## Part A: Core MR Methodology

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| **Item** | **Category** | **Question** | **Evaluation Criteria** |
| **A1** | **Data Sources** | Are Exposure and Outcome GWAS described with source, ancestry, and sample size? | **Score 1 if ALL of the following are clearly reported for BOTH exposure GWAS and outcome GWAS:**   * Study name or consortium or cohort clearly stated * Exact sample sizes provided * Ancestry composition reported   **Score 0 if ANY of the following:**   * Missing source, ancestry, and sample size for either exposure GWAS or outcome GWAS * Vague description (ancestry is only stated as “predominantly European” or “most participants European” without numeric percentages or without explicit statement) |
| **A2** | **Instrument Selection - Threshold** | Is genome-wide significance threshold applied and clearly justified? | **Score 1 if ANY of the following are clearly reported:**   * A p-value threshold of p < 5×10⁻⁸ is explicitly stated for selecting instruments * A different p-value threshold is clearly stated AND justified (e.g., “We used p < 1×10⁻⁵ due to limited sample size”)   **Score 0 if ANY of the following:**   * A different p-value threshold was used but no justification is provided * No p-value threshold is reported at all   **Mark N/A if:**   * The study uses a **single SNP instrument**, for which threshold selection does not apply. |
| **A3** | **Instrument Selection - Parameters** | Are linkage disequilibrium (LD) pruning or clumping parameters specified? | **Score 1 if ALL of the following are explicitly reported:**   * LD selection method (e.g., pruning or clumping) * r² threshold (e.g., r² < 0.01) * Distance parameter/window size (e.g., 10,000kb)   **Score 0 if ANY of the following:**   * LD method is not specified (“independent SNPs” alone with no further detail) * r² threshold is missing * Distance/window parameter is missing   **Mark N/A if:**   * The study uses a **single SNP instrument**. |
| **A4** | **Instrument Selection - Reference Panel** | Is the LD reference panel named and its population specified? | **Score 1 if BOTH of the following are reported:**   * Reference panel is explicitly named (e.g., “1000 Genomes Phase 3”) * The population subset or ancestry is specified (e.g., “European”)   **Score 0 if ANY of the following:**   * Reference panel is not identified at all * Reference panel is only vaguely described (e.g., “a standard reference panel”) * Population subset or ancestry is not specified * If panel is only used for imputation/QC or LDSC and **not** for MR instrument selection   **Mark N/A if:**   * The study uses a **single SNP instrument**. |
| **A5** | **Instrument Strength - Reporting** | Are numeric measures of instrument strength reported? | **Score 1 if ANY of the following are clearly reported:**   * F-statistics provided for each instrument OR a mean/overall F-statistic reported * R² (variance explained) reported for the instrument(s) * Both F-statistics and R² reported   **Score 0 if ANY of the following:**   * Instrument strength is mentioned qualitatively without numeric values (e.g., “strong instruments”) * No F-statistic or R² reported * Instrument strength not mentioned at all |
| **A6** | **Instrument Strength - Adequacy** | Are instrument strength metrics adequate (i.e. meeting conventional thresholds)? | **Score 1 if ANY of the following are true:**   * Mean or overall F-statistic is ≥ 10 * All individual SNP F-statistics are ≥ 10   **Score 0 if ANY of the following:**   * Mean or overall F-statistic is <10 * Any individual SNP F-statistic is < 10 * Weak instrument bias is explicitly acknowledged   **Mark N/A if:**   * A3a = 0 (i.e., if no numeric F-statistics or R² are reported) |
| **A7** | **MR Assumptions** | Are instrumental variable (IV) assumptions explicitly stated and empirically evaluated? | **Score 1 if BOTH are met:**   * IV assumptions (relevance, independence, exclusion restriction) **explicitly named or discussed** * At least one empirical assessment of assumptions is performed and reported, such as ANY of: * Confounder association testing (e.g., PhenoScanner lookup, covariate balance checks) * Pleiotropy tests (e.g., MR-Egger intercept, MR-PRESSO global test) * Negative control analyses * Steiger directionality tests   **Score 0 if ANY of the following:**   * IV assumptions are not mentioned * No empirical assessment or sensitivity test of assumptions is performed or reported |
| **A8** | **Harmonization** | Are effect alleles harmonized between datasets? | **Score 1 if AT LEAST ONE approach clearly described:**   * Automated harmonization using named functions/packages (e.g., TwoSampleMR harmonise\_data(), MungeSumstats) * Manual harmonization with specific steps described * Strand flip correction explicitly mentioned * Ambiguous SNP removal or frequency-based inference described   **Score 0 if ANY of the following:**   * No harmonization mentioned * Only vague statement without method description   **Mark N/A if:**   * The study is 1-sample MR |
| **A9** | **Palindromic SNPs** | Are palindromic SNPs (A/T or C/G) handled and reported appropriately? | **Score 1 if ANY of the following are clearly reported:**   * Automated harmonization using a tool that is documented to handle palindromic SNPs (e.g., TwoSampleMR harmonise\_data()) is explicitly named. * Palindromic SNPs are excluded from the analysis * Allele frequency threshold for resolving strand ambiguity is **explicitly stated** (e.g., “MAF <0.42”). * Reference-based alignment of palindromic SNPs using a **named reference panel** (e.g., 1000 Genomes) is described.   **Score 0 if ANY of the following:**   * Palindromic SNPs are not mentioned * Method of handling palindromic SNPs is not specified   **Mark N/A if:**   * The study is 1-sample MR |
| **A10** | **Sample Overlap** | Is sample overlap appropriately addressed? | **For 2-sample MR - Score 1 if ANY of the following are present:**   * Sample overlap discussed (e.g., “none” or “minimal” or “public GWAS datasets with no known overlap”) * Sample overlap adjusted using appropriate methods (e.g., CAUSE, MR-RAPS adjustment)   **For 1-sample MR - Score 1 if ANY of the following are present:**   * Overlap justified * Appropriate method used (e.g., two-stage least squares (2SLS) or equivalent method) * Appropriate software mentioned (e.g., ivreg, ivpack)   **Score 0 if ANY of the following:**   * Sample overlap not discussed * Sample overlap not adjusted |
| **A11** | **Confounder Control** | Are confounder limitations acknowledged, or covariates controlled for appropriately? | **For 2-sample MR - Score 1 if ANY of the following:**   * Explicit acknowledgment that individual-level covariates cannot be adjusted in summary-level MR * Discussion of residual confounding or population stratification as a study limitation * Reporting of methods for controlling population stratification control (e.g., genomic principal components in GWAS)   **For 1-sample MR - Score 1 if ANY of the following:**   * Covariate adjustment methods are clearly described * List of standard covariates (e.g., age, sex, principal components) included in models * Method for covariate selection is described   **Score 0 if ANY of the following:**   * For 2-sample MR: No acknowledgement of confounder limitations * For 1-sample MR: No description of covariate adjustment and no justification |
| **A12** | **Outlier Detection** | Are outlier instruments systematically identified and sensitivity analysis performed? | **Score 1 if ALL of the following criteria are met:**   * Systematic outlier detection method applied, such as: MR-PRESSO, leave-one-out analysis, radial MR, Cook's distance, MVMR-cML, contamination mixture model * The method is clearly named and adequately described (e.g., parameters, thresholds) * Results are presented both before and after removing outliers, showing effect estimates with and without exclusions * Impact of outlier removal is discussed, including whether estimates changed materially or conclusions were affected   **Score 0 if ANY of the following:**   * No systematic outlier detection method was applied. * The method is applied but not named or described. * Results after outlier removal are not presented. * The impact of removing outliers is not discussed.   **Mark N/A if:**   * The analysis used a **single SNP instrument** |
| **A13** | **Sensitivity Analyses - Testing** | Are sensitivity analyses performed to test for pleiotropy or heterogeneity? | **Score 1 if ANY of the following methods were applied:**   * MR-Egger regression * Weighted median or weighted mode estimator * MR-PRESSO (global test or outlier test) * Heterogeneity tests (Cochran's Q, I² statistic) * Radial MR with modified Q-statistic * Contamination mixture methods (e.g., MR-Mix, CAUSE)   **Score 0 if ANY of the following:**   * No sensitivity analysis was performed * Sensitivity analyses were only described in theory but not performed |
| **A14** | **Sensitivity Analyses - Reporting** | Are sensitivity analysis results reported and interpreted? | **Score 1 if ALL of the following are met:**   * Results from sensitivity analysis are clearly reported (e.g. effect estimates, confidence intervals, p-values) * Results are interpreted in text, discussing consistency or divergence with main estimates   **Score 0 if ANY of the following:**   * Sensitivity analysis were mentioned but results are not reported * Results shown but not interpreted * No mention of sensitivity analysis |
| **A15** | **Robust Estimators - Use** | Are alternative MR estimators used beyond inverse-variance weighted (IVW)? | **Score 1 if:**   * At least one alternative estimator used (e.g., Weighted median, Weighted mode, MR-Egger, MR-RAPS, GSMR) AND results reported   **Score 0 if:**   * Only IVW OR no results for alternative estimators |
| **A16** | **Robust Estimators - Results** | Are results consistent across multiple MR estimators? | **Score 1 if ANY of the following are present:**   * Results consistent and compared across MR estimators * Discordant results discussed with potential explanations   **Score 0 if ANY of the following:**   * Results are inconsistent * Results not discussed   **Mark N/A if:**   * Only one estimator used |
| **A17** | **Statistical Power** | Is statistical power assessed or sample size justified? | **Score 1 if ANY of the following are reported:**   * Formal power calculation is presented * Minimum detectable effect size calculated (e.g., “80% power to detect OR > 1.15”) * Discussion of sample sizeadequacy or limitations stated * Reference to power calculation tools/software (e.g., mRnd, MR Power)   **Score 0 if ANY of the following:**   * No power calculation or justification provided * No discussion of sample size or power limitations |

## Part B: Cross-Ancestry Extensions to MR Methodology

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| **Item** | **Category** | **Question** | **Evaluation Criteria** |
| **B1** | **Ancestry Reporting - Clarity** | Are the ancestries of participants clearly reported for both the exposure and outcome GWAS datasets? | **Score 1 if:**   * For **BOTH** exposure and outcome GWAS, ancestry is explicitly stated using standard terminology (e.g., European, East Asian, African, South Asian, Hispanic/Latino, Native American, Oceanian), clearly named specific populations   **Score 0 if ANY of these apply:**   * Ancestry not reported for either dataset * Only vague descriptors used (e.g., “diverse,” “multi-ethnic,” “international sample,” without details) * Only general geographic terms (e.g., “European countries,” “Asian region”) without explicit population labels |
| **B2** | **Ancestry Reporting - Composition** | For multi-ancestry GWAS, is a numeric breakdown of sample composition provided? | **Score 1 if:**   * The study reports the **numerical composition** (either counts or percentages) for each ancestry group **and** total sample size   **Score 0 if ANY of these apply:**   * Multi-ancestry GWAS is described but without any numerical composition * Only vague descriptors (“diverse”) without counts or percentages   **Mark N/A if:**   * Both exposure and outcome GWAS are single-ancestry |
| **B3** | **Cross-Ancestry Harmonization** | Is ancestry matching assessed or justified between the exposure and outcome GWAS datasets? | **Score 1 if ANY of the following:**   * Exposure and outcome GWAS are ancestry-matched * Ancestry mismatch is explicitly tested (e.g., heterogeneity or trans-ancestry comparisons) * Cross-ancestry replication or ancestry-stratified sensitivity analyses performed and reported   **Score 0 if ANY:**   * Mismatch is acknowledged but no formal testing or justification * No mention of ancestry matching considerations |
| **B4** | **LD Structure - Reference Panel** | Is an ancestry-appropriate LD reference panel used? | **Score 1 if ANY of the following are met:**   * For single-ancestry GWAS: The LD reference panel is explicitly named (e.g., “1000 Genomes Phase 3 EUR”) **AND** The panel is ancestry-matched to the GWAS population * For Multi-ancestry GWAS: The LD reference panel is explicitly named **AND** The authors report the numeric ancestry composition of the GWAS sample **AND** They provide a justification explaining that the reference panel covers the major ancestries present in the sample, where “major” ancestry is operationally defined as any ancestry (or combined ancestries) comprising ≥75% of the total GWAS sample, in accordance with GWAS Catalog Ancestry Reporting Standards (Morales et al., 2018). This threshold reflects current best practices for classification of predominant ancestry in large-scale genomic studies.   **Score 0 if ANY:**   * The LD reference panel is not named. * The panel is not ancestry-matched or appropriate for the GWAS population, with no explanation. * Multi-ancestry GWAS with no numeric breakdown of sample composition provided. Justification provided, but the referenced ancestries together account for **<75%** of the sample. * If panel is only used for imputation/QC or LDSC and not for MR instrument selection. |
| **B5** | **LD Structure - Parameters** | Are LD pruning or clumping parameters explicitly reported? | **Score 1 if ALL:**   * LD method clearly stated (pruning OR clumping) * r² threshold stated (e.g., r² < 0.01) * Distance/window parameter stated (e.g., 10,000kb)   **Score 0 if ANY missing:**   * Method not specified * No r² threshold * No distance parameter |
| **B6** | **Ancestry-Specific Instrument Strength** | Is instrument strength assessed separately by ancestry? | **Score 1 if ANY:**   * F-statistics OR R² reported separately for each ancestry in exposure GWAS * Weak instrument bias discussed in the context of ancestry-specific effects   **Score 0 if:**   * Only pooled instrument strength reported * No ancestry-specific strength metrics |
| **B7** | **Allele Frequency Validation** | Are minor allele frequencies (MAF) thresholds applied and reported separately by ancestry? | **Score 1 if ALL:**   * MAF thresholds stated per ancestry (e.g., "MAF > 0.01”) * Number of SNPs excluded by ancestry reported * Considerations of allele frequency differences discussed   **Score 0 if ANY:**   * No MAF thresholds stated * Only pooled MAF filtering * No mention of allele frequency validation |
| **B8** | **Instrument Transferability** | Is cross-ancestry instrument validity justified? | **Score 1 if ANY:**   * Replication in target ancestry. * LD or frequency comparison across ancestries with data presented. * Biological rationale provided (e.g., conserved pathways). * Citations to prior evidence of transferability.   **Score 0 if:**   * No justification or only general statements about “similarity”     **Mark N/A if:**   * The study is 1-sample MR |
| **B9** | **Phenotype Consistency - Definitions** | Are exposure and outcome phenotype definitions consistent across ancestries? | **Score 1 if:**   * For binary traits: Identical diagnostic criteria (e.g., ICD codes, clinical thresholds) * For continuous traits: Consistent measurement across ancestries   **Score 0 if ANY:**   * Inconsistent definitions without harmonization * No reporting of definitions by ancestry |
| **B10** | **Phenotype Consistency - Units** | Are measurement units consistent across ancestries or appropriately standardized? | **Score 1 if ANY:**   * Units are consistent across all ancestries * If inconsistent, conversions/transformations or standardizations are described   **Score 0 if ANY:**   * Units differ without clear conversion * Units not reported |
| **B11** | **Ancestry-Stratified Analysis - Reporting** | Are MR results reported separately by ancestry or tested for heterogeneity? | **Score 1 if ANY:**   * Stratified MR estimates presented * Formal heterogeneity tests (Cochran's Q, I²) performed * Meta-analyses across ancestries reported   **Score 0 if ANY:**   * Only pooled results reported without ancestry breakdown * Heterogeneity not assessed |
| **B12** | **Ancestry-Stratified Analysis - Interpretation** | Are ancestry-related differences in results interpreted? | **Score 1 if:**   * Population differences discussed * Heterogeneity results interpreted * Clinical or biological implications addressed   **Score 0 if:**   * Differences reported but not discussed * No interpretation of heterogeneity |
| **B13** | **Colocalization Analysis** | Is cross-ancestry colocalization assessed? | **Score 1 if ANY:**   * Formal colocalization methods applied (COLOC, eCAVIAR, SuSiE, FINEMAP) * High LD (e.g., r² > 0.8)) across ancestries demonstrated * Cross-ancestry variant-level concordance assessed   **Score 0 if:**   * No colocalization performed * Only general mentions without formal testing   **Mark N/A if**:   * The study is 1-sample MR |
| **B14** | **Ancestry-Specific Pleiotropy** | Is pleiotropy assessed separately by ancestry? | **Score 1 if ANY:**   * MR-Egger, MR-PRESSO, or radial MR performed separately by ancestry * Associations with confounders tested by ancestry * Negative control analysis performed by ancestry   **Score 0 if ANY:**   * Only pooled pleiotropy assessment * No ancestry-specific evaluation |
| **B15** | **Effect Size Interpretation** | Are effect sizes interpreted considering ancestry-specific contexts? | **Score 1 if ANY:**   * Differences in baseline risk across ancestries acknowledged * Clinical relevance by ancestry discussed * Limitations regarding generalizability explicitly addressed   **Score 0 if ANY:**   * No discussion of ancestry-specific relevance * Generalizability assumed without justification |