Mechanisms of Obesity

Theme I: Mechanisms of obesity and type 2 diabetes
Food For Thought 2023

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Swiss Re Institute

thebmj

University of BRISTOL

Acknowledgements and disclosures

Jane Blazeby
Chris Rogers
Graziella Mazza

The By-Band-Sleeve study is funded by the United Kingdom National Institute for Health Research (NIHR) HTA programme (ref: 09/127/53). The views and opinions expressed are those of the authors and do not necessarily reflect those of the HTA programme, the NIHR, the UK NHS or the Department of Health

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Jane Blazeby
Chris Rogers
Graziella Mazza

Roy Taylor
Michael E. J. Lean
Naveed Sattar
Alex McConnachie
Claudia-Martina Messow
Paul Welsh

Disclosures - none

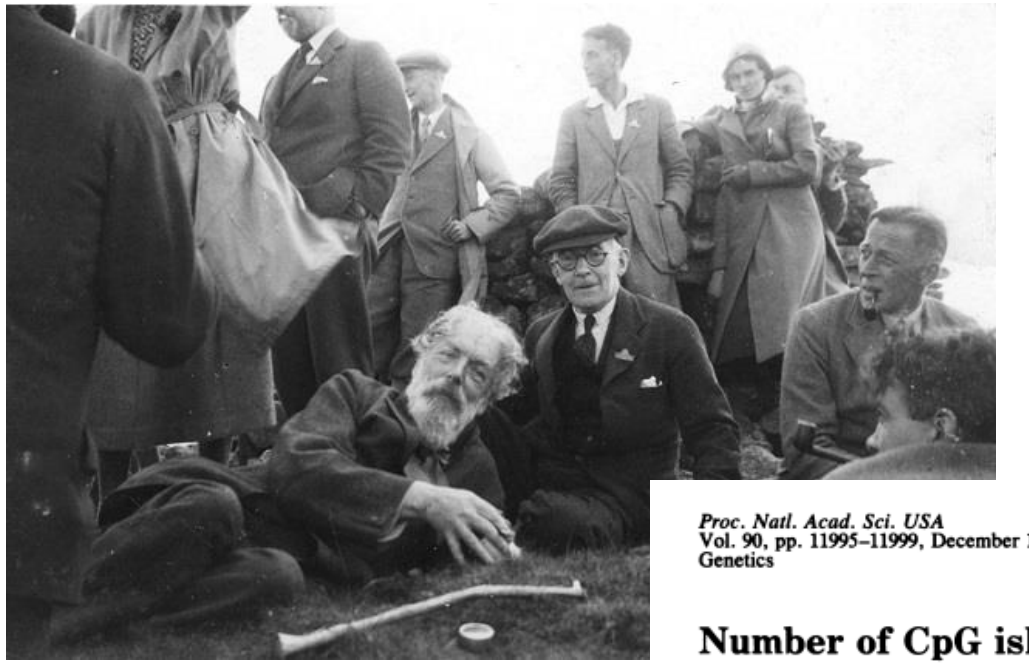
Overview

Conceptualising measures and mechanisms

One example to agree on… one which is challenging

Integrating evidence – helping mechanisms and implications

What can we take away which might open-up discussion?



D'Arcy Wentworth Thompson

On Growth and Form - 1917

Antequera & Bird

PNAS 1993

Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 11995–11999, December 1993
Genetics

Number of CpG islands and genes in human and mou

FRANCISCO ANTEQUERA AND ADRIAN BIRD

Institute of Cell and Molecular Biology, University of Edinburgh, King's Buildings, Edinburgh EH9 3JR, Scotland

Communicated by Stanley M. Gartler, September 17, 1993

ABSTRACT **Estimation of gene number in mammals is difficult due to the high proportion of noncoding DNA within the nucleus. In this study, we provide a direct measurement of the number of genes in human and mouse. We have taken advantage of the fact that many mammalian genes are associated with CpG islands whose distinctive properties allow their physical separation from bulk DNA. Our results suggest that there are ≈45,000 CpG islands per haploid genome in humans and 37,000 in the mouse. Sequence comparison confirms that about 20% of the human CpG islands are absent from the homologous mouse genes. Analysis of a selection of genes suggests that both human and mouse are losing CpG islands over evolutionary time due to *de novo* methylation in the germ line followed by CpG loss through mutation. This process appears to be more rapid in rodents. Combining the number of CpG islands with the proportion of island-associated genes, we estimate that the total number of genes per haploid genome is ≈80,000 in both organisms.**

their absolute number in hum
approach to the number of Cp
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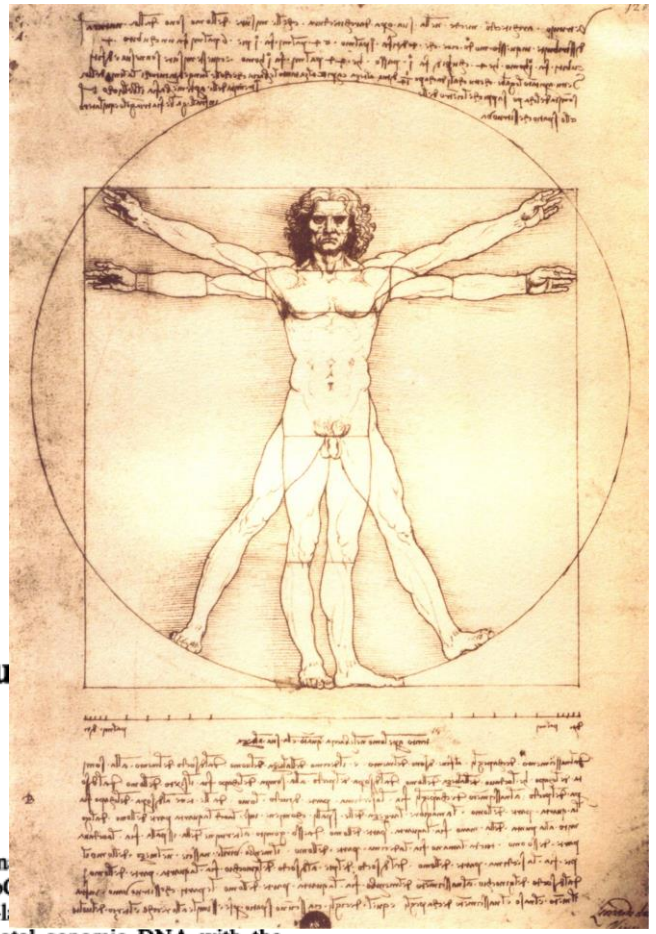
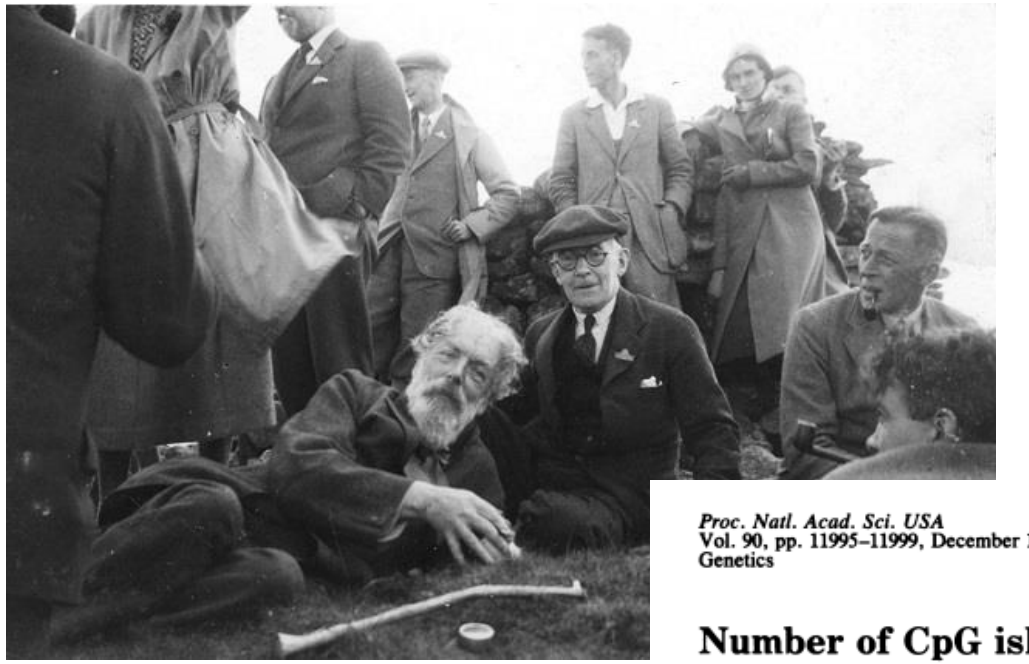
generated upon digestion of total genomic DNA with the methyl-sensitive restriction endonuclease *Hpa* II (8). An approximate figure of 30,000 CpG islands per haploid genome was suggested. Our results show significant differences between mouse and human that are relevant to our understanding of the origin and maintenance of CpG islands.

Because not all genes have CpG islands, the total number of genes cannot be deduced directly from their number. We have taken the study further by establishing the proportion of genes that are CpG island-associated. Combining the number of CpG islands per genome and the percentage of CpG island-associated genes, we obtain a direct estimate of the total number of genes in human and mouse.



Da Vinci c.1487

Vitruvian Man



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"In short, the form of an object is a "diagram of forces".

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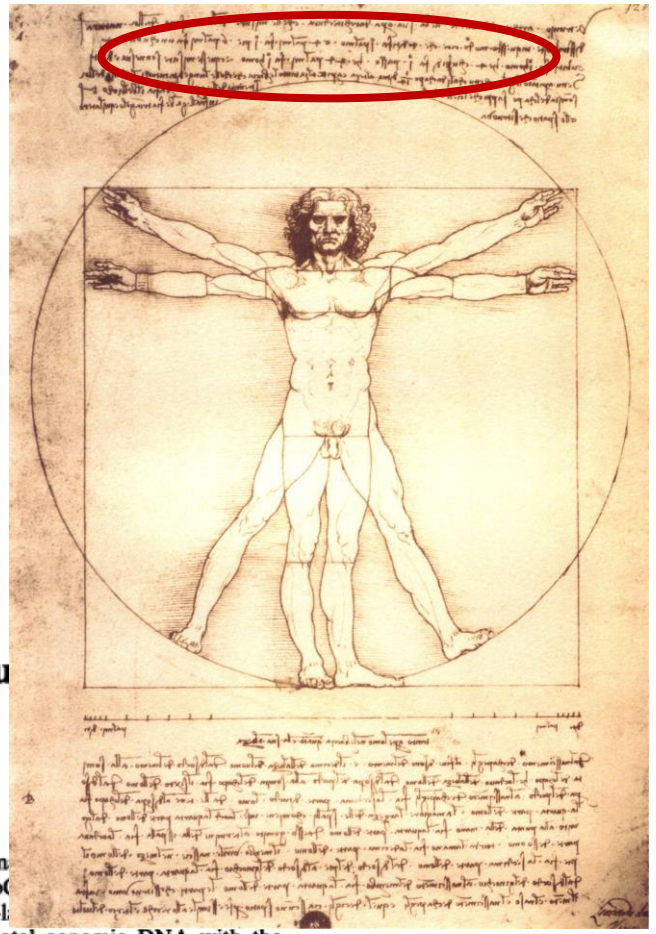

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The evidence is damming and the call for “mechanisms of” is natural

Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies

Prospective Studies Collaboration*

Summary

Background The main associations of body-mass index (BMI) with overall and cause-specific mortality can best be assessed by long-term prospective follow-up of large numbers of people. The Prospective Studies Collaboration aimed to investigate these associations by sharing data from many studies.

Lancet 2009; 373: 1083–96
Published Online
March 18, 2009
DOI:10.1016/S0140-

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults

Krishnan Bhaskaran, Ian Douglas, Harriet Forbes, Isabel dos-Santos-Silva, David A Leon, Liam Smeeth

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Background High body-mass index (BMI) predisposes to several site-specific cancers, but a large-scale systematic and detailed characterisation of patterns of risk across all common cancers adjusted for potential confounders has not previously been undertaken. We aimed to investigate the links between BMI and the most common site-specific cancers.

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Published Online
August 14, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60892-8

PLOS MEDICINE

RESEARCH ARTICLE

The global burden of disease attributable to high body mass index in 195 countries and territories, 1990–2017: An analysis of the Global Burden of Disease Study

Haijiang Dai[1,2], Tariq A. Alsalhe[3], Nasr Chalghaf[4,5], Matteo Riccò[6], Nicola Luigi Bragazzi[2]*, Jianhong Wu[2]*

Over 4 billion people may have overweight or obesity (BMI ≥25kg/m^2) by 2035… this reflects

An increase from 38% of the world’s population in 2020 to over 50

An increase in prevalence of obesity (BMI ≥30kg/m^2) from14% to 24%.

World Obesity Atlas – World Obesity Federation 2023

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BMJ

Original Article
EPIDEMIOLOGY/GENETICS

The Role of Inflammatory Cytokines as Intermediates in the Pathway from Increased Adiposity to Disease

Obesity

DOI: 10.1002/oby.23441

ORIGINAL ARTICLE
Epidemiology/Genetics

A multivariant recall-by-genotype study of the metabolomic signature of BMI

Obesity THE OBESITY SOCIETY WILEY

Published 18 July 2013)

RESEARCH

International Journal of Obesity

ARTICLE OPEN

Epidemiology and Population Health

Effects of adiposity on the human plasma proteome: observational and Mendelian randomisation estimates

Original Article
EPIDEMIOLOGY/GENETICS

Obesity

BMI and Mortality in UK Biobank: Revised Estimates Using Mendelian Randomization

Kaitlin H. Wade [1,2], David Carslake[1,2], Naveed Sattar[3], George Davey Smith[1,2], and Nicholas J. Timpson[1,2]

OPEN ACCESS Freely available online PLOS MEDICINE

The Effect of Elevated Body Mass Index on Ischemic Heart Disease Risk: Causal Estimates from a Mendelian Randomisation Approach

Børge G. Nordestgaard[1,2,3,4]*, Tom M. Palmer[5,6]*, Marianne Benn[1,2,4], Jeppe Zacho[1,2,4], Anne Tybjærg-Hansen[2,3,4,7], George Davey Smith[5,6], Nicholas J. Timpson[5,6]*

International Journal of Obesity (2011) 35, 300–308

www.nature.com/ijo

ORIGINAL ARTICLE

C-reactive protein levels and body mass index: elucidating direction of causation through reciproca Mendelian randomization

NJ Timpson[1], BG Nordestgaard[2,3], RM Harbord[1,4], J Zacho[2,3], TM Frayling[5,6], A Tybjærg-Hansen[2,7] and G Davey Smith[1]

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 3, 2009
Published online on November 3, 2008; doi: 10.1359/JBMR.081109

How Does Body Fat Influence Bone Mass in Childhood? Randomization Approach

Nicholas J Timpson,[1] Adrian Sayers,[2] George Davey-Smith,[1] and Jonathan H T

Obesity

Does Greater Adiposity Increase Blood Pressure and Hypertension Risk?

Mendelian Randomization Using the *FTO/MC4R* Genotype

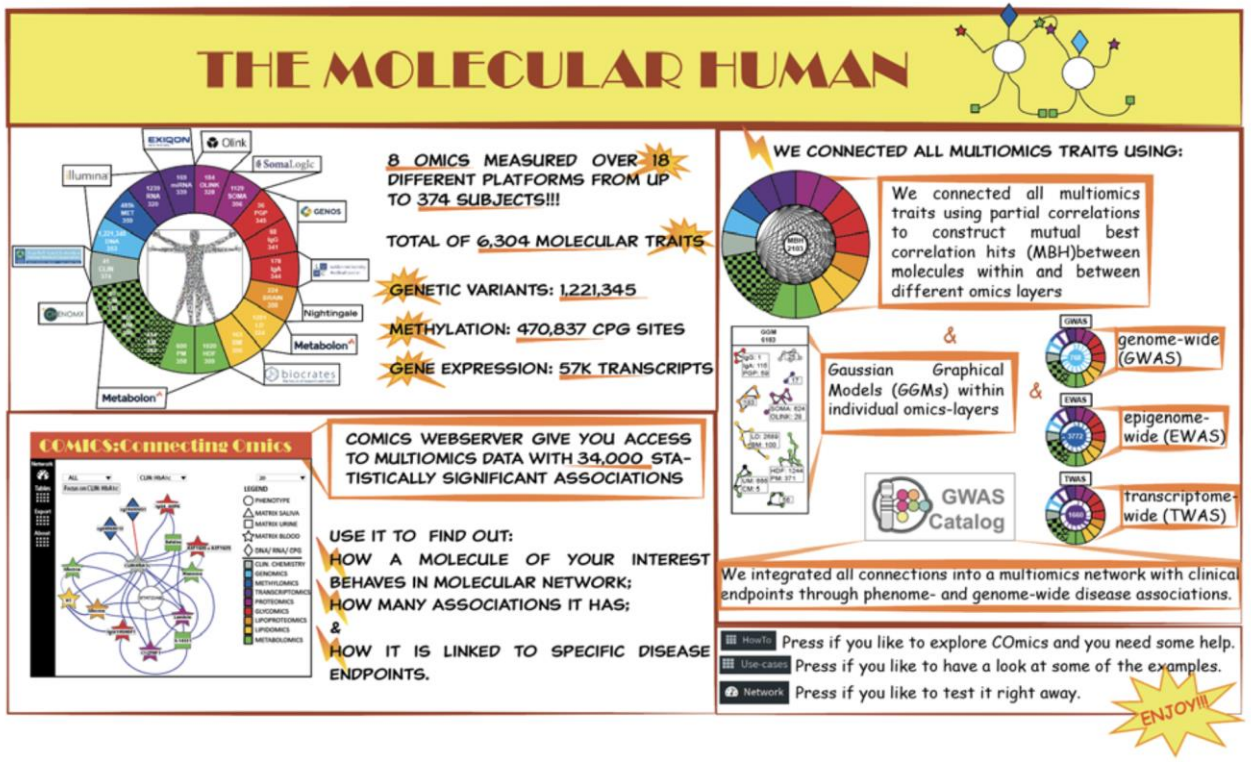
Nicholas J. Timpson, Roger Harbord, George Davey Smith, Jeppe Zacho, Anne Tybjærg-Hansen, Børge G. Nordestgaard

PLOS MEDICINE

RESEARCH ARTICLE

The blood metabolome of incident kidney cancer: A case–control study nested within the MetKid consortium

What kind of measurement and analytical world are we in right now?



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Director of Bioinformatics Core at
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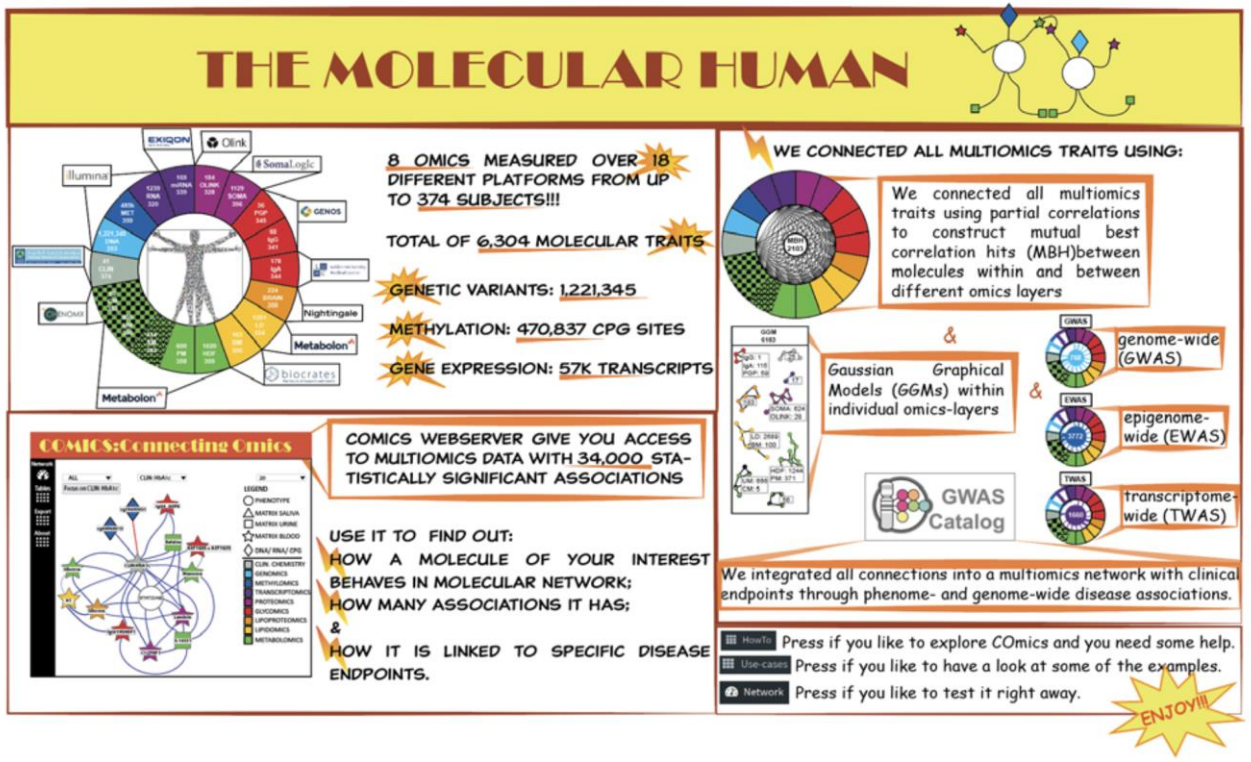

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Director of Bioinformatics Core at
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nature medicine
LETTERS
https://doi.org/10.1038/s41591-019-0665-2

Plasma protein patterns as comprehensive indicators of health

Stephen A. Williams[1,12*], Mika Kivimaki[2], Claudia Langenl
J. P. Casas[7], Claude Bouchard[8], Christian Jonasson[9], Mark A
Leigh Alexander[1], Jessica Ash[1], Tim Bauer[1], Jessica Chadwick[1]
Yolanda Hagar[1], Michael Hinterberg[1], Rachel Ostroff[1], Sophie
Nicholas J. Wareham[3,12]

nature genetics
Article
https://doi.org/10.1038/s41588-022-01270-1

Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases

Received: 14 March 2022
Accepted: 18 November 2022
Published online: 12 January 2023
Check for updates

Yiheng Chen[1,2], Tianyuan Lu[1,3,4], Ulrika Pettersson-Kymmer[5], Isobel D. Stewart[6], Guillaume Butler-Laporte[1,7], Tomoko Nakanishi[1,2,8,9], Agustin Cerani[1,7], Kevin Y. H. Liang[1,3], Satoshi Yoshiji[1,2,8,9], Julian Daniel Sunday Willett[1,3,10], Chen-Yang Su[1,11], Parminder Raina[12,13], Celia M. T. Greenwood[1,3,7,14], Yossi Farjoun[1,4,15,16], Vincenzo Forgetta[1,4], Claudia Langenberg[17,18,6], Sirui Zhou[1,2], Claes Ohlsson[19,20] & J. Brent Richards[1,2,4,7,21,22]

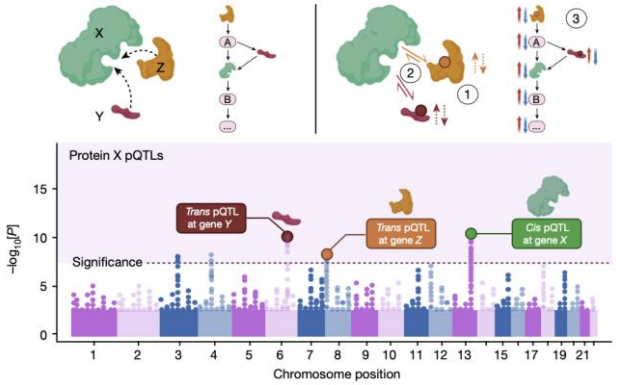
Article

Plasma proteomic associations with genetics and health in the UK Biobank

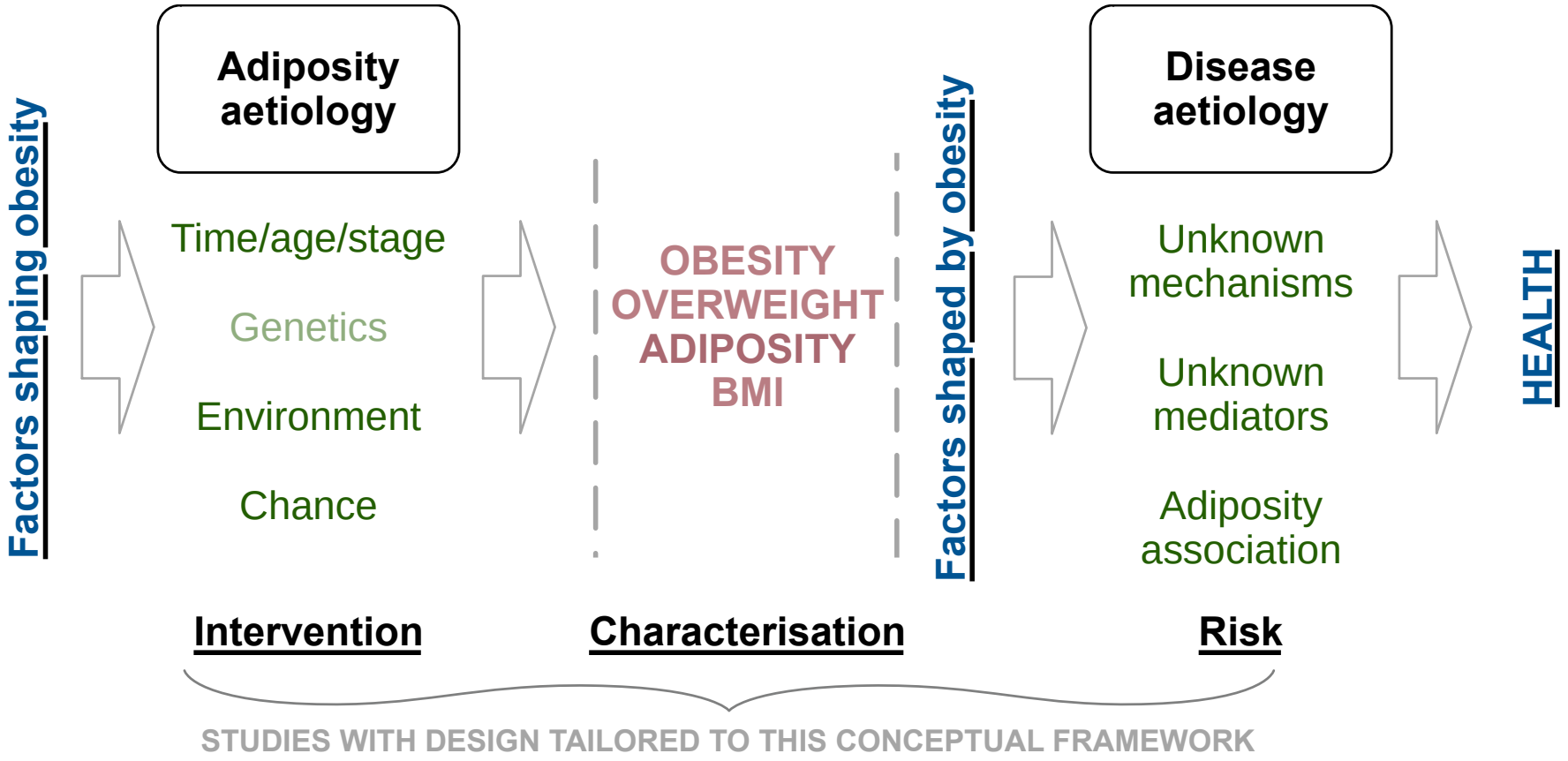
nature

Sun et al, October 2023

Ben Sun (Cambridge) & Chris Whelan (J&J)



…so what does this mean for “mechanisms of obesity”? Is it as easy as it sounds?



“Moving from measures to mechanisms: lessons in inference…”

Overview

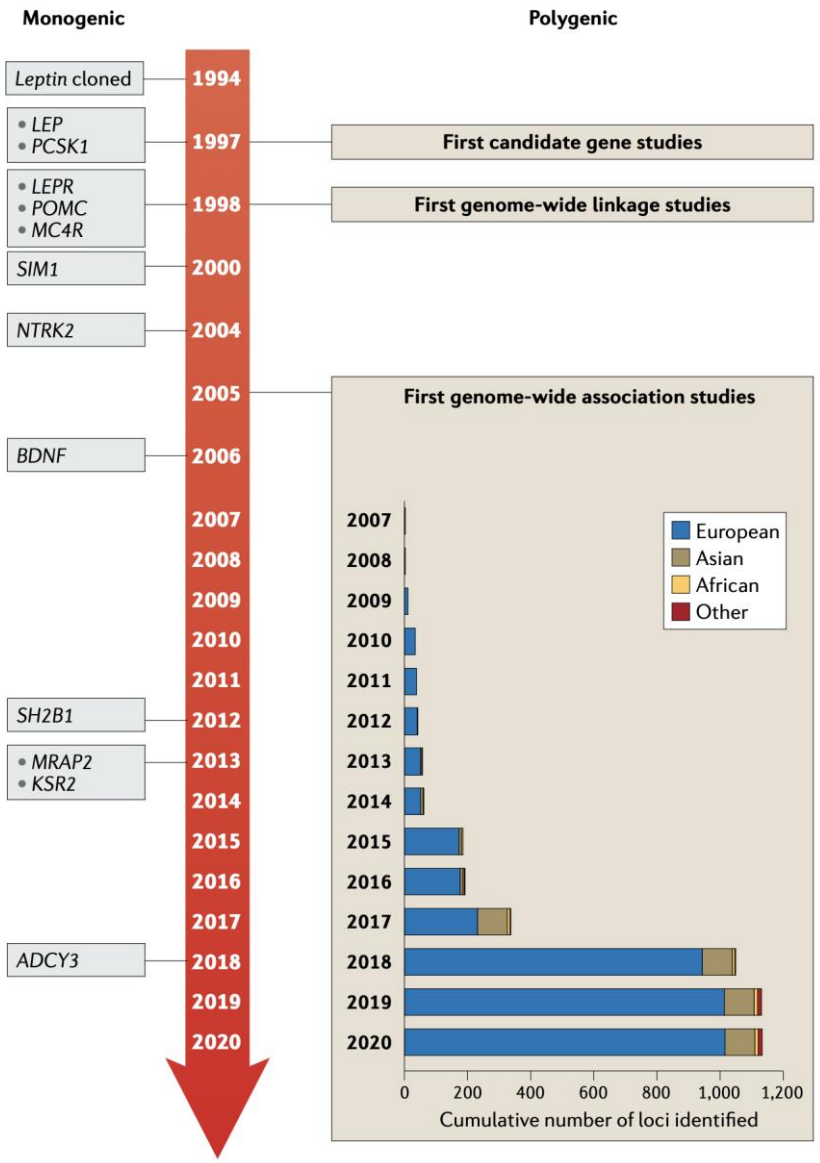
Conceptualising measures and mechanisms

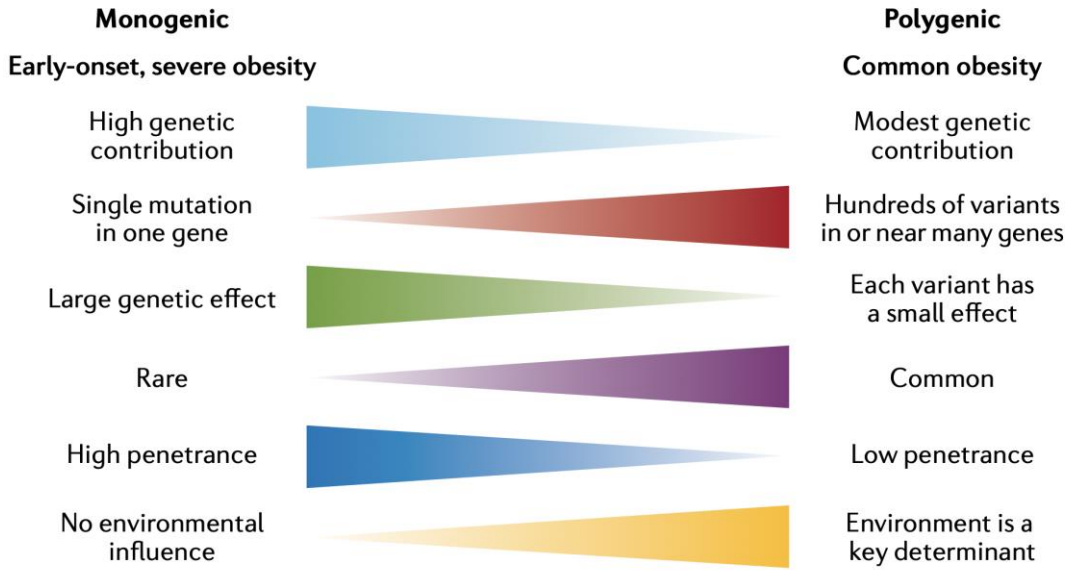
One example to agree on… one which is challenging

Integrating evidence – helping mechanisms and implications

What can we take away which might open-up discussion?

Genetic contributions to obesity

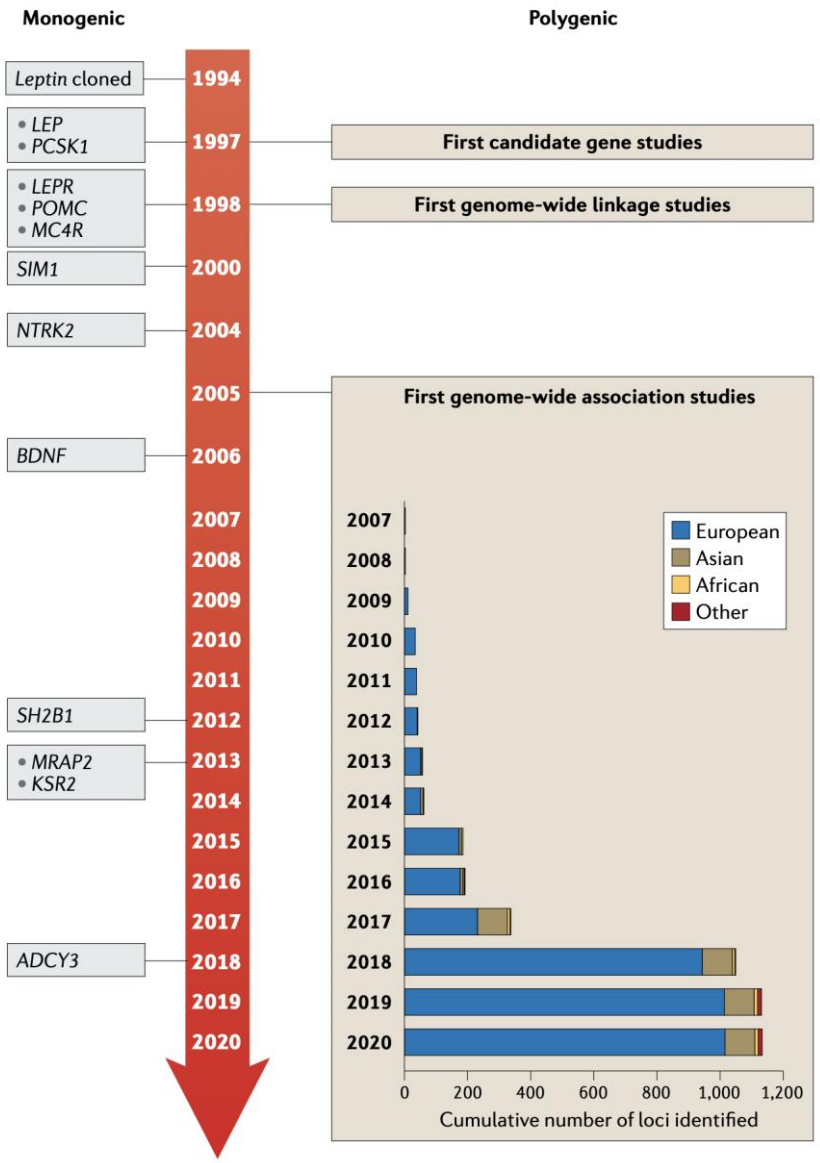




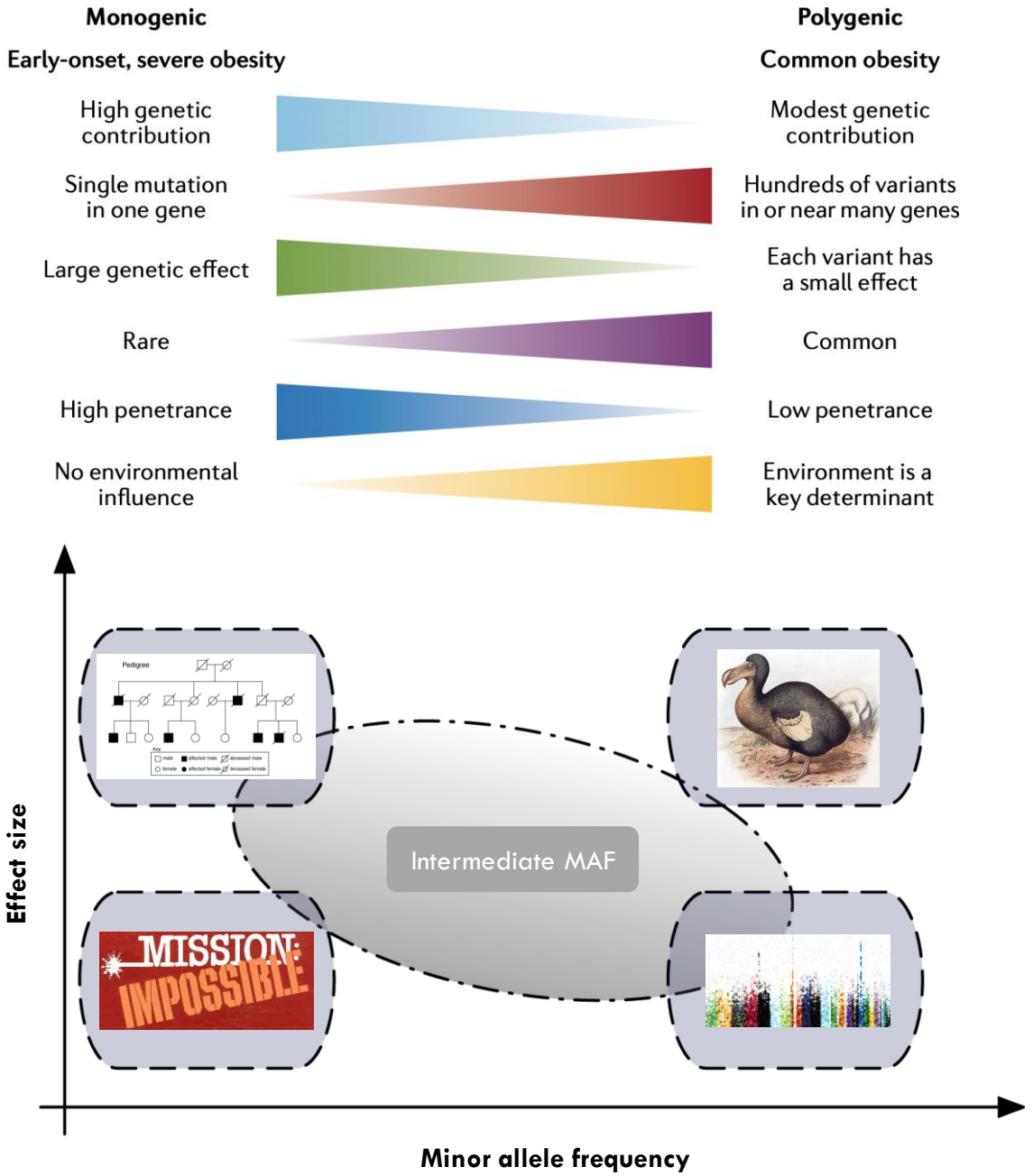
Nature Reviews Genetics 2022

Ruth Loos (Copenhagen) & Giles Yeo (Cambridge)

Genetic contributions to obesity



Loos & Yeo Nature Reviews Genetics 2022



Timpson et al Nature Reviews Genetics 2017

OXFORD

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

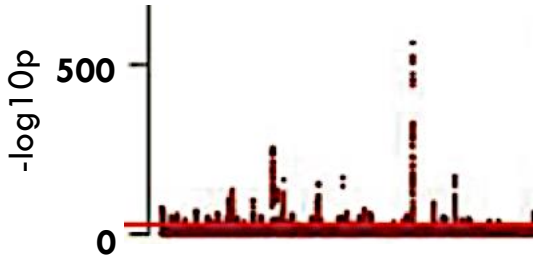
doi: 10.1093/hmg/ddy271
Advance Access Publication Date: 16 August 2018
Association Studies Article

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

GIANT CONSORTIUM



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

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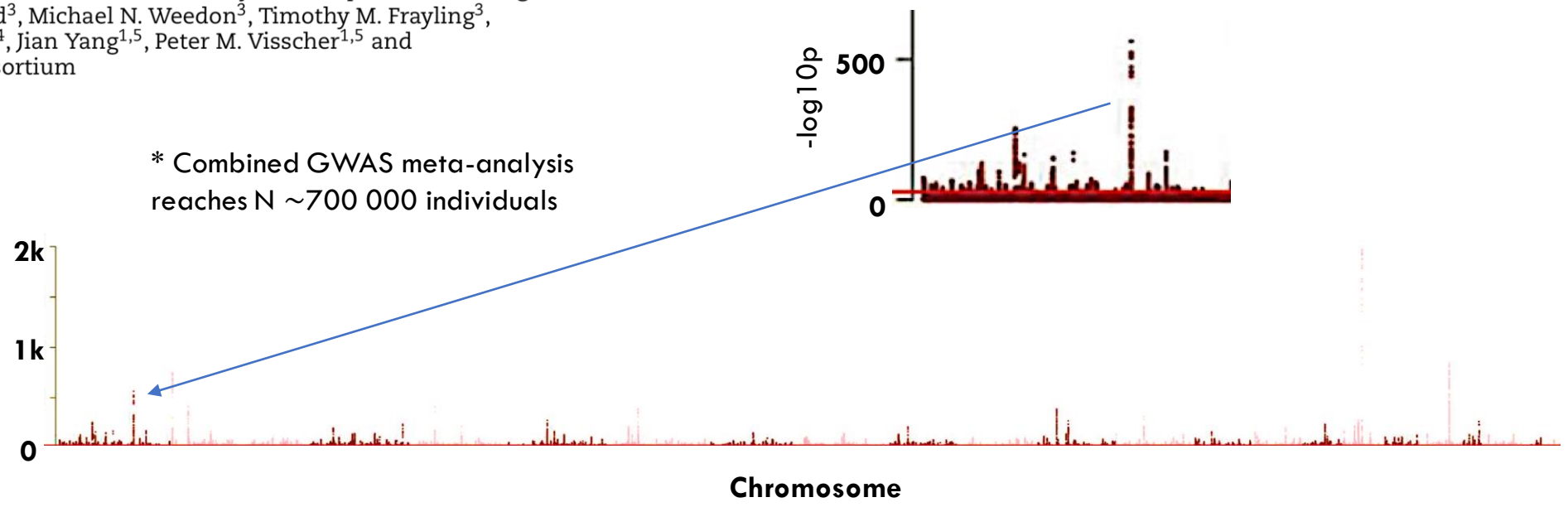
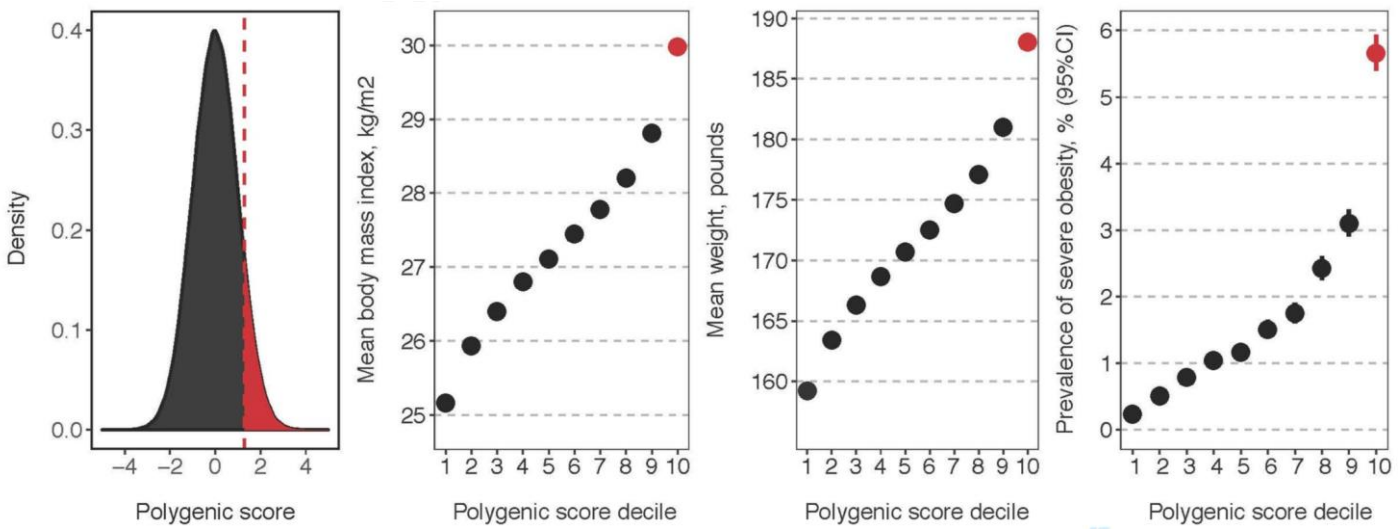


* >900 independent SNPs associated with BMI
* Genome-wide significant SNPs explain ~6.0% of the variance of BMI

Application of genetic risk scores as polygenic predictors

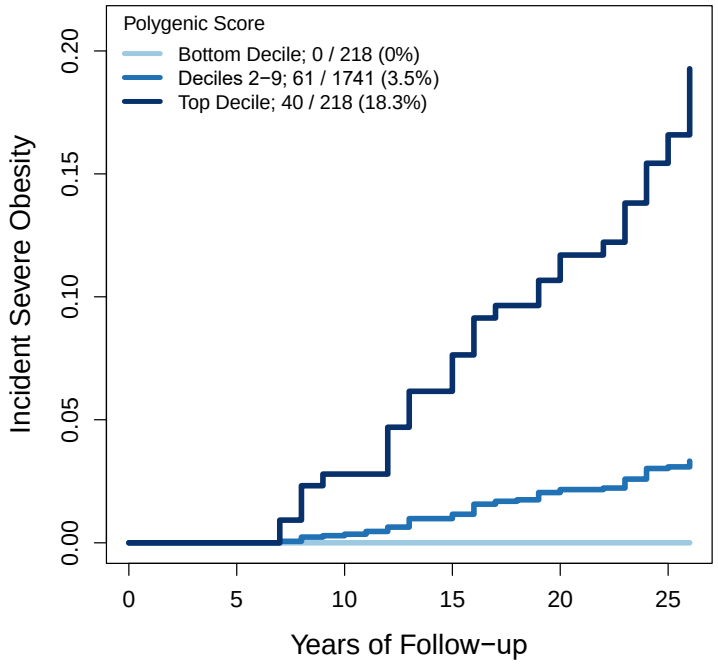


Polygenic score for body-mass index (BMI)

2,100,302 genetic variants

Tested in 119,951 **UK Biobank** participants

Validated it in 288,018 participants



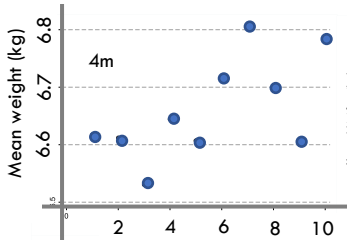
~2k young participants in **Framingham Offspring Study**

~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

Amit Khera (Boston) & Kaitlin Wade (Bristol)

Cell 2019



Children of the 90s
(ALSPAC)
www.bristol.ac.uk/alspac

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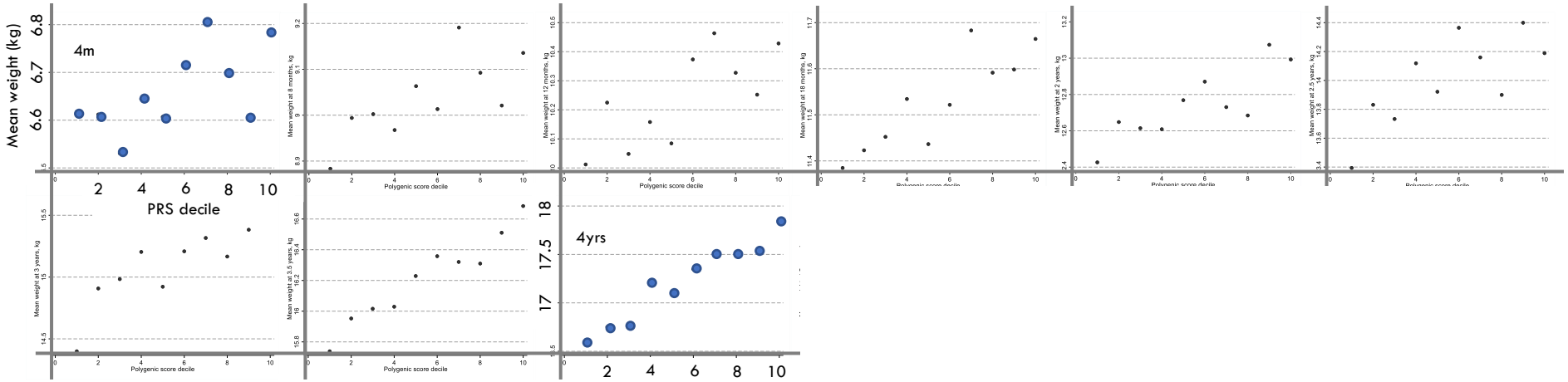

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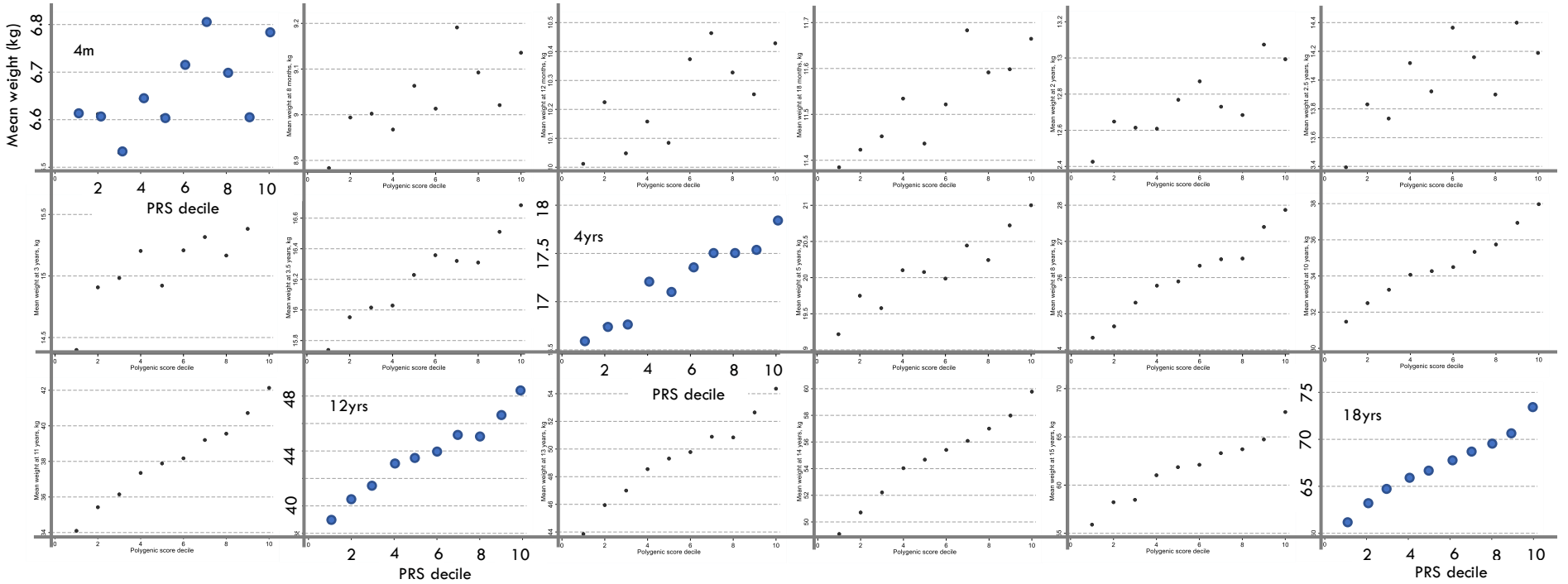

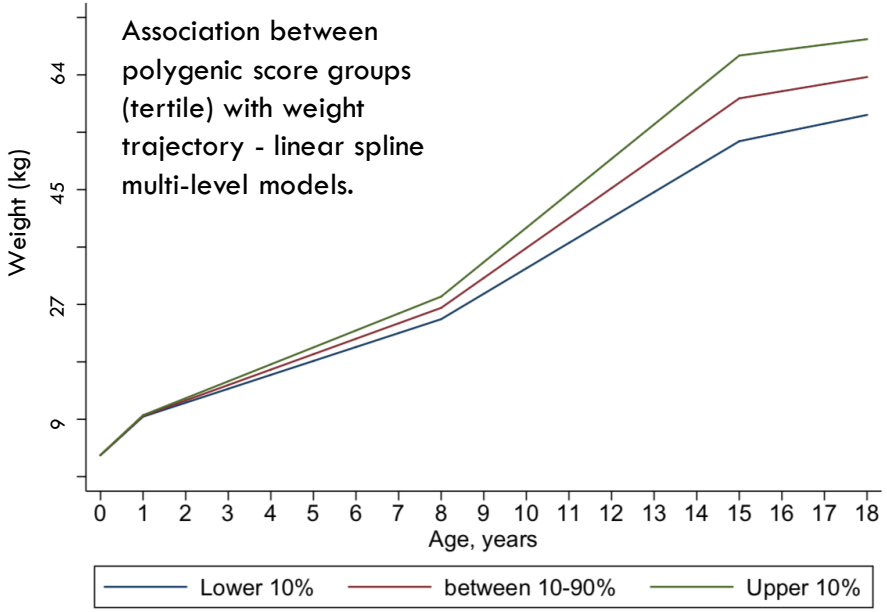

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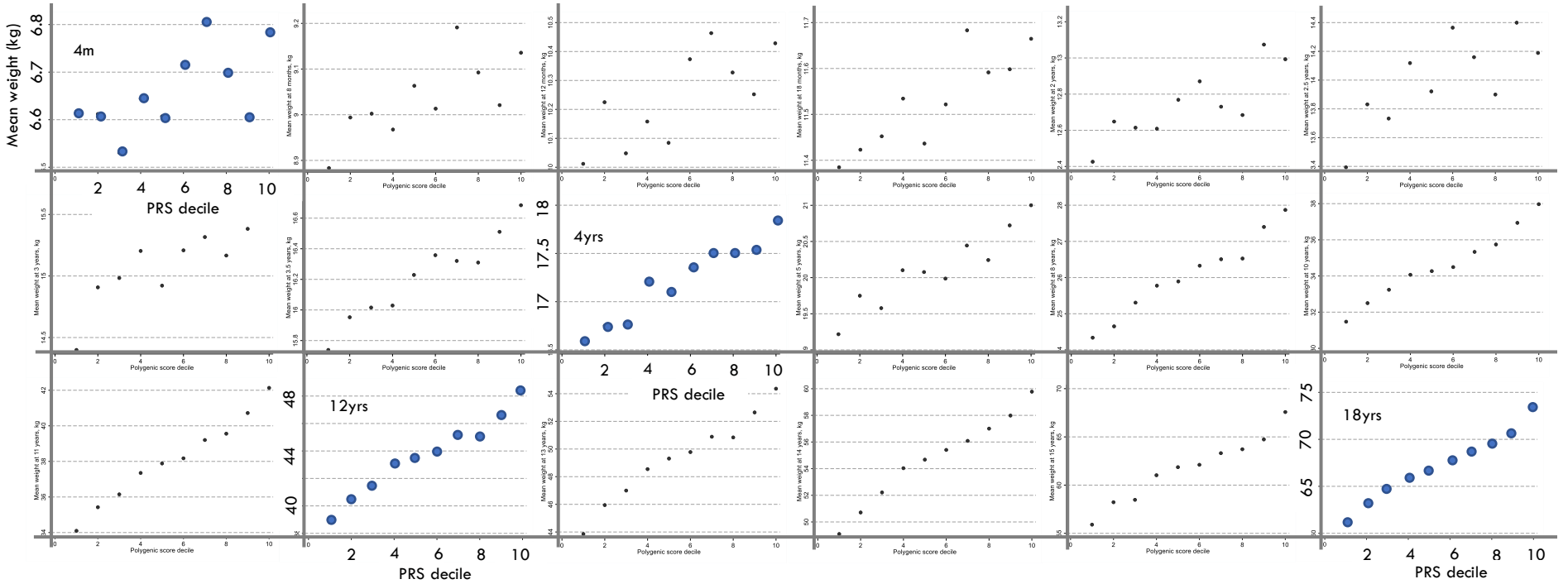

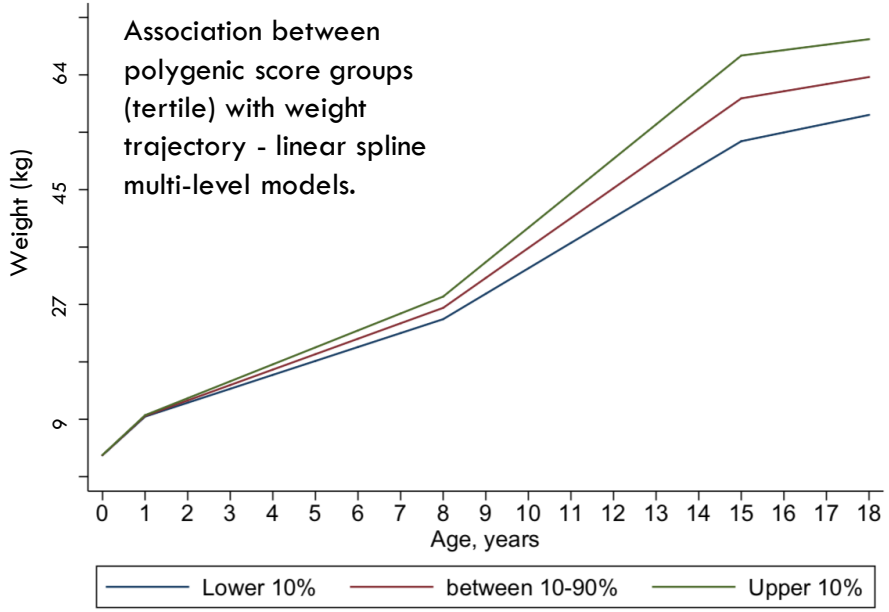

Sociodemographic factor	Estimate (95% CI)[1]	P-value
Family income (per week)	-0.03 (-0.06, -0.01)	0.002
Maternal highest qualification	-0.05 (-0.07, -0.03)	2.87×10^{-06}
Paternal highest qualification	-0.03 (-0.05, -0.01)	0.003
Household social class	0.02 (-0.002, -0.05)	0.07

Association between sociodem' factors and polygenic score

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

OXFORD

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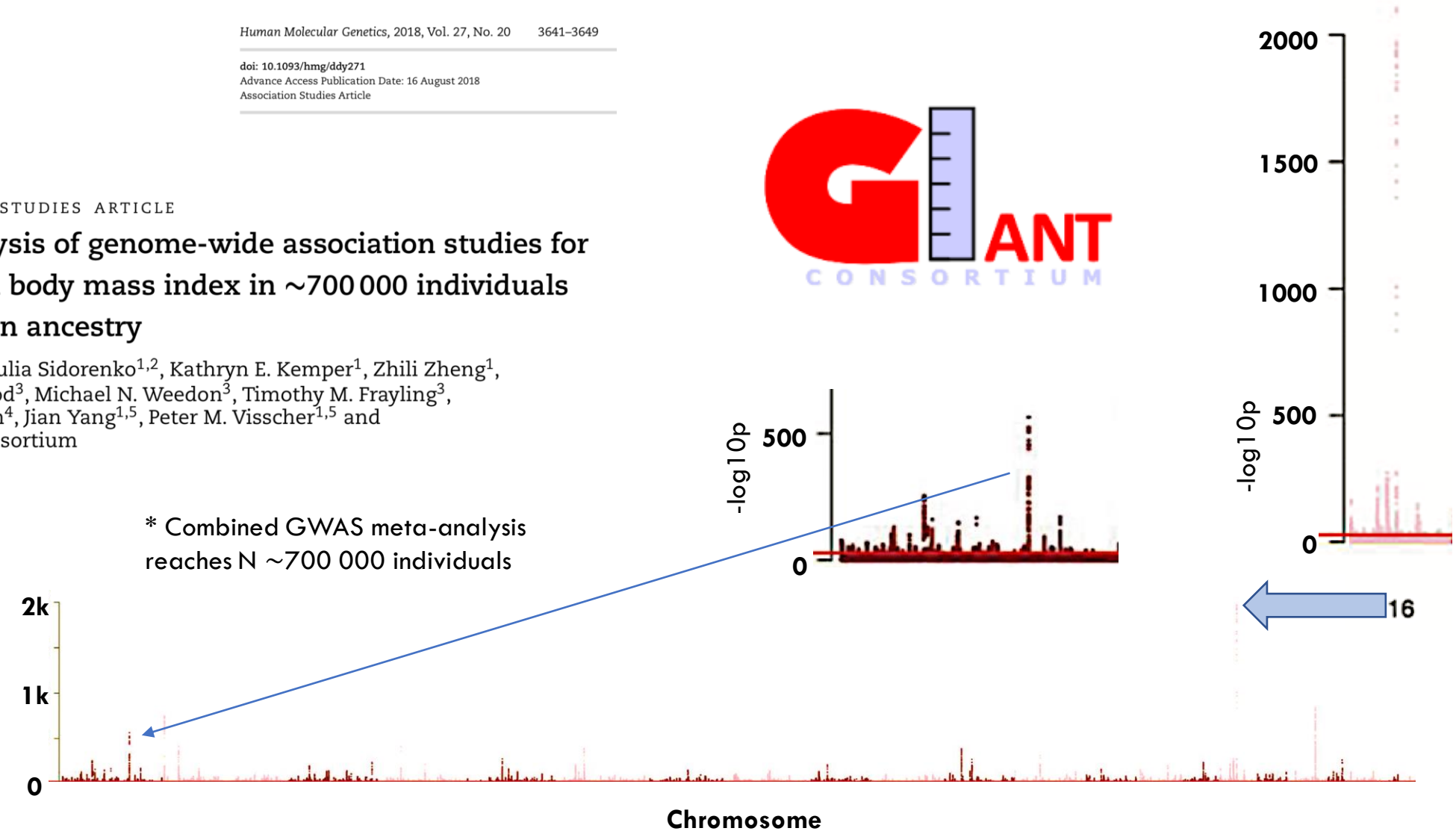
Meta-analysis of genome-wide association studies for height and body mass index in ~700 000 individuals of European ancestry

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



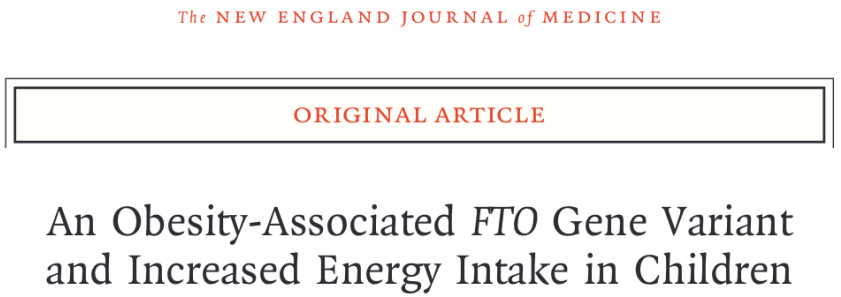
* Combined GWAS meta-analysis reaches N ~700 000 individuals

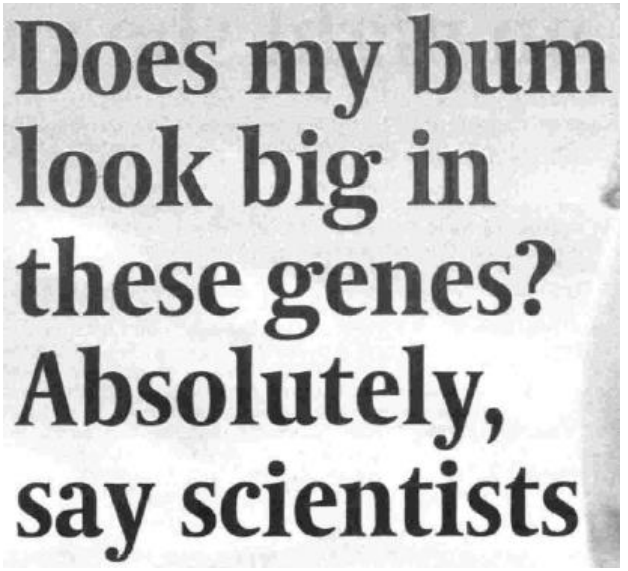
* >900 independent SNPs associated with BMI
* Genome-wide significant SNPs explain ~6.0% of the variance of BMI

What is less known is the aetiology of these signals

E.g. the fat mass and obesity related locus *FTO*, first reported in human in 2007

Was immediately implicated in possible associations with energy intake and dietary composition – though work was based on relatively small and imprecisely measured epidemiological data (Cecil et al 2008 & Timpson et al 2008).





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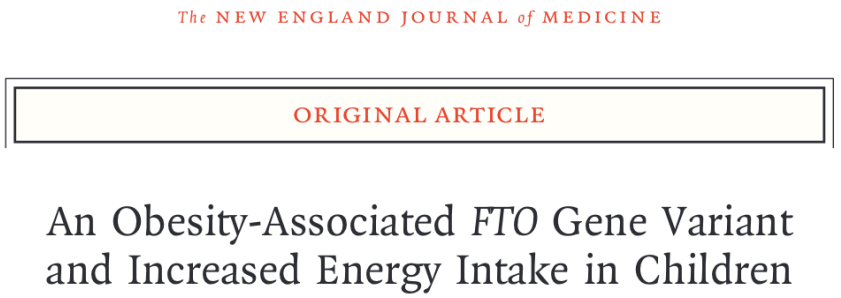
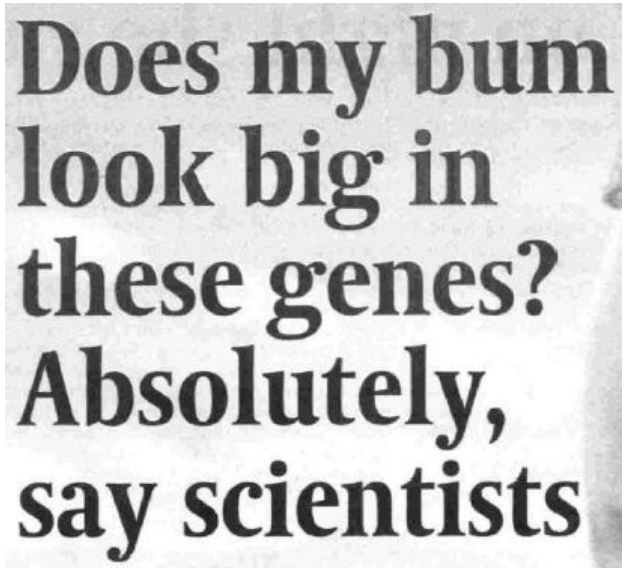
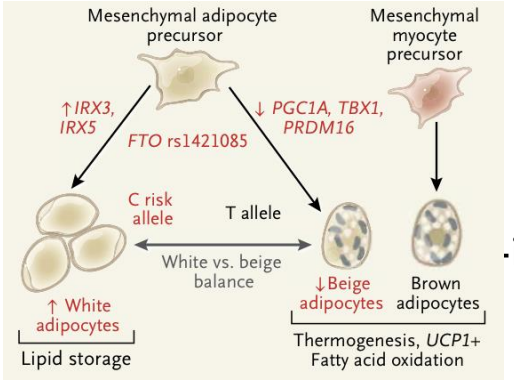




Since then, work concentrating on apparently functional "*FTO*" alleles (which have an impact on the expression of local genes IRX3/5 during early adipogenesis) has suggested repression of mitochondrial thermogenesis in adipocyte precursor cells

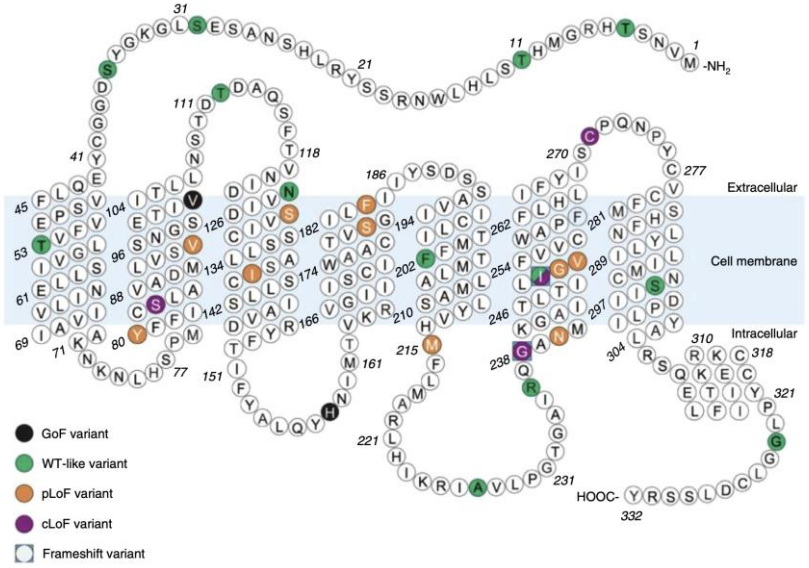


shift from heat producing adipocytes to energy-storing
pocytes with a reduction in thermogenesis, as well as an increase
in lipid storage or thermogenic capacity and resistance to high-fat
-induced adiposity (Claussnitzer et al 2015 & Zang et al 2023).

Can rare variants help to get closer to aetiology?

Kaitlin Wade (Bristol), Steve O'Rahilly & Brian Lam (Cambridge)

Using identified rare variants in ***MC4R*** to assess impact and frequency



G-protein coupled, seven-transmembrane receptor expressed widely in the central nervous system.

Binding of its natural agonists results in the suppression of food intake and activation of a subset of autonomic neurons of the sympathetic nervous system.

Severe early-onset obesity has been reported in multiple affected members of several families who only carried heterozygote LoF mutation, but not all...

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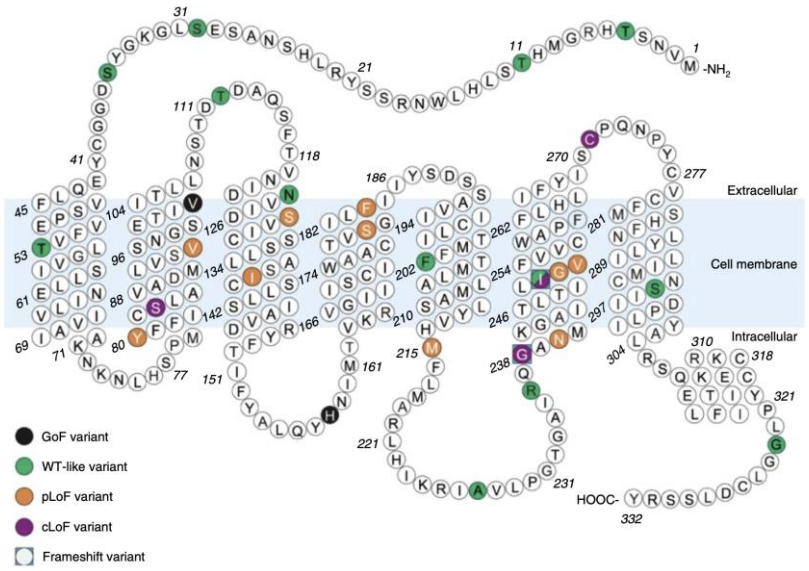
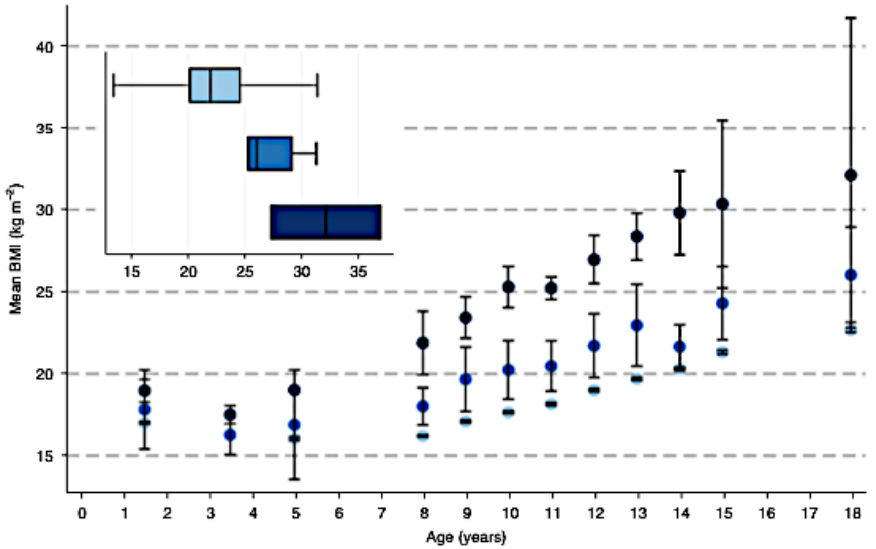


MC4R LoF mutations associated with BMI across the life course. Further, these are effects which exceed polygenic contributions.



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

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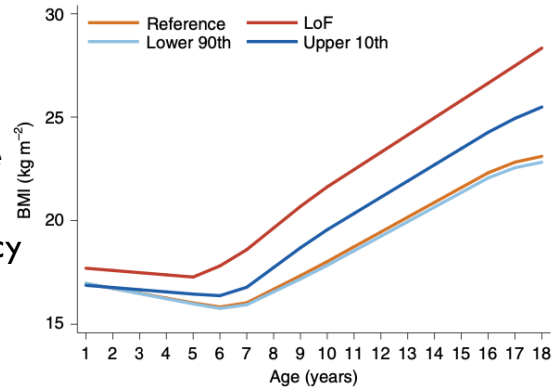
Heterozygous mutations that impair the function of the *MC4R* gene may very well be found in several millions of people worldwide a frequency of

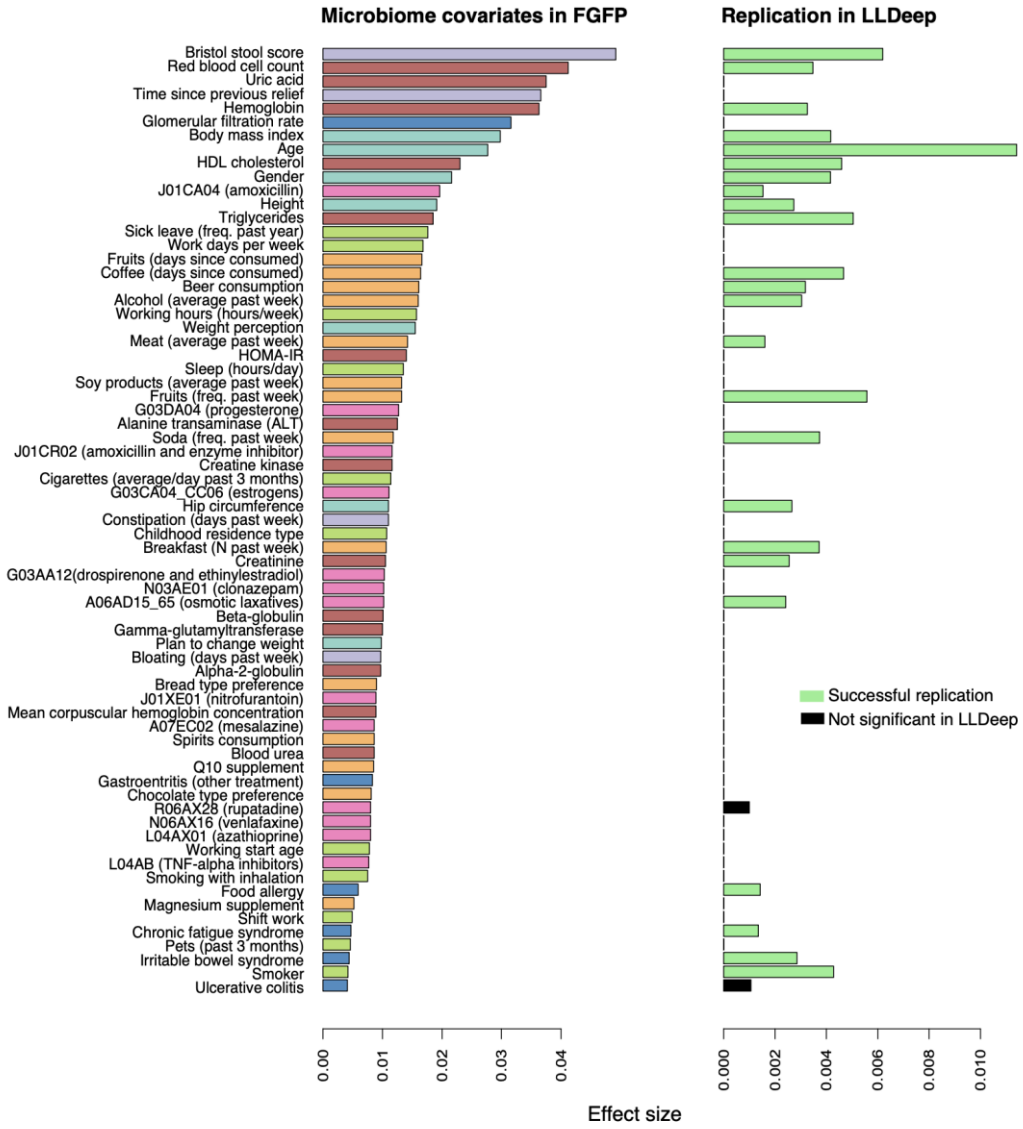
~1 in 340

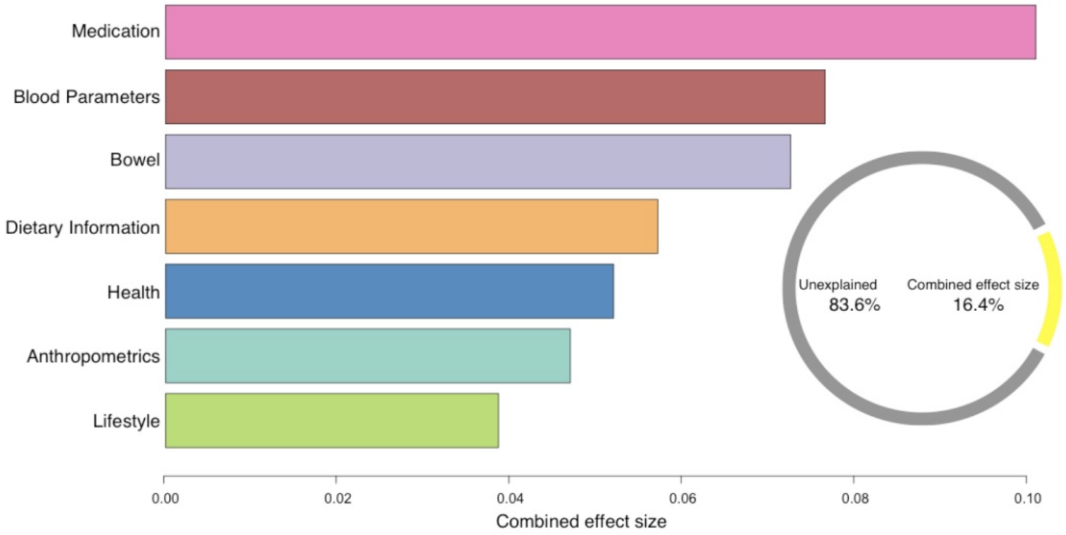


Wade et al Nat Med 2021

More challenging… the microbiome and potential role(s) in obesity

David Hughes (Pennington Biomed')
& Jeroen Raes (Leuven)

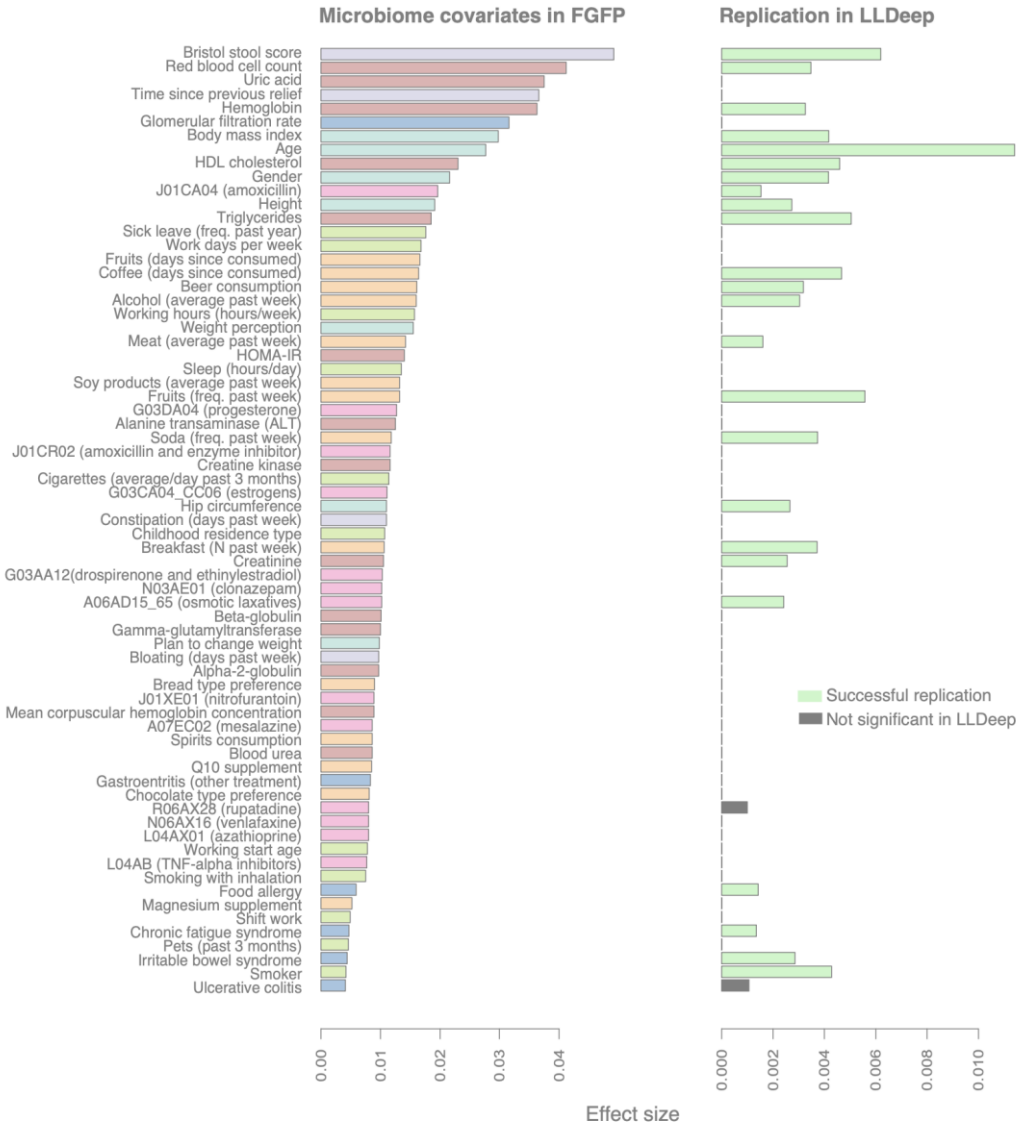


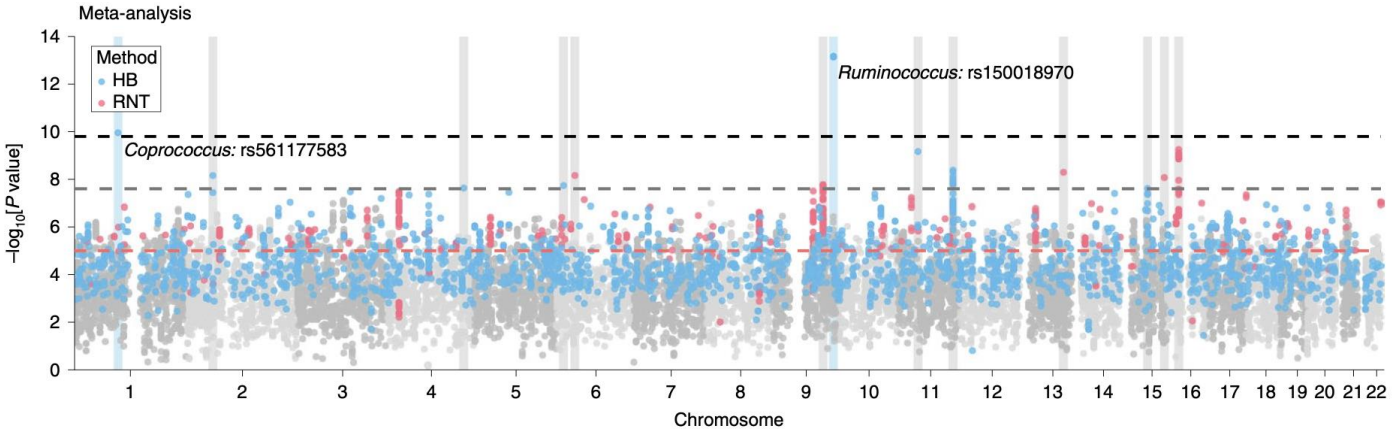


% community variation
(All covariates correlated with alpha-diversity measures & taxa abundances)

Falony et al, Science 2016

More challenging… the microbiome and potential role(s) in obesity





Faecal 16S ribosomal RNA gene sequences and host genotype data.

Flemish Gut Flora Project ($n = 2{,}223$), FoCus, $n = 950$ & PopGen, $n = 717$)

Two associations achieved a study-level threshold of $P = 1.57 \times 10^{-10}$

Ruminococcus and rs150018970 near *RAPGEF1* on chr 9

Coprococcus and rs561177583 within *LINC01787* on chr 1

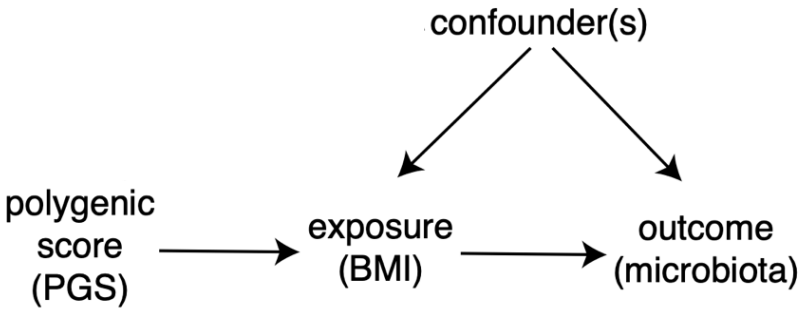
Exploratory analyses were undertaken using 11 other genome-wide associations ($P < 2.5 \times 10^{-8}$) gave one signal - rs4988235 (*MCM6/LCT*) and *Bifidobacterium*.

Evidence of signal overlap with other genome-wide association studies (age at menarche and cardiometabolic traits).

Falony et al, Science 2016

Hughes et al, Nat Micro 2020

More challenging… the microbiome and potential role(s) in obesity



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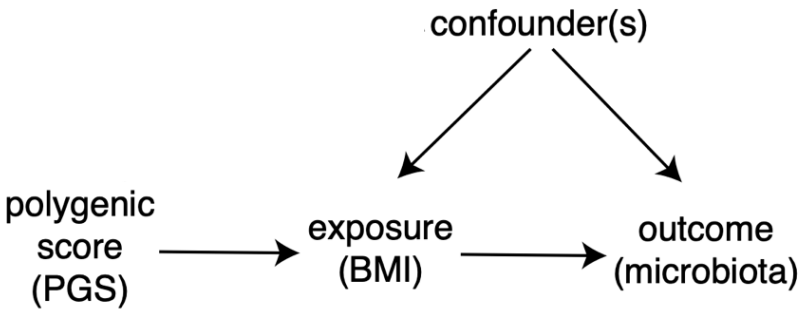


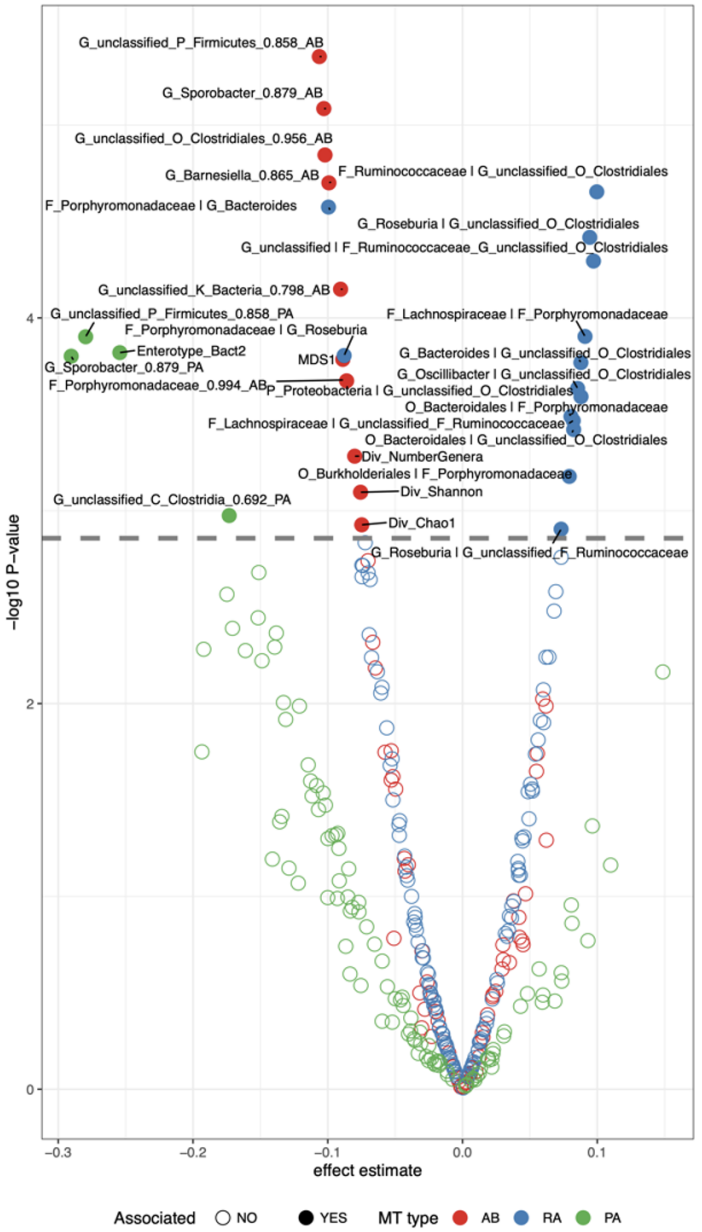
Observational and MR effect estimates were showed concordance.

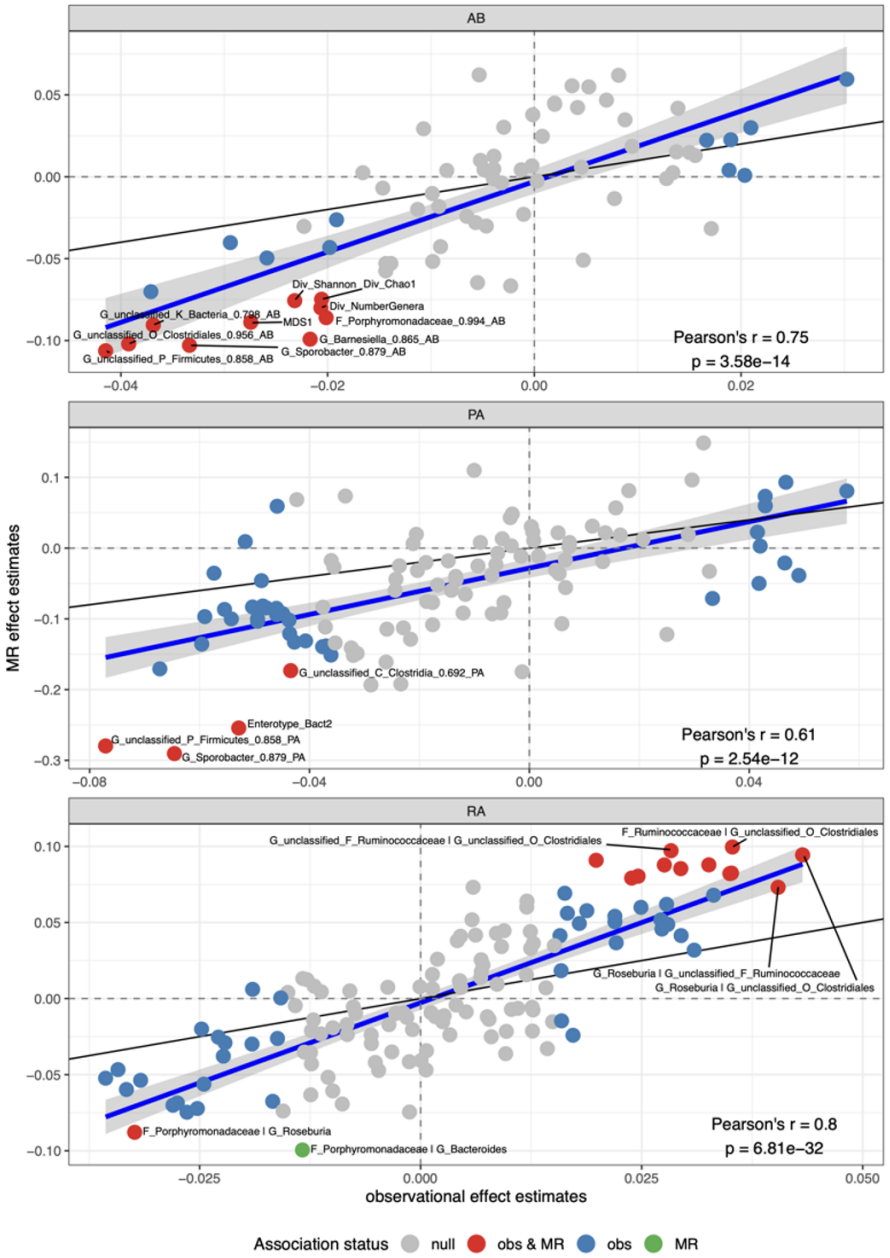
A total of 28 microbiome traits presented evidence to suggest that BMI causally influences variation.

This included (with increases in BMI):

- reduction in diversity
- decrease in the abundance of genera
- altered family/genus ratios across microbiome traits.
- altered odds of assignment to enterotypes

Hughes et al, **unpublished**





Overview

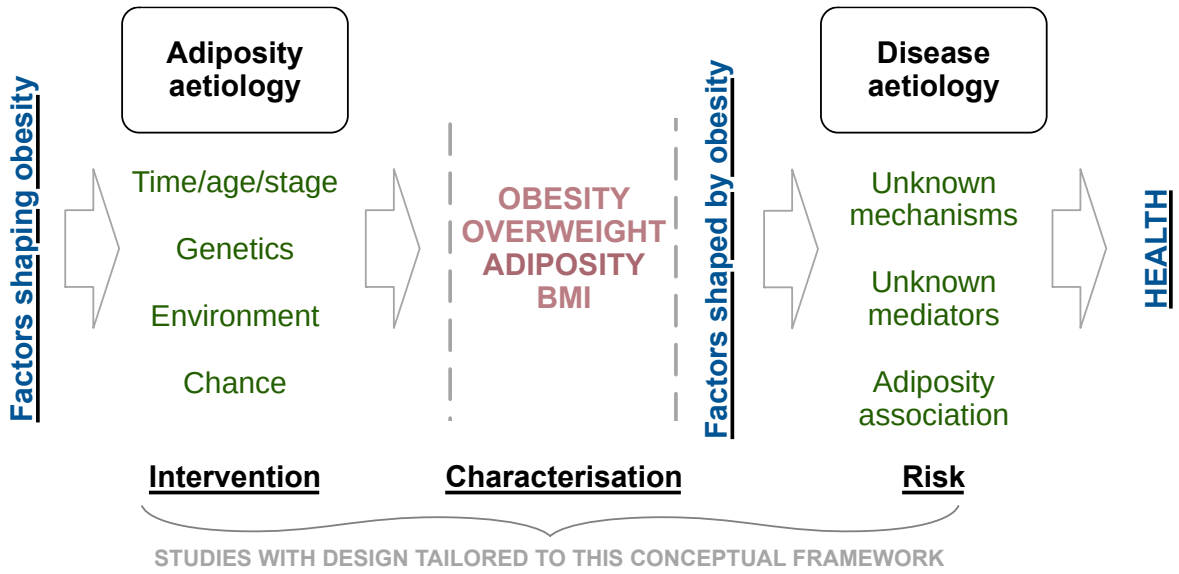
Conceptualising measures and mechanisms

One example to agree on… one which is challenging

Integrating evidence – helping mechanisms and implications

What can we take away which might open-up discussion?

Integrating evidence – studying both sides of the problem



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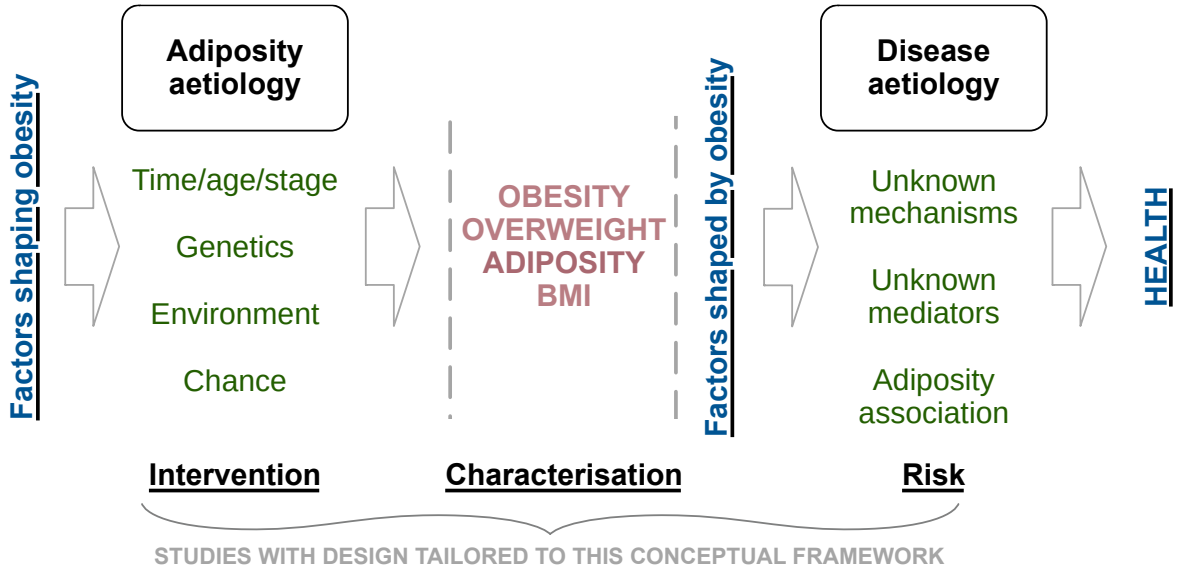
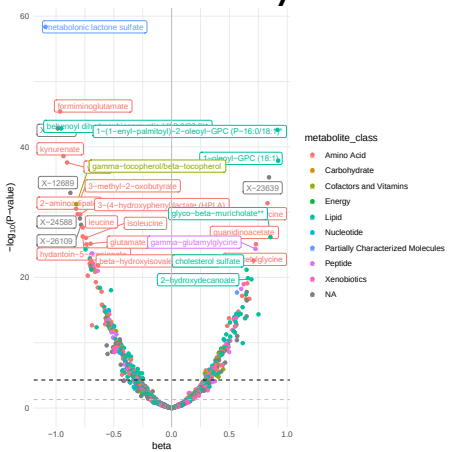


Question –> can we turn to areas where we are aware of the origins of weight change/obesity reduction and use these simultaneously comment on the mechanisms associated with obesity?

DiRECT
Diabetes Remission Clinical Trial

Roy Taylor/Mike Lean/Naveed Sattar



By-Band-Sleeve
BUILDING EVIDENCE TOGETHER

Jane Blazeby/Maddy Smith/Laura Corbin/David Hughes

…3 inferences from independent data sources…

DiRECT
Diabetes Remission Clinical Trial

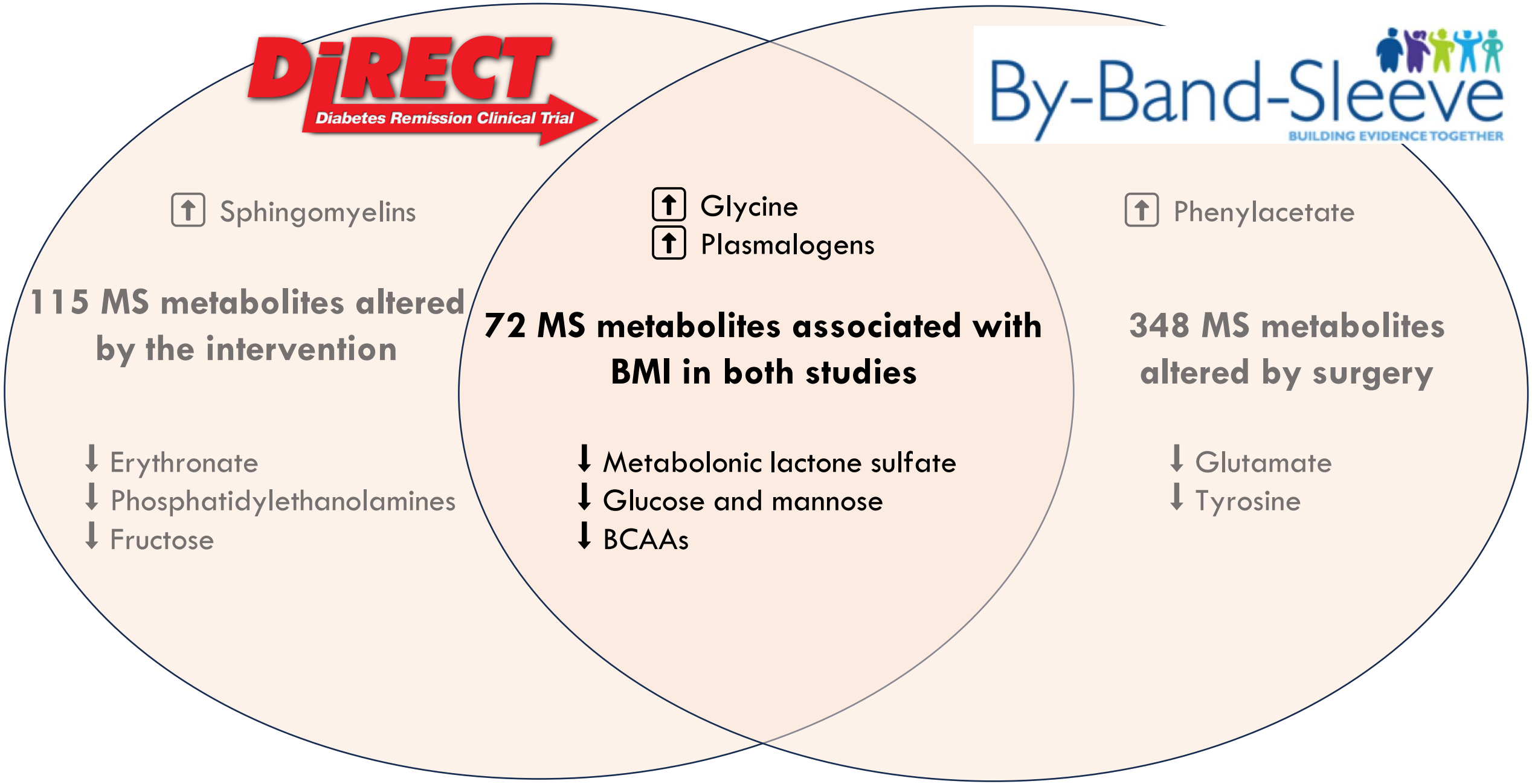
↑ Sphingomyelins

↑ Glycine
↑ Plasmalogens

115 MS metabolites altered by the intervention

↓ Erythronate
↓ Phosphatidylethanolamines
↓ Fructose

↓ Metabolonic lactone sulfate
↓ Glucose and mannose
↓ BCAAs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72 MS metabolites associated with BMI in both studies
↓ Metabolonic lactone sulfate
↓ Glucose and mannose
↓ BCAAs
↑ Phenylacetate
348 MS metabolites altered by surgery
↓ Glutamate
↓ Tyrosine

Integrating evidence – studying both sides of the problem

72 MS metabolites associated with BMI in both studies

Comparing the metabolic footprint of surgery-induced weight-loss to dietary restriction-induced weight-loss

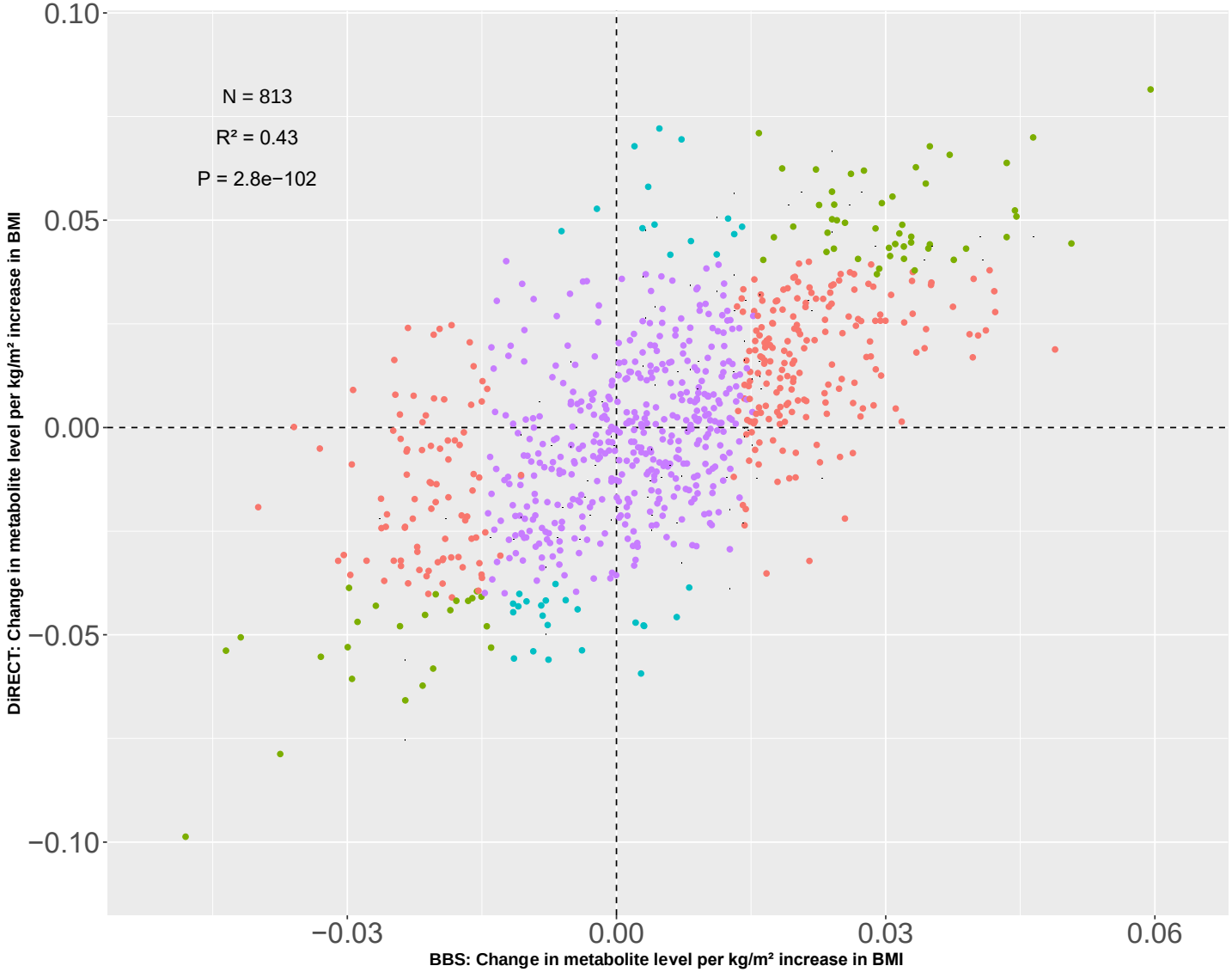
Estimates are on a BMI-scale, change in metabolite abundance per kg/m^2 increase in BMI

- Associated in both studies
- Associated in BBS only
- Associated in DiRECT only
- Not associated with BMI

Surprising overlap – unified by weight loss?

>8% metabolites are associated with BMI in *both* studies.

>38% metabolites are associated with one or other intervention.



Smith et al, **unpublished**

Consistent signal across BBS, DiRECT and MR (known metabolites)

Units here are standardised rank transformed metabolites per unit of BMI (kg/m^2)

Metabolite	Super Pathway	Sub Pathway	BBS effect (SE, p)	DiRECT effect (SE, p)	Pop' effect (SE, p)
glutamate	Amino Acid	Glutamate Metabolism	0.034 (0.003, 2.21E-24)	0.044 (0.009, 2.34E-06)	0.377 (0.054, 2.97E-12)
hydroxyasparagine**	Amino Acid	Alanine and Aspartate Metabolism	0.043 (0.003, 2.05E-41)	0.046 (0.009, 2.69E-07)	0.341 (0.049, 5.73E-12)
cortolone glucuronide (1)	Lipid	NA	0.045 (0.003, 1.41E-36)	0.052 (0.010, 1.43E-07)	0.321 (0.057, 1.42E-08)
aspartate	Amino Acid	Alanine and Aspartate Metabolism	0.031 (0.003, 1.66E-20)	0.038 (0.009, 4.38E-05)	0.282 (0.055, 3.70E-07)
2,3-dihydroxy-5-methylthio-4-pentenoate (DMTPA)*	Amino Acid	NA	0.033 (0.003, 3.12E-26)	0.046 (0.009, 1.03E-06)	0.273 (0.053, 2.44E-07)
5-methylthioadenosine (MTA)	Amino Acid	Polyamine Metabolism	0.026 (0.003, 1.05E-14)	0.061 (0.010, 7.76E-10)	0.270 (0.056, 1.48E-06)
N2,N2-dimethylguanosine	Nucleotide	Purine Metabolism, Guanine containing	0.051 (0.003, 7.59E-52)	0.0443 (0.010, 6.17E-06)	0.269 (0.053, 4.59E-07)
alpha-ketoglutarate	Energy	TCA Cycle	0.025 (0.003, 6.34E-13)	0.057 (0.010, 9.90E-09)	0.260 (0.058, 6.49E-06)
N4-acetylcytidine	Nucleotide	Pyrimidine Metabolism, Cytidine containing	0.033 (0.004, 3.63E-19)	0.041 (0.010, 4.56E-05)	0.254 (0.062, 3.76E-05)
1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)*	Lipid	Plasmalogen	-0.029 (0.003, 3.54E-17)	-0.061 (0.010, 1.83E-09)	-0.261 (0.061, 2.00E-05)
1-(1-enyl-palmitoyl)-GPC (P-16:0)*	Lipid	Lysoplasmalogen	-0.0234 (0.004, 2.48E-10)	-0.066 (0.009, 3.2E-11)	-0.277 (0.061, 7.04E-06)
1-linoleoyl-GPC (18:2)	Lipid	Lysophospholipid	-0.028 (0.004, 2.31E-14)	-0.047 (0.010, 1.46E-06)	-0.281 (0.057, 7.51E-07)
1-oleoyl-GPC (18:1)	Lipid	Lysophospholipid	-0.043 (0.003, 2.48E-33)	-0.051 (0.010, 3.20E-07)	-0.290 (0.057, 3.71E-07)
3beta-hydroxy-5-cholestenoate	Lipid	Sterol	-0.030 (0.004, 2.24E-16)	-0.053 (0.009, 2.91E-08)	-0.294 (0.058, 3.63E-07)
1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)*	Lipid	Plasmalogen	-0.050 (0.003, 3.89E-50)	-0.099 (0.009, 4.65E-25)	-0.321 (0.059, 5.24E-08)

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PhenoScanner V2

A database of human genotype-phenotype associations

Genetic variants associated with these metabolites are *also* related to:

- Blood omics traits (platelet volume/count)
- Overall mass, fluid regulation, corpuscular volume, cholesterol
- eGFR creatinine, kidney function
- Self reported malabsorption/urate/primary sclerosing cholangitis/gout
- Lipid profile (inverse associations with HDLs)
- Fatty acid profile (arachidonic/linoleic), lipid profile (triglycerides), cell count
- Blood omics traits (platelet count)
- Fatty acid profile (arachidonic/linoleic), lipid profile CRP, glucose, "metabolic syndrome"

Inference?? Not necessarily metabolites as a cause of these effects or downstream outcomes, but metabolites as circulating markers of shared biology (e.g. as Hartnup's is to niacin deficiency)

Overview

Conceptualising measures and mechanisms

One example to agree on… one which is challenging

Integrating evidence – helping mechanisms and implications

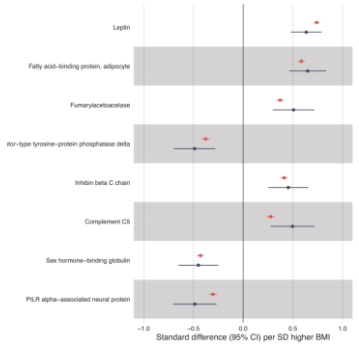
What can we take away which might opens-up discussion?

What are we learning about “mechanisms of obesity”?

STUDY VIGNETTES

V1

PROTEOMICS

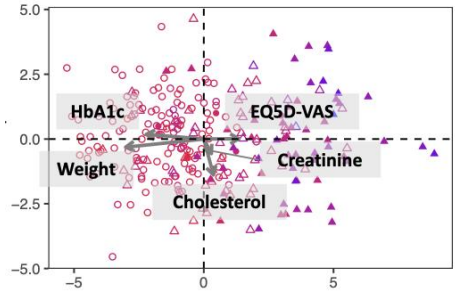


Genotype derived BMI variation

Mendelian randomisation

V2

METABOLOMICS

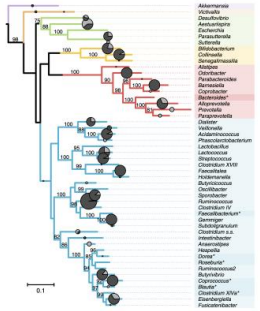


Intervention effect (weight change)

Weight loss intervention

V3

MICROBIOME



Microbiome genotypes

Genomewide association

What are we learning about “mechanisms of obesity”?

Disease

Behaviour

Metabolism

Environment

Appetite

Physiology

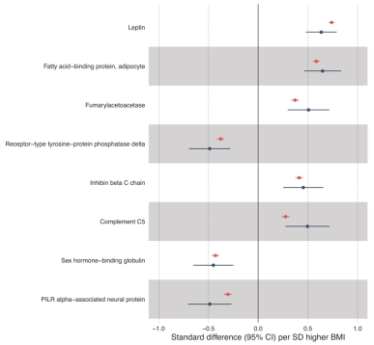
INFERENCE

OBESITY / OVERWEIGHT
ADIPOSITY / BMI

STUDY VIGNETTES

V1

PROTEOMICS

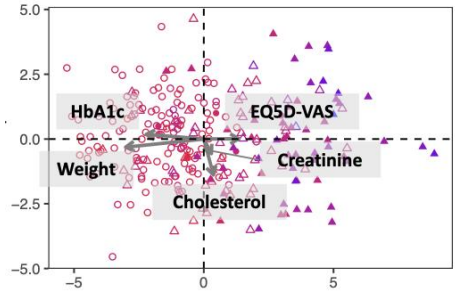


Genotype derived
BMI variation

Mendelian
randomisation

V2

METABOLOMICS

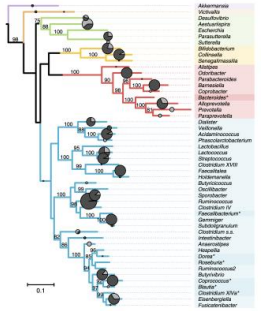


Intervention effect
(weight change)

Weight loss
intervention

V3

MICROBIOME



Microbiome
genotypes

Genomewide
association

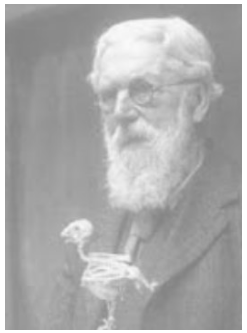
What are we learning about “mechanisms of obesity”?

In bringing these thoughts together…

Are we dealing with “mechanisms of” or in reality observed “mechanisms associated with obesity”?

If it is the latter, we need to illustrate both sides of a more fluid approach to inference.

Lancet Diabetes & Endocrinology Commission on the Definition and Diagnosis of Clinical Obesity



“In our opinion, the question of whether obesity is a disease or merely a condition conveying risk for future ailments is ill conceived because it presumes an implausible all-or-nothing scenario, in which obesity (ie, excess adiposity) is either always or never a disease. Logic and evidence suggest that obesity can be both a risk factor and, sometimes, a disease in and of itself …

…clinical definition of obesity based on distinctive clinical manifestations that reflect the impact of excess adiposity per se on normal functioning of organs and the entire individual is still missing"

Rubino et al, March 2023

What are we learning about “mechanisms of obesity”?

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Differing studies, study designs and data frames provide different inference:

Genetic contributions – have primacy, but are often signals and not clear biology

New omics measures – are often “just” phenotypes and need appropriate interpretation

Interventions which are effective can help to sort the order of effects and responses

What are we learning about “mechanisms of obesity”?

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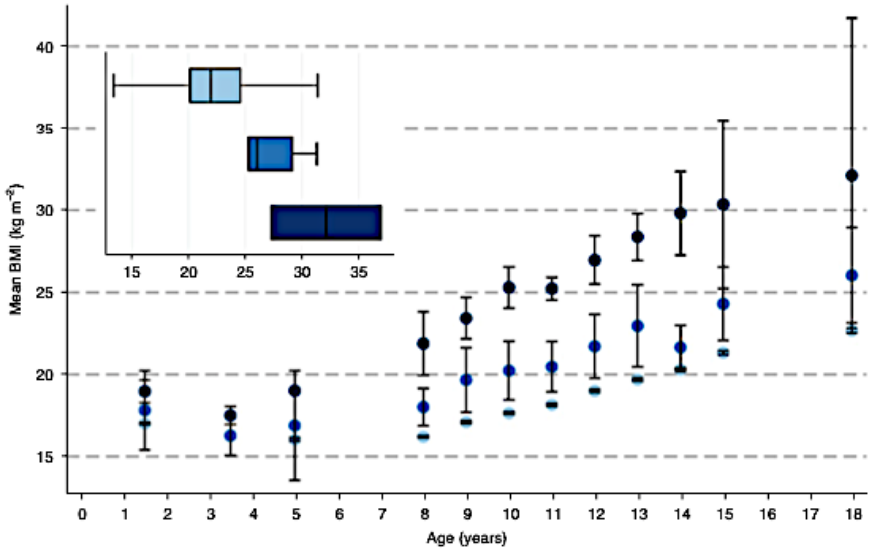
There will be ***other factors*** which are key nuances not considered here:

The failure of “obesity” as a category and BMI as a measure – heterogeneity and idiopathy

Other potential modulators – pharma’, nutritional composition, susceptibility, longitudinal variation

Using identified rare variants in ***MC4R & MC3R*** to assess impact and frequency

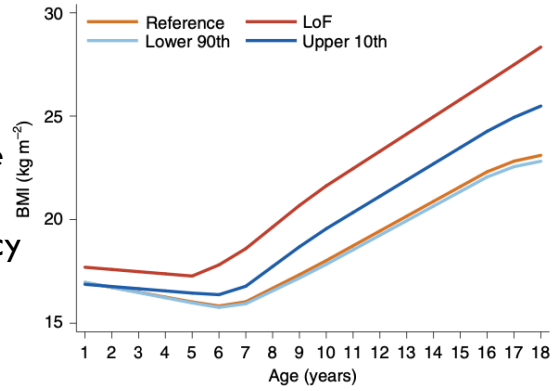
MC4R LoF mutations associated with BMI across the life course. Further, these are effects which exceed polygenic contributions.



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

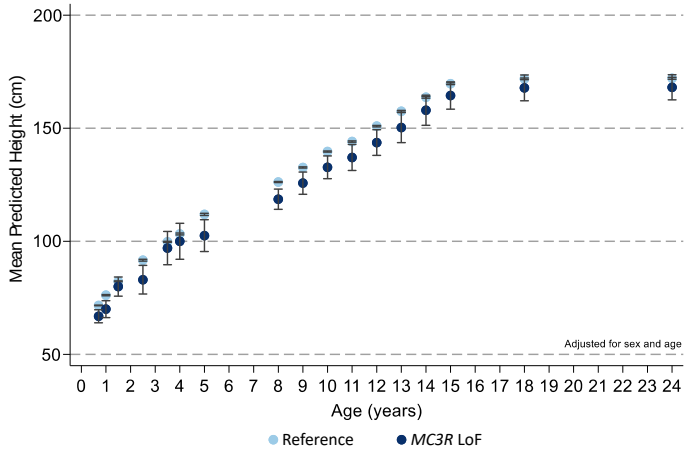
Heterozygous mutations that impair the function of the *MC4R* gene may very well be found in several millions of people worldwide a frequency of

~1 in 340

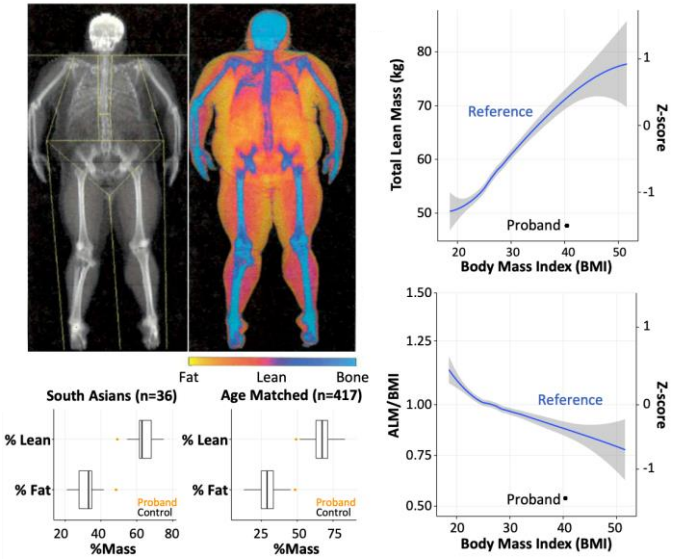


Wade et al Nat Med 2021

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



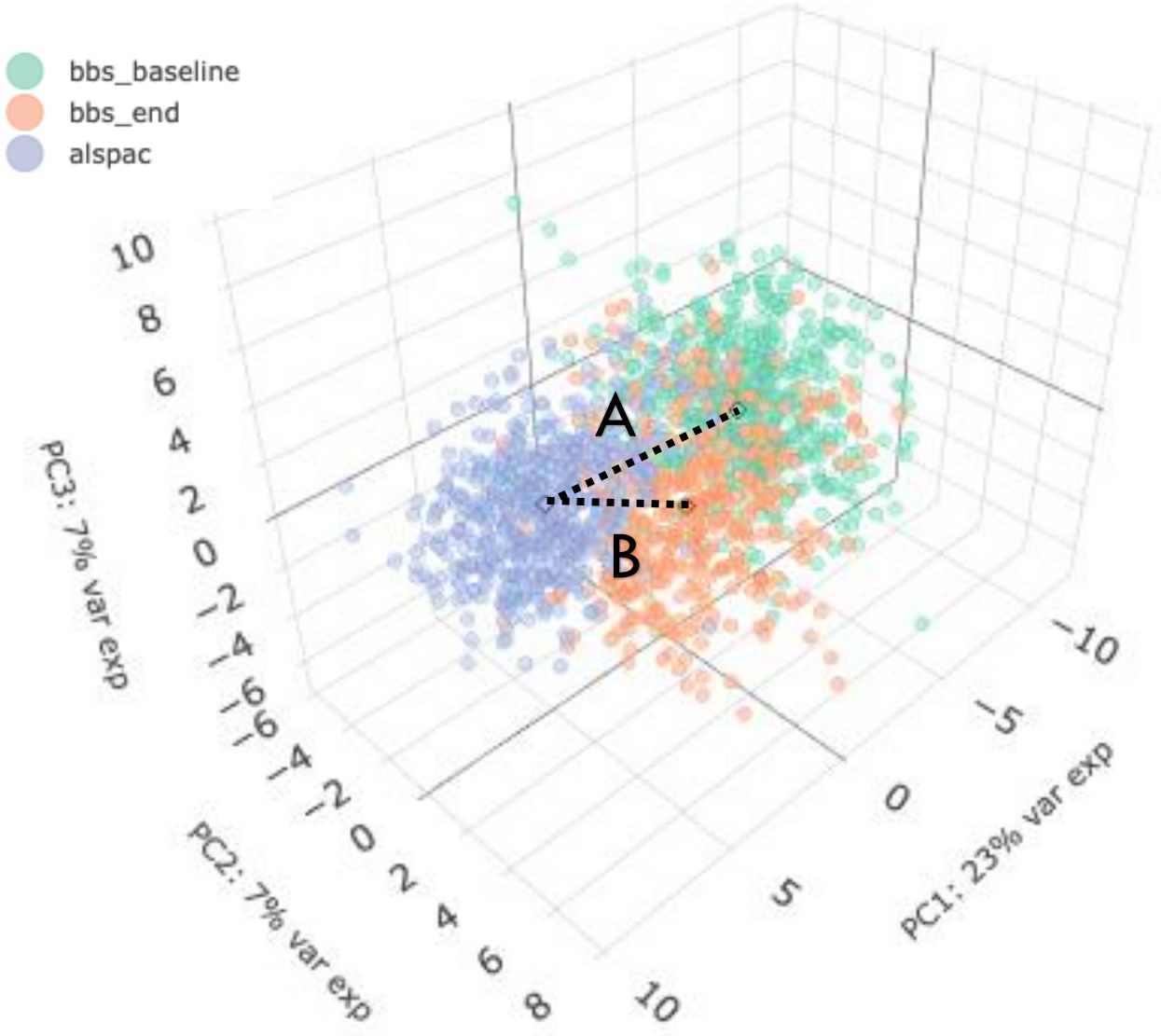
Genes & Health (G&H) stuc
two rare, homozygous non-
synonymous mutations p.M9
and p.G240W.



Lam et al Nat 2021

Integrating evidence – studying both sides of the problem

Bringing in metabolite data from a general population:
Do the levels of those 72 metabolites get closer to those of a general population post-surgery?



A = distance from pre-surgery to ALSPAC
B = distance from post-surgery to ALSPAC
Score = A/B

Score > 1 means post-surgery is more similar to ALSPAC than pre-surgery is

The 72 metabolites we selected (red line) perform better than random groups of 72 metabolites.