**Presenting MR estimates**

MR estimates are the effect of one unit of the exposure on the outcome. The units of exposure and outcome may not always be in easily interpretable “natural” units, but can be converted into more familiar units, if you can determine the units used for exposure and outcome.

1. **Commonly used units in genetic studies**

Genetic studies of continuous quantities are usually obtained using linear regression and give estimates in terms of effect sizes, also called z-scores, standard deviations or rank normalized (IRNT). These may be effect sizes of the original measurements or the original measurements may have been transformed, for example log transformed, before being standardized into effect sizes.

Genetic studies of dichotomous (binary) quantities usually use logistic regression and give estimates in logodds, but sometimes use linear regression and give estimates of the difference in probability of an event.

1. **Sources of information about the units used in a genome wide association study (GWAS)**

To interpret an MR estimate, you need to find the units for exposure and outcome, which may be given in the following places

* 1. the publication(s) for the relevant GWAS,
     1. the regression method and the units are usually in the methods, supplementary methods or other supplementary files
  2. websites where unpublished and published GWAS are curated
     1. Ben Neale UK Biobank files http://www.nealelab.is/uk-biobank, bearing in mind
        1. Round 1 files date from 2017
        2. Round 2 files date from 2018
        3. Multi-ancestry files date from 2020
     2. MRC-IEU <https://gwas.mrcieu.ac.uk/datasets/>
     3. Finngen https://www.finngen.fi/en/for\_researchers

1. **Conversion of estimates into different units**

Conversion, if at all, varies according to the units of the exposure and outcome. The information given below concerns the beta coefficient. Conversions can sometimes also be applied to the standard error (se), and the 95% confidence interval can be obtained as beta plus or minus 1.96 times the se, i.e., assuming a normal distribution. However, MR-Base/TwoSampleMR use a t-distribution for the MR-Egger confidence interval while MendelianRandomization uses a normal distribution.

The main possibilities for combinations of units are below with examples of conversion:

* Continuous exposure in effect size and outcome in logodds
  + Present as the association of x with y, which is the odds ratio of y per change in one effect size of x, because almost all outcomes are rare, then give a footnote with the standard deviation (SD) of x. For example, if the beta for x on y in 0.33, then convert to odds ratio (OR) by exponentiating, i.e., exp(0.33), which gives 1.39, so the OR is 1.39 per effect size of x. If you want to give the estimate in “natural” units of x, the table below gives examples of the conversion

**Example of conversion from SD units to natural units when x linear and y is in logodds**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SBP (x) in effect size on stroke (y) in logodds | OR per SD of SBP | SD of SBP in mmHg | OR per 1 mmHg of SBP is OR to the power 1/SD | OR per SD of SBP is OR per 1 mmHg to the power SD |
| 0.33 | 1.39 | 20 | 1.39 1/20 = 1.017 | 1.017 20 = 1.39 |
| 0.33 | 1.39 | 10 | 1.39 1/10 = 1.034 | 1.034 10 = 1.39 |
| 0.33 | 1.39 | 0.5 | 1.39 2 = 1.93 | 1.93 0.5 = 1.39 |

* Continuous exposure (x) and outcome (y) in effect sizes of natural units or logged units
  + Present as the association of x with y where the beta is the change in effect size of y per change in one effect size of x, then give a footnote showing the standard deviation of x and y. For example, if the beta for x on y is 0.33, then when x increases by an effect size y increases by 0.33 of an effect size. If the standard deviation (SD) of x and y were both 1 then for each unit increase of x y increases by 0.33. If you want to give the estimate in “natural” units, the table below gives examples of the conversion.

**Example of conversion between units when x and y are continuous**

|  |  |  |  |
| --- | --- | --- | --- |
| Beta for SBP (x) in effect size on lipids (y) in effect size | SD of SBP in mmHg | SD of lipids in mmol/L | beta per 1 mmHg of SBP on 1 mmol/L lipids is original beta divided by SD of SBP all times SD of lipids |
| 0.33 | 20 | 1 | (0.33/20) x 1 = 0.017 |
| 0.33 | 20 | 20 | (0.33/20) x 20 = 0.33 |
| 0.33 | 20 | 2 | (0.33/20) x 2= 0.033 |
| 0.33 | 1 | 2 | (0.33/1) x 2= 0.66 |

* Continuous exposure in effect size and outcome in probability
* Give as the association of x with y is odds ratio of y per change in one effect size of x. Convert the beta to an odds ratio using the following approximation, odds ratio is 1 + beta/(k(1-k)), where k is the lifetime probability of the outcome (1). For example if beta is 0.03 and k is 0.05, then the odds ratio is 1+ (0.03/(0.05(0.95)) which is 1.67. Then the standard error can be obtained from the logodds and the original outcome p-value, as follows
  + outcome beta in logodds is log(1+outcome beta in probability/(k\*(1-k)))
  + outcome se in logodds is abs(outcome beta in logodds/qnorm(outcome p value/2))

**A note on dichotomous exposures**

It may seem better to use a dichotomous exposure because the effect of the exposure may be non-linear. However, a dichotomous exposure has three disadvantages

1. Dichotomizing inevitably reduces power because it throws away variability, so the instruments will be weaker
2. A dichotomous exposure is more open to selection bias because greater weight will be given to the strata with more events, which are usually in older people. Genetic studies in older people are more open to selection bias from survival than genetic studies in younger people. So the instruments may be biased.
3. An apparently non-linear relation with age may be the result of selection bias

So, it may be better to use a continuous exposure and explain in the limitations whether a linear relation is plausible and what would be the consequences of non-linearity for the interpretation.

**Lifespan - a tricky outcome**

Finally, a particularly tricky unit is the one used for lifespan, specifically parental attained age, provided by Pilling (2), which is based on parental survival. It is in time lost, i.e., a positive estimate means worse survival. The estimate per unit of the exposure given by Pilling can be converted into years of life lost (3), as follows

1. Multiply by 10 to convert to years, an actuarial convention (3)
2. Multiply by an adjustment factor to allow for children only having half of their genetic endowment from each parent. For mothers and fathers together the adjustment factor is 1.9699, for mothers it is 2.5863 and for fathers it is 2.2869 (3)

1. Lloyd-Jones LR, Robinson MR, Yang J, Visscher PM. Transformation of Summary Statistics from Linear Mixed Model Association on All-or-None Traits to Odds Ratio. Genetics. 2018;208(4):1397-408.

2. Pilling LC, Kuo CL, Sicinski K, Tamosauskaite J, Kuchel GA, Harries LW, et al. Human longevity: 25 genetic loci associated in 389,166 UK biobank participants. Aging (Albany NY). 2017;9(12):2504-20.

3. Timmers PR, Mounier N, Lall K, Fischer K, Ning Z, Feng X, et al. Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. Elife. 2019;8.