The Avon Longitudinal Study of Parents and Children

A longitudinal and multi-generation platform for collaborative research

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University of BRISTOL

CHILDREN OF THE 90S

wellcome

Supported by NIHR

MRC Medical Research Council

Acknowledgements:

Wellcome Trust

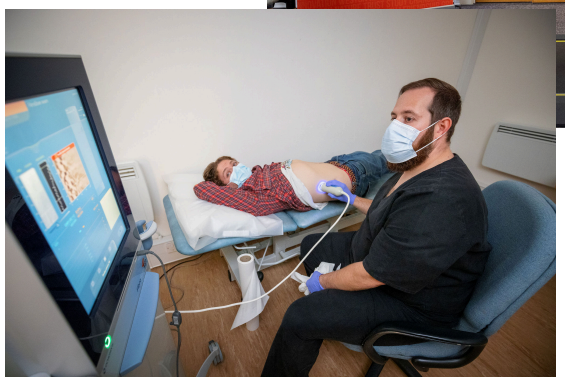
Medical Research Council

University of Bristol

Research community – our users

ALSPAC team

ALSPAC participants



ALSPAC

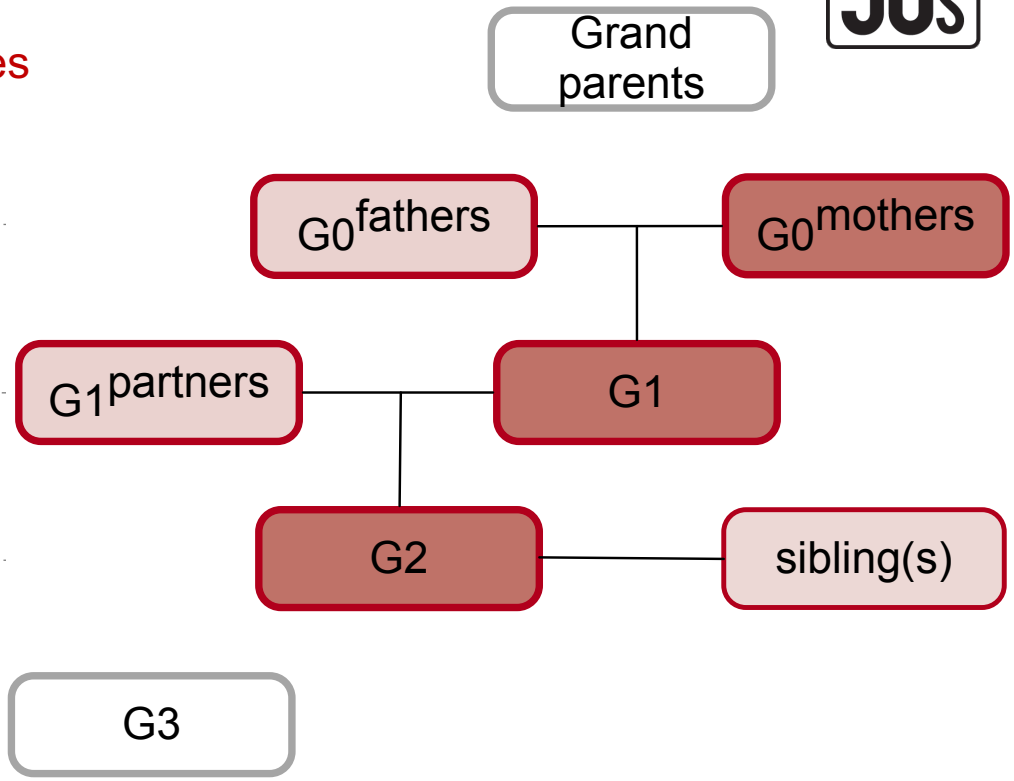
>30k participants, >1.2million bio-samples, >80k variables,
30 years of deep longitudinal study, just under 1,000 (979) researchers,
>2500 papers
18-20 proposals/month for data/samples

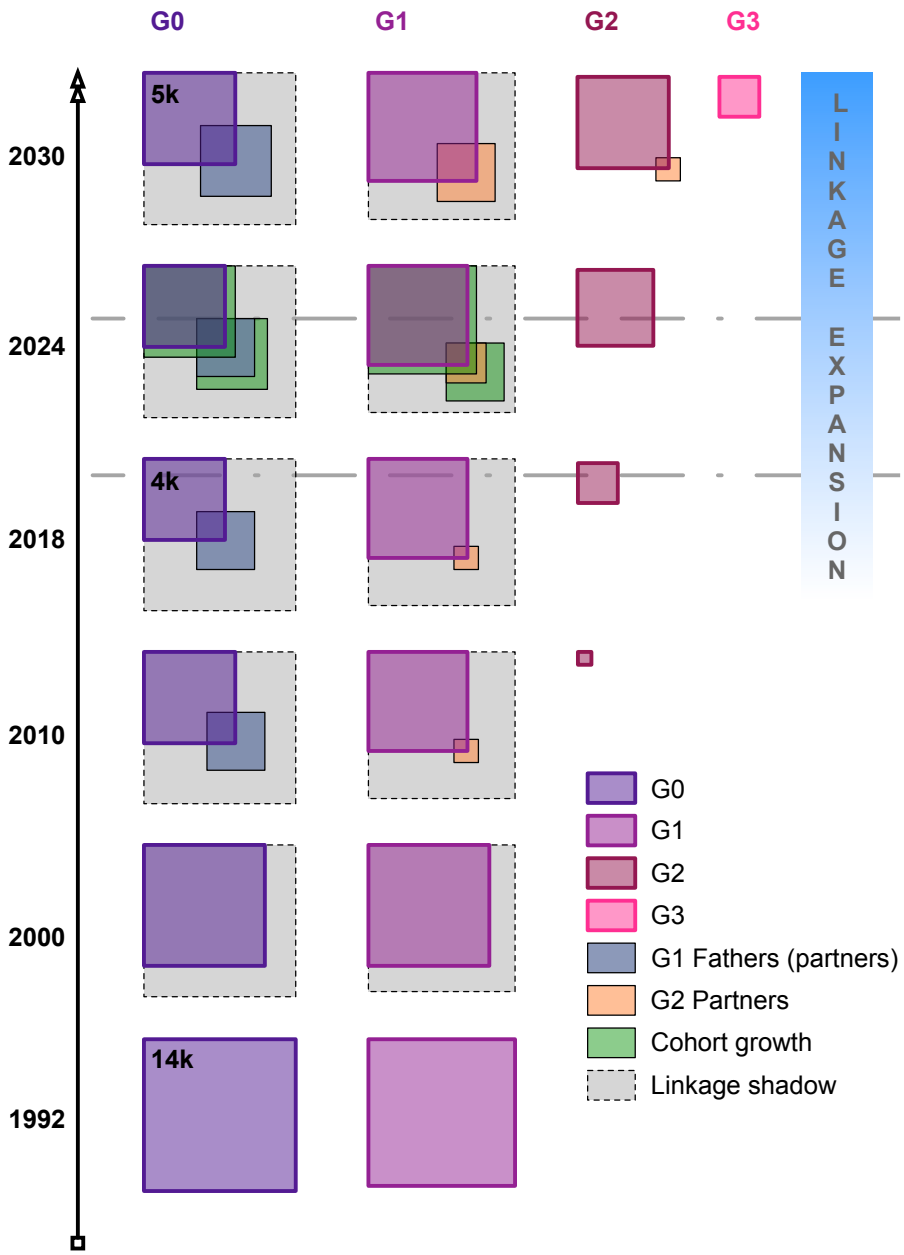
>14541 pregnancies, 75% of all
Linkage consented and >8000 active

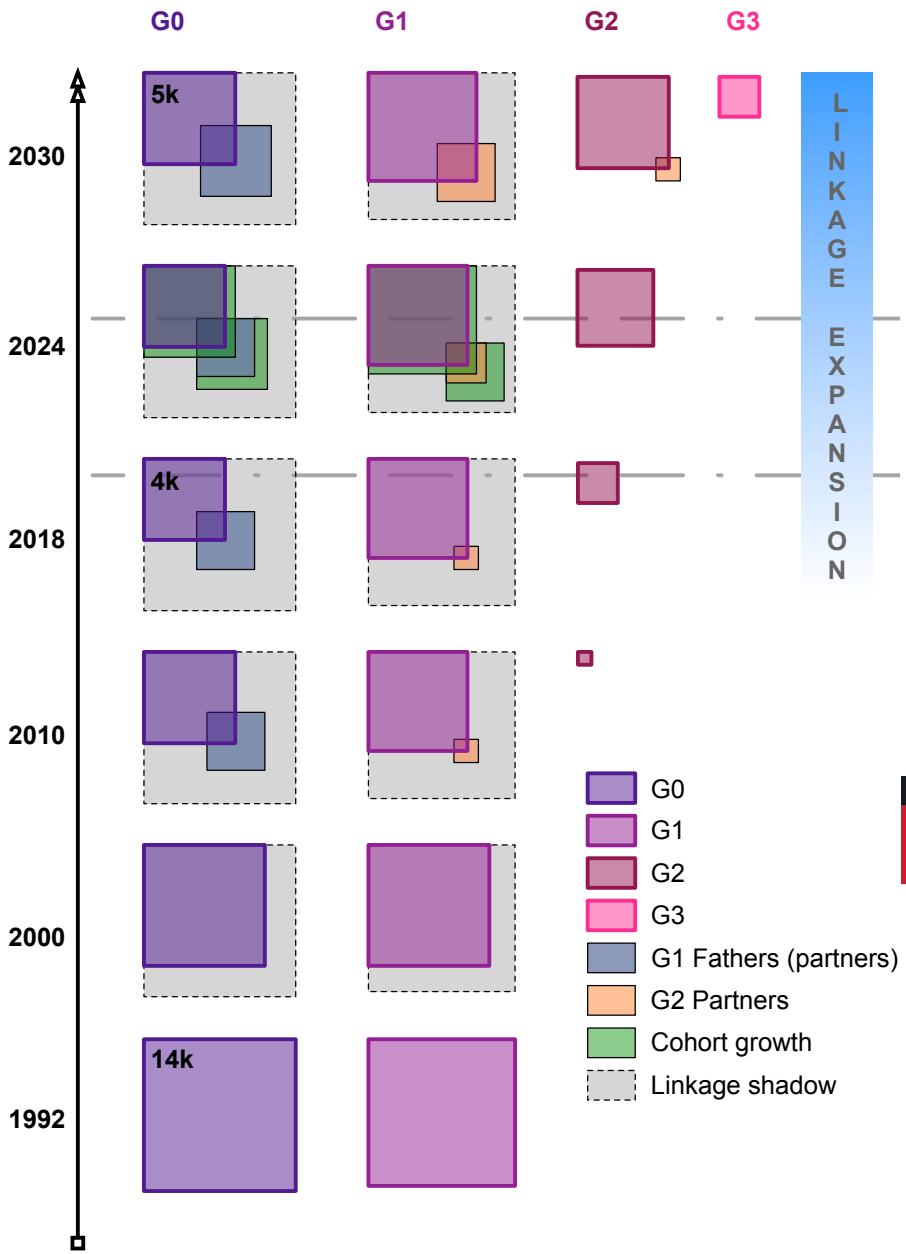
>9k at 8yrs, >6k at 18yr, 4.5k stable
>80% linked and 6500 active

>1200 new pregnancies
3300 pregnancies over next 5 years
Linkage consented

(Eldest G2 already 12
G3 likely over the next 5 years)




G0
G1
G2
G3
2030
2024
2018
2010
2000
1992
5k
4k
14k
LINKAGE EXPANSION
G0
G1
G2
G3
G1 Fathers (partners)
G2 Partners
Cohort growth
Linkage shadow



COHORT PROFILE

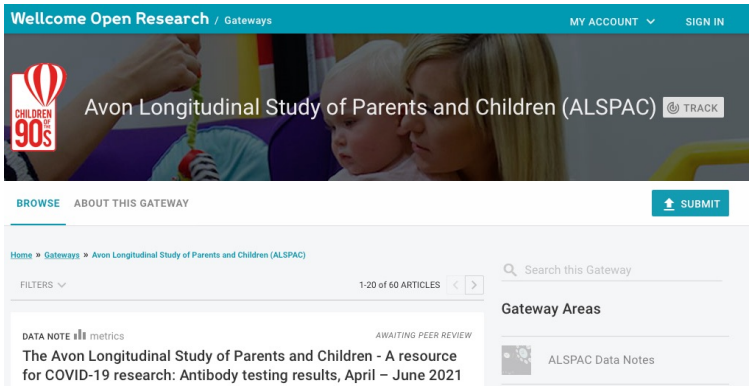
Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort

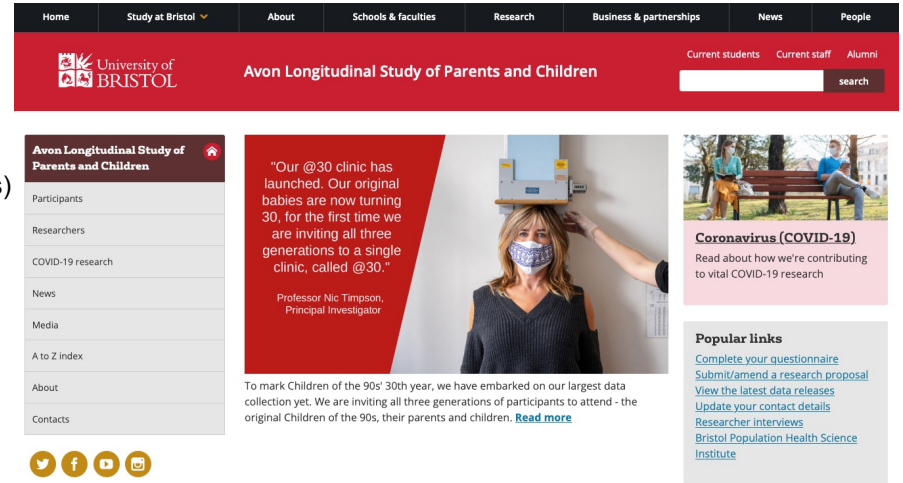
Abigail Fraser,[1,2] Corrie Macdonald-Wallis,[1,2] Kate Tilling,[2] Andy Boyd,[2] Jean Golding,[2] George Davey Smith,[1,2] John Henderson,[2] John Macleod,[2] Lynn Molloy,[2] Andy Ness,[3] Susan Ring,[2] Scott M Nelson[4] and Debbie A Lawlor[1,2]*

COHORT PROFILE

Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children

Andy Boyd,[1]* Jean Golding,[2] John Macleod,[1] Debbie A Lawlor,[3] Abigail Fraser,[3] John Henderson,[1] Lynn Molloy,[1] Andy Ness,[4] Susan Ring[1] and George Davey Smith[3]





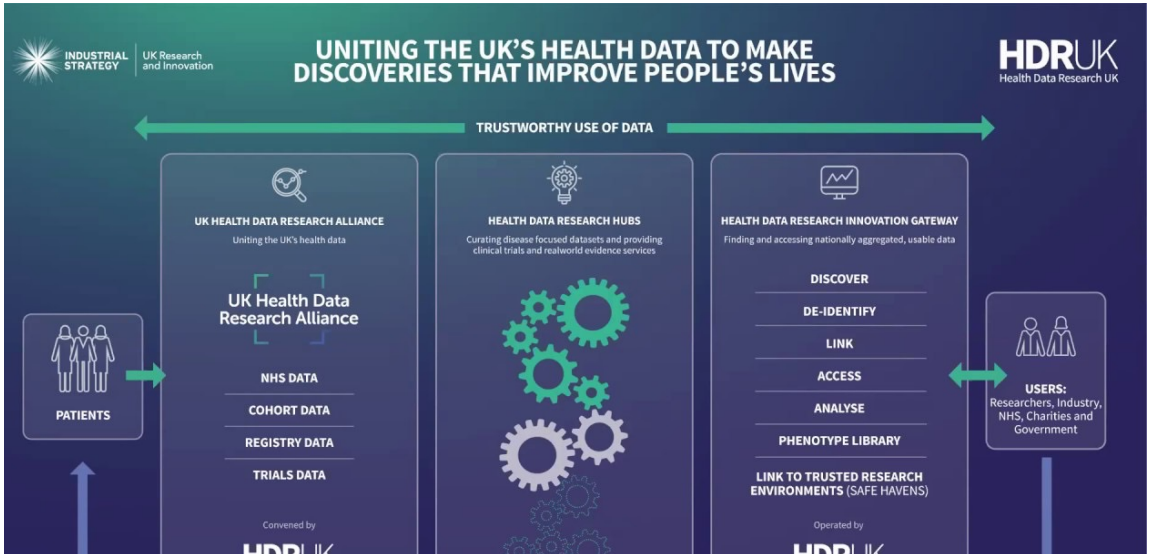
Visibility and Access

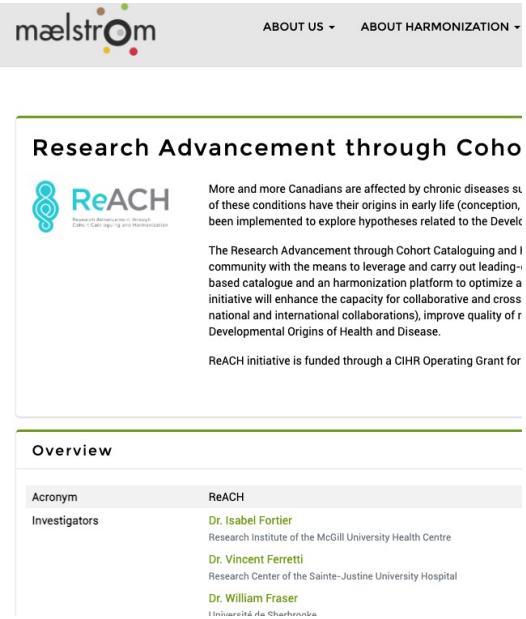
ALSPAC AVON LONGITUDINAL STUDY OF PARENTS

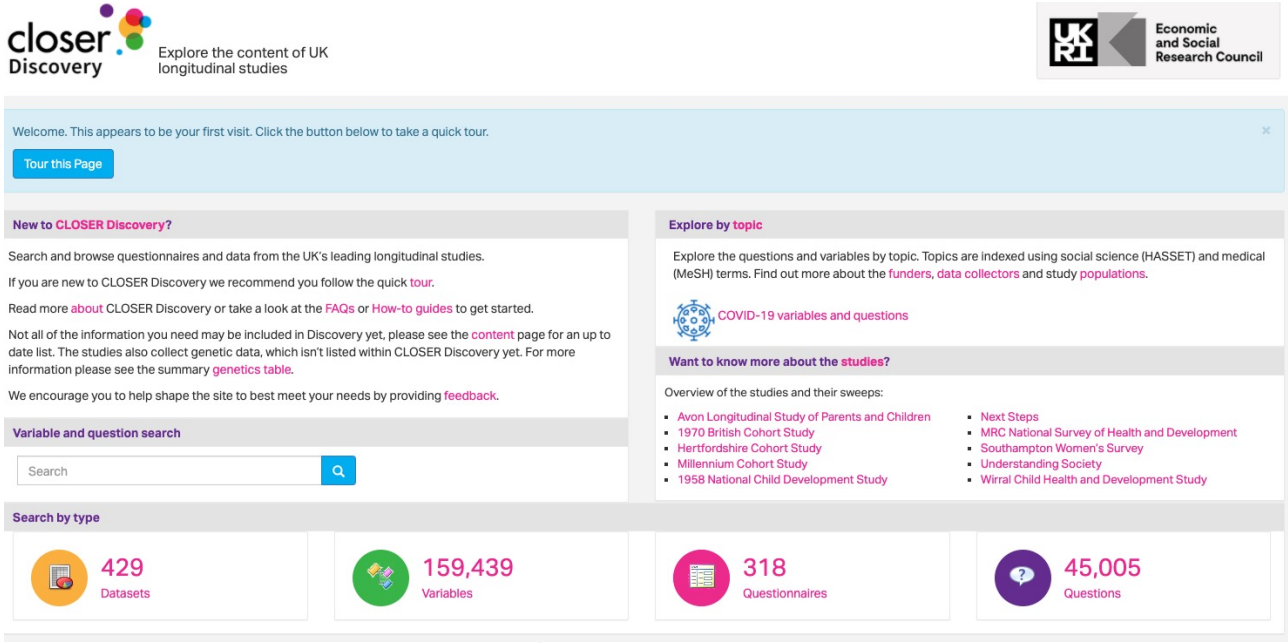
Access Policy

v. 13.0

February 2021







Visibility and Access

http://www.bristol.ac.uk/alspac/researchers/our-data/

http://variables.alspac.bris.ac.uk/

ALSPAC variables search tool | About | Variables

Freely browse available ALSPAC data by variable name

Show 10 entries

Search:

	Dataset	Variable	Details	Counts	Type	Release	Label 1	Label 2	Label 3
1	FOF1_3a	mult_dad	Entry is a duplicate - Remove if only looking at fathers: FOF1	2034	numeric	Current	Clinic	Adult	
2	FOF1_3a	ff1a005a	Arrival time of participant (hour): FOF1	2034	numeric	Current	Clinic	Adult	
3	FOF1_3a	ff1a005b	Arrival time of participant (minutes): FOF1	2034	numeric	Current	Clinic	Adult	
4	FOF1_3a	ff1a006	Reception Clinic Staff: FOF1	2034	numeric	Current	Clinic	Adult	
5	FOF1_3a	ff1a007	Reception Fieldworker: FOF1	2034	numeric	Current	Clinic	Adult	

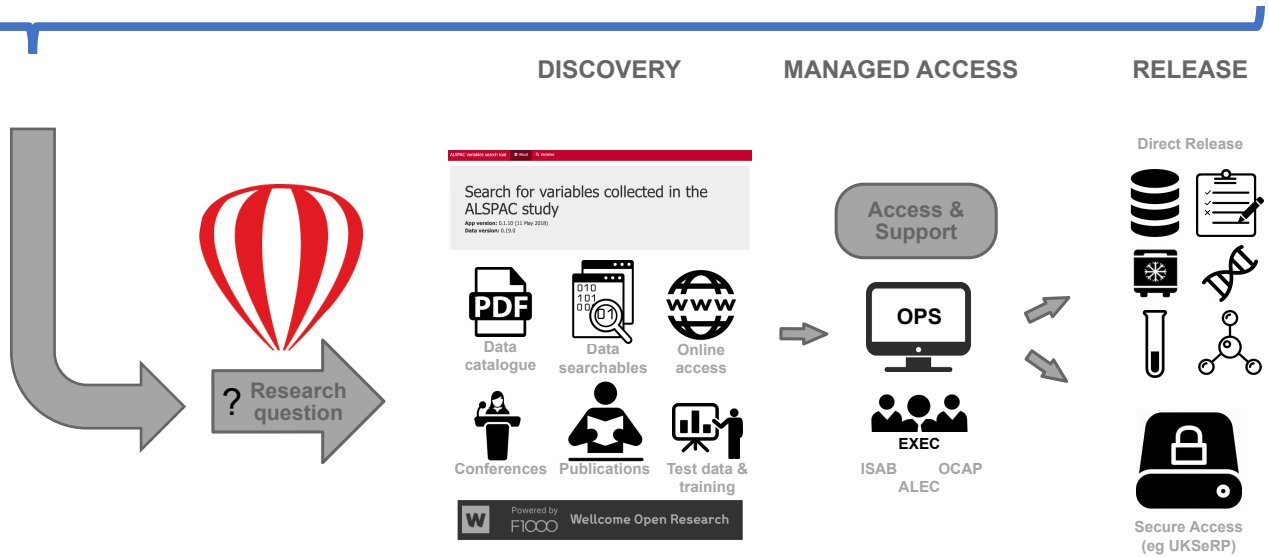
Instructions

Use the search box to filter on keywords or terms. Click on rows to select those variables. Click the Download button to download a csv of the variables that you have selected.

If there is anything you cannot find, please consult the data dictionary or variables catalog . You can also get help from the team at ALSPAC-data@bristol.ac.uk .

Note: Sometimes the sample counts presented here will be inaccurate - consult the data dictionary data dictionary for accurate summary data for each of the variables

Note: High dimensional biological data including genetic variants, DNA methylation measures and gene expression measures are not included in this tool. You can find out more about sample availability here

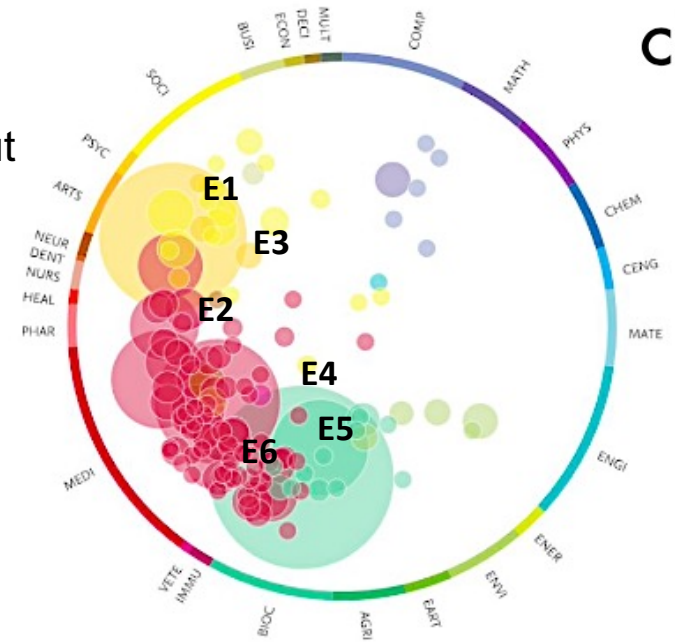


Current output from ALSPAC

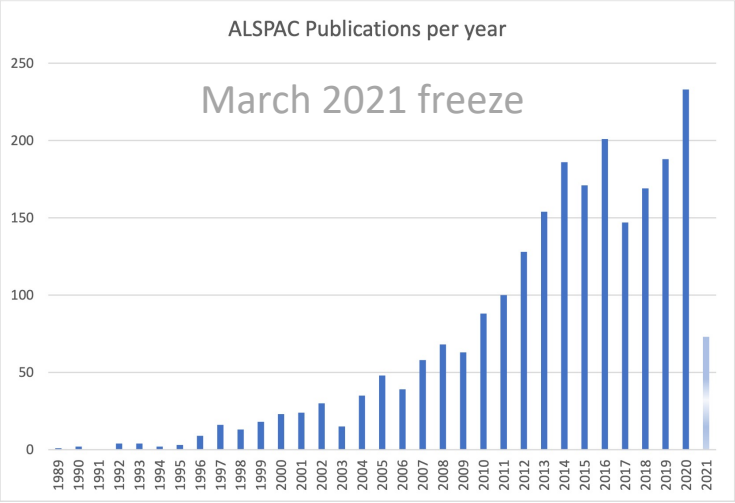
Medicine/molecular epidemiology contribution, but there are other major areas of activity.

Metrics are useful to illustrate this and guide activity – for example, we work to promote ALSPAC use with social scientists and to engage with methods and approaches aligned to social science studies.

Good overlap between social and medical sciences.



COMP	Computer Science	PHAR	Pharmacology, Toxicology and Pharmaceutics
MATH	Mathematics	HEAL	Health Professions
PHYS	Physics and Astronomy	NURS	Nursing
CHEM	Chemistry	DENT	Dentistry
CENG	Chemical Engineering	NEUR	Neuroscience
MATE	Materials Science	ARTS	Arts and Humanities
ENGI	Engineering	PSYC	Psychology
ENER	Energy	SOCI	Social Sciences
ENVI	Environmental Science	BUSI	Business, Management and Accounting
EART	Earth and Planetary Sciences	ECON	Economics, Econometrics and Finance
AGRI	Agricultural and Biological Sciences	DECI	Decision Sciences
BIOC	Biochemistry, Genetics and Molecular Biology	MULT	Multidisciplinary
IMMU	Immunology and Microbiology		
VETE	Veterinary		
MEDI	Medicine		



https://service.elsevier.com/app/answers/detail/a_id/12007/supporthub/scopus/

Exemplar 1. The anthropology of cohorts themselves – ethnography and participation

Sahra Gibbon
UCL

Why do Families Participate in Cohort Research:

- Pilot study research examining multi-generational birth cohort participation
- Method: ethnographic interview with 'paired participants' (G0 parent and G1 adult child who had own child(ren)enrolled in G2)
- 'Becoming Intergenerational in Birth Cohorts: kinship and the remaking of participation' Sahra Gibbon and Rosie Mathers (2021) *Somatosphere* March 18th

Biosocial Lives of Birth Cohorts (2021-2025):

- 4-year Investigator Award examining Biosocial research in 4 birth cohorts (ALSPAC, Generation R-Rotterdam, Generation 21-Porto, Pelotas Birth Cohort Study – Brazil) as knowledge, social practice and **participation**
- Using ethnographic and participatory research methods to examine the experience and meaning of birth cohort participation
- All arguably "biomedical", but where new data may illuminate other fields and help the interpretation of data collected within studies.

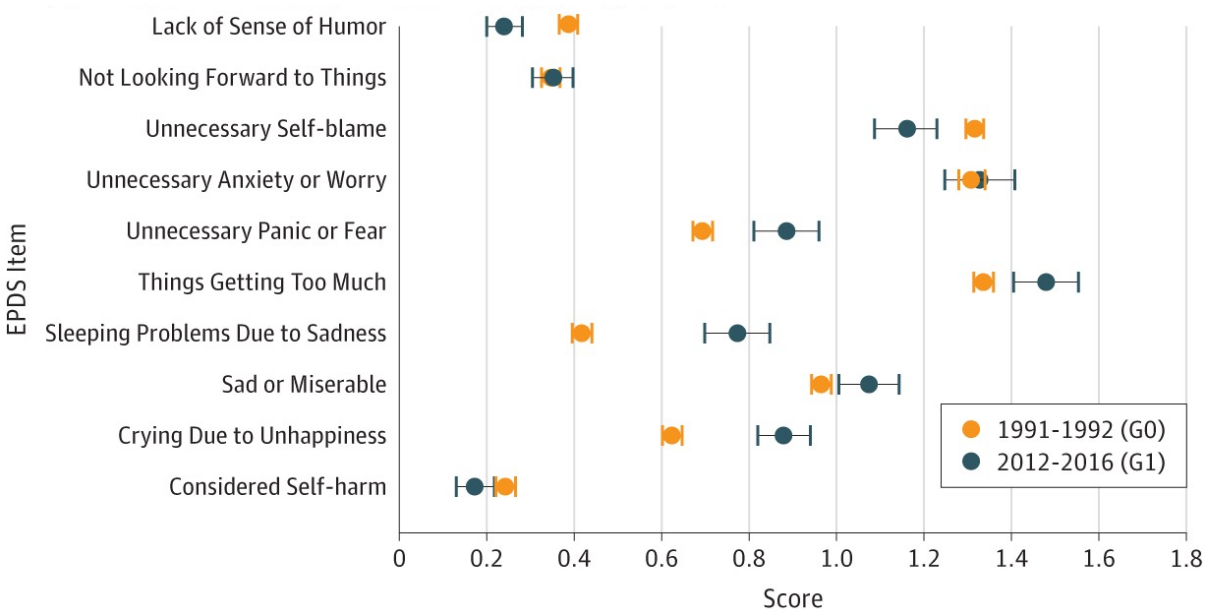
Exemplar 2. Mental health and longitudinal population study data

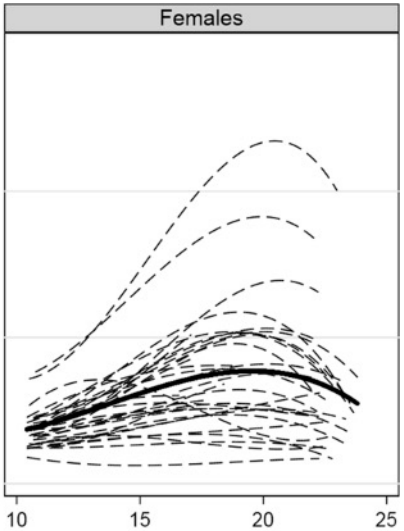
Mental health is receiving great attention and is measured in great detail in longitudinal studies like ALSPAC – this also bridges organic and social domains and there is an opportunity to bring together data and researchers around this.

JAMA Network Open - Psychology 2018

Prevalence of Prenatal Depression Symptoms Among 2 Generations of Pregnant Mothers

The Avon Longitudinal Study of Parents and Children

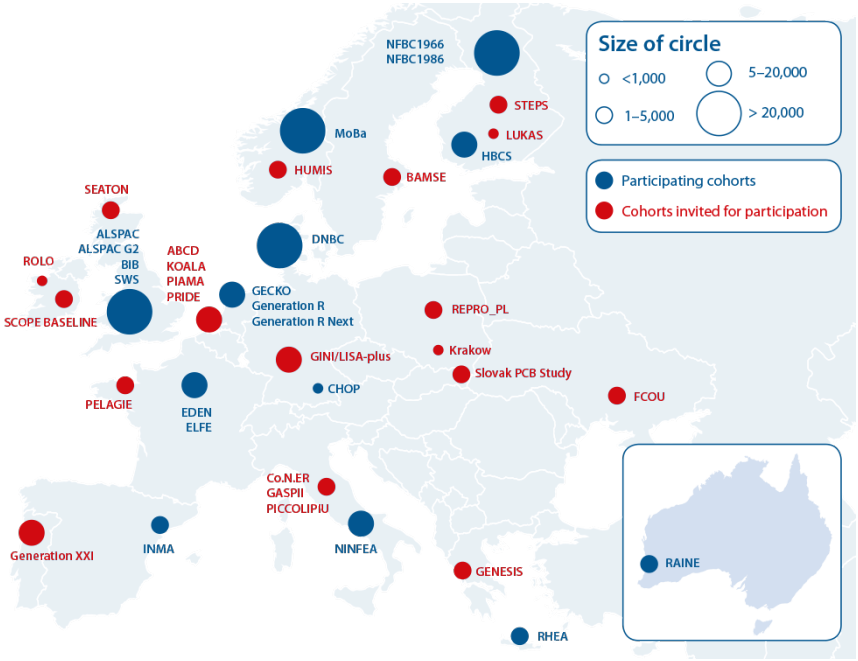




Alex Kwong
University of Edinburgh

Key point in the frequency and granularity of standardized data

Exemplar 3. Social inequality – measurement and implications



Tim Cadman
University of Bristol

Harmonised data on childhood for >250,000 children.

- Mental health outcomes at least 2 time points
- Data available for analysis via DataSHIELD

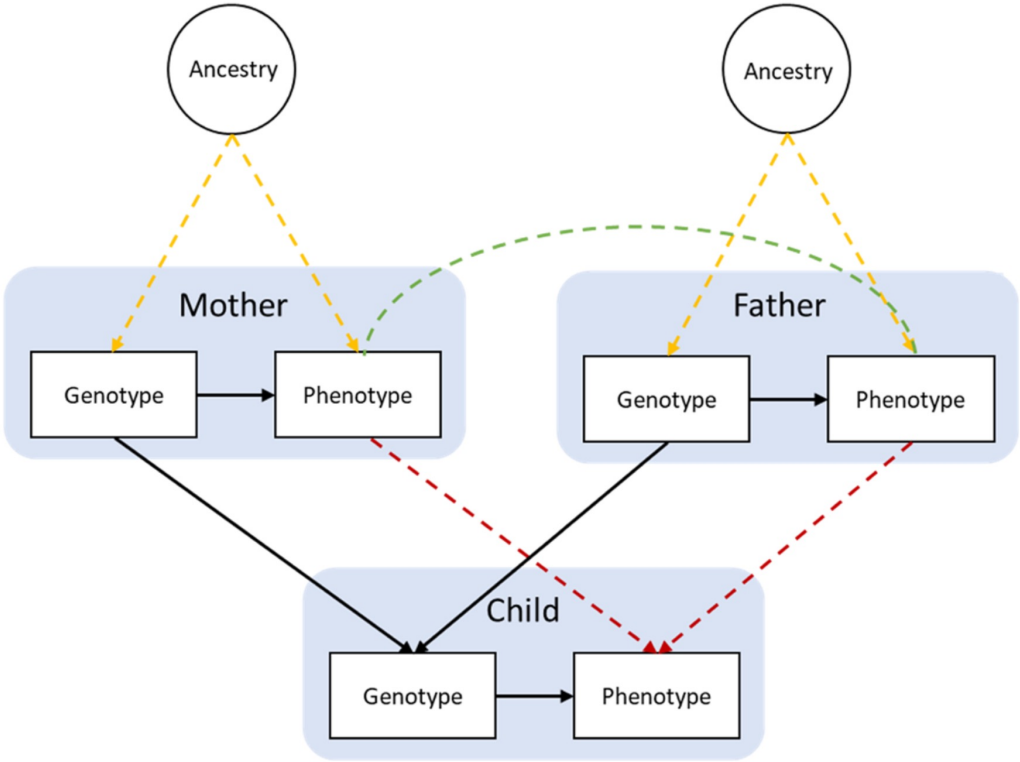
Consistent evidence that ***social inequalities in mental health*** are present from a young age for all cohorts

Inequalities reduce over time, but evidence that the rate of decrease slows and inequalities persist into middle childhood

Demonstrates ***meta-analysis of mental health trajectories*** across birth cohorts is possible:

a) Pros: making use of measurement at different times points across cohorts to model complete trajectories
b) Cons: non-equivalence of maternal education and mental health measurement.

Exemplar 4. The interplay between social and biomedical research – Certainly not only one direction



Tim Morris
University of Bristol

Population stratification - yellow

Dynastic effects - red

Assortative mating - green

(+ assortative mating by phenotype will lead to genotypic correlation!!)

"… population phenomena can bias estimates of genetic contributions to complex social phenotypes from samples of unrelated individuals. The presence of genetic association … may reflect confounding by underlying population phenomena including population stratification, assortative mating, and dynastic effects"

Morris et al Sci Adv. 2020

Exemplar 5. Deep-diving genetic architecture – common<->rare variants in cohorts

Cell

Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood

Kaitlin Wade
University of Bristol

ARTICLES
https://doi.org/10.1038/s41591-021-01349-y

nature medicine

Check for updates

Loss-of-function mutations in the melanocortin 4 receptor in a UK birth cohort

Ana Goncalves Soares
University of Bristol

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This Collection

MC3R links nutritional state to childhood growth and the timing of puberty

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Citation

Lam, B., Williamson, A., Finer, S., Day, F., Tadross, J. A., Goncalves Soares, A., Wade, K., et al. MC3R links nutritional state to childhood growth and the timing of puberty. *Nature* https://doi.org/10.17863/CAM.77325

Abstract

The state of somatic energy stores in metazoans is communicated to the brain, which regulates key aspects of behaviour, growth, nutrient partitioning and development1. The

Amit Khera
Mass Gen, Boston

Brian Lam
Metabolic Research Labs, University of Cambridge

OXFORD

Human Molecular Genetics, 2018, Vol. 27, No. 20 3641–3649

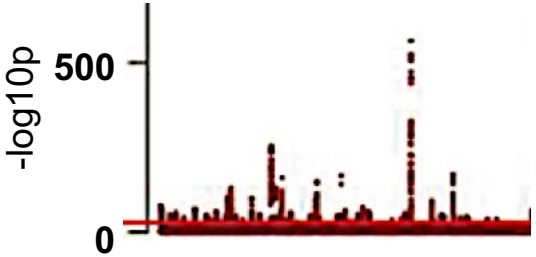
doi: 10.1093/hmg/ddy271
Advance Access Publication Date: 16 August 2018
Association Studies Article

ASSOCIATION STUDIES ARTICLE

Meta-analysis of genome-wide association studies for height and body mass index in ~700 000 individuals of European ancestry

Loic Yengo[1,*], Julia Sidorenko[1,2], Kathryn E. Kemper[1], Zhili Zheng[1], Andrew R. Wood[3], Michael N. Weedon[3], Timothy M. Frayling[3], Joel Hirschhorn[4], Jian Yang[1,5], Peter M. Visscher[1,5] and the GIANT Consortium

* Combined GWAS meta-analysis reaches N ~700 000 individuals



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GIANT CONSORTIUM

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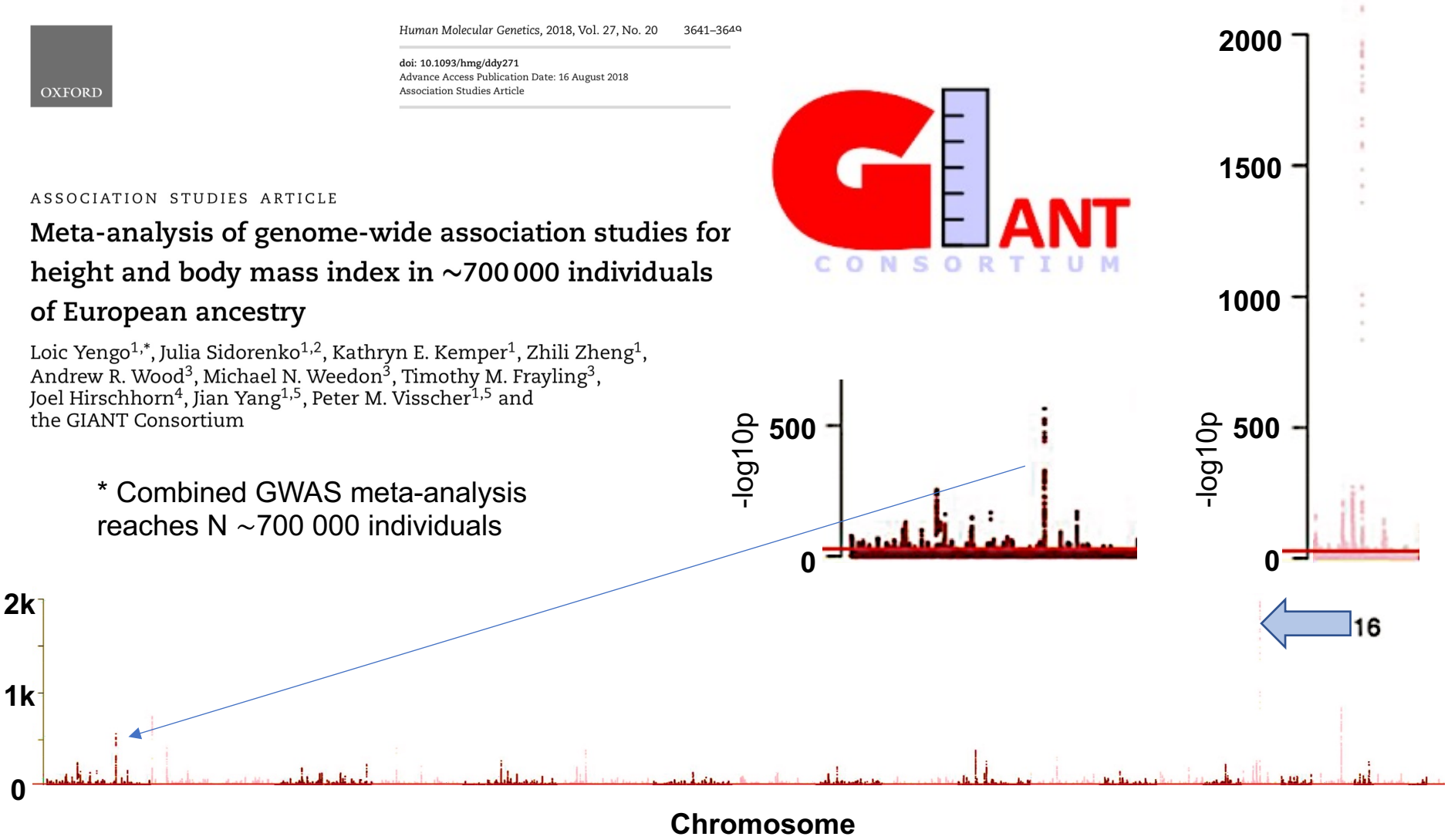
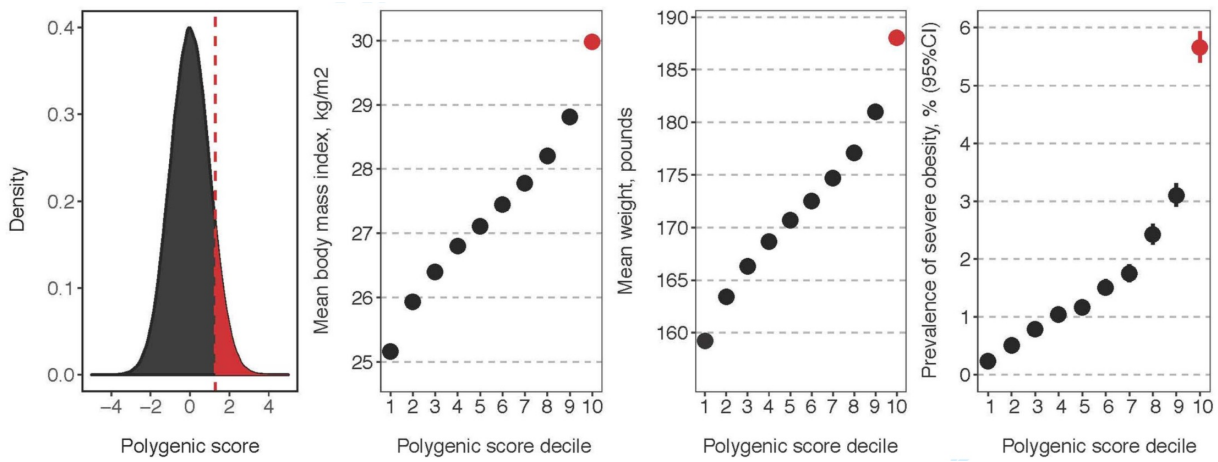


* >900 independent SNPs associated with BMI
* Genome-wide significant SNPs explain ~6.0% of the variance of BMI

Application of genetic risk scores in full form…

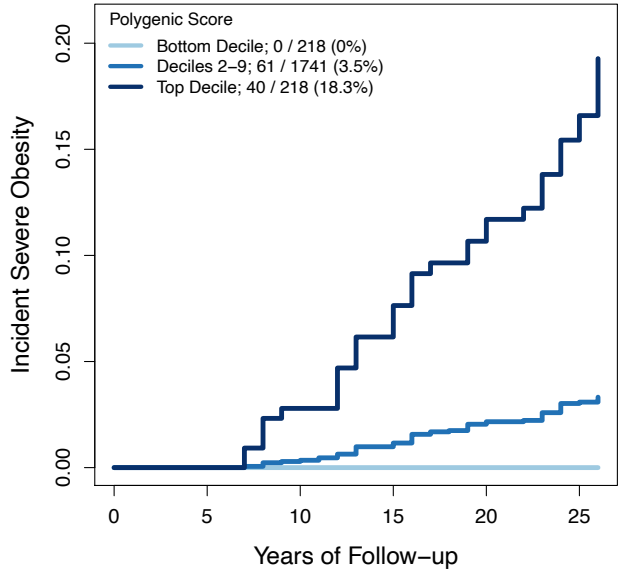


Polygenic score for body-mass index (BMI)

2,100,302 genetic variants

Tested in 119,951 UK Biobank participants

Validated it in 288,018 participants

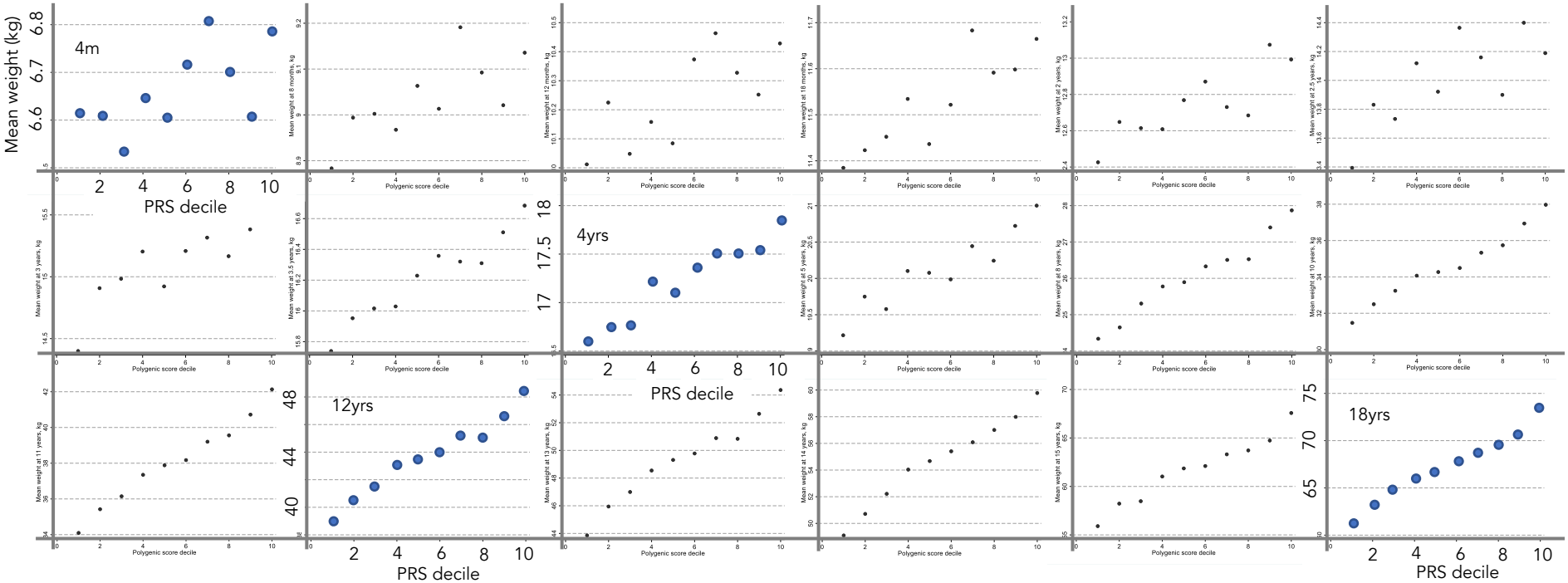


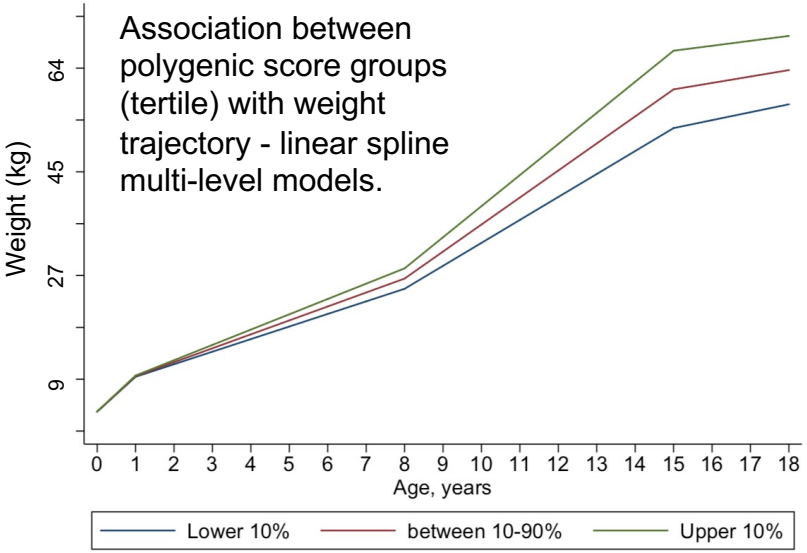
~2k young participants in Framingham Offspring Study

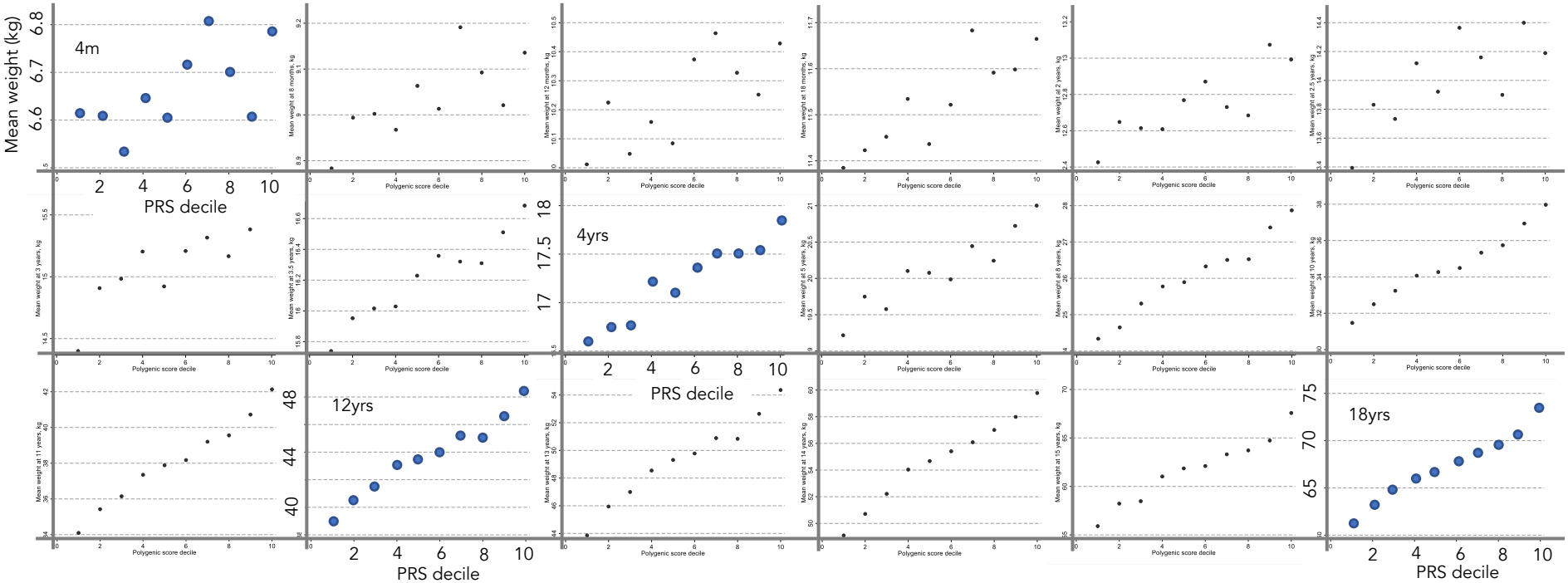
~3 kg/m2 higher BMI
~7kg higher weight
~4-fold increased risk for severe obesity
Increased risk cardiometabolic diseases & all-cause mortality

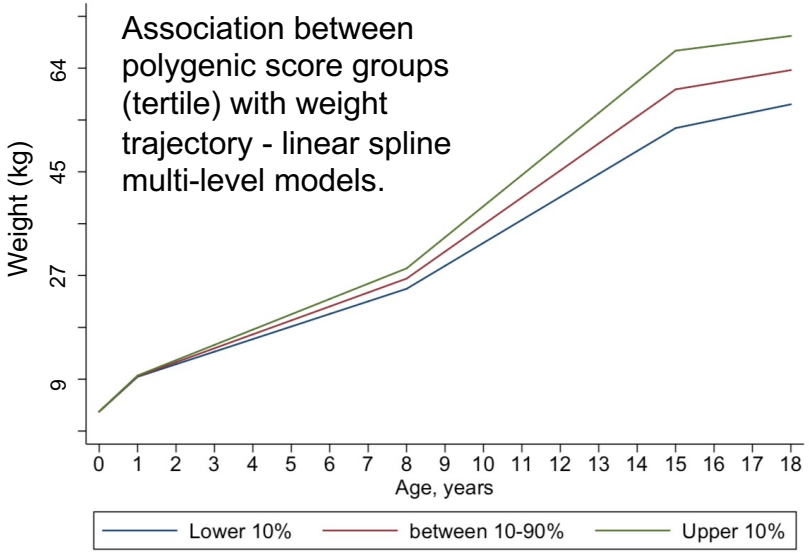
Severe obesity - 5-fold increased risk of bariatric surgery

Khera AV et all, Cell 2019


Mean weight (kg)
4m
4yrs
12yrs
18yrs
PRS decile
Polygenic score decile


Association between polygenic score groups (tertile) with weight trajectory - linear spline multi-level models.
Weight (kg)
Age, years
Lower 10%
between 10-90%
Upper 10%

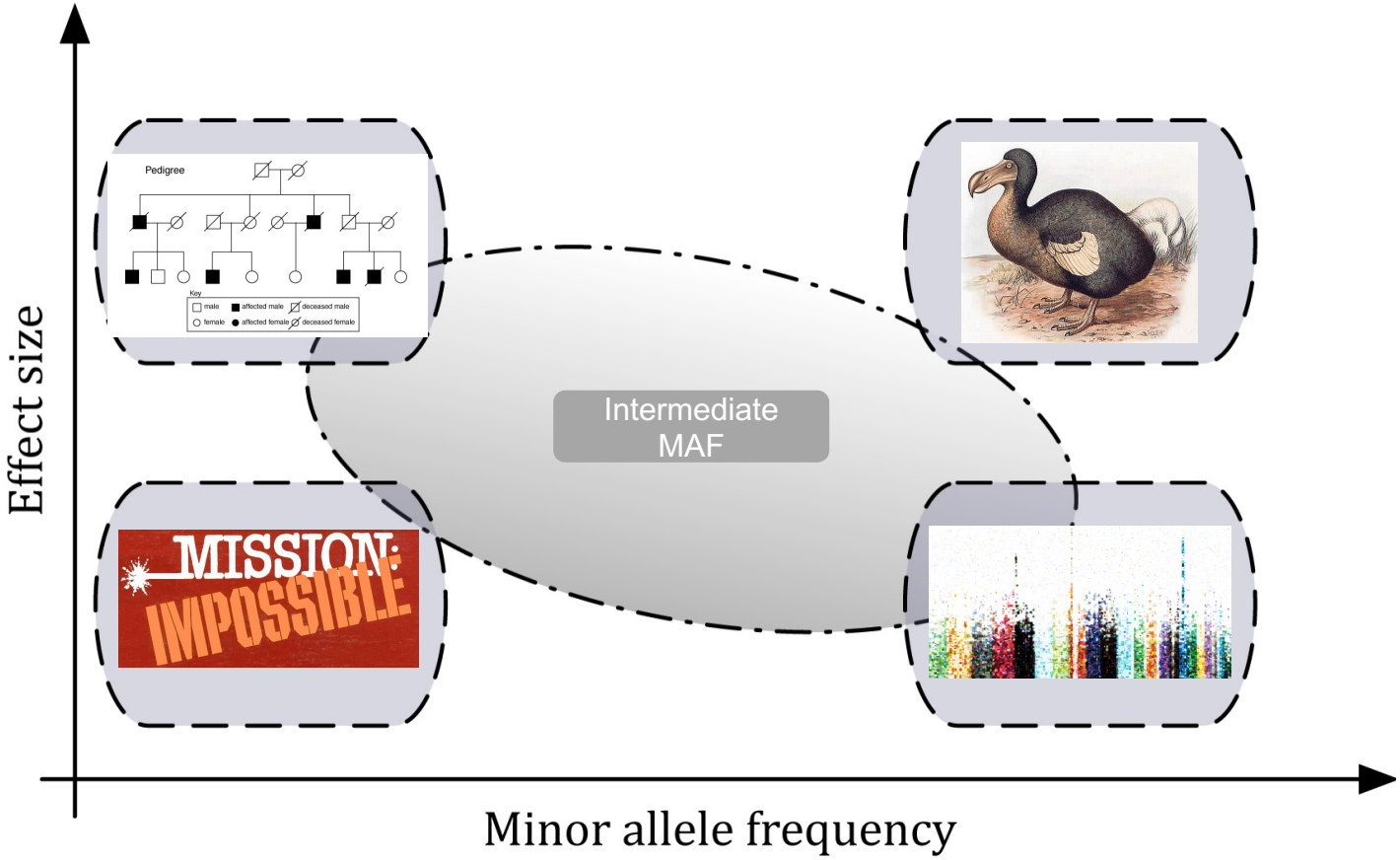




Sociodemographic factor	Estimate (95% CI)[1]	P-value
Family income (per week)	-0.03 (-0.06, -0.01)	0.002
Maternal highest qualification	-0.05 (-0.07, -0.03)	2.87×10^{-06}
Paternal highest qualification	-0.03 (-0.05, -0.01)	0.003
Household social class	0.02 (-0.002, -0.05)	0.07

Association between sociodem' factors and polygenic score

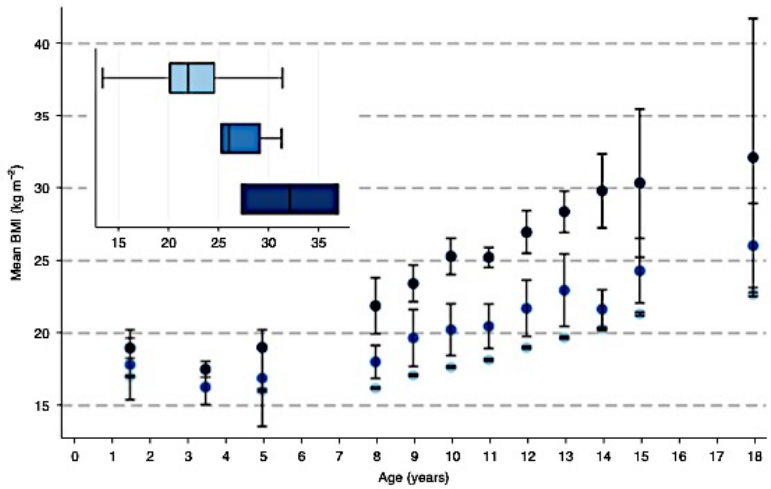
[1]Estimates represent the average change in the standardized polygenic score with each unit increase in the categorical sociodemographic factors


Effect size
Minor allele frequency
Intermediate MAF
Pedigree
Key
male
affected male
deceased male
female
affected female
deceased female
MISSION: IMPOSSIBLE

Using a pooled amplicon NG sequencing approach, identified rare variants in *MC4R* & *MC3R* can be examined re. frequency, function, longitudinal phenotype

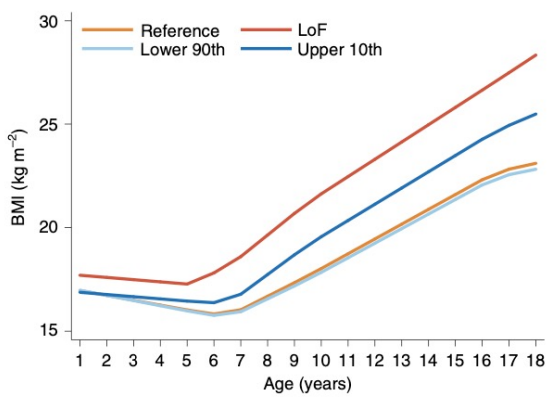
Using a pooled amplicon NG sequencing approach, identified rare variants in *MC4R* & *MC3R* can be examined re. frequency, function, longitudinal phenotype

MC4R LoF mutations associated with BMI across the life course. Further, these are effects which exceed polygenic contributions.



Reference, pLoF and cLoF groups are depicted in light, medium and dark blue, respectively.

Heterozygous mutations that impair the function of the *MC4R* gene may very well be found in several millions of people worldwide a frequency of ~1 in 340



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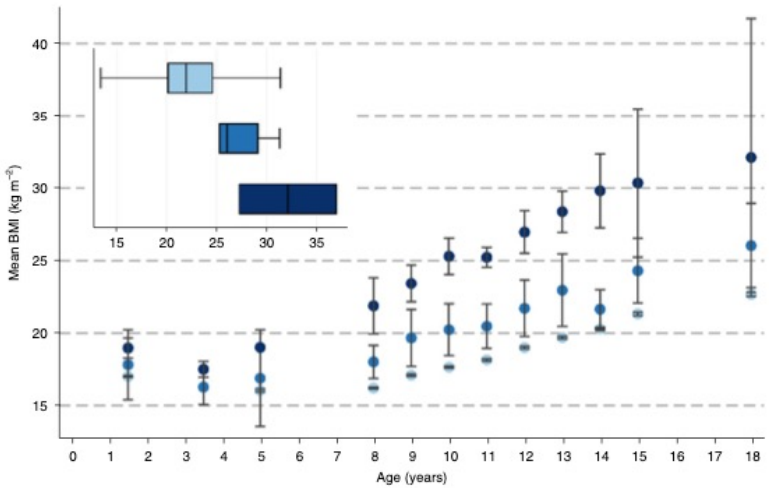

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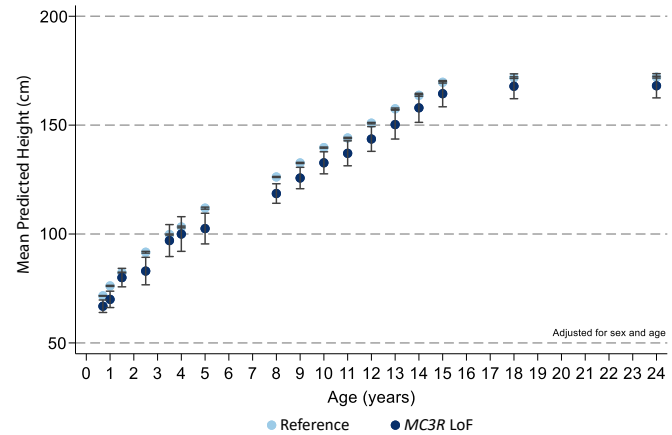
MC3R LoF mutations associated with lower height throughout childhood, adolescence and early adulthood, with a trend towards lower lean mass and lower weight.



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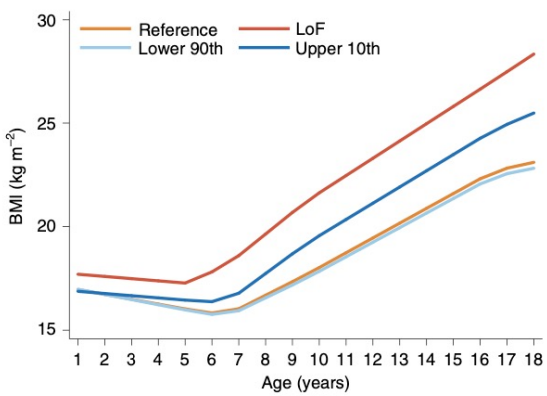
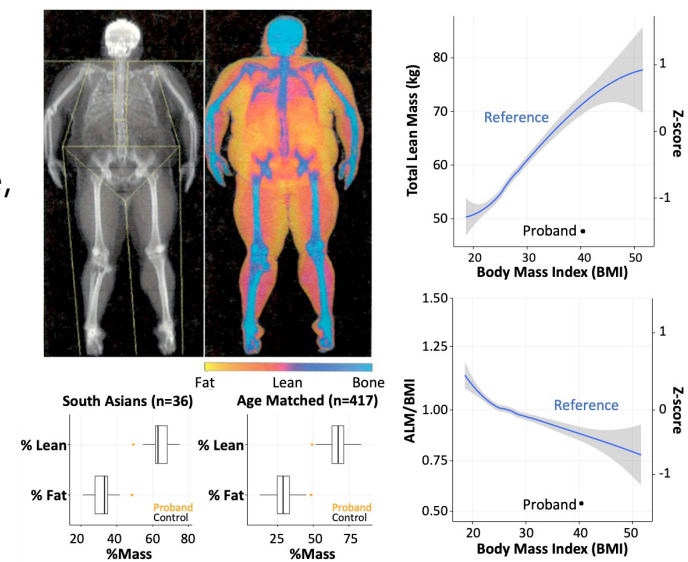


Genes & Health (G&H) study two rare, homozygous non-synonymous mutations p.M97I and p.G240W.



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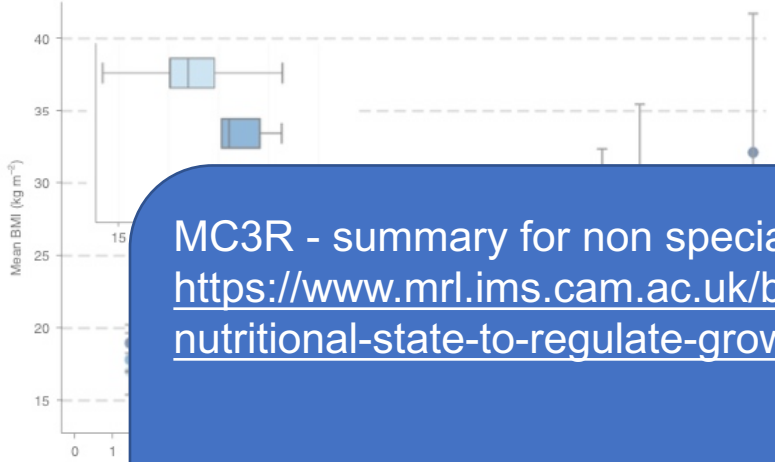
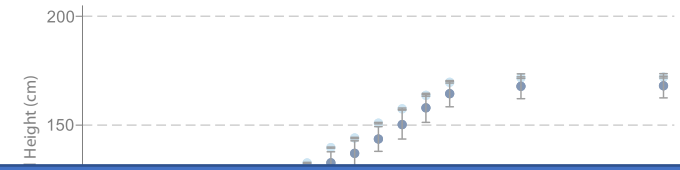


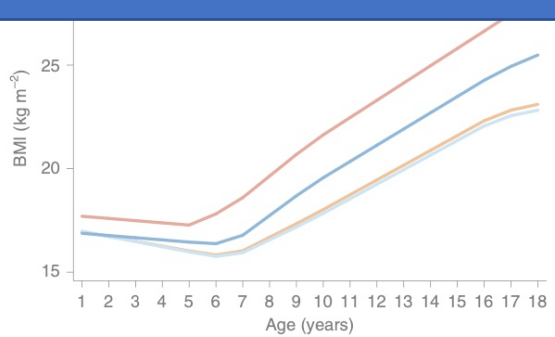


MC3R - summary for non specialists – https://www.mrl.ims.cam.ac.uk/blog/scientists-discover-how-our-brain-uses-nutritional-state-to-regulate-growth-and-age-at-puberty

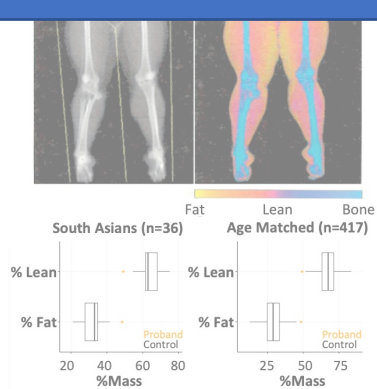
Steve O'Rahilly - blog on the way this story evolved – https://www.mrl.ims.cam.ac.uk/blog/the-long-story-on-mc3r-regulation-of-growth-and-age-at-puberty-how-we-did-it

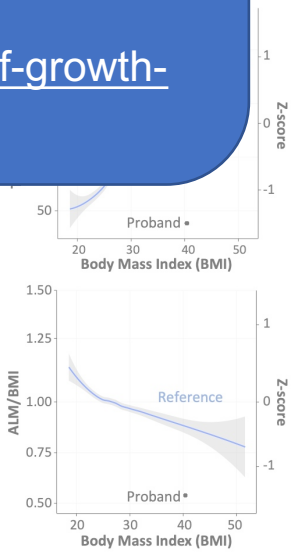
Reference, pl
blue, respect

Heterozygo
mutations that impair the function of the *MC4R* gene may very well be found in several millions of people worldwide a frequency of ~1 in 340

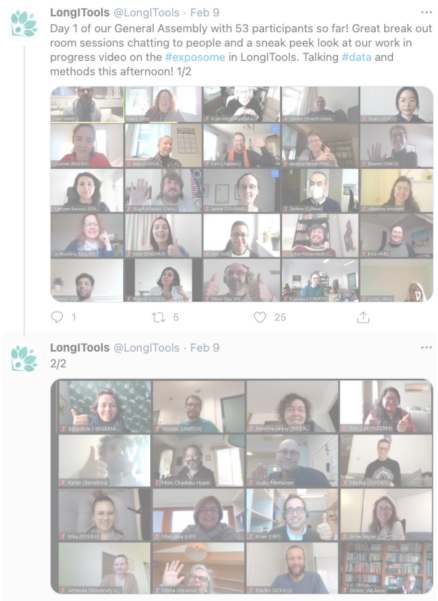


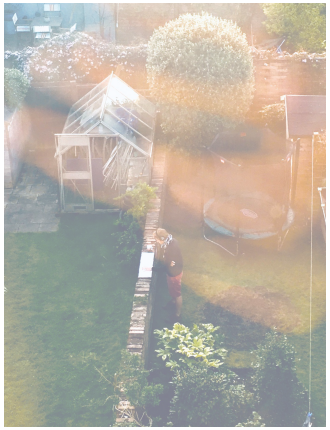
homozygous non-synonymous mutations p.M97I and p.G240W.

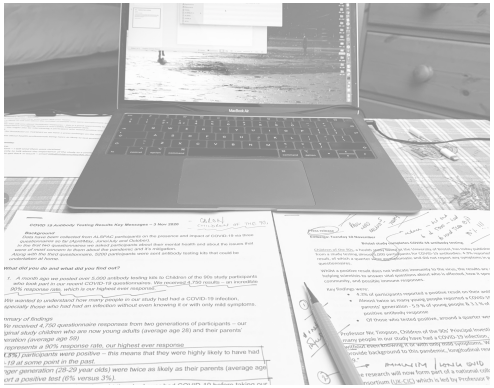


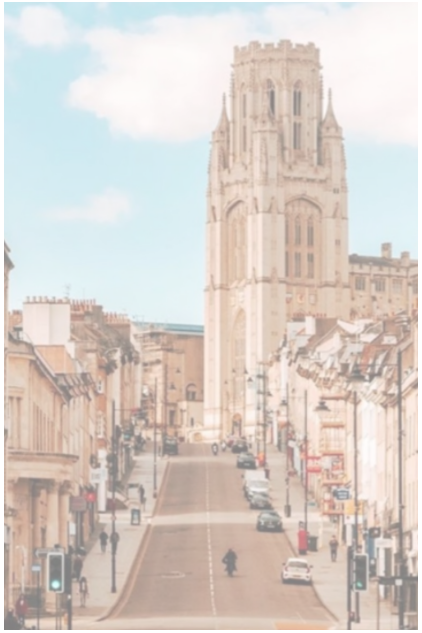


Exemplar 6. The implications of population events – SARS-CoV-2 & COVID-19





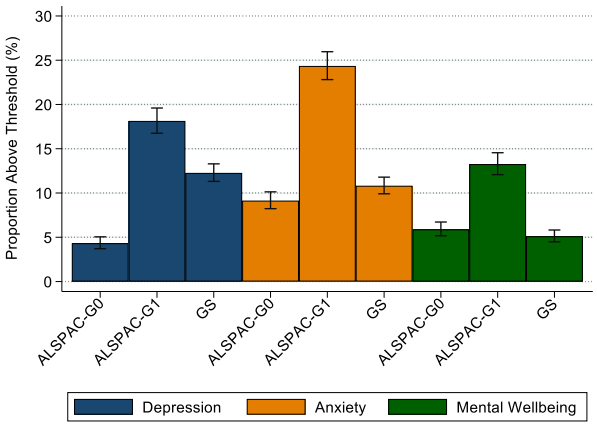


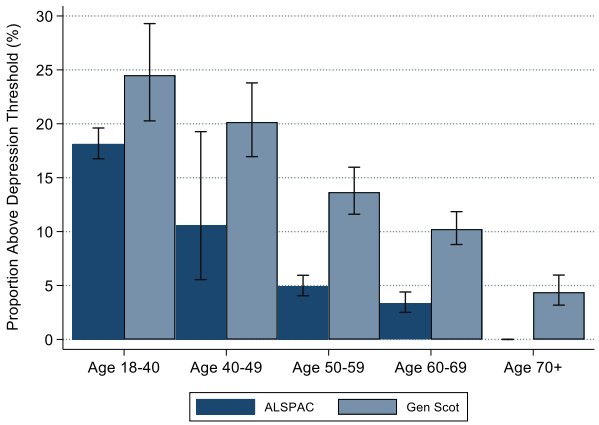


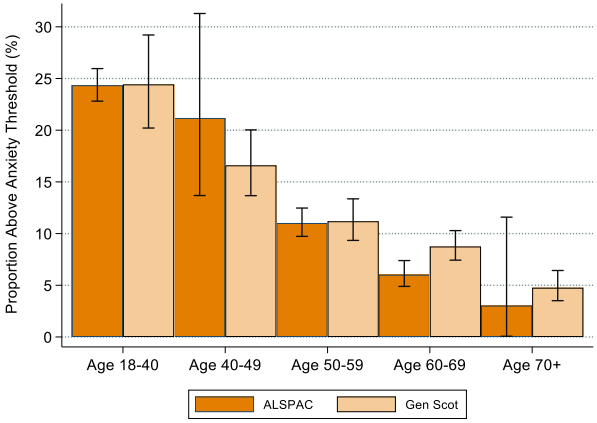
Mental health (MH) during COVID-19

Clear age gradients emerging across MH measures in *both* Generation Scotland and ALSPAC data from Q1

Alex Kwong
University of Bristol & Edinburgh







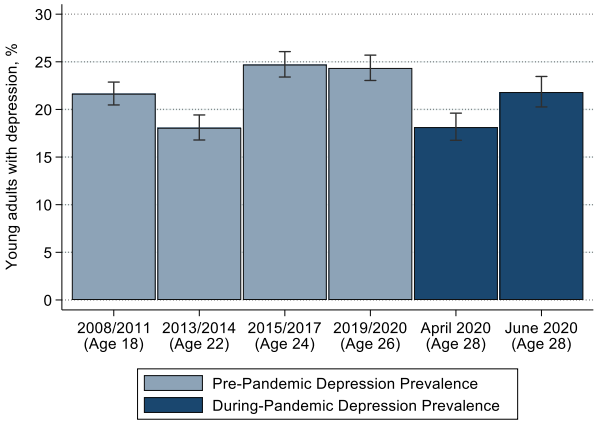
Depression, **anxiety** worse in in younger populations (ALSPAC-G0: n=3720; ALSPAC-G1: n=2850; GS: n= 4233)

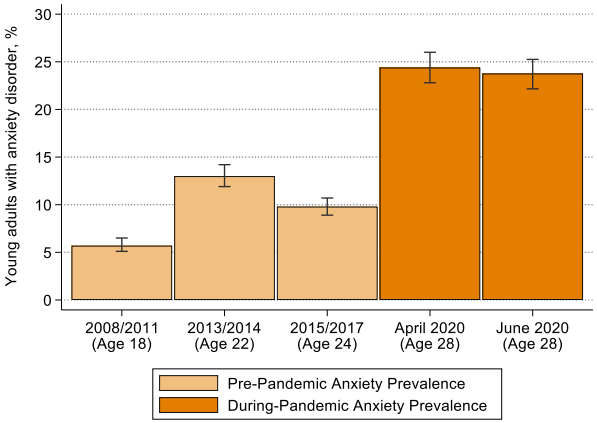
Depression measured by the Short Mood and Feelings Q in ALSPAC and Patient Health Questionnaire 9 in GS
Anxiety measured by the Generalised Anxiety Disorder Assessment in ALSPAC and GS

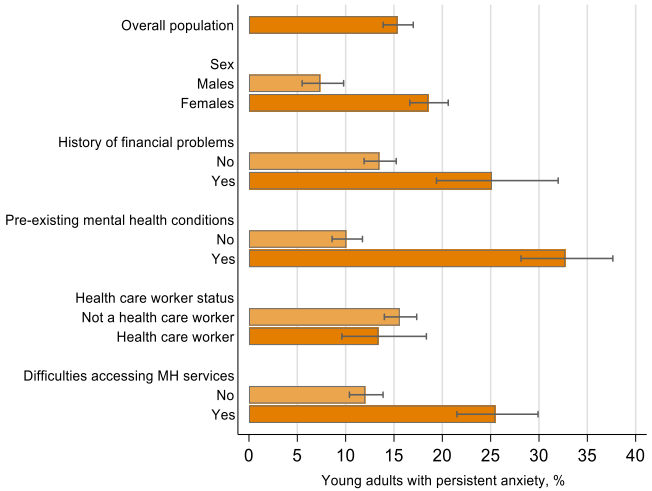
Kwong et al., Mental health during the COVID-19 pandemic in two longitudinal UK population cohorts. *Medrxiv*.

Longitudinal assessment of MH (in the young)

Specificity around anxiety and the persistence of this moving through lockdown and easing.







Left: **Depression** across COVID-19 is stable compared to previous waves in young ALSPAC
Middle: **Anxiety** is higher across COVID-19 compared to previous waves
Right: The proportion of young people with **anxiety** at both COVID-19 waves (persistent anxiety) by subgroups

Kwong et al., Longitudinal evidence for persistent anxiety in young adults through COVID-19 restrictions. *Wellcome Open Res 2020, **5**:195*

covid-19 questionnaire

https://www.bristol.ac.uk/alspac/researchers/wellcome-covid-19/

HDRUK
Health Data Research UK

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Our previous reports to SAGE

We work with The Strategic Advisory Group for Emergencies (SAGE) by providing SAGE with the prioritised health data research related to COVID-19.

- SAGE report – 2 November 2021
- SAGE report – 05 Oct 2021
- SAGE report – 07 Sep 2021
- SAGE report – 03 Aug 2021

covid-19 questionnaire

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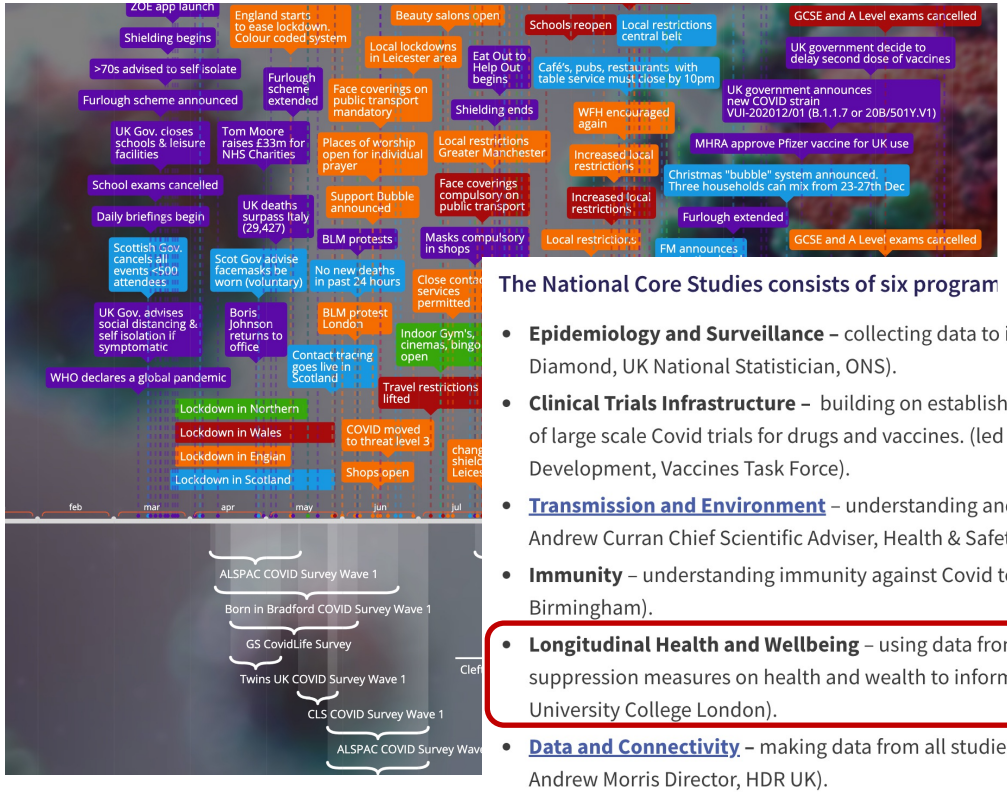


COVID-19 National Core Studies

The National Core Studies programme is enabling the UK to use health data and research to inform both our near and long-term responses to COVID-19, as well as accelerating progress to establish a world-leading health data and research infrastructure for the future.

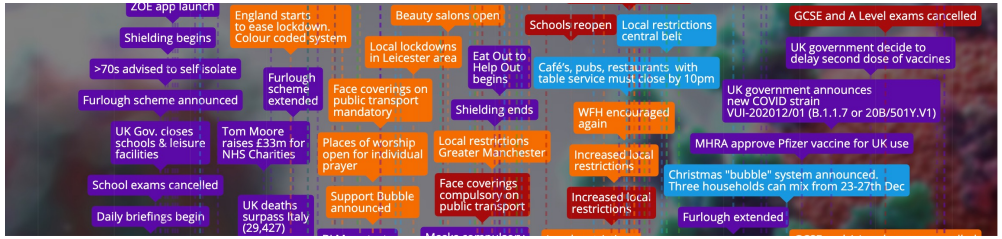
The National Core Studies consists of six program :

- **Epidemiology and Surveillance –** collecting data to inform safe level of restrictions and protection against imminent outbreaks (led by Ian Diamond, UK National Statistician, ONS).
- **Clinical Trials Infrastructure –** building on established NIHR infrastructure (and equivalent in Devolved Administrations) to accelerate delivery of large scale Covid trials for drugs and vaccines. (led by Patrick Chinnery, Clinical Director, MRC and Divya Chadha Manek, Head of Business Development, Vaccines Task Force).
- **Transmission and Environment** – understanding and mitigating transmission of the disease in workplace, transport and public places (led by Andrew Curran Chief Scientific Adviser, Health & Safety Executive).
- **Immunity** – understanding immunity against Covid to inform back-to-work policies (led by Paul Moss Professor of Haematology, University of Birmingham).
- **Longitudinal Health and Wellbeing** – using data from longitudinal studies to address the impact of COVID-19 and of associated viral suppression measures on health and wealth to inform mitigating strategies (led by Nishi Chaturvedi, Professor of Clinical Epidemiology, University College London).
- **Data and Connectivity –** making data from all studies available and accessible to inform decision makers and catalyse COVID-19 research (led by Andrew Morris Director, HDR UK).

"Pretty nice to be able to say "social science is super impactful, and strengthened by the capacity to compare patterns/relationships across contexts" – cohorts enable that…"

Gareth Griffith & Alex Kwong
Universities of Bristol & Edinburgh

covid-19 questionnaire



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BJPsych | The British Journal of Psychiatry (2021) 218, 334–343. doi: 10.1192/bjp.2020.242

CrossMark

Mental health before and during the COVID-19 pandemic in two longitudinal population cohorts

Alex S. F. Kwong*, Rebecca M. Pearson*, Mark J. Ad
Chloe Fawns-Ritchie, Helen Bould, Naomi Warne, Sta
Nadia Micali, Abraham Reichenberg, Matthew Hickm
Drew Altschul, Robin Flaig, Andrew M. McIntosh, Del
Nicholas J. Timpson*

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The British Journal of Psychiatry

Pre-pandemic mental health and disruptions to healthcare, economic and housing outcomes during the COVID-19 pandemic: evidence from 12 UK longitudinal studies

Published online by Cambridge University Press: **30 September 2021**

Giorgio Di Gessa, Jane Maddock, Michael J. Green, Ellen J. Thompson, Eoin McElroy, Helena L. Davies, Jessica Mundy, Anna J. Stevenson, Alex S. F. Kwong and Gareth J. Griffith ...Show all authors

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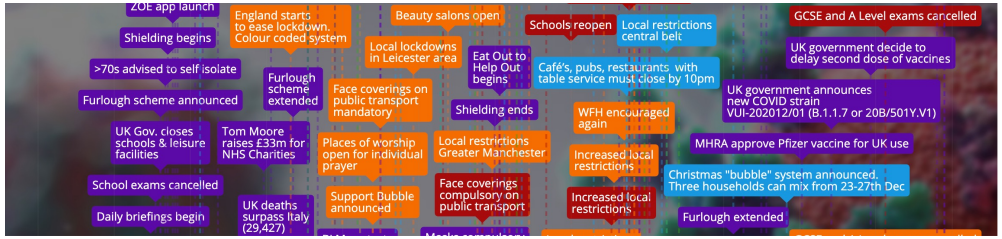

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Characterisation, determinants, mechanisms and consequences of the long-term effects of COVID-19: providing the evidence base for health care services

NIHR | National Institute for Health Research

UK Longitudinal Linkage Collaboration

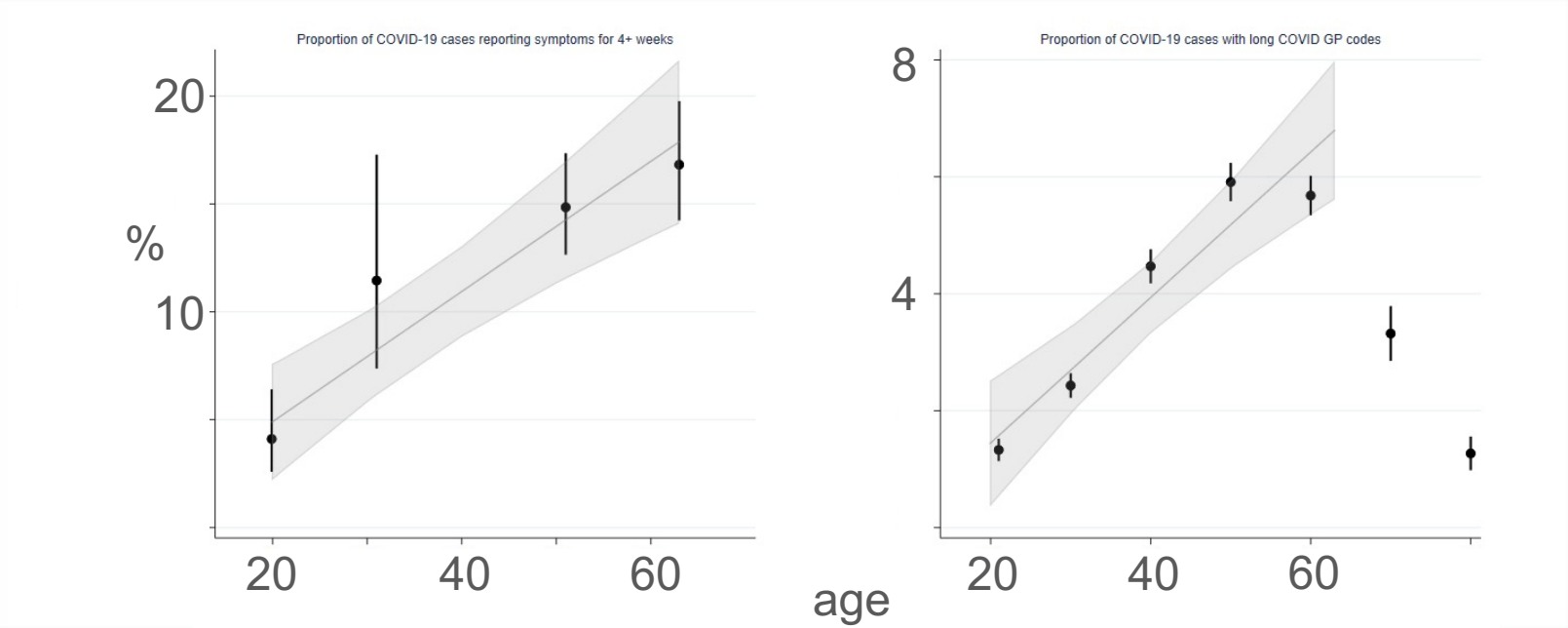
OpenSAFELY

Cohorts

Long COVID (part of SAGE briefing June/July)

Categorised by the UK's National Institute for Health Care and Excellence as acute COVID-19 (AC; lasting up to 4 weeks), ongoing symptomatic COVID-19 (**OSC**; from 4 to 12 weeks), and post-COVID-19 syndrome (**PCS**; over 12 weeks), with the latter two categories combined as 'long COVID'

Thompson et al, medRxiv 2021.06.24.21259277



LEFT - longitudinal studies - proportions reporting symptom length of four or more weeks in COVID-19 cases were ascertained from questionnaire responses.

RIGHT - in OpenSAFELY, proportions represent individuals within 10-year age categories who have long COVID codes in GP records.

COVID-19 Longitudinal Health and Wellbeing National Core Study

COVID-19 LONGITUDINAL HEALTH & WELLBEING NATIONAL CORE STUDY

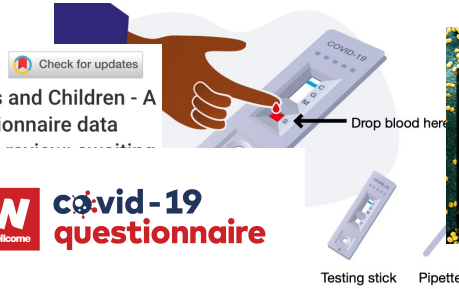
March/April 2020	October 2020	March 2021	Summer + 2021
Early, bespoke sample collection and analysis (UKCiC)	ORIENTGENE (REACT) ALSPAC/TUK/ Edinburgh/EXCEED/ BiB	**THRIVA** **10 studies** **~30k participants** **Ab results coupled with linkage and longitudinal data**	Primary data analysis of new THRIVA results Continuation of bespoke data collection/analysis Alignment with other enterprises to maximise value: CoCONNECT – ATLAS / ISARIC / PHOSP

UK Longitudinal Linkage Collaboration

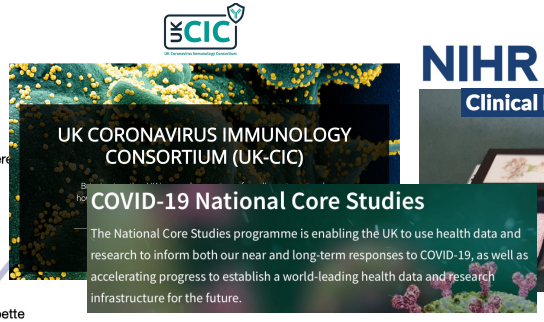
wellcome covid-19 questionnaire

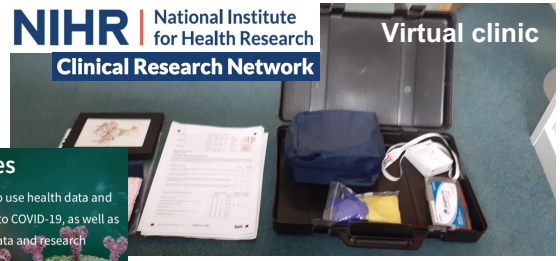
How to wrap up…?

IMPACT 1 – scientific advance – fast, policy relevant, dynamic data collection
IMPACT 2 – communication and engagement with the target population



wellcome covid-19 questionnaire





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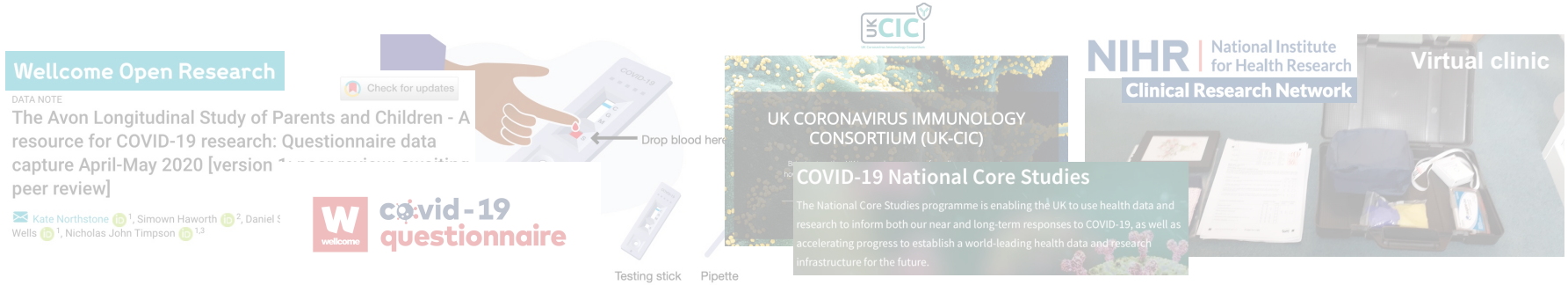
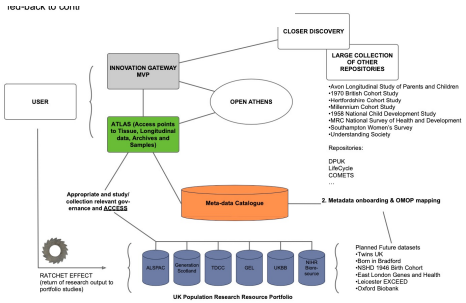
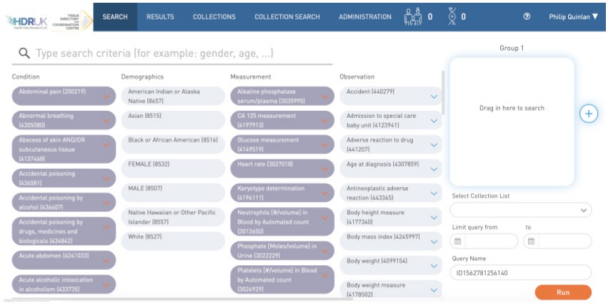
IMPACT 2 – communication and engagement with the target population



CHALLENGE 1 – post COVID_19 spotlight – engagement and maintenance
CHALLENGE 2 – visibility and access – from data collection to use





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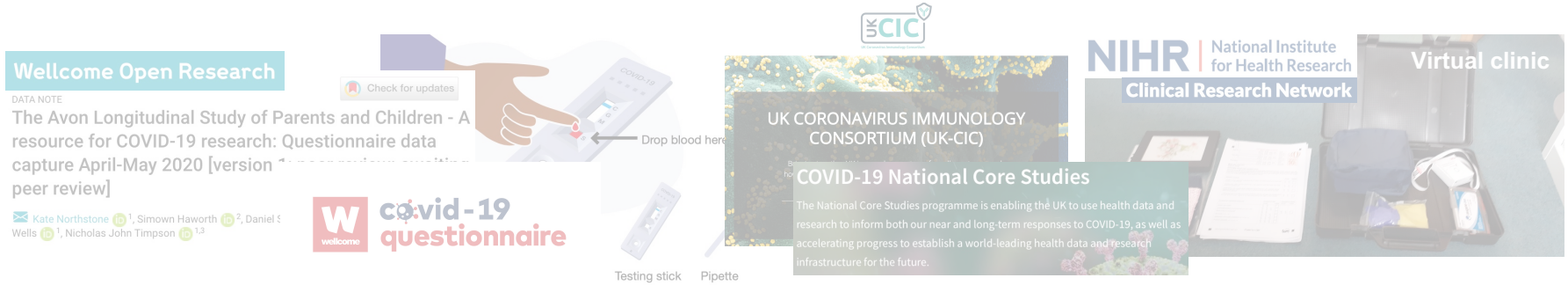

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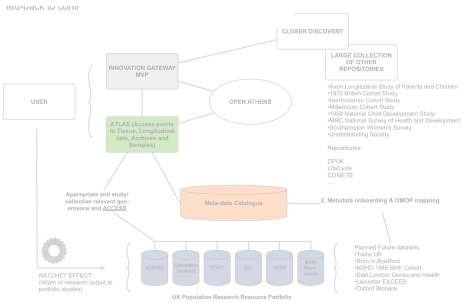
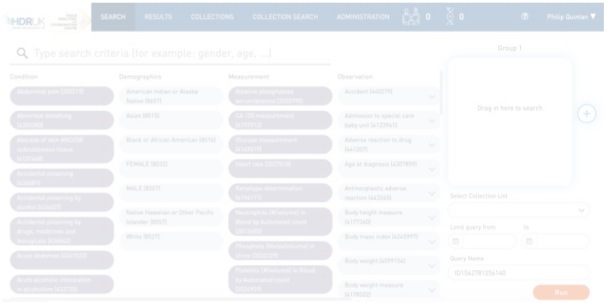
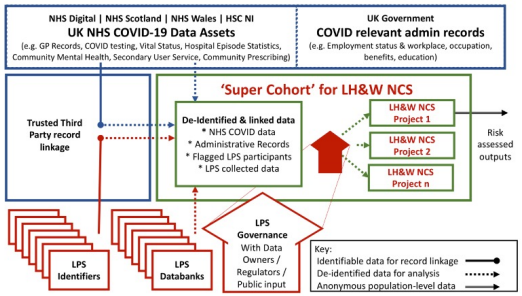
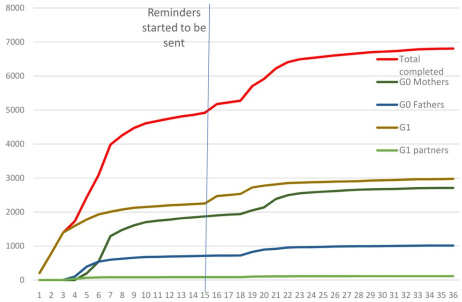




OPPORTUNITY 1 – EHRs and the synergy of scale and bespoke design
OPPORTUNITY 2 – capturing a public understanding of data and research





Potency of longitudinal studies – dynamy and utility amongst other resource types

Investment and support required – maintenance is critical, but requires justification

Headlines when out of the spotlight – needs energy and stakeholder engagement

Breadth and capacity of studies like HUNT, MoBa, HUSK, Tromso, NHS & ALSPAC!

PLEASE reach out and help us to think imaginatively about multi-domain analyses…

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