DMRdb: a disease-centric Mendelian randomization database for systematically assessing causal relationships of diseases with genes, proteins, CpG sites, metabolites and other diseases

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Correlation ≠ Causation

- In medical research, we often observe statistical correlations between certain factors and diseases. But this does not mean that these factors will cause disease.

High BMI → Diabetes?
High cholesterol → heart disease?
Smoking → lung cancer?
📌 Are these relationships truly causal, or are they just co-occurring?

Misled by Confounding Variables

- Intersting Problem:
  - Study has shown that there is a positive correlation between ice cream sales and the number of shark attacks.
  - In this example, **climate** is the confounding factor, affecting both ice cream sales and shark attacks.

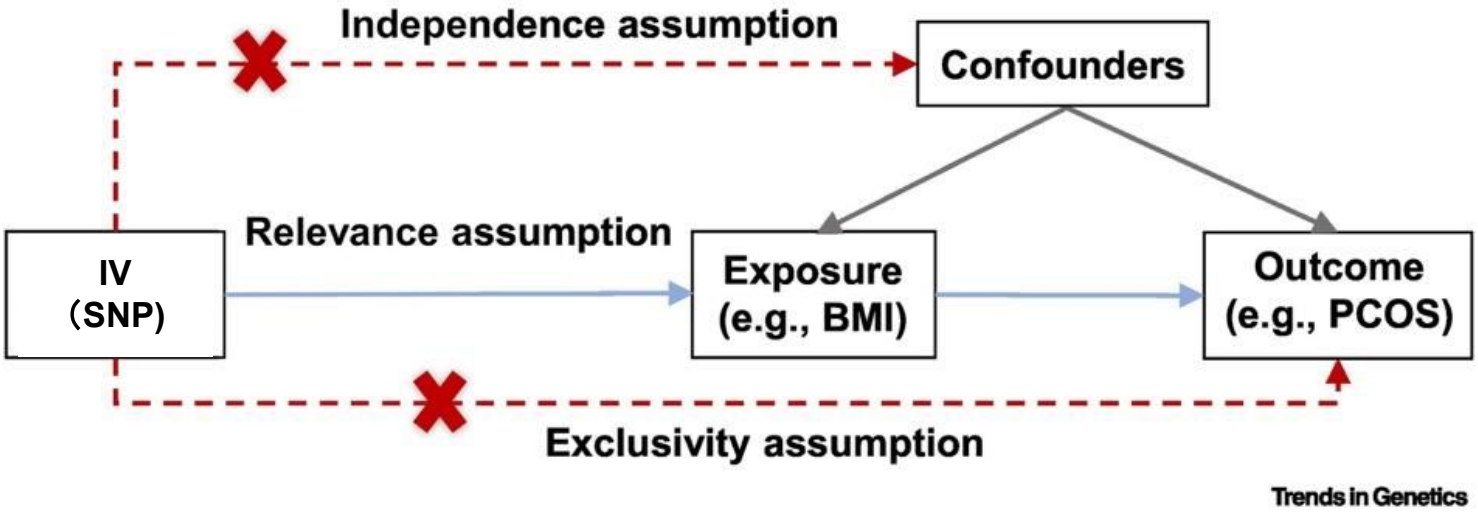
Limitations of Traditional Methods

- **R**andomized **C**ontrolled **T**rial, **RCT**
  - RCT is costly and has ethical limitations.
  - Observational studies are easily affected by confounding factors.

Nature’s version of a randomized trial

- Uses genetic variants (SNPs) as **Instrumental Variables**.
- Genes are randomly inherited at conception.
- SNPs are innate and not affected by the environment.

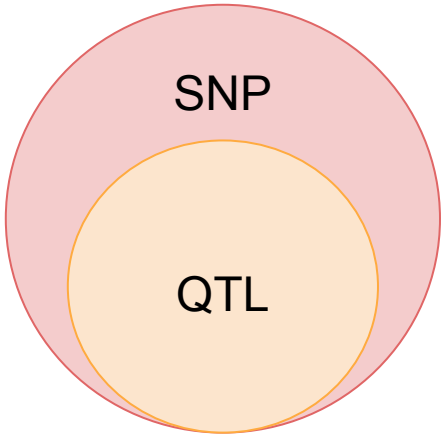
What's Mendelian Randomization?



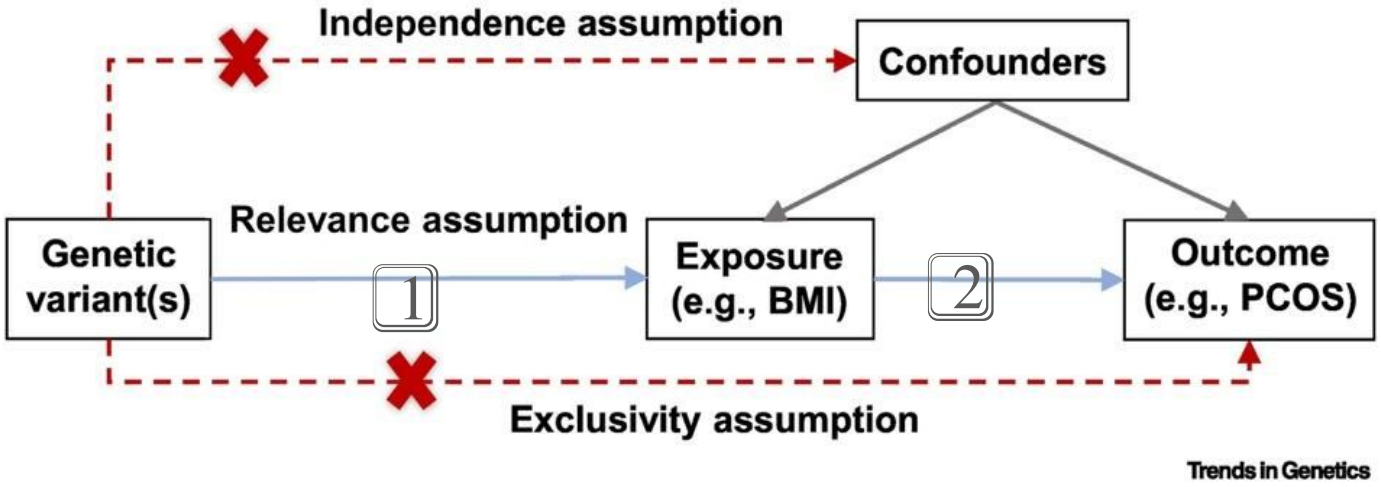
SNP/QTL(Quantitative Trait Loci)?

- QTL : A SNP that is associated with a measurable trait

- Depending on the trait, we have:
  - **eQTL**: affects gene expression
  - **pQTL**: affects protein levels
  - **meQTL**: affects DNA methylation
  - **mQTL**: affects metabolites



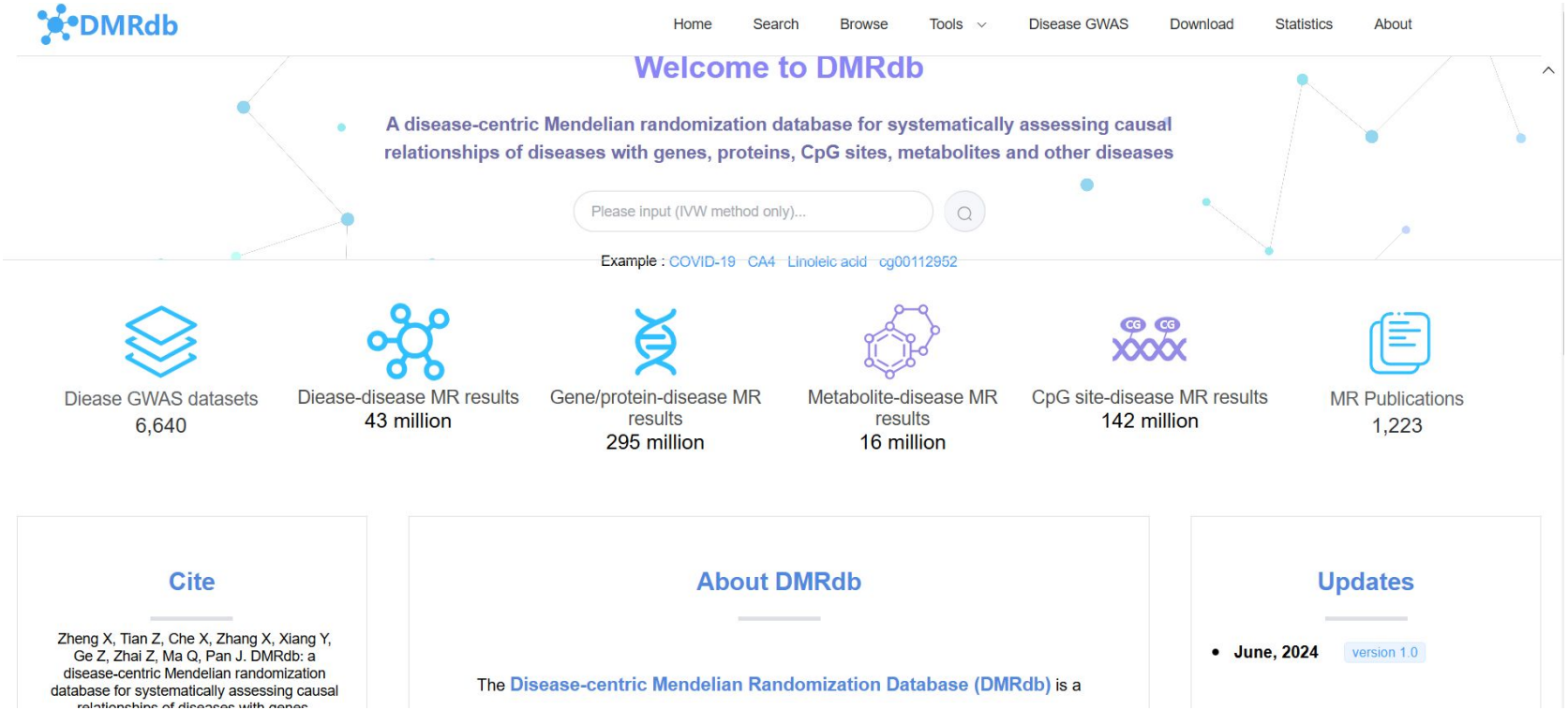
Hard parts in realizing Mendelian Randomization



Data collection

- UK Biobank
- **MRC IEU**
- **GWAS Catalog**
- **FinnGen**
- GoDMC
- UCSC Genome Browser
- **IEU GWAS database**
- eQTLGen consortium

About the website



Search notes

Result Type :

☑ Our Analysis Results ☐ Published Results

Study ID :

DMR1.....

Exposure :

Disease + COVID-19 (RELEASE 4), Alzheimer's disease...

Exposure ID :

DGWAS-1911, eqtl-a-ENSG00000141510, prot-a-10...

Outcome :

Disease +

Outcome ID :

DGWAS...

Analysis type :

☑ Disease-Disease ☐ eQTL-Disease ☐ pQTL-Disease ☐ Metabolite-Disease ☐ CpGsite-Disease

Methods :

☑ Inverse variance weighted ☑ Inverse variance weighted (multiplicative random effects) ☑ Inverse variance weighted (fixed effects) ☐ Simple mode ☐ MR Egger ☐ Simple median ☐ Wald ratio

Nsnp (greater than) :

OR :

Select

P-value for results (less than):

0.001

Example Submit Reset

SEARCH RESULT

Table Praph Heatmap

sort by current page

ID	ID exposure	ID outcome	Exposure	Outcome	Methods	Nsnp	Beta	SE	P-value	OR
DMR5611	DGWAS-5603	DGWAS-1	COVID-19 (RELEASE 4)	Hypothyroidism, strict autoimmune	Inverse variance weighted (fixed effects)	3	0.08	0.04	0.035	1.09
DMR12215	DGWAS-5603	DGWAS-10	COVID-19 (RELEASE 4)	Cholelithiasis	Inverse variance weighted (multiplicative random effects)	3	0.03	0.01	0.0043	1.03
DMR18866	DGWAS-5607	DGWAS-100	COVID-19 (RELEASE 4)	Wet age-related macular degeneration	Inverse variance weighted (multiplicative random effects)	2	-0.08	0.01	1.7e-8	0.92
DMR32368	DGWAS-5603	DGWAS-1001	COVID-19 (RELEASE 4)	Iron deficiency	Inverse variance weighted (multiplicative random effects)	3	0.52	0.19	0.005	1.69
DMR45871	DGWAS-5607	DGWAS-1003	COVID-19 (RELEASE 4)	Drug-induced cataract	Inverse variance weighted	2	-0.82	0.34	0.016	0.44

Detailed Disease GWAS information

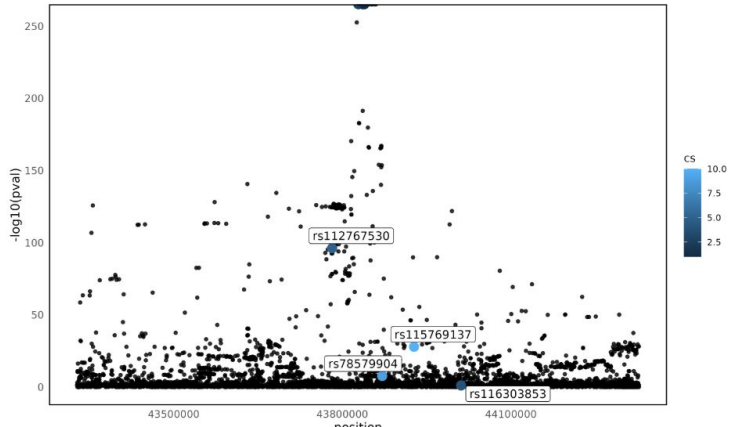
Diease GWAS id	DGWAS-10
Original Traits	Cholelithiasis
Category	Diseases of the digestive system
Sources	finngenR10
Original ID	finngen_R10_K11_CHOLELITH
Consortium	
Ncases	40191
Ncontrols	361641
Nsamples	401832
Nsnp	22669128
Population	European
Build	GRCh38

Fine mapping | Individual SNPs | Manhattan plot | QQ plot | SNP-density plot

• **SNPs that are most likely to be causal**

SNPs	Variable probabilities	Credible sets	Chr	Position	Effect allele	Other allele	nearest genes	P-Value	Beta	SE	EAF	samplesize
rs112767530	1	5	2	43781848	T	C	DYNC2LI1	5.60e-97	-0.219574	0.010507	0.172968	401832
rs114938914	1	3	2	43828371	T	C	ABCG5	0.00e+0	0.61997	0.0124862	0.0818171	401832
rs78579904	1	9	2	43870875	G	A	ABCG8	2.06e-8	-0.160467	0.0286182	0.0194024	401832
rs115445558	1	2	2	43835959	C	G	ABCG5	0.00e+0	0.629562	0.0122804	0.0842594	401832
rs115769137	1	10	2	43927549	A	C	LRPPRC	1.18e-28	-0.196359	0.0176818	0.0542492	401832
rs116303853	1	4	2	44011216	C	G	LRPPRC	7.09e-2	0.0247764	0.0137192	0.0841574	401832
rs11887534	1	1	2	43839108	C	G	ABCG8	0.00e+0	0.631352	0.012256	0.0842581	401832

• **Causal SNPs in the locus plot**



Advantage

Suitable for:

- Beginners who want to understand how GWAS SNPs influence diseases.
- Researchers who want a rough understanding of relationships before conducting experiments.
- Individuals without a statistical background who want a quick overview of MR analysis without requiring precise results.

Advantage

Key Features:

- Data sourced from multiple websites with a large sample size.
- Various MR analysis methods available.
- Multiple easy-to-use calculation tools.
    - Quick mapping of **rsIDs** and **chromosome positions**.
    - Power calculation capabilities.

Limitation and issues

- The **paper does not clearly explain** the full functionality of DMRdb.
- The **website lacks maintenance**, leading to usability issues.
- **Many features are unavailable** or not functioning properly.
- There is **no mention in the paper** regarding data standardization or whether the downloaded data is pre-standardized.
- **Slow data loading** affects usability and efficiency.

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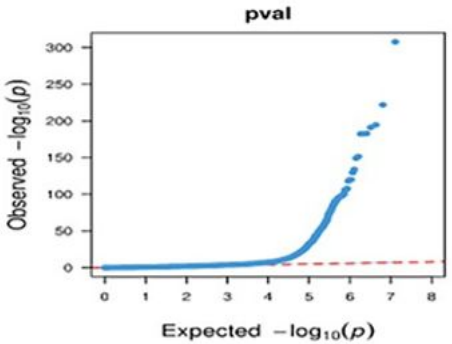
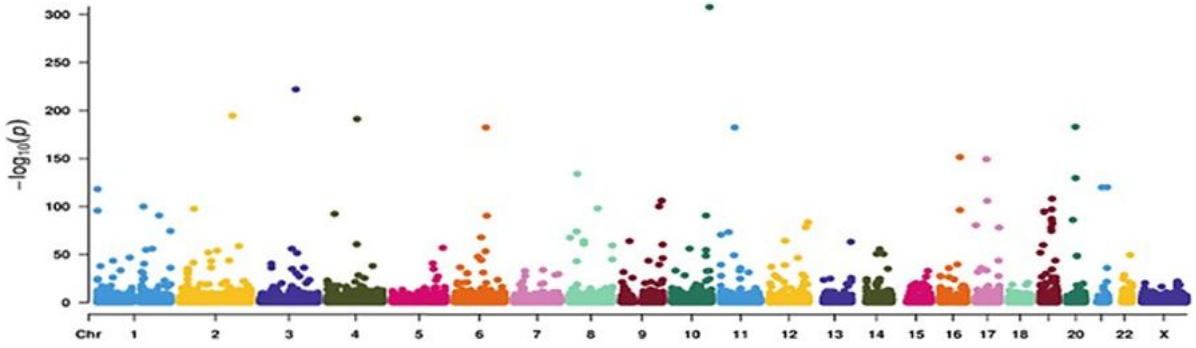
Sources	finngenR10
Original ID	finngen_R10_K11_CHOLELITH
Sex	Males and Females
Ncases	40191
Ncontrols	361641
Nsamples	401832
Nsnp	22669128
Population	European

SNP	Chromosome	Position	Effect Allele	Other Allele	Beta	EAF	P-value	SE	MR Keep
rs12741965	1	3865266	A	C	0.0472627	0.186897	0.0000017	0.0098757	TRUE
rs10907282	1	16183644	G	A	0.0456852	0.724381	0.000000129	0.0086518	TRUE
rs35176086	1	25512737	T	A	0.0425767	0.44867	3.89E-08	0.00774727	TRUE
rs61768918	1	37073881	A	G	0.109827	0.0240749	0.00000695	0.0244323	TRUE
rs4660585	1	41927330	A	G	0.0569994	0.702272	2.01E-11	0.00850109	TRUE
rs535574487	1	95195898	A	G	0.462088	0.00135797	0.00000213	0.0974665	TRUE
rs7550711	1	109540264	T	C	0.0889442	0.0563855	5.19E-08	0.0163357	TRUE
rs11205354	1	150276693	A	C	-0.035759	0.441954	0.00000456	0.00780036	TRUE
rs1127313	1	154583949	A	G	0.0528545	0.462039	7.49E-12	0.00771818	TRUE
rs12140076	1	180267389	A	G	-0.092049	0.0382288	0.00000775	0.0205832	TRUE





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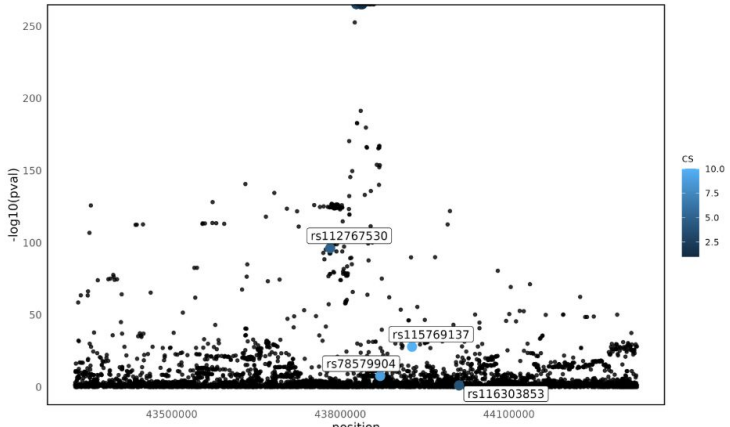

Missing

- Manhatten plot
- QQ plot