**Table 1** Summary of some existing MR methods

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Design | Instrumental variable | effect  assumption | effect assumption | Estimation procedure | Individual or summary data |
| PrediXcan1 | Two-sample | Correlated | Elastic net | N/A | Two-stage | Both |
| TWAS2 | Two-sample | Correlated | BSLMM | N/A | Two-stage | Both |
| SMR3 | Two-sample | Univariate | Fixed effect | N/A | Two-stage | Summary |
| GSMR4 | Two-sample | Near-independent | Fixed effect | N/A | Two-stage | Summary |
| MR-Egger13 | Two-sample | Independent | Fixed effect | Equal effect size | Two-stage | Summary |
| CoMM20 | Two-sample | Correlated | Normal | N/A | MLE | Individual |
| CaMMEL26 | Two-sample | Correlated | Fixed effect | Normal | Variational Bayes | Summary |
| Kang et al.27 | One-sample | Correlated | Fixed effect | Lasso | Two-stage | Individual |
| MRMix32 | Two-sample | Independent | Normal Mixture | Normal Mixture | Estimating equation | Summary |
| Berzuini et al.33 | One-sample | Correlated | Fixed effect | Horseshoe | MCMC | Individual |
| LDA MR-Egger35 | Two-sample | Correlated | Fixed effect | Equal effect size | Two-stage | Summary |
| **PMR-Egger** | **Two-sample** | **Correlated** | **Normal** | **Equal** **effect size** | **MLE** | **Both** |

Methods are categorized based on the experimental design (two-sample vs one-sample vs both), the characterizes of selected instrumental variables (univariate vs multiple independent vs multiple correlated), effect size assumption, effect size assumption, estimation/inference procedure (ratio-based vs two-stage estimation vs maximum likelihood vs Bayesian), and input data type (individual-level vs summary). The categorization of inference procedure generally follows ref [5]. In the inference procedure, the two-stage estimation procedure comprises two regression stages: the first-stage regression of the exposure on the instrumental variables, and the second-stage regression of the outcome on the fitted values of the exposure from the first stage. Some inference procedures, such as the inverse variance weighted (IVW) procedure (e.g. MR-Egger13) or the ratio method (e.g. for SMR3) are categorized as two-stage procedure here, as both are asymptotically equivalent to a two‐stage estimation procedure in the case of independent instruments. We only list MR methods that directly take input instruments into the model; many MR methods that performs various selection procedures on the instruments (e.g. Guo et al28) are not included in the table. Some recently developed methods that only test for horizontal pleiotropy, such as GLIDE30, MR-PRESSO21 and modified second-order weighting of Cohran’s Q statistic24,25, are not included in the table.