MetaboAnalyst 6.0

-- a unified platform for metabolomics data processing, analysis and interpretation

Causal Analysis using Mendelian randomization

2024-03-10

Module Overview

This module offers functions to estimate the causal relationship between metabolites and phenotypes through Mendelian randomization (MR) analysis.

- ✓ There are many metabolomics-based genome-wide association studies (mGWAS) conducted to understanding the genetic regulations of metabolites in complex phenotype.
- ✓ By leveraging those SNP-tagged metabolites and summary statistics from public GWAS repositories, we can now test potential causal relationships between those genetically influenced metabolites and a disease outcome of interest using the well-established two-sample Mendelian randomization method.
- ✓ MR can estimate whether a relationship between a metabolite and a phenotype is causal, while reduce the impact of confounding factors and reverse causality that often plague observational studies.

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1. Introduction

Background

- It is now possible to estimate causal relationship between metabolites and a phenotype of interest.
- If a metabolite is causal for a given disease, genetic variants which influence the levels of that metabolite, either directly or indirectly, should result in a higher risk of the disease.

Data Formats

- No data upload required
- Users select an exposure (i.e., metabolites) and an outcome (i.e., diseases) of interest from the available options from our built-in databases

Expected Results

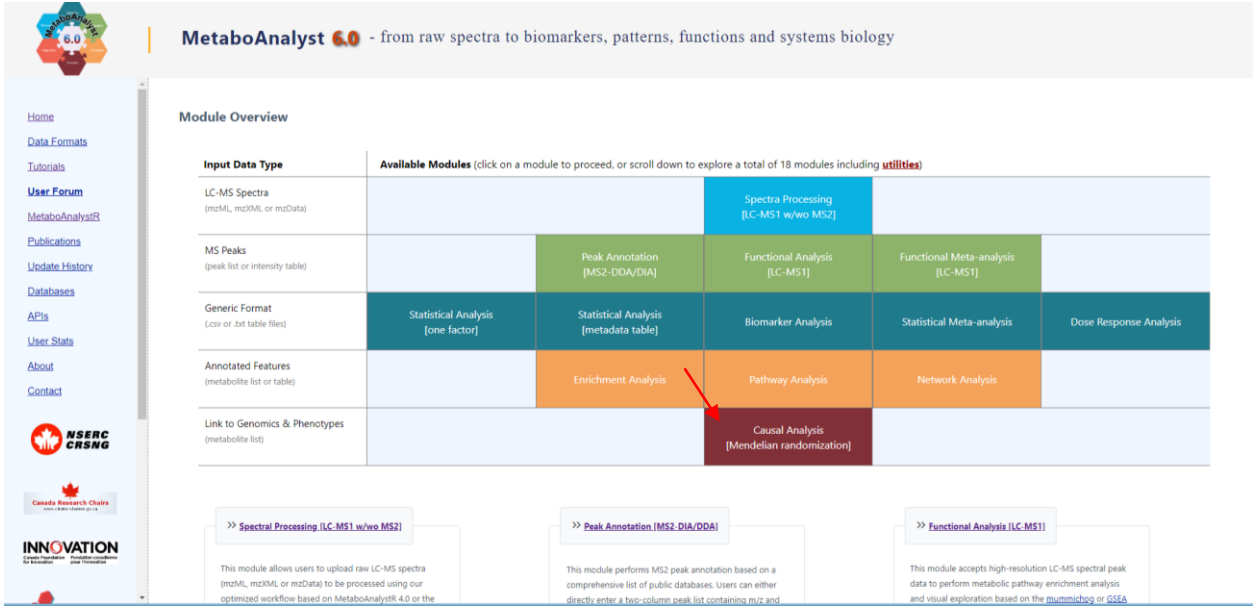
This module provides user comprehensive results on potential causal relationships between exposure-outcome based on two-sample MR

i. Intermediate results from harmonization steps

ii. The results from various statistical routines to estimate the causal effects and associated diagnostic and visualization plots

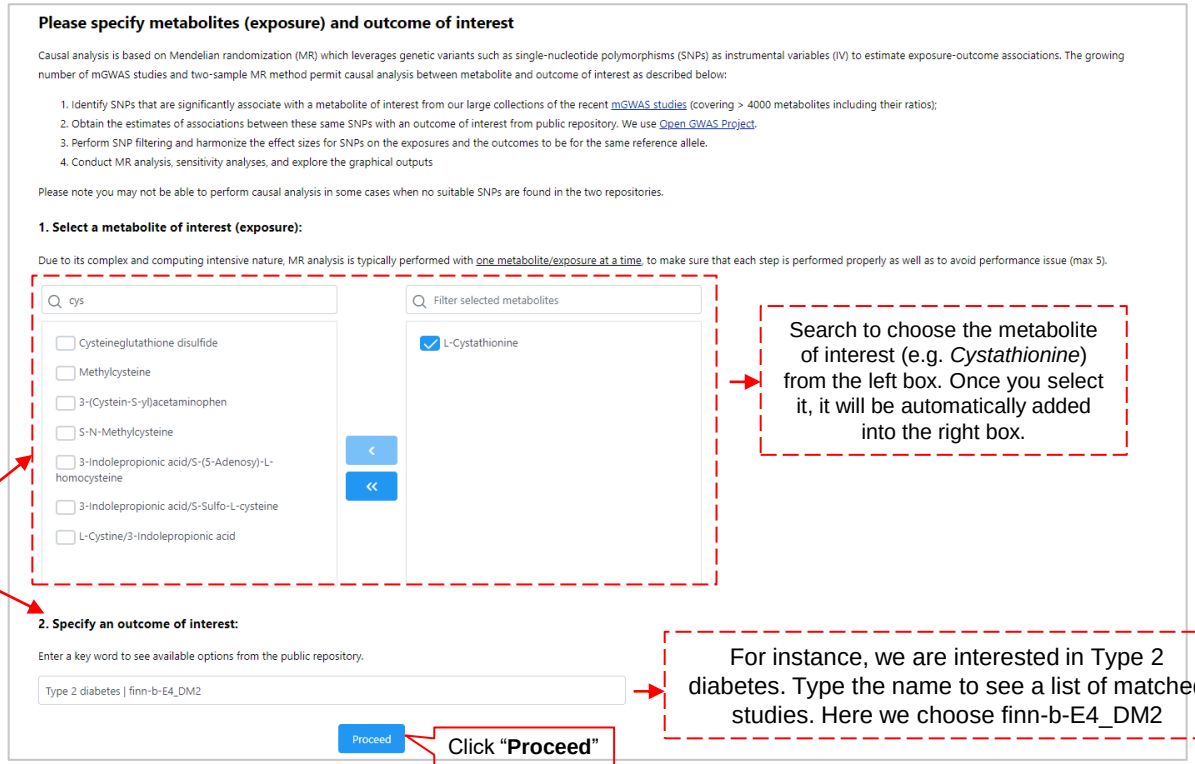
2. Choose the Module

Go to MetaboAnalyst (https://www.metaboanalyst.ca), and select the module



3. Causal Analysis via two-sample Mendelian randomisation (2SMR)

3.1 Specify metabolite and phenotype of interest



Users should first select an exposure (i.e., metabolites) and an outcome (i.e., diseases) of interest.

Search to choose the metabolite of interest (e.g. *Cystathionine*) from the left box. Once you select it, it will be automatically added into the right box.

For instance, we are interested in Type 2 diabetes. Type the name to see a list of matched studies. Here we choose finn-b-E4_DM2

Click "**Proceed**" to continue

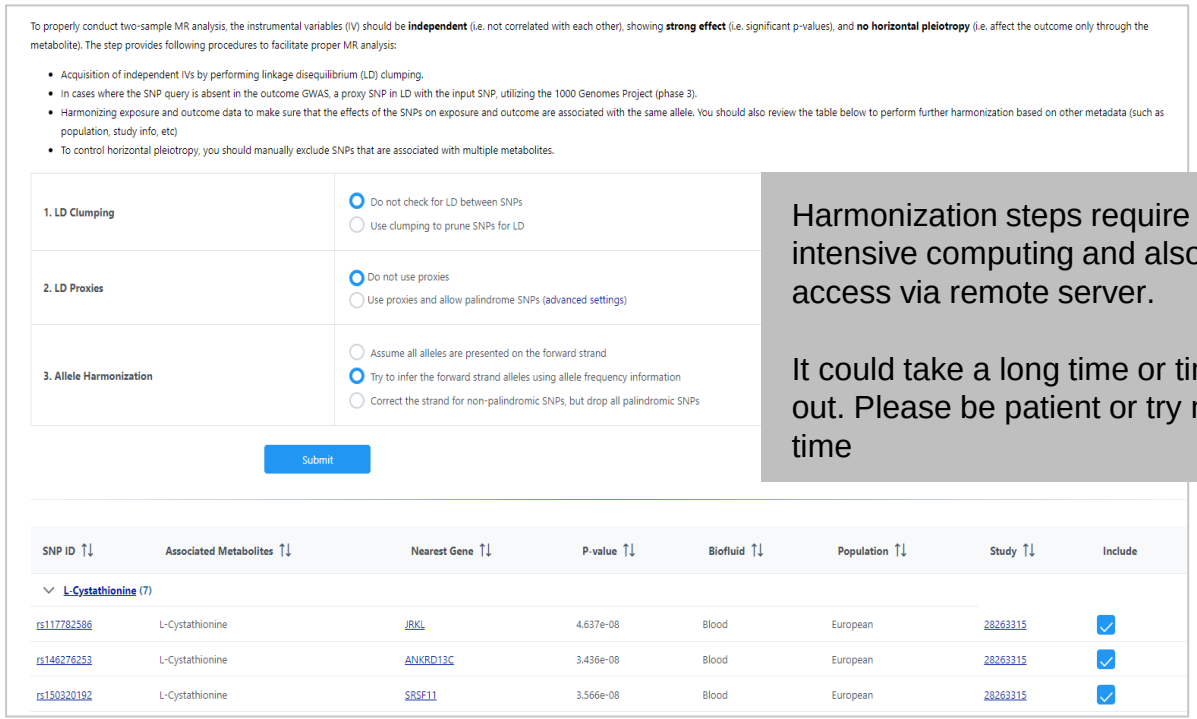
3.2 SNP filtering and harmonization

- Multiple SNPs could be identified as potential instrumental variables (IV) from the mGWAS and GWAS studies.

- To perform proper 2SMR, the IVs should be
  - Independent (i.e. not correlated with each other)
  - Showing strong effect (i.e. significant p-values)
  - No horizontal pleiotropy (i.e. affect the outcome only through the metabolite).

- Users need to carefully examine SNPs and apply different filtering and harmonization methods for each criterion

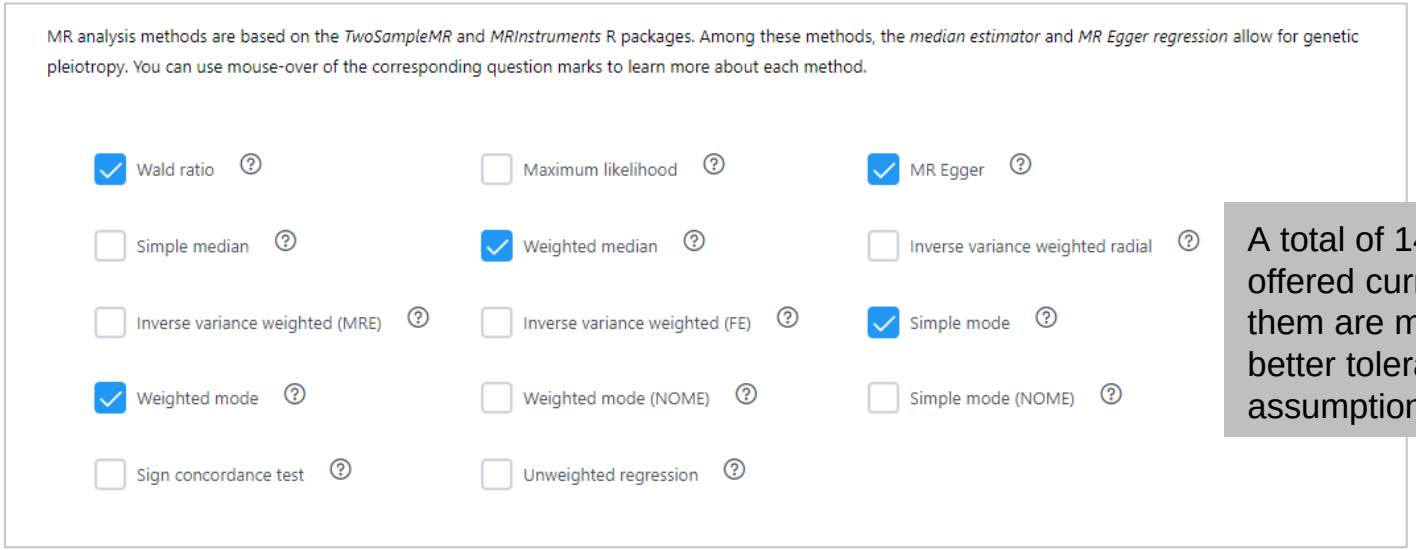
3.2 SNP Filtering and harmonization



Harmonization steps require intensive computing and also access via remote server.

It could take a long time or time out. Please be patient or try more time

3.3 Select statistical methods



A total of 14 MR methods are offered currently. Some of them are more robust and can better tolerate violations of the assumptions to certain degree

- Mouse over the question marks for each method to see their main features.
- You can also find more detailed introduction on the forum: https://omicsforum.ca/t/what-are-the-differences-between-the-mr-analysis-methods/1045

3.4 Mendelian randomization results

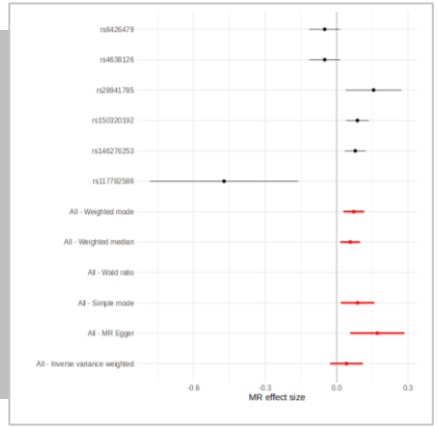
L-Cystathionine

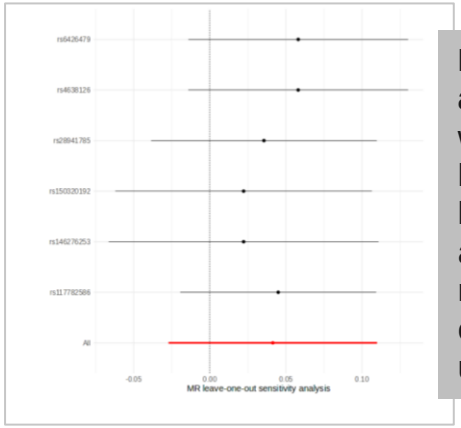
Methods	SNP Count	Causal Effect Estimates			Heterogeneity Tests			Horizontal Pleiotropy		
		Beta	SE	P value	Q	Q_df	Q_pval	Egger Intercept	SE	P value
Inverse variance weighted	6	0.041396	0.034939	0.23609	35.367	5	1.2709e-06	-	-	-
MR Egger	6	0.17071	0.057839	0.041906	14.006	4	0.0072767	-0.1179	0.047732	0.068948
Simple mode	6	0.088203	0.032068	0.040286	-	-	-	-	-	-
Weighted median	6	0.057145	0.021665	0.0083484	-	-	-	-	-	-
Weighted mode	6	0.072379	0.0219	0.021358	-	-	-	-	-	-

- The MR results are organized per metabolite (exposure).
- For metabolite, its shows the SNPs instrumental variables, along with their corresponding causal effect estimates, standard errors and p-values. Key values such as the MR-Egger regression intercept and its corresponding p-value are presented.
- Not all methods selected from the previous page would yield results depending of the data used.

3.4 Graphical outputs from MR analysis

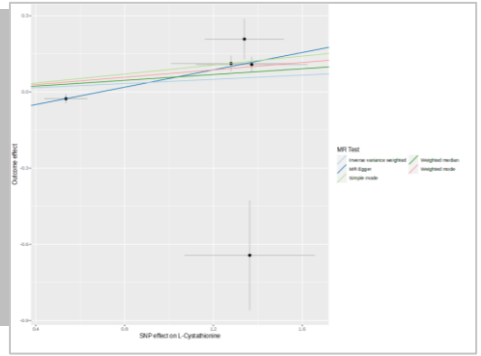
Forest plot compares the causal effect calculated using the methods that include all the SNPs to using each SNP separately.

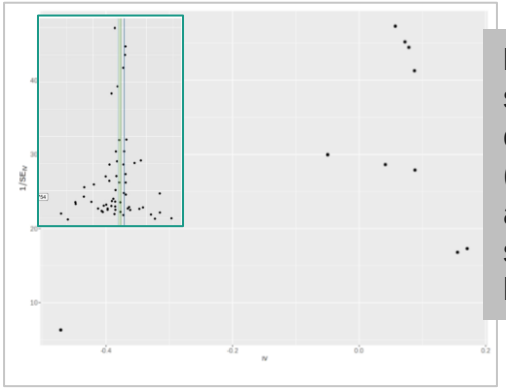




Leave one out sensitivity analysis: assesses whether a single SNP is having a disproportionately larger impact on an association. Each dot represents the MR analysis excluding that specific SNP using IVW method.

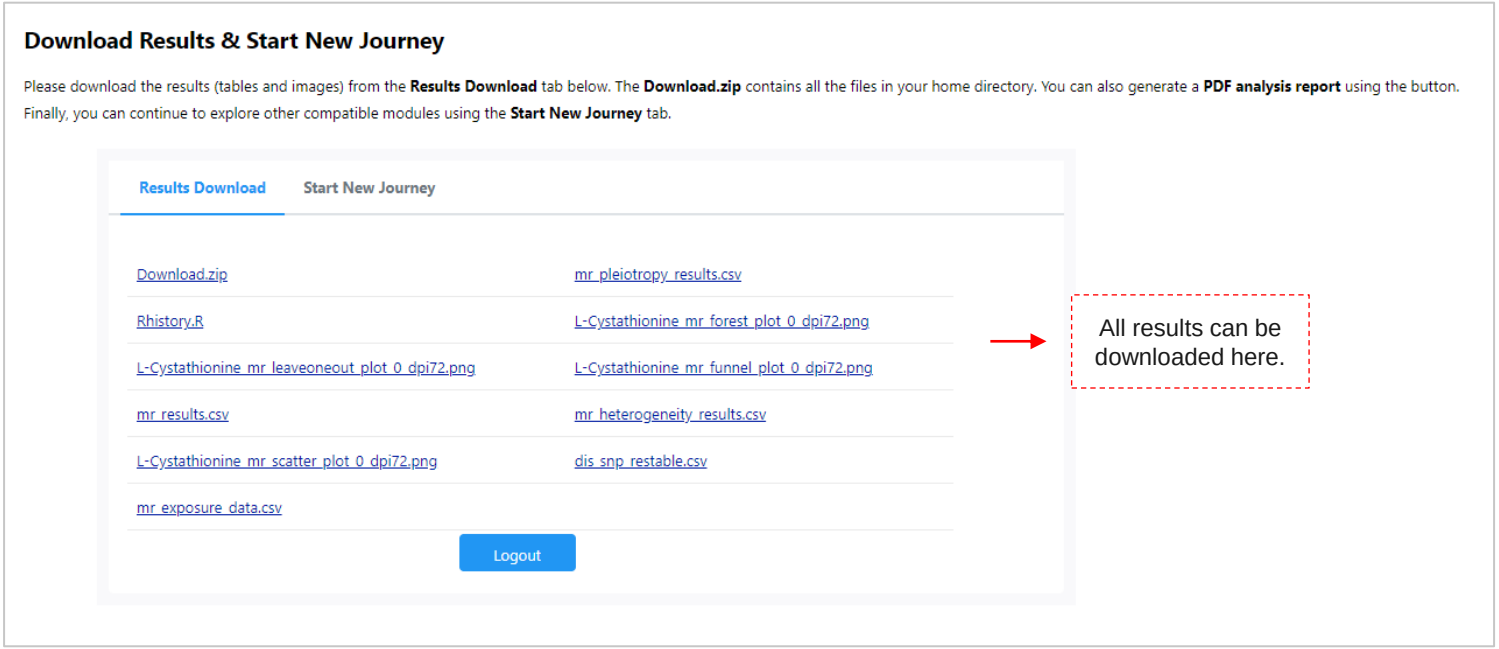
Scatter plot shows the relationships between SNP effects on exposure vs on the outcome. The slopes indicating the causal association





Funnel plot: Funnel shape will become more obvious with many SNPs (i.e. green box inset). Its asymmetry and wider spread may suggest horizontal pleiotropy.

4. Download Results



In summary

If you have any questions, please read/post into OmicsForum (www.omicsforum.ca)

Or contact us:

zhiqiang.pang[at]xialab.ca

jeff.xia[at]xialab.ca

- Two-sample MR analysis allows researchers to estimate potential causal relationships between a metabolite and a phenotype of interest based on public data (mGWAS and GWAS summary statistics)
- Performing 2MSR requires identification of suitable SNPs (i.e. instrument variables) and performing filtering and harmonization. The process is computing intensive and better start with one metabolite at a time
- The module offers various MR methods with different strengths and limitations. They may give different estimates. Carefully examine the graphical outputs are necessary to reach robust conclusions