# Case Study 1: Subjective wellbeing and cardiometabolic health

This case study demonstrates the rapid implementation of MR using MR-Base to identify a novel risk factor and enable transparency. It is based on work by Wootton et al that used MR-Base to investigate the association between subjective wellbeing and 11 measures of cardiometabolic health. [1]

## Methods

1. Access the platform (<http://mrbase.org>) and sign the data access agreement using a Google account.
2. Define the exposure by selecting the following from the MR-Base GWAS database. Specify the p-value threshold to be ‘5e-05’ and ensure ‘Perform clumping’ is ticked with the LD R squared value set to 0.001 and clumping distance set to 10000kb.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ID | Variable | First author (year) | Consortium | Sample size | Population | Sex |
| 1009 | Subjective wellbeing | Okbay (2016) [2] | SSGAC | 298420 | European | Males and females |

1. Define the outcome by selecting the following outcomes from the MR-Base GWAS database:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ID | Variable | First author (year) | Consortium | Sample size | Population | Sex |
| 2 | Body mass index | Locke (2015) [3] | GIANT | 339224 | Mixed | Males and females |
| 61 | Waist circumference | Shungin (2015) [4] | GIANT | 232101 | European | Males and females |
| 79 | Waist-to-hip-ratio | Shungin (2015) [4] | GIANT | 210082 | European | Males and females |
| 999 | Body fat | Lu (2016) [5] | - | 3228665 | 89% European | Males and females |
| 299 | HDL cholesterol | Willer (2013) [6] | GLGC | 187167 | Mixed | Males and females |
| 300 | LDL cholesterol | Willer (2013) [6] | GLGC | 173082 | Mixed | Males and females |
| 301 | Total cholesterol | Willer (2013) [6] | GLGC | 187365 | Mixed | Males and females |
| 798 | Myocardial infarction | Nikpay (2015) [7] | CARDIoGRAM plusC4D | 171875 | Mixed | Males and females |
| 7 | Coronary heart disease | Nikpay (2015) [7] | CARDIoGRAM plusC4D | 171875 | Mixed | Males and females |

1. Specify the analysis settings:

* Set LD clumping to ‘Do not check for LD between SNPs’ (as this was done in step 2)
* Specify that LD proxies are permitted with a minimum LD R squared value of 0.8 and ensure ‘Allow palindromic SNPs?’ is ticked with the MAF threshold set to 0.3
* Set allele harmonisation to ‘Attempt to align strands for palindromic SNPs’
* Select the MR Egger, weighted median, weighted mode and inverse variance weighted methods for analysis.

1. Perform the MR analysis and save the results, including the citations that are to be referenced in any published work arising from this analysis.

Note: result files are indexed according to the MR-Base IDs listed above.

## Analysis R code

MR-Base provides the analysis R code as an output. The R code for this analysis is provided below:

library(TwoSampleMR)

ao <- available\_outcomes()

exposure\_dat <- extract\_instruments(c('1009'),p1=5e-5)

outcome\_dat <- extract\_outcome\_data(exposure\_dat$SNP, c('2','61','79','999','300','301','299','7','798'), proxies = 1, rsq = 0.8, align\_alleles = 1, palindromes = 1, maf\_threshold = 0.3)

dat <- harmonise\_data(exposure\_dat, outcome\_dat, action = 2)

mr\_results <- mr(dat)

## References

1 Wootton RE, Lawn RB, Millard LAC, *et al.* Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: mendelian randomisation study. *BMJ* 2018;**362**:k3788. doi:10.1136/bmj.k3788

2 Okbay A, Baselmans BML, Neve J-ED, *et al.* Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet* 2016;**48**:624–33. doi:10.1038/ng.3552

3 Locke AE, Kahali B, Berndt SI, *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;**518**:197–206. doi:10.1038/nature14177

4 Shungin D, Winkler TW, Croteau-Chonka DC, *et al.* New genetic loci link adipose and insulin biology to body fat distribution. *Nature* 2015;**518**:187–96. doi:10.1038/nature14132

5 Lu Y, Day FR, Gustafsson S, *et al.* New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. *Nat Commun* 2016;**7**:10495. doi:10.1038/ncomms10495

6 Willer CJ, Schmidt EM, Sengupta S, *et al.* Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013;**45**:1274–83. doi:10.1038/ng.2797

7 Nikpay M, Goel A, Won H-H, *et al.* A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015;**47**:1121–30. doi:10.1038/ng.3396