The GLIDE package: Global and Individual Tests for Direct Effects in Mendelian randomization studies

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1 Introduction

"Mendelian randomization", an inferential method that uses germline genotypes as instrumental variables (IVs) to study the environmentally modifiable cause of human disease, has been increasingly popular in genetic epidemiology. Exploiting the random assortment of genes from parents to offsprings at the time of gamete formation, likened to "Nature′s randomized experiment." Mendelian randomization holds promise for removing confounding and reverse causation that loom over observational epidemiology. While conceptually appealing, skepticism has persisted on feasibility of strong assumptions required by Mendelian randomization, stated informally, that genetic variants are independent of confounders of the exposure disease relation, that genetic variants are associated with the exposure, preferably strongly, and that there is no direct effect from genetic variants to the disease other than the pathway through the exposure, also known as no "pleiotropy". Perhaps the Achilles′ heel for Mendelian randomization is potential pleiotropic effects among candidate genetic IVs, which can be sometimes plausible given complex biological pathways and networks. This threat to the validity of Mendelian randomization is heightened by the very practice of including a large number of risk variants to boost the strength of IVs. The GLIDE package performs the diagnostic tests for assessing global and individual variant pleiotropy in Mendelian randomization studies.

2 Main functions

We show an example analysis using simulation data that resemble the BMI analysis for GECCO presented in the paper [1]. Briefly the dataset contains genotype data for 75 SNPs and 20,000 subjects, as well as demographic variables including age, gender and 3 principal components for the parent genome-wide association study. First we load the example dataset:

```
> data(simdata)
> #The example dataset is a list composed of two dataframes.
> #simat stores 20,000 observations of 81 variables,
> #including outcome, 5 ajusting covariates, and 75 SNPs.
> simdat=simdata$simdat
> dim(simdat)
```

```
[1] 20000    81
```

```
> head(colnames(simdat),n=10)
```

```
 [1] "outcome" "pc1"     "pc2"     "pc3"     "age"     "sex"     "SNP1"   
 [8] "SNP2"    "SNP3"    "SNP4"   
```

```
> #coeff stores the 75 external regression cofficients.
> coeff=simdata$coeff
> head(coeff)
```

```
       coeff
SNP66 0.0192
SNP56 0.0230
SNP10 0.0229
SNP11 0.0307
SNP38 0.0174
SNP24 0.0402
```

```
>
```

We define the columns in simdat that contain genotype data:

```
> genotype_columns=which(grepl("^SNP",colnames(simdat)))
```

We next define the regression formula for outcome and adjusting covariates (variables to be adjusted for in addition to genotype variables, typically include age, gender, and principal components), as in other generic R regression functions:

```
> formula=as.formula("outcome~age+sex+pc1+pc2+pc3")
> formula
```

```
outcome ~ age + sex + pc1 + pc2 + pc3
```

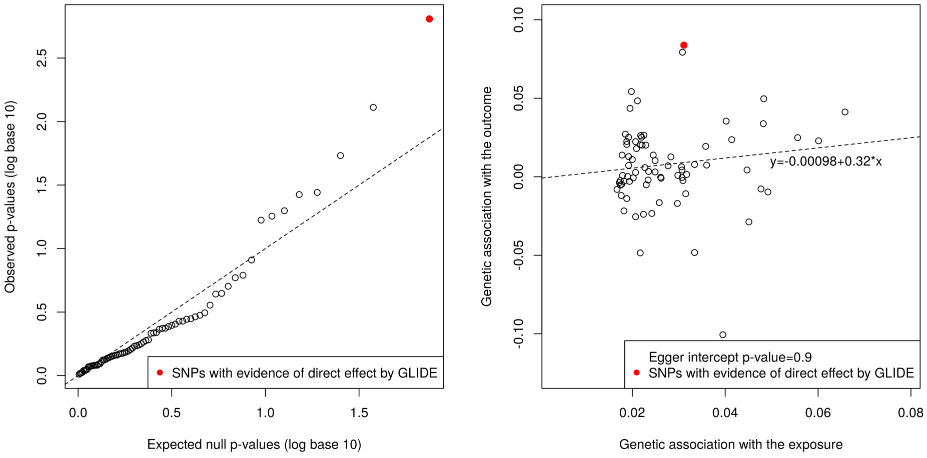
Much of computation time is spent in calculating the correlation matrix of the surrogate direct effects as defined in the paper [1]. When there are many SNPs to be evaluated as candidate instrumental variables, parallel computing can be deployed to speed up the glide function by setting the corenumber argument. If the requested number of cores is greater than number of cores available, GLIDE will user the latter number. GLIDE allows users to define a q-value cut-off that declares the significance of evaluating individual pleiotropy accounting for multiple testing. The default is qcutoff=0.2, to be conservative about validity of individual SNPs. Users can set the number of permutations for q-value computation. The default number is np=100,000. We then run the glide function with inputs as:

```
> out=glide(formula=formula,exposure_coeff=coeff,genotype_columns,data=sim
+           np=100000,qcutoff=0.2,parallel=TRUE,corenumber=1,verbose=TRUE)

GLIDE program starts at: 2024-10-24 06:31:17.352926
Warning message: 3 rows were removed due to missing data in age
Compute the correlation matrix at: 2024-10-24 06:31:24.50692
Total 75 SNPs...
There are 4 cores available in the machine.


Compute the null p-values at: 2024-10-24 06:31:32.736379

Compute the FWER and FDR values at: 2024-10-24 06:31:36.843201

GLIDE program ends at: 2024-10-24 06:31:39.653802

> head(out)

      observed_pvalue expected_pvalue    fwer   q_value   g_outcome
SNP60     0.001555538      0.01330764 0.11177 0.1184100  0.08377947
SNP48     0.007731389      0.02644120 0.43876 0.2899350 -0.04846745
SNP45     0.018526927      0.03954867 0.74925 0.4623800 -0.10059746
SNP49     0.036145821      0.05269381 0.93395 0.5619587  0.05428275
SNP43     0.037575697      0.06581008 0.94121 0.5619587  0.07930513
SNP3      0.050387996      0.07894376 0.97789 0.5619587  0.04835978
      g_outcome_variance
SNP60       0.0005712880
SNP48       0.0004120537
SNP45       0.0022840654
SNP49       0.0005370443
SNP43       0.0011821317
SNP3        0.0004534040
```

3 plot result

GLIDE provides two functions for plotting the results: the first shows the q-q plot of individual variant′s p-value for evaluating direct effects, the other shows the Egger regression plot with point estimates of genetic association with the exposure and the outcome. SNPs that were detected to have evidence of pleiotropy (for example, FDR<0.2) will be shown in both plots.

We draw the q-q plot for the example dataset: plot.glide(out). We draw the Egger plot for the example dataset: plot.egger(out,exposure_coeff=coeff). The figures are shown as follows: There is one SNP showing evidence of pleiotropy that may be deleted in the subsequent Mendelian randomization analysis.



4 session information

The version number of R and packages loaded for generating the vignette were:

```
R version 4.4.1 (2024-06-14)
Platform: x86_64-pc-linux-gnu
Running under: Ubuntu 24.04.1 LTS

Matrix products: default
BLAS:   /usr/lib/x86_64-linux-gnu/openblas-pthread/libblas.so.3
LAPACK: /usr/lib/x86_64-linux-gnu/openblas-pthread/libopenblasp-r0.3.26.so

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
 [3] LC_TIME=en_US.UTF-8        LC_COLLATE=C
 [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

time zone: Etc/UTC
tzcode source: system (glibc)

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
[1] GLIDE_1.0.5
```

```
loaded via a namespace (and not attached):
 [1] MASS_7.3-61       compiler_4.4.1    parallel_4.4.1    tools_4.4.1
 [5] maketools_1.3.1   buildtools_1.0.0  codetools_0.2-20  doParallel_1.0.1
 [9] iterators_1.0.14  foreach_1.5.2     knitr_1.48        xfun_0.48
[13] sys_3.4.3
```

References

[1] J. Y. Dai, U. Peters, X. Wang, J. Kocarnik, J. Chang-Claude, M. L. Slattery, A. Chan, M. Lemire, S. I. Berndt, G. Casey, M. Song, M. A. Jenkins, H. Brenner, A. P. Thrift, E. White, and L. Hsu. Diagnostics of pleiotropy in mendelian randomization studies: Global and individual tests for direct effects. *The American Journal of Human Genetics*, 2017, submitted.