

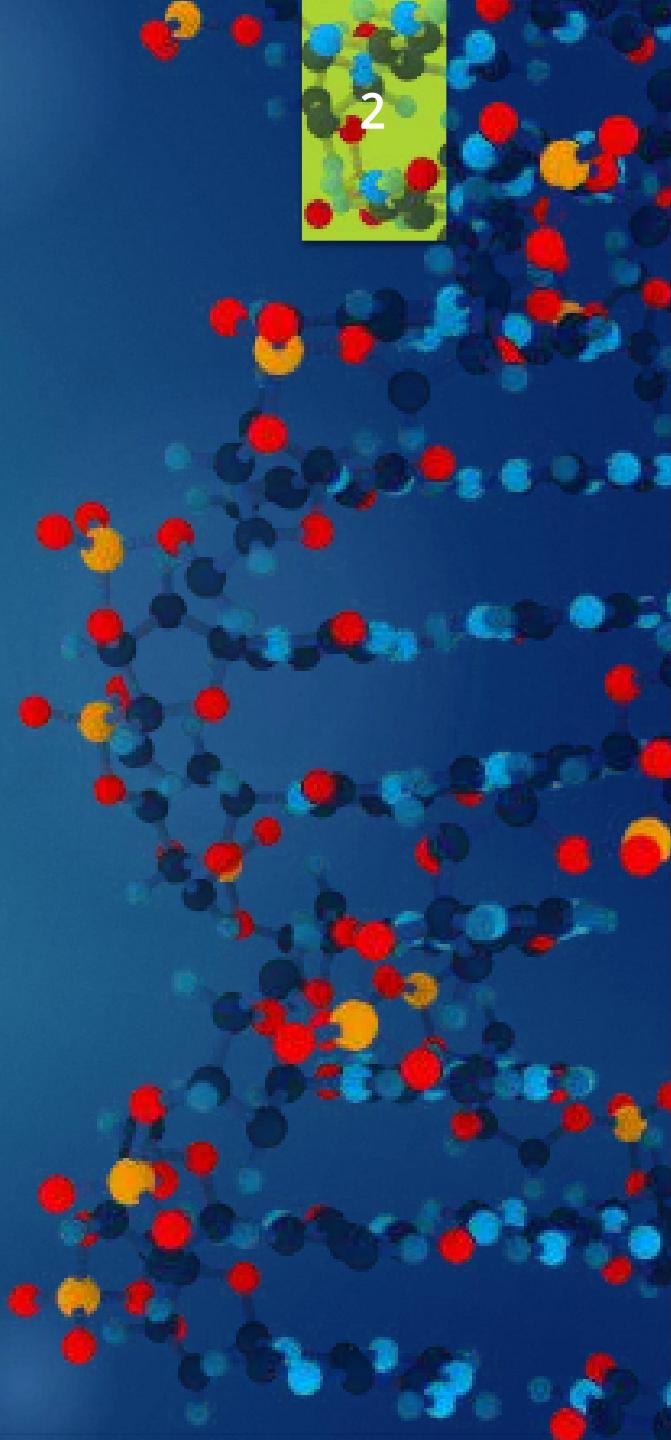
Celiac Disease Triggers

MATTHIJS KNIGGE



Overview

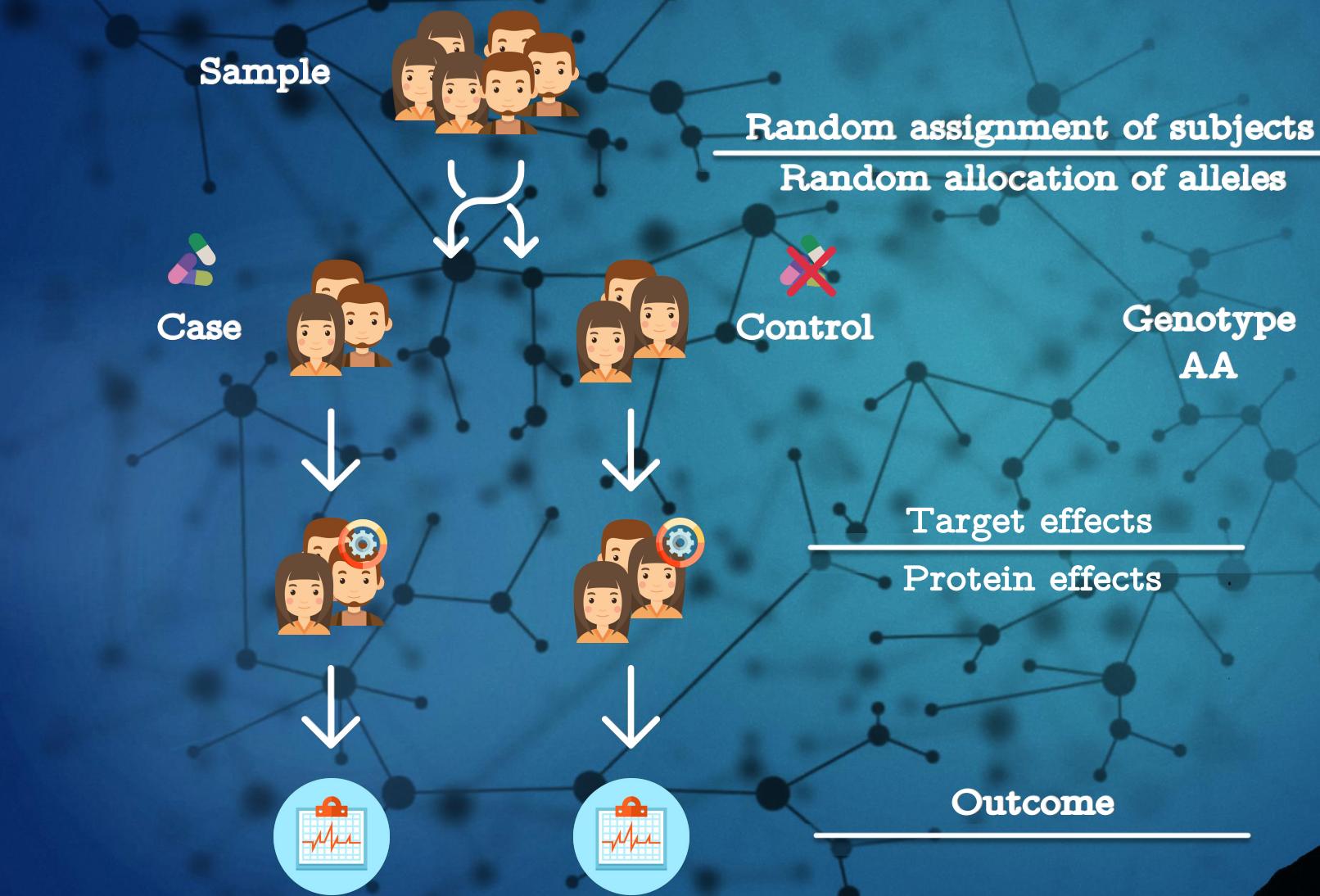
- ▶ Project goal
- ▶ Mendelian Randomization
- ▶ Methods
- ▶ Data
- ▶ Pipeline
- ▶ Preliminary results
- ▶ Future steps



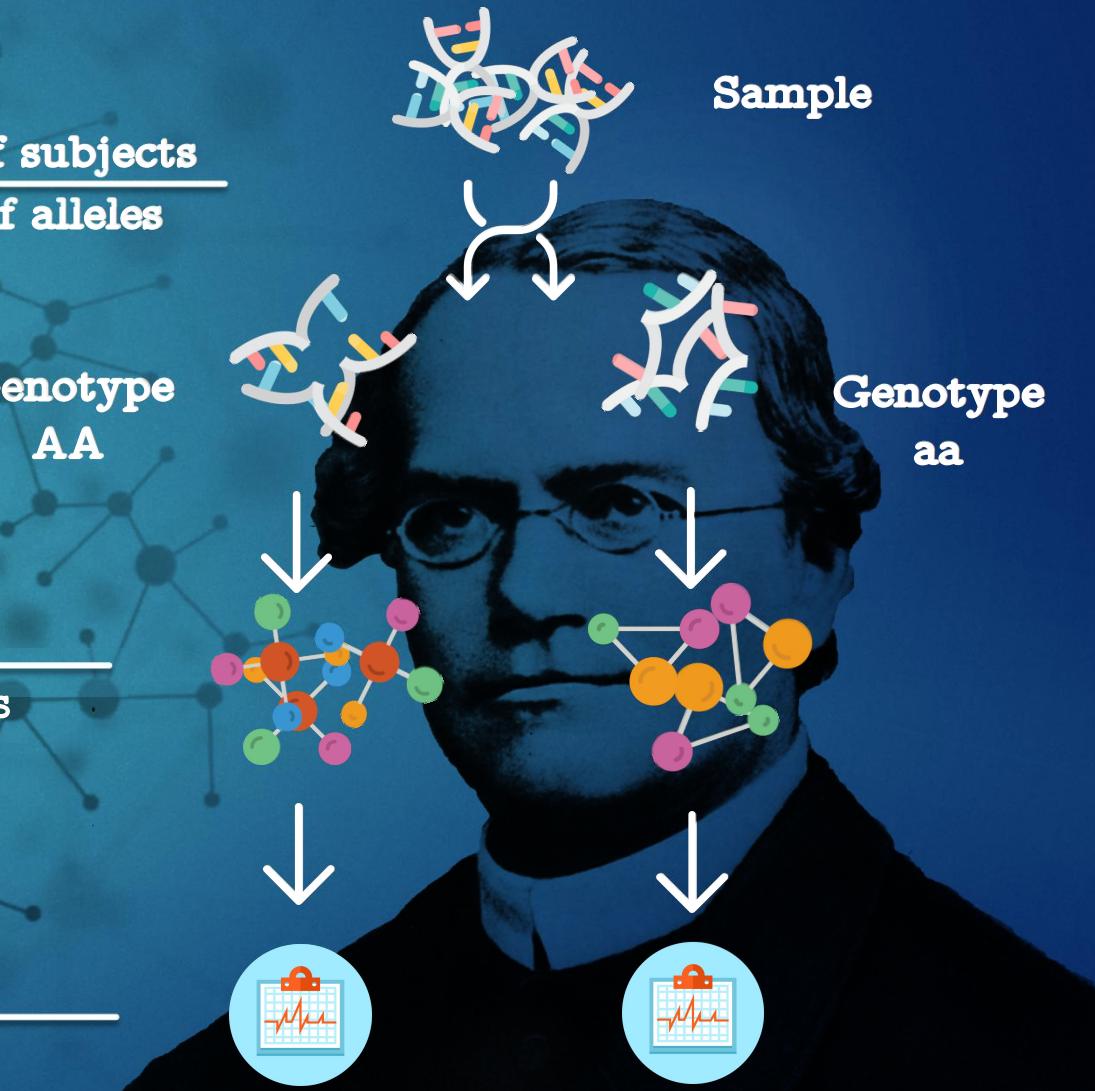
Project Goal

- ▶ Inspect > 60.000 clinical parameters to;
 - ▶ Find potential clinical parameters to evaluate causal effects on celiac disease
 - ▶ Identification of factors that cause or protect Celiac Disease

Randomized Controlled Trials (RCT)

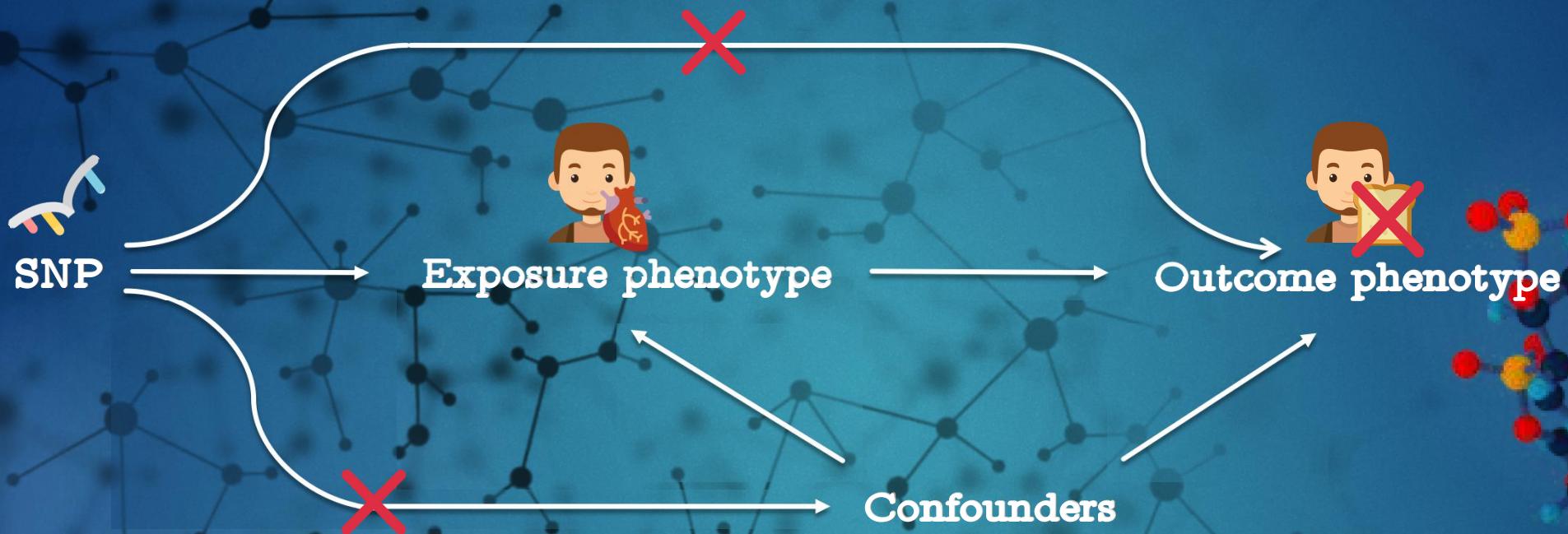


Mendelian Randomization (MR)



Mendelian Randomization setup

5



- ▶ Rules that need to be met before using a genetic variant in the MR framework
 - ▶ The genetic variant must be associated with the exposure of interest
 - ▶ The genetic variant must not be associated with confounders
 - ▶ The genetic variant may only affect the outcome through the exposure

Methods

Two-Sample MR



- Estimate causal effect between different samples
- Summary-level data from GWAS can be used



- Cannot test for confounding
- No overall causal estimate
- Assumes genetic variants are uncorrelated (not in linkage disequilibrium)



- Causal estimate between genetic variants

Inverse-Variance Weighted method (IVW)

- Overall causal estimate between exposure and outcome
- Summary-level data from GWAS can be used

- Assumes causal estimates provide independent evidence (no correlation)
- Cannot test for confounding

- Overall causal estimate between exposure and outcome

MR-egger method

- Can be deployed when the core assumptions do not hold.
- Can test for confounding (correlation between variants)
- Can test for a causal effect
- An estimate of the overall causal effect

- Needs 3 or more genetic variants
- Assumes genetic variants are uncorrelated
- Cannot distinguish between pleiotropy and a causal effect when genetic variants almost have equal estimates

- Overall causal estimate
- MR-egger causal test
- Overall pleiotropic effect

Bidirectional MR

- Can determine when genetic variant exhibits primary effect on the exposure, or the effect is secondary to the outcome

- difficulty in the presence of genetic variants that influence each other

- MR analysis in both directions, that ascertains direction of causal relationship

Data

	Type	Amount of Phenotypes	Direction
Celiac, Trynka 2011	GWAS Immunochip	1	Outcome
Celiac, Dubois 2010	GWAS Immunochip	1	Outcome
The NHGRI-EBI GWAS catalog	Published GWAS	2893	Exposure
MRbase Metabolite	GWAS on metabolites in whole blood	121	Exposure
MRbase Proteins	GWAS on protein levels whole blood	47	Exposure
MRbase Gene Expression levels	GWAS on gene identifiers in 44 different tissues	32432	Exposure
MRbase Methylation levels	GWAS on methylation levels in whole blood across 5 time points	33256	Exposure
Published GWAS	GWAS	1308	Exposure
Total		70059	

Pipeline



GWAS →

SNP	effect_allele	beta	se	p
rs61733845	T	0.03536714	0.04432255	2.465e-06
rs1320571	A	0.01882175	0.04265126	6.590e-01
...

Celiac 2011. Gosia Trynka et al



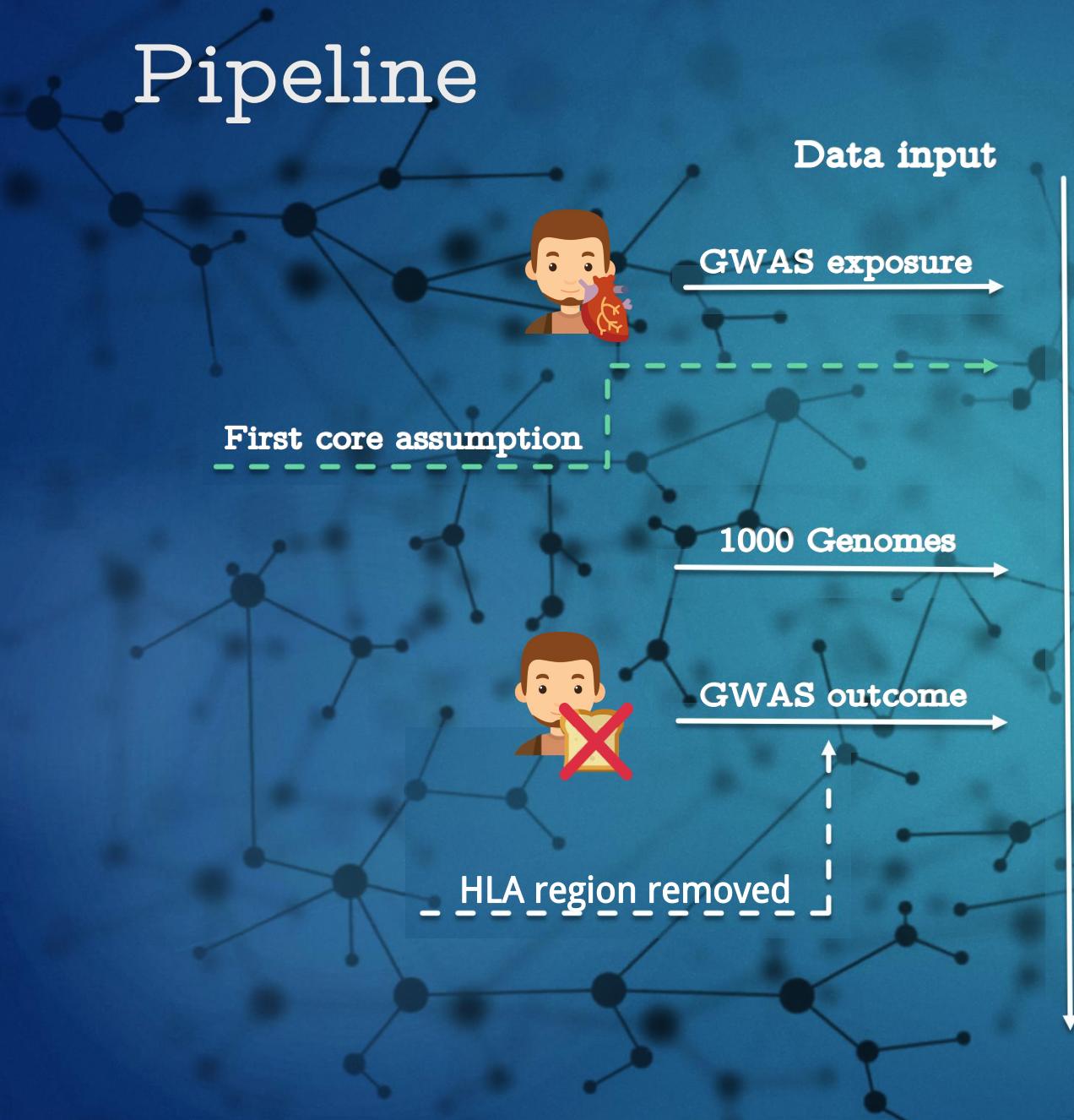
GWAS →

SNP	effect_allele	beta	se	p
rs314253	C	-0.0201900	0.002646	2.471-14
rs7775397	G	-0.0369352	0.004845	2.721e-14
...

HDL, LDL, Triglycerides. Willer CJ et al. Discovery and refinement of loci associated with lipid levels. Nat. Genet. 2013. doi:10.1038/ng.2797

Outcome = Celiac Disease, Exposure = HDL, LDL, Triglycerides

Pipeline



Operation

Select genome-wide significance on exposure

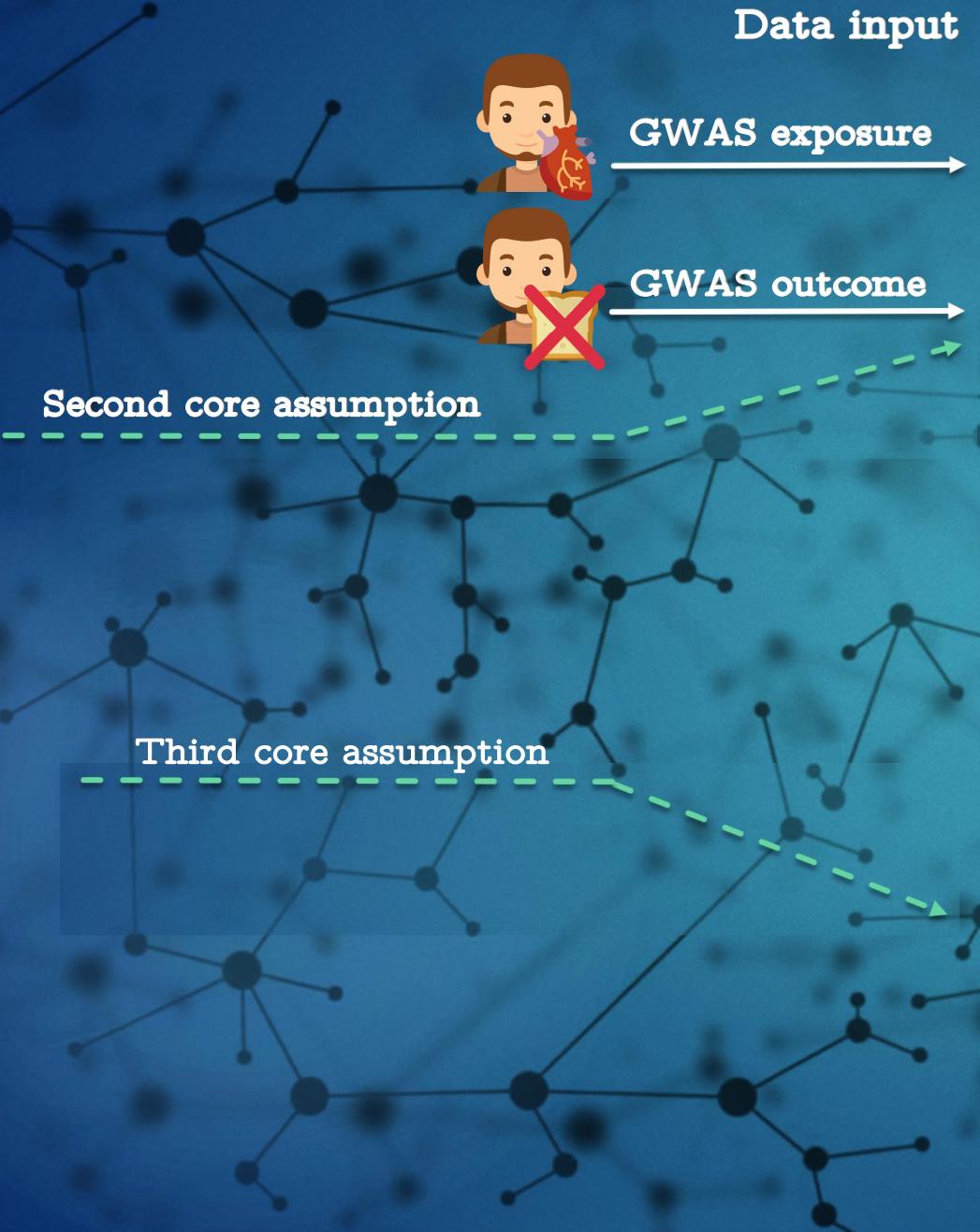
Remove variants without Beta/Log odds on exposure

Query missing alleles by reference on exposure

Find overlap between exposure and outcome

Harmonize Exposure on Outcome

- | - Positive align exposure
- | - Align outcome on exposure
- | - Remove palindromic SNPs



Operation

Clumping for proxy SNPs with PLINK

Perform Wald-method

Perform Inverse-Variance Weighted method

Perform MR-egger method

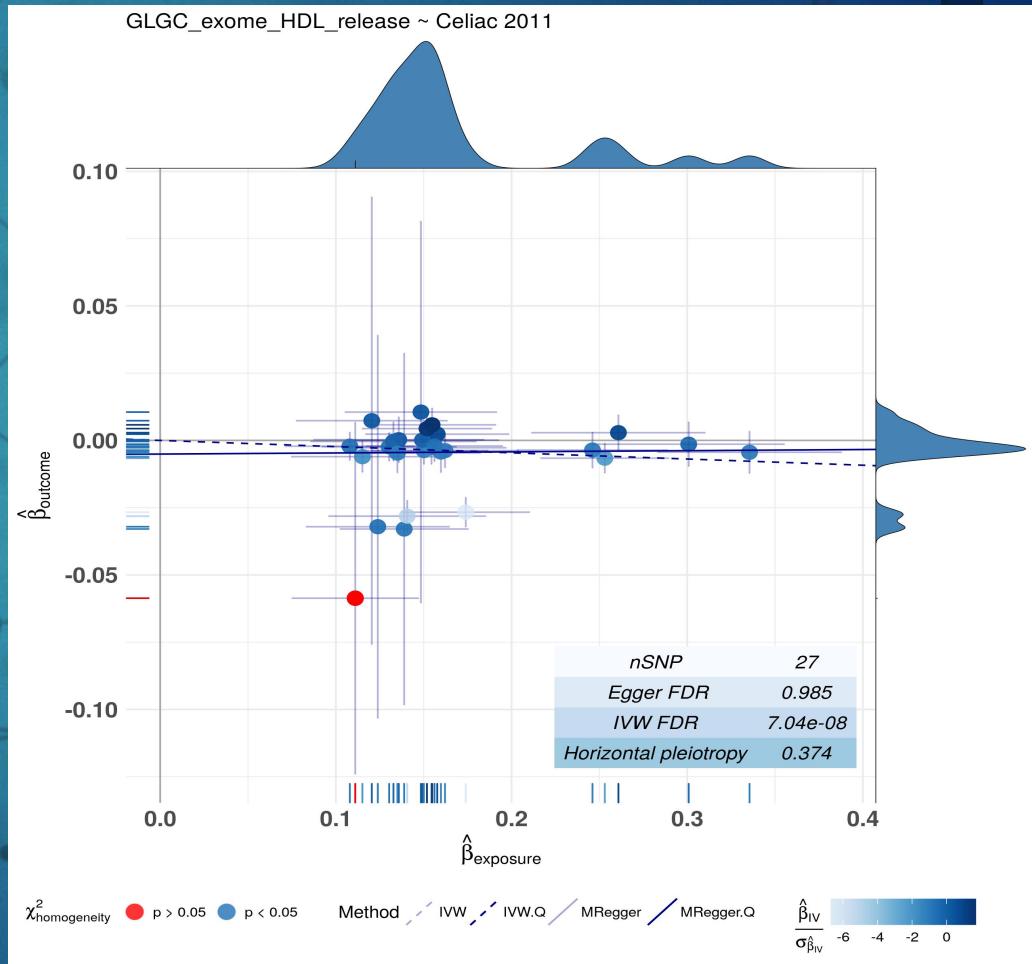
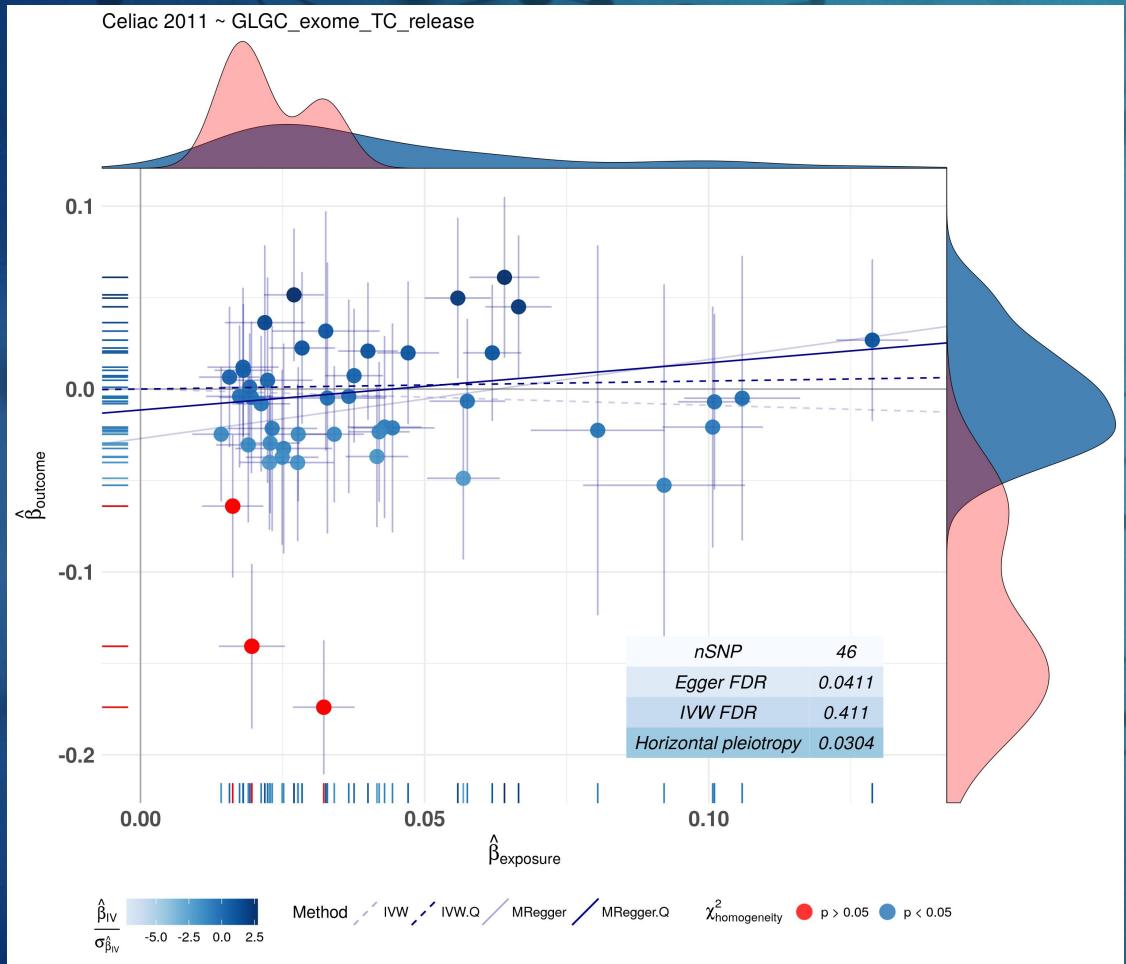
Perform Cochran's Q test

Perform Bidirectional MR

- Outcome becomes exposure
- Exposure becomes outcome

Preliminary results Bidirectional MR

► Celiac 2011, Gosia Trynka et. all



Preliminary results

- ▶ Celiac 2011, Gosia Trynka et. Al
 - ▶ 63 significant potential exposures
- ▶ Top 10

Exposure	IVW	Egger	nSNP
Rheumatoid_Arthritis_2014_24390342_hg 19	3.171316e-06	4.627945e-15	53
eo_baso_sum_build37_171771_20161212	1.361791e-05	8.413819e-08	28
eo_build37_172275_20161212	1.482109e-07	2.594648e-06	32
lymph_build37_171643_20161212	7.274596e-01	1.892860e-05	27
pct_build37_164339_20161212	5.517519e-08	2.612460e-05	19
plt_build37_166066_20161212	1.679860e-07	3.664932e-05	18
eo_p_build37_172378_20161212	2.691746e-04	1.070842e-03	27
pdw_build37_164433_20161212	8.302935e-03	1.199338e-03	14
hct_build37_173039_20161212	1.125320e-02	3.785512e-03	9
hgb_build37_172925_20161212	7.628868e-03	4.910752e-03	9

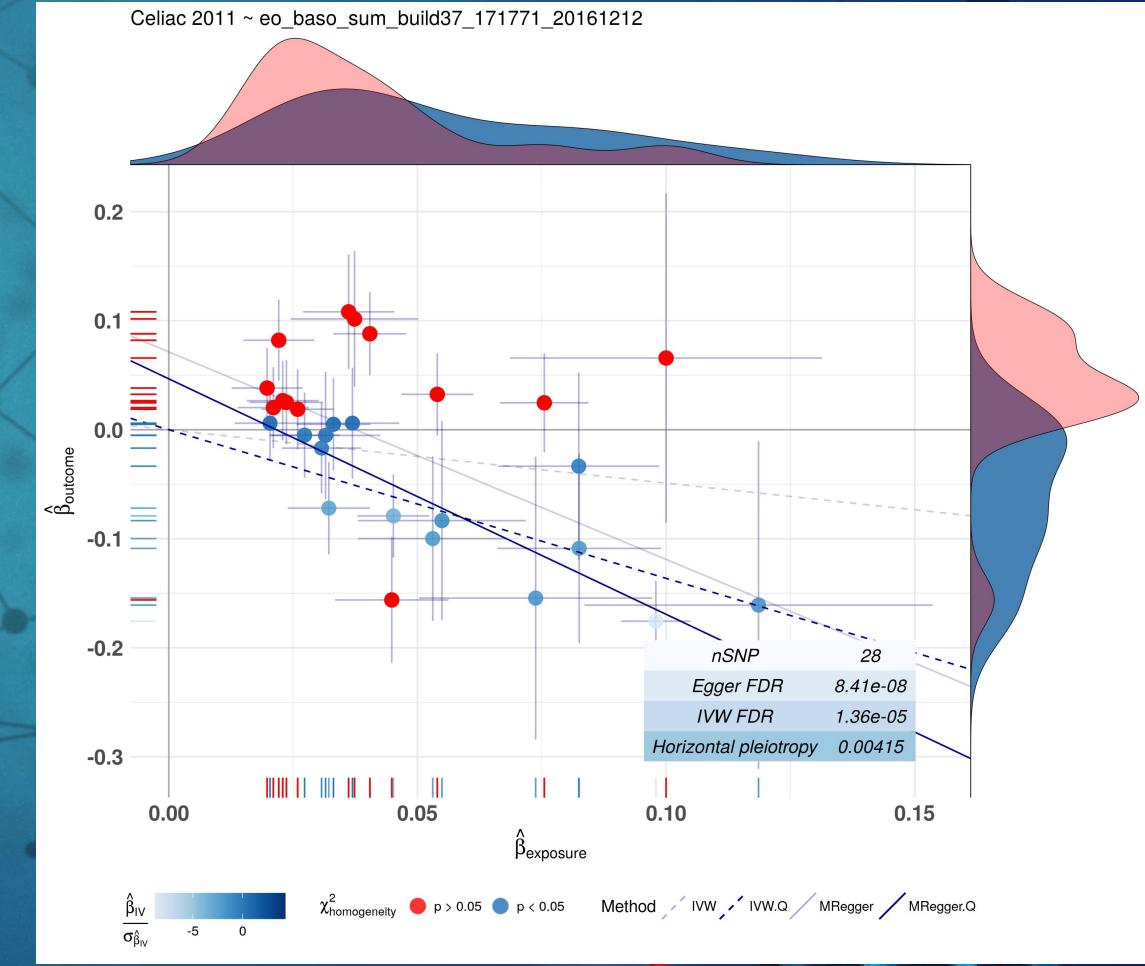
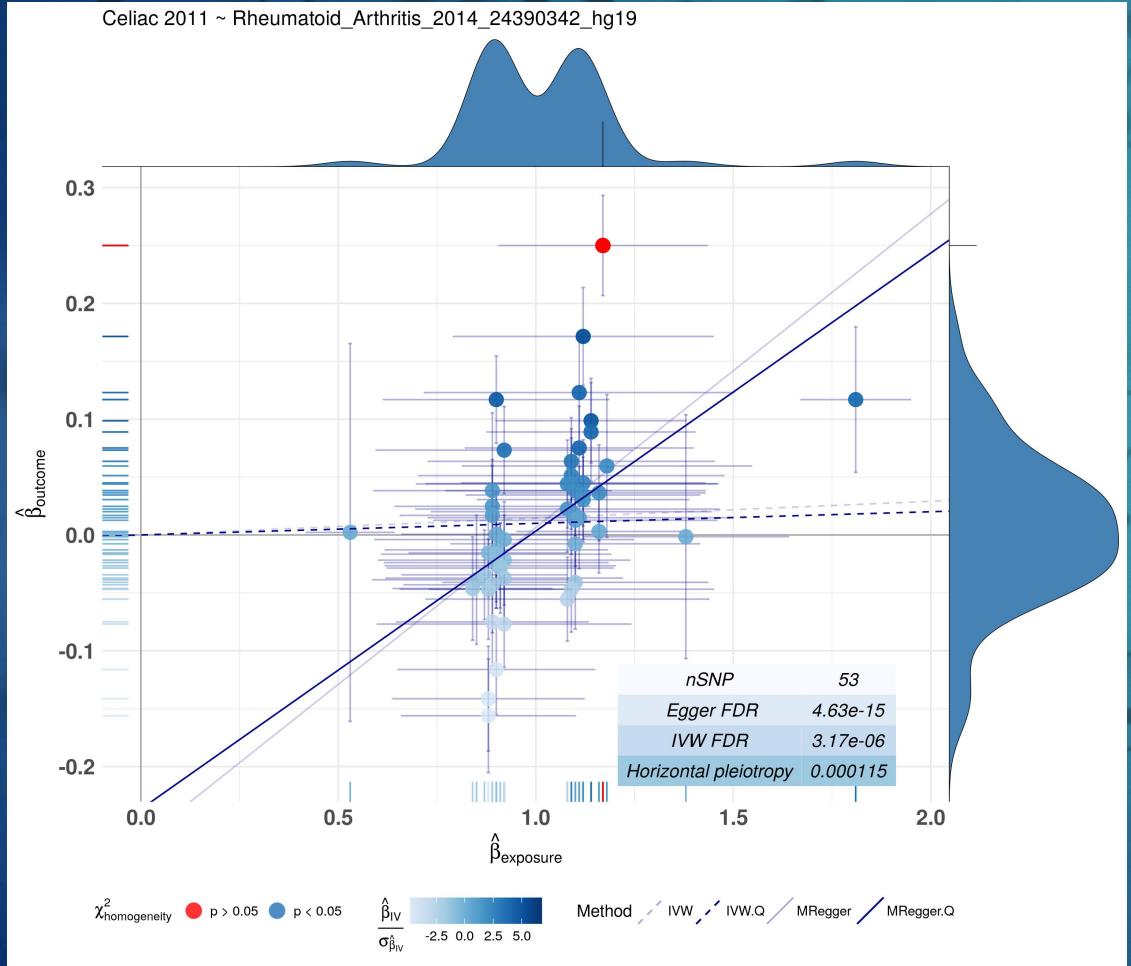
Preliminary results

- ▶ Celiac 2010, Patrick Dubois et. Al
 - ▶ 36 significant potential exposures
- ▶ Top 10

Exposure	IVW	Egger	nSNP
eo_build37_172275_20161212	2.457824e-05	0.0344422831	25
hct_build37_173039_20161212	3.635149e-01	0.0344422831	22
neut_p_gran_build37_170672_20161212	2.694008e-02	0.0344422831	25
eo_p_gran_build37_170536_20161212	6.095143e-03	0.0500008203	21
eo_baso_sum_build37_171771_20161212	6.892643e-06	0.0545461874	24
eo_p_build37_172378_20161212	3.581443e-03	0.0881148661	22
T1D_CC_2015_25751624_hg19	1.036351e-04	0.5464139213	24
Multiple_sclerosis_2011_21833088_hg19	2.899315e-02	0.5587373911	17
Packed_cell_volume_2012_23222517_hg18_hg19	4.829159e-02	0.5587373911	8
TR_trait31_2013_24074872_hg19	4.356029e-02	0.5924281553	19

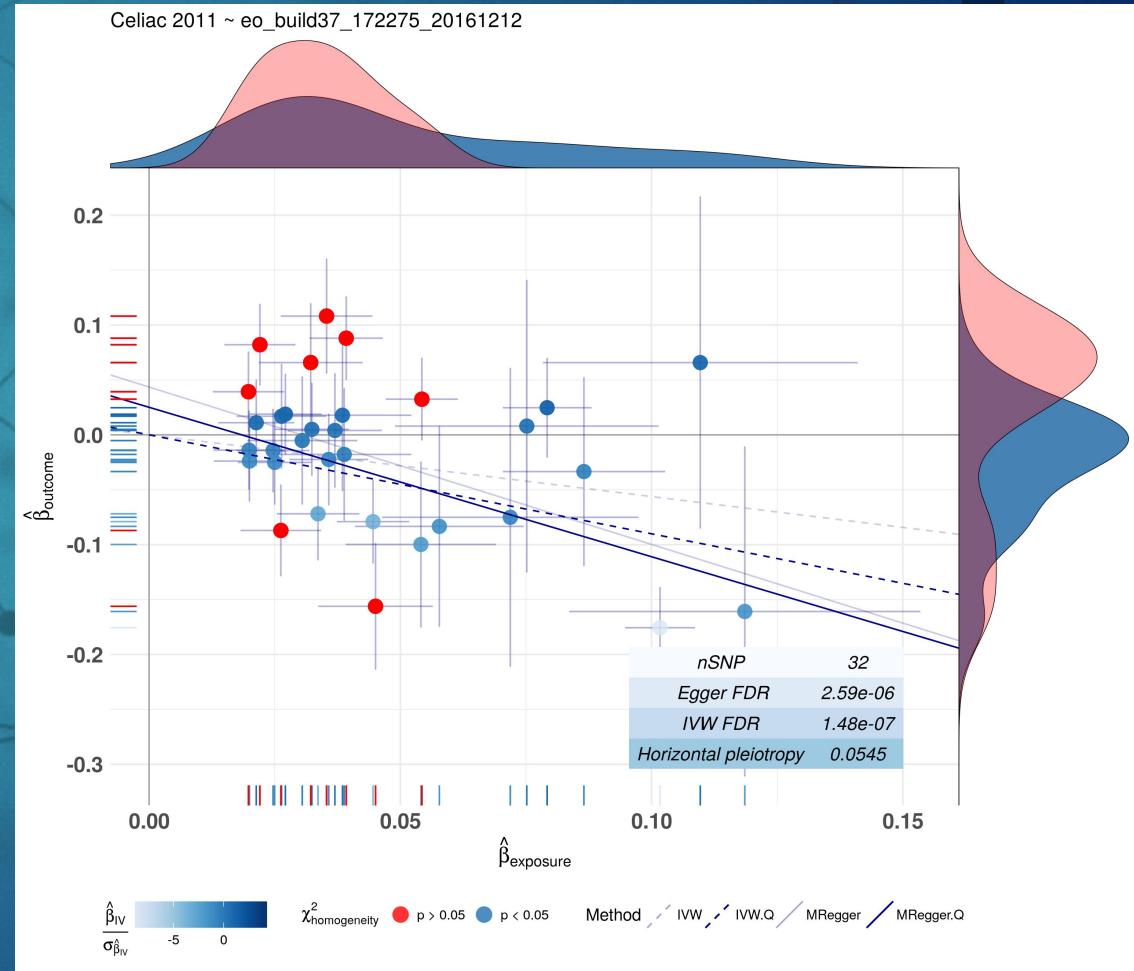
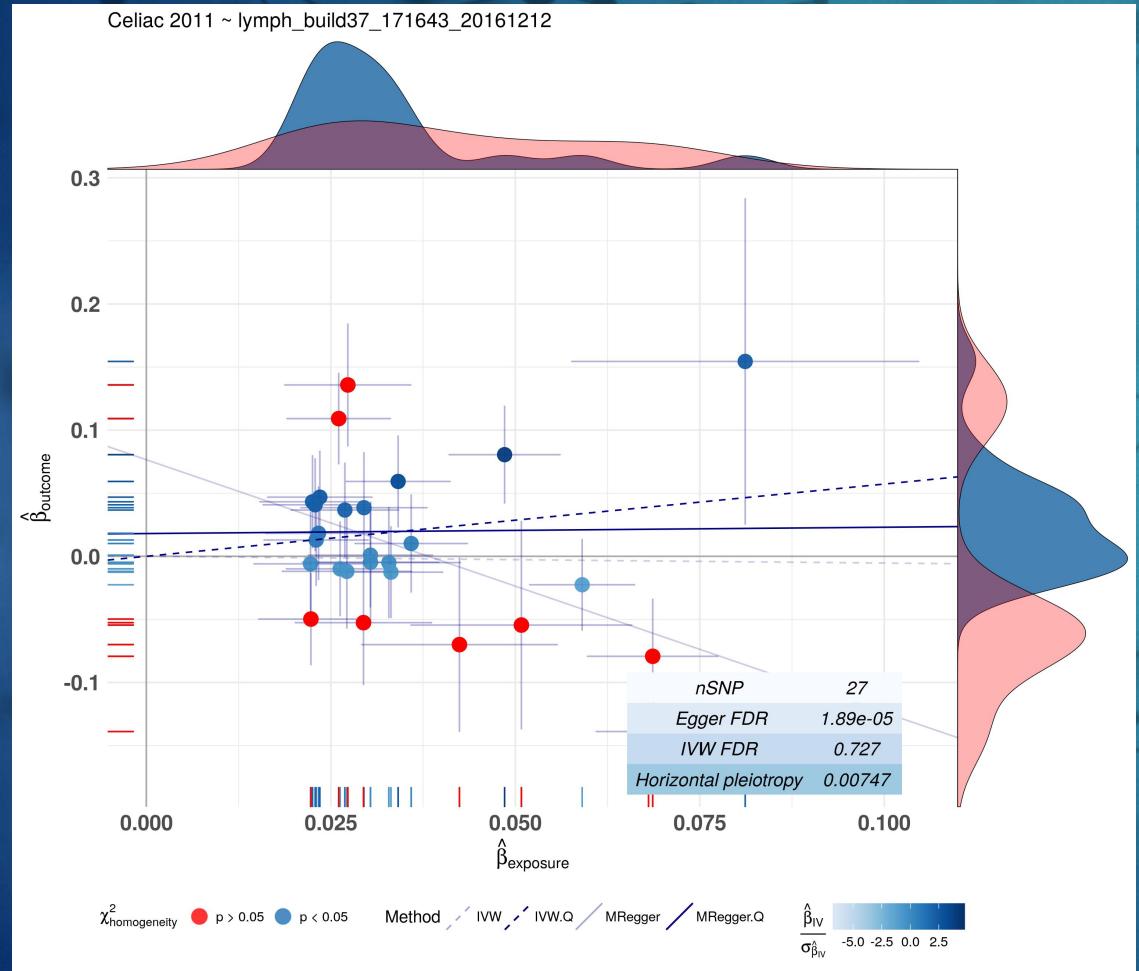
Preliminary results

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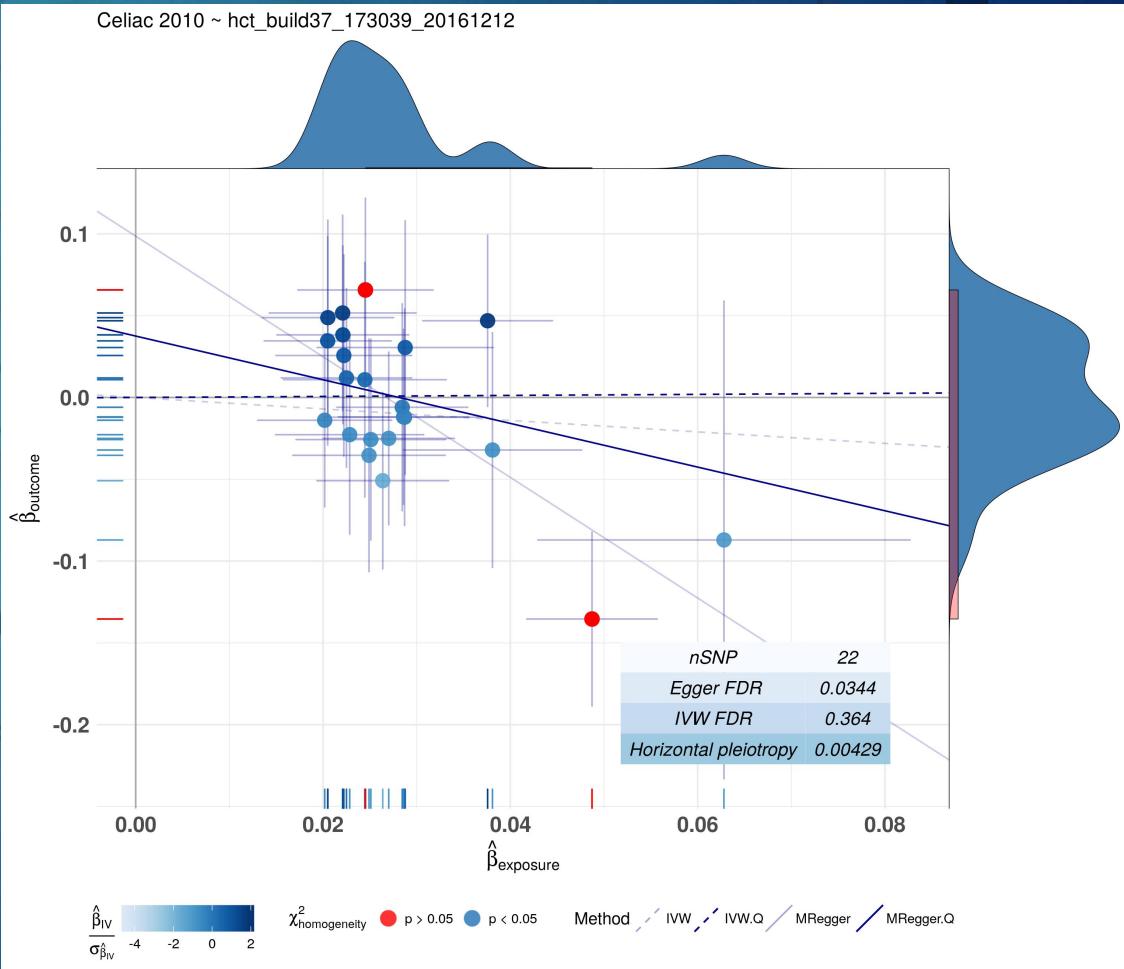
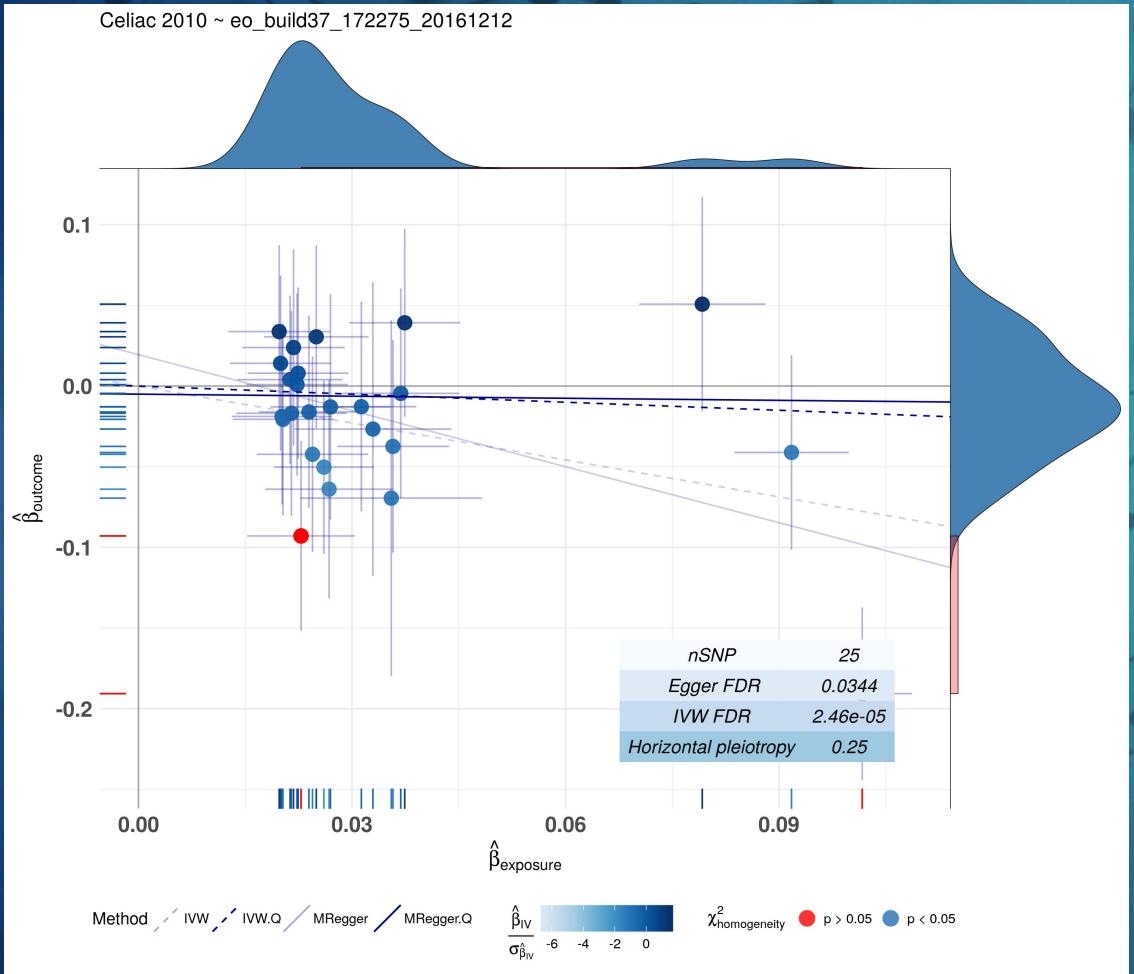
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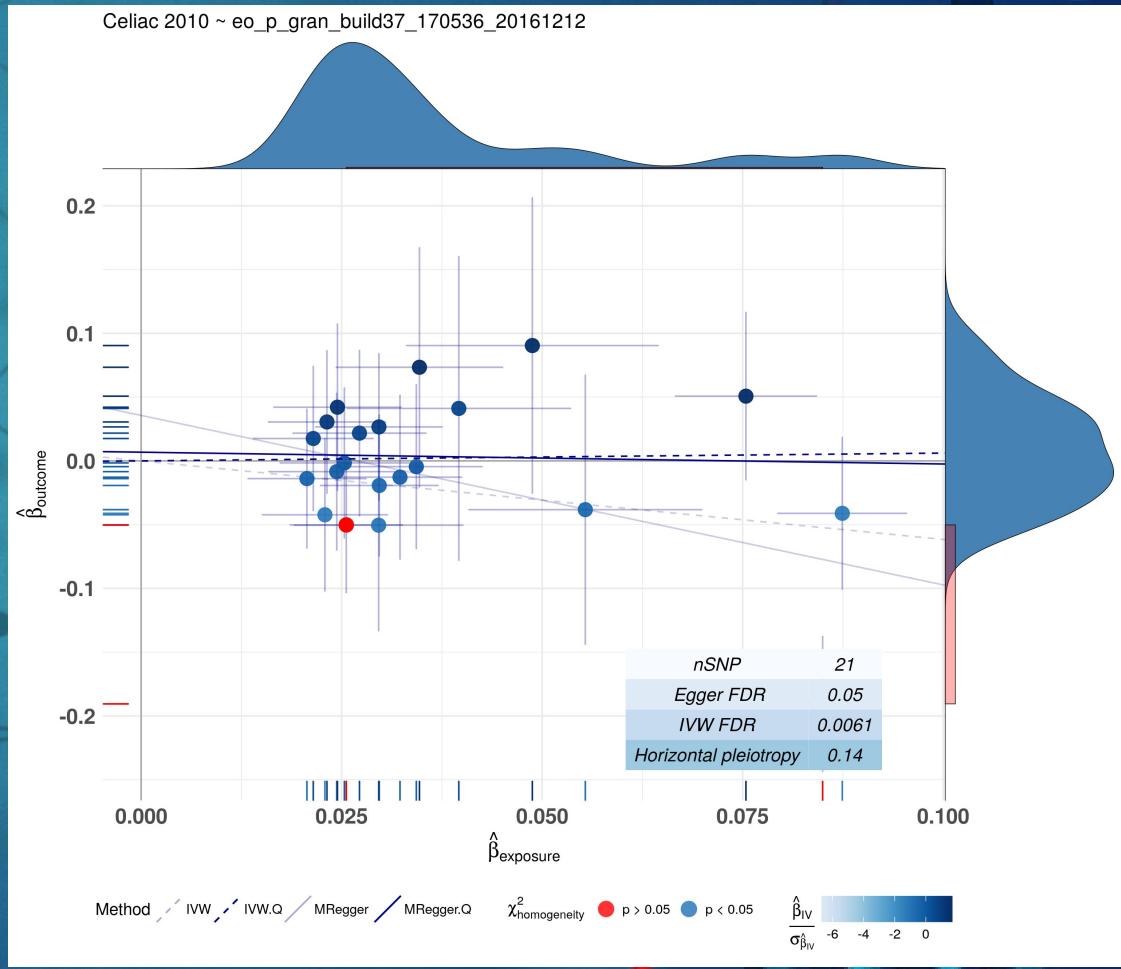
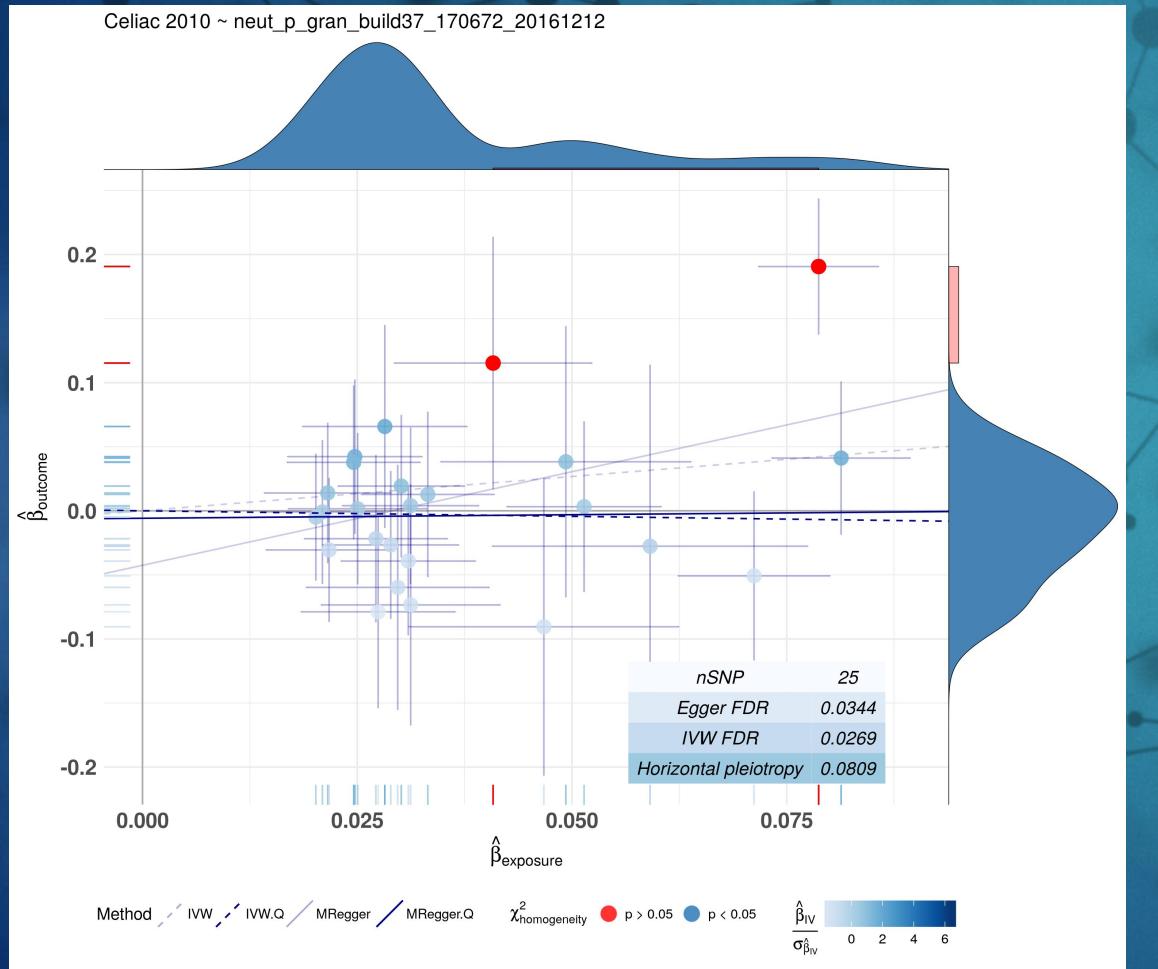
Preliminary results

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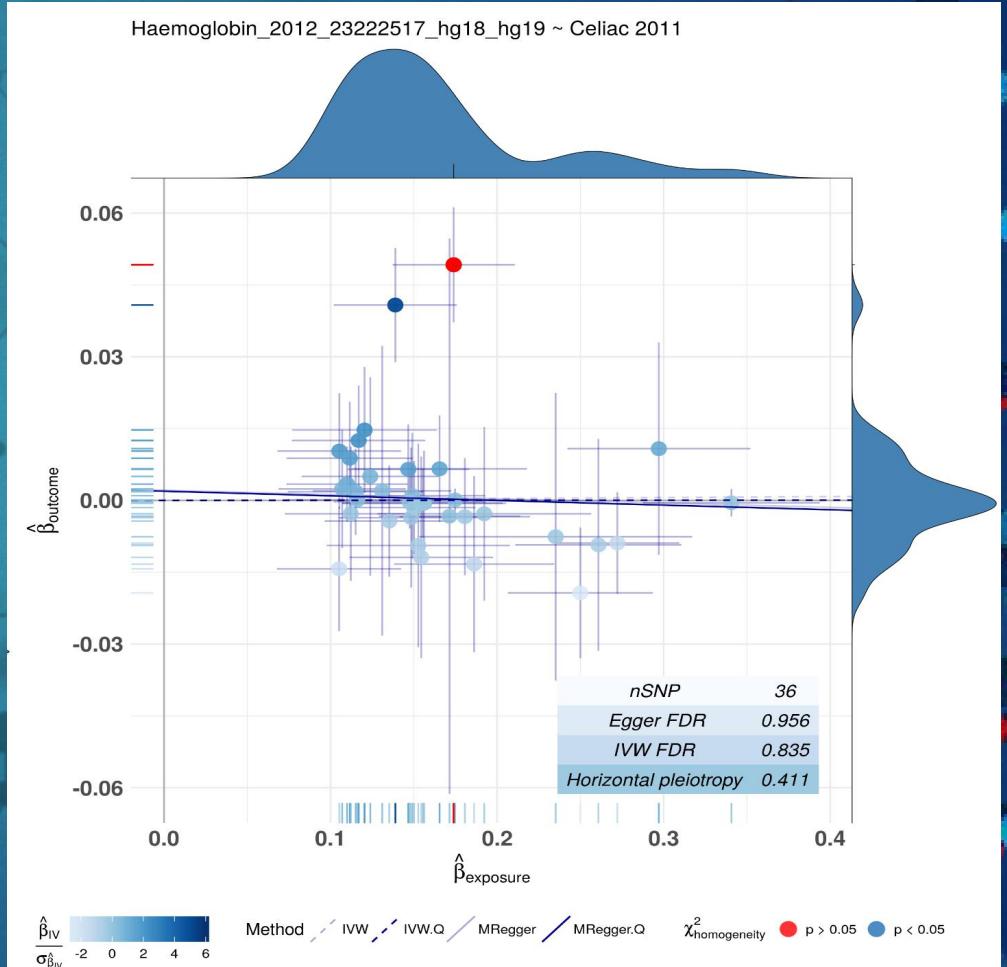
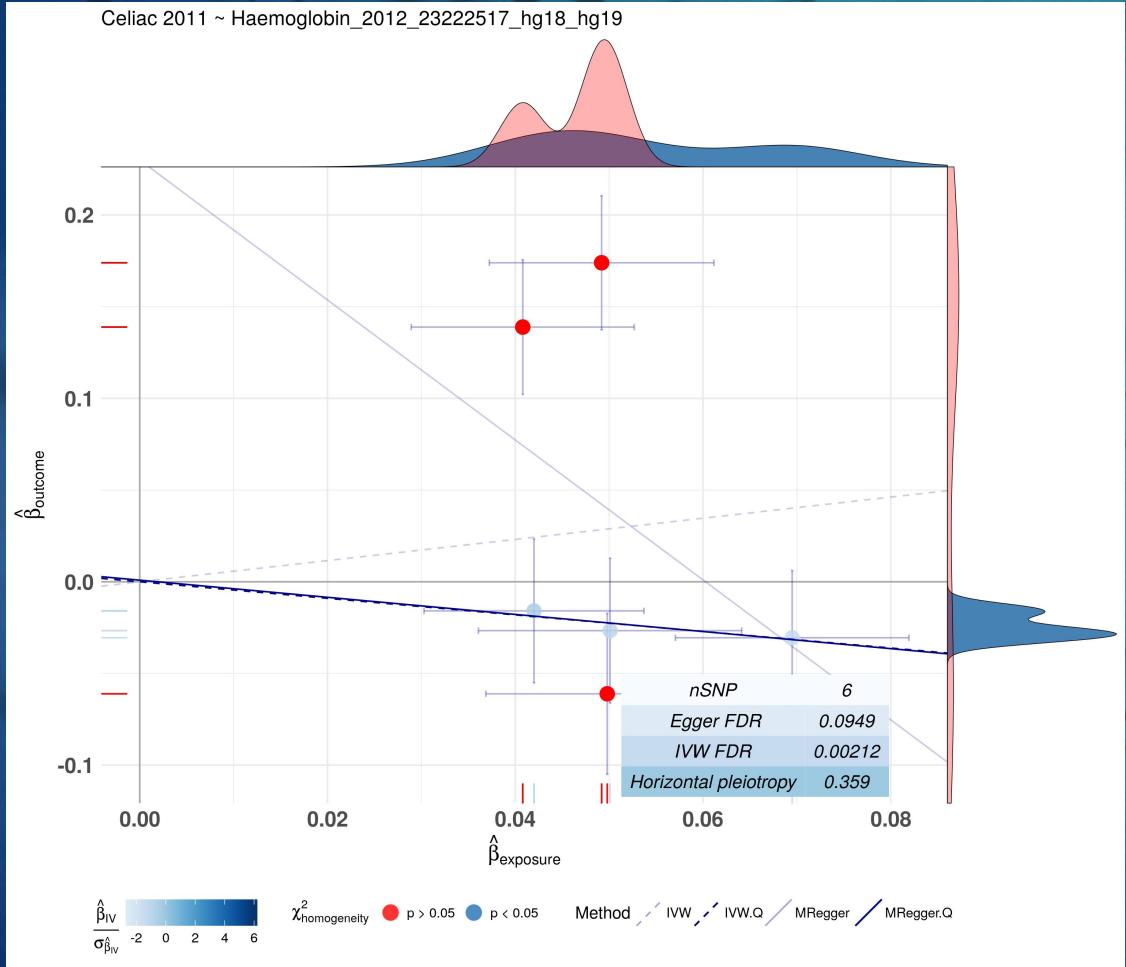
Preliminary results

► Celiac 2010, Patrick Dubois et. all



Preliminary results Bidirectional MR

► Celiac 2011, Gosia Trynka et. all



Future steps

- ▶ Predict significant hits in case-control studies
- ▶ Pathway analysis on SNPs in significant hits
- ▶ Network Mendelian Randomization