WHAT EXCITES THE FACULTY

LOIC YENGO

THE UNIVERSITY OF QUEENSLAND AUSTRALIA | CREATE CHANGE

What 'Love' got to do with it?

International Statistical Genetics Workshop

Boulder, March 8th 2019

Loïc Yengo

Program in Complex Trait Genomics

THE UNIVERSITY OF QUEENSLAND AUSTRALIA | IMB
Institute for Molecular Bioscience

THE UNIVERSITY OF QUEENSLAND AUSTRALIA | QBI
Queensland Brain Institute

Couples often assort on...

Education (r ~ 0.5)

Height (r ~ 0.2 - 0.3)

Resemblance of spouses = Assortative Mating (AM)

But also on...

- Body mass index
- Personality related traits
- Political preferences
- Diseases susceptibility
- Etc.

Evolutionary consequences of AM

- Fisher (1918), Wright (1921), Crow and Kimura (1970), Gimelfarb (1981, 1984).

- AM induces a **positive correlation between trait increasing alleles**.

- Consequence: **increase of genetic variance** (heritability).
- $var(a_1X_1 + a_2X_2) = a_1^2var(X_1) + a_2^2var(X_2) + \mathbf{2a_1a_2cov(X_1,X_2)}$

Why do we care about AM?

- Increase in genetic variance may lead to more extreme phenotypes in the population.

- AM create structures in the population that may engender health and socioeconomic inequalities.

How do we quantify it?

Chromosome	SNP	Tested Allele (A1)	Beta
1	rs1778789	A	0.01
2	rs67388911	G	-0.1
3	rs8800309	C	0.11
4	rs17777893	T	0.71

Summary Statistics from a reference GWAS

Individual level genotypes from a study **independent** of the reference GWAS

	ID_1	ID_2	…	ID_N
rs1778789	AA	AT	…	TT
rs67388911	GA	AA	…	GA
rs8800309	CC	CC	…	CC
rs17777893	GT	TT	…	GG

How do we quantify it?

Chromosome	SNP	Tested Allele (A1)	Beta
1	rs1778789	A	0.01
2	rs67388911	G	-0.1
3	rs8800309	C	0.11
4	rs17777893	T	0.71

Summary Statistics from a reference GWAS

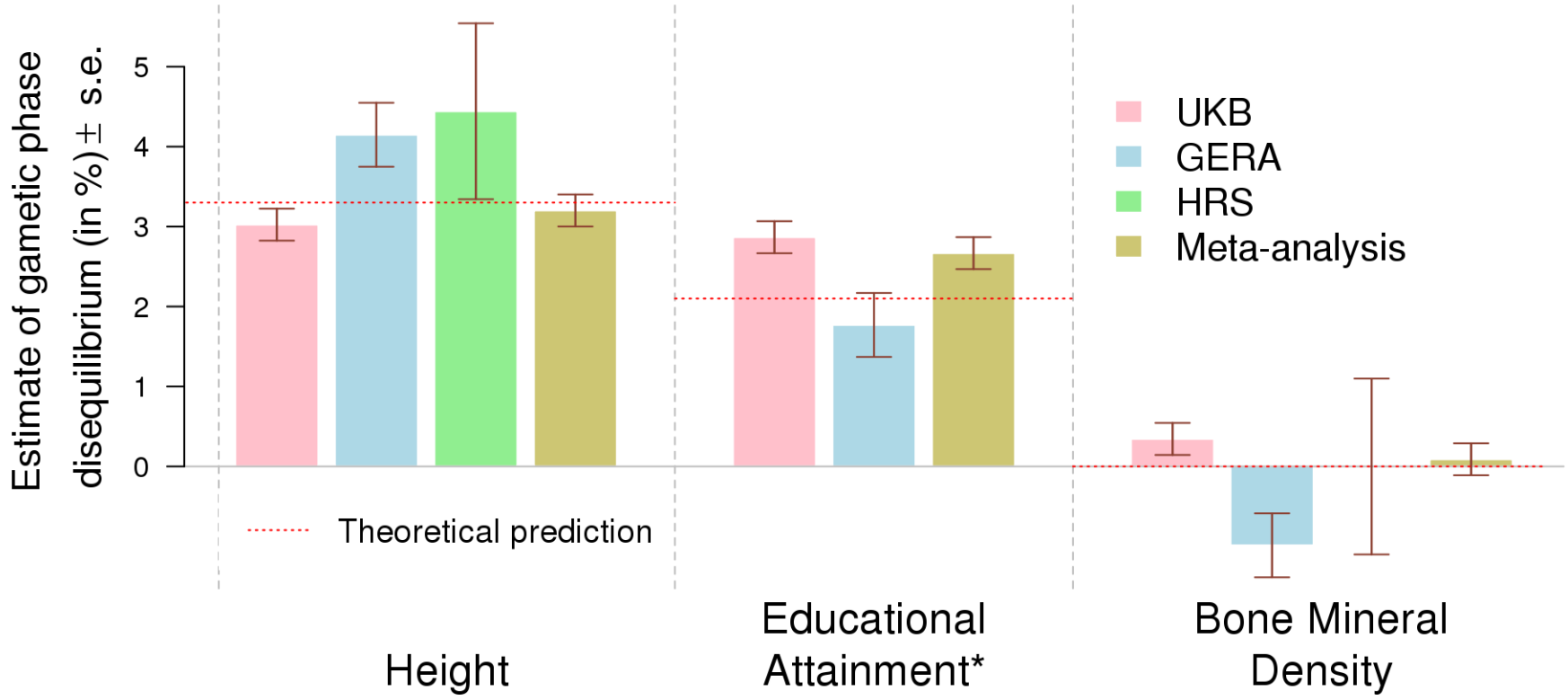
Individual level genotypes from a study independent of the reference GWAS

	ID_1	ID_2	…	ID_N
rs1778789	AA	AT	…	TT
rs67388911	GA	AA	…	GA
rs8800309	CC	CC	…	CC
rs17777893	GT	TT	…	GG

	Polygenic Score on odd chromosomes (So)	Polygenic Score on even chromosomes (Se)
ID_1	Beta(rs1778789) #A + Beta(rs8800309) #C	Beta(rs67388911) #G + Beta(rs17777893) #T
ID_2	Beta(rs1778789) #A + Beta(rs8800309) #C	Beta(rs67388911) #G + Beta(rs17777893) #T
…	…	…
ID_N	Beta(rs1778789) #A + Beta(rs8800309) #C	Beta(rs67388911) #G + Beta(rs17777893) #T

θ = S(o)~S(e) (regression) = cov(Se,So)/var(Se)

Significant GPD for height and Educational attainment



No signal for BMI, convergence?

What to know more?

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*]

Australian Government
Australian Research Council

The Sylvia & Charles Viertel Charitable Foundation

Australian Government
National Health and Medical Research Council

NIH

biobank uk

ACKNOWLEDGEMENTS

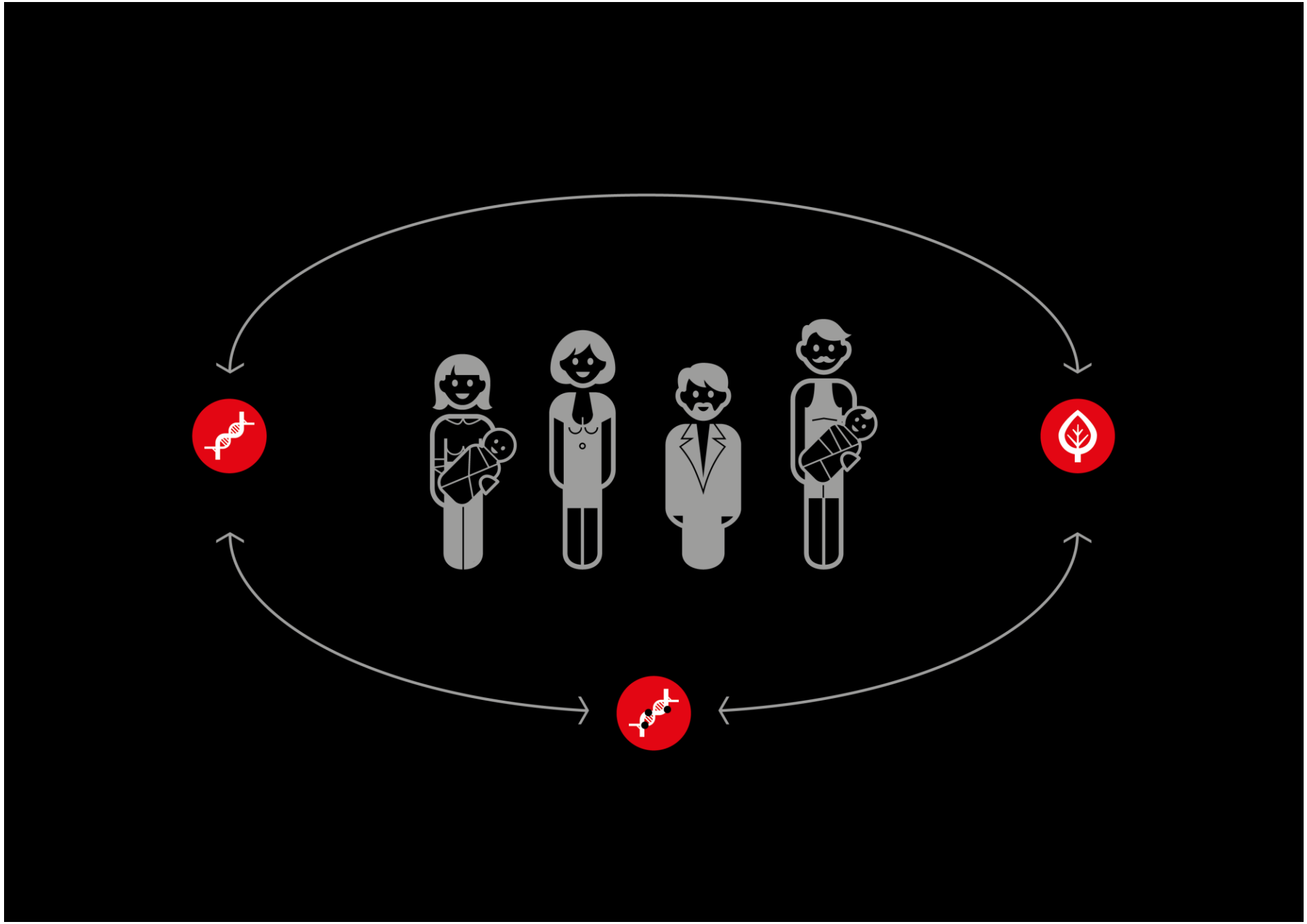
THANK YOU!

ICQG6

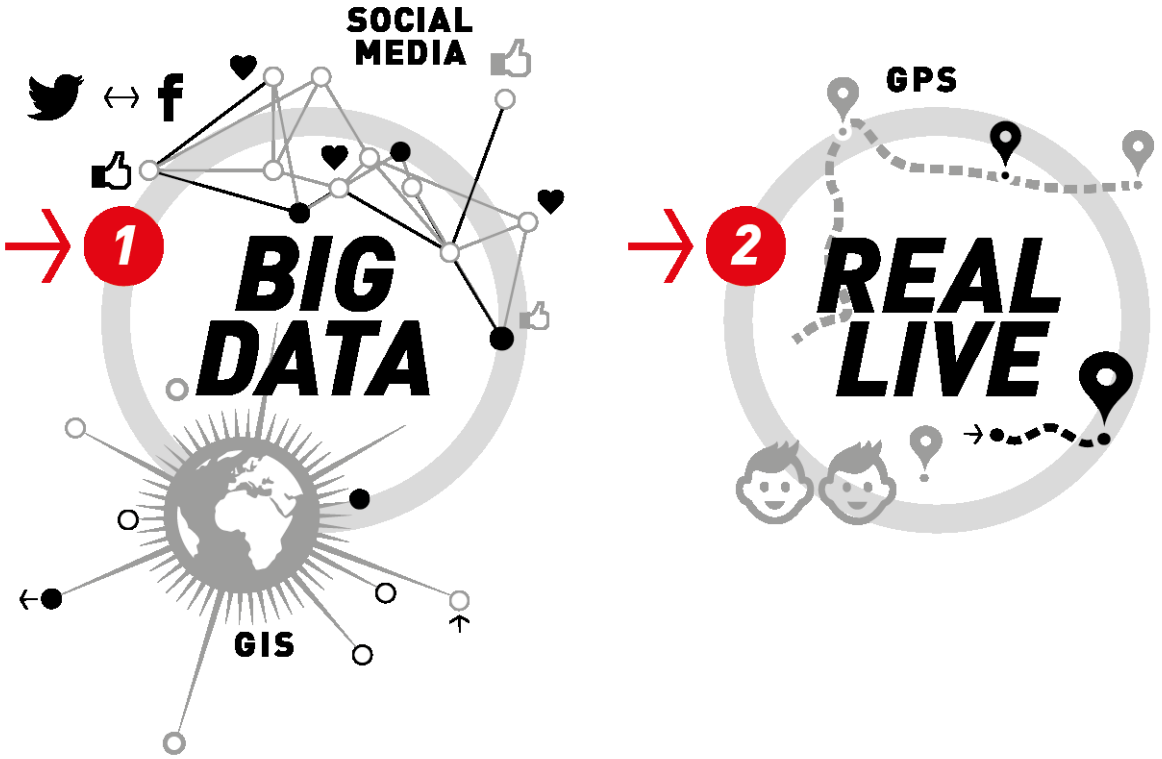
June 14th – 19th 2020, Brisbane, Australia

MEIKE BARTELS

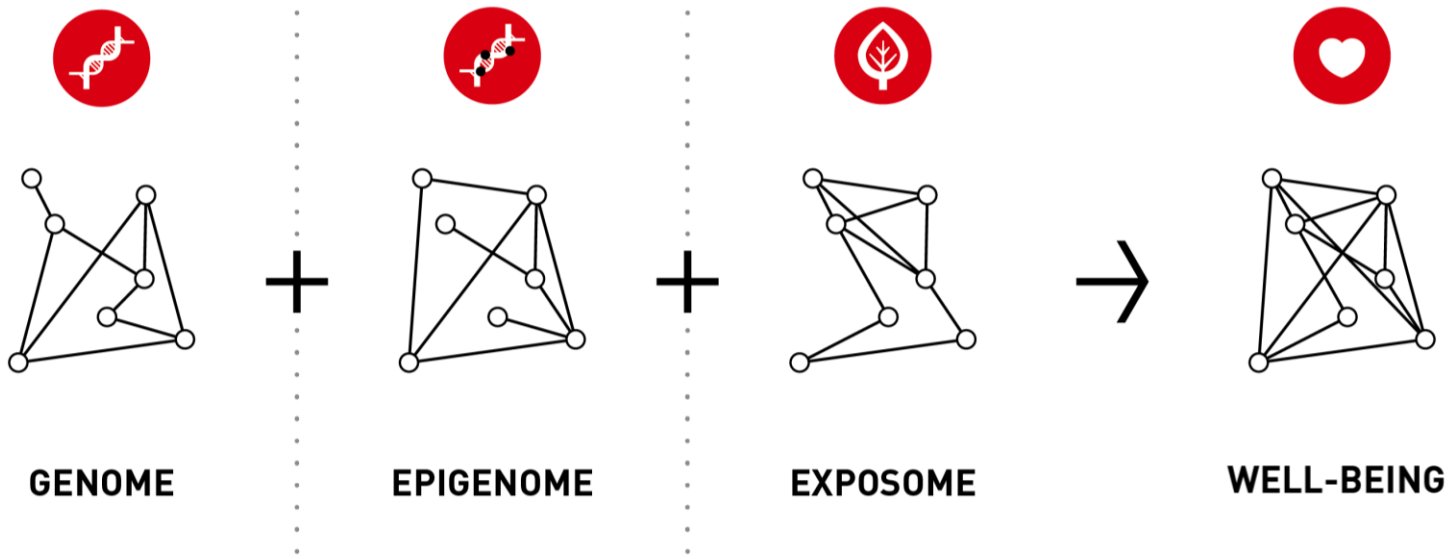
GENOME



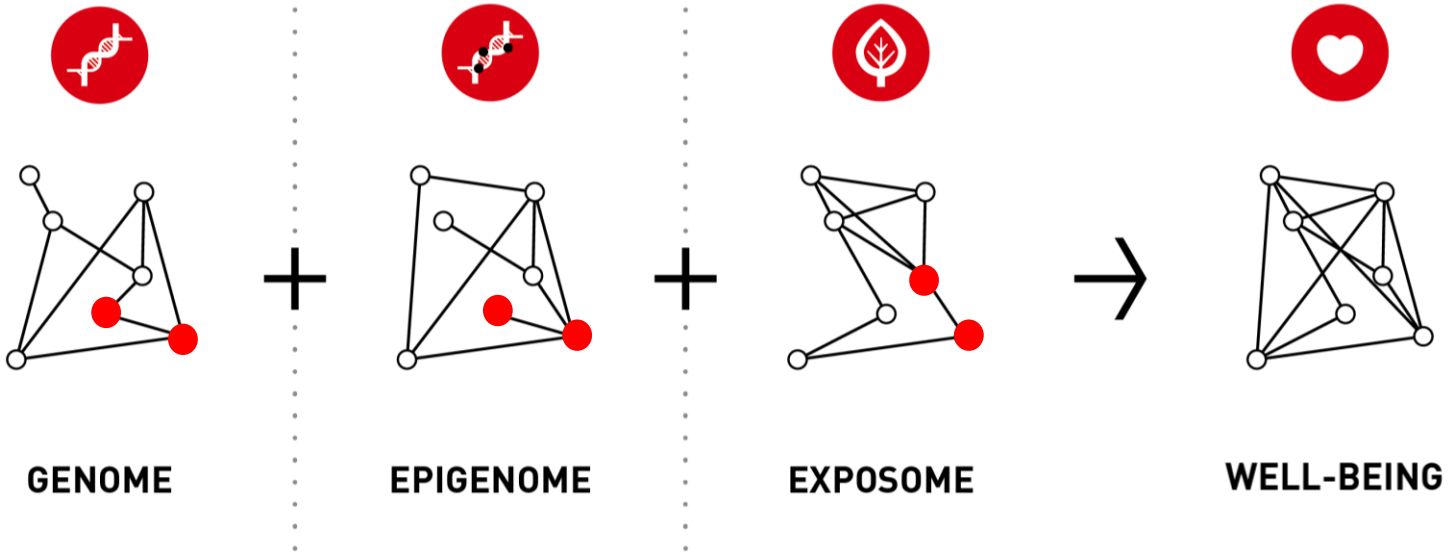
The Exposome



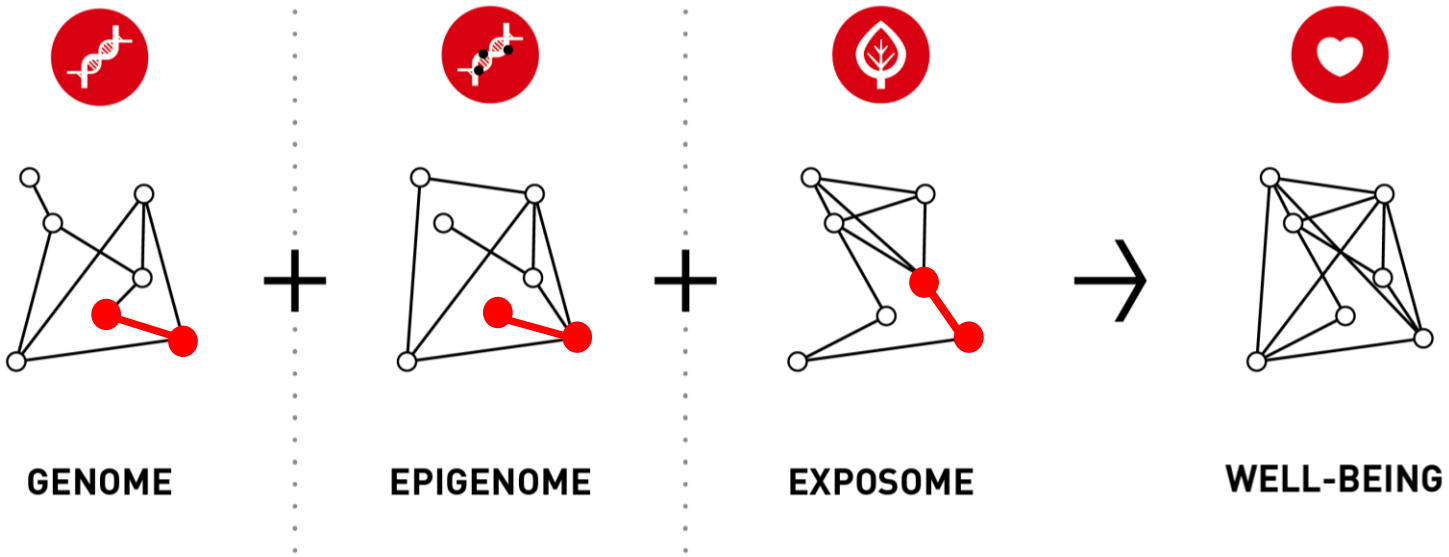
Network Integration



Network Integration



Network Integration



NICK MARTIN

Human Reproduction, Vol.25, No.6 pp. 1569–1580, 2010
Advanced Access publication on April 8, 2010 doi:10.1093/humrep/deq084

human reproduction

ORIGINAL ARTICLE *Reproductive genetics*

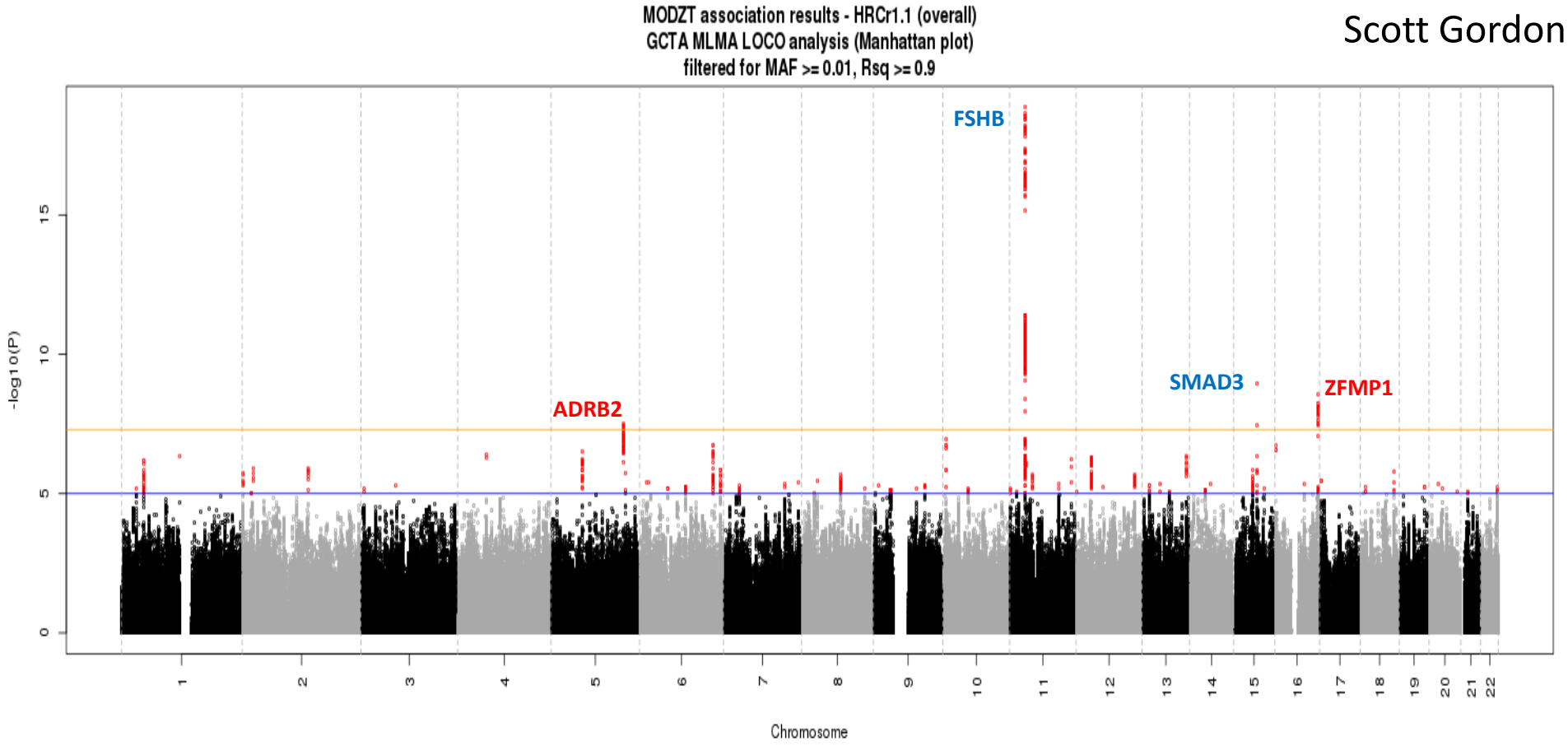
A genome wide linkage scan for dizygotic twinning in 525 families of mothers of dizygotic twins

Jodie N. Painter[1,*], Gonneke Willemsen[2], Dale Nyholt[1], Chantal Hoekstra[2], David L. Duffy[1], Anjali K. Henders[1], Leanne Wallace[1], Sue Healey[1], Lisa A. Cannon-Albright[3], Mark Skolnick[3], Nicholas G. Martin[1], Dorret I. Boomsma[2,†], and Grant W. Montgomery[1,†]

"Affected" sister-pair linkage study

QIMR	3,251 Mothers of DZ Twins	27,534 controls

Scott Gordon

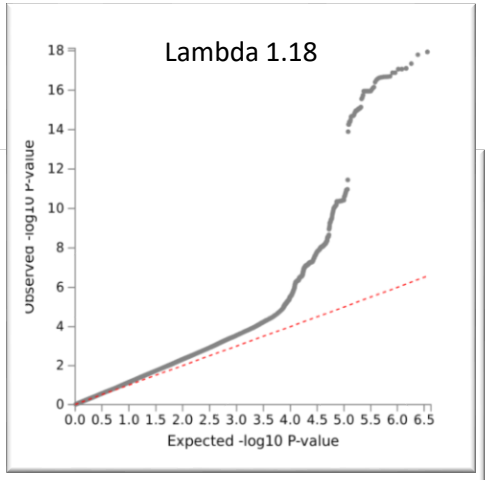


Manhattan plot for DZ Twinning

NTR-QIMR-MCTFR-WGHS-deCODEall

9598 MODZT “cases”, 363,756 controls

Note: small #cases implies large effect sizes!



FSHB Follicle stimulating hormone beta subunit
SMAD3 regulates gonadal responsiveness to FSH
ADRB2 (Adrenoceptor Beta 2) implicated in ovulation
ZFMP1 (Zinc finger FOG member 1): testicular cancer
IPO8 (Importin 8 required for TGF-β–activated Smad2/3 to translocate into the nucleus

Hamdi Mbarek

15 genes for DZT: 13 new; 13 have obvious function

					MODZT		MODZT+UKB (fixed effect)	MODZT+UKB (N-Weighted)
N	**Genes**	**Chr**	**Start**	**Stop**	**Gene based P**	**GWAS top SNP P**	**Gene based P**	**Gene based P**
1	FSHB	11	30252563	30256808	1.76E-10	7.31E-22	2.56E-11	1.31E-09
2	SMAD3	15	67356101	67487533	1.69E-07	1.91E-11	1.97E-08	3.69E-07
3	[redacted]	5	[redacted]		0.22	2.08E-08	0.44	0.42
4		8			3.61E-07	6.5E-09	2.34E-08	2.2E-07
5		16			2.05E-09	5.02E-10	6.16E-10	5.64E-07
6		5			5.78E-07		4.67E-07	2.35E-04
7		12			2.92E-08		2.27E-09	7.59E-08
8		17			6.10e-07		4.75E-07	2.84E-04
9		1			2.31E-05		2.59E-06	1.35E-04
10		2			8.56E-05		1.04E-06	1.36E-06
11		2			1.4E-04		1.48E-06	1.28E-06
12		8			2.03E-05		1.22E-06	6.75E-06
13		15			7.31E-06		6.35E-07	2.12E-05
14		2			0.024		1.45E-04	1.34E-06
15		4			0.022		1.73E04	2.72E-06

How well do these (PRS) predict

- **DZT in an out population (e.g. Iceland}**
- **Large differences in DZT rate between Africans, Europeans, Asians**
- **Large differences between early age (18) and late (37) MODZT**
- **Other female reproductive traits (menarche, menopause, age 1st kid, #kids)**
- **Female infertility**
- **Reproductive cancers (breast, ovarian, testicular, prostate)**
- **Evidence for selection at these loci (eugenic?, dysgenic?)**

HILARY MARTIN

Convergence of Mendelian and complex disease genetics

Hilary Martin

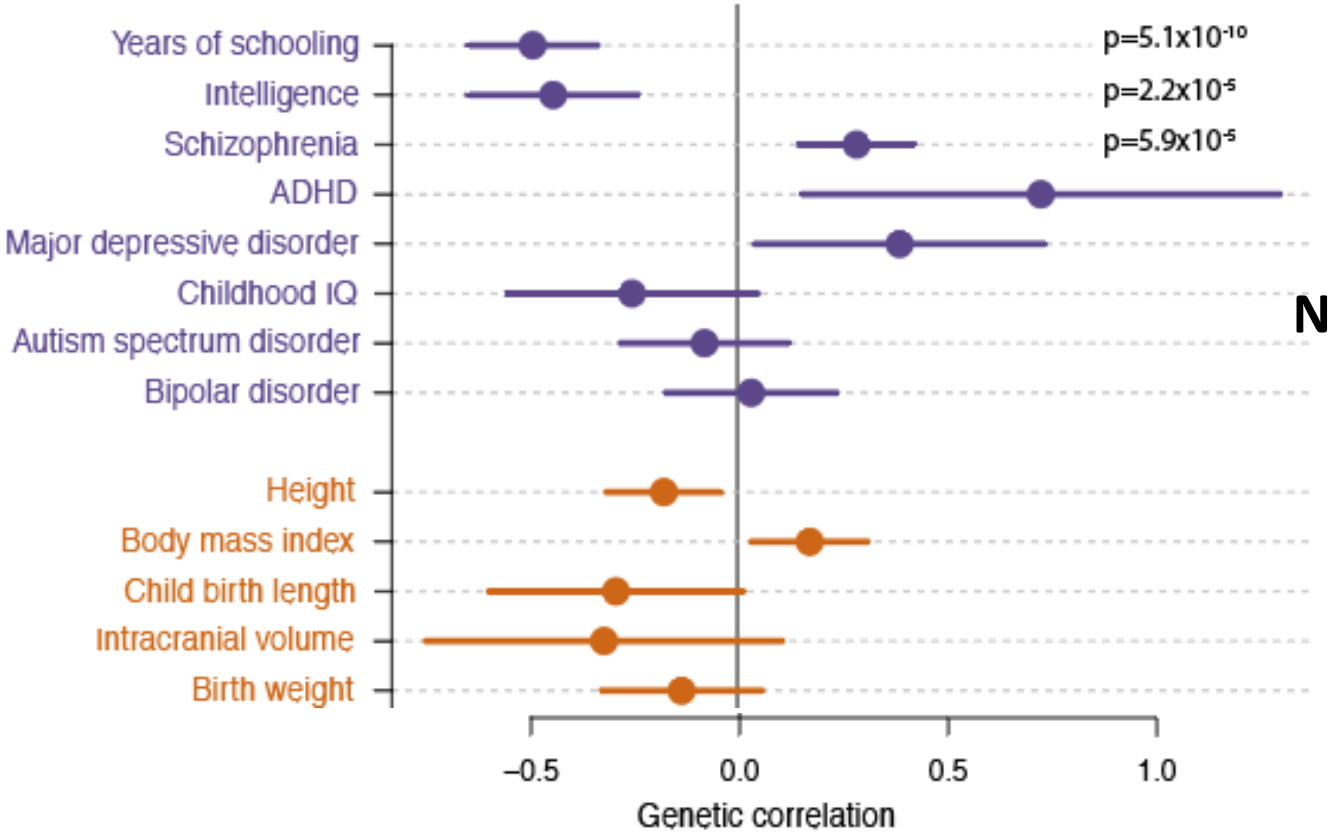
Wellcome Sanger Institute (near Cambridge, UK)

Mendelian versus complex disease genetics: a false dichotomy?

	Rare variants	**Common variants**
Mendelian diseases	Major role	?
Complex diseases	Some well-known examples (e.g. MODY), but don't account for much heritability	Major role

Common variants contribute to rare neurodevelopmental disorders previously assumed to be Mendelian

- ~7000 patients with rare, severe neurodevelopmental disorders in the Deciphering Developmental Disorders study versus ~9000 controls
- h^2_{SNP} **~8%** (for MAF>5%)
- replicated with polygenic scores in 1270 cases from Australia versus 1700 controls



LETTER

https://doi.org/10.1038/s41586-018-0566-4

Common genetic variants contribute to risk of rare severe neurodevelopmental disorders

Mari E. K. Niemi[1], Hilary C. Martin[1], Daniel L. Rice[1], Giuseppe Gallone[1], Scott Gordon[2], Martin Kelemen[1], Kerrie McAloney[2], Jeremy McRae[1], Elizabeth J. Radford[1-3], Sui Yu[4], Jozef Gecz[5,6], Nicholas G. Martin[2], Caroline F. Wright[7], David R. Fitzpatrick[8], Helen V. Firth[1,9], Matthew E. Hurles[1] & Jeffrey C. Barrett[1*]

No significant difference in any polygenic score between patients with versus without a "diagnostic" rare variant

Jeff Barrett

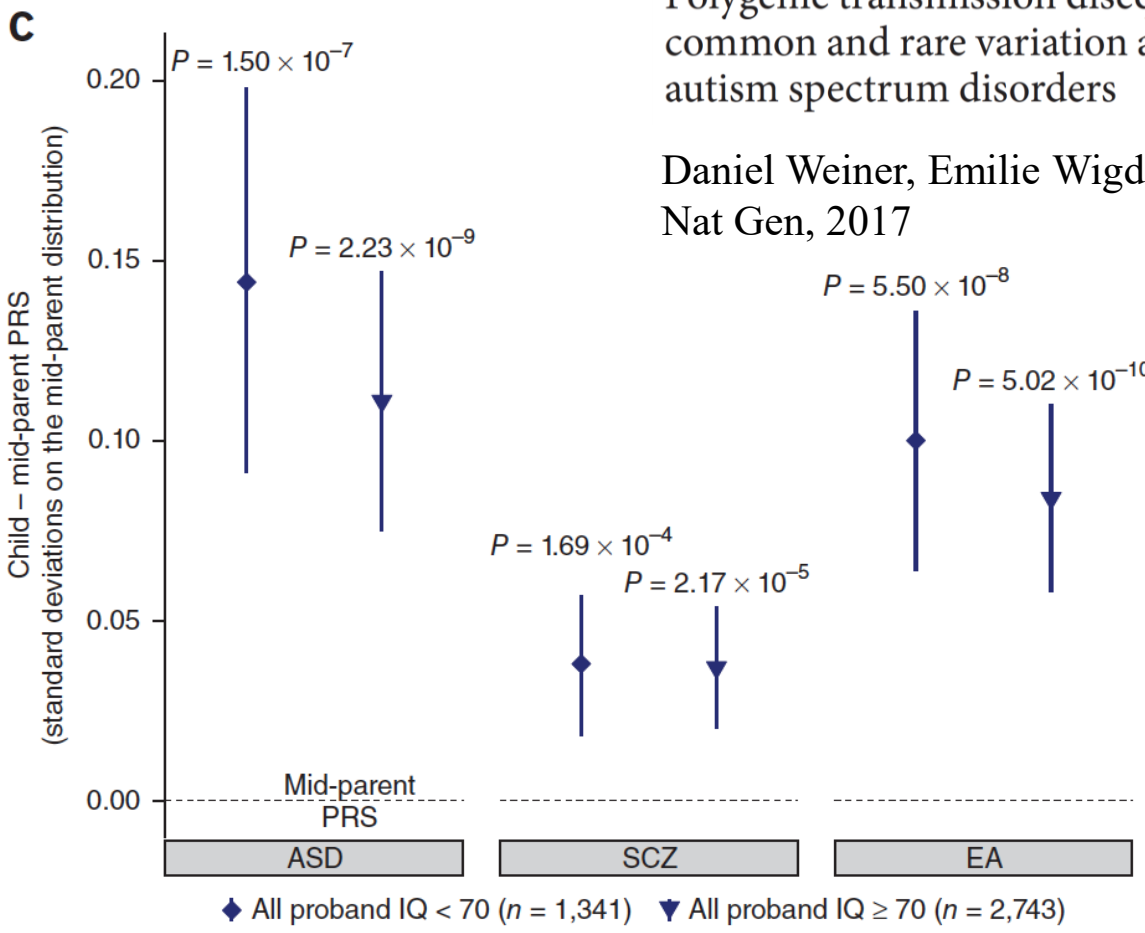
Mari Niemi

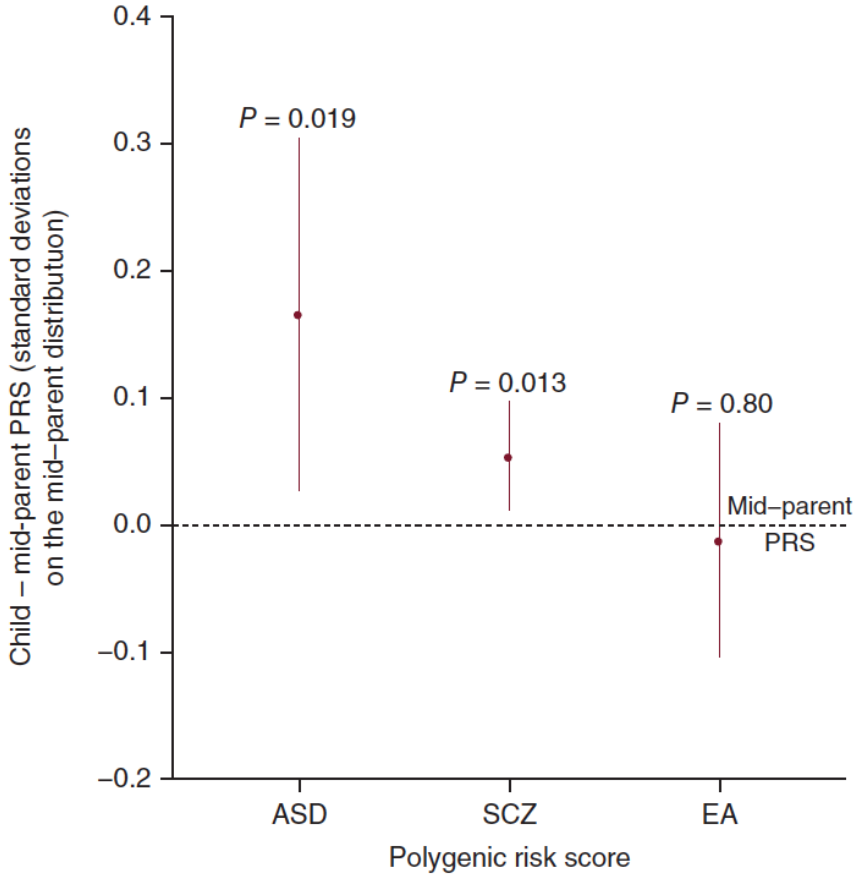
Polygenic transmission-disequilibrium test in autism

- Polygenic scores for autism, schizophrenia and educational attainment are significantly over-transmitted to autism patients, regardless of their IQ
- Still see over-transmission of autism and schizophrenia PRS to probands with a large-effect *de novo* mutation

Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders

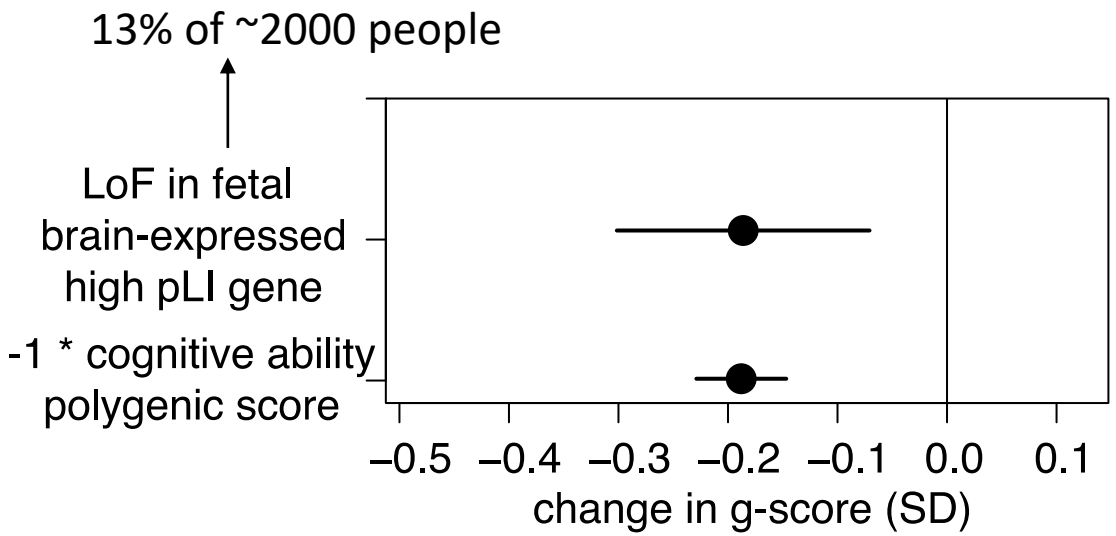
Daniel Weiner, Emilie Wigdor, …, Elise Robinson.
Nat Gen, 2017

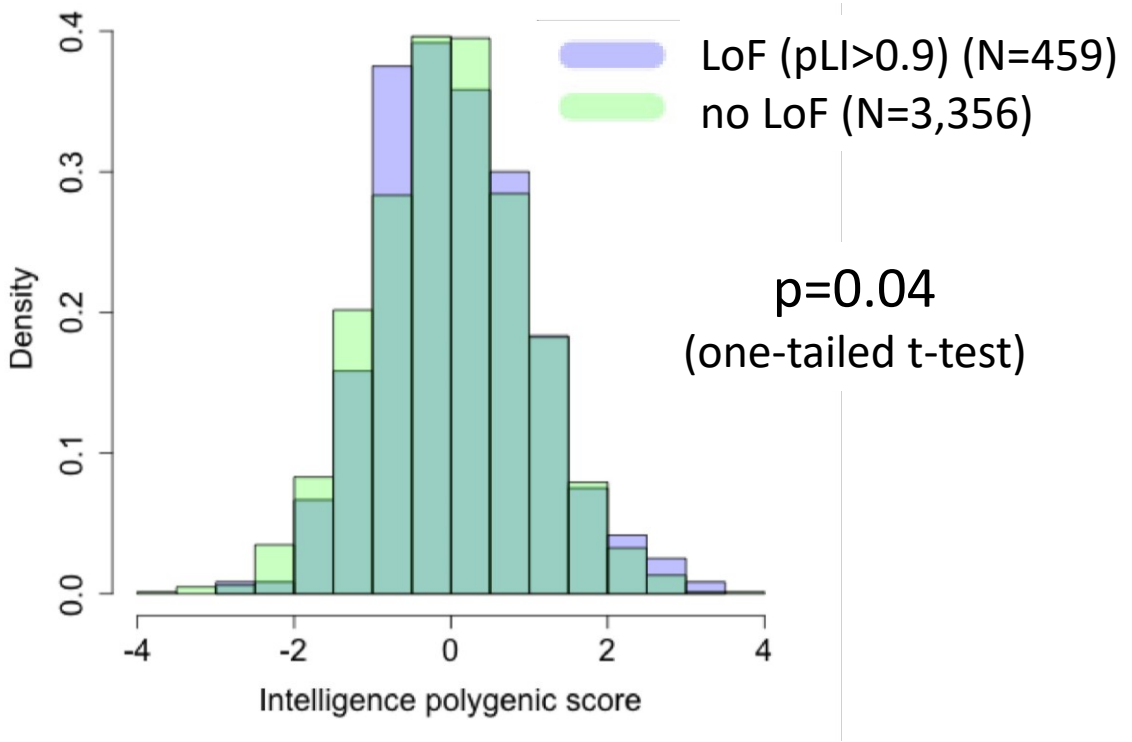




Common variants modifying penetrance of rare variants affecting cognition?

- rare loss-of-function variants in highly constrained genes increase risk of severe ID/DD and impact cognition in the general population
- **are people in healthy population cohorts protected against such variants by polygenic background?**
- preliminary work in INTERVAL, a cohort of healthy British blood donors





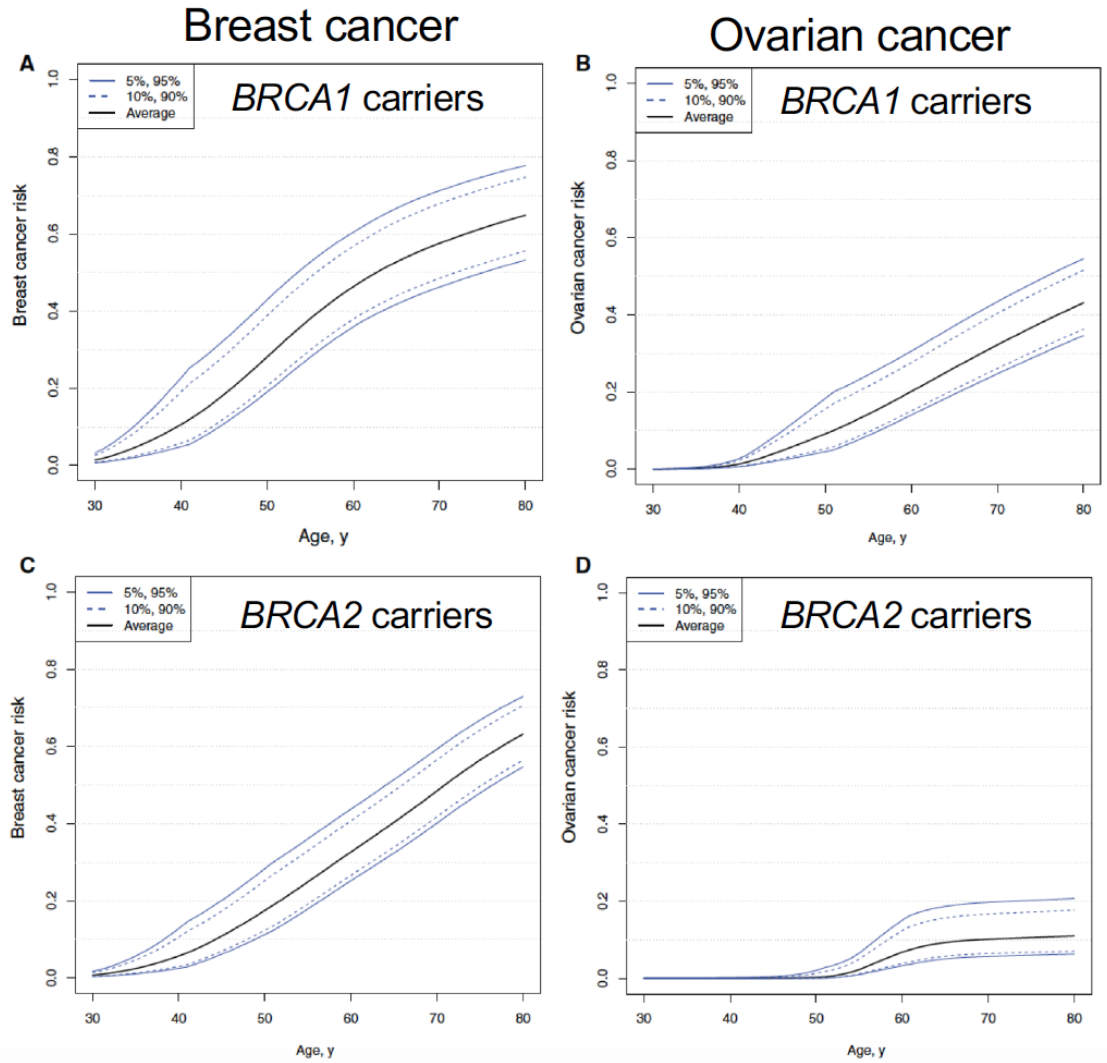
p=0.04
(one-tailed t-test)

ongoing collaboration with Andrea Ganna, Sali Farhan at Broad to expand sample size!

Mari Niemi, Eugene Gardner

Common variants modifying penetrance of rare variants in breast cancer

Predicted cancer risks by percentile of the polygenic risk scores



Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in *BRCA1* and *BRCA2* Mutation Carriers

Karoline B Kuchenbaecker, Lesley McGuffog, Daniel Barrowdale, Andrew Lee, Penny Soucy, Joe Dennis, Susan M Domchek, Mark Robson, Amanda B Spurdle, Susan J Ramus, ... Show more

JNCI: Journal of the National Cancer Institute, Volume 109, Issue 7, 1 July 2017, djw302, https://doi.org/10.1093/jnci/djw302

Open questions

- How much do low-frequency variants (e.g. MAF 0.1-5%) contribute to heritability of rare neurodevelopmental disorders?
- To what extent do common variants contribute to other rare disorders? e.g. heart defects
- Do polygenic scores and rare variants act additively on traits, or is there an interaction?
- Can we increase power to detect rare variants by conditioning on polygenic risk scores?
- To what extent can we improve polygenic prediction by incorporating rare variants? (as individual variants, or in aggregated groups)

Acknowledgements

Mari Niemi

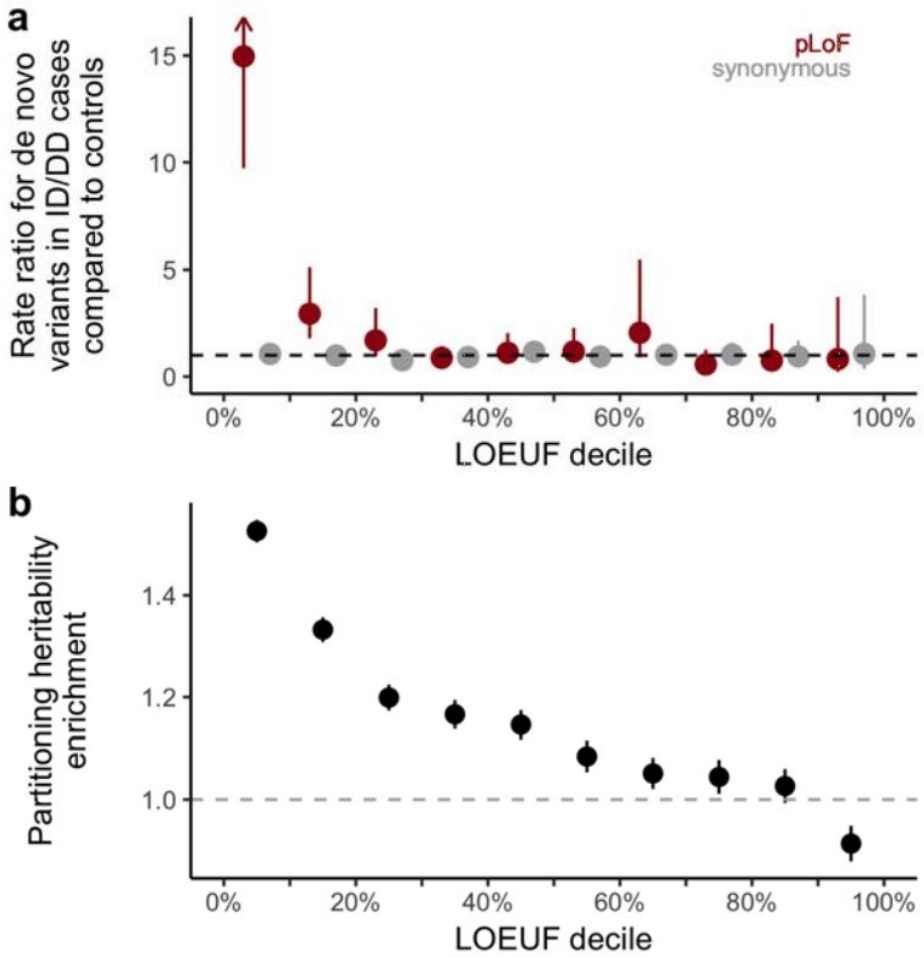
Eugene Gardner

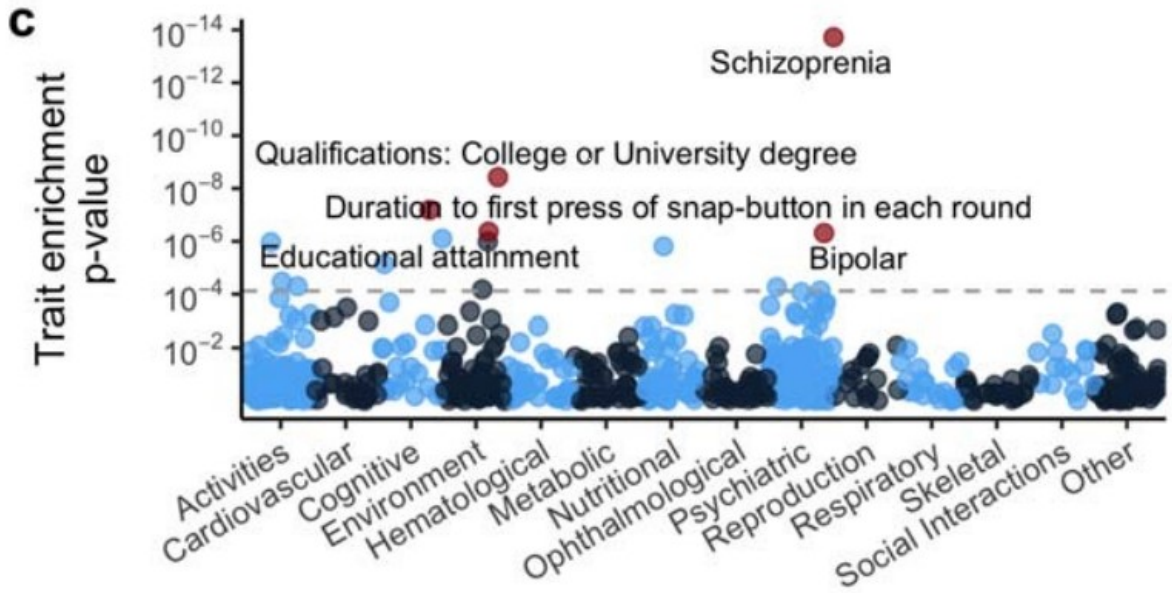
Jeff Barrett

Matt Hurles

For cognition and schizophrenia in particular, rare and common variant signals are enriched in highly constrained genes

High constrained genes: significantly depleted of loss-of-function variants in healthy people

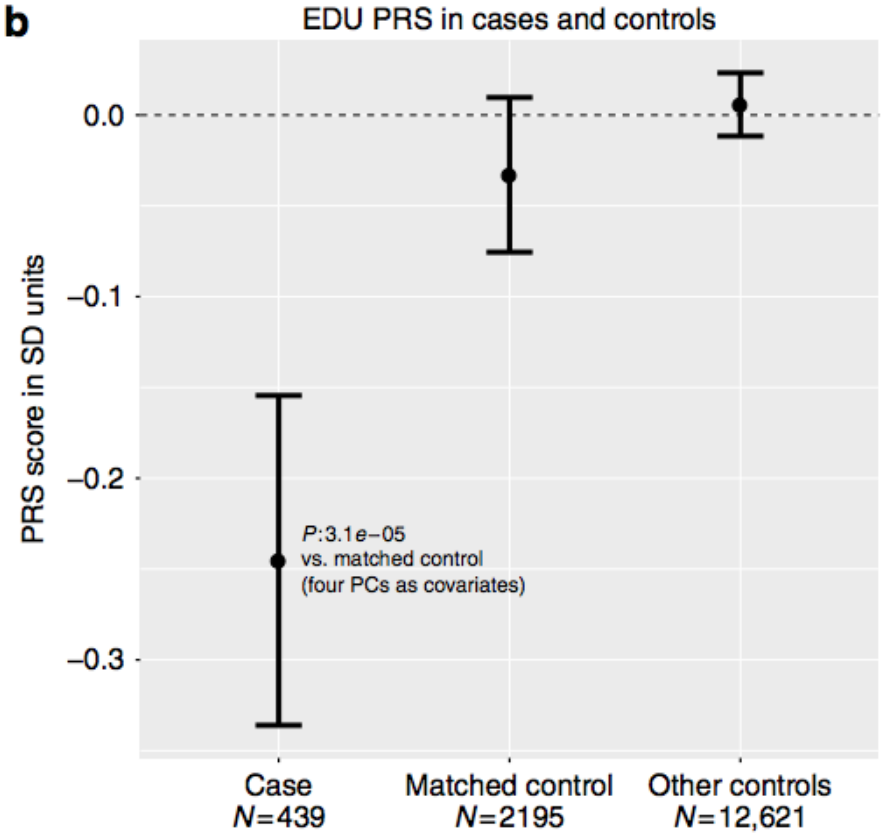


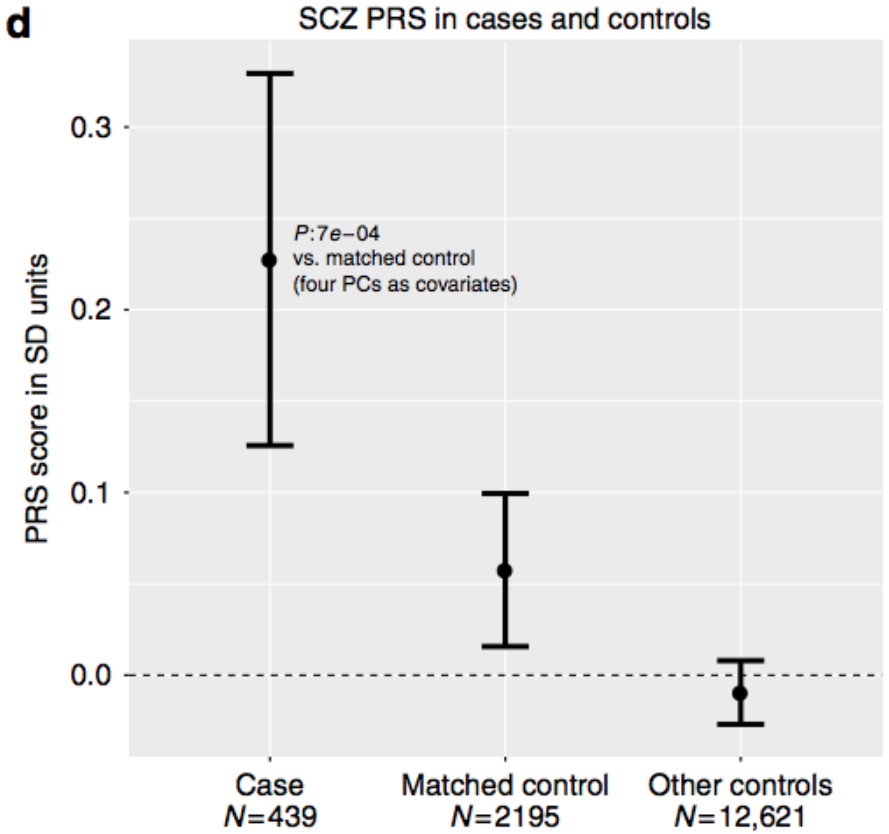


Karczewski et al, doi: http://dx.doi.org/10.1101/531210.

Common variants contribute to rare neurodevelopmental disorders previously assumed to be Mendelian

- 429 Finnish intellectual disability (ID) cases versus 2195 controls
- heritability explained by polygenic risk scores for EA is the highest in mild ID (2.2%) but lower for more severe ID (0.6%)





Contribution of rare and common variants to intellectual disability in a sub-isolate of Northern Finland

Mitja I. Kurki[1,2,3], Elmo Saarentaus[3], Olli Pietiläinen[2,4], Padhraig Gormley[1,2], Dennis Lal[1,2], Sini Kerminen[3], Minna Torniainen-Holm[3,5], Eija Hämäläinen[3], Elisa Rahikkala[6,7,8], Riikka Keski-Filppula[6,7,8], Merja Rauhala[9], Satu Korpi-Heikkilä[9], Jonna Komulainen-Ebrahim[10], Heli Helander[10], Päivi Vieira[10], Minna Männikkö[11,12], Markku Peltonen[5], Aki S. Havulinna[3,5], Veikko Salomaa[5], Matti Pirinen[3], Jaana Suvisaari[5], Jukka S. Moilanen[6,7,8], Jarmo Körkkö[9], Outi Kuismin[3,6,7,8], Mark J. Daly[1,2,3,13,14] & Aarno Palotie[1,2,3,13,14]

NATURE COMMUNICATIONS | (2019)10:410

MATT KELLER

Behavioral Genetics in the molecular age - answers to age old questions

Matthew Keller

CU Boulder

BG is interested in quantifying factors that cause individual differences

- Traditionally, we've done this using close relatives & twins
- Has been enormously successful and we've been able to make broad-brushed conclusions about genes & env.
- But these studies require strong assumptions about causes of relative similarity. For us who care about, e.g., VA:VNA, VF (familial variance from parental effects) VC (shared environmental effects), or AM (assortative mating), twin and family models can be biased and coarse
- We want ways to investigate old questions in new (and potentially less biased) ways
- Following are new ways to do this using molecular data

1. SNP data to estimate ~full *VA'*

- GREML is done on unrelated (distantly related) individuals – we don't require assumptions about causes of similarity between close relatives.
- As we move to very large sequence reference panels (e.g., TOPMed; n ~ 100k) – or to large sequence data itself, *VA'_GREML* should begin to approach VA. If *VA'_GREML* is much different than *VA'_twin*, something interesting is going on!
  - Upward biases in *VA'_twin*? De novo variants? Phenotypic heterogeneity?
- This is exciting: new and independent way of estimating VA. Via triangulation, we'll know ~ true VA soon.

2. SNP data to estimate allelic spectra of V(G) and COV(G)

- What is the mix of rare vs. common variants affecting trait variation? Important for study design and evolutionary interpretations.
- GREML models (previous slide) on imputed or sequence data, when done properly (multiple GRMs stratified by MAF and individual LD) can give us estimates of the allelic spectra
- These same methods can help us understand if rg is the same across the allelic spectra

3. SNP data to understand causes of spousal similarity

- Recent work* uses GREML and/or PRS to directly estimate the additive genetic correlation between mates
  - Spousal height correlation completely consistent with primary AM, but that of BMI is about ½ primary AM and ½ other factors (convergence? social homogamy?)
- This is exciting: assumptions about the cause of spousal similarity can now be empirically tested!

* Robinson et al., 2017

4. SNP data to investigate familial transmission

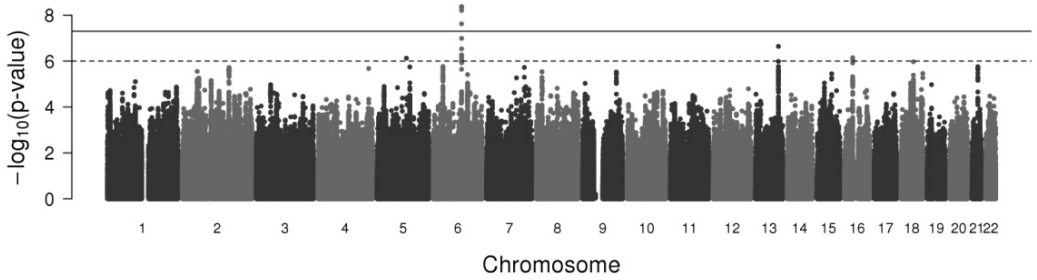
- Passive G-E correlations arise when genetic effects are not random with respect to env. effects
  - Most commonly: env. of offspring a function of parental phenotypes
- Comparing between- and within-family GWAS estimates can provide estimates of the importance of G-E covariance
- Similarly, looking at relationship between PRS of transmitted genome vs. PRS of untransmitted genome as a way to test parenting effects on offspring.

* Kong et al., 2018

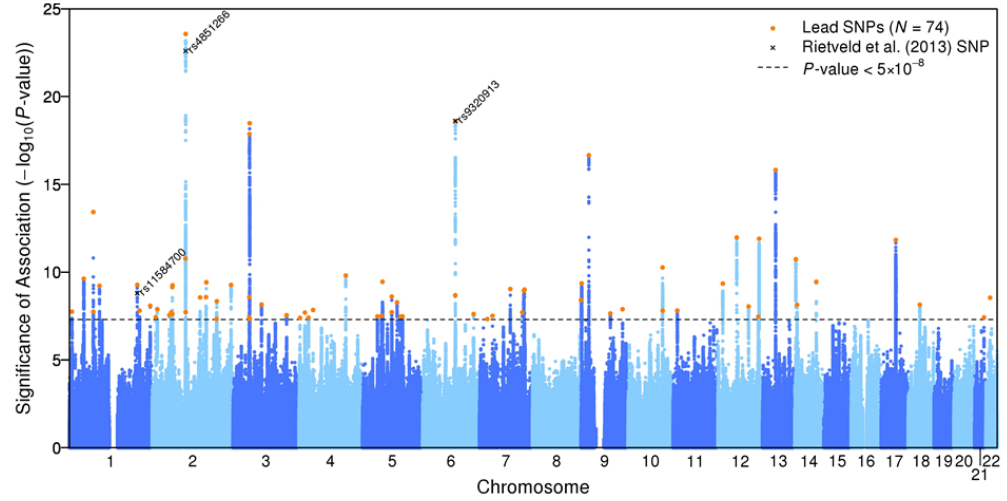
AYSU OKBAY

Integrating polygenic scores into social sciences

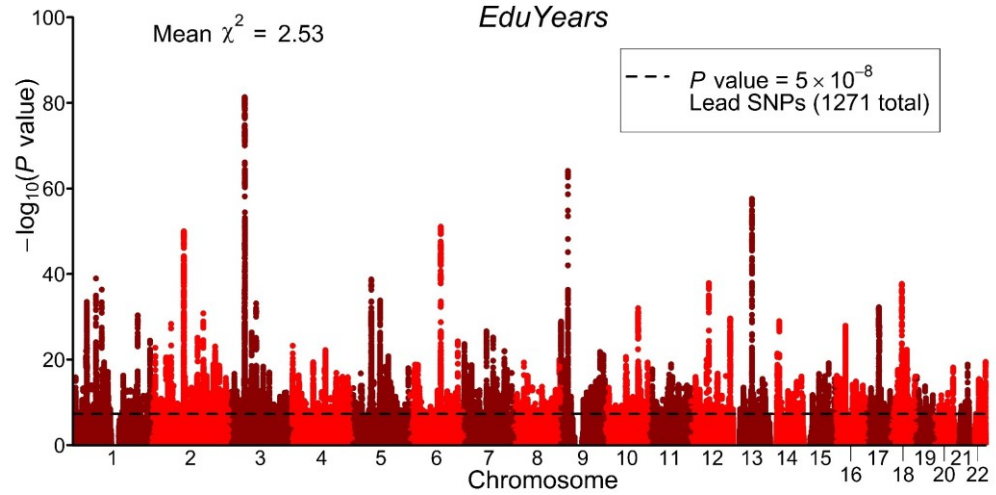
Aysu Okbay



EA1 (N=126,559), 3 hits

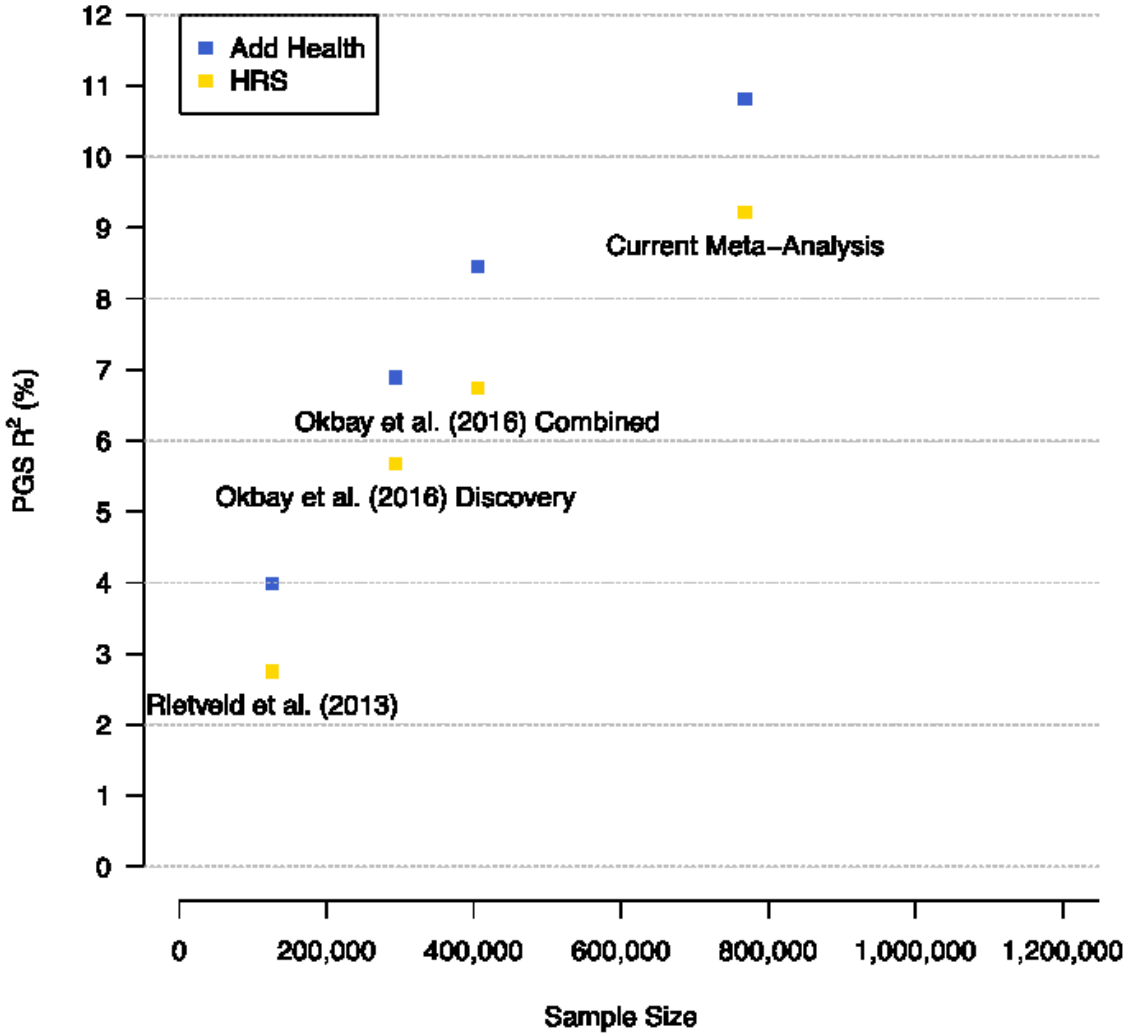


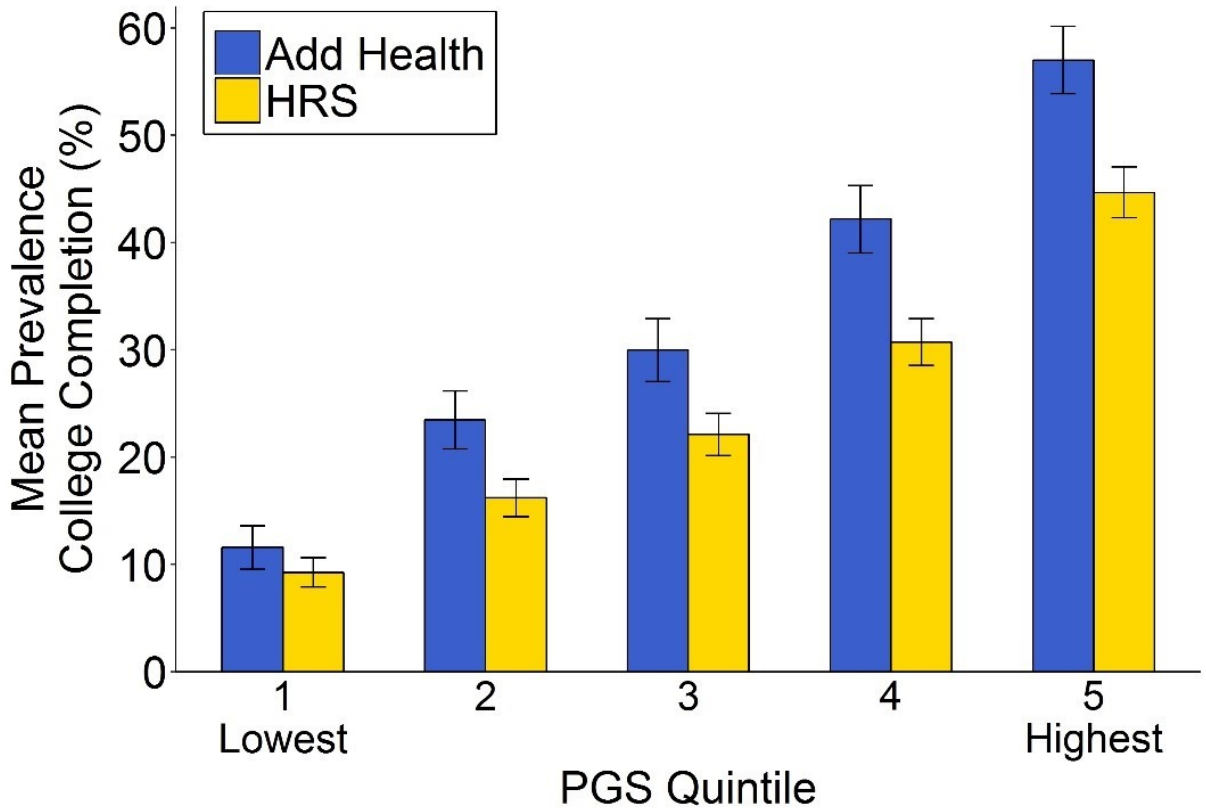
EA2 (N=293,723), 74 hits



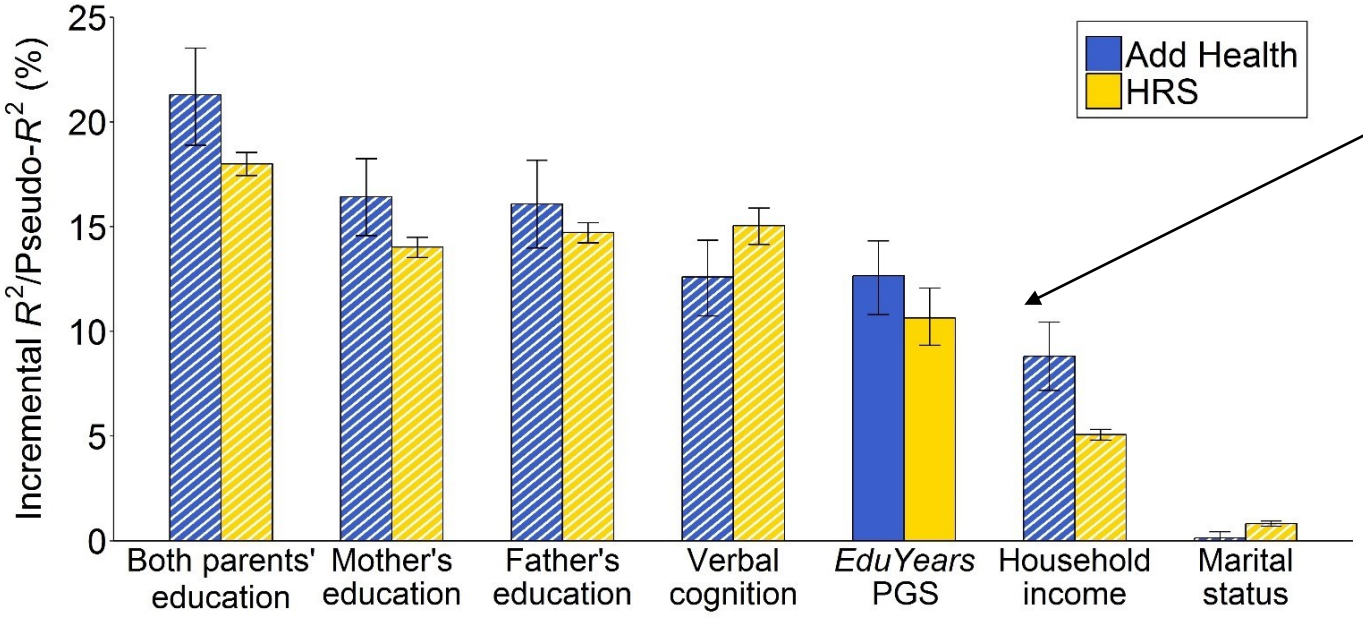
EA3 (N=1,131,881), 1,271

Educational attainment polygenic scores





Nearly as good as conventional controls in social science

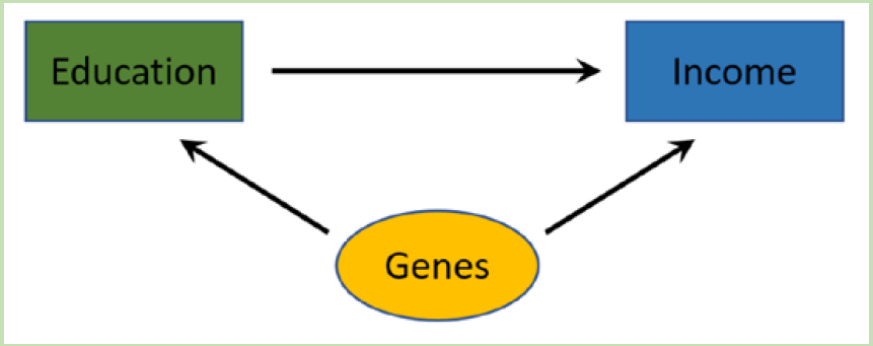


The EA score now predicts more than household income!

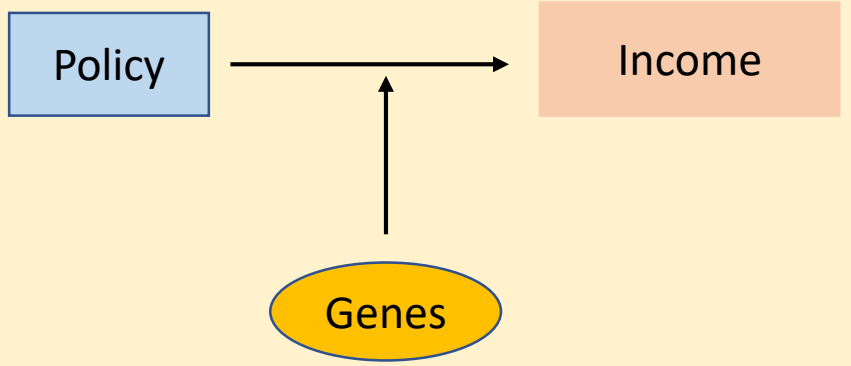
Makes many previously underpowered analyses feasible

Polygenic scores in social sciences

Genes as controls



Gene × environment interactions



Example: Policy evaluation

The Swedish educational reform:

- Increased compulsory schooling from 7 to 9 years
- Delayed ability tracking
- Was rolled out gradually generating quasi-experimental variation

Questions:

- Did the reform affect individuals in different EA PGS bins heterogeneously?
- Did the reform achieve what it meant to achieve? More equality?

Preliminary result:

- higher ability females were more likely to obtain a high school degree, which is beyond the new minimum established by the reform.

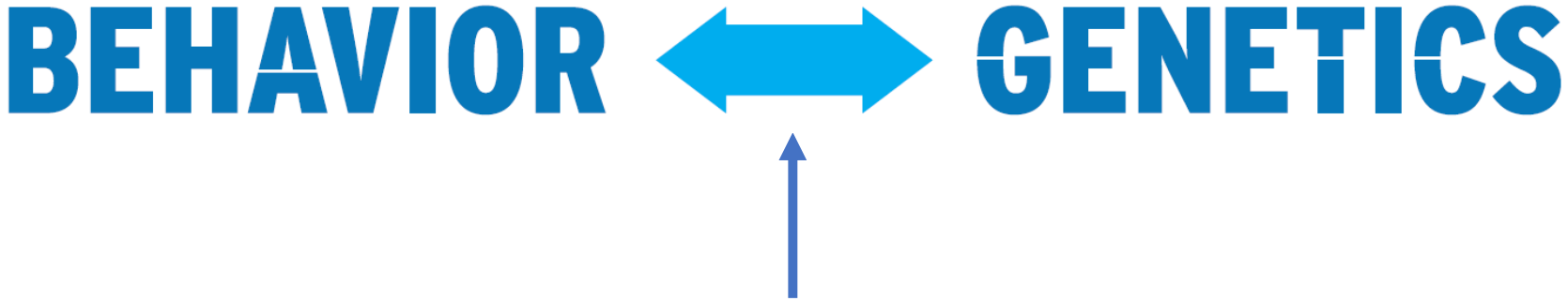
ABDEL ABDELLAOUI

BEHAVIOR ⟷ GENETICS

ABDEL ABDELLAOUI

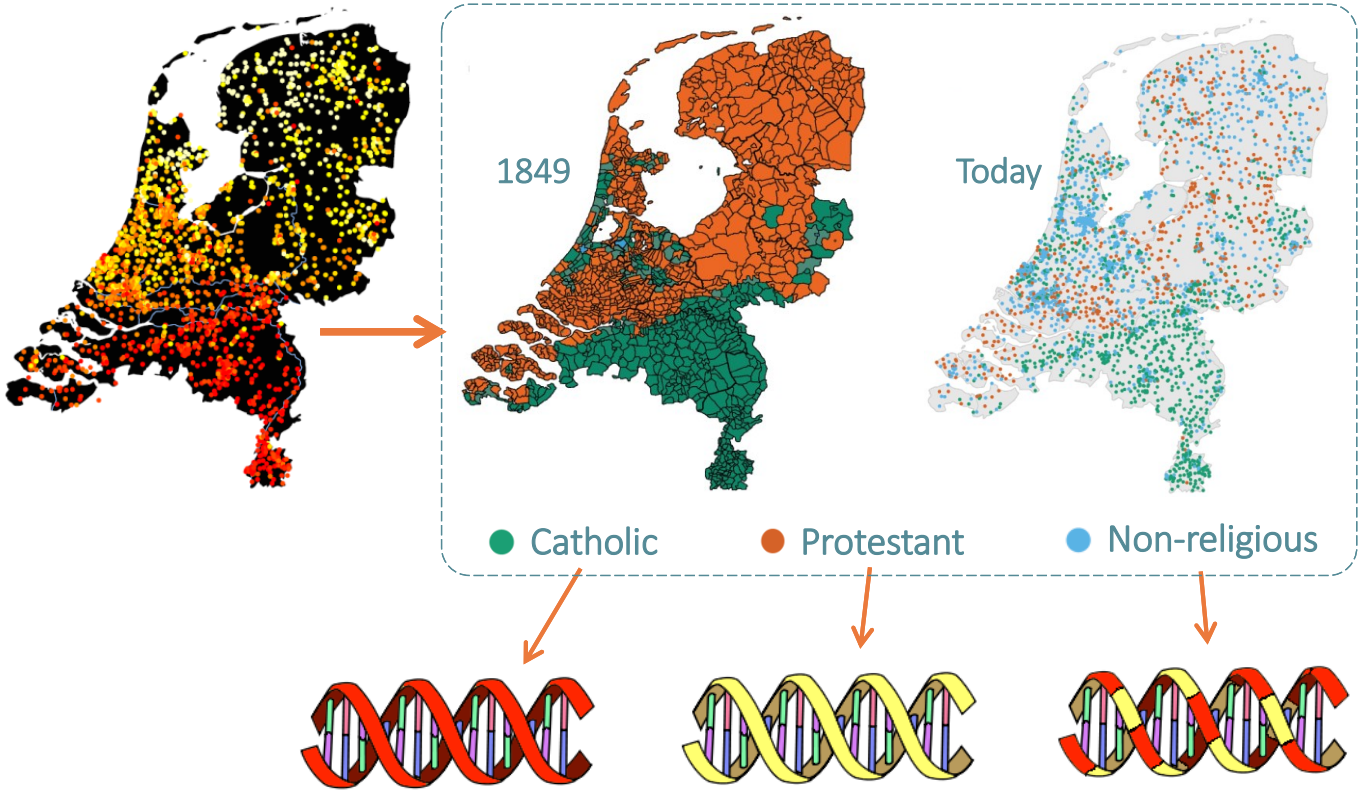
a.abdellaoui@amc.nl

dr_appie



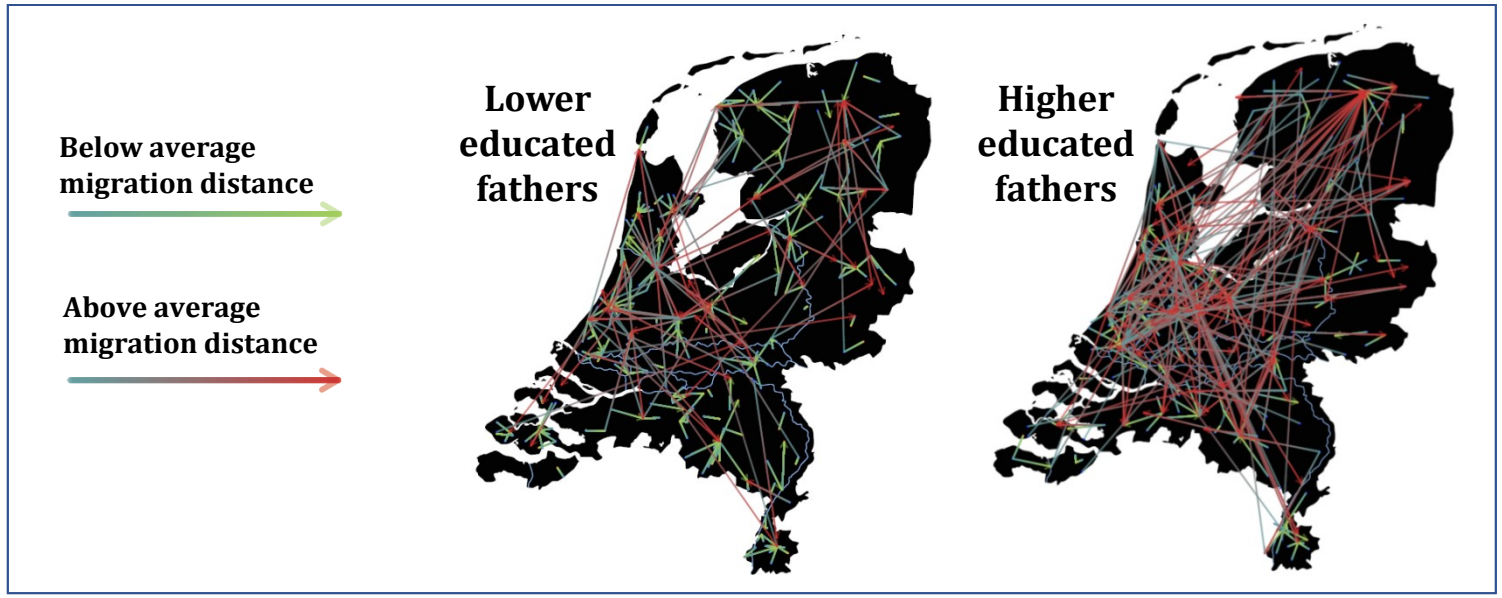
a.abdellaoui@amc.nl

dr_appie



Association Between Autozygosity and Major Depression: Stratification Due to Religious Assortment

Abdel Abdellaoui · Jouke-Jan Hottenga · Xiangjun Xiao · Paul Scheet · Erik A. Ehli · Gareth E. Davies · James J. Hudziak · Dirk J. A. Smit · Meike Bartels · Gonneke Willemsen · Andrew Brooks · Patrick F. Sullivan · Johannes H. Smit · Eco J. de Geus · Brenda W. J. H. Penninx · Dorret I. Boomsma



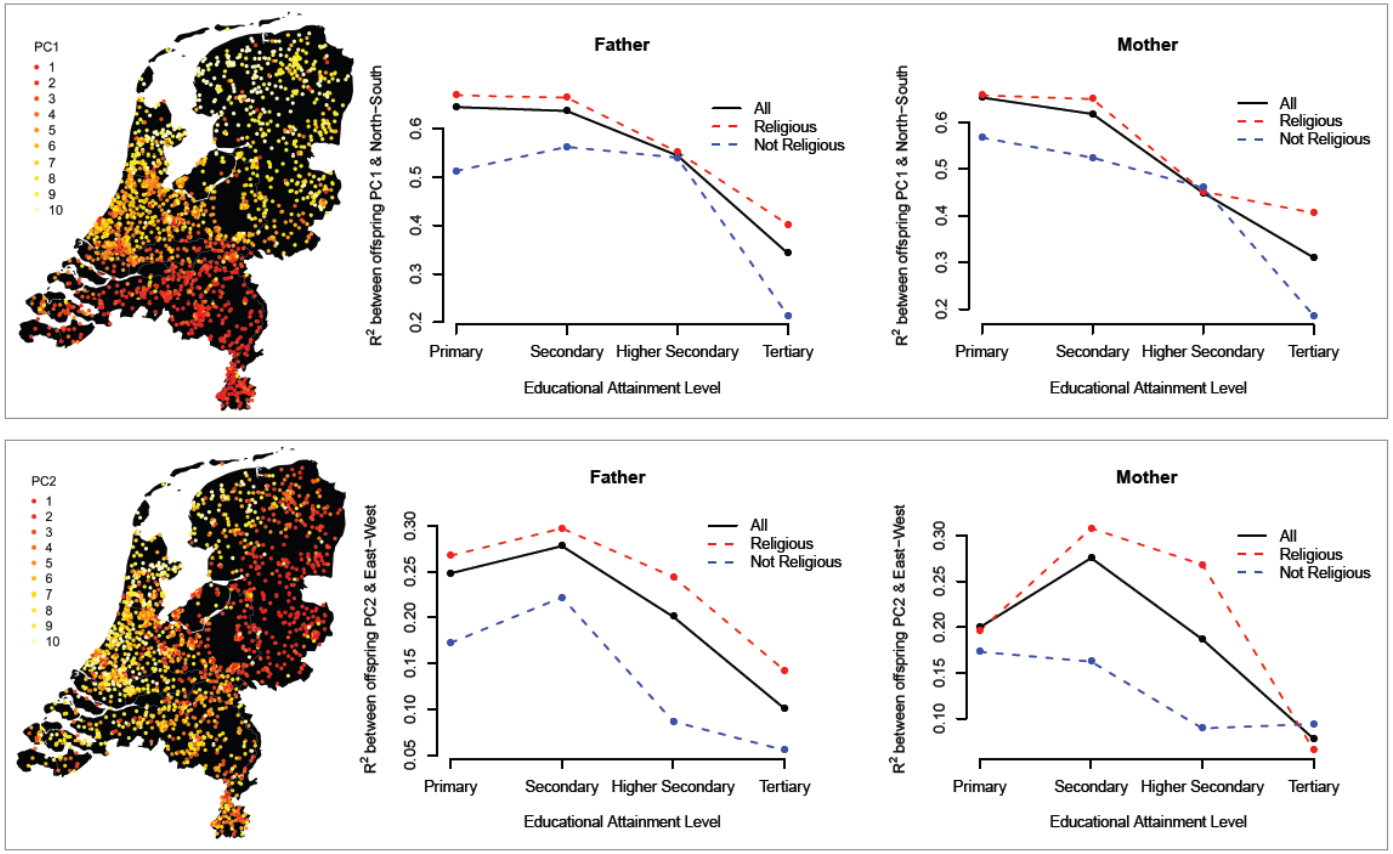
- Educational attainment was significantly associated with F_{roh} (inbreeding)
- But parental education was *much* more significantly associated with F_{roh}
- Why?
  - Higher educated parents **migrated** significantly more often and greater distances
  - There is strong **assortative mating** for educational attainment

RESEARCH ARTICLE

Educational Attainment Influences Levels of Homozygosity through Migration and Assortative Mating

Abdel Abdellaoui[1,2*], Jouke-Jan Hottenga[1], Gonneke Willemsen[1,3], Meike Bartels[1,2,3], Toos van Beijsterveldt[1], Erik A. Ehli[4], Gareth E. Davies[4], Andrew Brooks[5], Patrick F. Sullivan[6], Brenda W. J. H. Penninx[2,3,7], Eco J. de Geus[1,2,3], Dorret I. Boomsma[1,2,3]

Correlation between offspring ancestry and geography significantly decreased as parental education increased

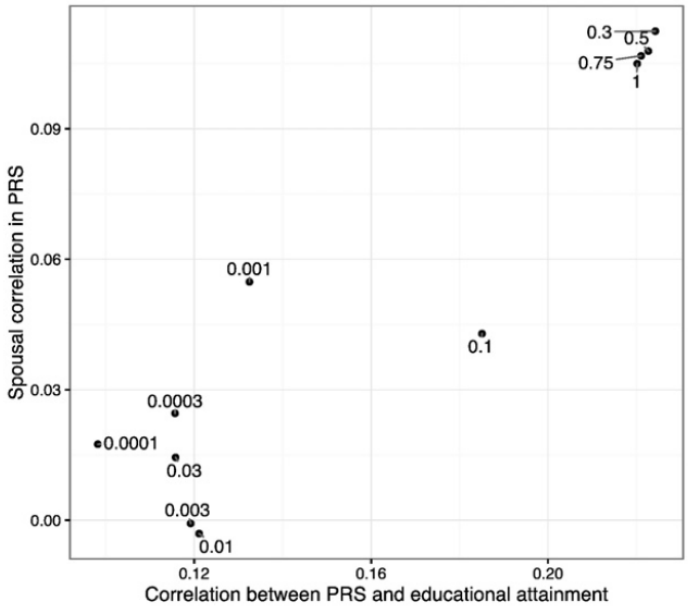


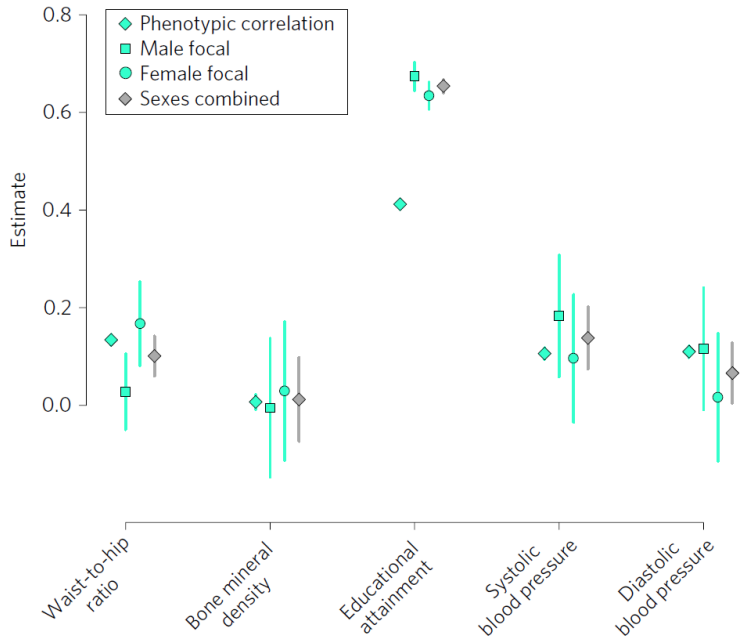
RESEARCH ARTICLE

Educational Attainment Influences Levels of Homozygosity through Migration and Assortative Mating

Abdel Abdellaoui[1,2*], Jouke-Jan Hottenga[1], Gonneke Willemsen[1,3], Meike Bartels[1,2,3], Toos van Beijsterveldt[1], Erik A. Ehli[4], Gareth E. Davies[4], Andrew Brooks[5], Patrick F. Sullivan[6], Brenda W. J. H. Penninx[2,3,7], Eco J. de Geus[1,2,3], Dorret I. Boomsma[1,2,3]

Assortative mating for educational attainment is measurable at the genetic level (with polygenic scores)





Assortative mating on educational attainment leads to genetic spousal resemblance for polygenic scores

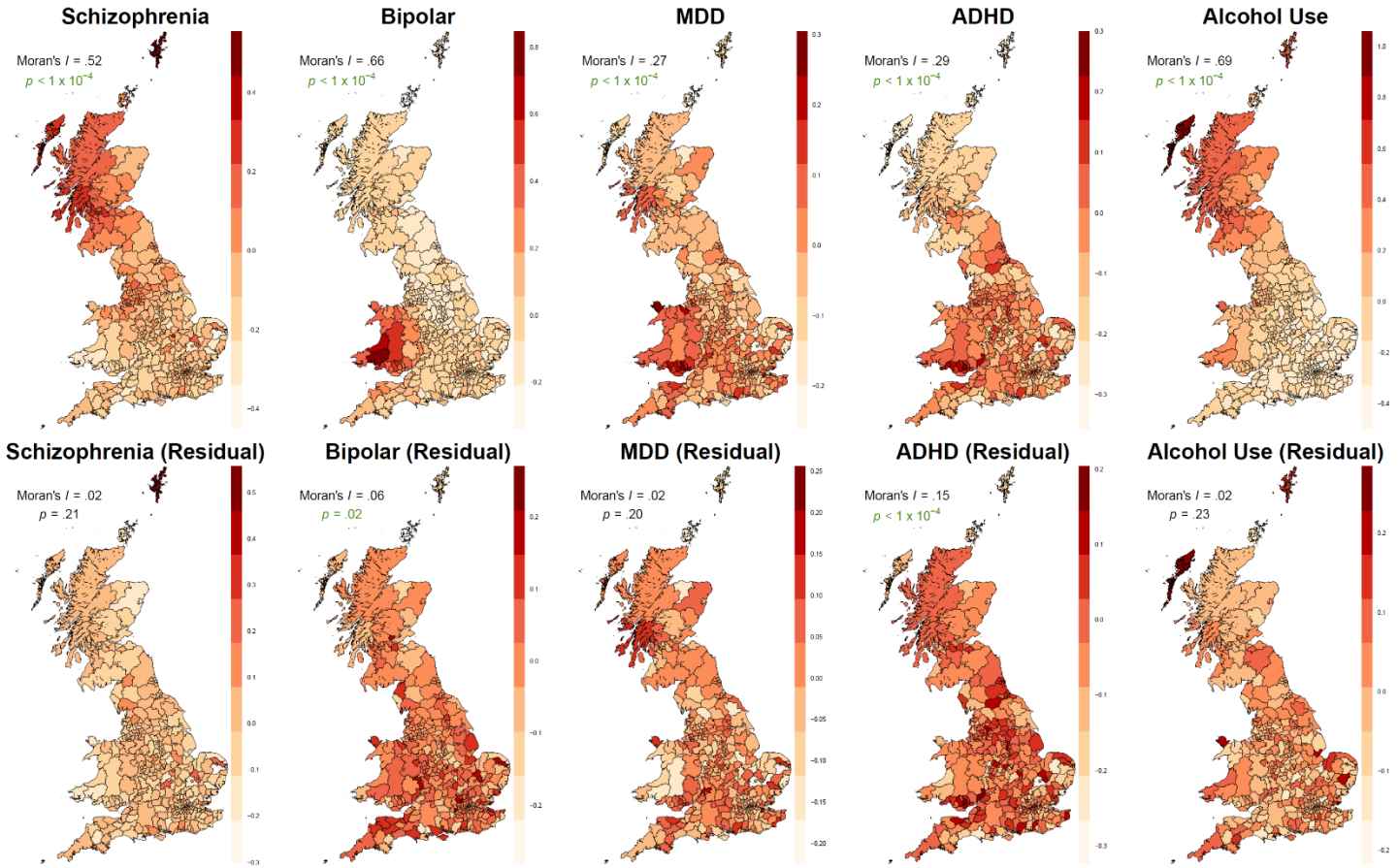
David Hugh-Jones [a,*,1], Karin J.H. Verweij [b,1], Beate St. Pourcain [c], Abdel Abdellaoui [b,*]

[a] Department of Economics, University of East Anglia, Research Park, Courtyard B, Norwich NR4 7TJ Norwich, England, United Kingdom
[b] Department of Biological Psychology, VU University, van der Boechorstraat 1, 1081 BT Amsterdam, The Netherlands
[c] Max Planck Institute for Psycholinguistics, Wundtlaan 1, 6525 XD Nijmegen, The Netherlands

Genetic evidence of assortative mating in humans

Matthew R. Robinson[1*], Aaron Kleinman[2], Mariaelisa Graff[3], Anna A. E. Vinkhuyzen[1], David Couper[4], Michael B. Miller[5], Wouter J. Peyrot[6], Abdel Abdellaoui[7], Brendan P. Zietsch[8], Ilja M. Nolte[9], Jana V. van Vliet-Ostaptchouk[9,10], Harold Snieder[9], The LifeLines Cohort Study[†], Genetic Investigation of Anthropometric Traits (GIANT) consortium[‡], Sarah E. Medland[11], Nicholas G. Martin[11], Patrik K. E. Magnusson[12], William G. Iacono[5], Matt McGue[5], Kari E. North[3,13], Jian Yang[1,14] and Peter M. Visscher[1,14*]

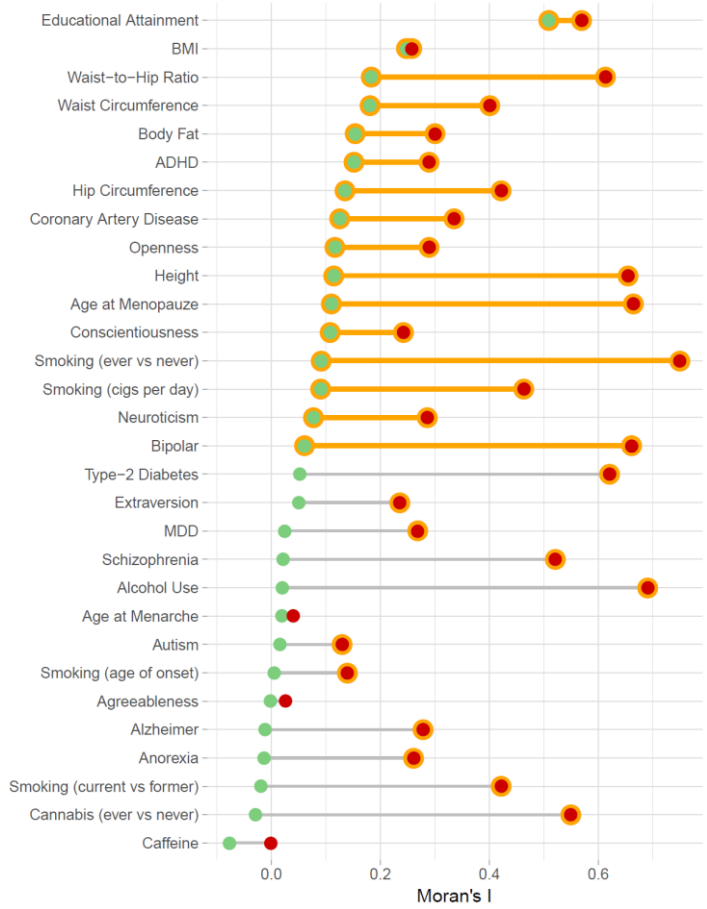
Polygenic scores, before and after regressing out 100 PCs



GENETIC CONSEQUENCES OF SOCIAL STRATIFICATION IN GREAT BRITAIN

Abdel Abdellaoui[1,], David Hugh-Jones[2], Kathryn E. Kemper[3], Yan Holtz[3], Michel G. Nivard[4], Laura Veul[1], Loic Yengo[3], Brendan P. Zietsch[5], Timothy M. Frayling[6], Naomi Wray[3,7], Jian Yang[3,7], Karin J.H. Verweij[1], Peter M. Visscher[3,7,*]*

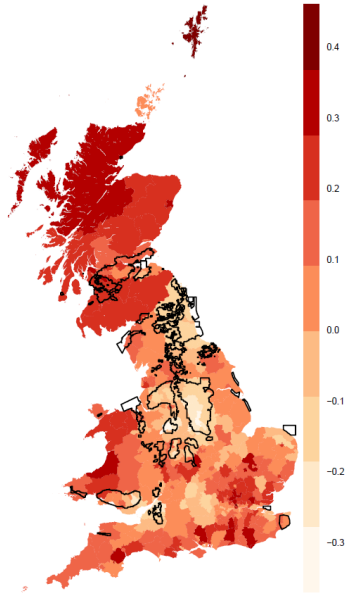
Spatial autocorrelation (i.e., geographic clustering) of 30 polygenic scores



- Uncorrected for PCs
- Corrected for 100 PCs

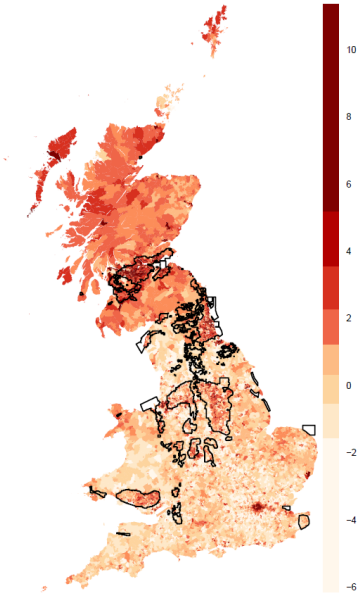
GENETIC CONSEQUENCES OF SOCIAL STRATIFICATION IN GREAT BRITAIN

Abdel Abdellaoui[1,], David Hugh-Jones[2], Kathryn E. Kemper[3], Yan Holtz[3], Michel G. Nivard[4], Laura Veul[1], Loic Yengo[3], Brendan P. Zietsch[5], Timothy M. Frayling[6], Naomi Wray[3,7], Jian Yang[3,7], Karin J.H. Verweij[1], Peter M. Visscher[3,7,*]*

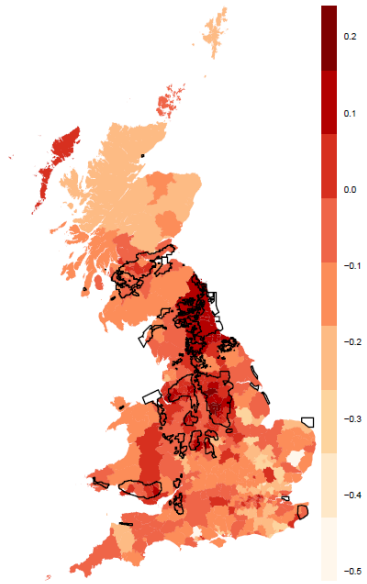


Educational Attainment Polygenic Score

(*EA3, without British cohorts*)



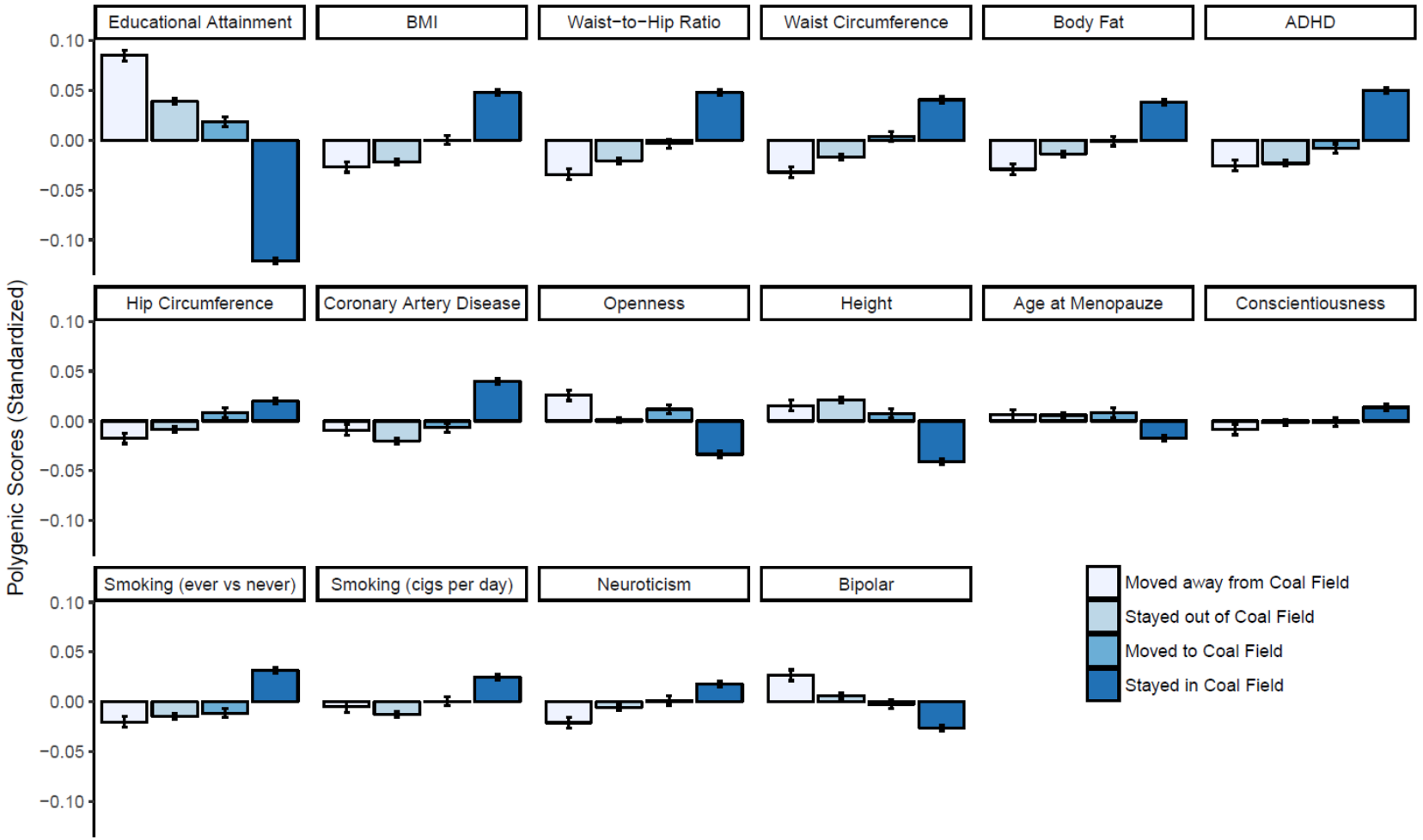
Townsend Index



Overall Health (phenotypic)

GENETIC CONSEQUENCES OF SOCIAL STRATIFICATION IN GREAT BRITAIN

Abdel Abdellaoui[1,], David Hugh-Jones[2], Kathryn E. Kemper[3], Yan Holtz[3], Michel G. Nivard[4], Laura Veul[1], Loic Yengo[3], Brendan P. Zietsch[5], Timothy M. Frayling[6], Naomi Wray[3,7], Jian Yang[3,7], Karin J.H. Verweij[1], Peter M. Visscher[3,7,*]*



GENETIC CONSEQUENCES OF SOCIAL STRATIFICATION IN GREAT BRITAIN

Abdel Abdellaoui[1,], David Hugh-Jones[2], Kathryn E. Kemper[3], Yan Holtz[3], Michel G. Nivard[4], Laura Veul[1], Loic Yengo[3], Brendan P. Zietsch[5], Timothy M. Frayling[6], Naomi Wray[3,7], Jian Yang[3,7], Karin J.H. Verweij[1], Peter M. Visscher[3,7,*]*

BEHAVIOR ⟷ GENETICS

Migration

Mate Choice

a.abdellaoui@amc.nl

dr_appie

KATRINA GRASBY

DAVID EVANS

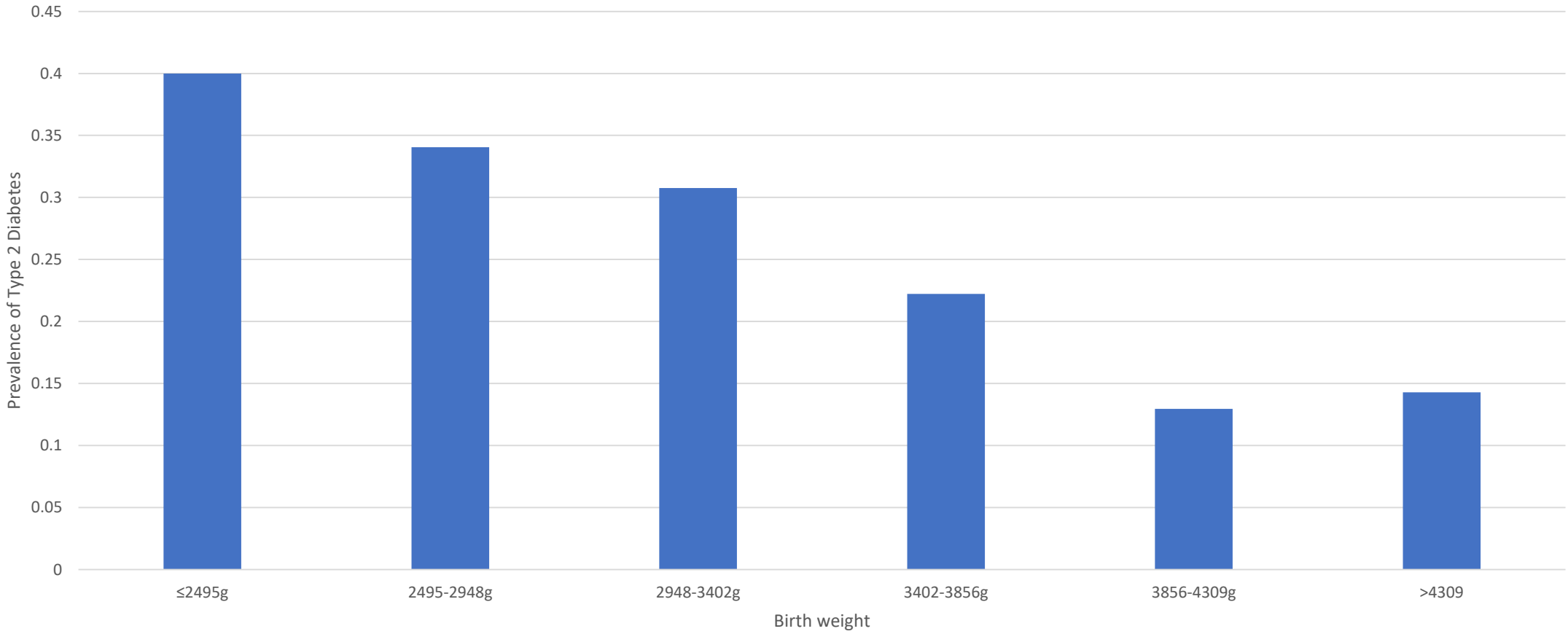
Using Genetics to Investigate the Developmental Origins of Health and Disease

David Evans

University of Queensland

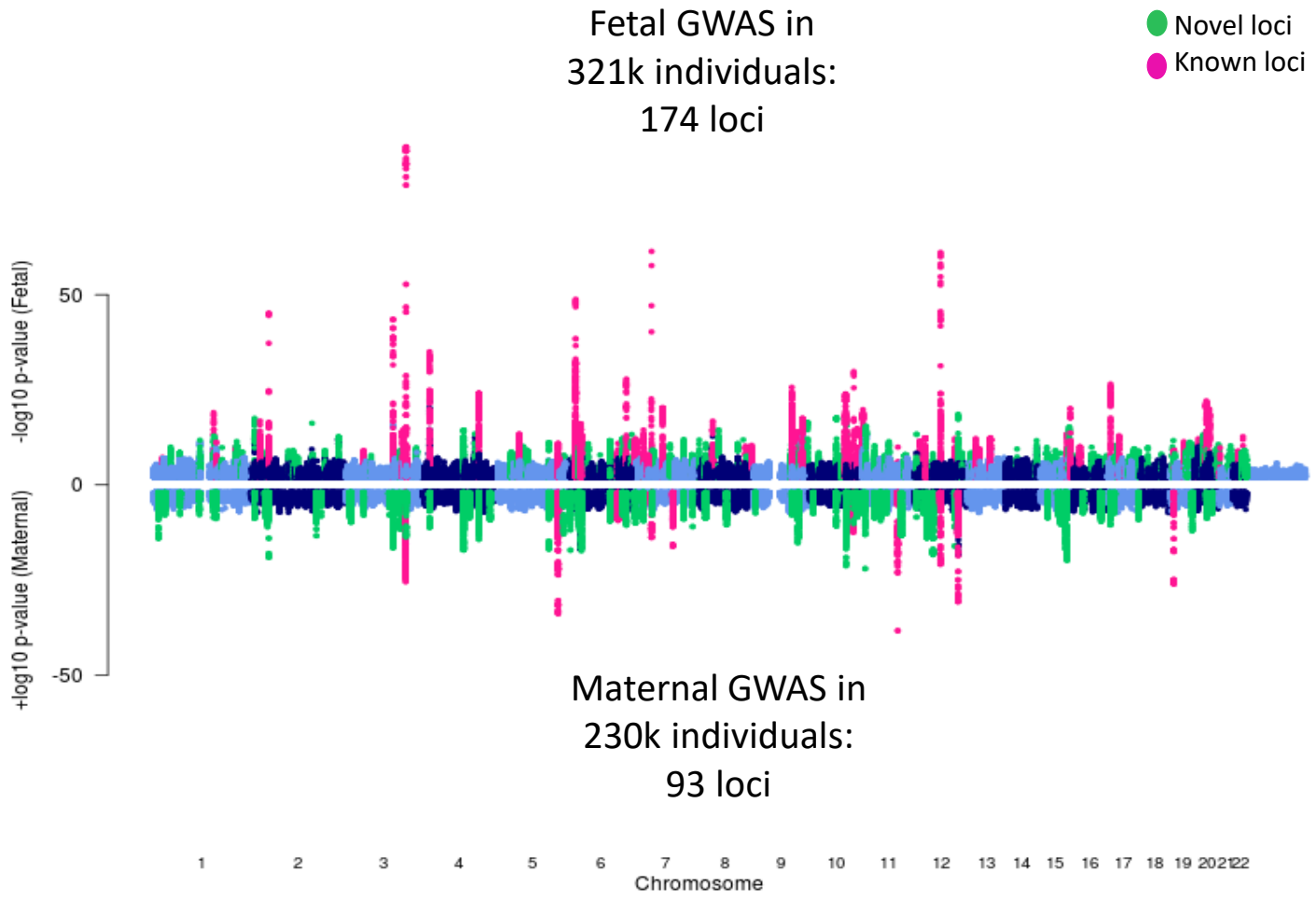
University of Bristol

Prevalence of Impaired Glucose Tolerance or T2D in 64 year old men in the UK



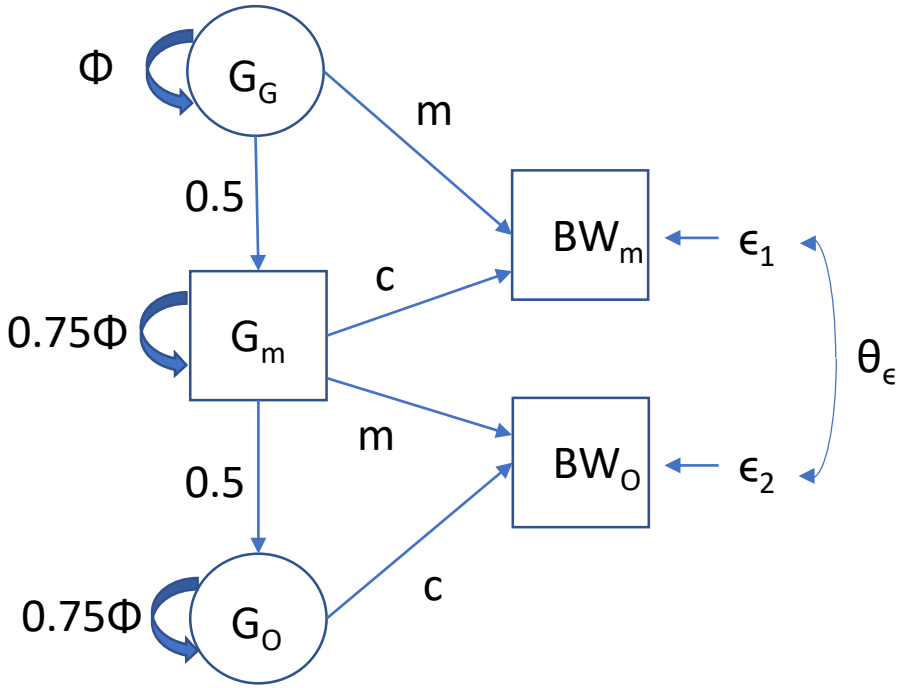
Hales et al. (1991)

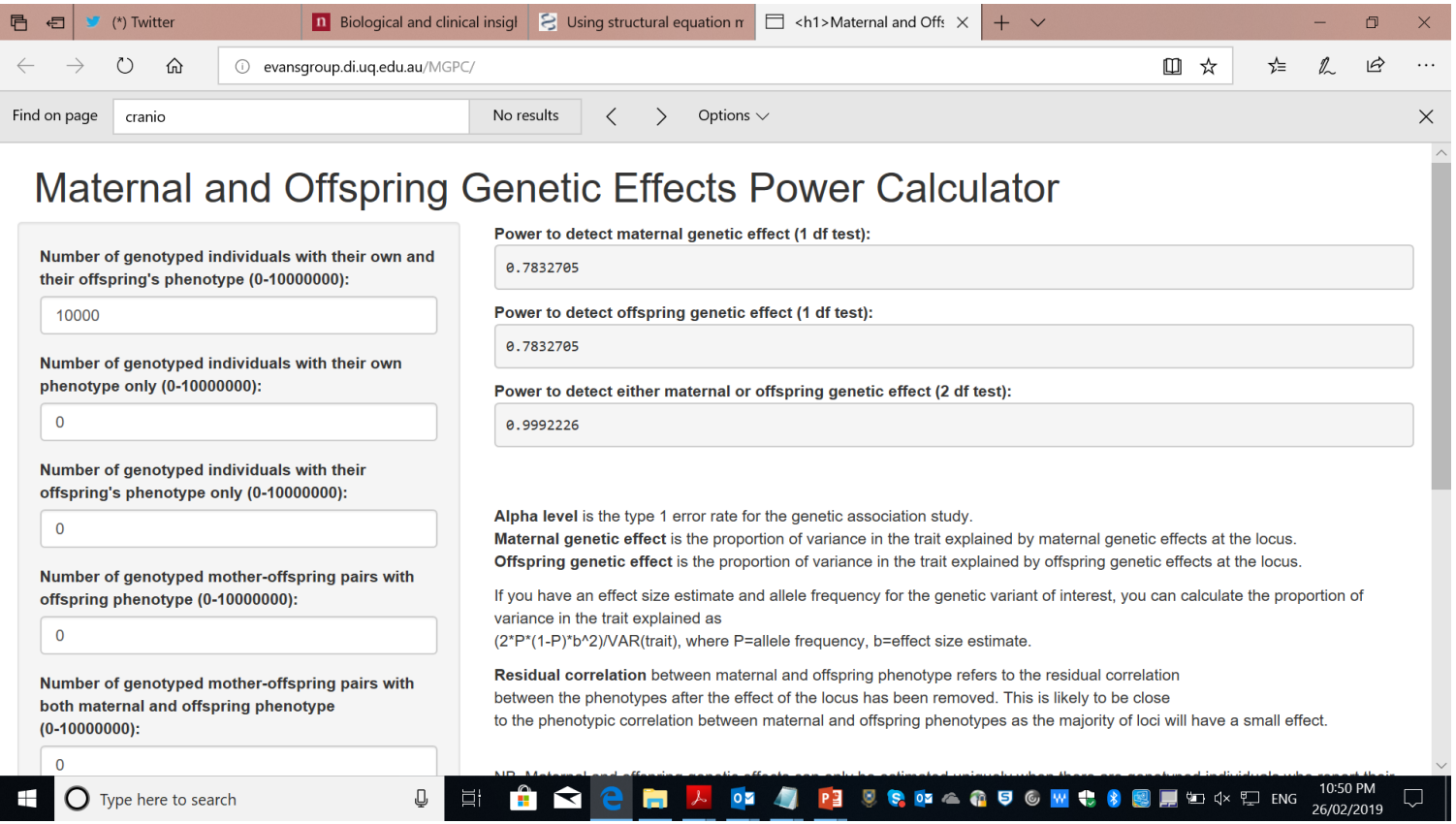
GWAS Analysis of Birthweight in UKBB and EGG



- Birthweight GWAS reflects a mixture of maternal and fetal genetic effects
- Unrelated individuals*

Disentangling Mother and Child Effects on Birth Weight





Behavior Genetics
https://doi.org/10.1007/s10519-018-9944-9

ORIGINAL RESEARCH

Calculating Power to Detect Maternal and Offspring Genetic Effects in Genetic Association Studies

Gunn-Helen Moen[1,2] · Gibran Hemani[3,4] · Nicole M. Warrington[5] · David M. Evans[3,4,5]

Received: 21 August 2018 / Accepted: 11 December 2018

Abstract
Offspring outcomes are a function of maternal genetics operating on the intrauterine and postnatal environment, offspring genetics and environmental factors. Partitioning genetic effects into maternal and offspring components requires genotyped mother–offspring pairs or genotyped individuals with phenotypic information on themselves and their offspring. We performed asymptotic power calculations and data simulations to estimate power to detect maternal and offspring genetic effects under a range of different study designs and models. We also developed the "Maternal and offspring Genetic effects Power Calculator" (M-GPC), an online utility which allows users to estimate the power to detect maternal and offspring genetic effects in their own studies. We find that approximately 50,000 genotyped mother–offspring pairs will be required to detect realistically sized maternal or offspring genetic effects (> 0.1% variance explained) with appreciable power (power > 90%, $\alpha = 5 \times 10^{-8}$, two degree of freedom test), whereas greater than 10,000 pairs will be required to determine whether known genetic loci have maternal and/or offspring genetic effects (power > 78%, $\alpha = 0.05$). The structural equation modelling framework espoused in this manuscript provides a natural method of combining different data structures including those present in large scale biobanks in order to maximize power to detect maternal and offspring genetic effects. We conclude that the sample sizes required to detect maternal or offspring genetic effects that explain realistic proportions of the trait variance with appreciable power are achievable and within the range of current research consortia.

Keywords Genetic association · GWAS · Maternal effects · Offspring effects · Fetal effects · Power

Introduction

Offspring phenotypes, including perinatal outcomes such as birthweight, length at birth and other anthropometric measurements, are thought to be a product of maternal genetics, offspring genetics and environmental factors. In this manuscript, we define maternal genetic effects as the causal influence of the maternal genotype on the offspring phenotype (Wolf and Wade 2009). Maternal genetic effects arise when the mother makes a contribution to the phenotype of her progeny over and above that which results from the genes she contributes to the zygote (Mather and Jinks 1982). Thus, our definition focuses on the effect of the maternal genome and is distinct from mitochondrial inheritance and genetic effects due to imprinting. In contrast, we define offspring genetic effects as those genetic effects on the offspring's phenotype that are directly mediated by the offspring's genome, which is comprised of 50% of alleles inherited from their mother and 50% from their father.

Edited by Tinca Polderman.

Nicole M Warrington and David M Evans joint senior authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10519-018-9944-9) contains supplementary material, which is available to authorized users.

✉ Gunn-Helen Moen
g.h.o.moen@studmed.uio.no

[1] Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Postbox 4959, Nydalen, 0424 Oslo, Norway

[2] Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

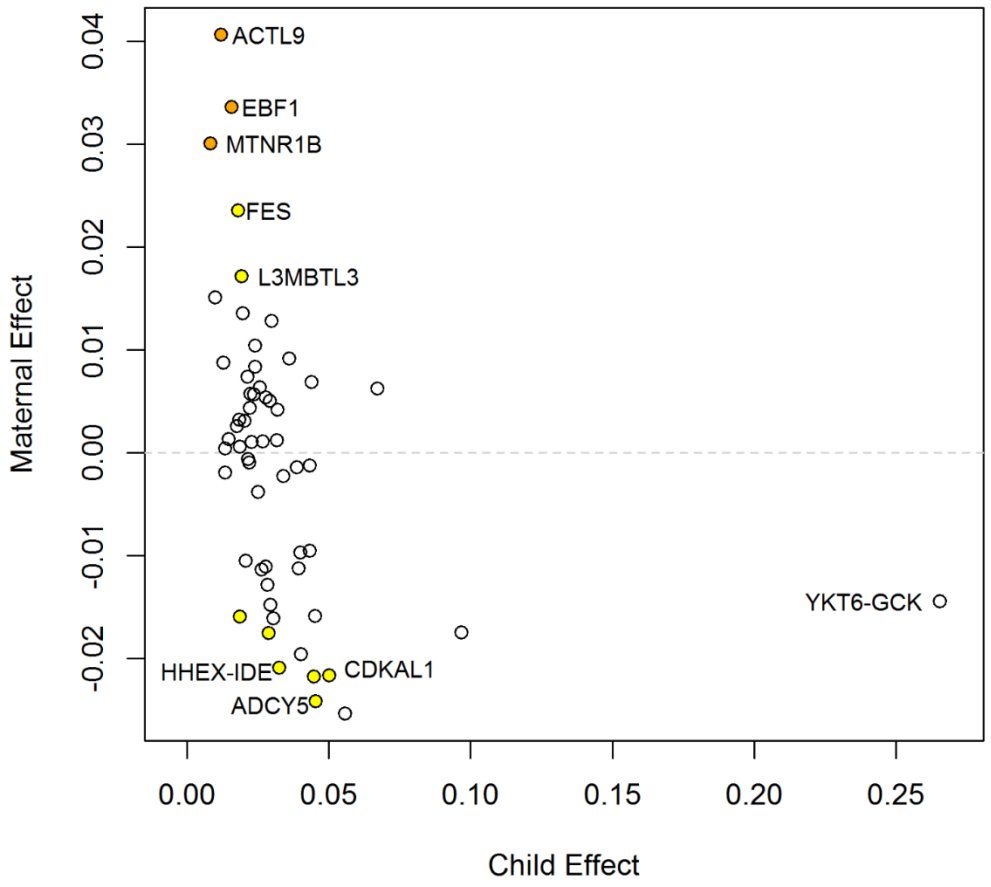
[3] Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK

[4] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

[5] Translational Research Institute, University of Queensland Diamantina Institute, Brisbane, Australia

Published online: 02 January 2019

Maternal vs Fetal Effects for Birth Weight SNPs



International Journal of Epidemiology, 2018, 1229–1241
doi: 10.1093/ije/dyy015
Advance Access Publication Date: 13 February 2018
Original article

Methods

Using structural equation modelling to jointly estimate maternal and fetal effects on birthweight in the UK Biobank

Nicole M Warrington,[1] Rachel M Freathy,[2,3] Michael C Neale[4] and David M Evans[1,3,5]*

[1]University of Queensland Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, QLD, Australia, [2]Institute of Biomedical and Clinical Science, University of Exeter Medical School, University of Exeter, Royal Devon and Exeter Hospital, Exeter, UK, [3]Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK, [4]Virginia Institute for Psychiatric and Behavioral Genetics, Departments of Psychiatry and Human & Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA, [5]School of Social and Community Medicine, University of Bristol, Bristol, UK

*Corresponding author. MRC Integrative Epidemiology Unit, University of Bristol, Oakfield House, Oakfield Grove, Clifton, BS82BN, UK. E-mail: dave.evans@bristol.ac.uk

Editorial decision 16 January 2018; Accepted 25 January 2018

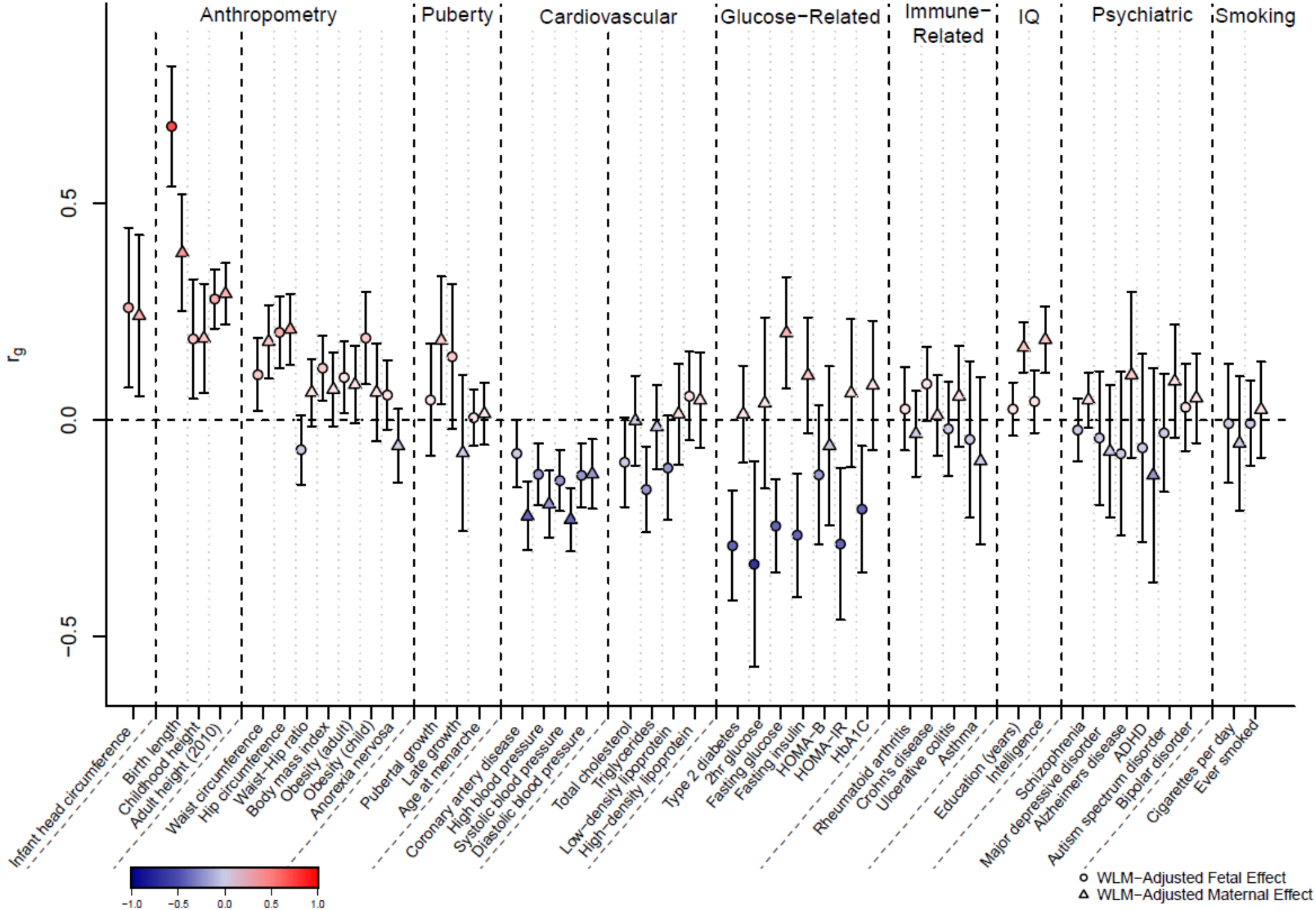
Abstract

Background: To date, 60 genetic variants have been robustly associated with birthweight. It is unclear whether these associations represent the effect of an individual's own genotype on their birthweight, their mother's genotype, or both.

Methods: We demonstrate how structural equation modelling (SEM) can be used to estimate both maternal and fetal effects when phenotype information is present for individuals in two generations and genotype information is available on the older individual. We conduct an extensive simulation study to assess the bias, power and type 1 error rates of the SEM and also apply the SEM to birthweight data in the UK Biobank study.

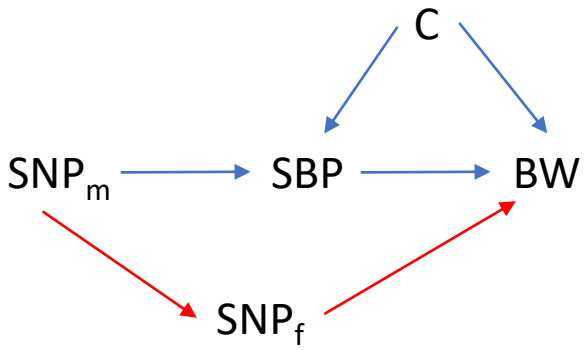
Results: Unlike simple regression models, our approach is unbiased when there is both a maternal and a fetal effect. The method can be used when either the individual's own phenotype or the phenotype of their offspring is not available, and allows the inclusion of summary statistics from additional cohorts where raw data cannot be shared. We show that the type 1 error rate of the method is appropriate, and that there is substantial statistical power to detect a genetic variant that has a moderate effect on the phenotype and reasonable power to detect whether it is a fetal and/or a maternal effect. We also identify a subset of birthweight-associated single nucleotide polymorphisms (SNPs) that have opposing maternal and fetal effects in the UK Biobank.

Conclusions: Our results show that SEM can be used to estimate parameters that would be difficult to quantify using simple statistical methods alone.

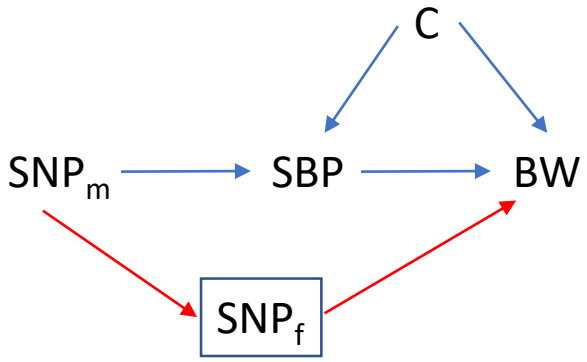

Anthropometry
Puberty
Cardiovascular
Glucose−Related
Immune−Related
IQ
Psychiatric
Smoking
r_g
0.5
0.0
−0.5
Infant head circumference
Birth length
Childhood height
Adult height (2010)
Waist circumference
Hip circumference
Waist−Hip ratio
Body mass index
Obesity (adult)
Obesity (child)
Anorexia nervosa
Pubertal growth
Late growth
Age at menarche
Coronary artery disease
High blood pressure
Systolic blood pressure
Diastolic blood pressure
Total cholesterol
Triglycerides
Low−density lipoprotein
High−density lipoprotein
Type 2 diabetes
2hr glucose
Fasting glucose
Fasting insulin
HOMA−B
HOMA−IR
HbA1C
Rheumatoid arthritis
Crohn's disease
Ulcerative colitis
Asthma
Education (years)
Intelligence
Schizophrenia
Major depressive disorder
Alzheimers disease
ADHD
Autism spectrum disorder
Bipolar disorder
Cigarettes per day
Ever smoked
−1.0
−0.5
0.0
0.5
1.0
WLM−Adjusted Fetal Effect
WLM−Adjusted Maternal Effect

Estimating Causal Effects of Maternal SBP on Offspring Birthweight

(1)



(2)



(3) (i) SNP$_m$ → SBP

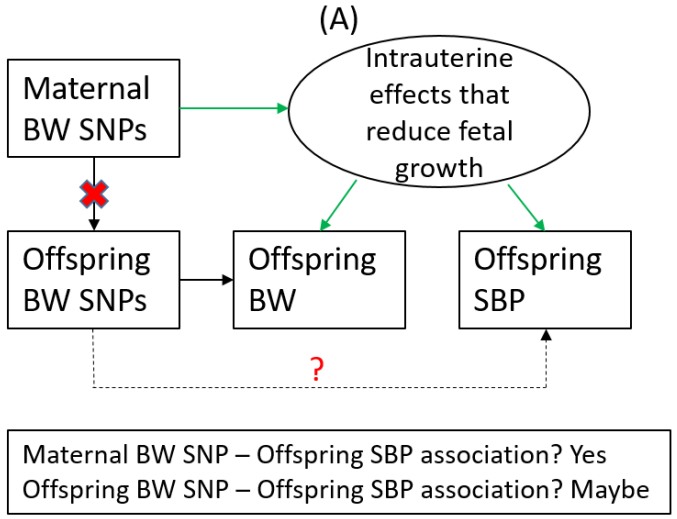
(ii) SNP$_m$ → BW

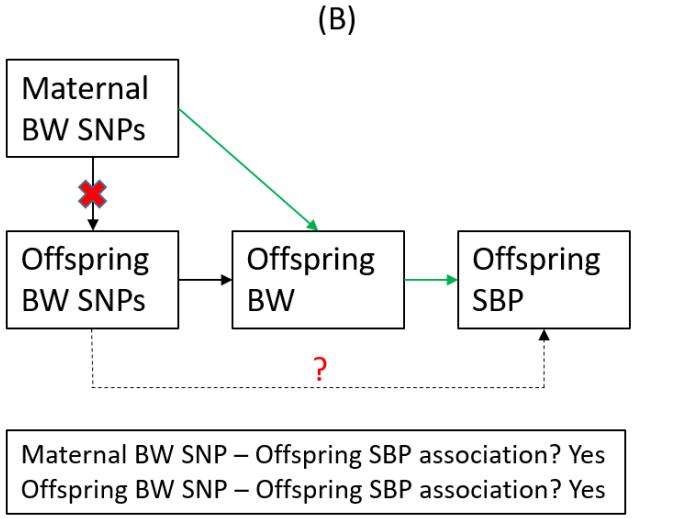
SNP$_f$ → BW

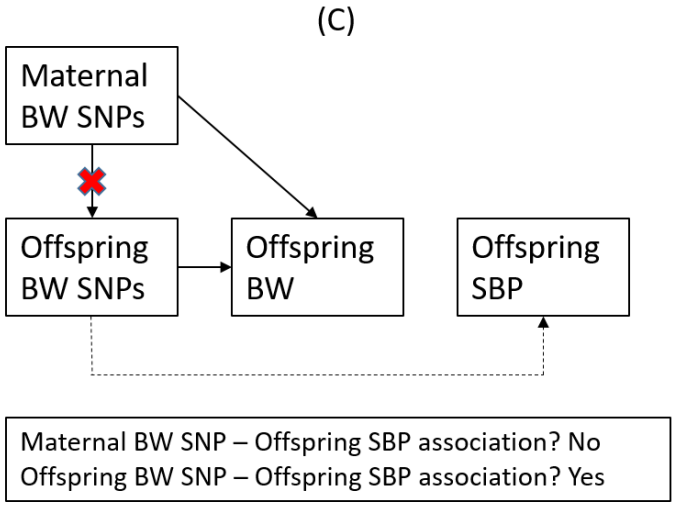
Maternal Exposure phenotype	Outcome	Number of SNPs	Beta	SE	P-value
Systolic blood pressure (mmHg)	Maternal effect on BW (unconditional)	68	-0.0158	0.0022	6.13E-10
	Fetal effect on BW (unconditional)	68	-0.0082	0.0020	1.43E-04
	Maternal effect on BW (adjusted)	68	-0.0148	0.0021	1.98E-09
	Fetal effect on BW (adjusted)	68	-0.0008	0.0019	6.70E-01

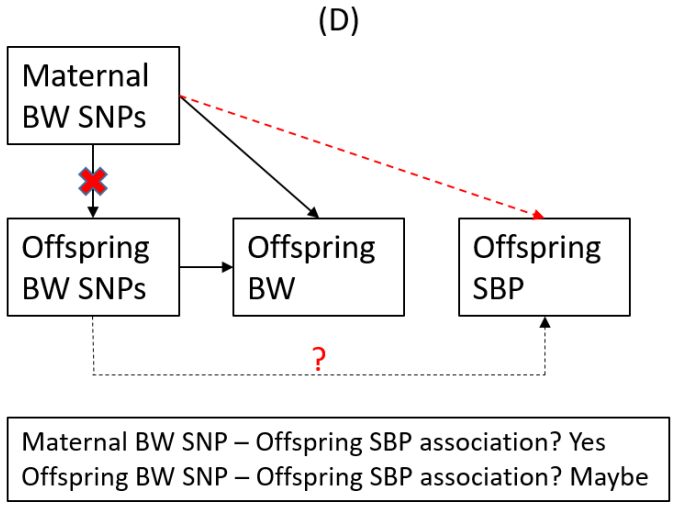
- No confounding from offspring genotype
- Very large sample sizes

Using Maternal Effects to Investigate the Effect of Birth Weight on Later Life Outcomes









Relationship between maternal and child SNPs, offspring birthweight (BW) and systolic blood pressure (SBP). Each model provides an explanation for the negative genetic correlation between birthweight and SBP observed in Horikoshi et al (2016). SNPs may exert maternal and/or fetal genetic effects on birthweight. A red cross indicates a blocked path due to conditioning on offspring/maternal genotype. The dashed black path represents the possibility of genetic pleiotropy mediated through the fetal genome. The dashed red path represents possible postnatal effects of maternal SNPs.

International Journal of Epidemiology, 2019, 1–15
doi: 10.1093/ije/dyz019
Original article

Original article

Elucidating the role of maternal environmental exposures on offspring health and disease using two-sample Mendelian randomization

David M Evans [1,2,3]* Gunn-Helen Moen,[4,5] Liang-Dar Hwang,[1] Debbie A Lawlor[2,3,6] and Nicole M Warrington[1]

[1]University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Queensland, Australia, [2]Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK, [3]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK, [4]Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway, [5]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway and [6]Bristol NIHR Biomedical Research Centre, Bristol, UK

*Corresponding author. University of Queensland Diamantina Institute, University of Queensland, Queensland, QLD 4102, Australia. E-mail: d.evans1@uq.edu.au.

Editorial decision 23 January 2019; Accepted 8 February 2019

Abstract

Background: There is considerable interest in estimating the causal effect of a range of maternal environmental exposures on offspring health-related outcomes. Previous attempts to do this using Mendelian randomization methodologies have been hampered by the paucity of epidemiological cohorts with large numbers of genotyped mother–offspring pairs.

Methods: We describe a new statistical model that we have created which can be used to estimate the effect of maternal genotypes on offspring outcomes conditional on offspring genotype, using both individual-level and summary-results data, even when the extent of sample overlap is unknown.

Results: We describe how the estimates obtained from our method can subsequently be used in large-scale two-sample Mendelian randomization studies to investigate the causal effect of maternal environmental exposures on offspring outcomes. This includes studies that aim to assess the causal effect of *in utero* exposures related to fetal growth restriction on future risk of disease in offspring. We illustrate our framework using examples related to offspring birthweight and cardiometabolic disease, although the general principles we espouse are relevant for many other offspring phenotypes.

Conclusions: We advocate for the establishment of large-scale international genetics consortia that are focused on the identification of maternal genetic effects and committed to the public sharing of genome-wide summary-results data from such efforts. This information will facilitate the application of powerful two-sample Mendelian randomization studies of maternal exposures and offspring outcomes.

LETTER

doi:10.1038/nature19806

Genome-wide associations for birth weight and correlations with adult disease

Momoko Horikoshi[1,2]*, Robin N. Beaumont[3]*, Felix R. Day[4]*, Nicole M. Warrington[5,6]*, Marjolein N. Kooijman[7,8,9]*, Juan Fernandez-Tajes[3]*, Bjarke Feenstra[10], Natalie R. van Zuydam[1,2], Kyle J. Gaulton[1,11], Niels Grarup[12], Jonathan P. Bradfield[13], David P. Strachan[14], Ruifang Li-Gao[15], Tarunveer S. Ahluwalia[12,16,17], Eskil Kreiner[16], Rico Rueedi[18,19], Leo-Pekka Lyytikäinen[20,21], Diana L. Cousminer[22,23,24], Ying Wu[25], Elisabeth Thiering[26,27], Carol A. Wang[6], Christian T. Have[12], Jouke-Jan Hottenga[28], Natalia Vilor-Tejedor[29,30,31], Peter K. Joshi[32], Eileen Tai Hui Boh[33], Ioanna Ntalla[34,35], Niina Pitkänen[36], Anubha Mahajan[1], Elisabeth M. van Leeuwen[8], Raimo Joro[37], Vasiliki Lagou[1,38,39], Michael Nodzenski[40], Louise A. Diver[41], Krina T. Zondervan[1,42], Mariona Bustamante[29,30,31,43], Pedro Marques-Vidal[44], Josep M. Mercader[45], Amanda J. Bennett[2], Nilufer Rahmioglu[1], Dale R. Nyholt[46], Ronald C. W. Ma[47,48,49], Claudia H. T. Tam[47], Wing Hung Tam[50], CHARGE Consortium Hematology Working Group†, Santhi K. Ganesh[51], Frank J. A. van Rooij[8], Samuel E. Jones[3], Po-Ru Loh[52,53], Katherine S. Ruth[3], Marcus A. Tuke[3], Jessica Tyrrell[3,54], Andrew R. Wood[3], Hanieh Yaghootkar[3], Denise M. Scholtens[40], Lavinia Paternoster[55,56], Inga Prokopenko[1,57], Peter Kovacs[58], Mustafa Atalay[37], Sara M. Willems[8], Kalliope Panoutsopoulou[59], Xu Wang[23], Lisbeth Carstensen[10], Frank Geller[10], Katharina E. Schraut[32], Mario Murcia[31,60], Catharina E. M. van Beijsterveldt[28], Gonneke Willemsen[28], Emil V. R. Appel[12], Cilius E. Fonvig[22,61], Caecilie Trier[22,61], Carla M. T. Tiesler[26,27], Marie Standl[26], Zoltán Kutalik[19,62], Silvia Bonàs-Guarch[45], David M. Hougaard[63,64], Friman Sánchez[45,65], David Torrents[45,66], Johannes Waage[16], Mads V. Hollegaard[63,64]‡, Hugoline G. de Haan[15], Frits R. Rosendaal[15], Carolina Medina-Gomez[7,8,67], Susan M. Ring[55,56], Gibran Hemani[55,56], George McMahon[56], Neil R. Robertson[1,2], Christopher J. Groves[3], Claudia Langenberg[4], Jian'an Luan[4], Robert A. Scott[4], Jing Hua Zhao[4], Frank D. Mentch[13], Scott M. MacKenzie[41], Rebecca M. Reynolds[68], Early Growth Genetics (EGG) Consortium†, William L. Lowe Jr[69], Anke Tönjes[70], Michael Stumvoll[38,39], Virpi Lindi[27], Timo A. Lakka[37,71,72], Cornelia M. van Duijn[8], Wieland Kiess[73], Antje Körner[38,73], Thorkild I. A. Sørensen[55,56,74,75], Harri Niinikoski[76,77], Katja Pahkala[36,78], Olli T. Raitakari[36,79], Eleftheria Zeggini[59], George V. Dedoussis[35], Yik-Ying Teo[33,80,81], Seang-Mei Saw[33,82], Mads Melbye[10,83,84], Harry Campbell[32], James F. Wilson[32,85], Martine Vrijheid[29,30,31], Eco J. C. N. de Geus[28,86], Dorret I. Boomsma[28], Haja N. Kadarmideen[87], Jens-Christian Holm[12,61], Torben Hansen[12], Sylvain Sebert[57,88,89], Andrew T. Hattersley[3], Lawrence J. Beilin[90], John P. Newnham[4], Craig E. Pennell[6], Joachim Heinrich[26,91], Linda S. Adair[92], Judith B. Borja[93,94], Karen L. Mohlke[25], Johan G. Eriksson[95,96,97], Elisabeth Widén[32], Mika Kähönen[98,99], Jorma S. Viikari[100,101], Terho Lehtimäki[20,21], Peter Vollenweider[44], Klaus Bønnelykke[16], Hans Bisgaard[16], Dennis O. Mook-Kanamori[15,102,103], Albert Hofman[7,8], Fernando Rivadeneira[7,8,67], André G. Uitterlinden[7,8,67], Charlotta Pisinger[104], Ohul Pedersen[12], Christine Power[105], Elina Hyppönen[105,106,107], Nicholas J. Wareham[4], Hakon Hakonarson[13,23,108], Eleanor Davies[41], Brian R. Walker[68], Vincent W. V. Jaddoe[7,8,9], Marjo-Riitta Järvelin[88,89,109,110], Struan F. A. Grant[13,23,108,111], Allan A. Vaag[83,112,113], Debbie A. Lawlor[55,56], Timothy M. Frayling[3], George Davey Smith[55,56], Andrew P. Morris[1,114,115]§, Ken K. Ong[4,116]§, Janine F. Felix[7,8,9]§, Nicholas J. Timpson[55,56]§, John R. B. Perry[4]§, David M. Evans[5,55,56]§, Mark I. McCarthy[1,2,117]§ & Rachel M. Freathy[3,55]§

A list of affiliations appears in the online version of this paper.

Birth weight (BW) has been shown to be influenced by both fetal and maternal factors and in observational studies is reproducibly associated with future risk of adult metabolic diseases including type 2 diabetes (T2D) and cardiovascular disease[1]. These life-course associations have often been attributed to the impact of an adverse early life environment. Here, we performed a multi-ancestry genome-wide association study (GWAS) meta-analysis of BW in 153,781 individuals, identifying 60 loci where fetal genotype was associated with BW ($P < 5 \times 10^{-8}$). Overall, approximately 15% of variance in BW was captured by assays of fetal genetic variation. Using genetic association alone, we found strong inverse genetic correlations between BW and systolic blood pressure ($R_g = -0.22$, $P = 5.5 \times 10^{-13}$), T2D ($R_g = -0.27$, $P = 1.1 \times 10^{-6}$) and coronary artery disease ($R_g = -0.30$, $P = 6.5 \times 10^{-9}$). In addition, using large-cohort datasets, we demonstrated that genetic factors were the major contributor to the negative covariance between BW and future cardiometabolic risk. Pathway analyses indicated that the protein products of genes within BW-associated regions were enriched for diverse processes including insulin signalling, glucose homeostasis, glycogen biosynthesis and chromatin remodelling. There was also enrichment of associations with BW in known imprinted regions ($P = 1.9 \times 10^{-4}$). We demonstrate that life-course associations between early growth phenotypes and adult cardiometabolic disease are in part the result of shared genetic effects and identify some of the pathways through which these causal genetic effects are mediated.

We combined GWAS data for BW from 153,781 individuals representing multiple ancestries from 37 studies across three components (Extended Data Fig. 1 and Supplementary Table 1): (i) 75,891 individuals of European ancestry from 30 studies; (ii) 67,786 individuals of European ancestry from the UK Biobank; and (iii) 10,104 individuals of diverse ancestries (African American, Chinese, Filipino, Surinamese, Turkish and Moroccan) from six studies. Within each study, BW was *Z*-score transformed separately in males and females after excluding non-singletons and premature births and adjusting for gestational age where available. Genotypes were imputed using reference panels from the 1000 Genomes (1000G) Project[2] or combined 1000G and UK10K projects[3] (Supplementary Table 2). We performed quality control assessments to confirm that the distribution of BW was consistent across studies, irrespective of the data collection protocol, and confirmed that self-reported BW in the UK Biobank showed genetic and phenotypic associations consistent with those seen for measured BW in other studies[4] (Methods).

We identified 60 loci (of which 59 were autosomal) associated with BW at genome-wide significance ($P < 5 \times 10^{-8}$) in either the European

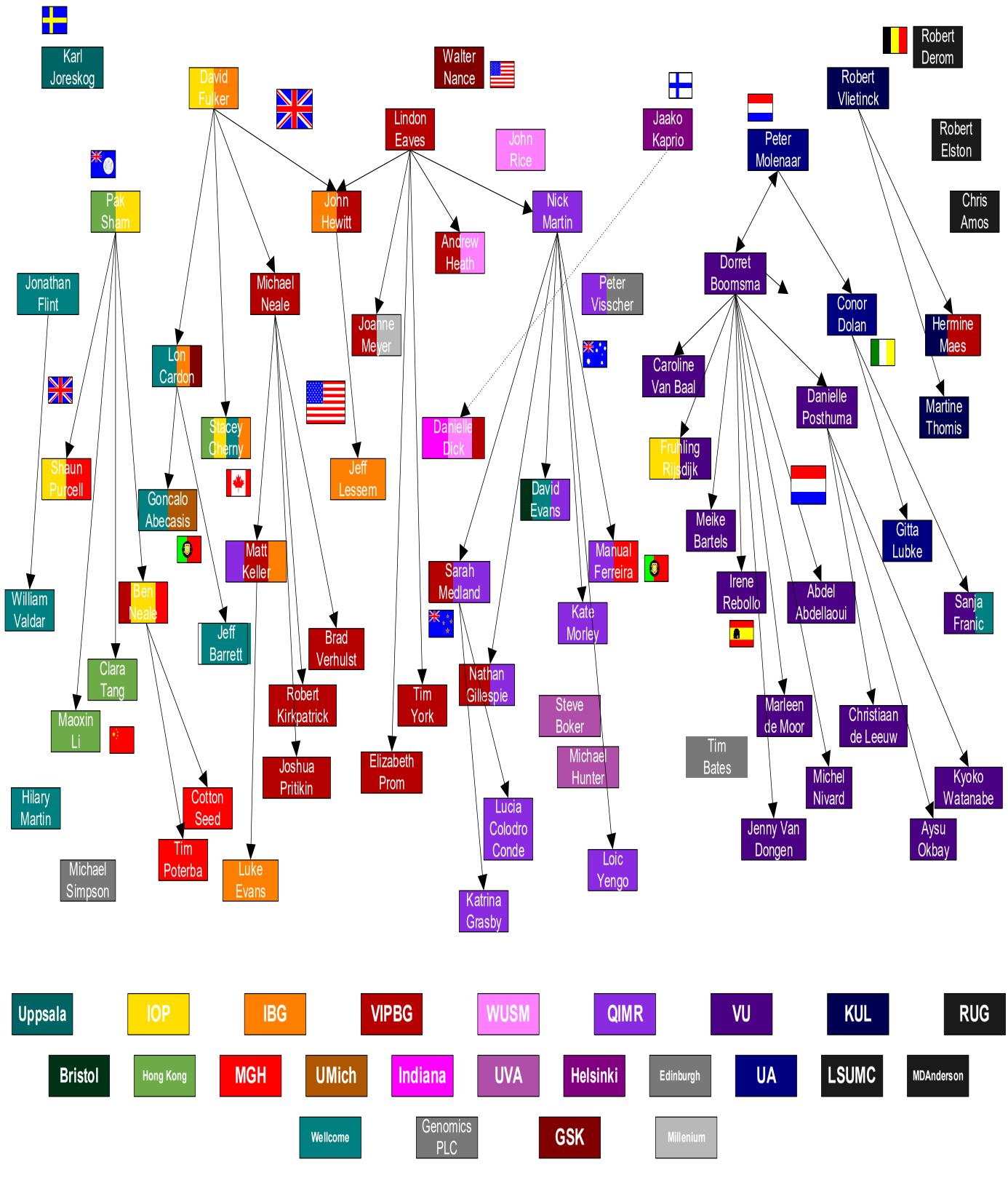
Title:

Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors

Authors and affiliations:

Nicole M Warrington[1,a], Robin N Beaumont[2,a], Momoko Horikoshi[3,4,5,a], Felix R Day[6,a], Øyvind Helgeland[7,8,9,a], Charles Laurin[10,11], Jonas Bacelis[12], Shouneng Peng[13,14], Ke Hao[13,14], Bjarke Feenstra[15], Andrew R Wood[2], Anubha Mahajan[3,4], Jessica Tyrrell[2,16], Neil R Robertson[3,4], N William Rayner[3,4,17], Zhen Qiao[1], Gunn-Helen Øiseth Moen[18,19], Marc Vaudel[8], Carmen J Marsit[20], Jia Chen[21], Michael Nodzenski[22], Theresia M Schnurr[23], Mohammad H Zafarmand[24,25], Jonathan P Bradfield[26,27], Niels Grarup[23], Marjolein N Kooijman[28,29,30], Ruifang Li-Gao[31], Frank Geller[15], Tarunveer S Ahluwalia[23,32,33], Lavinia Paternoster[10], Rico Rueedi[34,35], Ville Huikari[36], Jouke-Jan Hottenga[37,38,39], Leo-Pekka Lyytikäinen[40], Alana Cavadino[41,42], Sarah Metrustry[43], Diana L Cousminer[44,45], Ying Wu[46], Elisabeth Thiering[47,48], Carol A Wang[49], Christian T Have[23], Natalia Vilor-Tejedor[50,51], Peter K Joshi[52], Jodie N Painter[53], Ioanna Ntalla[54], Ronny Myhre[55], Niina Pitkänen[56], Elisabeth M van Leeuwen[29], Raimo Joro[57], Vasiliki Lagou[3,58,59], Rebecca C Richmond[10,11], Ana Espinosa[60,61,62,63], Sheila J Barton[64], Hazel M Inskip[64,65], John W Holloway[66], Loreto Santa-Marina[60,67,68], Xavier Estivill[69,70], Wei Ang[71], Julie A Marsh[71], Christoph Reichetzeder[72,73], Letizia Marullo[74], Berthold Hocher[72,75], Kathryn L Lunetta[76,77], Joanne M Murabito[77,78], Caroline L Relton[10,11,79], Manolis Kogevinas[60,61,62,63], Leda Chatzi[80], Catherine Allard[81], Luigi Bouchard[81,82,83], Marie-France Hivert[84,85,86], Ge Zhang[87,88,89], Louis J Muglia[87,88,89], Jani Heikkinen[90], Early Growth Genetics (EGG) Consortium[b], Camilla S Morgen[91], Antoine HC van Kampen[92,93], Barbera DC van Schaik[92], Frank D Mentch[26], Claudia Langenberg[6], Jian'an Luan[6], Robert A Scott[6], Jing Hua Zhao[6], Gibran Hemani[10,11], Susan M Ring[10,11], Amanda J Bennett[4], Kyle J Gaulton[3,94], Juan Fernandez-Tajes[3], Natalie R van Zuydam[3,4], Carolina Medina-Gomez[28,29,95], Hugoline G de Haan[31], Frits R Rosendaal[31], Zoltán Kutalik[34,96], Pedro Marques-Vidal[97], Shikta Das[42], Gonneke Willemsen[37,38,39], Hamdi Mbarek[37,38,39,98], Martina Müller-Nurasyid[99,100,101], Marie Standl[47], Emil V R Appel[23], Cilius E Fonvig[23,102,103], Caecilie Trier[23,102], Catharina EM van Beijsterveldt[38], Mario Murcia[60,104], Mariona Bustamante[60,61,62], Silvia Bonas-Guarch[105], David M Hougaard[106], Josep M Mercader[105,107,108], Allan Linneberg[109,110], Katharina E Schraut[52], Penelope A Lind[53], Sarah E Medland[53], Beverley M Shields[111], Bridget A Knight[111], Jin-Fang Chai[112], Kalliope Panoutsopoulou[17], Meike Bartels[37,38,39], Friman Sánchez[105,113], Jacob Stokholm[32], David Torrents[105,114], Rebecca K Vinding[32], Sara M Willems[29], Mustafa Atalay[57], Bo L Chawes[32], Peter Kovacs[115], Inga Prokopenko[3,116], Marcus A Tuke[2], Hanieh Yaghootkar[117], Katherine S Ruth[2], Samuel E Jones[2], Po-Ru Loh[118,119], Anna Murray[2], Michael N Weedon[2], Anke Tönjes[120], Michael Stumvoll[115,120], Kim F Michaelsen[121], Aino-Maija Eloranta[57], Timo A Lakka[57,122,123], Cornelia M van Duijn[29], Wieland Kiess[124], Antje Körner[115,124], Harri Niinikoski[125,126], Katja Pahkala[56,127], Olli T Raitakari[56,128], Bo Jacobsson[7,12], Eleftheria Zeggini[17], George V Dedoussis[129], Yik-Ying Teo[112,130,131], Seang-Mei Saw[112,132], Grant W Montgomery[53], Harry Campbell[52], James F Wilson[52,133], Tanja GM Vrijkotte[24], Martine Vrijheid[60,61,62], Eco JCN de Geus[37,38,39], M Geoffrey Hayes[134], Haja N Kadarmideen[135], Jens-Christian Holm[23,102], Lawrence J Beilin[136], Craig E Pennell[47], Joachim Heinrich[47,137], Linda S Adair[138], Judith B Borja[139,140], Karen L Mohlke[46], Johan G Eriksson[141,142,143], Elisabeth E Widén[90], Andrew T Hattersley[2,111], Tim D Spector[43], Mika Kähönen[144], Jorma S Viikari[145,146],

- Two year postdoctoral position
- One year postdoctoral position
- PhD position


Karl Joreskog
David Fulker
Walter Nance
Lindon Eaves
John Rice
Jaako Kaprio
Robert Derom
Robert Vlietinck
Robert Elston
Peter Molenaar
Chris Amos
Pak Sham
John Hewitt
Nick Martin
Andrew Heath
Jonathan Flint
Michael Neale
Peter Visscher
Dorret Boomsma
Conor Dolan
Hermine Maes
Joanne Meyer
Lon Cardon
Caroline Van Baal
Danielle Posthuma
Martine Thomis
Stacey Cherny
Danielle Dick
Fruhling Rijsdijk
Shaun Purcell
Jeff Lessem
David Evans
Meike Bartels
Gitta Lubke
Goncalo Abecasis
Manual Ferreira
Irene Rebollo
Abdel Abdellaoui
Sanja Franic
Matt Keller
Sarah Medland
William Valdar
Ben Neale
Kate Morley
Jeff Barrett
Brad Verhulst
Clara Tang
Nathan Gillespie
Marleen de Moor
Christiaan de Leeuw
Steve Boker
Robert Kirkpatrick
Tim York
Maoxin Li
Tim Bates
Michel Nivard
Kyoko Watanabe
Michael Hunter
Joshua Pritikin
Elizabeth Prom
Hilary Martin
Cotton Seed
Lucia Colodro Conde
Jenny Van Dongen
Aysu Okbay
Tim Poterba
Loic Yengo
Michael Simpson
Luke Evans
Katrina Grasby
Uppsala
IOP
IBG
VIPBG
WUSM
QIMR
VU
KUL
RUG
Bristol
Hong Kong
MGH
UMich
Indiana
UVA
Helsinki
Edinburgh
UA
LSUMC
MDAnderson
Wellcome
Genomics PLC
GSK
Millenium

34th International Statistical Genetics Workshop – Boulder CO 2020

Monday	Tuesday	Wednesday	Thursday	Friday
Intro 2 Unix & R	plink & GRMs	GWAS & genetic data formats	LD score regression & genetic correlation	Simulation
Causes of Variation	ACE: from twins to GRMs	Multivariate Models	Developmental Models	Genomic SEM
Biometrical Genetics	Binary & Ordinal Data & Measurement	Genetic Factor Models	Direction of Causation DOC	Model Assumptions & Extended Pedigrees
OpenMx: Regression & tools 4 SEM	Multilevel Models	GREML in OpenMx	PRS & Mendelian Randomization MR	Statistical Power
ACE Model (full script + umx)	Heterogeneity: Sex & GxE interaction	GW-SEM	Combined DOC-MR	Lightning Rounds

Thank you for participating! See you next year?!