

Package ‘mvfmr’

February 9, 2026

Type Package

Title Functional Multivariable Mendelian Randomization

Version 0.1.0

Description Implements Multivariable Functional Mendelian Randomization (MV-FMR) to estimate time-varying causal effects of multiple longitudinal exposures on health outcomes. Extends univariable functional Mendelian Randomization (MR) (Tian et al., 2024 <[doi:10.1002/sim.10222](https://doi.org/10.1002/sim.10222)>) to the multivariable setting, enabling joint estimation of multiple time-varying exposures with pleiotropy and mediation scenarios. Key features include: (1) data-driven cross-validation for basis component selection, (2) handling of mediation pathways between exposures, (3) support for both continuous and binary outcomes using Generalized Method of Moments (GMM) and control function approaches, (4) one-sample and two-sample MR designs, (5) bootstrap inference and instrument diagnostics including Q-statistics for overidentification testing. Methods are described in Fontana et al. (2025) <[doi:10.48550/arXiv.2512.19064](https://doi.org/10.48550/arXiv.2512.19064)>.

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Encoding UTF-8

Depends R (>= 3.5.0)

Imports fdapace, ggplot2 (>= 3.0.0), parallel, doParallel, foreach, pROC, progress, glmnet, gridExtra, stats

Suggests dplyr, tidyr, testthat (>= 3.0.0), knitr, rmarkdown

VignetteBuilder knitr

RoxygenNote 7.3.1

NeedsCompilation no

Author Nicole Fontana [aut, cre],
Francesca Ieva [aut, ths],
Piercesare Secchi [aut, ths]

Maintainer Nicole Fontana <nicole.fontana@polimi.it>

Repository CRAN

Date/Publication 2026-02-09 13:30:09 UTC

Contents

| | |
|--|----|
| mvfmr-package | 2 |
| AUTOMATIC_Multi_FMVMR_twosample_simple | 2 |
| cf_logit | 3 |
| fmvmr_separate_twosample | 4 |
| fmvmr_twosample | 5 |
| getX_multi_exposure | 6 |
| getX_multi_exposure_mediation | 7 |
| getY_multi_exposure | 8 |
| gmm_lm_onesample | 9 |
| gmm_twosample_simple | 9 |
| IS | 10 |
| mvfmr | 10 |
| mvfmr_separate | 12 |
| Separate_Multi_FMVMR_twosample_simple | 13 |

| | |
|--------------|-----------|
| Index | 15 |
|--------------|-----------|

| | |
|---------------|--|
| mvfmr-package | <i>mvfmr: Multivariable Functional Mendelian Randomization</i> |
|---------------|--|

Description

Implements Multivariable Functional Mendelian randomization to estimate time-varying causal effects of multiple correlated longitudinal exposures.

Author(s)

Nicole Fontana

| | |
|--|--|
| AUTOMATIC_Multi_FMVMR_twosample_simple | <i>Two-sample joint multivariable FMR (internal)</i> |
|--|--|

Description

Two-sample joint multivariable FMR (internal)

Usage

```
AUTOMATIC_Multi_FMVMR_twosample_simple(
  Gmatrix,
  res1,
  res2,
  by_used,
  sy_used,
  ny_used,
  max_nPC1 = NA,
  max_nPC2 = NA,
  X1Ymodel = NA,
  X2Ymodel = NA,
  basis = "eigenfunction"
)
```

Arguments

| | |
|----------|---|
| Gmatrix | Genetic instrument matrix from the exposure sample ($N \times J$) |
| res1 | FPCA result for exposure 1 |
| res2 | FPCA result for exposure 2 |
| by_used | Vector of SNP-outcome effect estimates (betas) from the outcome GWAS, length J |
| sy_used | Vector of standard errors for SNP-outcome effects, length J |
| ny_used | Sample size of the outcome GWAS |
| max_nPC1 | Maximum number of principal components to retain for exposure 1 (NA = select automatically) |
| max_nPC2 | Maximum number of principal components to retain for exposure 2 (NA = select automatically) |
| X1Ymodel | True effect model for X1 on Y (for simulation only) |
| X2Ymodel | True effect model for X2 on Y (for simulation only) |
| basis | Basis type for functional representation: "eigenfunction" or "polynomial" |

Value

List with separate estimation results for both exposures

| | |
|----------|---|
| cf_logit | <i>Control function for logit model</i> |
|----------|---|

Description

Control function for logit model

Usage

```
cf_logit(
  X,
  Y,
  Z,
  alpha = 1,
  nfolds = 10,
  standardize = TRUE,
  use_lasso = FALSE
)
```

Arguments

| | |
|-------------|--|
| X | Matrix of exposure principal components (N x K) |
| Y | Binary outcome vector (0/1, length N) |
| Z | Genetic instrument matrix (N x J) |
| alpha | Elastic net mixing parameter (1=lasso, 0=ridge) |
| nfolds | Number of cross-validation folds for lambda selection |
| standardize | Standardize variables before fitting |
| use_lasso | Use LASSO regularization in first stage. If FALSE, uses OLS. |

Value

List with gmm_est, gmm_se, variance_matrix, gmm_pval

fmvmr_separate_twosample

Two-Sample Separate Univariable Functional MR

Description

Separate estimation for each exposure using outcome GWAS summary statistics. For single exposure: set G2 = NULL, by2 = NULL, sy2 = NULL.

Usage

```
fmvmr_separate_twosample(
  G1_exposure,
  G2_exposure = NULL,
  fpca_results,
  by_outcome1,
  by_outcome2 = NULL,
  sy_outcome1,
  sy_outcome2 = NULL,
  ny_outcome,
```

```

    max_nPC1 = NA,
    max_nPC2 = NA,
    true_effects = NULL,
    verbose = TRUE
  )

```

Arguments

| | |
|--------------|---|
| G1_exposure | Genetic instrument matrix from exposure 1 ($N \times J1$) |
| G2_exposure | Genetic instrument matrix from exposure 2 ($N \times J2$) or NULL for single exposure |
| fpca_results | List of 2 FPCA objects |
| by_outcome1 | SNP-outcome betas for exposure 1 instruments |
| by_outcome2 | SNP-outcome betas for exposure 2 instruments or NULL |
| sy_outcome1 | Standard errors for exposure 1 |
| sy_outcome2 | Standard errors for exposure 2 or NULL |
| ny_outcome | Outcome GWAS sample size |
| max_nPC1 | Maximum number of principal components to retain for exposure 1 (NA = automatically determined) |
| max_nPC2 | Maximum number of principal components to retain for exposure 2 (NA = automatically determined) |
| true_effects | List containing true effects for exposure 1 and exposure 2 (simulation only) |
| verbose | Print progress messages and diagnostics during computation |

Value

fmvmr_separate_twosample object

| | |
|-----------------|---|
| fmvmr_twosample | <i>Two-Sample Joint Multivariable Functional MR</i> |
|-----------------|---|

Description

Joint estimation using outcome GWAS summary statistics. Simplified approach: only needs by, sy, ny (not individual outcome data).

Usage

```

fmvmr_twosample(
  G_exposure,
  fpca_results,
  by_outcome,
  sy_outcome,
  ny_outcome,

```

```

    max_nPC1 = NA,
    max_nPC2 = NA,
    true_effects = NULL,
    verbose = TRUE
  )

```

Arguments

| | |
|--------------|---|
| G_exposure | Genetic instrument matrix from the exposure sample ($N \times J$) |
| fPCA_results | List of 2 FPCA objects |
| by_outcome | Vector of SNP-outcome effect estimates (betas) from the outcome GWAS, length J |
| sy_outcome | VVector of standard errors for SNP-outcome effects, length J |
| ny_outcome | Sample size of the outcome GWAS |
| max_nPC1 | Maximum number of principal components to retain for exposure 1 (NA = automatically determined) |
| max_nPC2 | Maximum number of principal components to retain for exposure 2 (NA = automatically determined) |
| true_effects | List containing true effects for exposure 1 and exposure 2 (simulation only) |
| verbose | Print progress messages and diagnostics during computation |

Value

fmvmr_twosample object

getX_multi_exposure *Generate multi-exposure data with genetic instruments*

Description

Generate multi-exposure data with genetic instruments

Usage

```

getX_multi_exposure(
  N = 10000,
  J = 30,
  ZXmodel = "A",
  nSparse = 10,
  NT = 1000,
  TT = 50,
  shared_effect = TRUE,
  separate_G = FALSE,
  shared_G_proportion = 0.15
)

```

Arguments

| | |
|---------------------|---|
| N | Sample size |
| J | Number of genetic instruments |
| ZXmodel | Model type (currently not used) |
| nSparse | Number of sparse observations per subject |
| NT | Number of points |
| TT | Max observation period |
| shared_effect | Whether X1 and X2 share confounding |
| separate_G | Whether to use separate instruments for each exposure |
| shared_G_proportion | Proportion of shared instruments (0-1) |

Value

List with X1, X2 sparse data and genetic instruments

getX_multi_exposure_mediation

Generate multi-exposure mediation data with genetic instruments

Description

Generate multi-exposure mediation data with genetic instruments

Usage

```
getX_multi_exposure_mediation(
  N = 10000,
  J = 30,
  ZXmodel = "A",
  nSparse = 10,
  mediation_strength = 0.3,
  separate_G = FALSE,
  shared_G_proportion = 0,
  mediation_type = "linear"
)
```

Arguments

| | |
|---------|---|
| N | Sample size |
| J | Number of genetic instruments per exposure |
| ZXmodel | Model type (currently not used, kept for compatibility) |
| nSparse | Number of sparse observations per subject |

mediation_strength Strength of mediation X1 -> X2 (default 0.3)

separate_G Whether to use separate instruments for each exposure

shared_G_proportion Proportion of shared instruments (0-1)

mediation_type Character. Type of mediation effect: "linear" (default), "nonlinear", or "time_varying".

Value

List with same structure as getX_multi_exposure()

getY_multi_exposure *Generate outcome from exposures*

Description

Generate outcome from exposures

Usage

```
getY_multi_exposure(
  RES,
  X1Ymodel = "1",
  X2Ymodel = "1",
  X1_effect = TRUE,
  X2_effect = TRUE,
  outcome_type = "continuous"
)
```

Arguments

RES Output from getX_multi_exposure() or getX_multi_exposure_mediation()

X1Ymodel Effect model for X1 (0-9)

X2Ymodel Effect model for X2 (0-9)

X1_effect Include X1 effect?

X2_effect Include X2 effect?

outcome_type "continuous" or "binary"

Value

Data frame with outcome Y

`gmm_lm_onesample` *GMM estimation for continuous outcome*

Description

GMM estimation for continuous outcome

Usage

```
gmm_lm_onesample(X, Y, Z, beta0 = NA)
```

Arguments

| | |
|-------|--|
| X | Matrix of exposure principal components (N x K) |
| Y | Outcome vector (length N) |
| Z | Genetic instrument matrix (N x J) |
| beta0 | Initial values for beta (default NA, uses zero initialization) |

Value

List with `gmm_est`, `gmm_se`, `variance_matrix`, `gmm_pval`, `Q_stat`, `Q_pval`

`gmm_twosample_simple` *Two-sample GMM*

Description

Two-sample GMM

Usage

```
gmm_twosample_simple(bx, by, sy, ny)
```

Arguments

| | |
|----|---|
| bx | Matrix J x K of first-stage coefficients (SNP -> PC associations) |
| by | Vector length J of outcome GWAS betas |
| sy | Vector length J of outcome GWAS standard errors |
| ny | Outcome GWAS sample size |

Value

List with `gmm_est`, `gmm_se`, `variance_matrix`, `gmm_pval`, `Q_stat`, `Q_df`, `Q_pval`

IS *Calculate F-statistics and Q-statistic for instrument strength (internal)*

Description

Calculate F-statistics and Q-statistic for instrument strength (internal)

Usage

```
IS(J, K, PC, datafull, Y = NULL)
```

Arguments

| | |
|----------|--|
| J | Number of genetic instruments |
| K | Number of exposures |
| PC | Vector of indices indicating which columns in datafull correspond to the principal components |
| datafull | Data frame containing instruments (first J columns) and principal components (subsequent columns) [G, X] |
| Y | Optional outcome vector; if provided, Q-statistic for overidentification is calculated) |

Value

Matrix with columns: PC (component index), RR (R-squared), FF (F-statistic), cFF (conditional F-statistic). If Y is provided, additional columns: Qvalue (Hansen's J overidentification test statistic), df (degrees of freedom for Q-test), pvalue (p-value for Q-test from chi-squared distribution).

mvfmr *Joint Multivariable Functional Mendelian Randomization*

Description

Joint Multivariable Functional Mendelian Randomization

Usage

```
mvfmr(
  G,
  fpca_results,
  Y,
  outcome_type = c("continuous", "binary"),
  method = c("gmm", "cf", "cf-lasso"),
  nPC1 = NA,
```

```

max_nPC1 = NA,
nPC2 = NA,
max_nPC2 = NA,
improvement_threshold = 0.001,
bootstrap = FALSE,
n_bootstrap = 100,
n_cores = parallel::detectCores() - 1,
true_effects = NULL,
X_true = NULL,
verbose = FALSE
)

```

Arguments

| | |
|-----------------------|--|
| G | Genetic instrument matrix (N x J) |
| fPCA_results | List with two FPCA objects from fdapace (res1 and res2) |
| Y | Outcome vector |
| outcome_type | Type of outcome: "continuous" for numeric outcomes, "binary" for 0/1 outcomes |
| method | Estimation method: "gmm" (Generalized Method of Moments), "cf" (control function), or "cf-lasso" (control function with Lasso) |
| nPC1 | Fixed number of principal components to retain for exposure 1 (NA = select automatically) |
| max_nPC1 | Maximum number of principal components to retain for exposure 1 (NA = automatically determined) |
| nPC2 | Fixed number of principal components to retain for exposure 2 (NA = select automatically) |
| max_nPC2 | Maximum number of principal components to retain for exposure 2 (NA = automatically determined) |
| improvement_threshold | Minimum cross-validation improvement required to add an additional principal component |
| bootstrap | Whether to compute confidence intervals using bootstrap resampling |
| n_bootstrap | Number of bootstrap replicates (only used if bootstrap = TRUE) |
| n_cores | Number of CPU cores to use for parallel computations |
| true_effects | List with true_effect1 and true_effect2 (simulation only) |
| X_true | List with X1_true and X2_true curves (simulation only) |
| verbose | Print progress and diagnostic messages during computation |

Value

mvfmr object with:

- coefficients - Estimated beta coefficients
- vcov - Variance-covariance matrix

- effects - List with effect1 and effect2 curves
- nPC_used - Components selected (nPC1, nPC2)
- diagnostics - F-statistics, instrument diagnostics
- performance - MISE, coverage (if true effects provided)

mvfmr_separate

*Separate Univariable Functional Mendelian Randomization***Description**

Separate Univariable Functional Mendelian Randomization

Usage

```
mvfmr_separate(
  G1,
  G2,
  fpca_results,
  Y,
  outcome_type = c("continuous", "binary"),
  method = c("gmm", "cf", "cf-lasso"),
  nPC1 = NA,
  max_nPC1 = NA,
  nPC2 = NA,
  max_nPC2 = NA,
  improvement_threshold = 0.001,
  bootstrap = FALSE,
  n_bootstrap = 100,
  n_cores = parallel::detectCores() - 1,
  true_effects = NULL,
  X_true = NULL,
  verbose = FALSE
)
```

Arguments

| | |
|--------------|--|
| G1 | Genetic instrument matrix for exposure 1 |
| G2 | Genetic instrument matrix for exposure 2, or NULL if only a single exposure is analyzed |
| fpca_results | List of FPCA objects |
| Y | Outcome vector |
| outcome_type | Type of outcome: "continuous" for numeric outcomes, "binary" for 0/1 outcomes |
| method | Estimation method: "gmm" (Generalized Method of Moments), "cf" (control function), or "cf-lasso" (control function with Lasso) |

| | |
|-----------------------|---|
| nPC1 | Fixed number of principal components to retain for exposure 1 (NA = select automatically) |
| max_nPC1 | Maximum number of principal components to retain for exposure 1 (NA = automatically determined) |
| nPC2 | Fixed number of principal components to retain for exposure 2 (NA = select automatically) |
| max_nPC2 | Maximum number of principal components to retain for exposure 2 (NA = automatically determined) |
| improvement_threshold | Minimum cross-validation improvement required to add an additional principal component |
| bootstrap | Whether to compute confidence intervals using bootstrap resampling |
| n_bootstrap | Number of bootstrap replicates (only used if bootstrap = TRUE) |
| n_cores | Number of CPU cores to use for parallel computations |
| true_effects | List with true_effect1 and true_effect2 (simulation only) |
| X_true | List with X1_true and X2_true curves (simulation only) |
| verbose | Print progress and diagnostic messages during computation |

Value

fmvmr_separate object

Separate_Multi_FMVMR_twosample_simple

Separate univariable two-sample FMR (internal)

Description

Separate univariable two-sample FMR (internal)

Usage

```
Separate_Multi_FMVMR_twosample_simple(
  Gmatrix1,
  Gmatrix2 = NULL,
  res1,
  res2,
  by_used1,
  by_used2 = NULL,
  sy_used1,
  sy_used2 = NULL,
  ny_used,
  max_nPC1 = NA,
  max_nPC2 = NA,
```

```

X1Ymodel = NA,
X2Ymodel = NA,
basis = "eigenfunction"
)

```

Arguments

| | |
|----------|---|
| Gmatrix1 | Genetic instrument matrix from exposure 1 ($N \times J1$) |
| Gmatrix2 | Genetic instrument matrix from exposure 2 ($N \times J2$) or NULL |
| res1 | FPCA result for exposure 1 |
| res2 | FPCA result for exposure 2 |
| by_used1 | Vector of SNP-outcome effect estimates (betas for X1) from the outcome GWAS, length J |
| by_used2 | Vector of SNP-outcome effect estimates (betas for X2) from the outcome GWAS, length J or NULL |
| sy_used1 | Vector of standard errors for SNP-outcome effects for X1, length J |
| sy_used2 | Vector of standard errors for SNP-outcome effects for X2, length J or NULL |
| ny_used | Sample size of the outcome GWAS |
| max_nPC1 | Maximum number of principal components to retain for exposure 1 (NA = select automatically) |
| max_nPC2 | Maximum number of principal components to retain for exposure 2 (NA = select automatically) |
| X1Ymodel | True effect model for X1 on Y (for simulation only) |
| X2Ymodel | True effect model for X2 on Y (for simulation only) |
| basis | Basis type for functional representation: "eigenfunction" or "polynomial" |

Value

List with separate estimation results for both exposures

Index

`_PACKAGE` (mvfmr-package), [2](#)

`AUTOMATIC_Multi_FMVMR_twosample_simple`,
[2](#)

`cf_logit`, [3](#)

`fmvmr_separate_twosample`, [4](#)
`fmvmr_twosample`, [5](#)

`getX_multi_exposure`, [6](#)
`getX_multi_exposure_mediation`, [7](#)
`getY_multi_exposure`, [8](#)
`gmm_lm_onesample`, [9](#)
`gmm_twosample_simple`, [9](#)

`IS`, [10](#)

`mvfmr`, [10](#)
`mvfmr-package`, [2](#)
`mvfmr_separate`, [12](#)

`Separate_Multi_FMVMR_twosample_simple`,
[13](#)