

# Integrative Mendelian randomization for detecting exposure-by-group interactions using group-specific and combined summary statistics

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## Introduction

This vignette provides an introduction to the `int2MR` package. The R package `int2MR` implements the `int2MR` method for detecting both direct exposure-outcome effect within comparison group and reference group and exposure-group interaction effect.

Before installing `int2MR`, ensure that you have the `devtools` package installed. The package also requires `rstan` for Bayesian modeling. To install the development version of `int2MR`, run:

```
# Load devtools package
library(devtools)
```

```
## Loading required package: usethis
```

```
# Install the int2MR package from GitHub
install_github("Likeli-Ke/int2MR")
```

```
## Downloading GitHub repo Likeli-Ke/int2MR@HEAD
```

```
##
```

```
## -- R CMD build -----
```

```
##    checking for file '/private/var/folders/q8/w_3t37sj42q7724cbdb6l_c0000gn/T/RtmpKA09J4/remotesa
```

```
## - preparing 'int2MR':
```

```
##    checking DESCRIPTION meta-information ... v    checking DESCRIPTION meta-information
```

```
## - checking for LF line-endings in source and make files and shell scripts
```

```
## - checking for empty or unneeded directories
```

```
## - building 'int2MR_0.1.0.tar.gz'
```

```
##
```

```
##
```

```
# Load the int2MR package
library(int2MR)
```

## Input Data Format

The `int2MR` package supports two types of GWAS summary statistics:

- **Three-sample data:** Utilizes three separate IV-to-outcome GWAS statistics.

- **Two-sample data:** Utilizes two IV-to-outcome GWAS summary statistics.

To detect the exposure-group interaction effect, it is essential that the proportion of the comparison group (denoted as  $\rho$ ) varies among the provided GWAS summary statistics.

## Data Requirements

Your input data should include:

- **Number of IVs** (instrumental variables)
- **Point estimates** and **squared standard errors** for:
  - IV-to-outcome effects
  - IV-to-exposure effects
- **Proportion of the comparison group ( $\rho$ )** in each IV-to-outcome GWAS summary statistic.

Load the example datasets provided with the package as follows:

```
data(example_3sample_data)
data(example_2sample_data)
```

For further details on the example data formats included with the package, consult the help pages.

```
help(example_3sample_data)
help(example_2sample_data)
```

## Running Examples

This section demonstrates how to run `int2MR` using simulated data. Two examples are provided: one for three-sample data and one for two-sample data.

### Example 1: Three-Sample Data

In this example, we perform an analysis on simulated three-sample data. The parameters include:

- **model\_type:** “3sample”
- **Prior distributions:** Inverse gamma priors with a shape and scale of 0.1
- **MCMC Settings:** 2 chains, 10000 iterations with a warm-up period of 2500 iterations, and an `adapt_delta` of 0.95.

```
result_3sample <- int2MR(data_list_3sample = example_3sample_data,
  model_type = "3sample",
  prior_inv_gamma_shape = 0.1,
  prior_inv_gamma_scale = 0.1,
  chains = 2, iter = 10000, warmup = 2500,
  adapt_delta = 0.95)
```

```
## Loading required package: rstan
```

```
## Loading required package: StanHeaders

##
## rstan version 2.32.7 (Stan version 2.32.2)

## For execution on a local, multicore CPU with excess RAM we recommend calling
## options(mc.cores = parallel::detectCores()).
## To avoid recompilation of unchanged Stan programs, we recommend calling
## rstan_options(auto_write = TRUE)
## For within-chain threading using 'reduce_sum()' or 'map_rect()' Stan functions,
## change 'threads_per_chain' option:
## rstan_options(threads_per_chain = 1)

## Trying to compile a simple C file

## Running /Library/Frameworks/R.framework/Resources/bin/R CMD SHLIB foo.c
## using C compiler: 'Apple clang version 16.0.0 (clang-1600.0.26.6)'
## using SDK: ''
## clang -arch arm64 -I"/Library/Frameworks/R.framework/Resources/include" -DNDEBUG -I"/Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/StanHeaders/include"
## In file included from <built-in>:1:
## In file included from /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/StanHeaders/include:
## In file included from /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/RcppEigen/include:
## In file included from /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/RcppEigen/include/Eigen/src/Core:
## 679 | #include <cmath>
##      |          ^~~~~~
## 1 error generated.
## make: *** [foo.o] Error 1
```

```
# Display the results for the three-sample analysis
result_3sample$result_3sample
```

```
##      est_beta  se_beta    pval_beta est_beta_int se_beta_int pval_beta_int
## 1 0.1967906 0.0320366 8.114063e-10 -0.1387293 0.05635197 0.01382276
##      total_effect pval_total
## 1 0.05806123 0.11119
```

## Example 2: Two-Sample Data

This example demonstrates an analysis using simulated two-sample data. The configuration is similar to the three-sample analysis, with `model_type` set to “2sample”.

```
result_2sample <- int2MR(data_list_2sample = example_2sample_data,
  model_type = "2sample",
  prior_inv_gamma_shape = 0.1,
  prior_inv_gamma_scale = 0.1,
  chains = 2, iter = 10000, warmup = 2500,
  adapt_delta = 0.95)
```

```
## Trying to compile a simple C file
```

```

## Running /Library/Frameworks/R.framework/Resources/bin/R CMD SHLIB foo.c
## using C compiler: 'Apple clang version 16.0.0 (clang-1600.0.26.6)'
## using SDK: ''
## clang -arch arm64 -I"/Library/Frameworks/R.framework/Resources/include" -DNDEBUG -I"/Library/Frameworks/R.framework/Resources/include"
## In file included from <built-in>:1:
## In file included from /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/StanHeaders/include/stan/math/prim/mat/fun/eigen.h:1:
## In file included from /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/RcppEigen/include/Eigen/Core:1:
## /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/library/RcppEigen/include/Eigen/src/Core/Matrix.h:679:1: error: expected ';' after struct definition
##   679 | #include <cmath>
##       |         ^~~~~~
## 1 error generated.
## make: *** [foo.o] Error 1

```

```

# Display the results for the two-sample analysis
result_2sample$result_2sample

```

```

##   est_beta    se_beta    pval_beta est_beta_int se_beta_int pval_beta_int
## 1 0.191453 0.03606459 1.104622e-07  -0.1440905   0.0569437   0.01139313
##   total_effect pval_total
## 1   0.04736241 0.2823961

```