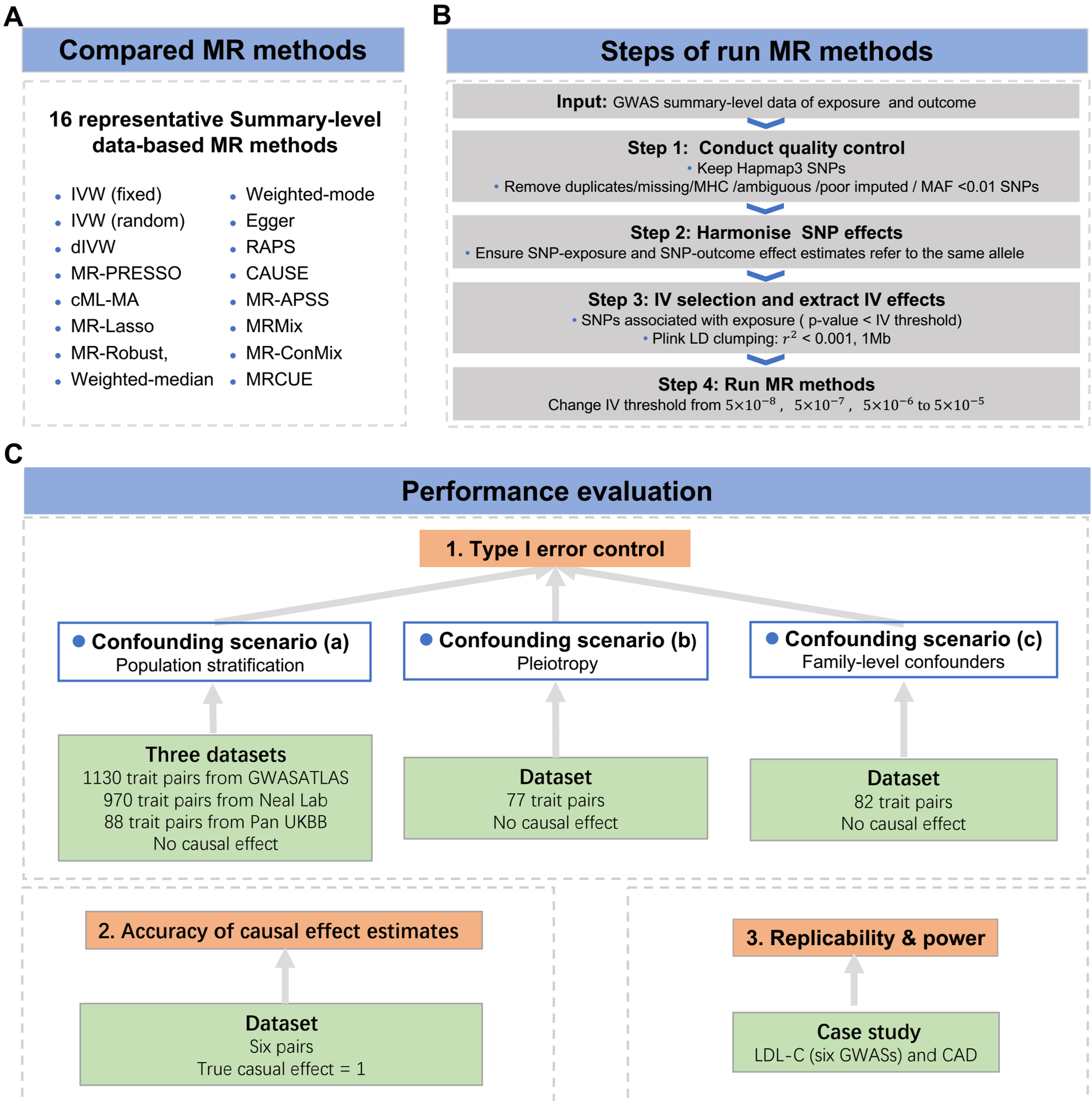
A
Compared MR methods
16 representative Summary-level data-based MR methods
IVW (fixed)
IVW (random)
dIVW
MR-PRESSO
cML-MA
MR-Lasso
MR-Robust,
Weighted-median
Weighted-mode
Egger
RAPS
CAUSE
MR-APSS
MRMix
MR-ConMix
MRCUE
B
Steps of run MR methods
Input: GWAS summary-level data of exposure and outcome
Step 1: Conduct quality control
Keep Hapmap3 SNPs
Remove duplicates/missing/MHC /ambiguous /poor imputed / MAF <0.01 SNPs
Step 2: Harmonise SNP effects
Ensure SNP-exposure and SNP-outcome effect estimates refer to the same allele
Step 3: IV selection and extract IV effects
SNPs associated with exposure (p-value < IV threshold)
Plink LD clumping: r^2 < 0.001, 1Mb
Step 4: Run MR methods
Change IV threshold from 5×10^{-8}, 5×10^{-7}, 5×10^{-6} to 5×10^{-5}
C
Performance evaluation
1. Type I error control
Confounding scenario (a)
Population stratification
Confounding scenario (b)
Pleiotropy
Confounding scenario (c)
Family-level confounders
Three datasets
1130 trait pairs from GWASATLAS
970 trait pairs from Neal Lab
88 trait pairs from Pan UKBB
No causal effect
Dataset
77 trait pairs
No causal effect
Dataset
82 trait pairs
No causal effect
2. Accuracy of causal effect estimates
Dataset
Six pairs
True casual effect = 1
3. Replicability & power
Case study
LDL-C (six GWASs) and CAD