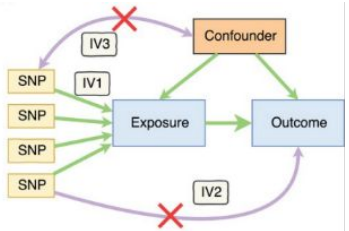
mGWAS-Explorer 2.0 Tutorial

– Crohn's disease case study

Goal for this tutorial

- Identify the **causal** associations between **metabolites** and **Crohn's disease**

MR Concept

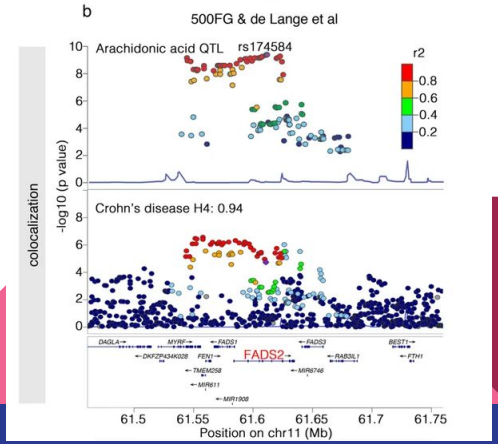


- **Mendelian randomization (MR)** is a research method that uses genetic variants as natural experiments to examine probable **causal** relationships between exposure risk factor and disease outcome.
- Compared to conventional observational research, MR is less susceptible to confounding and reverse causality.
- Assumptions:
  - Relevance assumption (IV1): the instruments must be associated with the exposure risk factor
  - Exclusion restriction assumption (IV2): the only way the IVs influence the outcome is through the relevant exposure risk factor
  - Independence assumption (IV3): the IVs must not associate with confounders

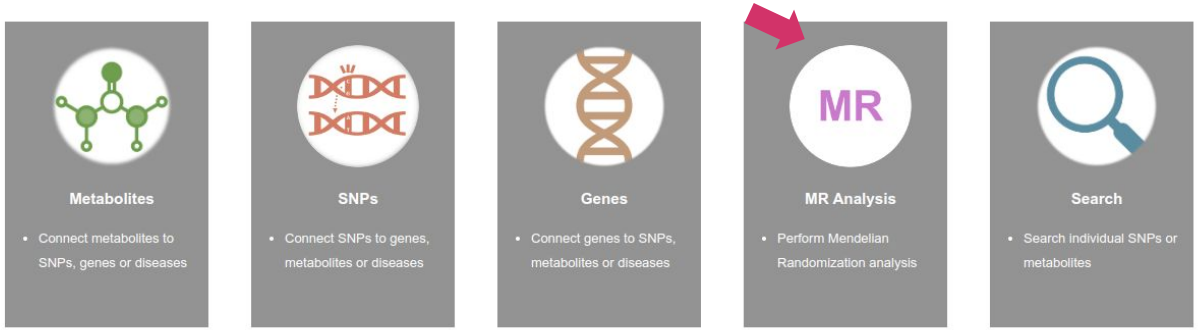
(Hemani et al. eLife vol. 7 e34408. 30 May. 2018)

Background

- Colocalization analysis between **arachidonic acid** mQTL and **Crohn's disease** GWAS's profile strongly supported the hypothesis that arachidonic acid share common genetic variants with Crohn's disease (Chu et al., 2021)
- Therefore, we applied the **Mendelian randomization** method to test the **causal effect** of arachidonic acid on Crohn's disease using mGWAS-Explorer 2.0



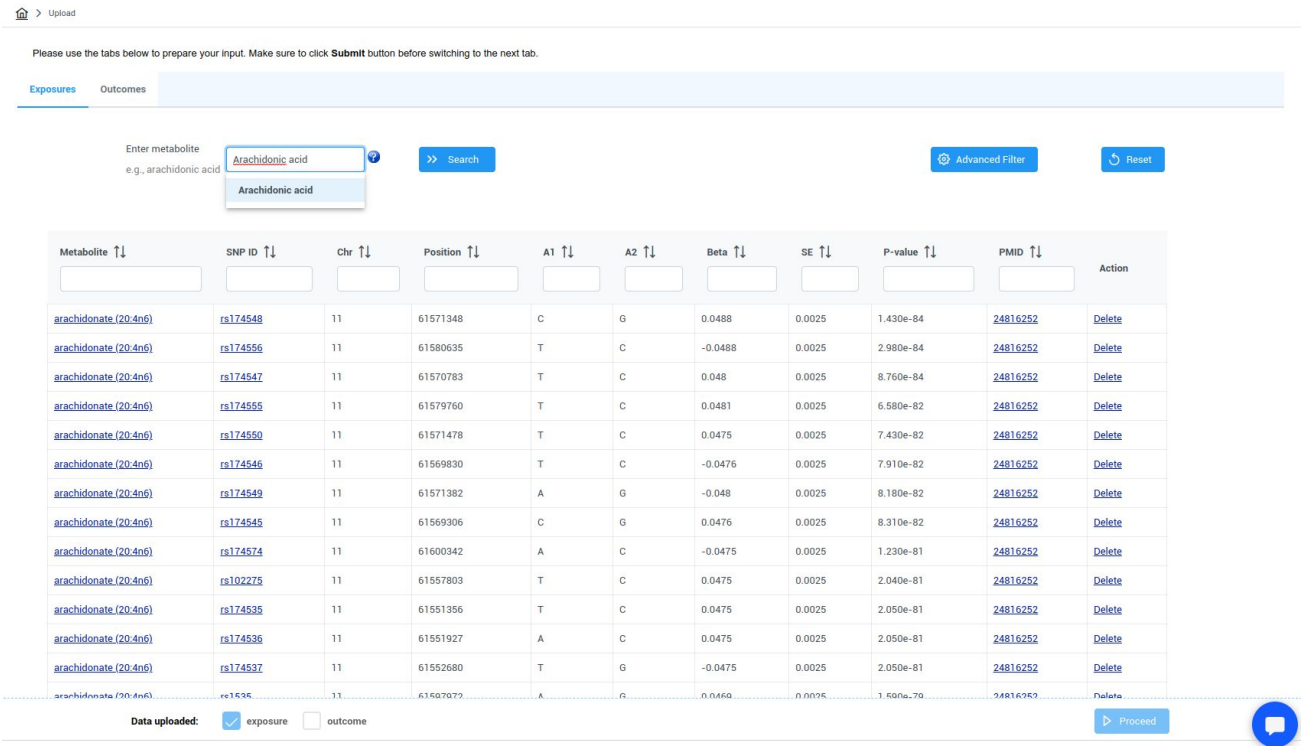
Starting up



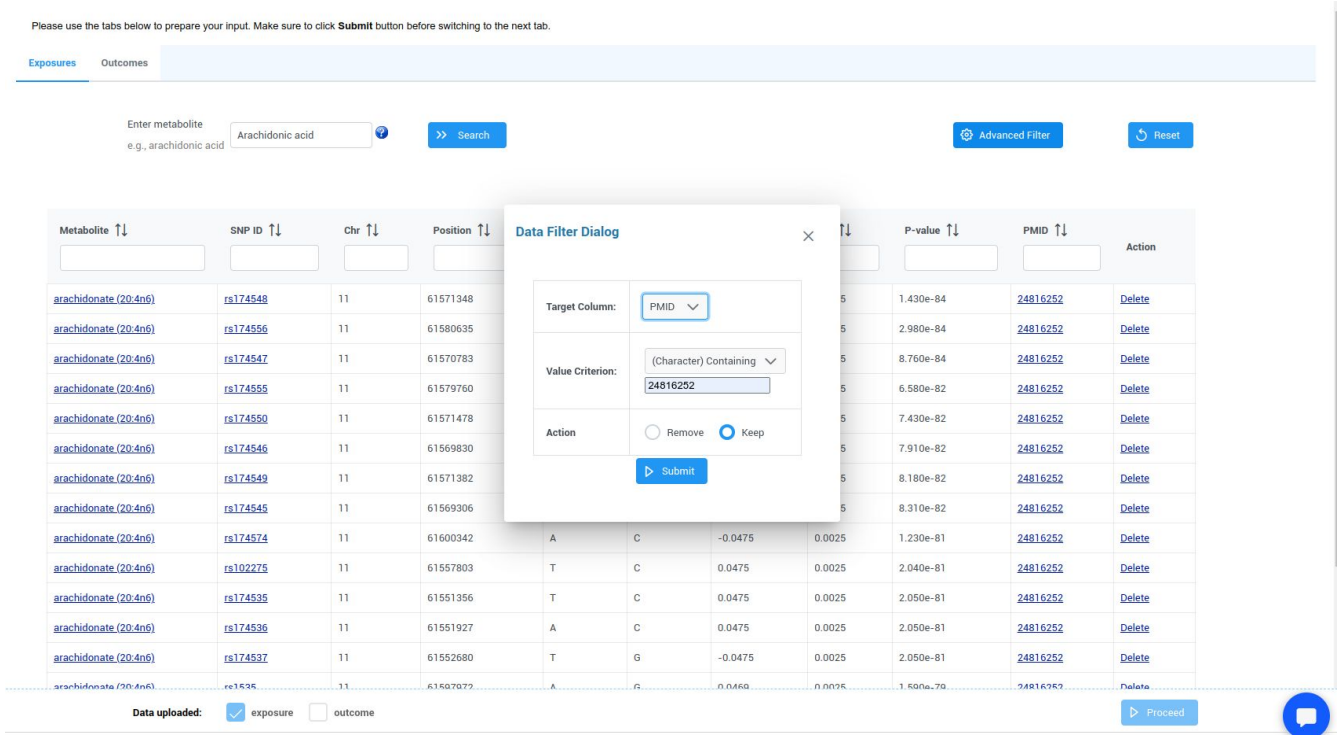
- Go to the mGWAS-Explorer homepage (www.mgwas.ca)
- Click on the “MR” button to enter the data upload page for MR module

Exposure data (metabolite)

1. Copy and paste “Arachidonic acid” in the search box
2. Select from the drop-down list
3. Click “Search” button

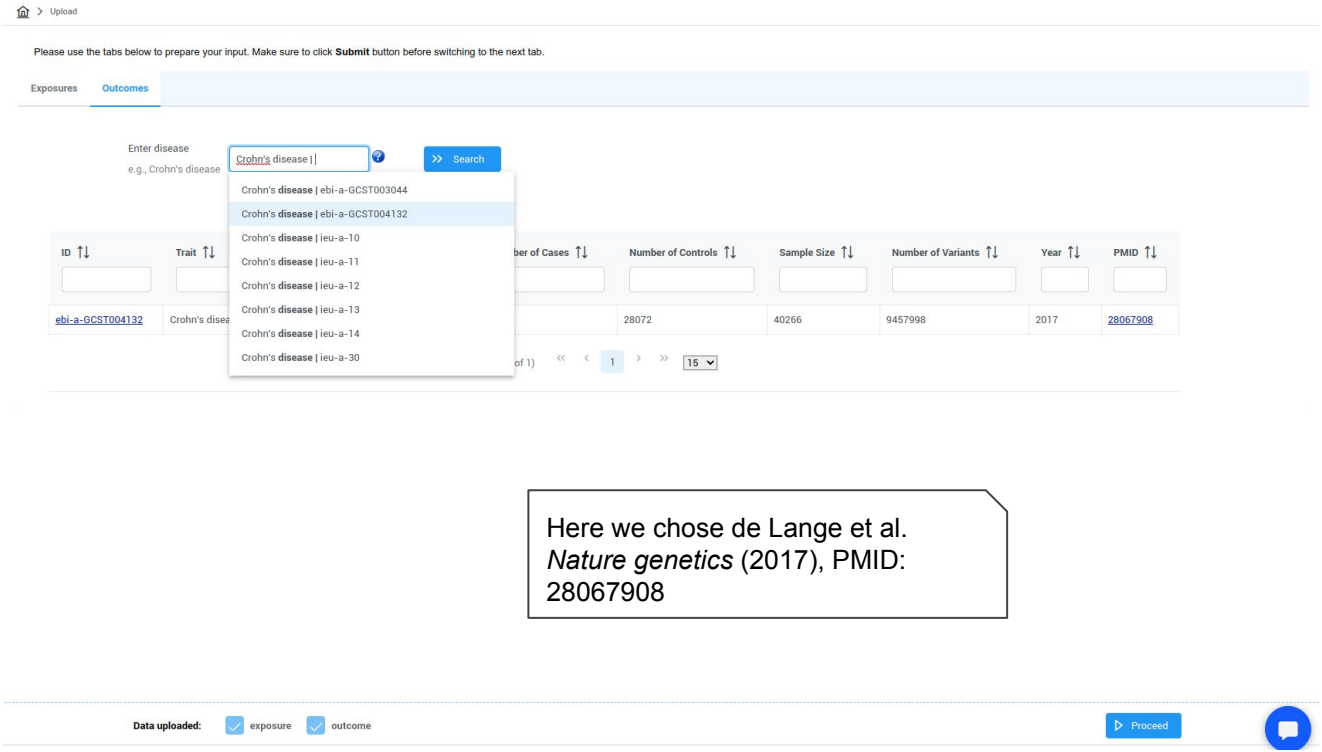


- Note: use advanced filter to select a mGWAS study
  - Here we chose Shin et al. *Nature genetics* (2014), PMID: 24816252



Outcome data (disease)

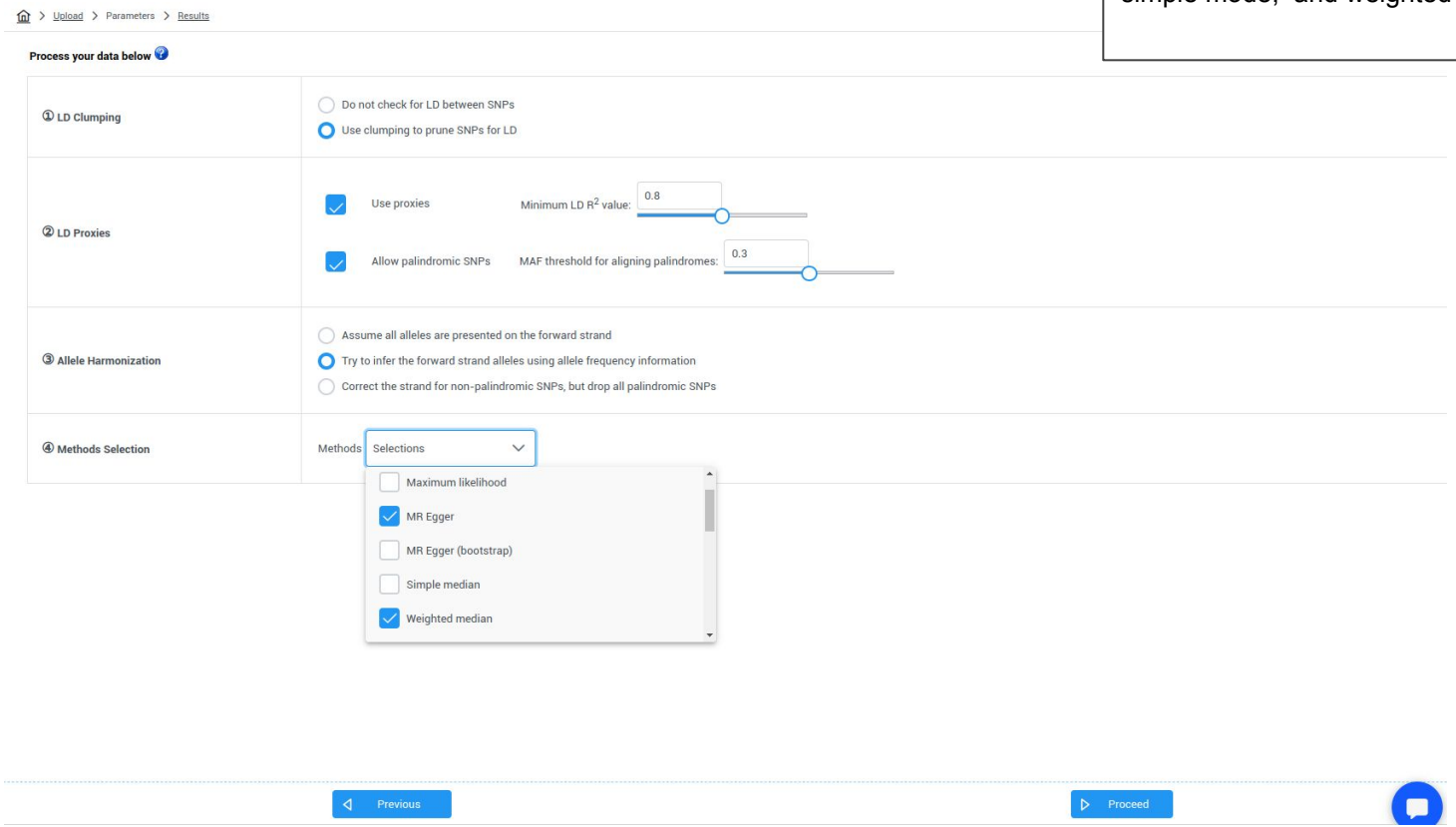
1. Copy and paste “Crohn’s disease” in the search box
2. Select from the drop-down list
3. Click “Search” button
4. After both exposure and outcome data are uploaded, click “Proceed” button



Here we chose de Lange et al. *Nature genetics* (2017), PMID: 28067908

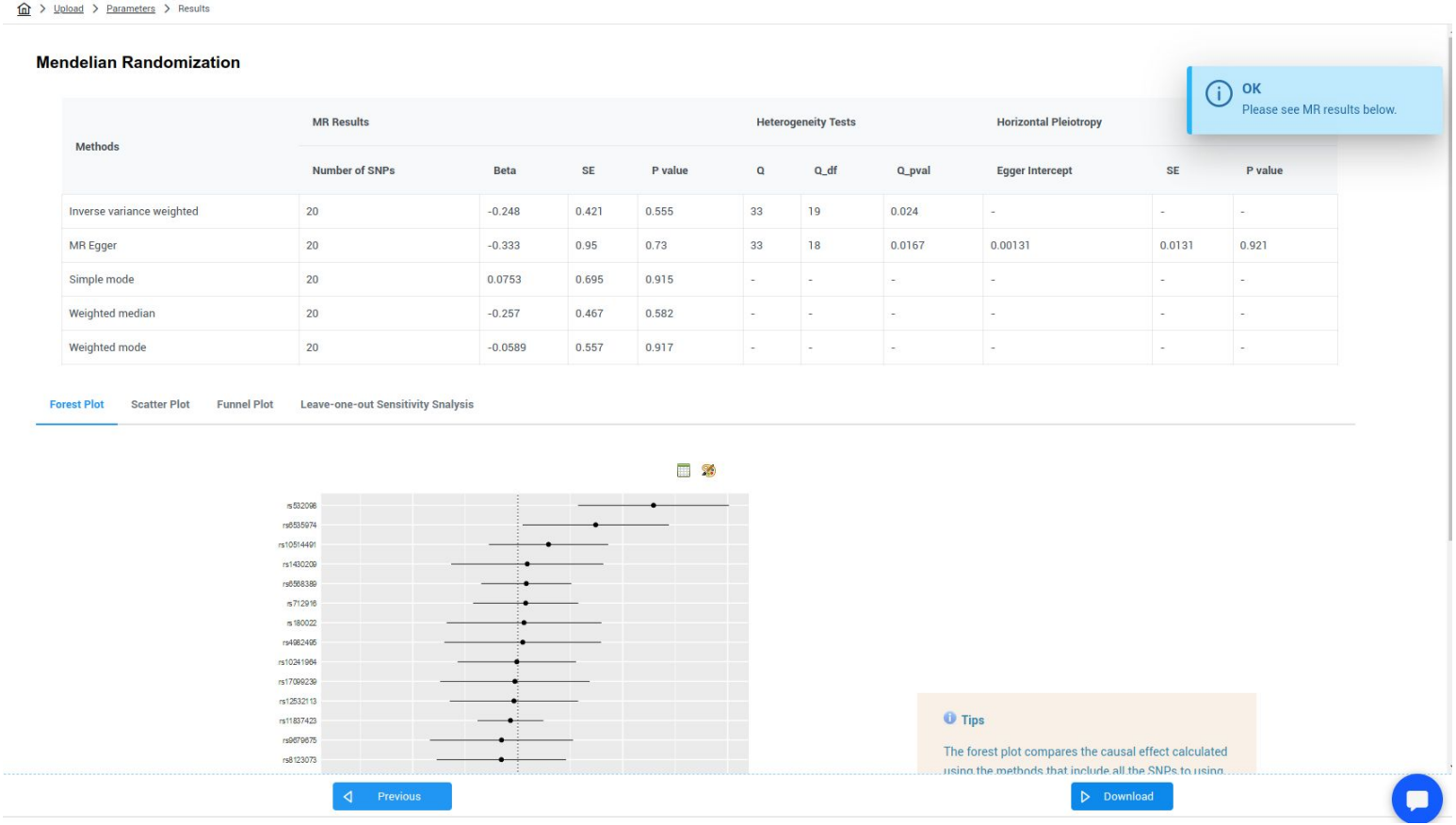
Run MR

Here we chose five commonly used MR methods: MR Egger, weighted median, Inverse variance weighted, simple mode, and weighted mode



MR results

Users can toggle between tabs to view different plots.

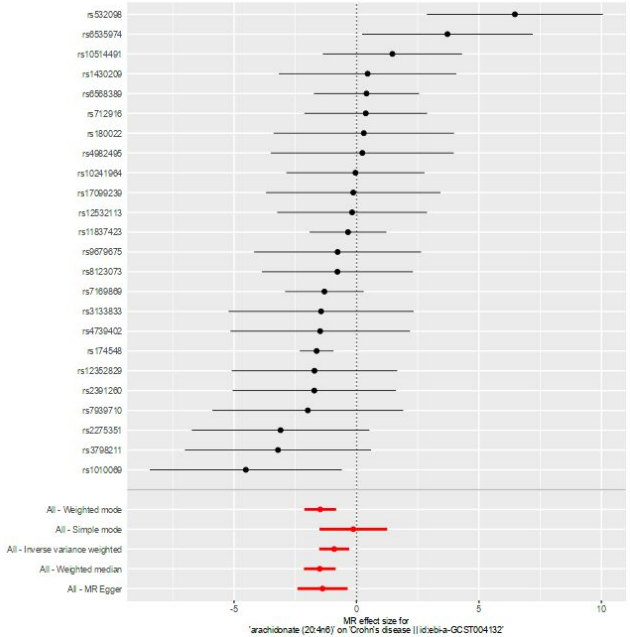


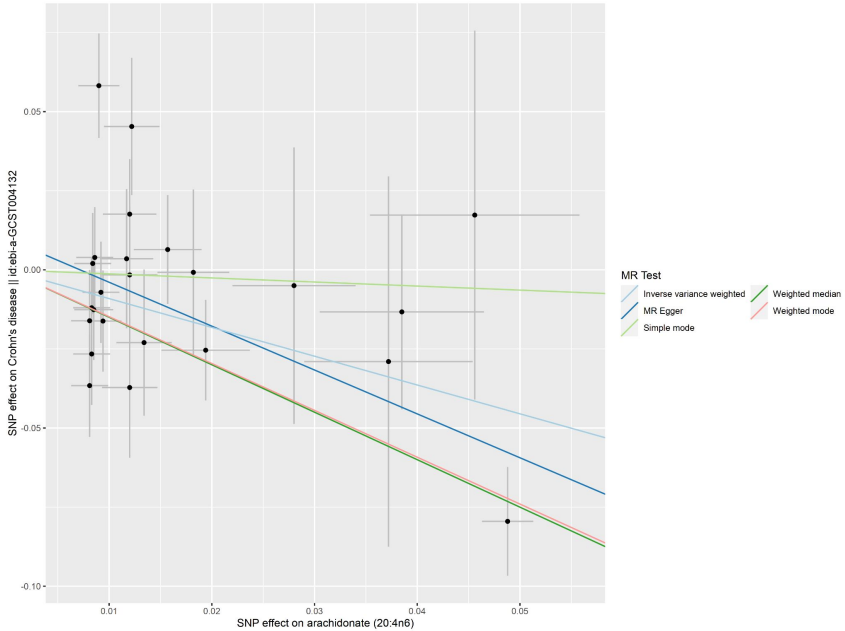
Methods	MR Results				Heterogeneity Tests			Horizontal Pleiotropy		
	Number of SNPs	Beta	SE	P value	Q	Q_df	Q_pval	Egger Intercept	SE	P value
Inverse variance weighted	20	-0.248	0.421	0.555	33	19	0.024	-	-	-
MR Egger	20	-0.333	0.95	0.73	33	18	0.0167	0.00131	0.0131	0.921
Simple mode	20	0.0753	0.695	0.915	-	-	-	-	-	-
Weighted median	20	-0.257	0.467	0.582	-	-	-	-	-	-
Weighted mode	20	-0.0589	0.557	0.917	-	-	-	-	-	-

MR results

Methods	MR Results			
	Number of SNPs	Beta	SE	P value
Inverse variance weighted	24	-0.91	0.313	0.0036
MR Egger	24	-1.39	0.523	0.0146
Simple mode	24	-0.128	0.646	0.844
Weighted median	24	-1.5	0.335	7.55e-06
Weighted mode	24	-1.48	0.322	0.000126

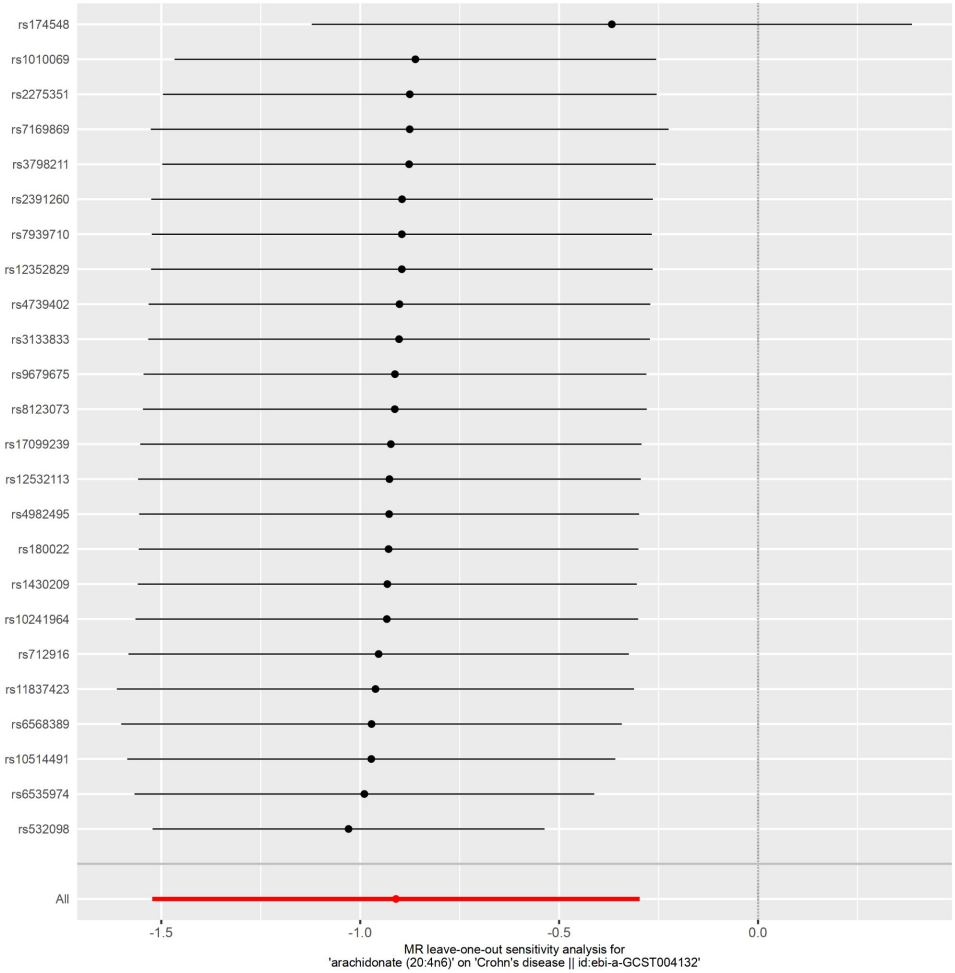
Consistently shows that the decrease in **arachidonic acid** level had a causal effect on **Crohn's disease**





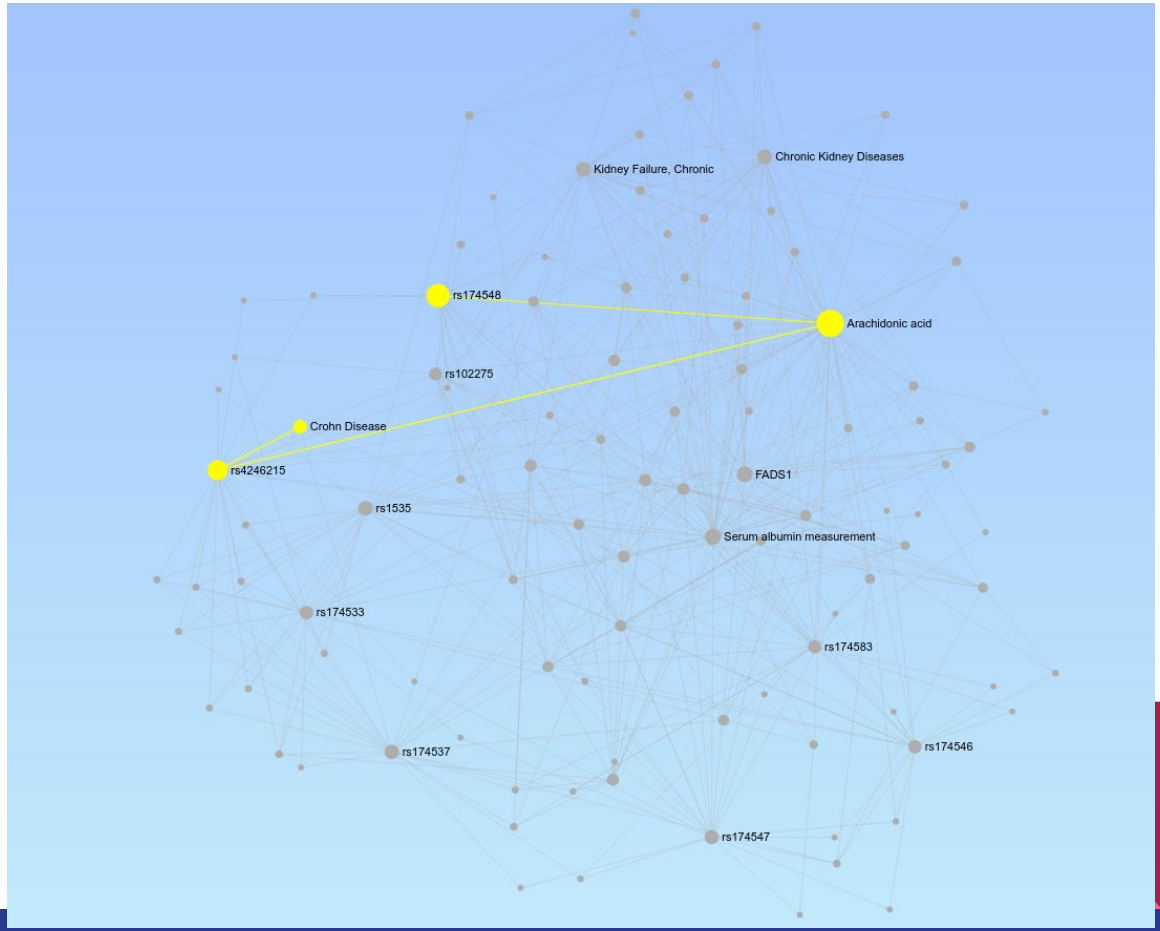
Leave-one-out plot

- Each black point represents the MR method applied to estimate the causal effect of AA on CD excluding that particular SNP from the analysis
- Exclusion of **rs174548** leads to larger changes in the result



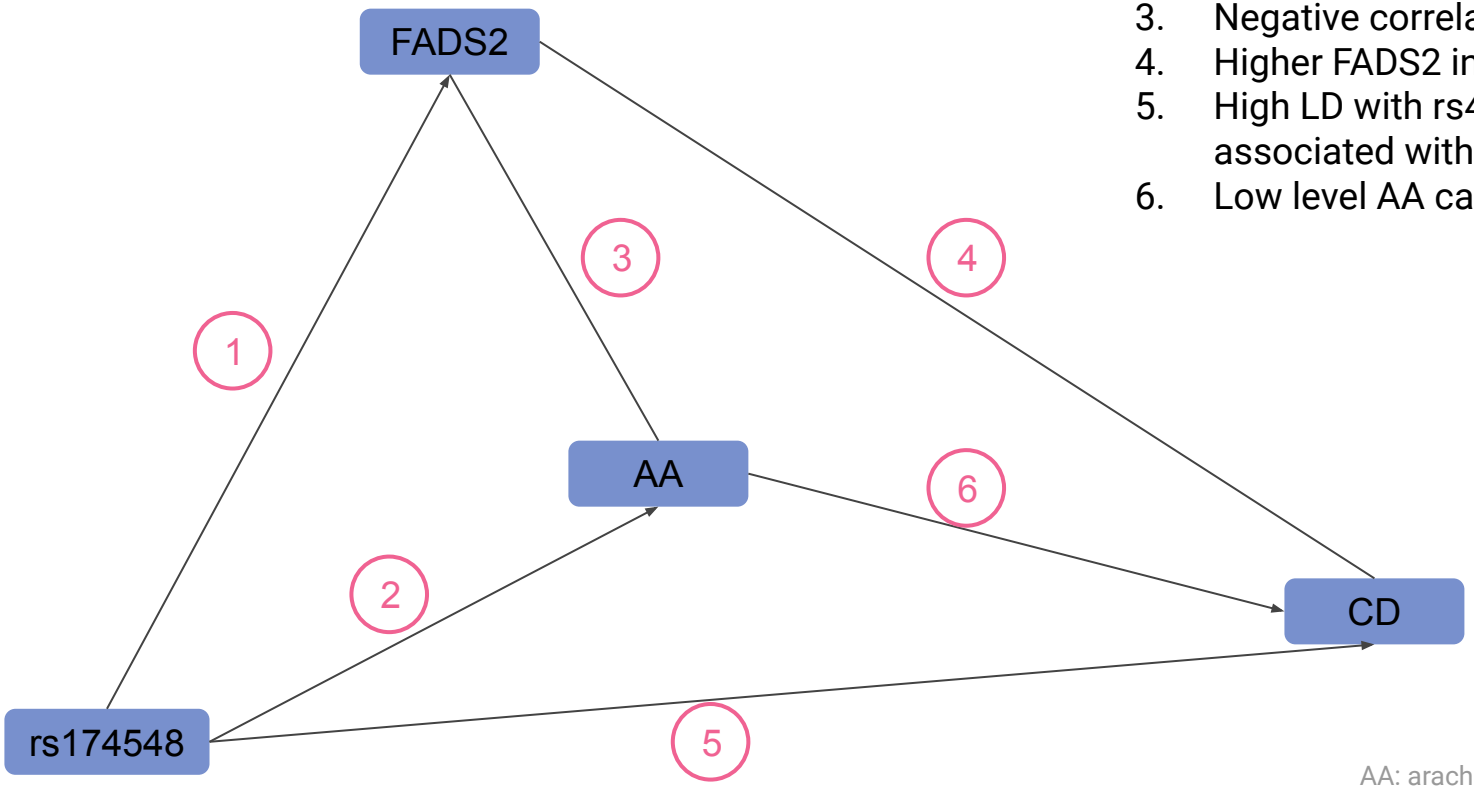
Network-mapping

- Input:
  - rs174548
    - SNP-metabolite
    - SNP-gene (EUR, r^2>0.7)
    - SNP-disease
  - arachidonic acid
    - metabolite-SNP
    - metabolite-gene
    - metabolite-disease
- Degree filter > 1
- Shortest path view



Mechanistic link

1. Higher FADS2 level (allele G), eQTL
2. Lower AA level (allele G)
3. Negative correlation
4. Higher FADS2 in CD
5. High LD with rs4246215, associated with CD
6. Low level AA causal to CD



AA: arachidonic acid;
CD: Crohn's disease

In summary

mGWAS-Explorer 2.0 is able to provide multiple evidence that arachidonic acid is causally associated with Crohn’s disease, suggesting it is a potential therapeutic target.