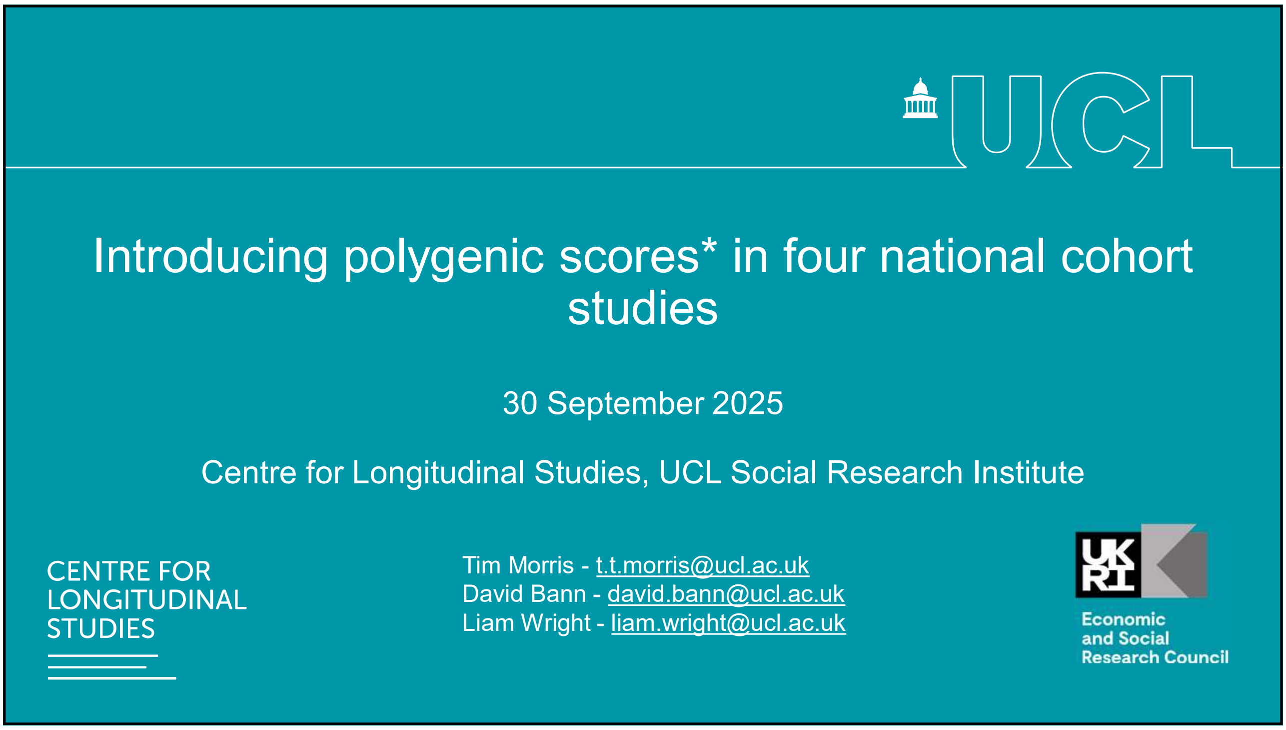

Introducing polygenic scores* in four national cohort studies

30 September 2025

Centre for Longitudinal Studies, UCL Social Research Institute

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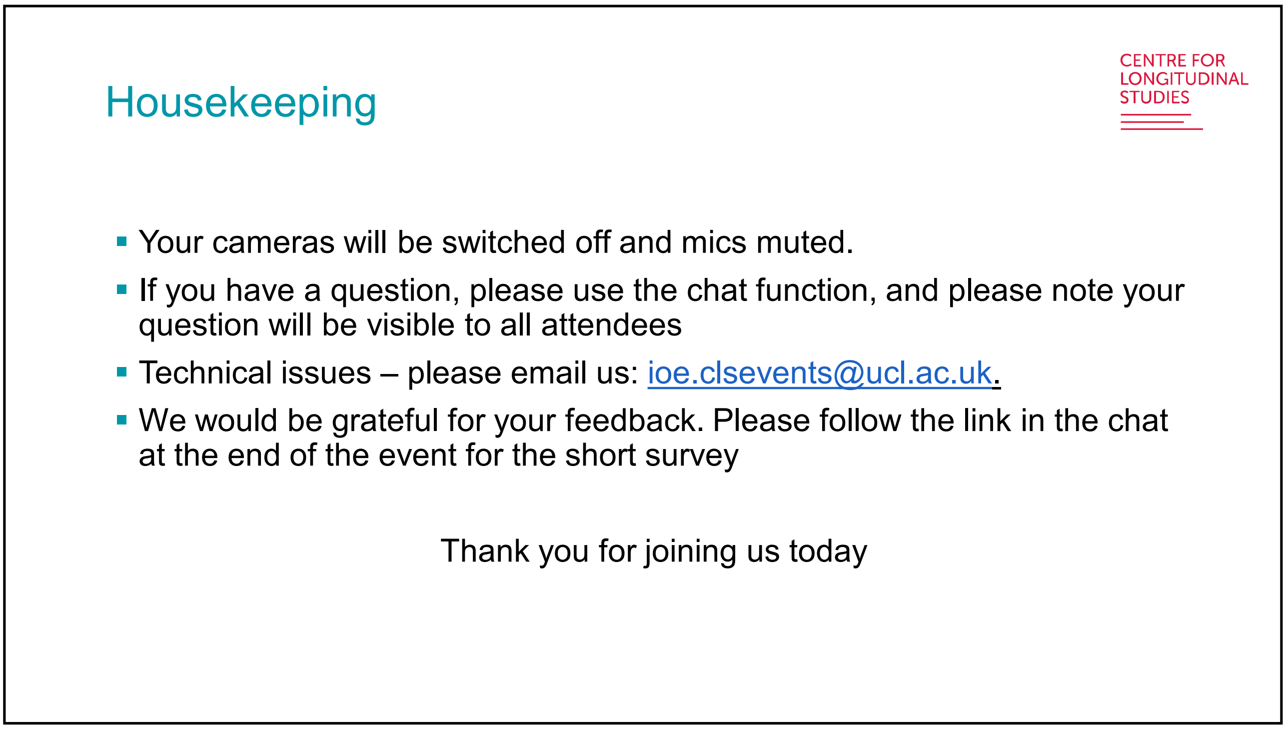
STUDIES

Tim Morris - t.t.morris@ucl.ac.uk
David Bann - david.bann@ucl.ac.uk
Liam Wright - liam.wright@ucl.ac.uk

Economic
and Social
Research Council

1



Housekeeping

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- Your cameras will be switched off and mics muted.
- If you have a question, please use the chat function, and please note your question will be visible to all attendees
- Technical issues – please email us: ioe.clsevents@ucl.ac.uk.
- We would be grateful for your feedback. Please follow the link in the chat at the end of the event for the short survey

Thank you for joining us today

2

Outline

CENTRE FOR
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- Introduction to CLS cohorts + value to research
- Generation of polygenic indexes
- Polygenic indexes available from CLS
- Access and resources
- Examples of research using the polygenic indexes
- Q&A

Introduction to CLS cohort studies

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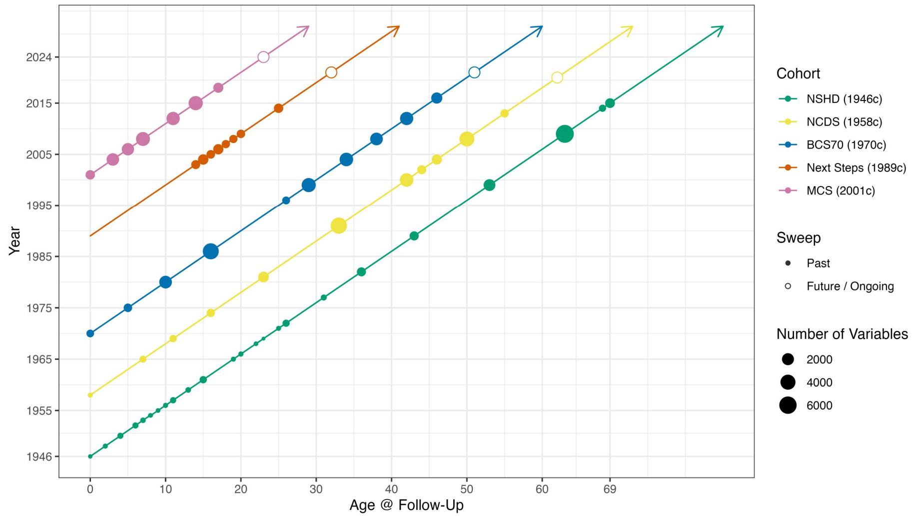

cls.ucl.ac.uk

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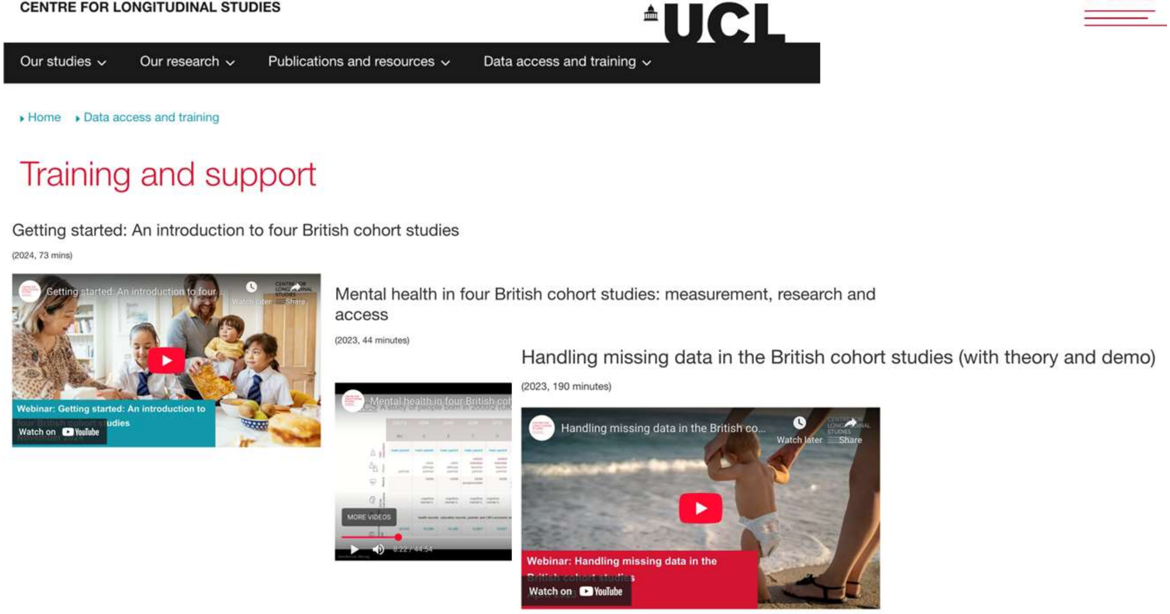
CENTRE FOR LONGITUDINAL STUDIES

Our studies ⌄ Our research ⌄ Publications and resources ⌄ Data access and training ⌄

‣ Home ‣ Data access and training

Training and support

Getting started: An introduction to four British cohort studies

(2024, 73 mins)

Mental health in four British cohort studies: measurement, research and access

(2023, 44 minutes)

Handling missing data in the British cohort studies (with theory and demo)

(2023, 190 minutes)

Value: genetically informed research

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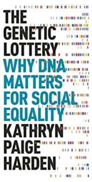
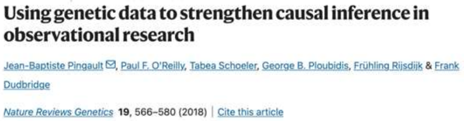
Useful re: environment or genes…eg,

- G x E interactions (eg, age, cohort, environment)
- Accounting for confounding
- Instrumental variables (MR)
- Help measurement eg, approximating unmeasured exposures
- Improving prediction
- …

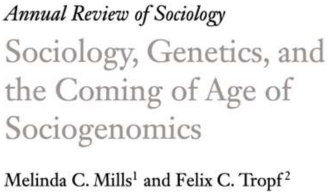


Harden KP. 2021.


Using genetic data to strengthen causal inference in observational research

Jean-Baptiste Pingault, Paul F. O'Reilly, Tabea Schoeler, George B. Ploubidis, Frühling Rijsdijk & Frank Dudbridge

Nature Reviews Genetics 19, 566–580 (2018) | Cite this article


Annual Review of Sociology

Sociology, Genetics, and the Coming of Age of Sociogenomics

Melinda C. Mills[1] and Felix C. Tropf[2]


ANNUAL REVIEW OF ECONOMICS Volume 4, 2012

Review Article

The Promises and Pitfalls of Genoeconomics

Benjamin et al 2012

Value: cohorts with genetic data

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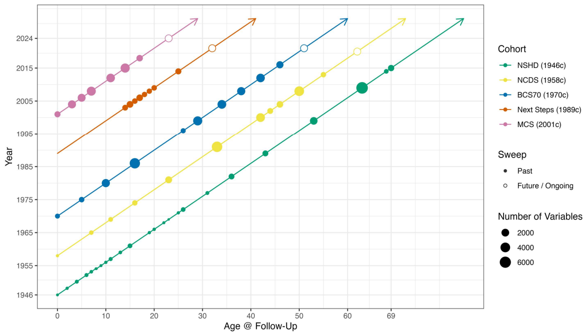
wrt other datasets e.g., biobanks

1. Rich phenotypic data
2. Life course / longitudinal research
3. Comparative across generations
4. National sample + representation
5. Mother-father-offspring trios (MCS)



Shireby et al 2025 Data Resource profile

https://cls-genetics.github.io/

Phenotypic data

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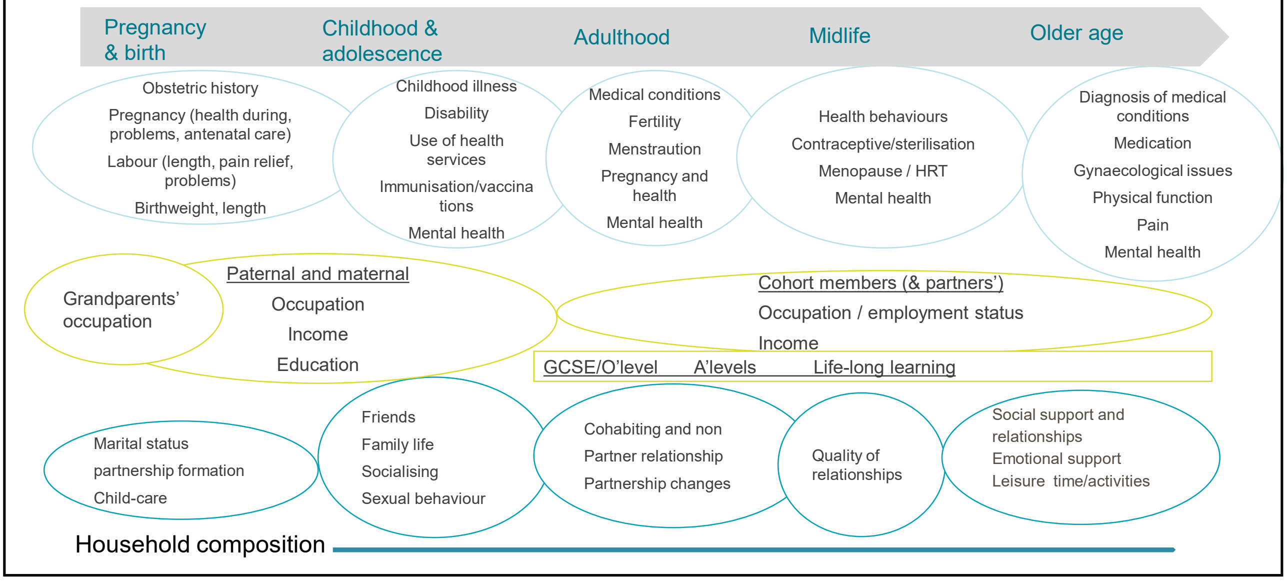

Pregnancy & birth
Childhood & adolescence
Adulthood
Midlife
Older age

Obstetric history
Pregnancy (health during, problems, antenatal care)
Labour (length, pain relief, problems)
Birthweight, length

Childhood illness
Disability
Use of health services
Immunisation/vaccinations
Mental health

Medical conditions
Fertility
Menstruation
Pregnancy and health
Mental health

Health behaviours
Contraceptive/sterilisation
Menopause / HRT
Mental health

Diagnosis of medical conditions
Medication
Gynaecological issues
Physical function
Pain
Mental health

Grandparents' occupation

Paternal and maternal
Occupation
Income
Education

Cohort members (& partners')
Occupation / employment status
Income

GCSE/O'level A'levels Life-long learning

Marital status
partnership formation
Child-care

Friends
Family life
Socialising
Sexual behaviour

Cohabiting and non
Partner relationship
Partnership changes

Quality of relationships

Social support and relationships
Emotional support
Leisure time/activities

Household composition

Generation of polygenic indexes

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Genetic data

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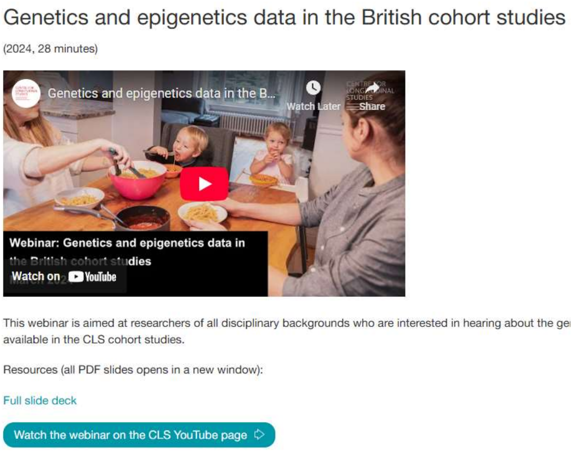
- Blood & saliva samples
- Imputed to TOPMed panel
- Consistent QC process across cohorts

Genetics webinar



Genetics and epigenetics data in the British cohort studies

(2024, 28 minutes)

This webinar is aimed at researchers of all disciplinary backgrounds who are interested in hearing about the ge
available in the CLS cohort studies.

Resources (all PDF slides opens in a new window):

Full slide deck

Watch the webinar on the CLS YouTube page

https://cls.ucl.ac.uk/data-access-training/training-and-support/

Sampled participants

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Cohort	Age sample taken	N total cohort	N responded to biosample wave	N alive & in UK at wave	N imputed + QC'd	Response rate (%)	PGI available
1958c NCDS	44*	18,558	9,377	15,971	6,396	40	6,396
1970c BCS	46	17,006	8,581	16,577	5,598	33.8	5,361
1989-90c Next Steps	32	16,122	7,279	15,358	1,568	10.2	1,272
2001c Millennium cohort (cohort members)	14	19,517	11,859	18,575	7,841	42.3	7,836*

Millennium Cohort Study	Sample
offspring	7,836
mothers	7,777
fathers	4,634
offspring - mother duos	6,426
offspring - father duos	3,802
offspring – mother - father trios	3,117

Polygenic indexes

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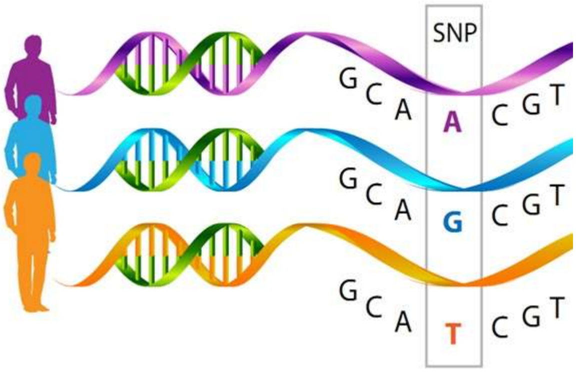
- Designed to summarise the *known* genetic predisposition for a trait
- Calculated as count and effect sizes of individual variants
- Dependent on the trait and population measured in the GWAS
- Normally distributed in population



Rayner, 2018

Polygenic indexes

CENTRE FOR
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STUDIES

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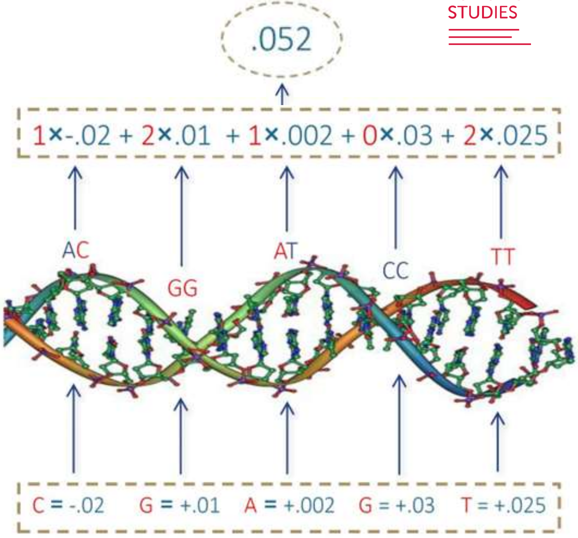

Abdellaoui, 2021

Polygenic indexes

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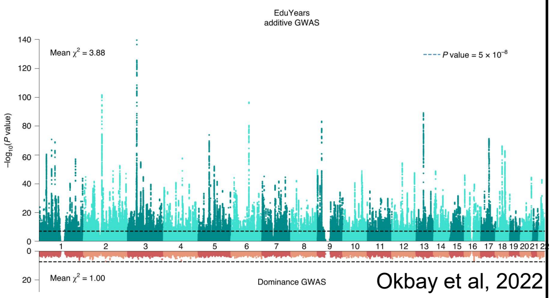
- Generated with PRSice2 (Choi et al, 2019)
- SNPs clumped to avoid overcounting signals (250kb, r² > 0.1)
- Polygenic indexes generated at 5 thresholds
- Generated for cohorts independently and for the harmonised cohort genotype data



Okbay et al, 2022

Predictive power

Threshold	Example SNPs for Height in MCS
5x10-08	5,739
1x10-05	9,507
0.01	30,029
0.05	46,249
1	121,034

Reliability

Polygenic indexes

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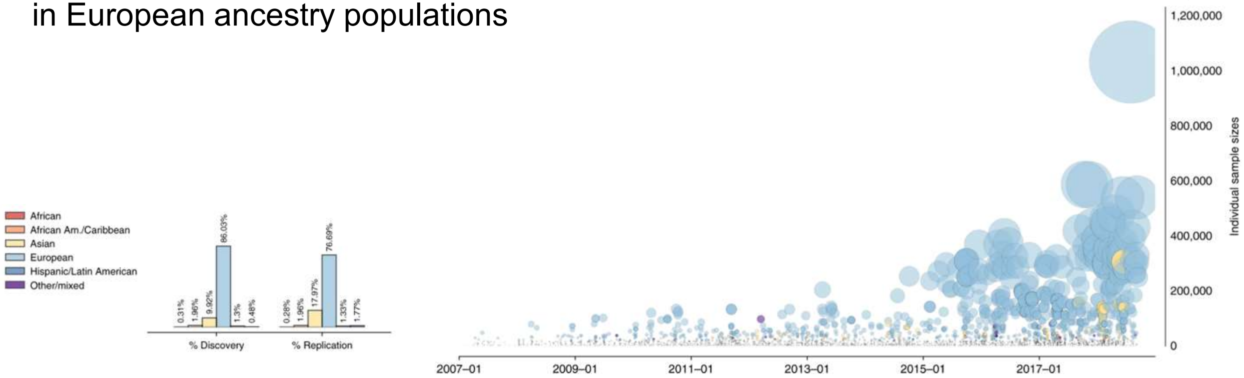
- WEIRD samples dominate research
- Restricted to participants of 'European ancestry'
- Ancestry inferred by genetic similarity to people in a large reference dataset (1000 Genomes Phase 3)
- Genetic studies have been overwhelmingly conducted in European ancestry populations



Mills & Rahal, 2019

Code pipeline

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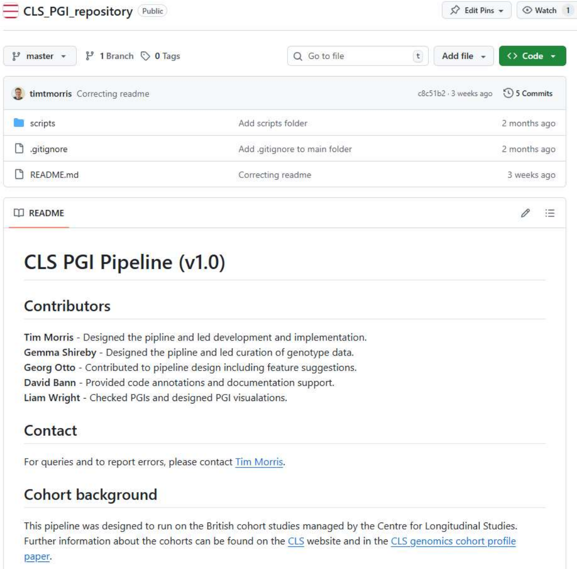
- Full code pipeline available on GitHub at https://github.com/CLS-Data/CLS_PGI_repository
- Pipeline can be cloned and run in other (cohort) datasets



timtmorris Correcting readme c8c51b2 · 3 weeks ago

scripts	Add scripts folder	2 months ago
.gitignore	Add .gitignore to main folder	2 months ago
README.md	Correcting readme	3 weeks ago

CLS PGI Pipeline (v1.0)

Contributors

Tim Morris - Designed the pipline and led development and implementation.
Gemma Shireby - Designed the pipline and led curation of genotype data.
Georg Otto - Contributed to pipeline design including feature suggestions.
David Bann - Provided code annotations and documentation support.
Liam Wright - Checked PGIs and designed PGI visualations.

Contact

For queries and to report errors, please contact Tim Morris.

Cohort background

This pipeline was designed to run on the British cohort studies managed by the Centre for Longitudinal Studies. Further information about the cohorts can be found on the CLS website and in the CLS genomics cohort profile paper.

Polygenic indexes available from CLS

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Polygenic indexes

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Currently…

44 traits over 7 domains:

- Anthropometrics
- Brain structure and cognition
- Health behaviours
- Mental health
- Personality
- Physical health
- Social outcomes

Substance abuse	Birth weight	Diet	Hypertension
ADHD	Blood pressure	Education	Major depressive disorder
Age at initiation of smoking	Body fat distribution	Externalising problems	Neuroticism
Age at menopause	Body Mass Index (adulthood)	Extraversion	Openness to experience
Agreeableness	Body Mass Index (childhood)	Fasting blood glucose	Parental Lifespan
Alcoholic drinks per week	Cigarettes per day	Grip strength	Parkinson's disease
Alzheimer's Disease	Cognition	HbA1c	Rheumatoid arthritis
Anxiety	Conscientiousness	Height	Schizophrenia
Asthma	Coronary artery disease	Hippocampal volume	Type 1 Diabetes
Autism spectrum disorder	C-reactive protein	Household Income	Type 2 Diabetes
Bipolar disorder	Depressive symptoms	Human Longevity	Waist circumference

Polygenic indexes

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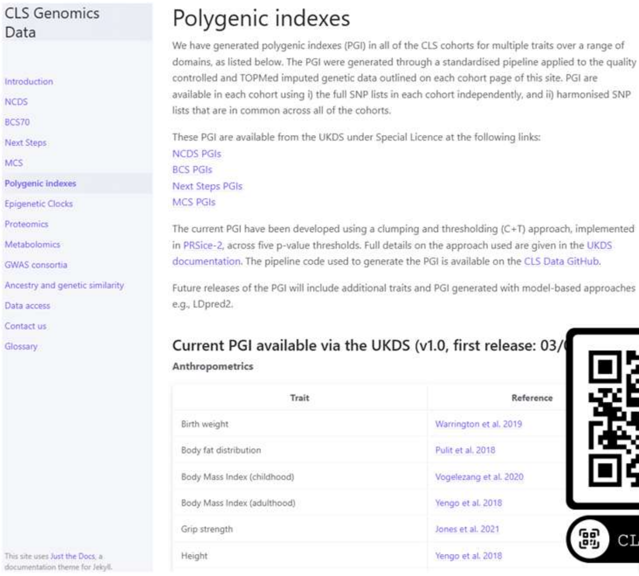
Currently…

44 traits over 7 domains:

- Anthropometrics
- Brain structure and cognition
- Health behaviours
- Mental health
- Personality
- Physical health
- Social outcomes



CLS Genomics Data

- Introduction
- NCDS
- BCS70
- Next Steps
- MCS
- **Polygenic indexes**
- Epigenetic Clocks
- Proteomics
- Metabolomics
- GWAS consortia
- Ancestry and genetic similarity
- Data access
- Contact us
- Glossary

This site uses Just the Docs, a documentation theme for Jekyll.

Polygenic indexes

We have generated polygenic indexes (PGI) in all of the CLS cohorts for multiple traits over a range of domains, as listed below. The PGI were generated through a standardised pipeline applied to the quality controlled and TOPMed imputed genetic data outlined on each cohort page of this site. PGI are available in each cohort using i) the full SNP lists in each cohort independently, and ii) harmonised SNP lists that are in common across all of the cohorts.

These PGI are available from the UKDS under Special Licence at the following links:
NCDS PGIs
BCS PGIs
Next Steps PGIs
MCS PGIs

The current PGI have been developed using a clumping and thresholding (C+T) approach, implemented in PRSice-2, across five p-value thresholds. Full details on the approach used are given in the UKDS documentation. The pipeline code used to generate the PGI is available on the CLS Data GitHub.

Future releases of the PGI will include additional traits and PGI generated with model-based approaches e.g., LDpred2.

Current PGI available via the UKDS (v1.0, first release: 03/

Anthropometrics

Trait	Reference
Birth weight	Warrington et al. 2019
Body fat distribution	Pulit et al. 2018
Body Mass Index (childhood)	Vogelezang et al. 2020
Body Mass Index (adulthood)	Yengo et al. 2018
Grip strength	Jones et al. 2021
Height	Yengo et al. 2018

CLS GitHub

Polygenic indexes

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All PGI have been created for:

1. Each cohort independently
2. Restricting to harmonised 'SNP list'

Threshold	Height SNPs in MCS	Height SNPs in MCS (harmonised)
5x10-08	5,739	5,521
1x10-05	9,507	9,090
0.01	30,029	28,226
0.05	46,249	43,037
1	121,034	109,176

Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry FREE

Loic Yengo, Julia Sidorenko, Kathryn E Kemper, Zhili Zheng, Andrew R Wood, Michael N Weedon, Timothy M Frayling, Joel Hirschhorn, Jian Yang, Peter M Visscher ...
Show more

Human Molecular Genetics, Volume 27, Issue 20, 15 October 2018, Pages 3641–3649, https://doi.org/10.1093/hmg/ddy271

Example PGI - height

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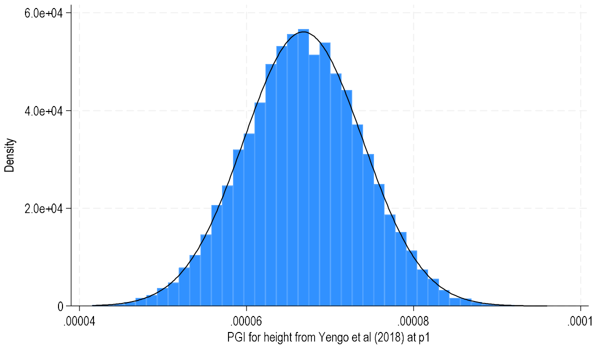

NCDS

nvht16 - Height in metres at 16 years

Threshold	Sex R2 (%)	Sex + PGI R2 (%)	PGI Δ R2 (%)
5x10-08	29.51	46.83	17.32
1x10-05	29.51	48.39	18.88
0.01	29.51	49.74	20.23
0.05	29.51	49.69	20.18
1	29.51	49.67	20.16

What do the PGIs look like?

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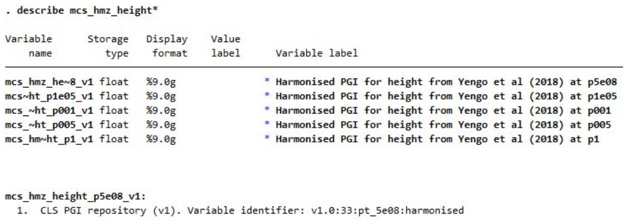
Consistent variable naming convention:

- Cohort
- If harmonised dataset
- Trait
- p value threshold
- PGI repository version

mcs_hmz_height_p5e08_v1



```
. describe mcs_hmz_height*

Variable      Storage   Display    Value
    name         type    format    label      Variable label
------------------------------------------------------------------------------------------
mcs_hmz_he~8_v1 float   %9.0g                * Harmonised PGI for height from Yengo et al (2018) at p5e08
mcs~ht_p1e05_v1 float   %9.0g                * Harmonised PGI for height from Yengo et al (2018) at p1e05
mcs_~ht_p001_v1 float   %9.0g                * Harmonised PGI for height from Yengo et al (2018) at p001
mcs_~ht_p005_v1 float   %9.0g                * Harmonised PGI for height from Yengo et al (2018) at p005
mcs_hm~ht_p1_v1 float   %9.0g                * Harmonised PGI for height from Yengo et al (2018) at p1


mcs_hmz_height_p5e08_v1:
  1.  CLS PGI repository (v1). Variable identifier: v1.0:33:pt_5e08:harmonised
```

Access and resources

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Data access

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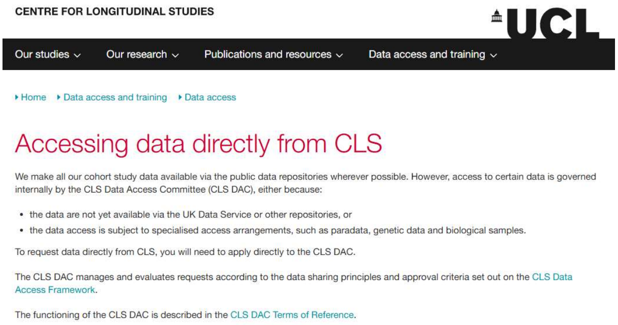
STUDIES

Raw genetic data



Accessing data directly from CLS

We make all our cohort study data available via the public data repositories wherever possible. However, access to certain data is governed internally by the CLS Data Access Committee (CLS DAC), either because:

- the data are not yet available via the UK Data Service or other repositories, or
- the data access is subject to specialised access arrangements, such as paradata, genetic data and biological samples.

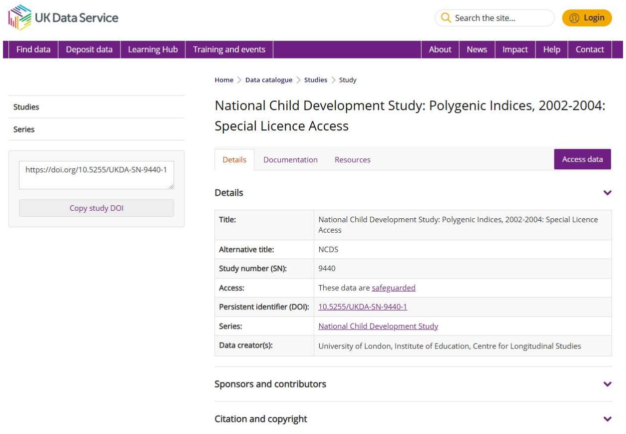
To request data directly from CLS, you will need to apply directly to the CLS DAC.

The CLS DAC manages and evaluates requests according to the data sharing principles and approval criteria set out on the CLS Data Access Framework.

The functioning of the CLS DAC is described in the CLS DAC Terms of Reference.

https://cls.ucl.ac.uk/

PGIs



https://doi.org/10.5255/UKDA-SN-9440-1

National Child Development Study: Polygenic Indices, 2002-2004: Special Licence Access

Details

Title:	National Child Development Study: Polygenic Indices, 2002-2004: Special Licence Access
Alternative title:	NCDS
Study number (SN):	9440
Access:	These data are safeguarded
Persistent identifier (DOI):	10.5255/UKDA-SN-9440-1
Series:	National Child Development Study
Data creator(s):	University of London, Institute of Education, Centre for Longitudinal Studies

Sponsors and contributors

Citation and copyright

https://ukdataservice.ac.uk/

Data access

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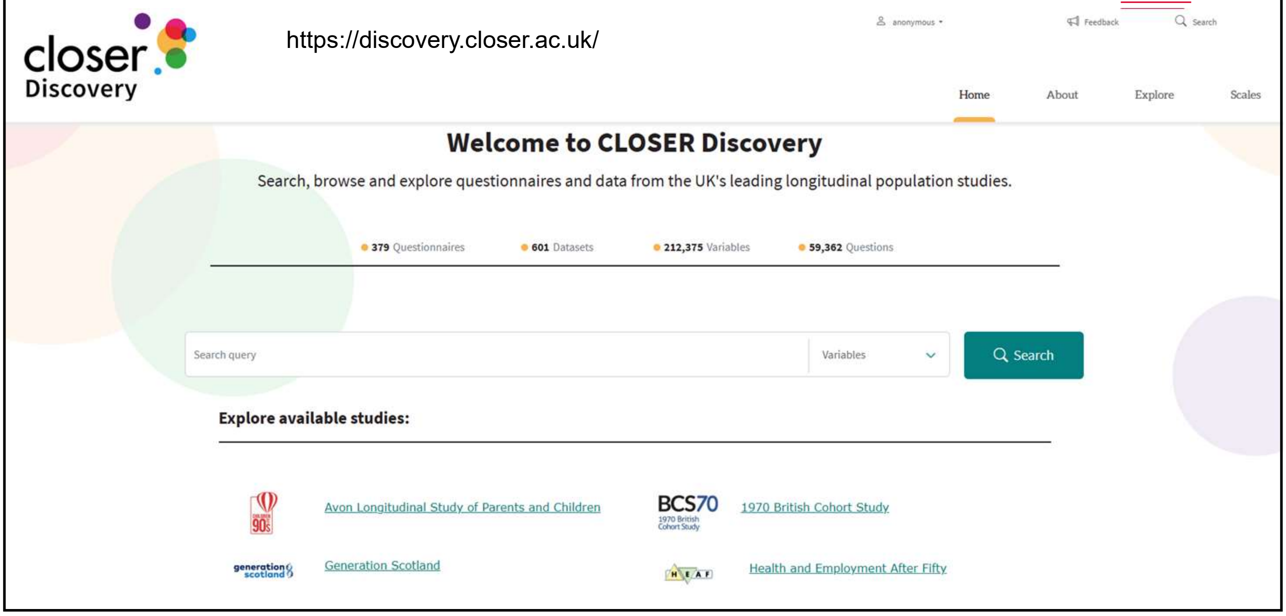

https://discovery.closer.ac.uk/

Welcome to CLOSER Discovery

Search, browse and explore questionnaires and data from the UK's leading longitudinal population studies.

- **379** Questionnaires
- **601** Datasets
- **212,375** Variables
- **59,362** Questions

Explore available studies:

- Avon Longitudinal Study of Parents and Children
- 1970 British Cohort Study
- Generation Scotland
- Health and Employment After Fifty

Data access

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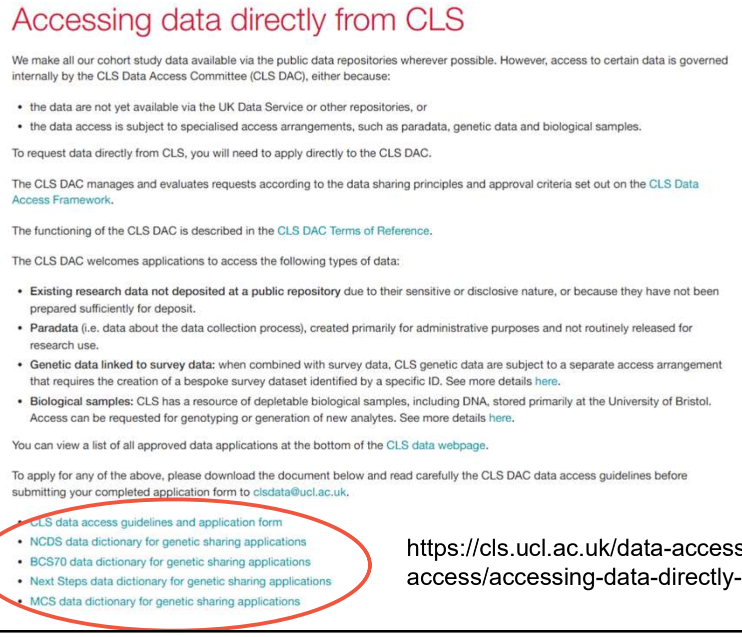
STUDIES



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The functioning of the CLS DAC is described in the CLS DAC Terms of Reference.

The CLS DAC welcomes applications to access the following types of data:

- **Existing research data not deposited at a public repository** due to their sensitive or disclosive nature, or because they have not been prepared sufficiently for deposit.
- **Paradata** (i.e. data about the data collection process), created primarily for administrative purposes and not routinely released for research use.
- **Genetic data linked to survey data:** when combined with survey data, CLS genetic data are subject to a separate access arrangement that requires the creation of a bespoke survey dataset identified by a specific ID. See more details here.
- **Biological samples:** CLS has a resource of depletable biological samples, including DNA, stored primarily at the University of Bristol. Access can be requested for genotyping or generation of new analytes. See more details here.

You can view a list of all approved data applications at the bottom of the CLS data webpage.

To apply for any of the above, please download the document below and read carefully the CLS DAC data access guidelines before submitting your completed application form to clsdata@ucl.ac.uk.

- CLS data access guidelines and application form
- NCDS data dictionary for genetic sharing applications
- BCS70 data dictionary for genetic sharing applications
- Next Steps data dictionary for genetic sharing applications
- MCS data dictionary for genetic sharing applications

https://cls.ucl.ac.uk/data-access-training/data-access/accessing-data-directly-from-cls/

Resources

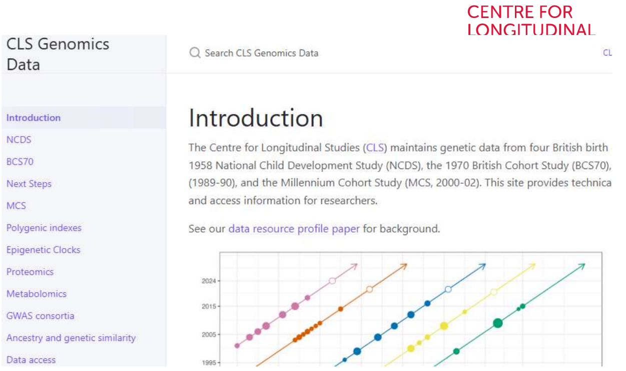
- CLS genomics GitHub for ‘living documentation’

  https://cls-genetics.github.io

- IJE Data Resource profile
  https://academic.oup.com/ije/article/54/5/dyaf141/8237599

CLS GitHub

Cohort profile



CENTRE FOR LONGITUDINAL

CLS Genomics Data

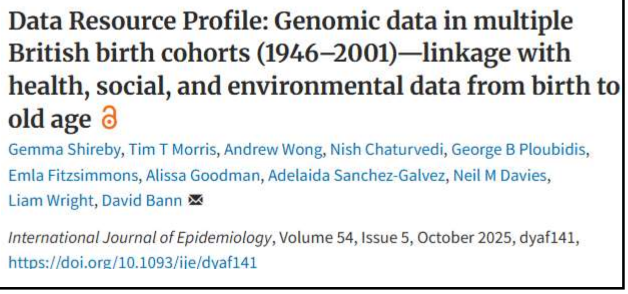
Search CLS Genomics Data

- Introduction
- NCDS
- BCS70
- Next Steps
- MCS
- Polygenic indexes
- Epigenetic Clocks
- Proteomics
- Metabolomics
- GWAS consortia
- Ancestry and genetic similarity
- Data access

Introduction

The Centre for Longitudinal Studies (CLS) maintains genetic data from four British birth 1958 National Child Development Study (NCDS), the 1970 British Cohort Study (BCS70), (1989-90), and the Millennium Cohort Study (MCS, 2000-02). This site provides technica and access information for researchers.

See our data resource profile paper for background.



Data Resource Profile: Genomic data in multiple British birth cohorts (1946–2001)—linkage with health, social, and environmental data from birth to old age

Gemma Shireby, Tim T Morris, Andrew Wong, Nish Chaturvedi, George B Ploubidis, Emla Fitzsimmons, Alissa Goodman, Adelaida Sanchez-Galvez, Neil M Davies, Liam Wright, David Bann ✉

International Journal of Epidemiology, Volume 54, Issue 5, October 2025, dyaf141, https://doi.org/10.1093/ije/dyaf141

Examples of research using the polygenic indexes

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Exemplar #1: Gene x Environment Interaction in Education

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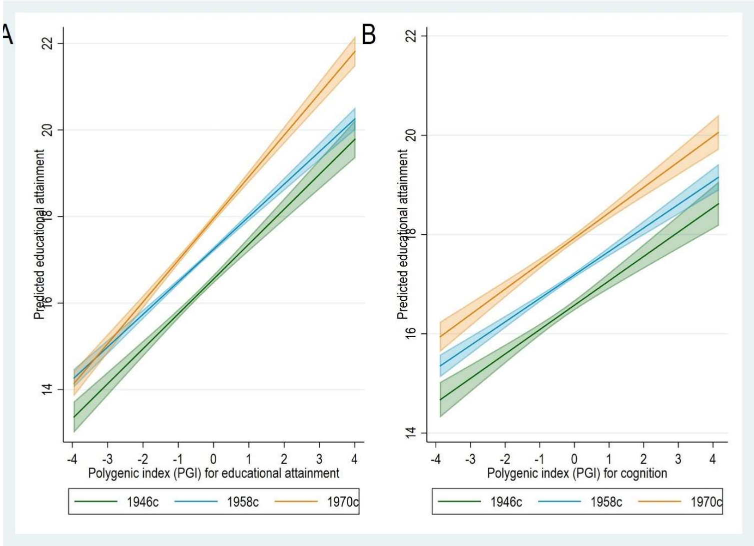

Morris et al, 2025

Exemplar #1: Gene x Environment Interaction in Education

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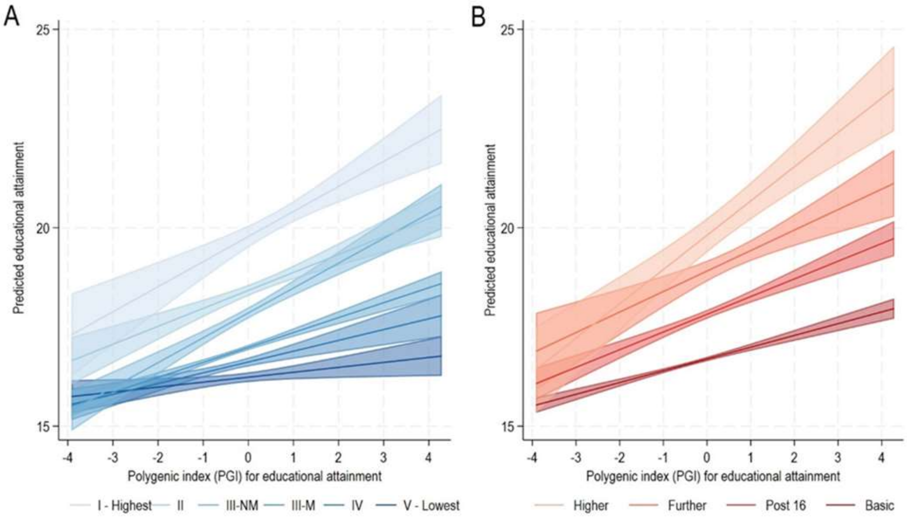

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Exemplar #1: Gene x Environment Interaction in Education

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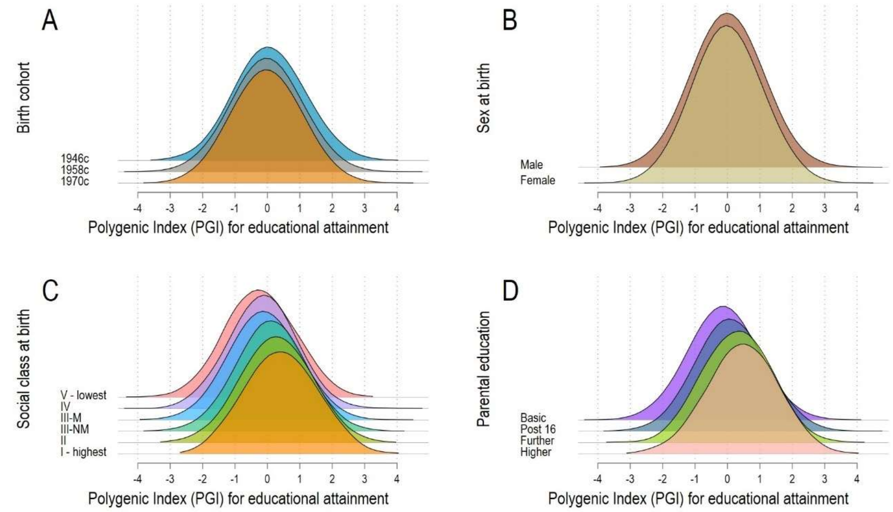

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Exemplar #2: Gene x Environment Interaction in Obesity

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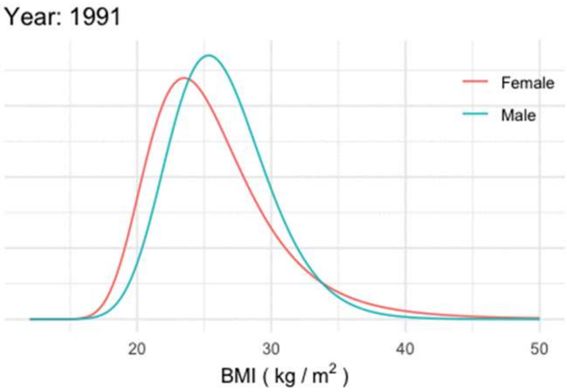
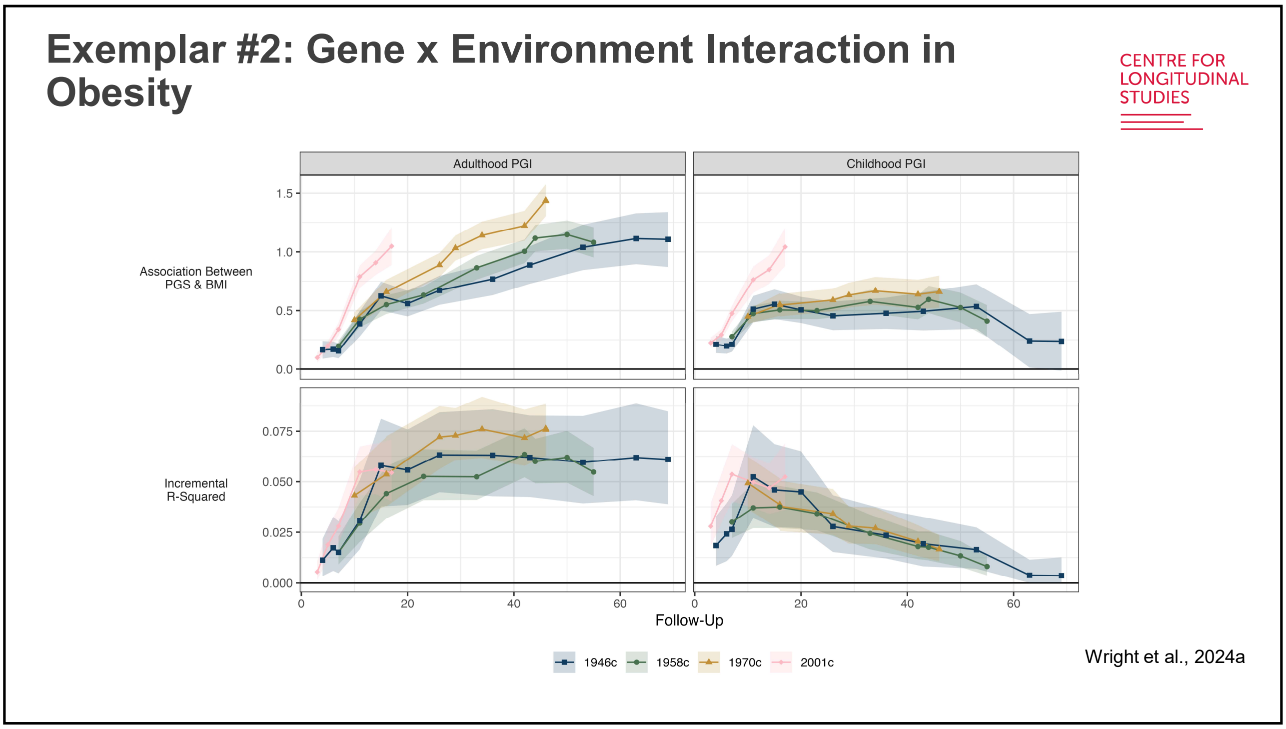


Wright et al., 2024a



Exemplar #2: Gene x Environment Interaction in Obesity

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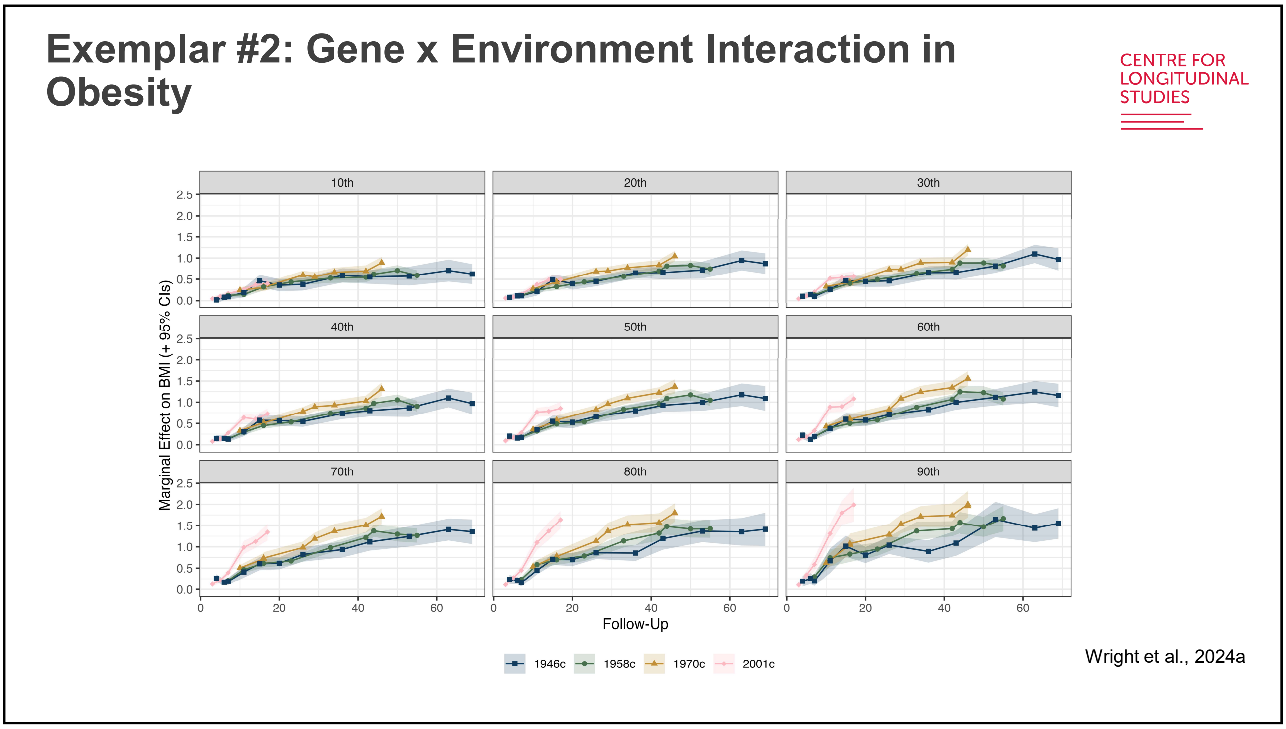
Wright et al., 2024a



Exemplar #2: Gene x Environment Interaction in Obesity

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Wright et al., 2024a

The Confounding of Genes and Family Environments

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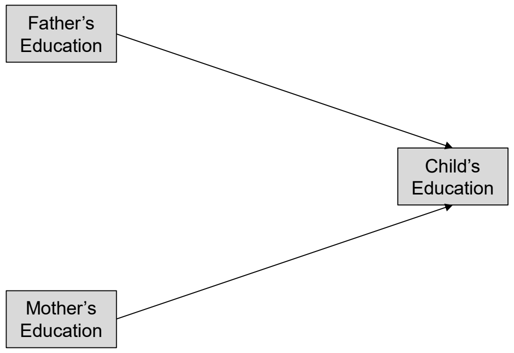
Father's
Education

Child's
Education

Mother's
Education

The Confounding of Genes and Family Environments

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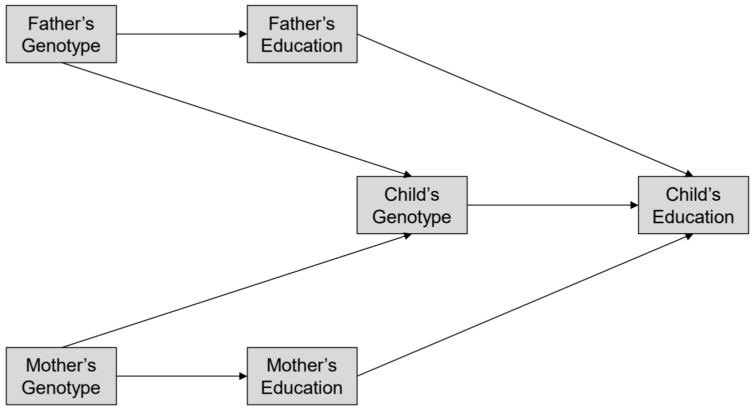
Father's
Genotype

Father's
Education

Child's
Genotype

Child's
Education

Mother's
Genotype

Mother's
Education

Indirect genetic effects

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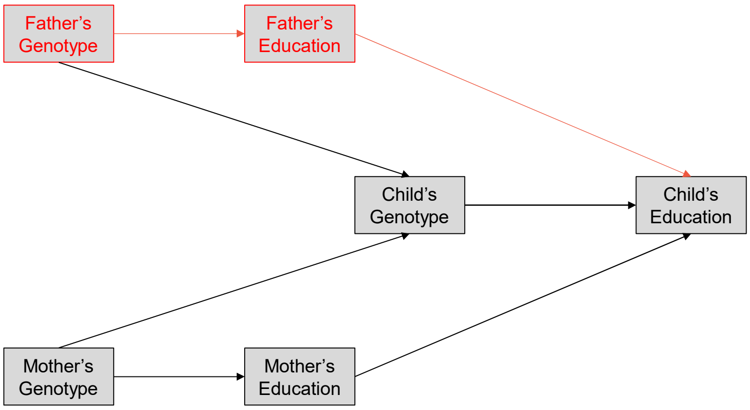

Father's Genotype

Father's Education

Child's Genotype

Child's Education

Mother's Genotype

Mother's Education

Indirect genetic effects

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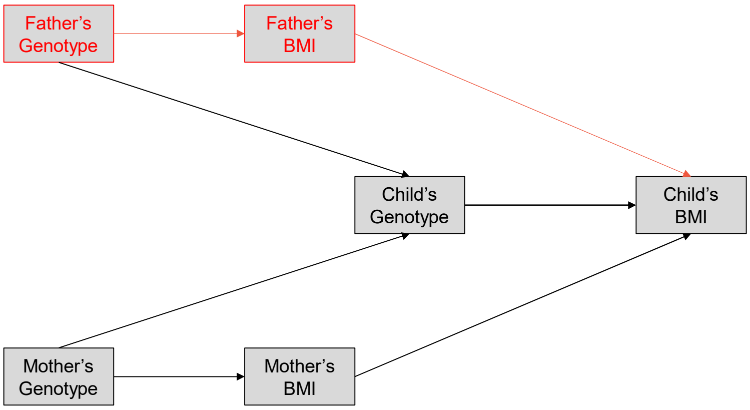

Father's Genotype

Father's BMI

Child's Genotype

Child's BMI

Mother's Genotype

Mother's BMI

Exemplar #3: Genetic Nurture of BMI

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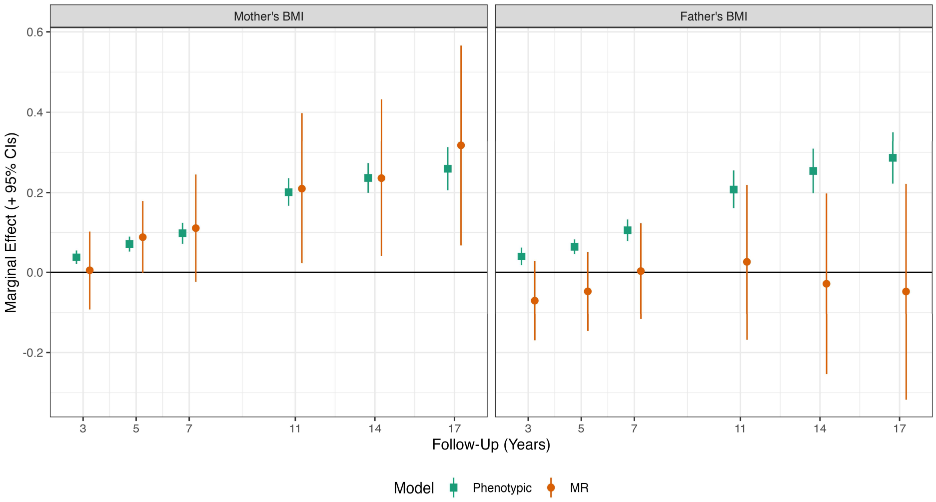

Wright et al., 2024b

Indirect genetic effects

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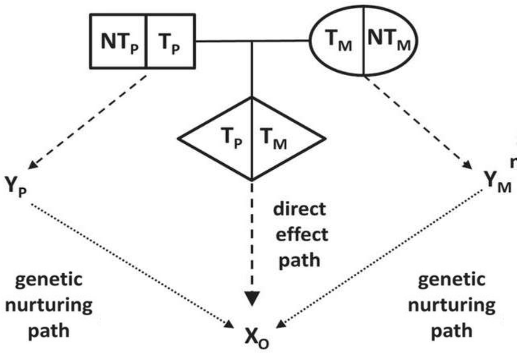

Kong et al., 2018

Acknowledgements

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