Annual review – year 1

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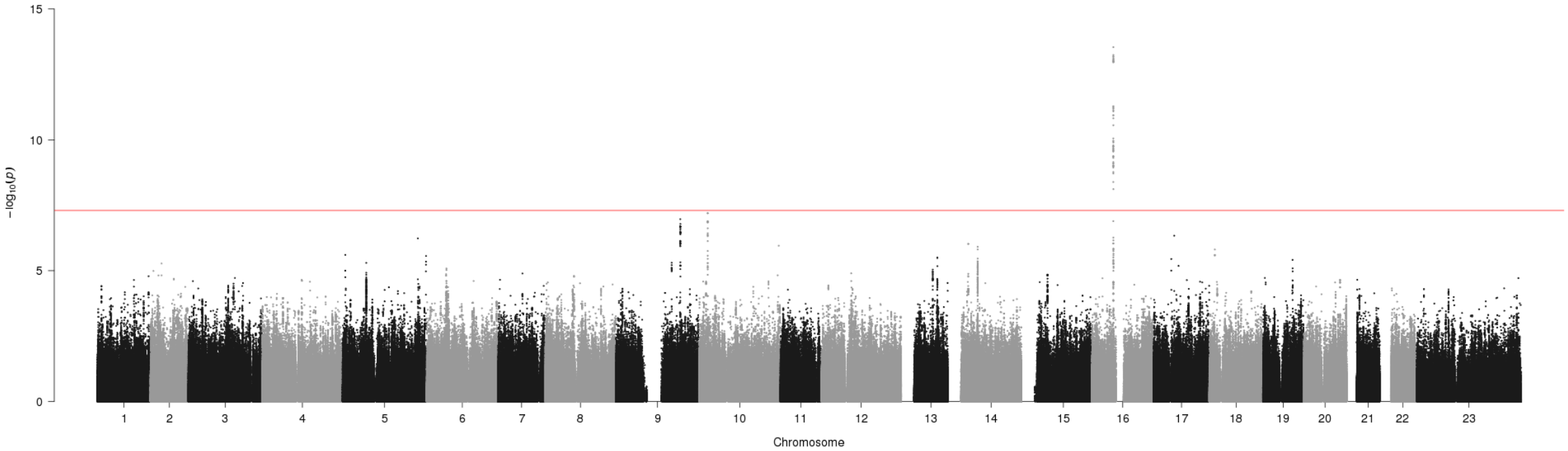
Medical Research Council Integrative Epidemiology Unit

Thursday, 19 December 2019

Genome wide association study of glycosuria

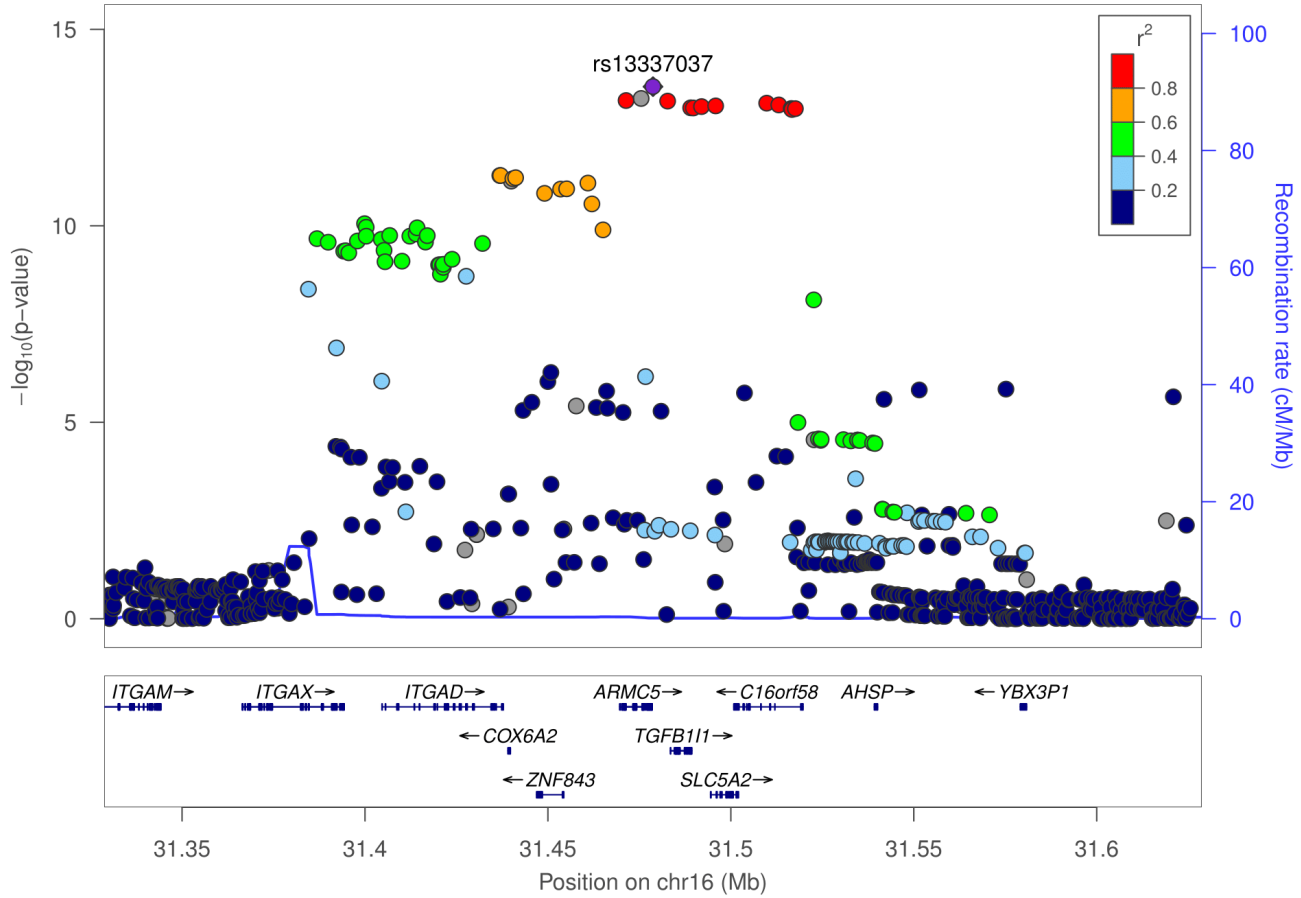


- Performed GWAS using ALSPAC data - lead SNP = rs13337037
  - OR: 1.42; 95% CI: 1.29 - 1.55; P = 2.88×10^{-14}
- Independently tested association in NFBC
  - OR: 1.25; 95% CI: 1.10 - 1.43; P = 9.8×10^{-4}
- Performed meta-analysis - lead SNP = rs13337037
  - OR: 1.38; 95% CI: 1.30 - 1.45; P = 3.09×10^{-16}

Genome wide association study of glycosuria

			Glycosuria and traits				Lead SNP and traits			
Trait	n	n_cases	beta	95%_CI_lower	95%_CI_upper	P_value	beta	95%_CI_lower	95%_CI_upper	P_value
Stix test	7176	282	3.83	3.39	4.26	6.84E-67	0.50	0.32	0.68	2.82E-08
BMI	6544		0.91	0.67	1.14	3.80E-14	0.18	0.03	0.32	1.64E-02
Underweight	284	6260	-0.08	-0.28	0.11	0.6	-0.03	-0.22	0.16	0.7
Normalweight	4934	1610	-0.33	-0.47	-0.19	5.13E-06	-0.07	-0.16	0.02	1.19E-01
Overweight	994	5550	0.23	0.06	0.40	6.66E-03	0.08	-0.03	0.18	1.54E-01
Obese1	230	6314	0.49	0.19	0.80	1.41E-03	0.08	-0.13	0.28	4.71E-01
Obese2	102	6442	0.88	0.46	1.31	5.27E-05	0.12	-0.18	0.43	4.23E-01
Frequency of water drunk in one week	5764		0.00	-0.13	0.13	9.98E-01	0.11	0.03	0.18	6.84E-03
Thrush (ever)	1264	3556	0.01	-0.04	0.25	9.28E-01	-0.08	-0.18	0.02	1.35E-01
Thursh (pregnancy)	828	5857	0.22	0.04	0.39	1.43E-02	-0.07	-0.18	0.05	2.67E-01
Urinary infection (ever)	1845	2901	0.03	-0.12	0.18	7.16E-01	-0.05	-0.14	0.04	2.97E-01
Urinary infection (pregnancy)	6314	371	0.86	0.64	1.08	2.16E-14	-0.13	-0.30	0.04	1.44E-01
Urinating at night	2703	2132	0.08	0.03	0.13	2.05E-03	-0.01	-0.04	0.02	4.43E-01
Hypertension (ever)	5848	986	0.46	0.30	0.62	2.61E-08	0.04	-0.07	0.14	5.12E-01
Hypertension (pregnancy)	275	702	-0.16	-0.47	0.16	3.38E-01	-0.05	-0.28	0.17	6.31E-01
Gestational hypertension	6233	1063	-0.16	-0.47	0.16	3.38E-01	-0.05	-0.28	0.17	6.31E-01
Preeclampsia	7296	162	1.16	0.81	1.51	7.86E-11	0.15	-0.09	0.39	2.31E-01

Genome wide association study of glycosuria



Exp Ther Med. 2016 Aug; 12(2): 649–652.
Published online 2016 May 25. doi: [10.3892/etm.2016.3388]
PMCID: PMC4950299
PMID: 27446256

Novel *SLC5A2* mutation contributes to familial renal glucosuria: Abnormal expression in renal tissues

Lei Yu,[1] Ping Hou,[2] Guo-Ping Liu,[1] and Hong Zhang[2]

A recurrent deletion in the SLC5A2 gene including the intron 7 branch site responsible for familial renal glucosuria

Xiangzhong Zhao, Li Cui, Yanhua Lang, Ting liu, Jingru Lu, Cui Wang, Sylvie Tuffery-Giraud, Irene Bottillo, Xinsheng Wang & Leping Shao

Scientific Reports **6**, Article number: 33920 (2016) | Download Citation

Influence of Familial Renal Glycosuria Due to Mutations in the *SLC5A2* Gene on Changes in Glucose Tolerance over Time

Emilia Ottosson-Laakso, Tiinamaija Tuomi, Björn Forsén, Monika Gullström, Per-Henrik Groop, Leif Groop, Petter Vikman

Published: January 6, 2016 • https://doi.org/10.1371/journal.pone.0146114

Chapter 1 - systematic review

	MR terms	Adiposity terms	MR & Adiposity
Medline	8,001 / 42,142	1,668,470	1,058 / 3,469
Embase	14,164 / 37,037	1,557,903	1,928 / 3,564
BiorXiv	564	-	564

Original Investigation | Cardiology

November 16, 2018

Association Between Obesity and Cardiovascular Outcomes

A Systematic Review and Meta-analysis of Mendelian Randomization Studies

Haris Riaz, MD[1]; Muhammad Shahzeb Khan, MD[2]; Tariq Jamal Siddiqi, MBBS[3]; et al

Author Affiliations | Article Information

JAMA Netw Open. 2018;1(7):e183788. doi:10.1001/jamanetworkopen.2018.3788

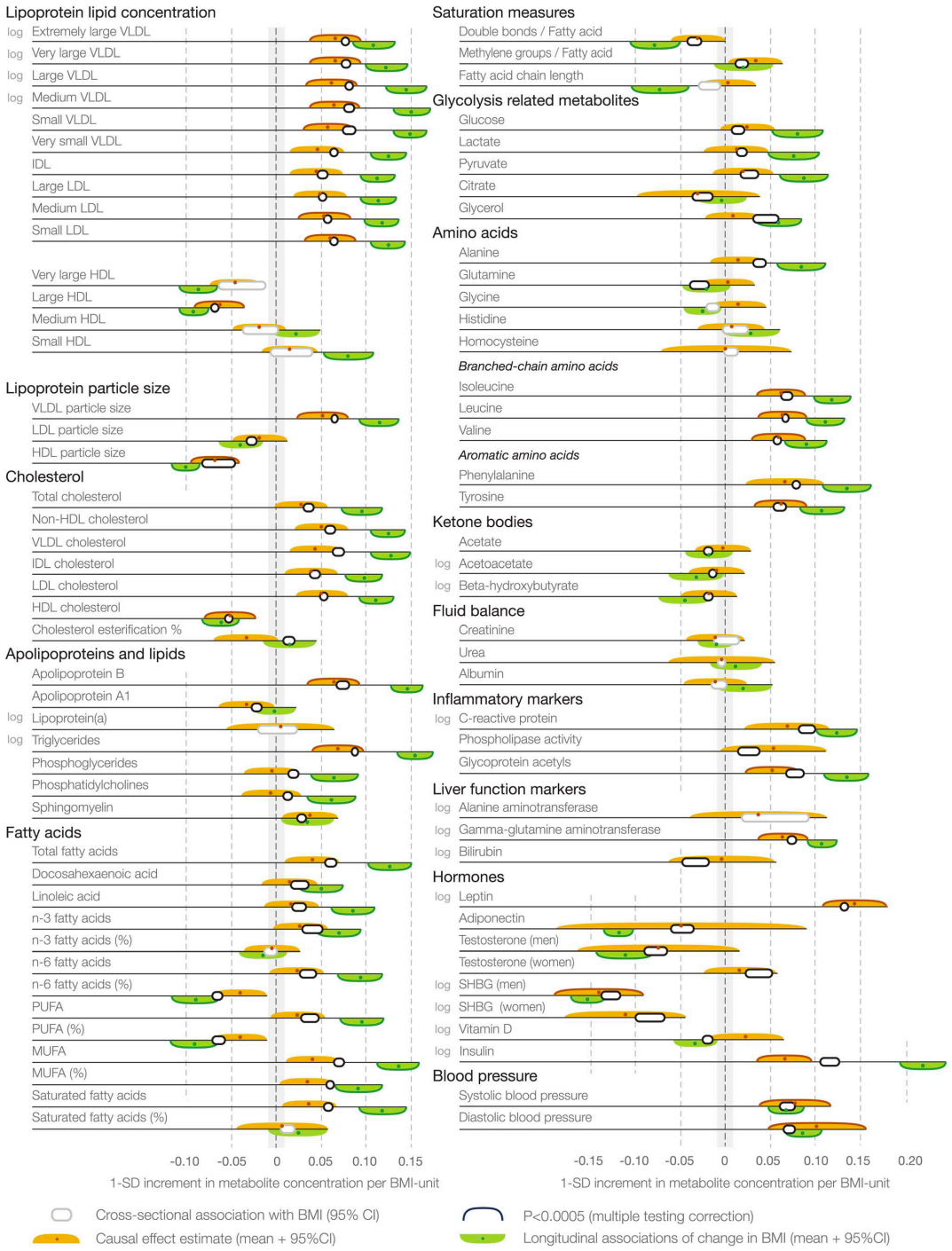
Titles screened	Full text	Review	Meta-analysis
2,511	27	7	5

- Inclusion
  - BMI or WHRadjBMI
  - & CAD, stroke, T2D
  - & OR with 95% CI
- Results (1SD higher BMI)
  - T2D: OR 1.67 (1.3-2.1); P < 0.001; I^2 = 93%; n = 461 871
  - CAD: OR 1.20 (1-1.4); P = 0.03; I^2 = 87%; n = 570 261
  - Stroke: OR 1.02 (1-1.1); P = 0.65; I^2 = 0%; n = 228 816

Adiposity and metabolites – Peter Wurtz

- 82 metabolic measures (NMR)
- Triangulation approach
  - Observational (bi-directional)
  - MR (weighted genetic risk score; 32 SNPs)
  - Weight change

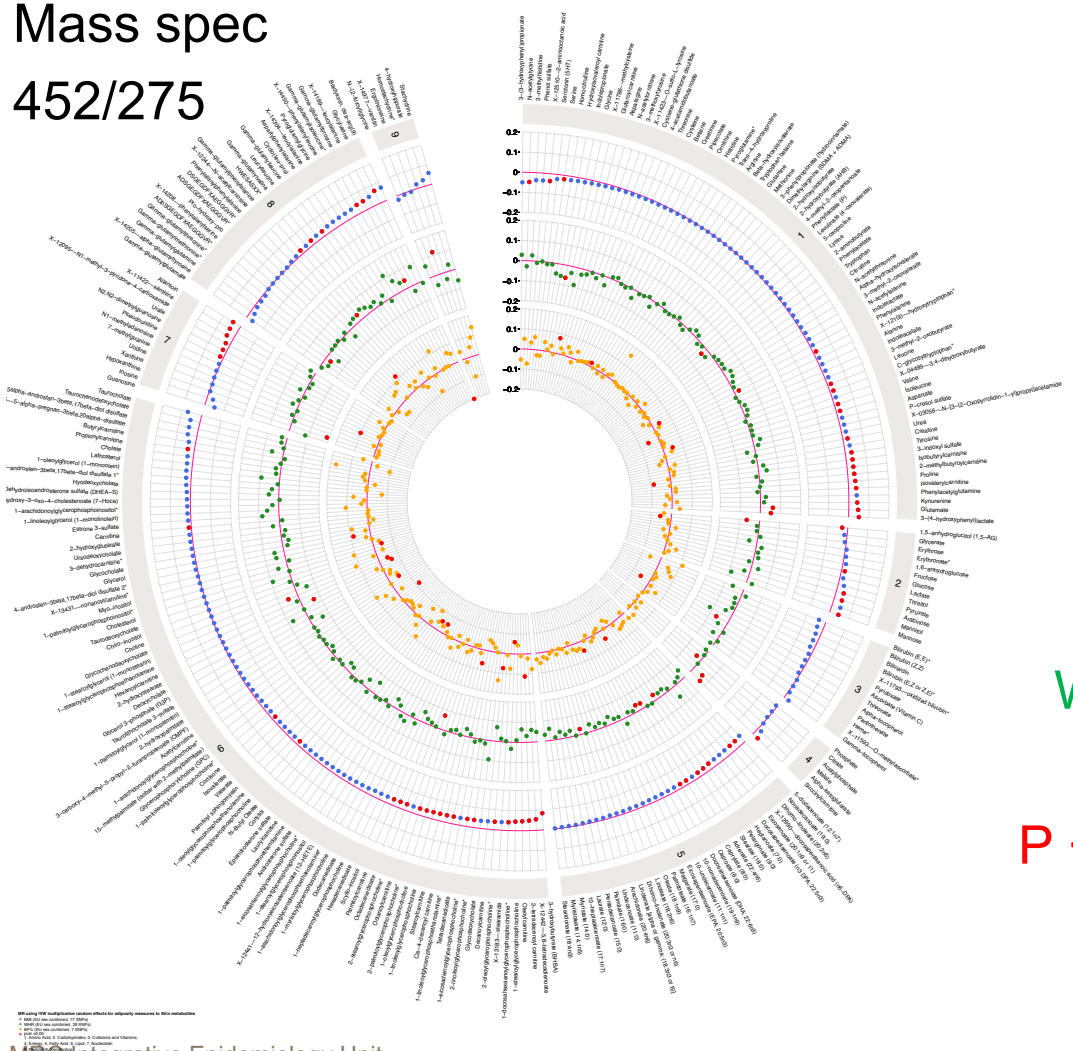
- Obs and MR do not significantly differ (p > 0.0005)
- MR estimates
  - Positive: VLDL and LDL lipids, branched-chain and aromatic amino acids, inflammatory markers, leptin, insulin, and blood pressure.
  - Inverse: Large HDL lipid concentration, HDL particle size, sex hormone–binding globulin.



Measures of adiposity and metabolites – step one

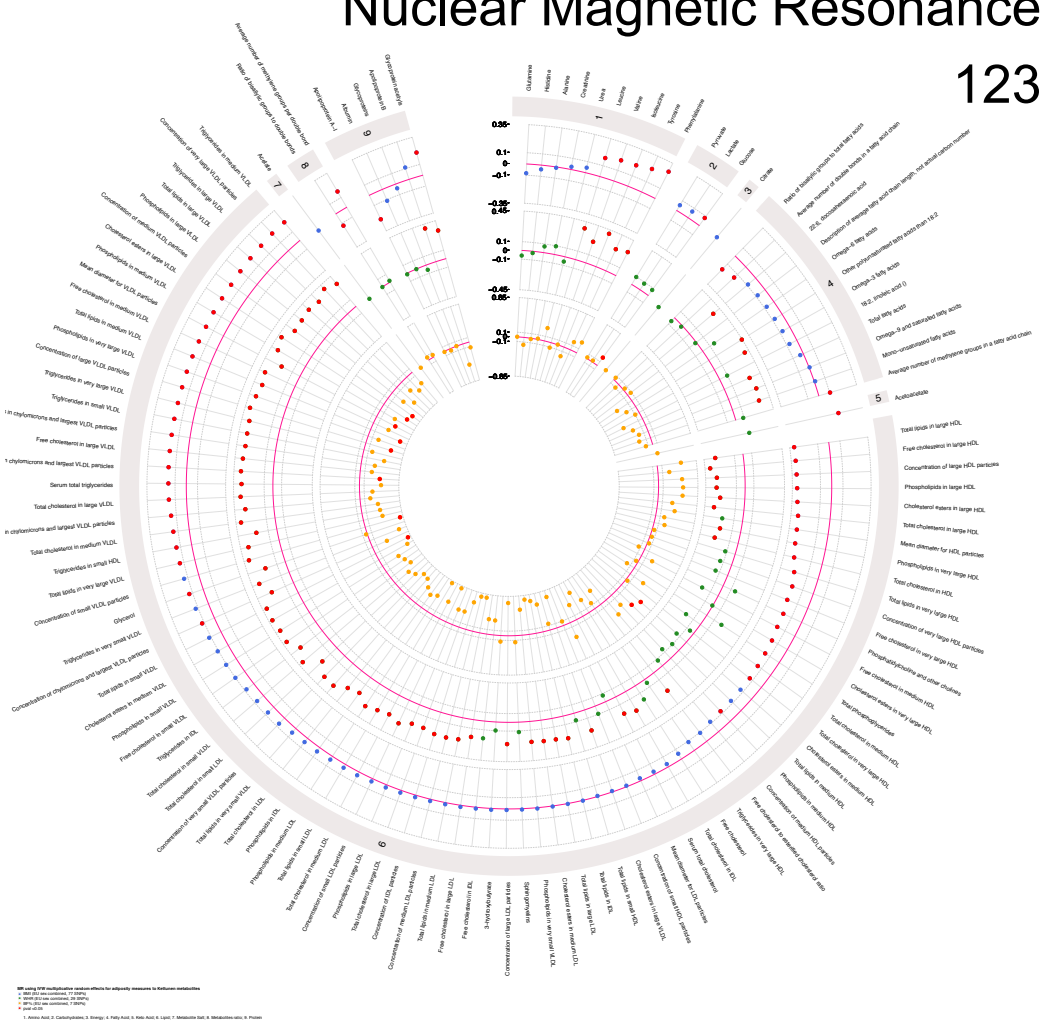
Mass spec

452/275



Nuclear Magnetic Resonance

123

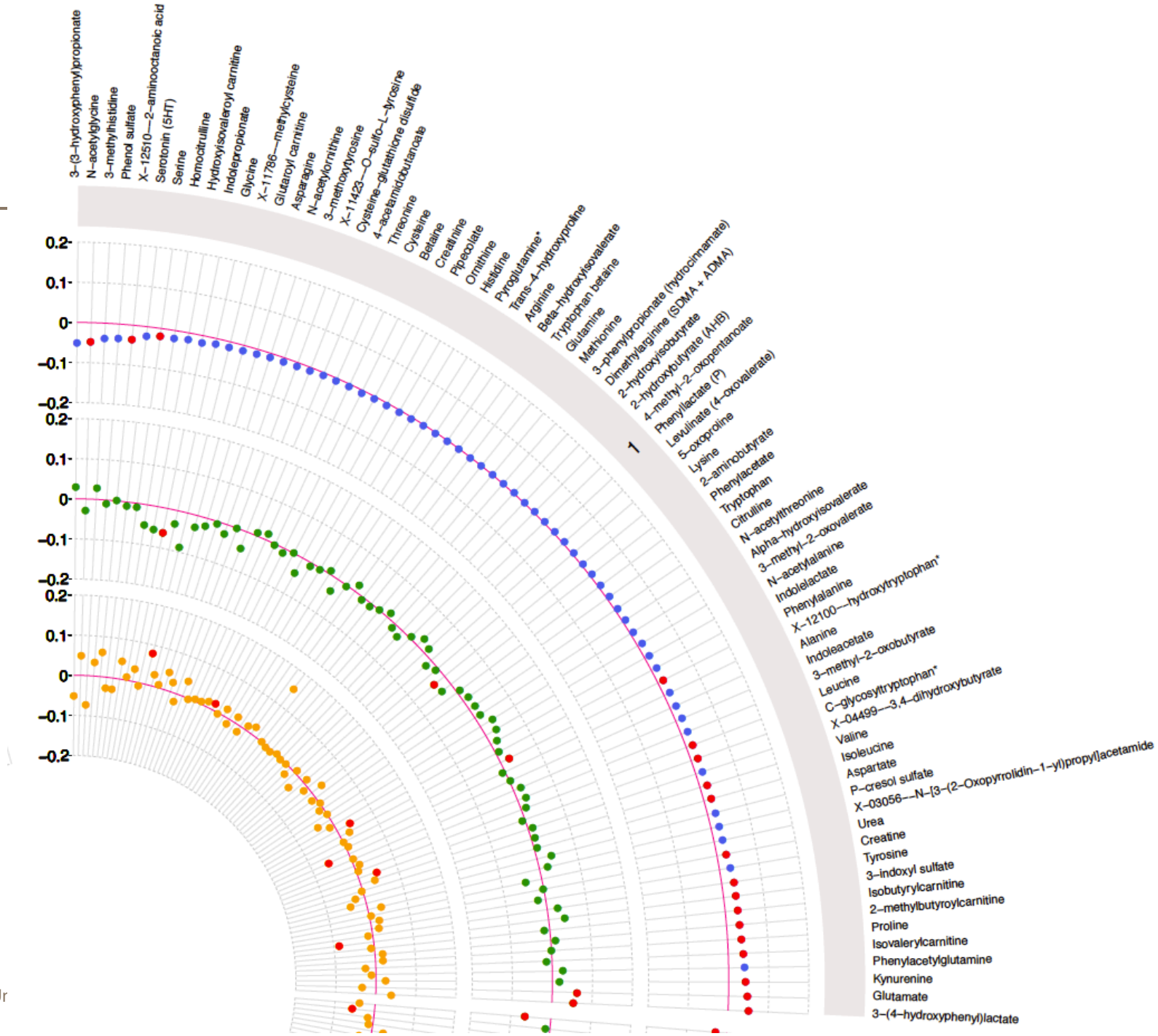


BMI

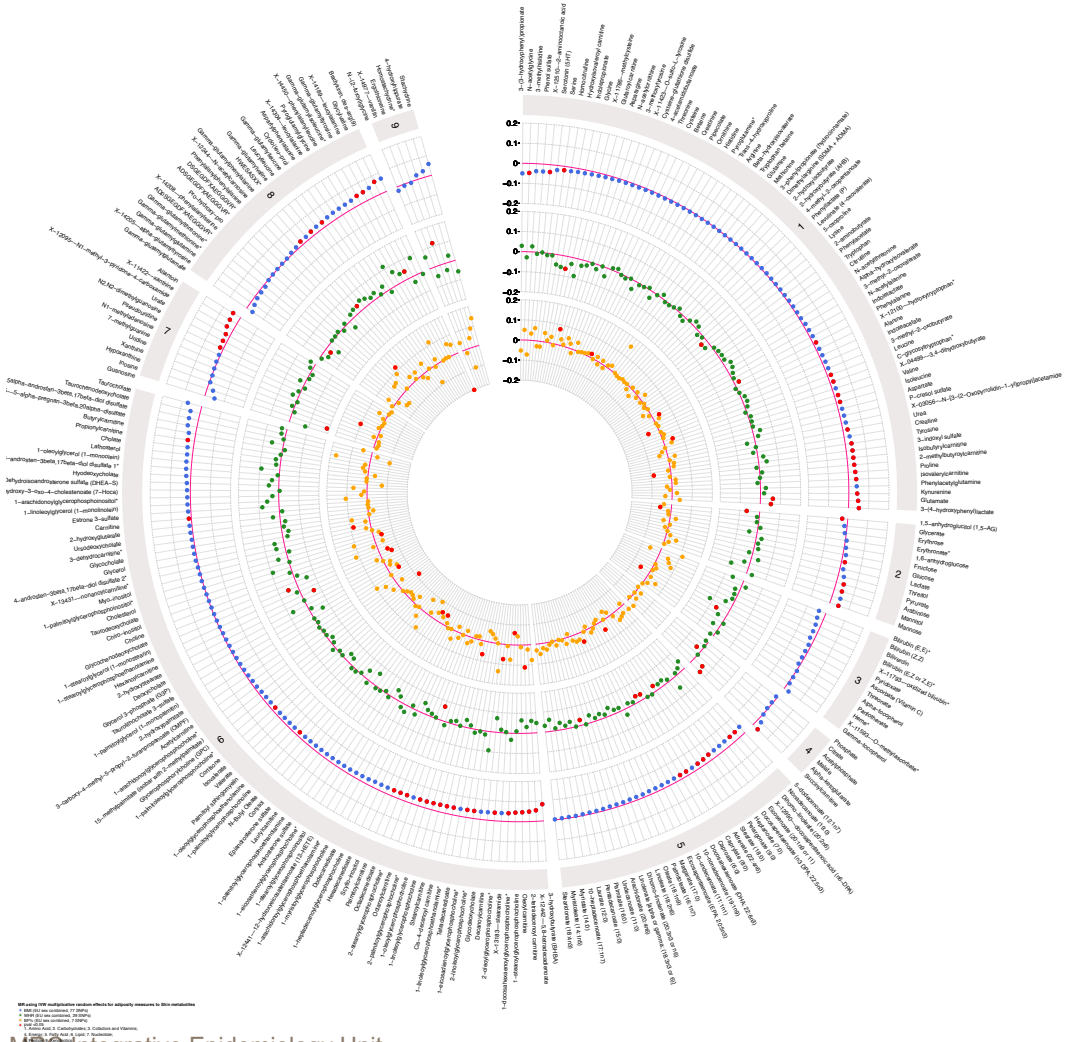
WHR

BF

P < 0.05


3-(3-hydroxyphenyl)propionate
N-acetylglycine
3-methylhistidine
Phenol sulfate
X-12510---2-aminooctanoic acid
Serotonin (5HT)
Serine
Homocitrulline
Hydroxyisovaleroyl carnitine
Indolepropionate
Glycine
X-11786---methylcysteine
Glutaroyl carnitine
Asparagine
N-acetylornithine
3-methoxytyrosine
X-11423---O-sulfo-L-tyrosine
Cysteine-glutathione disulfide
4-acetamidobutanoate
Threonine
Cysteine
Betaine
Creatinine
Pipecolate
Ornithine
Histidine
Pyroglutamine*
Trans-4-hydroxyproline
Arginine
Beta-hydroxyisovalerate
Tryptophan betaine
Glutamine
Methionine
3-phenylpropionate (hydrocinnamate)
Dimethylarginine (SDMA + ADMA)
2-hydroxyisobutyrate
2-hydroxybutyrate (AHB)
4-methyl-2-oxopentanoate
Phenylactate (P)
Levulinate (4-oxovalerate)
5-oxoproline
Lysine
2-aminobutyrate
Phenylacetate
Tryptophan
Citrulline
N-acetylthreonine
Alpha-hydroxyisovalerate
3-methyl-2-oxovalerate
N-acetylalanine
Indolelactate
Phenylalanine
X-12100---hydroxytryptophan*
Alanine
Indoleacetate
3-methyl-2-oxobutyrate
Leucine
C-glycosyltryptophan*
X-04499---3,4-dihydroxybutyrate
Valine
Isoleucine
Aspartate
P-cresol sulfate
X-03056---N-[3-(2-Oxopyrrolidin-1-yl)propyl]acetamide
Urea
Creatine
Tyrosine
3-indoxyl sulfate
Isobutyrylcarnitine
2-methylbutyroylcarnitine
Proline
Isovalerylcarnitine
Phenylacetylglutamine
Kynurenine
Glutamate
3-(4-hydroxyphenyl)lactate
0.2
0.1
0
-0.1
-0.2
1

Measures of adiposity and metabolites – step-two



Metabolite SNPs

Disease

MR visualisation tool

MR Visualisation Tool

Online tool for visualising MR results • Adminstrated by University of Bristol • 2018

Read our paper

The MR-Vis tool:

The **MR-Vis** application allows you to visualise results of the Mendelian Randomisation (MR) experiments mainly using the effective ***circular plots***. Then, you can download your generated plots in a format suitable for publications.

Input Data:

You can either upload your own MR results or use our example data to explore the functions of the MR-Vis tool:

- (•) **Upload your MR results**
- ( ) Use our example data

Example data:

Describe Our MR Experiments …

About | Data Viewer | Visualisation | Exposure SNPs

Current Version: Beta 0.2

Last Update: 4th July 2018

This online tool has been developed to visualise **MR results**, mainly using circular plots, and to allow users to **download generated figures** in a high-quality format.

The **MR-Vis** was developed and is maintained by the MRC Integrative Epidemiology Unit (IEU) at the School of Population Health Science (PHS), the University of Bristol.

Contacts:

Queries can be directed to: Dr. Osama Mahmoud (o.mahmoud@bristol.ac.uk).

Acknowledgments:

This tool was developed by Dr. Osama Mahmoud and Prof. Nicholas J Timpson, with assistance from Dr. David A Hughes, Dr. Kaitlin Wade, Mr. Matthew Lee and Dr. Laura J Corbin.

This website was created in R v3.5.0 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) using the package 'shiny' (Winston Chang, Joe Cheng, JJ Allaire, Yihui Xie and Jonathan McPherson (2017). shiny: Web Application Framework for R. R package version 1.0.0).

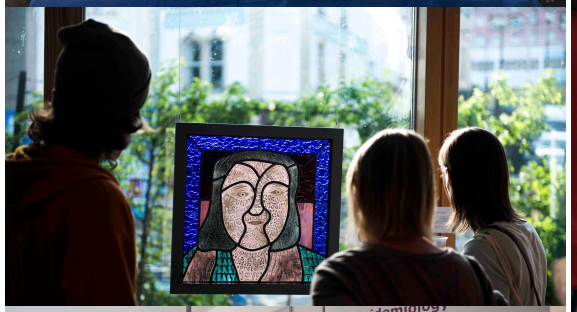
Creation of this app was greatly aided by Circlize, whose code is freely available and was used as a reference point in the creation of this app. We would like to thank the authors for making their code available for others.

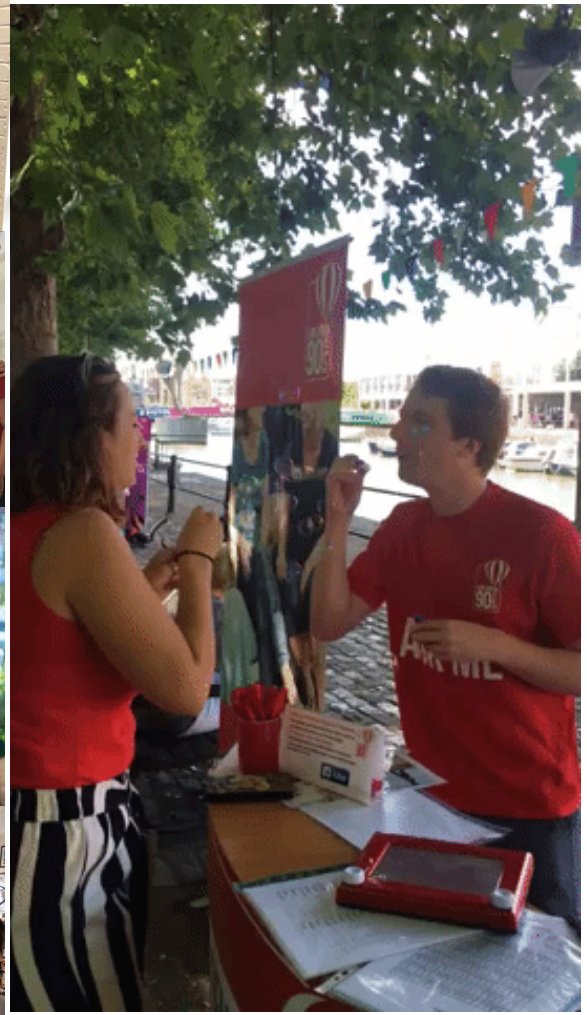
Ongoing and future work

- Tim Frayling work
  - Favourable adiposity & BMI
  - GRS -> metabolites
- Flemish Gut Flora Project
  - Observational analysis
  - Prediction using GRSs
  - One-sample MR
- Metabolite profile/groupings
  - Factor analysis
  - Partial least squares
  - Biological priors

Training etc.

- Courses year 1
  - stats / R / STATA / Linear & Logistic regression / MR / Linux / programming
- Courses year 2
  - Mediation analysis / Genetic epidemiology / Multiple imputation / Repeated measures
- Posters/presentations
  - GW4 congress (poster/talk) / Pop Health Science Symposium (poster) / GW4 orientation (talk)
- Public engagement

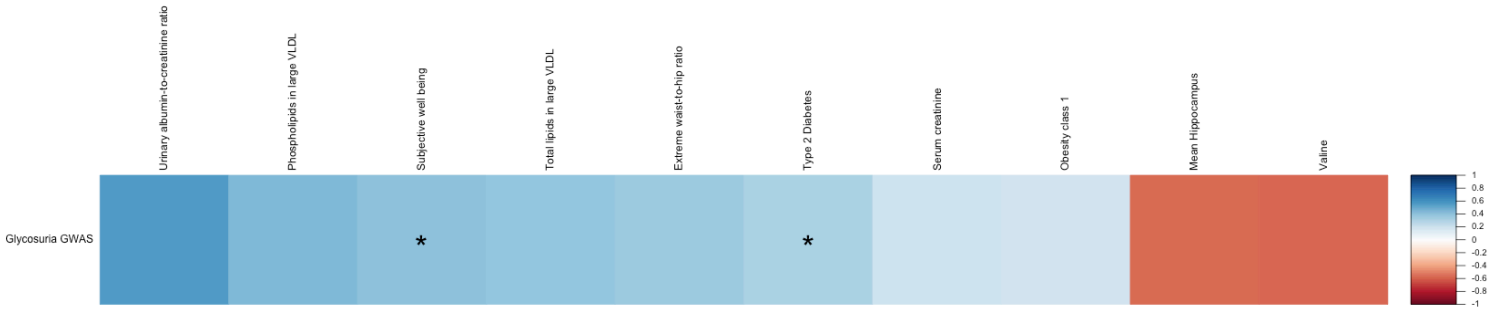


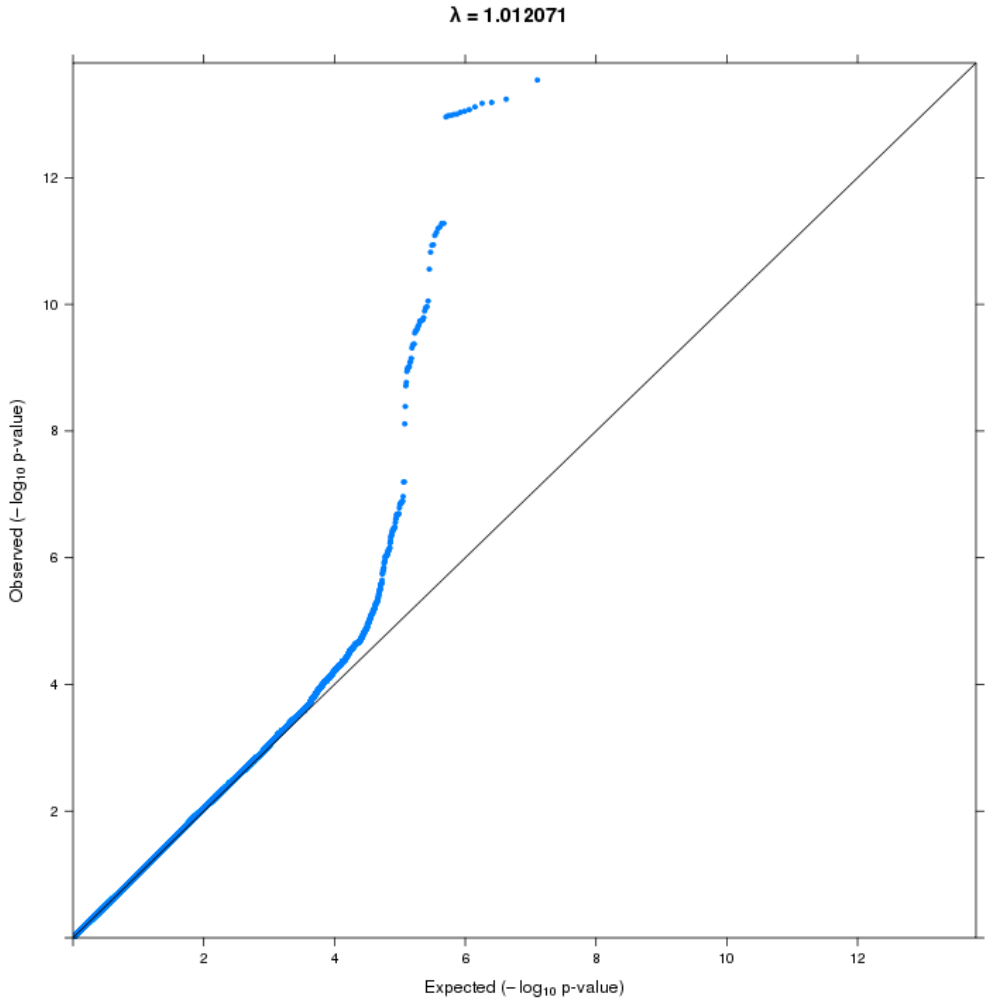


Acknowledgements

Kaitlin Wade
David Hughes
Charlie Hatcher
Laura Corbin
Osama Mahmoud
Nancy McBride
Nic Timpson
Luke McGuinness
Tom B

GWAS


Urinary albumin-to-creatinine ratio
Phospholipids in large VLDL
Subjective well being
Total lipids in large VLDL
Extreme waist-to-hip ratio
Type 2 Diabetes
Serum creatinine
Obesity class 1
Mean Hippocampus
Valine
Glycosuria GWAS
*
*
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1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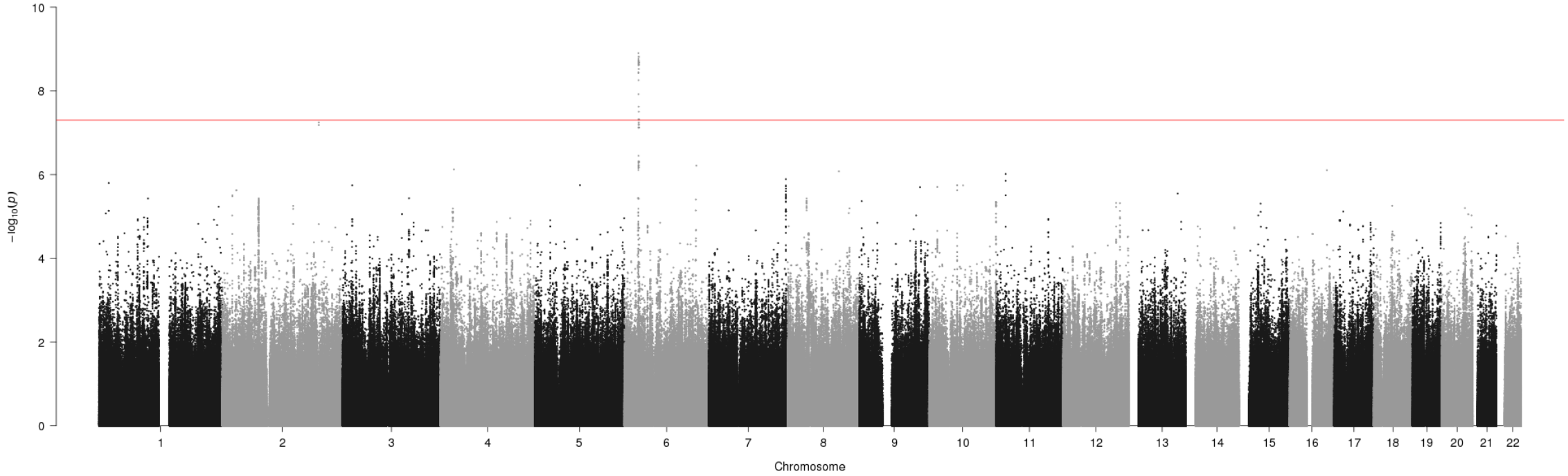
Observed (− log10 p-value)
Expected (− log10 p-value)
2
4
6
8
10
12


10
8
6
4
2
0
$-\log_{10}(p)$
1
2
3
4
5
6
7
8
9
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11
12
13
14
15
16
17
18
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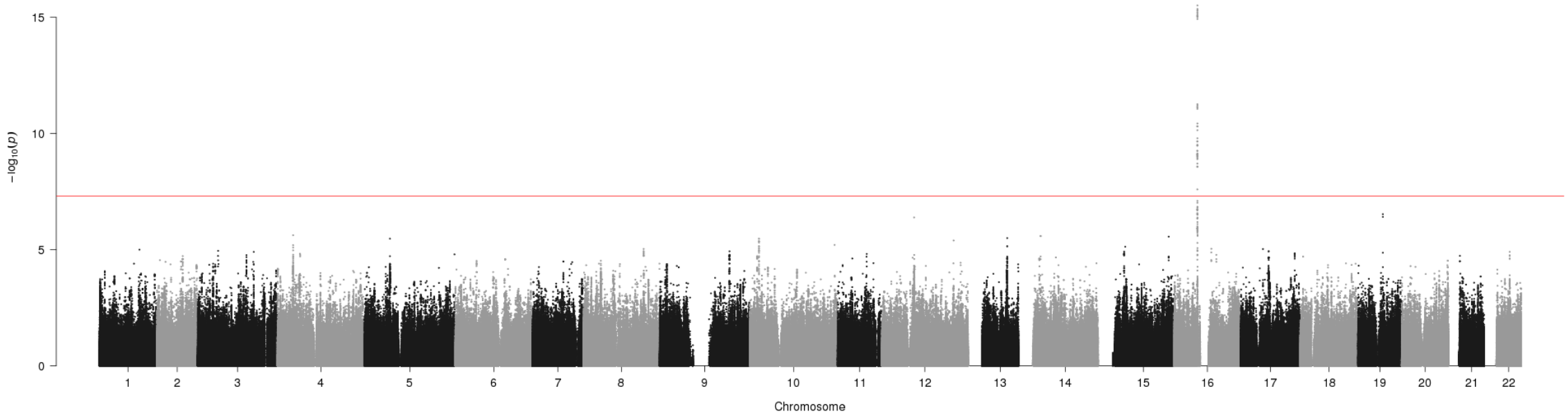
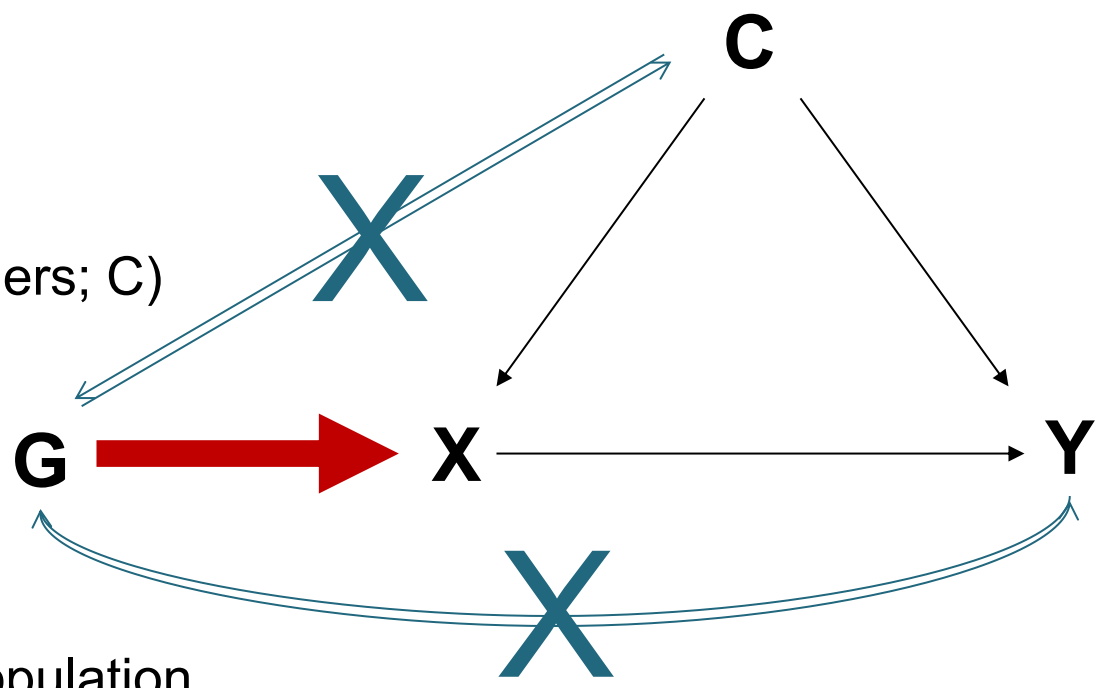
20
21
22
Chromosome


15
10
5
0
$-\log_{10}(p)$
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome

Mendelian randomization

1. The IV is associated with X
2. The IV is independent of confounders
3. The IV is independent of the outcome (Y) conditional on the exposure X (and confounders; C)



4. Homogeneity, monotonicity, no interaction
   - The effect is homogeneous across the population
   - The instrument-exposure association is always in the same direction or null
   - The instrument doesn’t interact with confounders in terms of its effect on your exposure