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The proposed trans-ethnic MR method, TEMR, improves the statistical power and estimation accuracy of MR in populations with small GWAS datasets using only a public large-scale GWAS summary dataset. This study has important guiding significance for the discovery of new disease-related factors.

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ARTICLE

TEMR: Trans-ethnic mendelian randomization method using large-scale GWAS summary datasets

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Summary

Available large-scale genome-wide association study (GWAS) summary datasets predominantly stem from European populations, while sample sizes for other ethnicities, notably Central/South Asian, East Asian, African, Hispanic, etc., remain comparatively limited, resulting in low precision of causal effect estimations within these ethnicities when using Mendelian randomization (MR). In this paper, we propose a trans-ethnic MR method, TEMR, to improve the statistical power and estimation precision of MR in a target population that is underrepresented, using trans-ethnic large-scale GWAS summary datasets. TEMR incorporates trans-ethnic genetic correlation coefficients through a conditional likelihood-based inference framework, producing calibrated *p* values with substantially improved MR power. In the simulation study, compared with other existing MR methods, TEMR exhibited superior precision and statistical power in causal effect estimation within the target populations. Finally, we applied TEMR to infer causal relationships between concentrations of 16 blood biomarkers and the risk of developing five diseases (hypertension, ischemic stroke, type 2 diabetes, schizophrenia, and major depression disorder) in East Asian, African, and Hispanic/Latino populations, leveraging biobank-scale GWAS summary data obtained from individuals of European descent. We found that the causal biomarkers were mostly validated by previous MR methods, and we also discovered 17 causal relationships that were not identified using previously published MR methods.

Introduction

In recent years, the evolving landscape has witnessed a progressive expansion of large-scale genome-wide association studies (GWASs), leading to the widespread release and utilization of GWAS summary data among researchers. At the forefront of these developments is Mendelian randomization (MR),[1,2] a method that hinges on the use of publicly available GWAS summary data for causal inference. MR uses genetic variants as instrumental variables (IVs) to infer the causal effect of an exposure on an outcome. Three assumptions must be met: relevance (IVs are strongly associated with the exposure), exchangeability (IVs are independent of confounders among the exposure and outcome), and exclusion restriction (IVs affect the outcome only through the exposure). However, a noteworthy challenge is that the bulk of available large-scale datasets predominantly stem from European populations, such as the UK Biobank (UKB)[3–7] and the FinnGen consortium,[8] while sample sizes for other ethnicities, notably Central/South Asians, East Asians, Africans, Hispanics, etc., remain comparatively limited.[9–12] Taking the East Asian population as an example, despite the substantial data provided by BioBank Japan (BBJ),[11,12] Taiwan Biobank (TWB),[13] and China Kadoorie Biobank (CKB)[14] for the East Asian population (>100,000 individuals), the number of included participants falls short of those for the extensive datasets derived from individuals of European descent available from the UKB (>500,000 individuals) and the FinnGen consortium (>620,000 individuals). Moreover, the UKB incorporates a substantial amount of omics data, including imaging omics,[4] exomes,[5] proteomics,[6] and metabolomics.[7] BBJ, TWB, and CKB have significantly smaller sample sizes and may also lack some omics data.[12] Furthermore, omics databases dedicated to other ethnicities tend to exhibit relatively smaller sample sizes.[15–21] The potential inadequacy of GWAS summary data from smaller samples to furnish robust causal evidence for MR is apparent. Additionally, causal evidence derived from a substantial European population cannot be directly extrapolated to other ethnic groups due to diversity in the genetic structure between individuals of different ethnicities.[22,23] The unbalanced sample makeup across global populations may exacerbate disparities in genetic studies of non-European individuals. Therefore, it is crucial to propose a methodology that leverages the genetic correlations[24,25] among different ethnicities, harnessing the advantages of large European datasets to enhance the accuracy and statistical power of MR in estimating causal effects in underrepresented populations.

Numerous trans-ethnic MR (TEMR) analyses have been published, predominantly in applied research articles.[26–28] The common approach in these studies involves conducting separate MR analyses within distinct ethnic groups and subsequently comparing the nuances in the MR results between these groups. This is unfair for ethnicities

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with small sample sizes, as the statistical power of MR is much lower than that observed with large-sample-size studies. Methodological advancements have been made in cross-ethnic approaches within GWAS meta-analysis and the polygenic risk score (PRS). The published trans-ethnic meta-analysis approaches account for the similarity in allelic effects between the most closely related populations while allowing for heterogeneity between more diverse ethnic groups.[29–32] While trans-ethnic GWAS meta-analysis has the potential to improve the efficiency of identifying new loci by merging populations of different ethnicities, it operates at a mixed-population level and may not necessarily contribute to the discovery of genetic loci specific to particular ethnic groups. Trans-ethnic PRS prediction methods leverage shared genetic effects across ancestries to increase the accuracy of predicting the genetic predisposition of complex phenotypes in underrepresented populations.[33–35] However, these methods highlight that, regarding the improvement of the power to discover new loci or disease predictions, a noticeable gap in the current literature lies in the lack of attention given to methods facilitating the transfer of causal effects observed in MR studies across different ethnicities. Despite progress in various methodological aspects of trans-ethnic analysis, there remains an unexplored avenue concerning the migration of causal effects across ethnic groups in the context of MR.

In this paper, we propose an MR method based on multiple ethnic populations, TEMR, to improve the statistical power and estimation precision of MR in a target population that is underrepresented using trans-ethnic large-scale GWAS summary datasets. Under the framework of the conditional likelihood-based inference framework, TEMR bridges the causal effects of different ethnicities using a trans-ethnic genetic correlation coefficient, which is the correlation of Wald ratios for shared SNPs in different ethnic populations. In the simulation study, TEMR showed superior precision and power for causal effect estimation in the target population relative to the other seven methods in the case of continuous and binary outcome variables. Finally, we applied TEMR to infer causal relationships between concentrations of 16 blood biomarkers and the risk of developing five diseases (hypertension, ischemic stroke, type 2 diabetes [T2D], schizophrenia, and major depressive disorder [MDD]) in East Asian, African, and Hispanic/Latino populations, leveraging biobank-scale GWAS summary data taken from individuals of European descent.

Methods

TEMR model based on two ancestries

Figure 1 serves as a visual summary of the TEMR method and the framework for our case analysis. Consider a target dataset $\{G_1, X_1, Y_1\}$ from an underrepresented ancestry (e.g., East Asian ancestry) with a small sample size, where G_1 is an $n_1 \times p$ genotype matrix and X_1 and Y_1 are $n_1 \times 1$ phenotype/disease vectors, which represent the exposure and outcome, respectively. Now, we suppose that a biobank-scale dataset $\{G_2, X_2, Y_2\}$ (e.g., European ancestry) is also available, where G_2 is an $n_2 \times p$ genotype matrix and X_2 and Y_2 are $n_2 \times 1$ phenotype/disease vectors that represent exposure and outcome, respectively. We assume that $n_2 > n_1$. Since we are mainly interested in improving the statistical power of causal effect estimation in the target population by leveraging biobank-scale datasets from another auxiliary ancestry, we chose p independent IVs (SNPs) associated with at least one exposure in two ancestries (X_1 and X_2). We can obtain summary-level data on p SNPs from published GWASs, including β-coefficients ($\widehat{\beta}_{Y_{1j}}, \widehat{\beta}_{X_{1j}}$ and $\widehat{\beta}_{Y_{2j}}, \widehat{\beta}_{X_{2j}}$) and their standard errors ($\widehat{\sigma}^2_{Y_{1j}}, \widehat{\sigma}^2_{X_{1j}}$ and $\widehat{\sigma}^2_{Y_{2j}}, \widehat{\sigma}^2_{X_{2j}}$).

When the three core assumptions of MR are all satisfied, we can obtain the causal effect estimation using the Wald ratio for each SNP

$$\widehat{\beta}_{1j} = \frac{\widehat{\beta}_{Y_{1j}}}{\widehat{\beta}_{X_{1j}}}, \widehat{\beta}_{2j} = \frac{\widehat{\beta}_{Y_{2j}}}{\widehat{\beta}_{X_{2j}}}, j = 1, \ldots, p, \quad \text{(Equation 1)}$$

with their variances

$$\widehat{\sigma}^2_{\beta_{1j}} = \frac{\widehat{\beta}^2_{Y_{1j}} \times \widehat{\sigma}^2_{X_{1j}}}{\widehat{\beta}^4_{X_{1j}}} + \frac{\widehat{\sigma}^2_{Y_{1j}}}{\widehat{\beta}^2_{X_{1j}}}, \ \widehat{\sigma}^2_{\beta_{2j}} = \frac{\widehat{\beta}^2_{Y_{2j}} \times \widehat{\sigma}^2_{X_{2j}}}{\widehat{\beta}^4_{X_{2j}}} + \frac{\widehat{\sigma}^2_{Y_{2j}}}{\widehat{\beta}^2_{X_{2j}}}. \quad \text{(Equation 2)}$$

$\widehat{\beta}_{1j}$ and $\widehat{\beta}_{2j}$ are the causal effect estimates of exposure on outcome using the j-th SNPs in the target and auxiliary populations, respectively. We constructed the following multivariable normal distribution model for Wald ratios from two populations:

$$\begin{pmatrix} \widehat{\beta}_{1j} \\ \widehat{\beta}_{2j} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \begin{pmatrix} \widehat{\sigma}^2_{\beta_{1j}} & \rho_\beta \widehat{\sigma}_{\beta_{1j}} \widehat{\sigma}_{\beta_{2j}} \\ \rho_\beta \widehat{\sigma}_{\beta_{1j}} \widehat{\sigma}_{\beta_{2j}} & \widehat{\sigma}^2_{\beta_{2j}} \end{pmatrix} \right), \quad \text{(Equation 3)}$$

where β_1 and β_2 are the causal effects of exposure on outcome in the target and auxiliary populations, respectively. They can be the same or different. ρ_β is the trans-ethnic genetic correlation, which represents the correlation of the causal effects of one exposure on one outcome in two ancestries (e.g., Chinese and European), and it can be calculated using the Pearson correlation coefficient

$$\rho_\beta = \frac{cov(z_1, z_2)}{\sqrt{var(z_1) \cdot var(z_2)}}, \quad \text{(Equation 4)}$$

where z_1 and z_2 are the Z scores of p-dimensional Wald ratio vectors in two ancestries:

$$z_{1j} = \frac{\widehat{\beta}_{1j}}{\widehat{\sigma}_{\beta_{1j}}}, z_{2j} = \frac{\widehat{\beta}_{2j}}{\widehat{\sigma}_{\beta_{2j}}}, j = 1, \ldots, p. \quad \text{(Equation 5)}$$

We aimed to improve the statistical power of causal effect (β_1) estimation in the target population using the trans-ethnic genetic correlation (ρ_β), which connects the causal effects of two ethnicities. Based on model 3 (Equation 3) and the conditional normal distribution formula,[36] we have

$$\widehat{\beta}_{1j} \middle| \widehat{\beta}_{2j} \sim N\left(\beta_1 + \rho_\beta \widehat{\sigma}_{\beta_{1j}} \widehat{\sigma}^{-1}_{\beta_{2j}} \left(\widehat{\beta}_{2j} - \beta_2 \right), \widehat{\sigma}^2_{\beta_{1j}} - {\rho_\beta}^2 {\widehat{\sigma}_{\beta_{1j}}}^2 \right) \quad \text{(Equation 6)}$$

with its variance

$$var\left(\widehat{\beta}_{1j} \middle| \widehat{\beta}_{2j} \right) = \widehat{\sigma}^2_{\beta_{1j}} \left(1 - {\rho_\beta}^2 \right) < \widehat{\sigma}^2_{\beta_{1j}}. \quad \text{(Equation 7)}$$

Therefore, the variance of the j-th Wald ratio estimation $\widehat{\beta}_{1j}$ conditional on $\widehat{\beta}_{2j}$ is smaller than its original variance as the trans-ethnic genetic correlation ρ_β increases. Then, we obtained the conditional log likelihood function of model 8 (Equation 8),

$$Q(\beta_1) = \sum_j -p\ln(2\pi) - \frac{1}{2}\ln\left(\widehat{\sigma}^2_{\beta_{1j}} - {\rho_\beta}^2{\widehat{\sigma}_{\beta_{1j}}}^2\right) - \frac{1}{2}\frac{\left(\widehat{\beta}_{1j} - \beta_1 - \rho_\beta\widehat{\sigma}_{\beta_{1j}}\widehat{\sigma}^{-1}_{\beta_{2j}}\left(\widehat{\beta}_{2j} - \widehat{\beta}_2\right)\right)^2}{(1-{\rho_\beta}^2){\widehat{\sigma}_{\beta_{1j}}}^2},$$

(Equation 8)

where $\widehat{\beta}_2$ is obtained by inverse-variance weighting (IVW) or other effective MR methods using a large-scale dataset in the auxiliary population. We aimed to maximize the log conditional likelihood function using the Nelder-Mead method[37] to obtain the estimation of β_1. Then, we used the likelihood ratio test to perform hypothesis testing:

$$H_0 : \beta_1 = 0 \text{ vs. } H_1 : \beta_1 \neq 0, \quad \text{(Equation 9)}$$

with the testing statistics

$$\chi^2 = -2 \times \frac{Q(\widehat{\beta}_1)}{Q(0)} \sim \chi^2(1). \quad \text{(Equation 10)}$$

When there is horizontal pleiotropy, the third assumption of MR is violated, and causal effect estimation using the traditional Wald ratio is biased; therefore, we modeled the TEMR-Wald ratio as follows:

$$\beta_{1j} = \frac{\widehat{\beta}_{Y_{1j}} - \alpha_{1j}}{\widehat{\beta}_{X_{1j}}}, \beta_{2j} = \frac{\widehat{\beta}_{Y_{2j}} - \alpha_{2j}}{\widehat{\beta}_{X_{2j}}} \quad \text{(Equation 11)}$$

where α_{1j} represents horizontal pleiotropy and is unknown. Therefore, in the first step, we need to estimate α_{1j} and α_{2j} using MR-Egger regression.

(1) Separately estimate causal effects β_1^{Egger} and β_2^{Egger} for each ancestry using MR-Egger regression:

$$\begin{aligned}\widehat{\beta}_{Y_{1j}} &= \widehat{\beta}_{X_{1j}}\cdot\beta_1^{Egger} + \alpha_1 + \varepsilon_{1j}, \varepsilon_{1j} \sim N\left(0, \widehat{\sigma}^2_{Y_{1j}}\right)\\ \widehat{\beta}_{Y_{2j}} &= \widehat{\beta}_{X_{2j}}\cdot\beta_2^{Egger} + \alpha_2 + \varepsilon_{2j}, \varepsilon_{2j} \sim N\left(0, \widehat{\sigma}^2_{Y_{2j}}\right)\end{aligned} \quad \text{(Equation 12)}$$

(2) Separately estimate horizontal pleiotropy α_{1j} and α_{2j} in each ancestry using

$$\begin{aligned}\widehat{\alpha}_{1j} &= \widehat{\beta}_{Y_{1j}} - \widehat{\beta}_{X_{1j}}\cdot\widehat{\beta}_1^{Egger}\\ \widehat{\alpha}_{2j} &= \widehat{\beta}_{Y_{2j}} - \widehat{\beta}_{X_{2j}}\cdot\widehat{\beta}_2^{Egger}\end{aligned} \quad \text{(Equation 13)}$$

Then, we can obtain the estimations of the modified Wald ratios $\widehat{\beta}_{1j}$ and $\widehat{\beta}_{2j}$ by substituting $\widehat{\alpha}_{1j}$ and $\widehat{\alpha}_{2j}$ into Equation 11. Next, we used models 1, 3, 6, and 8 (Equations 1, 3, 6, and 8) to estimate β_1. The difference is that the $\widehat{\beta}_2$ in model 8 (Equation 8) is obtained by horizontal-pleiotropy-robust MR methods using a large-scale dataset in the auxiliary population.

TEMR model based on multiple ancestries

If there are $E > 2$ ancestries, the target dataset is $\{G_T, X_T, Y_T\}$, and the auxiliary datasets are $\{G_a, X_a, Y_a\}(a = 2, \ldots, E)$, then we set up the following multivariable normal distribution model using Wald ratios from E ancestries:

$$\begin{pmatrix}\widehat{\beta}_{Tj}\\ \widehat{\beta}_{Aj}\end{pmatrix} \sim N\left(\begin{pmatrix}\beta_T\\ \beta_A\end{pmatrix}, \begin{pmatrix}\widehat{\sigma}^2_{\beta_{Tj}} & \Sigma_{A1}\\ \Sigma_{1A} & \Sigma_{AA}\end{pmatrix}\right), \quad \text{(Equation 14)}$$

where $\widehat{\beta}_{Aj} = \begin{pmatrix}\widehat{\beta}_{2j}\\ \ldots\\ \widehat{\beta}_{Ej}\end{pmatrix}$, $\beta_A = \begin{pmatrix}\beta_2\\ \ldots\\ \beta_E\end{pmatrix}$, $\Sigma_{AA} = \begin{pmatrix}\widehat{\sigma}^2_{\beta_{2j}} & \ldots & \rho_{\beta_{(2,E)}}\widehat{\sigma}_{\beta_{2j}}\widehat{\sigma}_{\beta_{Ej}}\\ \ldots & \ldots & \ldots\\ \rho_{\beta_{(E,2)}}\widehat{\sigma}_{\beta_{Ej}}\widehat{\sigma}_{\beta_{2j}} & \ldots & \widehat{\sigma}^2_{\beta_{Ej}}\end{pmatrix}$

$\Sigma_{A1} = \left(\rho_{\beta_{(1,2)}}\widehat{\sigma}_{\beta_{1j}}\widehat{\sigma}_{\beta_{2j}} \ \ldots \ \rho_{\beta_{(1,E)}}\widehat{\sigma}_{\beta_{1j}}\widehat{\sigma}_{\beta_{Ej}}\right)$, $\Sigma_{1A} = {\Sigma_{A1}}^T$, and $\rho_{\beta_{(m,n)}} = \rho_{\beta_{(n,m)}}$. The conditional distribution of $\widehat{\beta}_{Tj}$ given $\widehat{\beta}_{Aj}$ is

$$\widehat{\beta}_{Tj}\left|\widehat{\beta}_{Aj} \sim N\left(\beta_T + \Sigma_{A1}\Sigma_{AA}^{-1}\left(\widehat{\beta}_{Aj} - \beta_A\right), \widehat{\sigma}^2_{\beta_{Tj}} - \Sigma_{A1}\Sigma_{AA}^{-1}\Sigma_{1A}\right)\right.. \quad \text{(Equation 15)}$$

Then, we obtained the estimation of β_T via maximum likelihood estimation using the Nelder-Mead method.

Due to the predominant representation of European individuals in public GWAS summary datasets, with smaller sample sizes for other ethnicities, our aim was to utilize information from the European population to improve the precision of causal effect estimation and testing efficacy for smaller sample populations. Furthermore, if our focus is exclusively on the Asian population, then the inclusion of other small-sample ethnicities could still contribute to enhancing the estimation of causal effects on the Asian population, although the contribution may not be as substantial as that from the European population.

Simulation settings

In our simulation study, we systematically evaluated the performance of TEMR through several steps. We first generated the GWAS summary statistics using trans-ethnic genetic correlation $\rho_{\beta_{(e_1,e_2)}}$:

$$\widehat{\beta}_{X_{ej}} \sim N(0.2, 0.05) \text{ for target population,}$$

$$\widehat{\beta}_{X_{ej}} \sim N(0.2, 0.03) \text{ for auxiliary population,}$$

$$\begin{pmatrix}\widehat{\beta}_{Y_{1j}}\\ \ldots\\ \widehat{\beta}_{Y_{Ej}}\end{pmatrix} \sim MVN\left(\begin{pmatrix}\widehat{\beta}_{X_{1j}}\beta_1\\ \ldots\\ \widehat{\beta}_{X_{Ej}}\beta_E\end{pmatrix}, \begin{pmatrix}\widehat{\sigma}^2_{Y_{1j}} & \ldots & \rho_{\beta_{(1,E)}}\widehat{\sigma}_{Y_{Ej}}\widehat{\sigma}_{Y_{1j}}\\ \ldots & \ldots & \ldots\\ \rho_{\beta_{(E,1)}}\widehat{\sigma}_{Y_{Ej}}\widehat{\sigma}_{Y_{1j}} & \ldots & \widehat{\sigma}^2_{Y_{Ej}}\end{pmatrix}\right),$$

where $\widehat{\sigma}^2_{Y_{ej}}$ was the variance of $\widehat{\beta}_{Y_{ej}}$. Then, we generated the Wald ratios ($\widehat{\beta}_{ej}$) for different ethnicities from the above GWAS summary statistics:

$$\widehat{\beta}_{ej} = \widehat{\beta}_{Y_{ej}} \Big/ \widehat{\beta}_{X_{ej}}, e = 1, \ldots, E$$

We considered scenarios where the causal effects were the same or different across different ethnicities, as well as situations where the causal effects were either zero ($\beta_e = 0$) or non-zero ($\beta_e = 0.05$). We also explored various scenarios, including different trans-ethnic genetic correlation coefficients between ethnicities. We considered the number of ethnicities to be $E = 2$ or $E = 4$, $\rho_{\beta_{(e_1,e_2)}}$ to vary from 0.1 to 0.9, and that the trans-ethnic genetic correlations are the same or different across different race pairs. Acknowledging the potential influence of genetic factors across diverse racial backgrounds, in this study, we aimed to

account for variations in genetic correlation. Furthermore, in an effort to optimize precision and statistical power, we systematically varied the number of SNPs ($p = 25$, 50, 100, and 200) while keeping the other parameters constant. This process allows us to determine how much the precision and statistical power of causal effect estimates can be significantly improved under different numbers of IVs. Finally, our simulation study was designed to encompass four distinct scenarios: one where pleiotropy was absent ($\gamma_{je} = 0$), another where balanced horizontal pleiotropy was present ($\gamma_{je} \sim U(-0.01, 0.01)$), a third scenario where directional horizontal pleiotropy was present ($\gamma_{je} \sim U(0, 0.01)$), and one where some IVs were weakly associated with the exposure ($\widehat{\beta}_{X_{ej}} \sim N(0, 0.01)$), especially when there were only several SNPs (e.g., 5 SNPs) significantly associated with exposure in the target population but a large number of SNPs (e.g., 95 SNPs) were significant in other populations. For $E = 2$, we set $\widehat{\sigma}_{Y_{ej}} \sim U(0.01, 0.13)$ for the target population and $\widehat{\sigma}_{Y_{ej}} \sim U(0.0002, 0.01)$ for the auxiliary population. For $E = 4$, we set $U(0.01, 0.13)$, $U(0.02, 0.12)$, $U(0.02, 0.25)$, and $U(0.0002, 0.01)$ for four populations. The smaller $\widehat{\sigma}_{Y_{ej}}$ represent the larger sample size. The $\widehat{\sigma}_{Y_{ej}}$ in different populations were set in terms of the standard errors of $\widehat{\beta}_{Y_{ej}}$ in the GWAS summary statistics of application. Table S14 lists the sample sizes and quantile ranges of $\widehat{\sigma}_{Y_{ej}}$ for five diseases in different populations. Taking hypertension as an example, the sample sizes were 2,703 (East Asian), 6,626 (African), 10,526 (Hispanic/Latino), and 337,199 (European), and the corresponding quantile ranges of standard errors were 0.08–0.10 (East Asian), 0.05–0.12 (African), 0.02–0.11 (Hispanic/Latino), and 0.0006–0.0013 (European). We then applied our TEMR method to estimate causal effects in the target population. To benchmark the performance of our approach, we conducted a comparative analysis with previously published MR methods[2] based on the Wald ratio, including the IVW method,[38] MR-Egger,[39] simple median,[40] weighted median,[41] simple mode,[42] and weighted mode.[43] By thoroughly examining these scenarios, we aimed to provide a comprehensive assessment of the performance and robustness of TEMR analysis under diverse genetic and phenotypic conditions.

The evaluation metrics include estimation bias, standard error, type I error for testing null causal effects, and statistical power for testing non-null causal effects. We utilized boxplots to demonstrate the results of bias and standard error, Q-Q plots to showcase the results of type I error, and bar charts to depict the results of statistical power. We also report the empirical coverage of 95% confidence intervals for causal effect estimation, and it is calculated by the bootstrap method.

Application

We applied TEMR to estimate the causal effects of several biomarkers on the risk of developing five diseases (hypertension, ischemic stroke, T2D, schizophrenia, and MDD) in the East Asian, African, and Hispanic/Latino populations, leveraging data from large European cohorts. We selected all blood biomarkers from the UKB that were consistently available across four ethnicities, focusing on 18 biomarkers that could be matched with data from the other populations. The diseases were chosen for their significant public health impact, high prevalence, and representative nature of the complex interplay between genetics and the environment. The GWAS summary data for the Asian population were mainly sourced from the BBJ, with a sample size of 170,000. For the African population, the data were mainly obtained from the Pan-UKB, with a sample size of 6,000, and for the Hispanic population, the data were obtained from the GWAS Catalog, with a sample size of 6,000. The GWAS summary data of the European population were derived from the UKB, with a sample size of 500,000. The details of the dataset information are shown in Table S7. First, for each trait, we chose significant SNPs based on the criterion of p values $<5\times10^{-8}$ in each ethnicity. Then, we obtained the union set of significant SNPs in four ethnicities. Next, we calculated the combined p value of four ethnicities for each SNP in the union set. The combined p value for j-th SNP was calculated by the Fisher's method[44,45]: $p_j = 2 \times (1 - \Phi(Z_j))$, where $Z_j = \sum_e Z_{je} = \sum_e \Phi^{-1}(1 - p_{je}/2)$, Φ was the standard normal cumulative distribution function, and p_{je} was the p value for the j-th SNP in the e-th ethnicity. Finally, we conducted the linkage disequilibrium (LD) clump process ($r^2 < 0.01$) based on the combined p value using the LD panel in the target ethnicity. For two SNPs with high LD, we kept the SNP with the smaller combined p value. After the above steps, we obtained the IVs for each target ethnicity. Then, we applied TEMR and six other MR methods for -ethnic MR analysis of the associations between concentrations of 16 biomarkers and the risk of developing five diseases. For each target population, we used the other three datasets as auxiliary datasets. The data used in our study were all publicly available and obtained written informed consent from all participants.

Results

Simulation

We conducted a series of simulation studies to evaluate the performance of the TEMR, comprising seven published MR methods. We assessed variations in the magnitudes of the following parameters in the scenarios of no pleiotropy and horizontal pleiotropy: causal effect, trans-ethnic genetic correlation, and the number of SNPs. We utilized boxplots to demonstrate the results of estimation bias and standard error, Q-Q plots to show the results of type I error, and bar charts to depict the results of statistical power. We also report the empirical coverage of 95% confidence intervals for causal effect estimation, and it is calculated by the bootstrap method.

Figure 2 shows the simulation results of causal effect estimation in the target population when there is one auxiliary population and no pleiotropy. The simulation results demonstrated nearly unbiased estimates of causal effects for TEMR, regardless of the alignment between causal effects in the auxiliary and target populations. TEMR also showed superior precision and power across a broad spectrum of scenarios relative to the other seven methods. The precision of TEMR incrementally improved as ρ_β increased. When $\rho_\beta < 0.4$, the precision of TEMR was similar to that of the IVW and weighted median estimation (WME) methods. However, when $\rho_\beta \geq 0.4$, the precision of TEMR surpassed that of the other seven methods (Figure 2A). Additionally, TEMR exhibited stable type I errors unaffected by variations in ρ_β or causal effects in the auxiliary population (Figures 2B and 2C). Moreover, the statistical power of TEMR significantly increased with increasing ρ_β, especially outperforming the other seven methods when $\rho_\beta \geq 0.4$ (Figures 2D and 2E). Specifically, when $\rho_\beta = 0.6$, there was a notable decrease in the

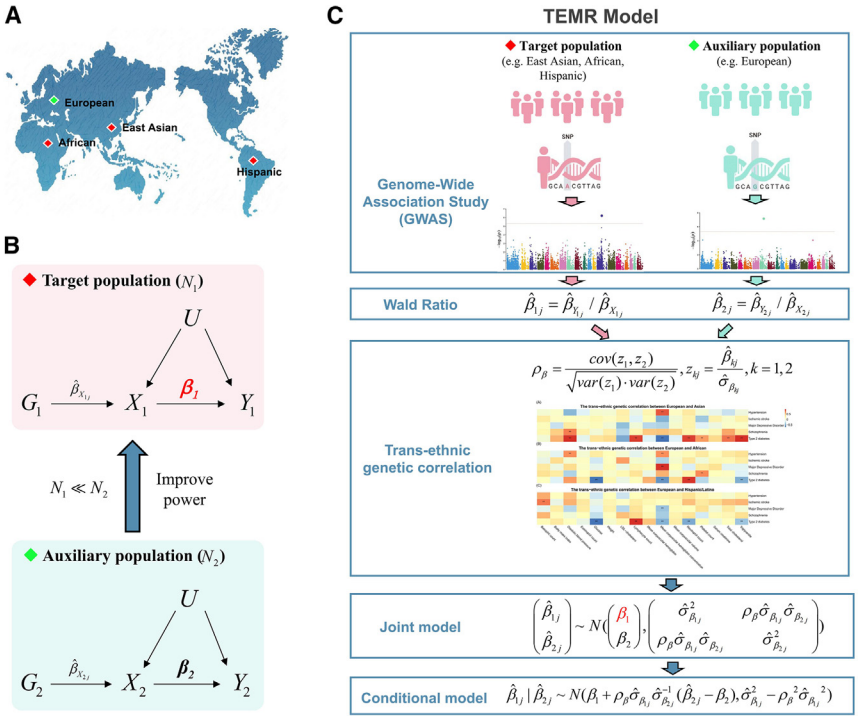

Figure 1. TEMR flowchart

(A) An example of multiple ethnicities, which also are the ethnicities in which we are interested in the applied example.

(B) The aim of TEMR is to improve the statistical power and estimation accuracy of MR in the target population only using trans-ethnic large-scale auxiliary dataset.

(C) Flowchart of TEMR model taking two ethnicities as example: one target population and one auxiliary population.

standard error of approximately 15%–20% and an increase in the power of approximately 20%. At a higher ρ_β, the standard error decreased by up to 50%, while the power improved by 40% (Table S1). The empirical coverage of 95% confidence intervals for causal effect estimations using TEMR were around 95% under any scenarios (Table 1), while the coverages of other methods including median-based and mode-based methods were a bit higher than 95%.

Then, we extended our simulation to a scenario in which horizontal pleiotropy, both balanced and directional, was present. In addition to achieving unbiased estimates of causal effects and stable type I errors, TEMR also maintained the advantages of precision and power, as described above (Figures 3 and S1), while other methods demonstrated biased causal effect estimations. When there was directional pleiotropy, the empirical coverage of 95% confidence intervals for TEMR and simple mode methods was around 95%, while other methods were far below 95% (Table S1). Furthermore, we also incorporated the scenario where the utilized SNPs were weak IVs, a common challenge in MR studies. Our results indicated that when the target population comprised over 90% of weak IVs, the variance of causal effect estimations across all methods saw a marked increase. However, the TEMR demonstrated decreasing variance, with its accuracy continuing to improve as ρ_β increased (Figure S2; Table S2). The empirical coverage of 95% confidence intervals for TEMR was a bit lower than 95%, while that of mode-based methods reached 1. This observation underscores the robustness and effectiveness of TEMR in the presence of weak IVs, highlighting its potential as a reliable method for estimating causal effects even under less-than-ideal conditions. Additionally, we validated our findings by generating individual-level data to calculate summary-level data and conducting similar simulations, which yielded consistent results (Figures S3 and S4).

To investigate the impact of the number of SNPs (Figure 4; Table S3) on the causal effect estimates, we first conducted a thorough exploration by varying the number of SNPs while maintaining other parameters at their initial settings. The simulation results indicated that an increase in the number of SNPs leads to greater precision and greater test power in the causal effect estimates derived from the TEMR analysis. While other methods also demonstrated improvements with more SNPs, the enhancement was not as pronounced as that observed with TEMR.

Additionally, we explored the causal effect estimates using TEMR when there was a negative genetic correlation between ethnic groups. The results indicated that precision and statistical power significantly improved as the absolute value of the genetic correlation increased, which was consistent with the aforementioned findings (Figures S5 and S6; Table S4).

Subsequently, we considered the case of multiple auxiliary populations, taking three auxiliary populations and one target population as an example, assuming uniform causal effects across different populations. In the absence of horizontal pleiotropy, TEMR produced nearly unbiased estimates of causal effects. The precision and statistical power of the TEMR analysis also increased as ρ_β increased; when $\rho_\beta \geq 0.4$, the precision and power of TEMR surpassed those of the other methods (Figure 5A). Specifically, when $\rho_\beta = 0.6$, there was a notable decrease in the standard error of approximately 15%–20% and an increase in the power of approximately 20%. At a higher ρ_β, the standard error decreased by up to 50%, while the power improved by 40% (Figure 5C). Furthermore, TEMR exhibited stable type I errors, which were unaffected by variations in ρ_β (Figure 5B). In cases involving horizontal pleiotropy, we obtained results consistent with our previous findings (Figure S7; Table S5). We also obtained consistent results

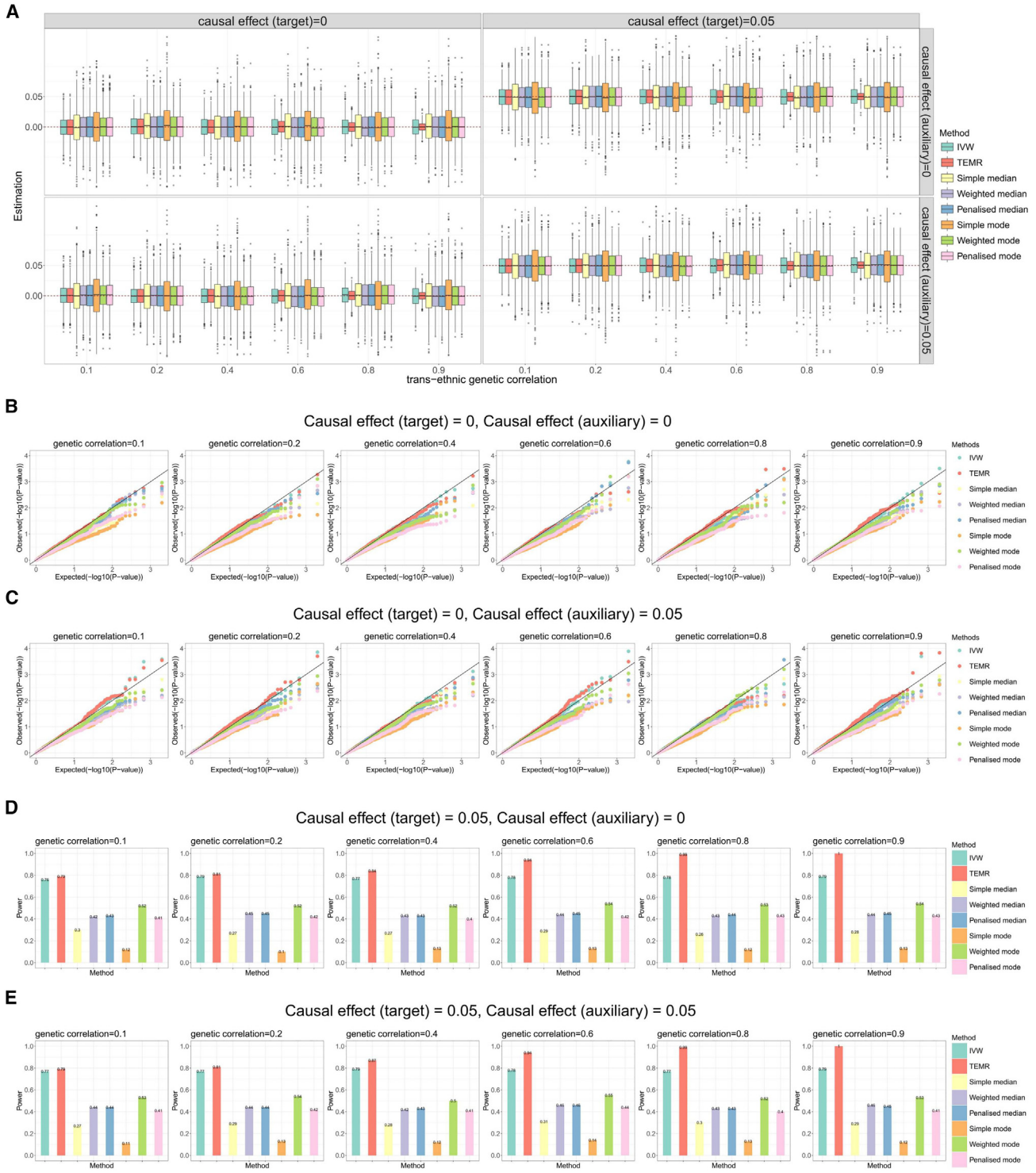

Figure 2. Simulation results for causal effect estimation in the target population when there is one auxiliary population (no pleiotropy)

(A) Boxplots show the performances of causal effect estimation in the target population.

(B and C) Q-Q plots show the performances of type I error rates of zero causal effect estimation in the target population when the causal effects of the auxiliary population are 0 and 0.05, respectively.

(D and E) Bar chart plots show the performances of statistical power of non-zero causal effect estimation in the target population when the causal effects of the auxiliary population are 0 and 0.05, respectively. IVW, inverse-variance weighted method.

when the genetic correlations were negative (Figures S8 and S9; Table S6). Moreover, compared to having only one auxiliary population, the precision (standard error) of the causal effect estimate obtained from three auxiliary populations also improved with the increase in genetic correlations, with an improvement of approximately 15% when

Table 1. Empirical coverage of 95% confidence intervals for causal effect estimation

β_1	β_2	ρ_β	IVW	TEMR	Simple median	Weighted median	Penalized median	Simple mode	Weighted mode	Penalized mode
0	0	0.1	0.958	0.952	0.979	0.979	0.968	0.989	0.962	0.970
0	0	0.2	0.954	0.946	0.976	0.976	0.962	0.983	0.962	0.975
0	0	0.4	0.953	0.944	0.979	0.979	0.966	0.980	0.967	0.985
0	0	0.6	0.955	0.946	0.975	0.975	0.965	0.987	0.968	0.977
0	0	0.8	0.963	0.932	0.976	0.976	0.970	0.985	0.975	0.984
0	0	0.9	0.963	0.934	0.975	0.975	0.962	0.985	0.960	0.980
0	0.05	0.1	0.951	0.938	0.974	0.974	0.965	0.981	0.959	0.980
0	0.05	0.2	0.946	0.946	0.978	0.978	0.967	0.984	0.956	0.983
0	0.05	0.4	0.957	0.942	0.977	0.977	0.966	0.981	0.962	0.974
0	0.05	0.6	0.954	0.954	0.975	0.975	0.968	0.977	0.964	0.985
0	0.05	0.8	0.963	0.926	0.984	0.984	0.960	0.980	0.956	0.977
0	0.05	0.9	0.948	0.922	0.977	0.977	0.962	0.984	0.963	0.981
0.05	0	0.1	0.950	0.926	0.980	0.980	0.970	0.981	0.961	0.976
0.05	0	0.2	0.963	0.938	0.985	0.985	0.967	0.988	0.964	0.983
0.05	0	0.4	0.958	0.932	0.980	0.980	0.962	0.982	0.970	0.983
0.05	0	0.6	0.961	0.952	0.966	0.966	0.973	0.987	0.971	0.986
0.05	0	0.8	0.951	0.926	0.980	0.980	0.963	0.995	0.965	0.979
0.05	0	0.9	0.954	0.928	0.973	0.973	0.964	0.983	0.960	0.978
0.05	0.05	0.1	0.954	0.940	0.970	0.970	0.964	0.987	0.962	0.979
0.05	0.05	0.2	0.957	0.946	0.980	0.980	0.959	0.980	0.969	0.979
0.05	0.05	0.4	0.964	0.944	0.976	0.976	0.969	0.987	0.964	0.982
0.05	0.05	0.6	0.944	0.946	0.985	0.985	0.973	0.991	0.971	0.984
0.05	0.05	0.8	0.950	0.936	0.976	0.976	0.963	0.981	0.966	0.984
0.05	0.05	0.9	0.953	0.935	0.977	0.977	0.966	0.988	0.965	0.982

$\rho_\beta = 0.9$. Furthermore, we also incorporated the scenario where the utilized SNPs exhibited weak IVs. The results indicated that when the target population comprised over 90% of weak IVs, the precision across all methods saw a marked increase. However, the TEMR demonstrated the decreasing variance of causal effect estimation, with its accuracy continuing to improve as ρ_β increased (Figure S10; Table S7).

Application

In this section, we applied TEMR to infer the causal relationships between different biomarkers and five diseases (hypertension, ischemic stroke, T2D, schizophrenia, and MDD) in the East Asian, African, and Hispanic/Latino populations, leveraging GWAS summary data from large European cohorts (Table S8). Initially, we identified 16 specific biomarkers that were significantly associated with at least 2 SNPs from a multitude of biomarkers. Then, we calculated the trans-ethnic genetic correlation for all pairs of biomarkers, and the results are shown in Figure 6 (Table S9). The results showed that there were trans-ethnic genetic correlations between the causal effects of all biomarkers and diseases in the four populations, which could be analyzed by TEMR. Among these, the absolute correlation coefficient of 19 pairs was 0.6 (total $16 \times 5 = 80$ pairs), which are shown in Figure 6.

Then, we performed TEMR and the other seven methods to explore the causal relationships between 16 biomarkers and five diseases. The results indicated that compared with the other seven methods, TEMR identified a greater number of biomarkers with significant causal associations with various outcomes (Figure 7). Among these, TEMR emerged as the method that identified the most significant biomarker pairs in target populations, with IVW following close behind (Table S10), and most of the significant biomarker pairs identified by the other methods were also detected by TEMR but with smaller p values. Notably, there were 5 significant relationships across different ethnic groups that were identified as significant in the TEMR analyses ($p < 0.000625$ [0.05/80]) but not identified in other MR methods: 3 causal relationships in East Asian and 2 causal relationships in Hispanic/Latino populations.

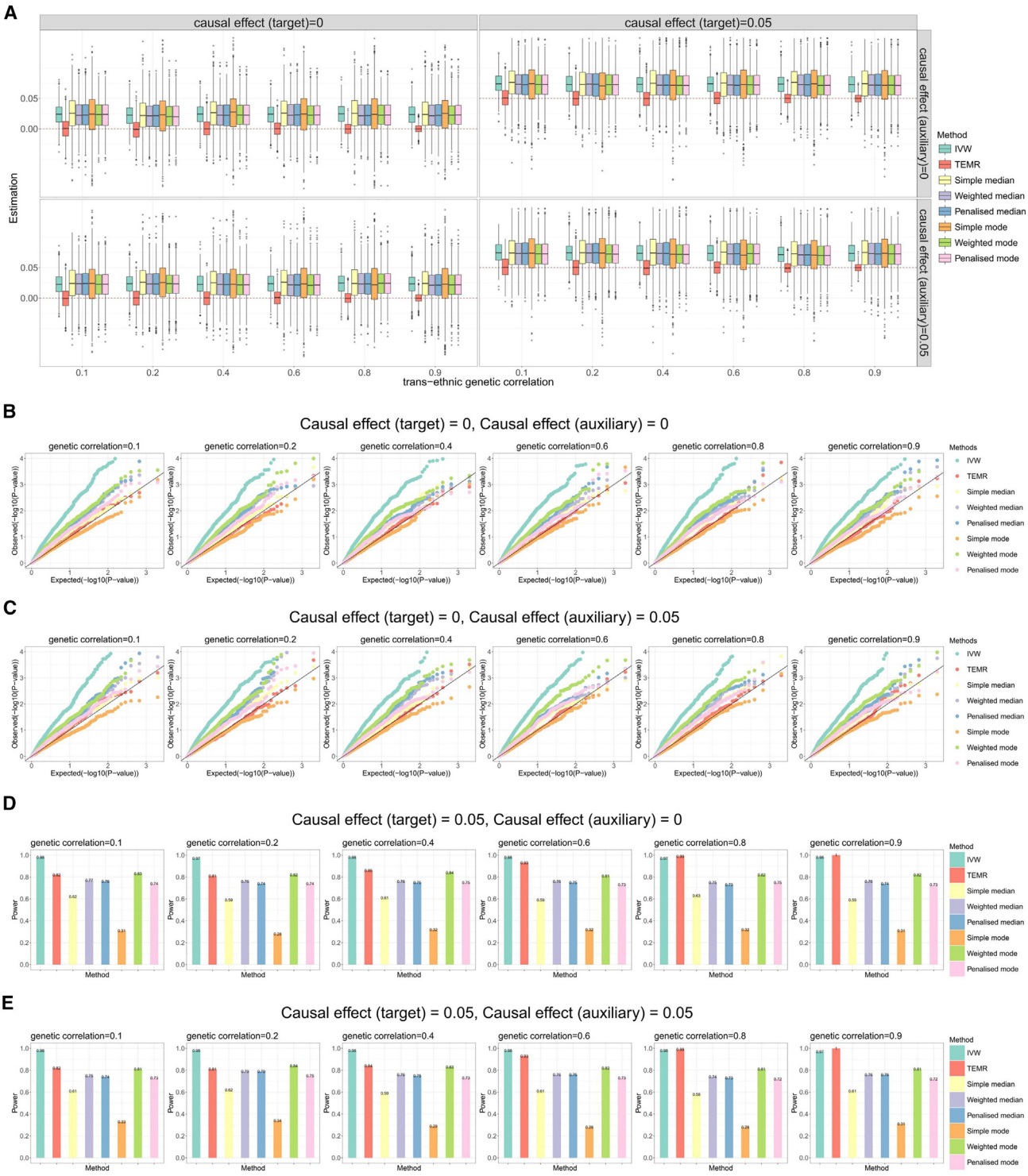

Figure 3. Simulation results for causal effect estimation in the target population when there is one auxiliary population (directional horizontal pleiotropy)

(A) Boxplots show the performances of causal effect estimation in the target population.

(B and C) Q-Q plots show the performances of type I error rates of zero causal effect estimation in the target population when the causal effects of the auxiliary population are 0 and 0.05, respectively.

(D and E) Bar chart plots show the performances of statistical power of non-zero causal effect estimation in the target population when the causal effects of the auxiliary population are 0 and 0.05, respectively. IVW, inverse-variance weighted method.

If we relax the threshold ($p < 0.05$), there were 17 relationships across different ethnic groups that were identified as significant in the TEMR analyses but not identified in other MR methods: 8 causal relationships in East Asian, 4 causal relationships in African, and 5 causal relationships in Hispanic/Latino populations.

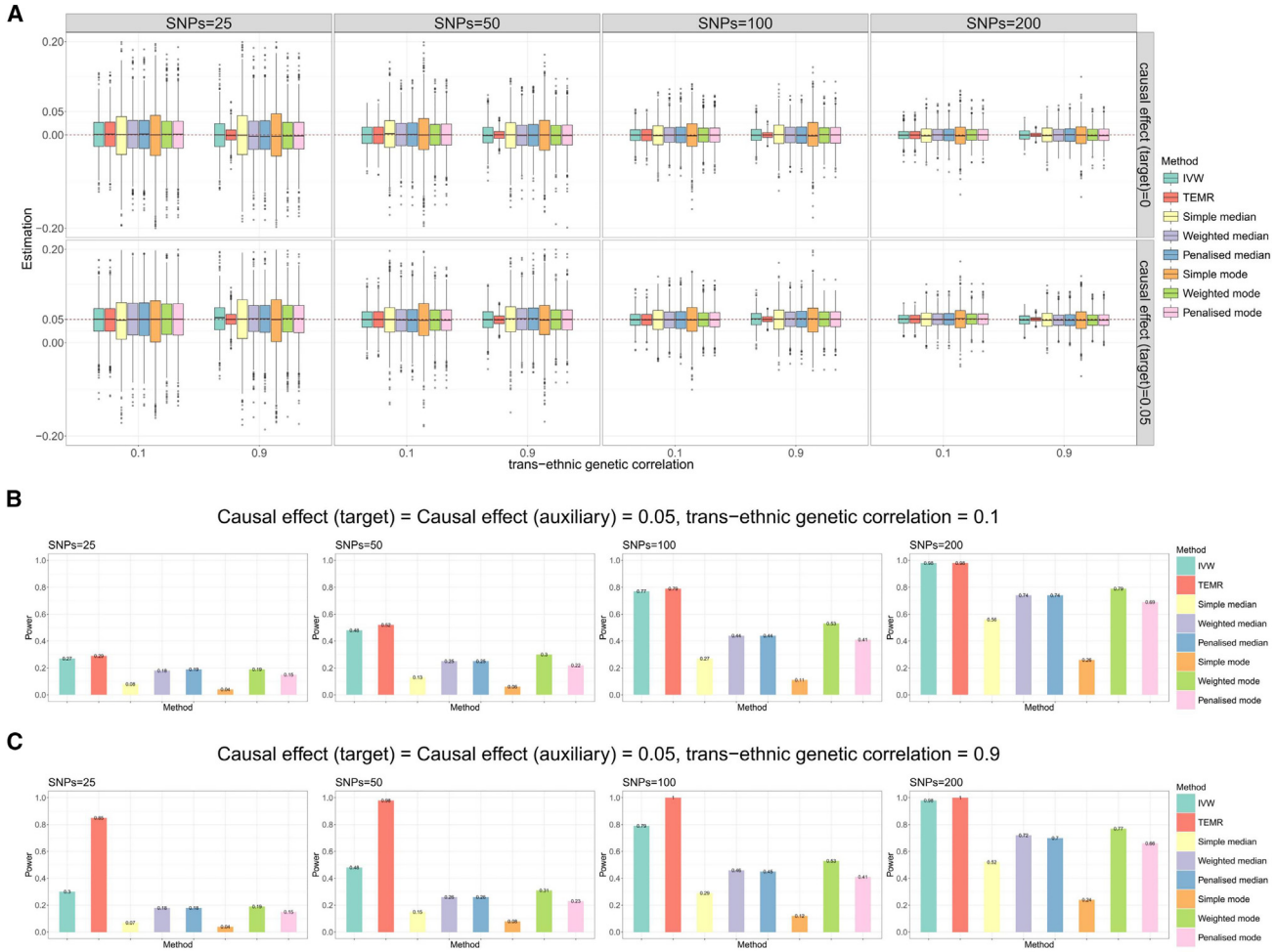

Figure 4. Simulation results for causal effect estimation in the target population with different numbers of SNPs
(A) Boxplots show the performances of causal effect estimation in the target population.
(B and C) Bar chart plots show the performances of statistical power of non-zero causal effect estimation in the target population. IVW, inverse-variance weighted method.

Firstly, for hypertension, the TEMR has revealed that a 1 SD increase of the basophil count (10^9 cells/L) was associated with a 0.26-fold decrease in the risk of hypertension in the East Asian population (odds ratio [*OR*] = 0.26; Table S11), and for every 1 SD mmol/L increase in glucose, the risk of hypertension increased by 2.16 times in the Hispanic/Latino population (*OR* = 2.16; Table S13). The physiological role of basophils in immune responses remains somewhat of an enigma despite being observed for many years, with some studies reporting that basophils have a negative regulatory effect in immune responses.[46,47] However, in recent years, multiple studies have suggested that higher basophil counts may also serve a protective role in the risk of developing various diseases. Lind et al. have suggested that in the European population, the higher basophil counts in patients with narcolepsy may represent a positive response of the immune system to narcolepsy. Liang et al. demonstrated that the basophil count in patients with systemic lupus erythematosus was significantly lower than that in healthy controls.[48–50] Basophils may contribute to the maintenance of vascular health by influencing the tone and function of blood vessels, and a balanced basophil count may aid in the healthy functioning of the vasculature. Fasting glucose is a standard measure for diabetes. Insulin resistance, common in diabetes, can lead to high blood pressure by increasing kidney's sodium retention, activating the nervous system, changing ion transport, and causing blood vessel wall thickening.[51,52] A retrospective cohort study from Japan has shown that higher fasting blood glucose was an independent risk factor for the development of hypertension.[53]

Next, for ischemic stroke, the TEMR found that DBP was a risk factor, that is, an increase of 1 SD mmHg in DBP resulted in a 2.06-fold increase in the risk of disease in East Asian population (*OR* = 2.06; Table S11) and a 1.06-fold increase in the Hispanic/Latino population (*OR* = 1.06; Table S13). Higher height (*OR* = 0.91; Table S11) and mean corpuscular hemoglobin (*OR* = 0.92; Table S11) were protected factors of ischemic stroke in East Asians. A 1 SD increase of triglyceride (10^9 cells/L) was associated with a 2.19-fold increase in the risk of ischemic stroke in the African population (*OR* = 2.19; Table S12). Elevated

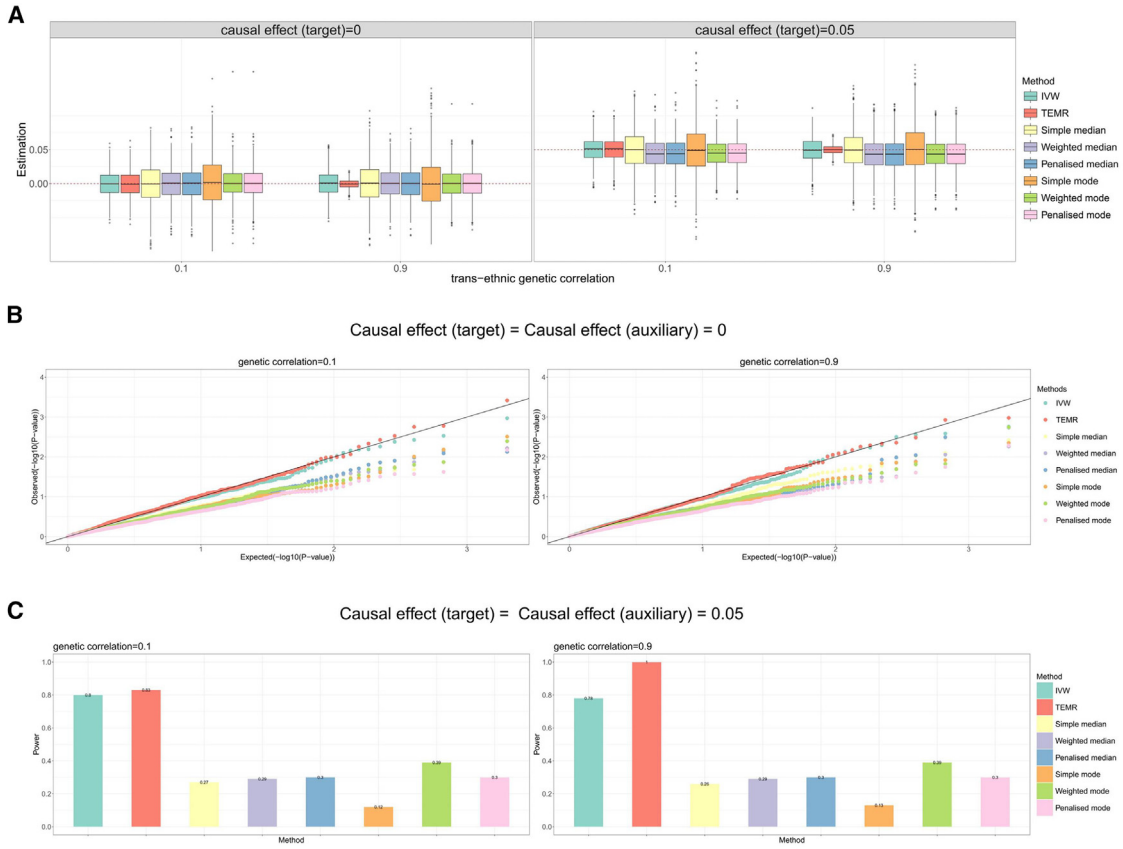

Figure 5. Simulation results for causal effect estimation in the target population when there are multiple auxiliary populations
(A) Boxplots show the performances of causal effect estimation in the target population.
(B) Q-Q plots show the performances of type I error rates of zero causal effect estimation in the target population.
(C) Bar chart plots show the performances of statistical power of non-zero causal effect estimation in the target population. IVW, inverse-variance weighted method.

DBP increases the stress on the blood vessel walls, which may lead to alterations in hemodynamics and, consequently, heighten the risk of thrombus formation.[54] Numerous studies in the European population have demonstrated a clear association between hypertension and the occurrence of ischemic stroke, highlighting the importance of blood pressure control in stroke prevention strategies.[54–56] Krieg et al. found that increased body height was negatively associated with coronary heart disease in Europeans.[57] A European cohort study indicated that elevated hemoglobin was also associated with increased mortality for ischemic stroke.[58] The Copenhagen City Heart Study found that the incidence of ischemic stroke increased with increasing levels of nonfasting triglycerides,[59] and this also supported the result of TEMR.

Additionally, with each 1 SD mmHg increase in DBP, the risk of MDD decreased by 44% in East Asian ($OR = 0.56$) and 43% in African ($OR = 0.57$) populations, while an increase of 1 SD mmol/L in TC led to a 1.25-fold increase in the risk of MDD ($OR = 1.25$) in the African population, and for every 1 SD mmol/L increase in glucose, the risk of MDD increased by a factor of 1.35 ($OR = 1.35$) in the East Asian population. Besides, for every 1 SD increase in neutrophil count (10^9 cells/L), the risk of schizophrenia increased by a factor of 1.91 in the Hispanic/Latino population ($OR = 1.91$; Tables S11–S13). For DBP, its protective role in MDD might be related to better cerebrovascular health, as adequate blood pressure is crucial for maintaining proper brain perfusion and oxygenation, which are essential for emotional regulation and mood stabilization.[60] Cholesterol is essential to axonal functioning and myelin formation in the central nervous system.[61] Coupled with biological plausibility, lipid profile disturbances have been reported in patients with MDD in the European population.[62,63] Elevated glucose concentrations are commonly linked to insulin resistance, a condition that can precipitate neurochemical imbalances within the brain. Specifically, it can disrupt the homeostatic equilibrium of key neurotransmitters, including glutamate and γ-aminobutyric acid (GABA), which play pivotal roles in the modulation of affect.[64,65] As the relationship between neutrophil count and the risk of developing schizophrenia is complex and not fully understood, some studies have suggested that increased neutrophil activity may be associated with a reduced risk of the disease, potentially due to its role in modulating inflammatory responses.[66,67]

Finally, for T2D, with each 1 SD increase in platelet count (10^9 cells/L), the risk of T2D decreases by 32% in East Asian

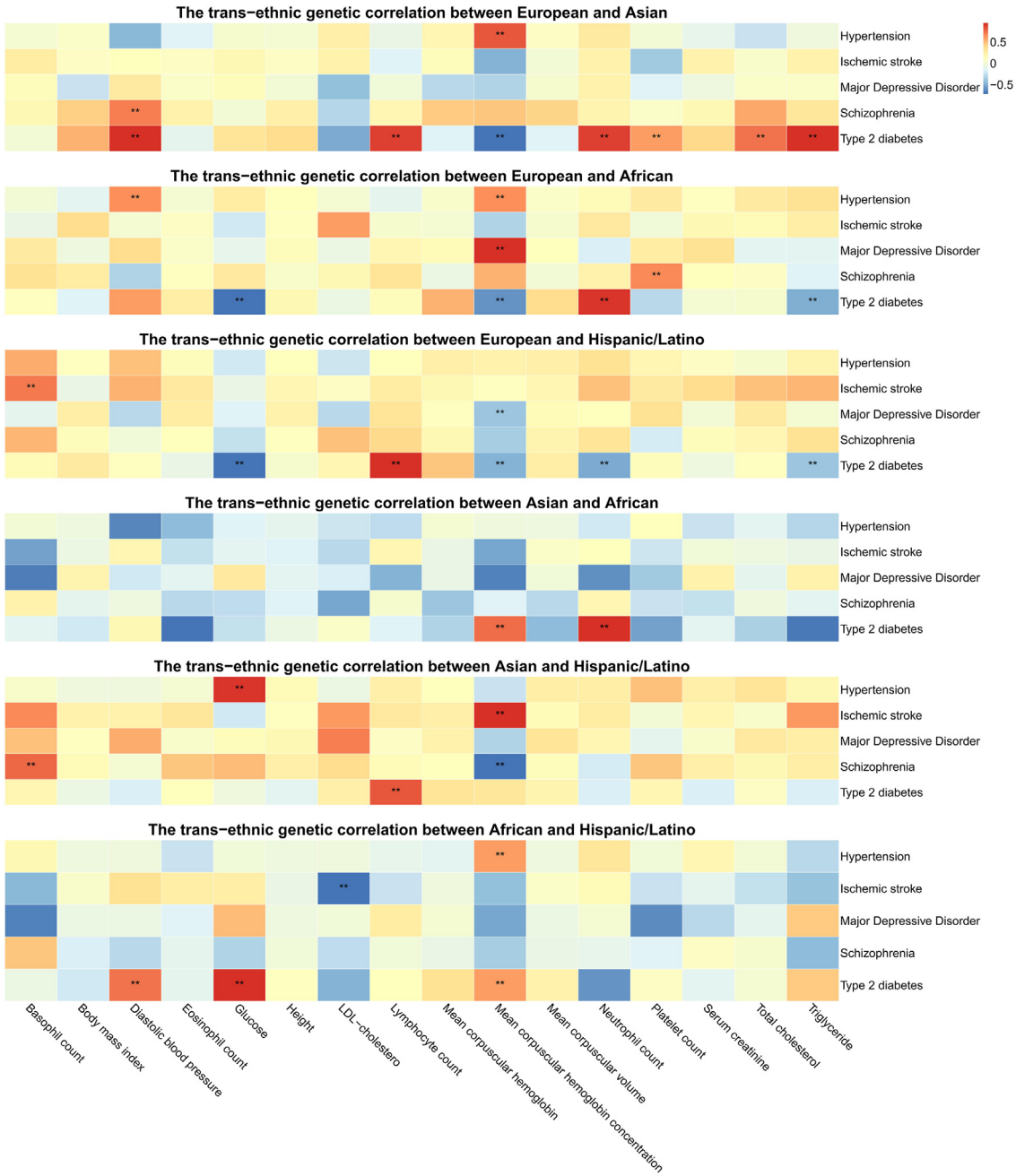

Figure 6. Heatmap of trans-ethnic genetic correlation for 16 biomarkers and four diseases

The color intensity indicates the strength of the correlation. Warmer colors, tending toward red, signify a correlation coefficient approaching 1, indicating a strong positive correlation. Conversely, cooler colors, leaning toward blue, denote a correlation coefficient nearing −1, suggesting a strong negative correlation. **$|\rho_\beta| > 0.6$.

($OR = 0.68$; Table S11) and 2% in Hispanic/Latino ($OR = 0.98$; Table S13) populations, an increase of each 1 SD in lymphocyte count (10^9 cells/L) leads to a 0.47-fold decrease of T2D risk in the Hispanic/Latino population ($OR = 0.47$; Table S13), and each 1 SD increase in mean corpuscular hemoglobin concentration (MCHC) (g/dL) leads to a 2.35-fold increase of T2D risk in the African population ($OR = 2.35$; Table S12), while BMI was considered as a risk factor in the East Asian population ($OR = 2.16$; Table S11). The protective role of platelet count might be related to the way platelets interact with insulin resistance and inflammation, which are key players in the pathogenesis of T2D. A study from Saudi Arabia indicated that, compared to the control group, the mean platelet volume in patients with T2D was significantly reduced.[68] Benjamin er al. found that increased MPV in Europeans was significantly associated with diabetes.[69] The causal relationship between lymphocyte count and T2D could be linked to the immune system's ability to modulate inflammation, which is crucial in maintaining glucose homeostasis.[70] Several lymphocyte subtypes were

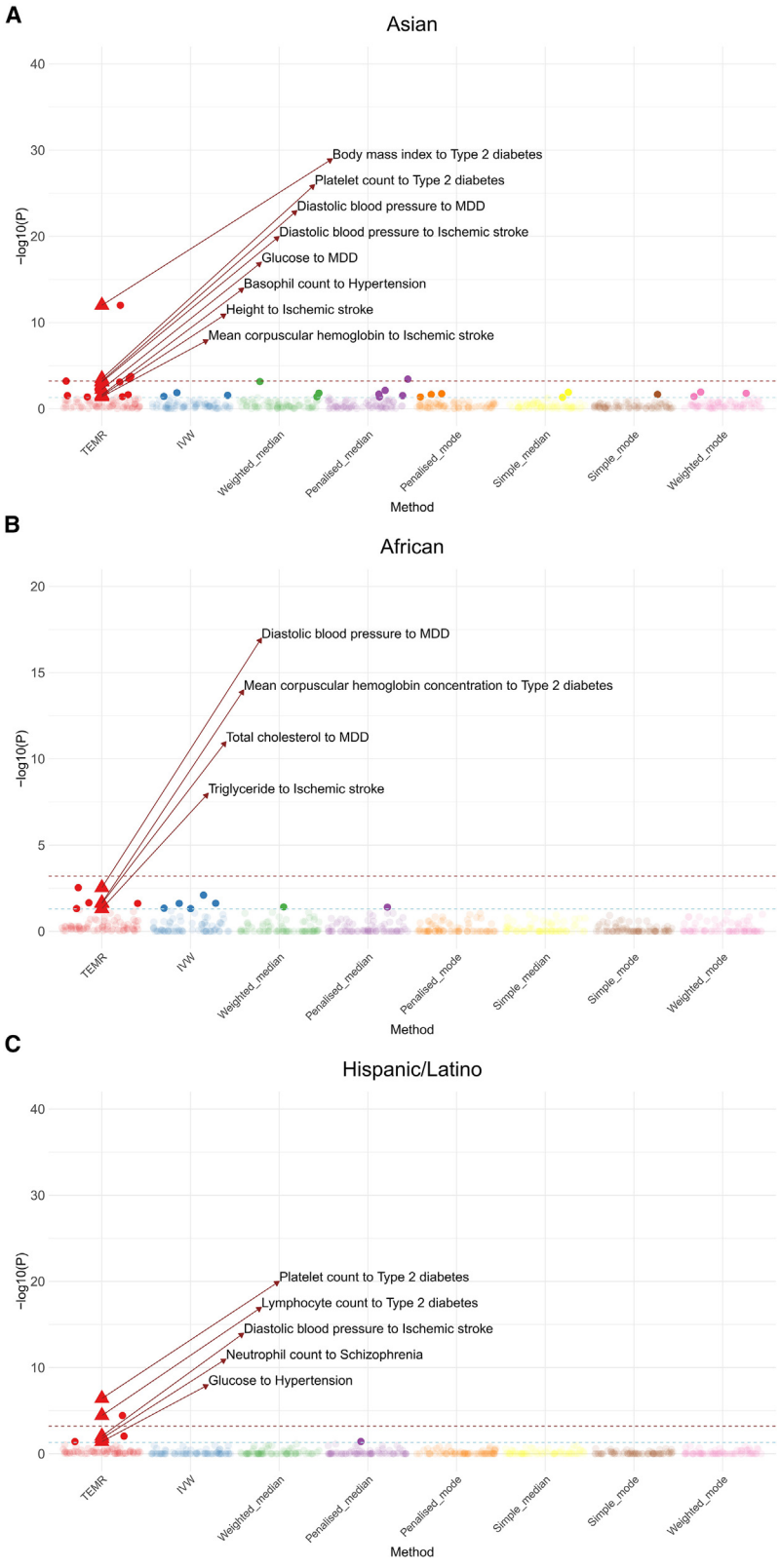

Figure 7. Results of trans-ethnic MR analysis for causal relationships from 16 biomarkers to four diseases

Different colors represent the $-\log_{10}(p)$ calculated by different methods. The triangle points represent the relationships that are significant in TEMR results but not significant in other methods. The solid or dashed points indicate whether the causal effects are significant ($p < 0.05$). In cases where the MR-Egger test suggests the presence of horizontal pleiotropy between biomarker pairs, the p values presented are those adjusted for such pleiotropy.

Discussion

In this paper, we propose a trans-ethnic MR method, TEMR, to improve the statistical power and estimation accuracy of MR in the target population using only trans-ethnic large-scale GWAS summary datasets. TEMR showed superior precision and power for causal effect estimation in the target population relative to other published MR methods in the simulation study. Leveraging biobank-scale GWAS summary data from Europeans, the inference of causal relationships between concentrations of 16 blood biomarkers and the risk of developing five diseases in East Asian, African, and Hispanic populations revealed 17 causal relationships that were not found using previously published MR methods.

TEMR bridges the causal effects of multiple ethnicities using a trans-ethnic genetic correlation coefficient. With the increase in trans-ethnic genetic associations, the statistical power of causal effects in the non-European population is significantly improved. Trans-ethnic genetic correlation measures the extent to which genetic variants influence phenotypes similarly across different populations. With the advent of genomic technologies, researchers were able to conduct GWASs of large cohorts from different ethnicities. These studies revealed that while there is substantial genetic variation between different populations, certain variants have similar frequencies and effects across groups. Numerous studies have shown that the genetic variants for many traits are highly correlated across different populations. Trans-ethnic genetic correlation is assessed using various methods, such as multi-ancestry GWAS, TWAS, and PRS prediction, and can be estimated by numerous methods, including LD score regression,[59] HDL,[76] GCTA-GREML,[77]

found to associated with the risk of T2D in Europeans.[71] The relationships of MCHC and T2D were not significant in the study based on Europeans.[72] Many studies have demonstrated that BMI was a risk factor for T2D in different populations.[73–75]

BOLT-REML,[78] and PAINTOR.[79] These methods can achieve much greater accuracy than Z score-based methods. In this paper, TEMR was conducted using a simple Z score method to obtain results quickly, and using these methods will improve the performance of TEMR. TEMR is suitable for traits with high genetic associations between different ethnicities. When the genetic association between traits is nearly zero, the TEMR method yields results similar to those obtained with traditional MR.

There are several limitations in our study. The impact of pleiotropy is an important topic in MR studies. Here, we consider the case of no pleiotropy or horizontal pleiotropy. For the latter, we proposed a two-step process to remove the pleiotropy effect from the traditional Wald ratio using MR-Egger regression, obtaining the TEMR-Wald ratio estimation. The limitation of this process is that it also requires the InSIDE assumption to be met, and the influence of correlated pleiotropy cannot be eliminated. An available solution is to detect outliers using published methods such as radial MR and MR-PRESSO and then remove them before conducting TEMR. In addition, when the data are obtained from people with multiple ethnicities, TEMR can improve the statistical power of causal effect estimation only in one target population, leveraging other target populations and the European population. In the future, we will extend TEMR to improve the statistical power of causal effect estimation in multiple target populations, leveraging only the European population. The degree of improvement in statistical power is closely related to the number of IVs and the magnitude of trans-ethnic genetic correlations.

In application, we use the GWAS summary statistics of Africans from the UKB. In general, there are (both genetic and environmental) differences between individuals of African ancestry living in developed countries (such as the UKB sample) and individuals living in Africa. Therefore, our results are restricted to the African population in the UKB but not to all African individuals, especially when we take African ancestry as the target population. When the African ancestry is the auxiliary population, regardless of which country the African population is from, TEMR can improve the statistical power of causal effect estimation in other target populations. In addition, all of the 17 associations identified by TEMR had previously been observed in either observational, cohort or MR studies based on Europeans. The results reveal that some relationships are only significant in one or two ancestries but not significant in other ancestries. This may be because the auxiliary datasets could not provide enough statistical power for TEMR to detect these relationships or due to genetic and environmental differences among ancestries that modify the causal associations between biomarkers and diseases.

In conclusion, we proposed a trans-ethnic MR method, TEMR, to improve the statistical power and estimation accuracy of MR in the target population using only a trans-ethnic large-scale GWAS summary dataset. This study has important guiding significance for the discovery of new disease-related factors.

Data and code availability

The GWAS summary data in the UKB are publicly available at UK Biobank: http://www.nealelab.is/uk-biobank. The GWAS summary data in BBJ are publicly available at BBJ: https://pheweb.jp/. The GWAS summary data in Pan-UKB are publicly available at Pan-UKB: https://pan.ukbb.broadinstitute.org/. Other GWAS summary data are publicly available at the IEU OpenGWAS project: https://gwas.mrcieu.ac.uk/ and GWAS Catalog: https://www.ebi.ac.uk/gwas/. All the analyses in our article were implemented by R software (v.4.3.2). R packages used in our analysis include *TwoSampleMR*, *MendelianRandomization*, *ggplot2*, *plinkbinr*, and *ieugwasr*. The TEMR package can be implemented by GitHub: https://github.com/hhoulei/TEMR. All the codes for simulation are uploaded in GitHub: https://github.com/hhoulei/TEMR_Simul.

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Author contributions

H.L. and F.X. conceived the study. L.H. contributed to the theoretical derivation with assistance from Z.Y. S.W. contributed to the data simulation. L.H. and S.W. contributed to the application. L.H. and S.W. wrote the manuscript with input from all other authors. All authors reviewed and approved the final manuscript.

Declaration of interests

The authors declare no competing interests.

Supplemental information

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