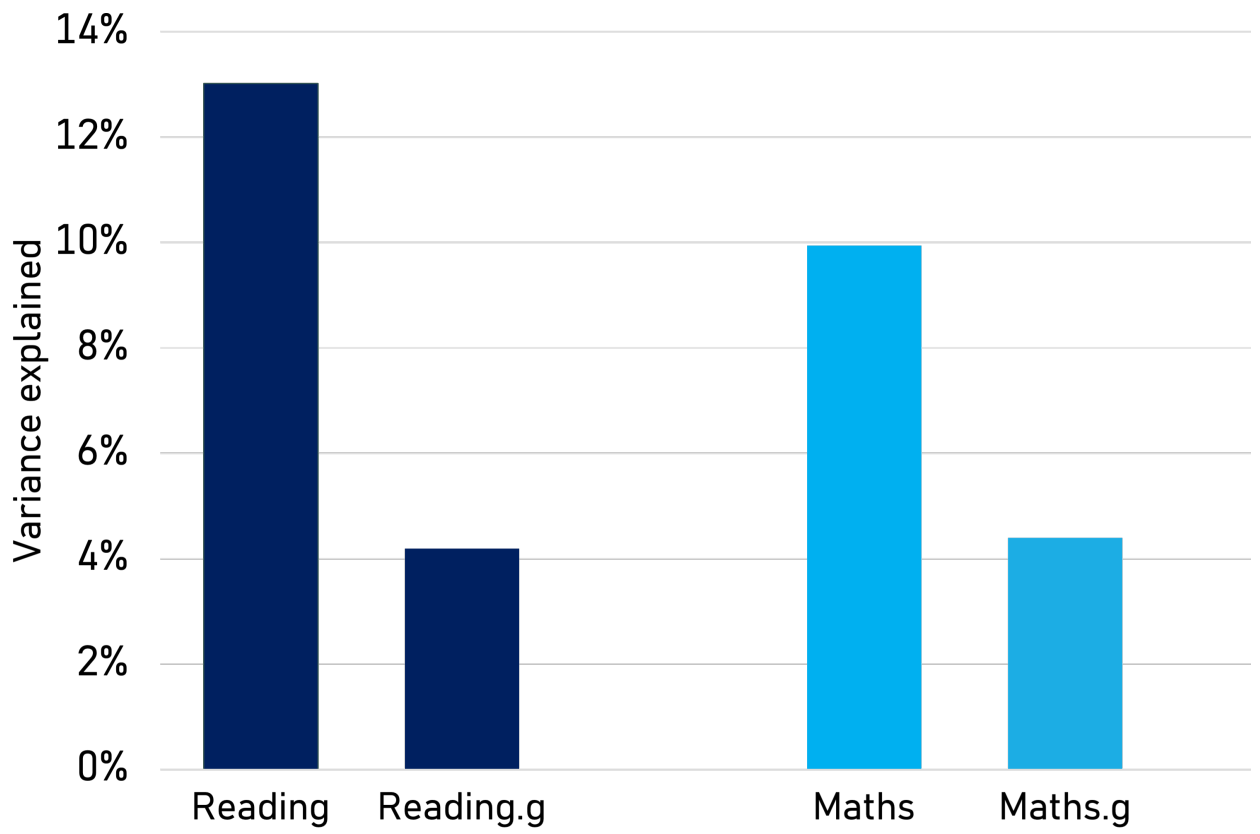
Allegrini et al 2019
Mol Psychiatry

Predicting educational achievement from DNA



Allegrini et al 202-
Plos Genetics

Multi-polygenic score analysis

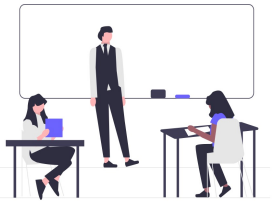


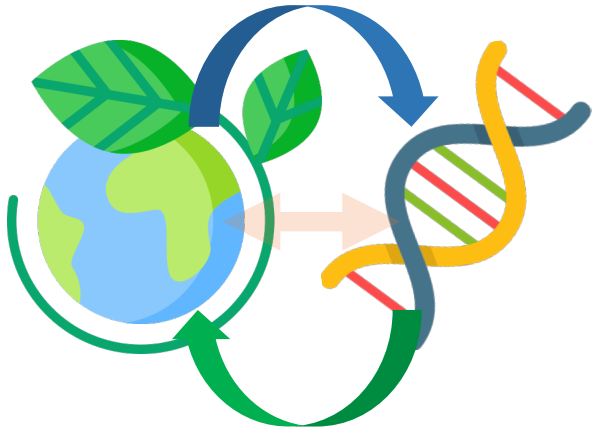
Procorpio et al. in prep

Transactional models: gene-environment correlation(rGE)

Passive

Evocative

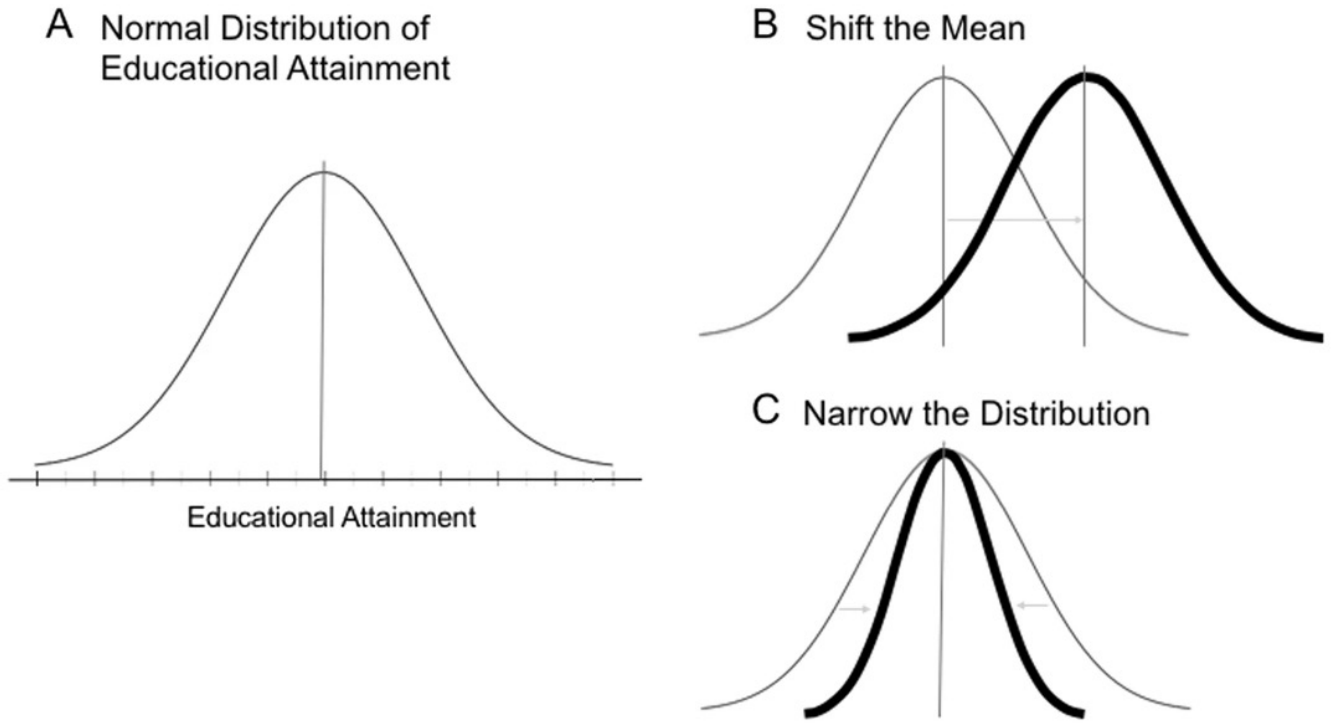




Active

Transactional model

Genetic research in the context of education



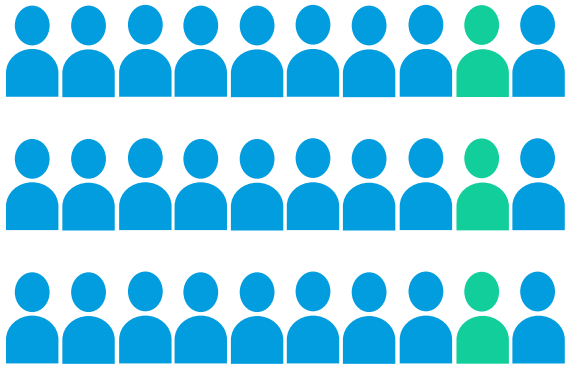
Sokolowski and Ansari, 2018
Npj Science of Learning

Genetics and the personalized education

- Educational curricula → embracing individual differences between students
- Future applications: Genetic information integrated into the development of early interventions, particularly as an additional tool to inform early screening → Many caveats

1 in 10 children

3 children in every classroom



World Health Organization

British Journal of Psychiatry, 2019

Study >28,000 adolescents in England

Above clinical cutoff for emotional, conduct problems, and hyperactivity

Deighton et.al, 2019

	2017		2020
5-16 y.o.	**11.6%**	→	**17.4%**
17-19 y.o.	**10.1%**	→	**17.4%**

NHS Digital, 2021

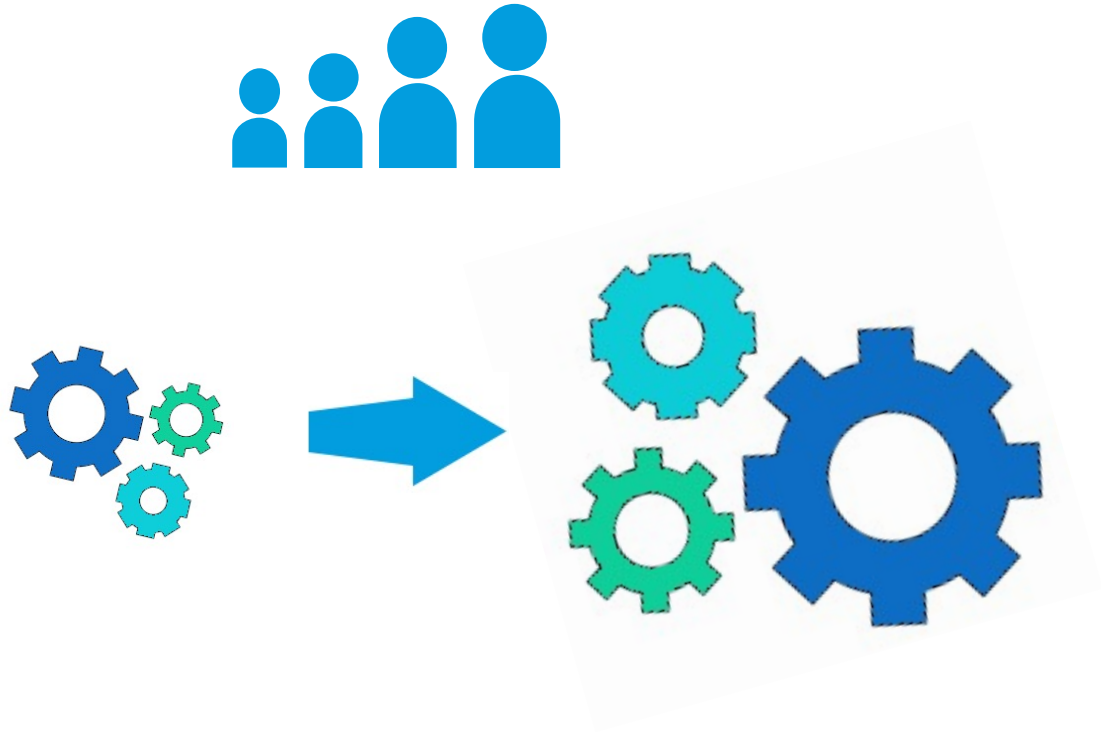
Increase of 63% by 2030

The NHS is not coping well

10% of children and young people (aged 5-16 years) have a clinically diagnosable mental health problem, yet 70% of children and adolescents who experience mental health problems have not had appropriate interventions at a sufficiently early age.

(Children's Society, 2008)

75% of those with a mental health condition start developing it before the age of 18



MQ Transforming mental health through research

What are the 10 ACEs?

- physical abuse
- sexual abuse
- psychological abuse
- physical neglect
- psychological neglect
- witnessing domestic abuse
- having a close family member who misused drugs or alcohol
- having a close family member with mental health problems
- having a close family member who served time in prison
- parental separation or divorce on account of relationship breakdown.

- *EIF report, 2020*

Fifteen Thousand Hours

Secondary Schools and Their Effects on Children

Michael Rutter
Barbara Maughan
Peter Mortimore
Janet Ouston

School environment and mental health

- Exams?
- Student-teacher relationships?
- School types?
- School resources?
- Neighborhood?

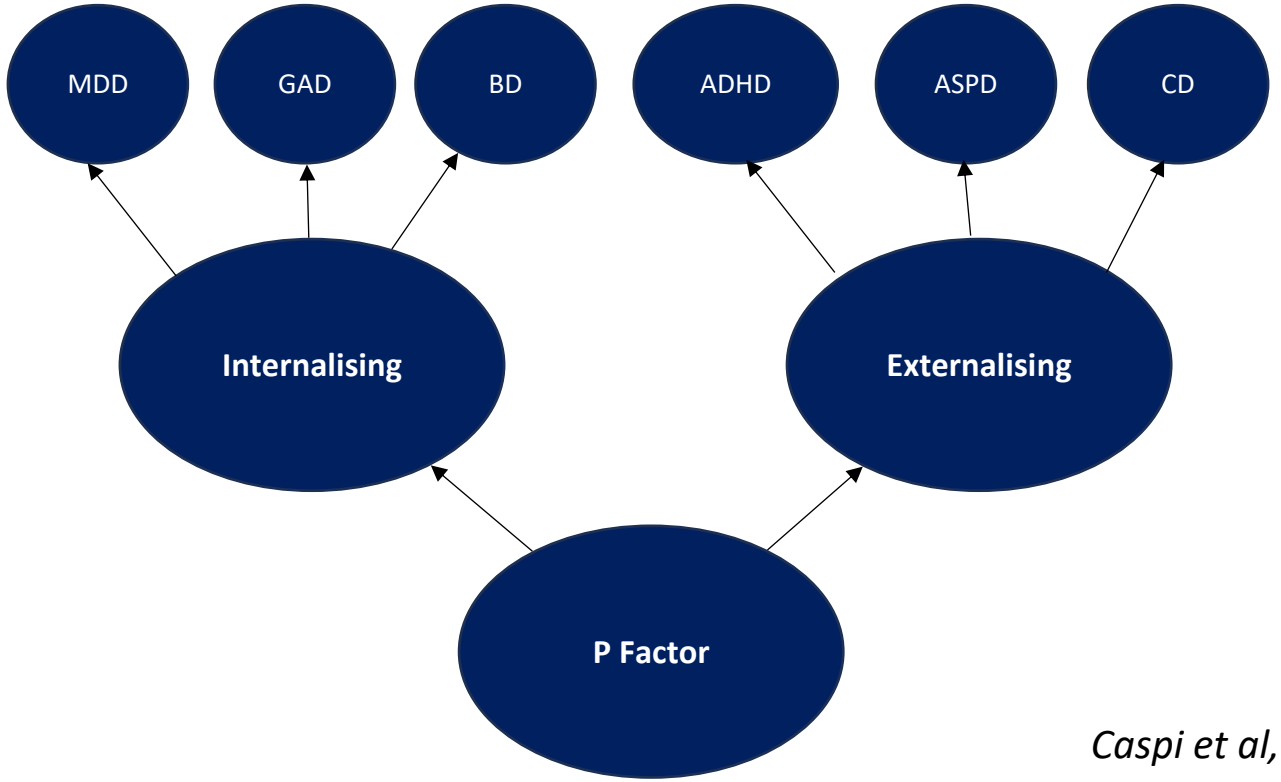
Twins Early Development Study (TEDS)

TEDS

Parent-, teacher- , and self-reported measures

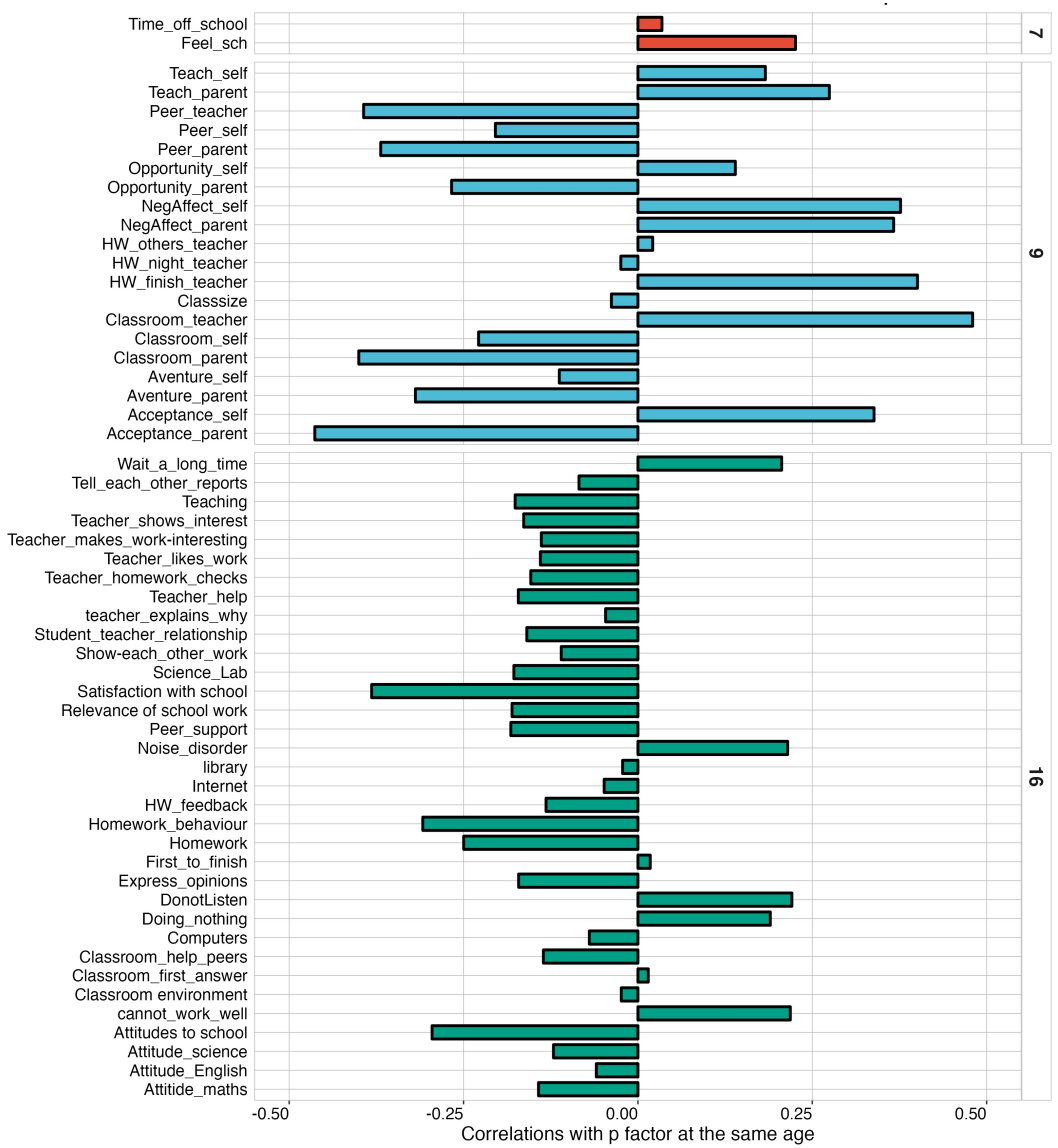
Collected when the twins were 7-21

P factor of psychopathology

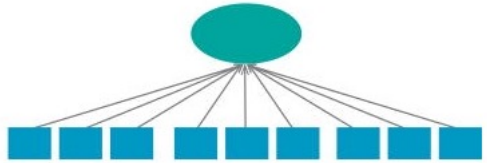


Caspi et al, 2014; Allegrini et al, 2020

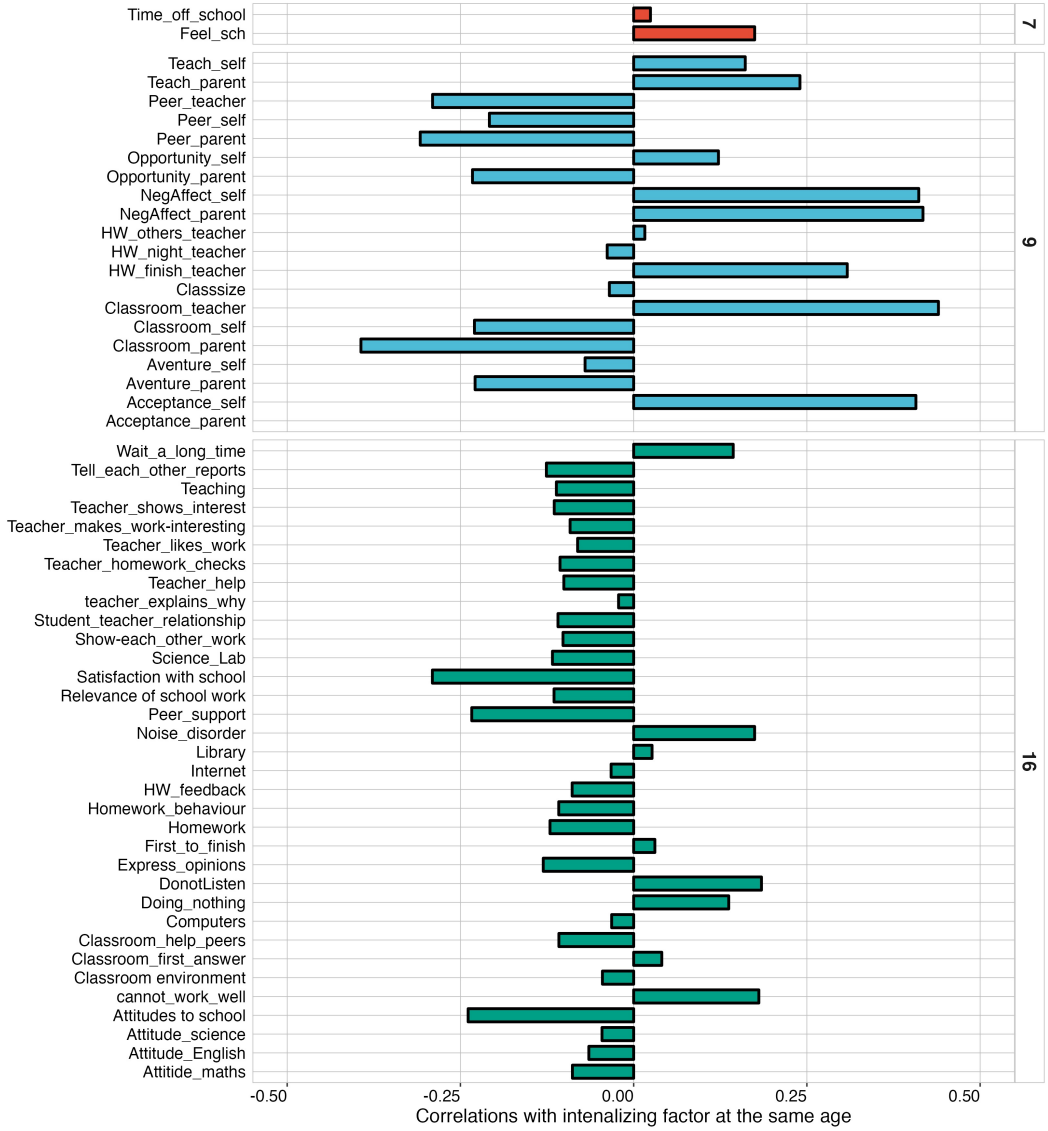
Associations between school environments and p-factor



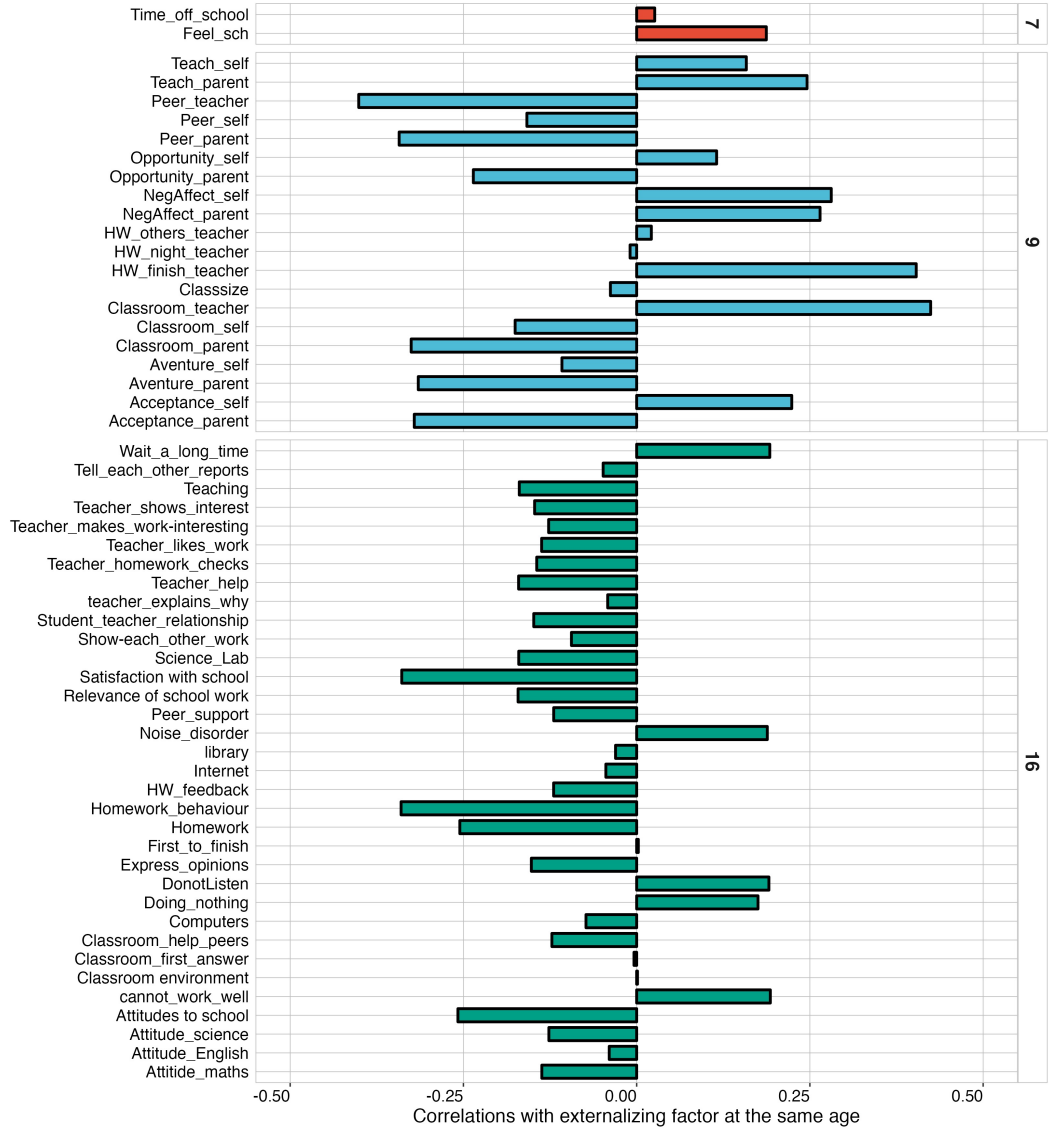
Subjective school experiences and p

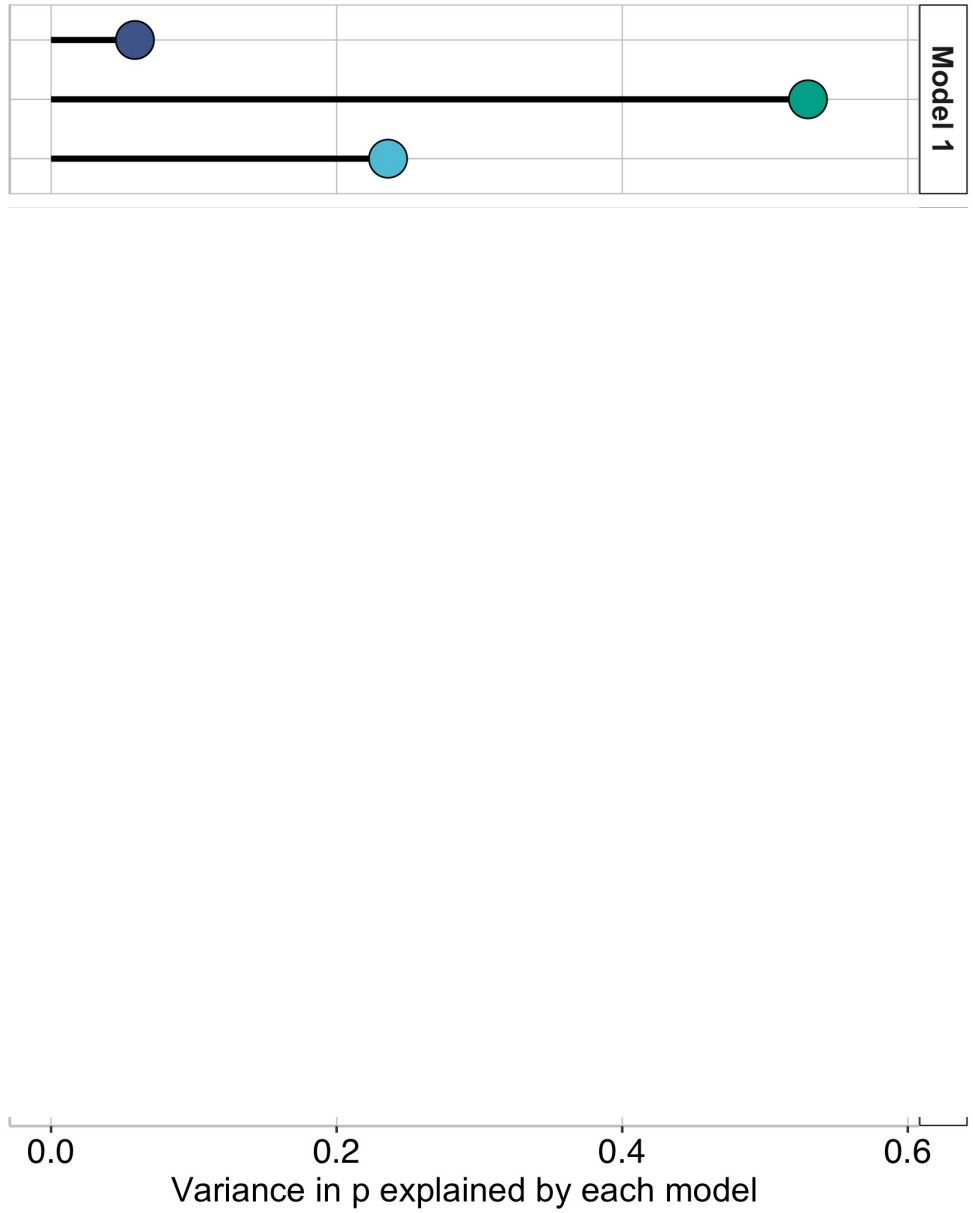


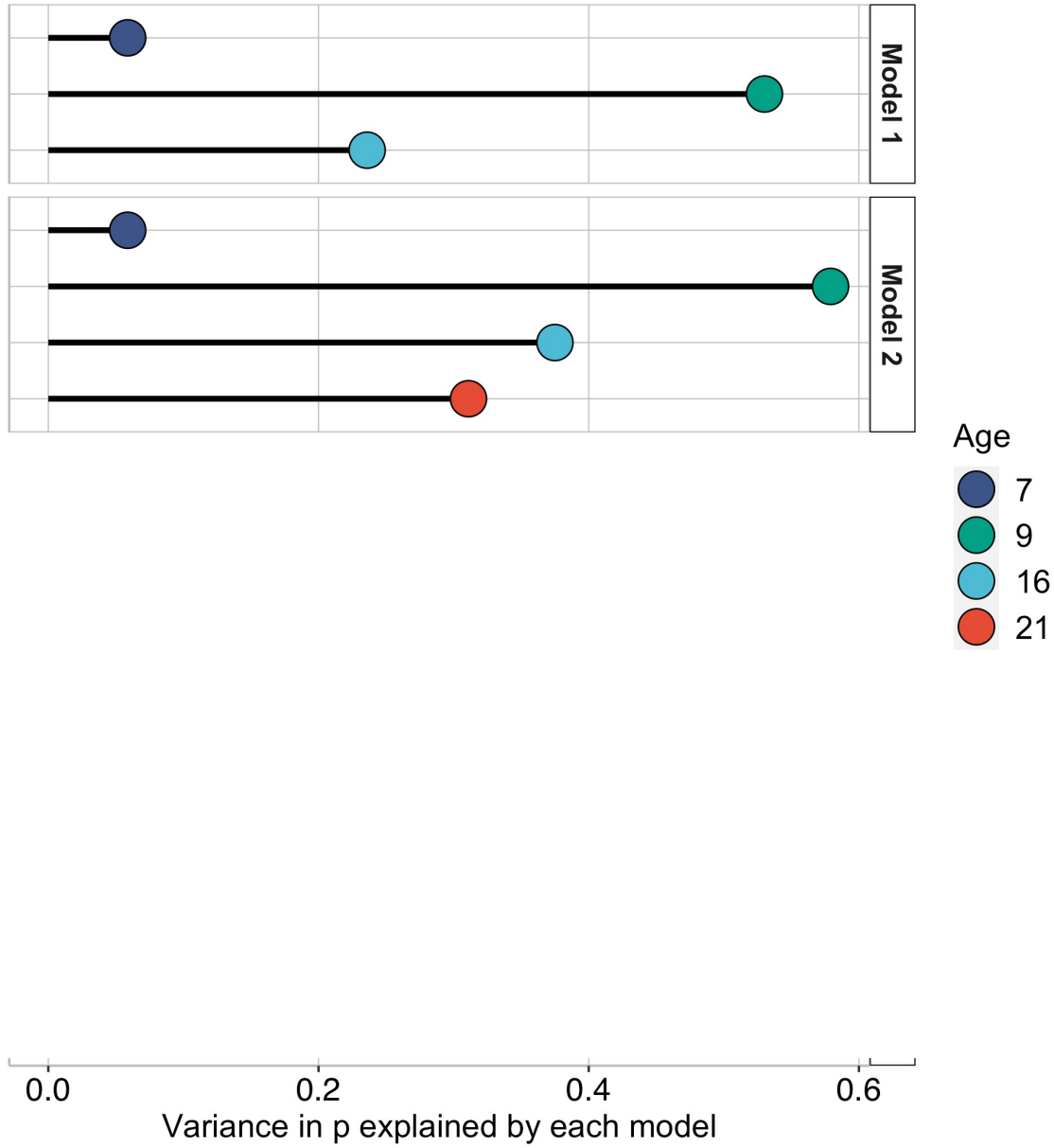
Associations between objective school environments and internalizing problems

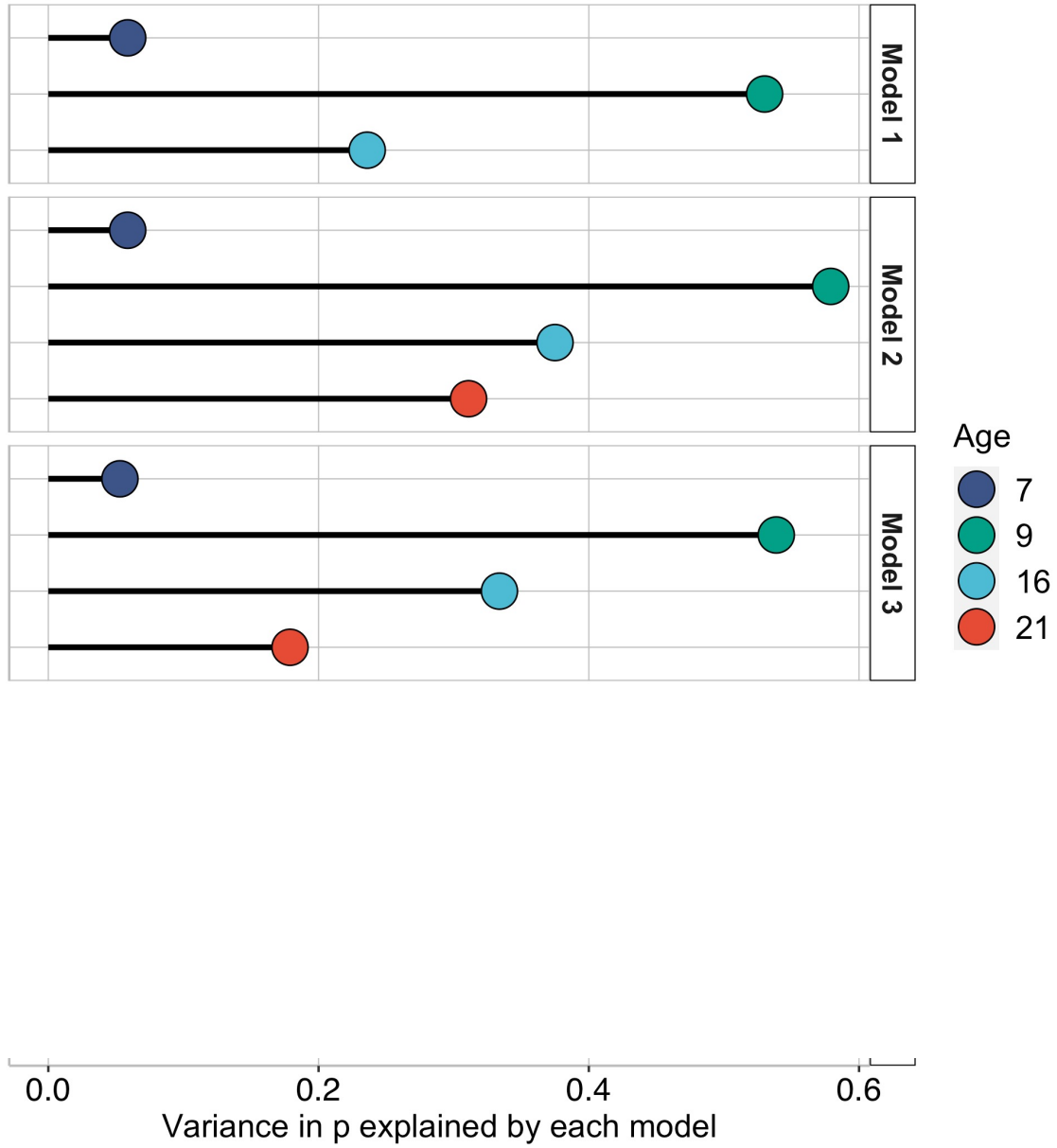


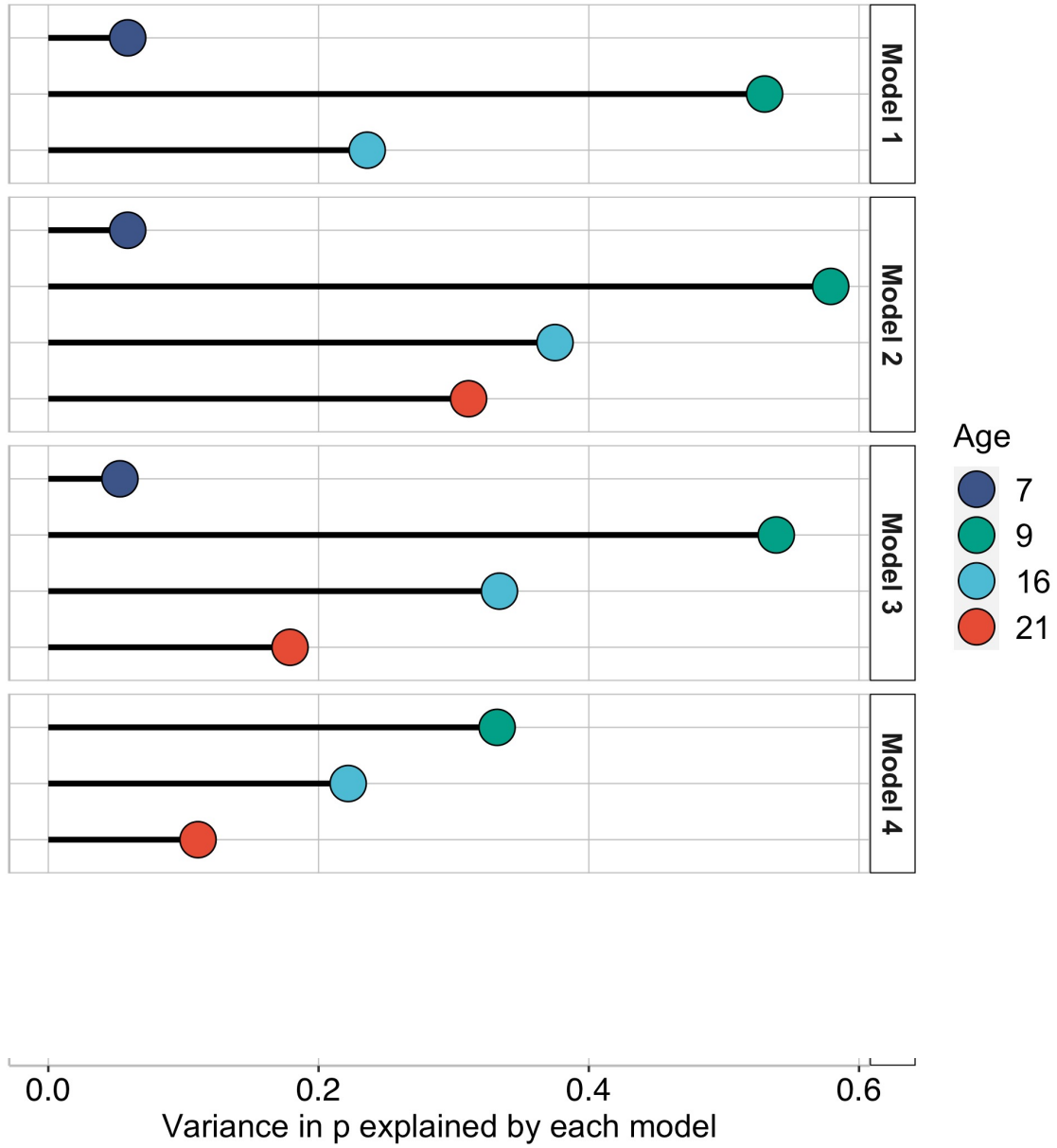
Associations between objective school environments and externalizing problems

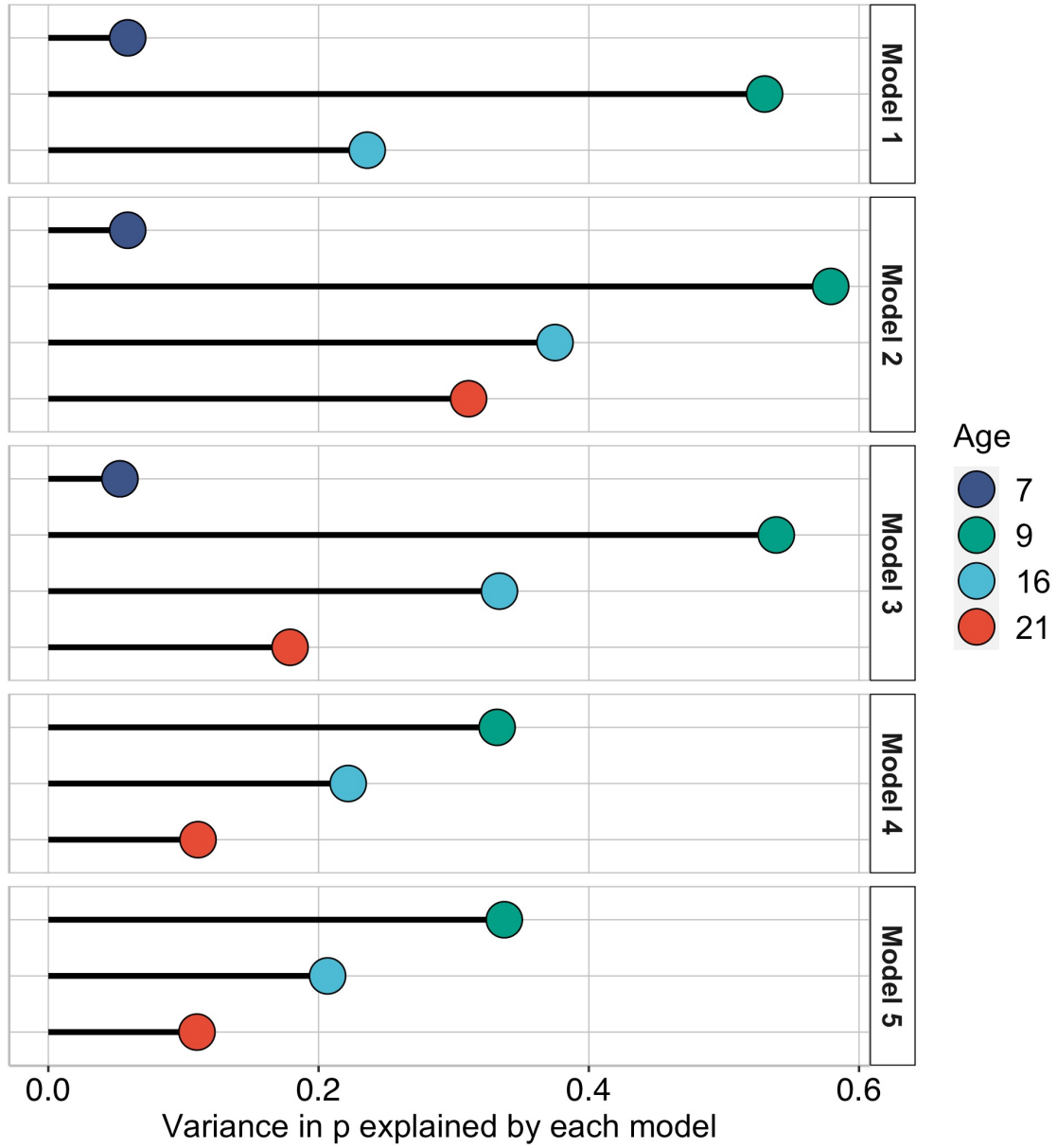



Model 1
Age
7
9
16
21
0.0
0.2
0.4
0.6
Variance in p explained by each model

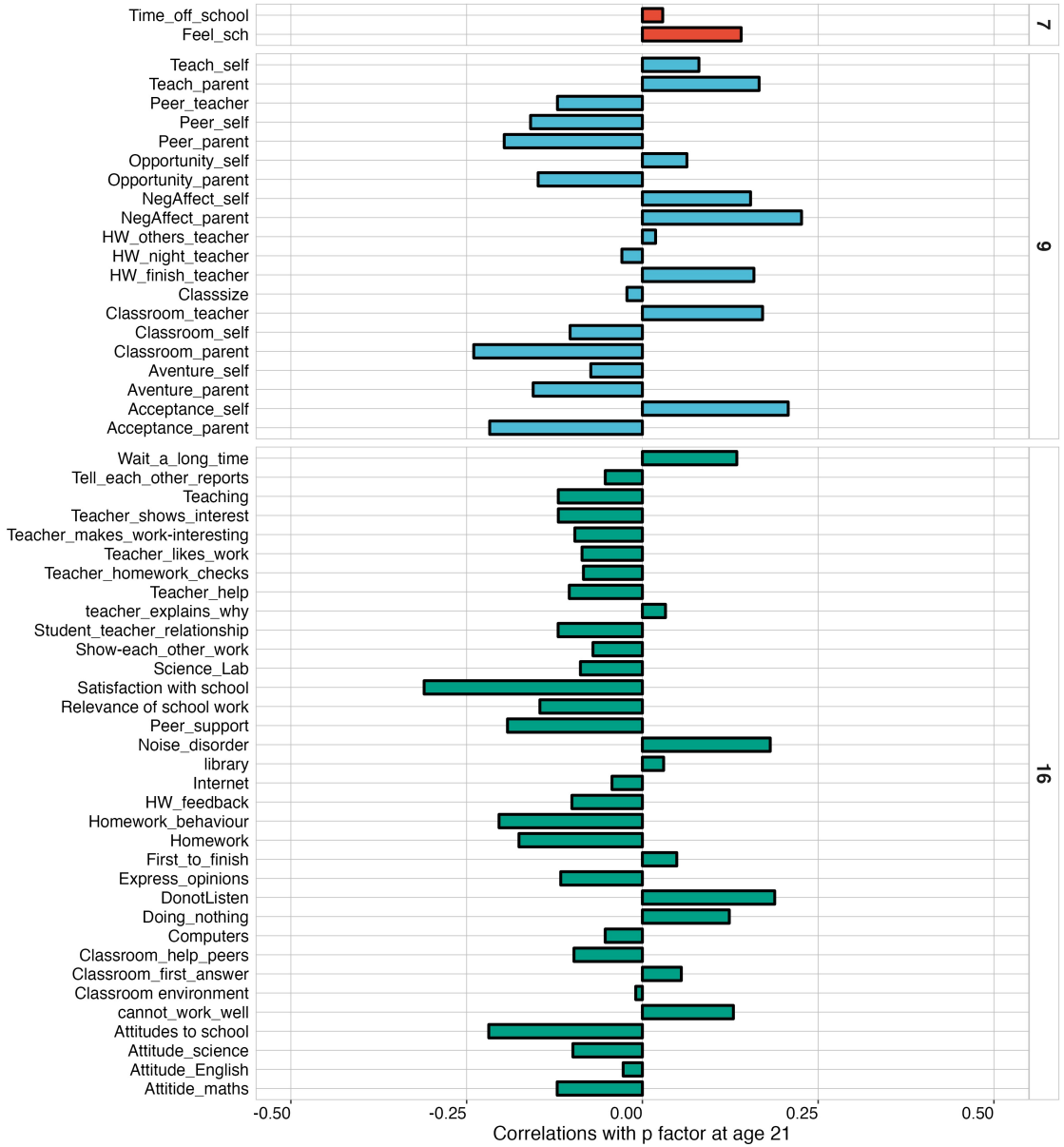

Model 1
Model 2
Age
7
9
16
21
0.0
0.2
0.4
0.6
Variance in p explained by each model


Model 1
Model 2
Model 3
Age
7
9
16
21
0.0
0.2
0.4
0.6
Variance in p explained by each model

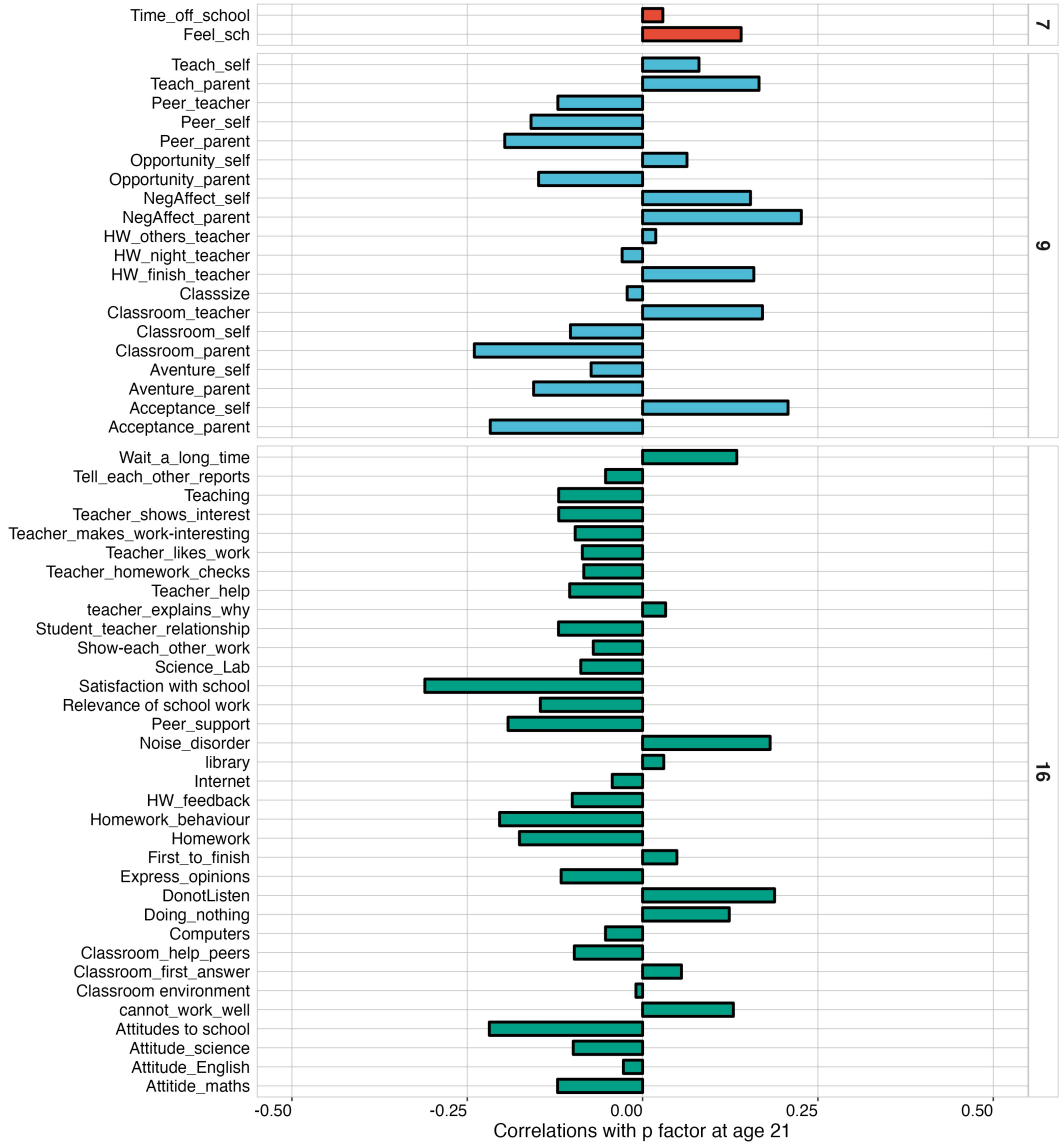

Model 1
Model 2
Model 3
Model 4
Age
7
9
16
21
0.0
0.2
0.4
0.6
Variance in p explained by each model


Model 1
Model 2
Model 3
Model 4
Model 5
0.0
0.2
0.4
0.6
Variance in p explained by each model
Age
7
9
16
21

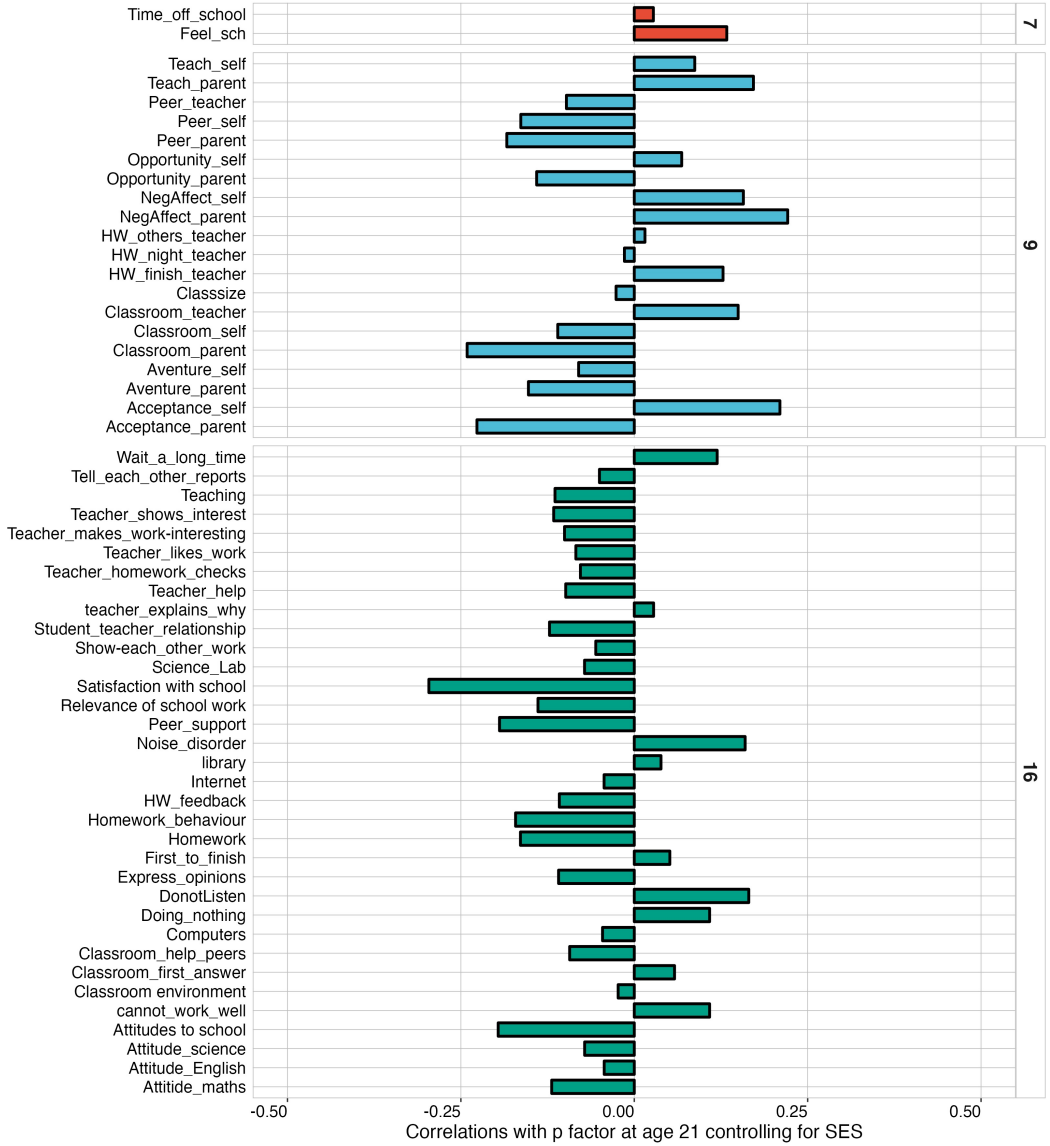
Associations between school environments and p-factor at age 21

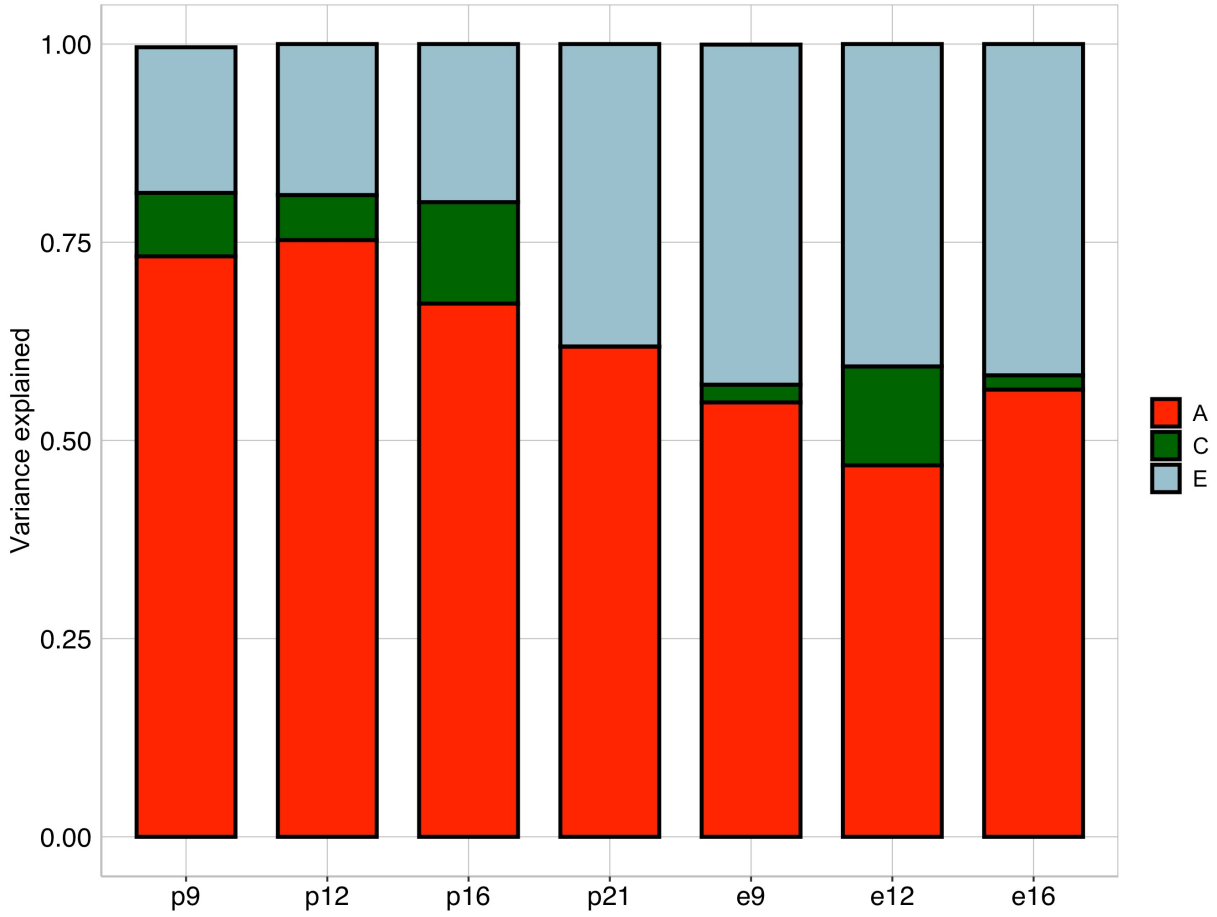


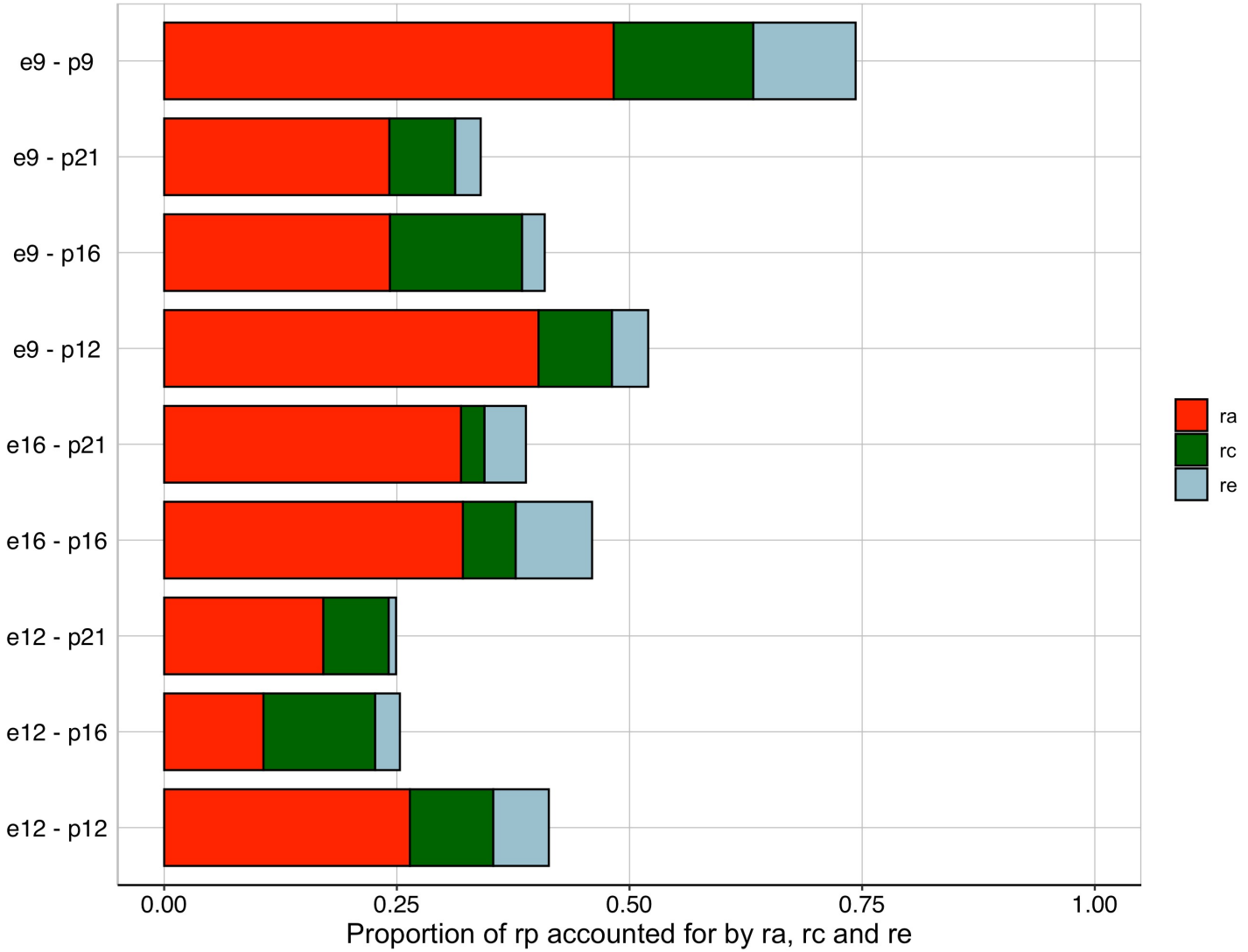
Associations between school environments and p factor at age 21



Associations between school environments and p factor at age 21 controlling for SES

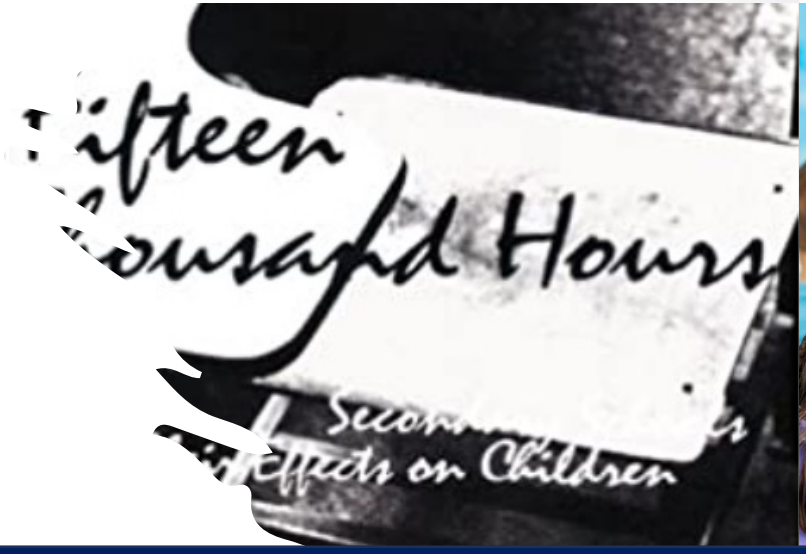



1.00
0.75
0.50
0.25
0.00
Variance explained
p9
p12
p16
p21
e9
e12
e16
A
C
E


e9 - p9
e9 - p21
e9 - p16
e9 - p12
e16 - p21
e16 - p16
e12 - p21
e12 - p16
e12 - p12
0.00
0.25
0.50
0.75
1.00
Proportion of rp accounted for by ra, rc and re
ra
rc
re

Conclusions

- School experiences are substantially associated with mental health even 10 years later
- Causality?
- Widespread rGE
- Interventions?



NPD data (ages 12-16, N=3,000-11,000)

School level data:

- Absences
- Persistent absentees
- Headcount (boys, girls, pupils)
- Number of qualified & non-qualified teachers
- Teacher-pupil ratio
- Free school meals
- Special education needs
- English as the first/second language

Individual level data:

- Absences

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Ofsted data (ages 12-16, N=3,500-4,500)

- Overall effectiveness
- Early years provision
- Pupils' attendance
- Pupils' attainment
- Behaviour and safety of pupils
- Quality of teaching
- Quality of learning progress
- Effectiveness of guidance and support
- Extent to which the curriculum meets the pupils' needs
- Leadership and management
- Effectiveness of school promoting euality opportunities
- Residential safety
- …and many others

Ofsted | Department for Education

Limitations

- Missing data and attrition
- Self-report & rater bias
- Diversity
- PRS explain a small proportion of variance in childhood mental health
- No information available about exam pressures

Future directions

- This research program is ongoing
- Use objective measures of school environment (National Pupil Database)
- Are some children differentially affected by school experiences → extreme analyses
- Are the links between school experiences and mental health mediated by parental expectations?
- Extend the present analyses to datasets outside the UK
- Triangulation

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TEDS

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CoDE Research Network

CoDE Lab
Cognition, Development & Education

We apply an interdisciplinary approach at the intersection of psychology, genetics and education to investigate individual differences in cognition, development and learning.

Group Leaders

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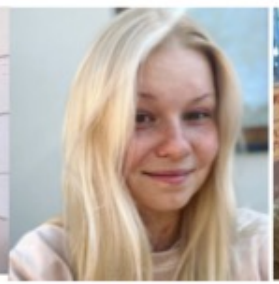
Dr Kaili Rimfeld

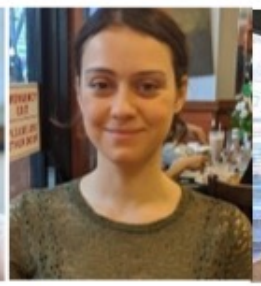
Dr Margherita Malanchini

The Team

Dr. Anna Suarez



Agnieszka Gidziela



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