Supplementary Materials

A novel random effect model for GWAS meta-analysis and its application to trans-ethnic meta-analysis

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1 Kernel Matrix K for Trans-Ethnic Meta-Analysis

In Section 2.3, we proposed two choices of $\mathbf{K}$ for trans-ethnic meta-analysis. In this section, we provide more details including their general structures. Suppose that the first n_1 studies belong to the first ancestry group, then followed by another n_2 belong to the second ancestry group, and so on. $n_1 + n_2 + \ldots + n_p = n$ is the total number of studies. Let A_t denote a set of indices for the studies in the t_{th} ancestry group, $t = 1, \ldots, p$. Corresponding to the way we arrange the input data, $A_1 = \{1, \ldots, n_1\}, A_2 = \{n_1+1, \ldots, n_1+n_2\}, \ldots, A_p = \{n_1+\ldots+n_{p-1}+1, \ldots, n_1+\ldots+n_{p-1}+n_p\}$. Using those notations, we propose two choices for $\mathbf{K}$, which can be summarized as follows:

Choice 1. Group-wise independent kernel structure

Define each entry of the $\mathbf{K}$ matrix as

$$K_{ij} = \begin{cases} 1 & \text{if } i, j \in A_t \text{ for some t} \in \{1, \ldots, p\} \\ 0 & \text{otherwise} \end{cases},$$

where $i, j \in \{1, \ldots, n\}$. The $\mathbf{K}$ matrix can be written as

$$\mathbf{K} = \left(\begin{array}{ccc|ccc|c|ccc} 1 & \dots & 1 & 0 & \dots & 0 & & 0 & \dots & 0 \\ & \vdots & & & \vdots & & \ddots & & \vdots & \\ 1 & \dots & 1 & 0 & \dots & 0 & & 0 & \dots & 0 \\ \hline 0 & \dots & 0 & 1 & \dots & 1 & & 0 & \dots & 0 \\ & \vdots & & & \vdots & & \ddots & & \vdots & \\ 0 & \dots & 0 & 1 & \dots & 1 & & 0 & \dots & 0 \\ \hline & \ddots & & & \ddots & & \ddots & & \ddots & \\ \hline 0 & \dots & 0 & 0 & \dots & 0 & \dots & 1 & \dots & 1 \\ & \vdots & & & \vdots & & \vdots & & \vdots & \\ 0 & \dots & 0 & 0 & \dots & 0 & \dots & 1 & \dots & 1 \end{array}\right)$$

2. Genetic similarity (F_{st}) kernel structure

Define each entry of the $\mathbf{K}$ matrix as

$$K_{ij} = 1 - \frac{F_{st_{tt'}}}{D}, \quad \text{with } D = \max_{t,t' \in \{1,\dots,p\}} \{F_{st_{tt'}}\},$$

where $i \in A_t$ for some $t \in \{1,\dots,p\}$, $j \in A_{t'}$ for some $t^{'} \in \{1,\dots,p\}$, and $F_{st_{tt'}}$ is the pairwise F_{st} between ancestry group t and $t^{'}$. Since $F_{st_{tt'}} \leq D, \forall\ t$ and $t^{'}$, as a consequence, $0 \leq K_{ij} \leq 1, \forall\ i$ and j. In general, the $\mathbf{K}$ matrix under this assumption can be written as

$$\mathbf{K} = \left(\begin{array}{ccc|ccc|c|ccc} 1 & \dots & 1 & 1-\frac{F_{st_{12}}}{D} & \dots & 1-\frac{F_{st_{12}}}{D} & & 1-\frac{F_{st_{1p}}}{D} & \dots & 1-\frac{F_{st_{1p}}}{D} \\ & \vdots & & & \vdots & & \ddots & & \vdots & \\ 1 & \dots & 1 & 1-\frac{F_{st_{12}}}{D} & \dots & 1-\frac{F_{st_{12}}}{D} & & 1-\frac{F_{st_{1p}}}{D} & \dots & 1-\frac{F_{st_{1p}}}{D} \\ \hline 1-\frac{F_{st_{21}}}{D} & \dots & 1-\frac{F_{st_{21}}}{D} & 1 & \dots & 1 & & 1-\frac{F_{st_{2p}}}{D} & \dots & 1-\frac{F_{st_{2p}}}{D} \\ & \vdots & & & \vdots & & \ddots & & \vdots & \\ 1-\frac{F_{st_{21}}}{D} & \dots & 1-\frac{F_{st_{21}}}{D} & 1 & \dots & 1 & & 1-\frac{F_{st_{2p}}}{D} & \dots & 1-\frac{F_{st_{2p}}}{D} \\ \hline & \ddots & & & \ddots & & \ddots & & \ddots & \\ \hline 1-\frac{F_{st_{p1}}}{D} & \dots & 1-\frac{F_{st_{p1}}}{D} & 1-\frac{F_{st_{p2}}}{D} & \dots & 1-\frac{F_{st_{p2}}}{D} & & 1 & \dots & 1 \\ & \vdots & & & \vdots & & \ddots & & \vdots & \\ 1-\frac{F_{st_{p1}}}{D} & \dots & 1-\frac{F_{st_{p1}}}{D} & 1-\frac{F_{st_{p2}}}{D} & \dots & 1-\frac{F_{st_{p2}}}{D} & & 1 & \dots & 1 \end{array}\right)$$

2 Derivation of the Hypothesis Test

After calculating the test statistic T, the next step is to obtain the corresponding p-value for assessing the association evidence. If we had just used the minimum p-value (which is denoted as our test statistic T) to assess significance, we would ignore the multiple comparisons between different p_ρ values, which would result in inflated type I error control. Thus, we derived the asymptotic distribution of T to obtain its p-value, details provided as follows:

Recall that the score test statistics can be written as:

$$S_\rho = (1-\rho)\widehat{\boldsymbol{\beta}}^{'}\widehat{\Sigma}^{-1}\mathbf{K}\widehat{\Sigma}^{-1}\widehat{\boldsymbol{\beta}} + \rho\widehat{\boldsymbol{\beta}}^{'}\widehat{\Sigma}^{-1}\mathbf{1}\mathbf{1}^{'}\widehat{\Sigma}^{-1}\widehat{\boldsymbol{\beta}}. \tag{1}$$

And for any given ρ, the null distribution of S_ρ can be closely approximated by

$$\sum_{j=1}^{n}\lambda_j\chi^2_{1,j}, \tag{2}$$

where $(\lambda_1,\ldots,\lambda_n)$ are the eigenvalues of $\widehat{\Sigma}^{-1/2}V_\rho\widehat{\Sigma}^{-1/2}$, and $\{\chi^2_{1,j}\}$ are independent χ^2_1 random variables.

Let $\mathbf{Z} = \widehat{\Sigma}^{-1/2}\mathbf{1}$ and $\mathbf{M} = \mathbf{Z}(\mathbf{Z}^{'}\mathbf{Z})^{-1}\mathbf{Z}^{'}$, then $\mathbf{M}$ is a projection matrix onto the space spanned by $\mathbf{Z}$. In addition, define $\mathbf{u} = \widehat{\Sigma}^{-1/2}\widehat{\boldsymbol{\beta}}$. Based on those notations, the first term of the right side of (1) can be written as:

$$\begin{aligned}
(1-\rho)\widehat{\boldsymbol{\beta}}^{'}\widehat{\Sigma}^{-1}\mathbf{K}\widehat{\Sigma}^{-1}\widehat{\boldsymbol{\beta}} &= (1-\rho)\mathbf{u}^{'}\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}\mathbf{u} \\
&= (1-\rho)\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\mathbf{u} \qquad (3)\\
&+ 2(1-\rho)\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}\mathbf{M}\mathbf{u} \qquad (4)\\
&+ (1-\rho)\mathbf{u}^{'}\mathbf{M}\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}\mathbf{M}\mathbf{u}, \qquad (5)
\end{aligned}$$

and the second term of the right side of (1) can be written as:

$$\begin{aligned}
\rho\widehat{\boldsymbol{\beta}}^{'}\widehat{\Sigma}^{-1}\mathbf{1}\mathbf{1}^{'}\widehat{\Sigma}^{-1}\widehat{\boldsymbol{\beta}} &= \rho\mathbf{u}^{'}\widehat{\Sigma}^{-1/2}\mathbf{1}\mathbf{1}^{'}\widehat{\Sigma}^{-1/2}\mathbf{u} \\
&= \rho\mathbf{u}^{'}\mathbf{M}\mathbf{Z}\mathbf{Z}^{'}\mathbf{M}\mathbf{u}. \qquad (6)
\end{aligned}$$

Following the derivation as in Lee et al. (2012), it can be easily shown that $(3)+(4) = (1-\rho)\kappa$

and $(5)+(6)=\tau(\rho)\eta_0$, where

$$\begin{aligned}
\kappa &= \mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\mathbf{u} \\
&+ 2\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}\mathbf{M}\mathbf{u}, \\
\tau(\rho) &= [a^2b(1-\rho)+\rho]/a. \\
\text{with} \quad a &= (\mathbf{Z}^{'}\mathbf{Z})^{-1},\ b=\mathbf{Z}^{'}\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}\mathbf{Z},\ \text{and}\ \eta_0=(\mathbf{Z}^{'}\mathbf{Z})^{-1}\mathbf{u}^{'}\mathbf{Z}\mathbf{Z}^{'}\mathbf{u}.
\end{aligned}$$

As a result, we have $S_\rho=(1-\rho)\kappa+\tau(\rho)\eta_0$.

The asymptotic distribution of S_ρ can be approximated as $(1-\rho)(\sum_{k=1}^{m}\lambda_k^{'}\eta_k+\zeta)+\tau(\rho)\eta_0$, since under the null, each elements of $\mathbf{u}$ has mean 0 and variance 1, $\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\mathbf{u}$ asymptotically follows $\sum_{k=1}^{m}\lambda_k^{'}\eta_k$, where $\{\lambda_1^{'},\ldots,\lambda_m^{'}\}$ are non-zero eigenvalues of $(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})$, η_ks are iid χ_1^2 random variables, $\eta_0=(\mathbf{Z}^{'}\mathbf{Z})^{-1}\mathbf{u}^{'}\mathbf{Z}\mathbf{Z}^{'}\mathbf{u}$ asymptotically follows χ_1^2 distribution. Furthermore, since $\mathbf{M}$ is a projection matrix, $(\mathbf{I}-\mathbf{M})\mathbf{u}$ and $\mathbf{M}\mathbf{u}$ are asymptotically independent. Therefore, $\zeta=2\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}\mathbf{M}\mathbf{u}$ satisfies the following conditions:

$$\begin{aligned}
E(\zeta) &= 0, \quad var(\zeta)=4trace(\widehat{\Sigma}^{-1/2}\mathbf{M}\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}), \\
corr(\eta_0,\zeta) &= 0, \quad \text{and} \quad corr(\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\mathbf{u},\zeta)=0
\end{aligned}$$

In addition, by asymptotic independence between $(\mathbf{I}-\mathbf{M})\mathbf{u}$ and $\mathbf{M}\mathbf{u}$, it can be shown that $\mathbf{u}^{'}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\mathbf{u}$ and $(\mathbf{Z}^{'}\mathbf{Z})^{-1}\mathbf{u}^{'}\mathbf{Z}\mathbf{Z}^{'}\mathbf{u}$ are also asymptotically independent. Since the Pearson correlation between κ and η_0 is zero, we can approximate S_ρ as the mixture of two independent variables. We can approximate the distribution of κ by using the moment matching or characteristic function inversion method (Davis, 1980) after adjusting for the extra variance term of ζ.

To estimate the distribution of $T=\min\{p_{\rho_1},\ldots,p_{\rho_b}\}$, let $q_{\min}(\rho)$ denote the $(1-T)$th percentile of the distribution of S_ρ for each ρ in the grid search. The p-value of T is

$$\begin{aligned}
1 &- P(S_{\rho_1}<q_{\min}(\rho_1),\ldots,S_{\rho_b}<q_{\min}(\rho_b)) \\
=1 &- E[P(\kappa<\min\{(q_{\min}(\rho_v)-\tau(\rho_v)\eta_0)/(1-\rho_v)\})|\eta_0], \qquad (7)
\end{aligned}$$

which can be obtained by one-dimensional numerical integration.

To sum up, our proposed method can be implemented through the following algorithm:

Step 1: Set a grid $0\le\rho_1\le\rho_2\le\ldots\le\rho_b\le 1$.

Step 2: Compute $S_{\rho_1},\ldots,S_{\rho_b}$ using equation (1).

Step 3: Compute $\mathbf{Z}$, $\mathbf{M}$, $\lambda_k^{'}$s, $\tau(\rho_i)$, and

$$\mu_S = \sum_{k=1}^{m} \lambda_k^{'}, \quad \sigma_\zeta = 2\sqrt{trace(\widehat{\Sigma}^{-1/2}\mathbf{M}\widehat{\Sigma}^{-1/2}\mathbf{K}\widehat{\Sigma}^{-1/2}(\mathbf{I}-\mathbf{M})\widehat{\Sigma}^{-1/2}\mathbf{K})}, \quad \text{and} \quad \sigma_S = \sqrt{2\sum_{k=1}^{m}(\lambda_k^{'})^2 + \sigma_\zeta^2}$$

Step 4: For each $\rho_i, i \in \{1,\ldots,b\}$, calculate p_{ρ_i} using equation (2), $T = \min\{p_{\rho_1},\ldots,p_{\rho_b}\}$ and $q_{min}(\rho_i)$

Step 5: Numerically integrate $F(\delta(x)|\lambda)f(x|\chi_1^2)$, where

$$\delta(x) = (\min\{(q_{min}(\rho_i) - \tau(\rho_i)x)/(1-\rho_v)\} - \mu_S)\frac{\sqrt{\sigma_S^2 - \sigma_\zeta^2}}{\sigma_S} + \mu_S,$$

$f(x|\chi_1^2)$ is the density function of χ_1^2, and $F(\delta(x)|\lambda)$ is a distribution function of a mixture of chi-square distribution $\sum \lambda_k^{'}\chi_k^2$. The p-value is found as

$$p - value = 1 - \int F(\delta(x)|\lambda)f(x|\chi_1^2)dx.$$

3 Using Z-scores instead of Effect-size Estimates

Based on p-values (p_i), sample sizes (n_i) and direction of effects (Δ_i), we can construct a signed Z-score $Z_i = \Phi^{-1}(1-p_i/2) * sign(\Delta_i)$ for each study, where $\Phi(\cdot)$ is the standard normal distribution function. Now we show how to transform the Z-scores as input data for our proposed method.

3.1 Continuous Traits

For continuous traits, the linear regression model can be written as

$$y_{ik} = \beta_0 + \beta_i g_{ik} + \epsilon_{ik},$$

where y_{ik} is a trait value of study i individual k, g_{ik} is a minor allele count, and $\epsilon_{ik} \sim N(0,\omega_i^2)$ is the error term. Let us denote $\boldsymbol{x}_{ik} = (1, g_{ik})$ and $\mathbf{X}_i = (\boldsymbol{x}_{i1},\ldots,\boldsymbol{x}_{in_i})^{'}$. Then the estimator of β_i follows the normal distribution

$$\widehat{\beta_i} \sim N(\beta_i, \sigma_i^2),$$

where $\sigma_i^2 = \omega_i^2(\mathbf{X}_i^{'}\mathbf{X}_i)_{2,2}^{-1}$ and $(\mathbf{X}_i^{'}\mathbf{X}_i)_{2,2}^{-1}$ is the (2,2) element of $(\mathbf{X}_i^{'}\mathbf{X}_i)^{-1}$. The two side p-value is $p_i = 1 - 2\Phi(|\widehat{\beta_i}/\sigma_i|)$, and thus the Z-score Z_i follows $N(\beta_i/\sigma_i, 1)$. This result implies that we

can reconstruct $\widehat{\beta}_i$ using a Z-score by estimating σ_i^2. Since

$$(\mathbf{X}_i^{'}\mathbf{X}_i)^{-1} = \frac{1}{n_i \sum_{k=1}^{n_i} g_{ik}^2 - (\sum_{k=1}^{n_i} g_{ik})^2} \begin{pmatrix} \sum_{k=1}^{n_i} g_{ik}^2 & -\sum_{k=1}^{n_i} g_{ik} \\ -\sum_{k=1}^{n_i} g_{ik} & n_i \end{pmatrix},$$

we then have under the Hardy-Weinberg equilibrium

$$\frac{n_i \omega_i^2}{n_i \sum_{k=1}^{n_i} g_{ik}^2 - (\sum_{k=1}^{n_i} g_{ik})^2} \approx \frac{\omega_i^2}{n_i 2q_i(1-q_i)},$$

where q_i is a minor allele frequency (MAF) for the corresponding queried SNP. As a result, under the Hardy-Weinberg equilibrium $\widehat{\beta}_i$ is equivalent to $\sqrt{\frac{\omega_i^2}{n_i 2q_i(1-q_i)}} Z_i$. With an additional assumption that the variance of error term (ω_i^2) are the same across studies, we can use

$$\tilde{\beta}_i = Z_i / \sqrt{n_i q_i (1-q_i)}$$

and its standard error

$$\tilde{\sigma}_i = 1 / \sqrt{n_i q_i (1-q_i)}$$

as inputs for our proposed method.

3.2 Binary Traits

For binary traits, the logistic regression model can be written as

$$logit Pr(y_{ik} = 1) = \beta_0 + \beta_i g_{ik}.$$

Asymptotically, $var(\widehat{\boldsymbol{\beta}}_i) = J^{-1}(\boldsymbol{\beta}_i)$, where $J(\boldsymbol{\beta}_i) = \sum_{k=1}^{n_i} \boldsymbol{x}_{ik} \boldsymbol{x}_{ik}^{'} \mu_{ik}(1-\mu_{ik})$, and $\mu_{ik} = \frac{\exp(\boldsymbol{\beta}_i^{'} \boldsymbol{x}_{ik})}{1+\exp(\boldsymbol{\beta}_i^{'} \boldsymbol{x}_{ik})}$. Since

$$\boldsymbol{x}_{ik} \boldsymbol{x}_{ik}^{'} = \begin{pmatrix} 1 & g_{ik} \\ g_{ik} & g_{ik}^2 \end{pmatrix},$$

we then have

$$J(\boldsymbol{\beta}_i) = \sum_{k=1}^{n_i} \frac{\exp(\boldsymbol{\beta}_i^{'} \boldsymbol{x}_{ik})}{[1+\exp(\boldsymbol{\beta}_i^{'} \boldsymbol{x}_{ik})]^2} \begin{pmatrix} 1 & g_{ik} \\ g_{ik} & g_{ik}^2 \end{pmatrix}.$$

If we use $r_i = n_{case,i}/n_i$ to denote the proportion of case samples for study i and assume that its effect size β_i is very small, then $\frac{\exp(\boldsymbol{\beta}_i^{'} \boldsymbol{x}_{ik})}{[1+\exp(\boldsymbol{\beta}_i^{'} \boldsymbol{x}_{ik})]^2} \approx r_i(1-r_i)$ for any $k \in \{1, \ldots, n_i\}$, and $J(\boldsymbol{\beta}_i)$ reduces to

$$J(\boldsymbol{\beta}_i) = r_i(1-r_i) \sum_{k=1}^{n_i} \begin{pmatrix} 1 & g_{ik} \\ g_{ik} & g_{ik}^2 \end{pmatrix} = r_i(1-r_i) \begin{pmatrix} n_i & \sum g_{ik} \\ \sum g_{ik} & \sum g_{ik}^2 \end{pmatrix}.$$

The remaining derivations then follow the same calculation as in the continuous traits case. As a result, for binary traits, the log odds ratio estimate $\widehat{\beta}_i$ is asymptotically equivalent to $Z_i/\sqrt{n_i r_i(1-r_i)q_i(1-q_i)}$. If all studies have similar ratios of cases and controls, the $r_i(1-r_i)$ term can be ignored. Therefore,

$$\tilde{\beta}_i = Z_i/\sqrt{n_i q_i(1-q_i)}$$

and its standard error

$$\tilde{\sigma}_i = 1/\sqrt{n_i q_i(1-q_i)}$$

can be used as inputs for both continuous and binary traits.

4 Estimation of Bayes factor thresholds corresponding to genome-wide p-value significance levels

We carried out 20 million null simulations for MANTRA to find Bayes factor thresholds corresponding to genome-wide p-value significance levels. Following our type I error simulations as in Section 3.1.1, each simulated dataset had 27 studies (9 ancestry groups in triplicate) and each study had 500 cases and 500 controls. We then applied MANTRA to those 20 million nulls to obtain Bayes factors, and calculated the empirical type I error rates as the proportion of Bayes factors (out of the 20 million) that were greater than a given Bayes factor threshold. When we used log10 Bayes factor = 5 as a threshold, the empirical type I error rate was 1.8×10^{-6} with the exact binomial confidence interval $(1.25 \times 10^{-6}, 2.4 \times 10^{-6})$. Supplementary Figure 1 plots the obtained empirical type I error rates (illustrated in -log10(empirical type I error rate) on the vertical axis) and the Bayes factors (illustrated in log10(Bayes' factor) on the horizontal axis).

Due to our limited computing resources, it would take us months to run MANTRA on billions of null simulations that are required to find a comparable Bayes factor threshold to the commonly used genome-wide significance level ($\alpha = 5 \times 10^{-8}$); therefore, we performed a regression analysis between the Bayes factor thresholds and the empirical type I error rates. We obtained the empirical type I error rates for a sequence of Bayes factor thresholds and fitted a linear regression model using -log10(Empirical type I error rate) as a response variable and the log10 Bayes' factor threshold as a predictor. The obtained regression intercept and slope are were 1.08577 (p-value $< 2 \times 10^{-16}$) and 0.98106 (p-value $< 2 \times 10^{-16}$) respectively. Based on those regression parameters, we estimated the Bayes factor threshold (on the log10 base) that corresponds to the genome-wide significance level as 6.34. We note that the estimated significance level from this linear model that corresponds to log10 Bayes factor = 5 was $\alpha = 1.0 \times 10^{-6}$, which is slightly lower than the observed significance level 1.8×10^{-6}. We employed both $\alpha = 1.8 \times 10^{-6}$ and 1.0×10^{-6} to the power simulations and found that the results were very similar (data not

shown).

To sum up, we defined the level of significance as a p-value less than 1.8×10^{-6}, or as a log10 Bayes factor larger than 5. We also employed the significance level as a p-value less than 5×10^{-8} or as a log10 Bayes factor larger than 6.34.

5 Supplementary Tables and Figures

Supplementary Table 1: Type-I error rate estimates at different α levels based on 100 million replicates. Each entry represents an estimated type I error rate calculated using the proportion of p-values smaller than the given level α. One integrated study was simulated per ancestry group, and each study had 1500 cases and 1500 controls.

	$\alpha = 10^{-2}$	10^{-3}	10^{-4}	10^{-5}	10^{-6}
TransMeta.Fst	1.051×10^{-2}	1.1×10^{-3}	1.079×10^{-4}	1.1×10^{-5}	1.05×10^{-6}
TransMeta.Indep	1.008×10^{-2}	0.9×10^{-3}	8.589×10^{-5}	7.4×10^{-6}	9.0×10^{-7}

Supplementary Table 2: Pairwise F_{st} values used for the T2D meta-analysis. The F_{st} values were extracted from Supplementary Table 6 of International HapMap 3 Consortium. (2010). Integrating common and rare genetic variation in diverse human populations. *Nature*, **467(7311)**, 52-58.

Ancestry	European	east Asian	south Asian	Mexican and Mexican-American
European	0	0.111	0.035	0.031
east Asian	0.111	0	0.077	0.070
south Asian	0.035	0.077	0	0.035
Mexican and Mexican-American	0.031	0.070	0.035	0

Supplementary Table 3: P-values and Bayes' factors of the six meta-analysis methods for the 24 SNPs with TransMeta.Fst p-value $< 5 \times 10^{-8}$ among the 69 SNPs from the T2D trans-ethnic meta-analysis data. Values in the parenthesis are the optimal ρ values for our proposed method. Values in the last column are the I^2 statistic for measuring the heterogeneity level.

SNP	F.ST (ρ)	INDEP(ρ)	FE	RE	RE-HE	Bayes	I^2
rs7903146	6.17e-77 (0.00)	3.59e-84 (0.25)	6.44e-75	2.89e-07	3.55e-76	74.13	0.83
rs10811661	4.42e-27 (1.00)	4.42e-27 (1.00)	1.11e-27	1.28e-24	2.74e-27	25.36	0.10
rs7756992	4.04e-26 (0.25)	3.57e-31 (0.25)	3.39e-26	2.19e-04	1.88e-27	24.87	0.81
rs3802177	6.55e-19 (0.09)	2.10e-19 (0.25)	1.61e-18	1.61e-18	3.39e-18	16.27	0
rs1111875	1.12e-18 (1.00)	1.33e-20 (0.25)	2.80e-19	2.49e-05	3.29e-19	17.12	0.65
rs4402960	5.51e-18 (0.25)	4.22e-18 (0.25)	7.50e-18	1.54e-17	1.55e-17	15.52	0.01
rs163184	4.12e-14 (1.00)	2.63e-14 (0.25)	1.03e-14	4.80e-07	1.64e-14	12.41	0.55
rs9936385	3.32e-12 (0.25)	9.15e-13 (0.25)	9.65e-13	3.01e-10	1.67e-12	10.63	0.11
rs7178572	5.70e-11 (0.25)	4.91e-11 (0.25)	1.47e-11	1.47e-11	2.45e-11	9.35	0
rs5215	1.25e-10 (1.00)	1.07e-10 (0.25)	3.12e-11	8.47e-05	3.24e-11	8.98	0.57
rs12571751	2.19e-10 (1.00)	2.43e-10 (1.00)	2.19e-10	2.19e-10	3.46e-10	8.22	0
rs1801282	3.86e-10 (1.00)	2.89e-10 (0.25)	4.24e-10	4.24e-10	6.41e-10	7.99	0
rs849135	3.88e-10 (0.00)	2.21e-10 (0.25)	1.06e-09	2.84e-03	1.07e-09	7.62	0.53
rs17791513	1.01e-09 (0.00)	1.11e-08 (0.09)	2.42e-08	4.71e-03	1.76e-08	6.60	0.65
rs4430796	1.06e-09 (1.00)	2.59e-09 (1.00)	1.16e-09	1.10e-07	1.71e-09	7.53	0.24
rs4458523	1.72e-09 (1.00)	1.79e-09 (1.00)	1.91e-09	1.91e-09	2.88e-09	7.32	0
rs11257655	2.06e-09 (1.00)	5.31e-09 (1.00)	1.92e-09	8.71e-04	2.22e-09	7.33	0.61
rs2943640	6.52e-09 (1.00)	6.63e-09 (1.00)	7.01e-09	7.01e-09	9.96e-09	6.73	0
rs7612463	8.25e-09 (1.00)	1.7e-08 (0.25)	6.28e-09	6.28e-09	9.21e-09	6.86	0
rs11717195	1.46e-08 (0.25)	3.17e-08 (1.00)	2.26e-08	2.26e-08	3.25e-08	6.20	0
rs4812829	2.09e-08 (0.00)	1.59e-08 (0.25)	4.21e-08	1.42e-04	5.98e-08	6.07	0.4
rs12970134	2.98e-08 (1.00)	4.79e-08 (1.00)	2.48e-08	2.48e-08	3.55e-08	6.06	0
rs10830963	2.98e-08 (0.25)	3.76e-08 (0.25)	1.99e-07	2.91e-03	2.48e-07	5.60	0.50
rs2261181	3.05e-08 (1.00)	7.51e-09 (0.25)	2.34e-08	1.31e-05	3.11e-08	6.24	0.27

Supplementary Table 4: Supplementary Table 3 continued: P-values and Bayes' factors of the six meta-analysis methods for the remaining 45 SNPs among the 69 SNPs from the T2D trans-ethnic meta-analysis data.

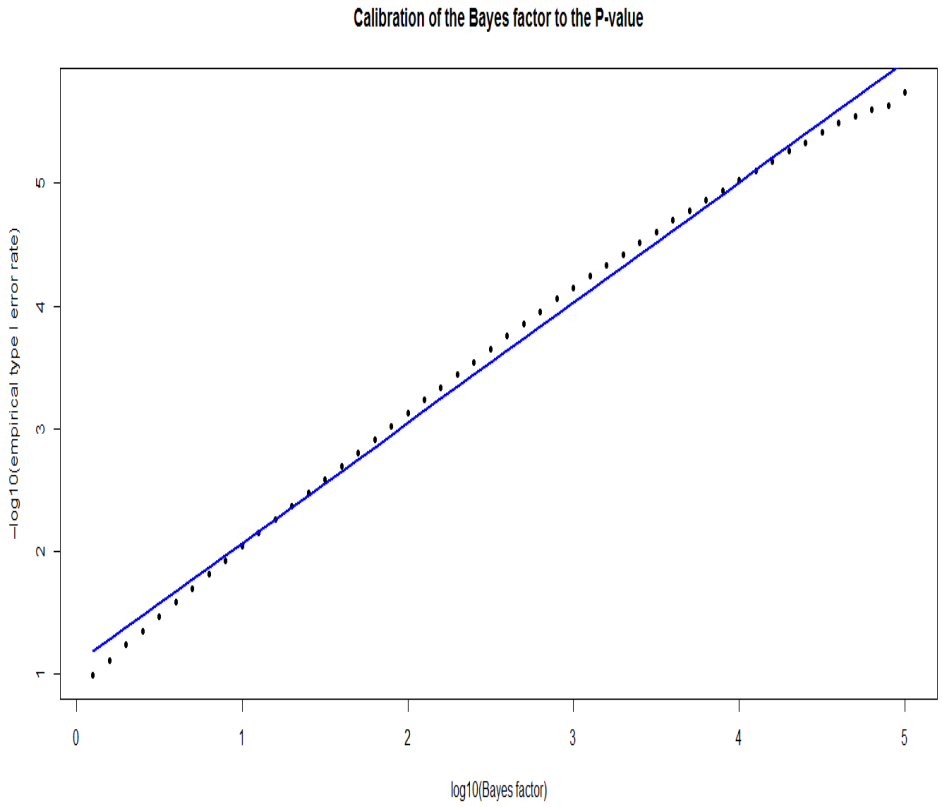
SNP	F.ST (ρ)	INDEP(ρ)	FE	RE	RE-HE	Bayes	I^2
rs7845219	6.56e-08 (1.00)	8.63e-08 (1.00)	5.84e-08	5.84e-08	8.57e-08	5.99	0
rs516946	6.57e-08 (0.09)	6.60e-08 (0.25)	1.11e-07	1.11e-07	1.63e-07	5.59	0
rs1552224	1.35e-07 (1.00)	7.71e-08 (0.25)	9.61e-08	2.11e-03	9.68e-08	5.81	0.63
rs17168486	3.86e-07 (1.00)	4.36e-07 (0.09)	3.74e-07	4.38e-03	3.65e-07	5.08	0.58
rs12899811	6.29e-07 (1.00)	1.40e-06 (1.00)	7.42e-07	2.05e-05	1.09e-06	4.74	0.16
rs2028299	6.48e-07 (1.00)	9.0e-07 (1.00)	7.741e-07	2.35e-04	9.09e-07	4.81	0.42
rs1535500	1.45e-06 (0.00)	1.53e-06 (0.25)	5.36e-06	1.13e-02	5.61e-06	4.10	0.52
rs3923113	1.96e-06 (0.25)	2.29e-06 (1.00)	2.31e-06	1.51e-02	5.47e-07	4.62	0.74
rs2796441	1.96e-06 (1.00)	2.43e-06 (1.00)	1.63e-06	1.63e-06	2.39e-06	4.42	0
rs2075423	2.03e-06 (1.00)	2.52e-06 (1.00)	2.17e-06	9.69e-04	3.17e-06	4.34	0.45
rs12427353	3.11e-06 (0.00)	3.13e-06 (0.25)	3.41e-06	3.41e-06	4.17e-06	4.14	0
rs243088	3.49e-06 (1.00)	3.56e-06 (0.25)	3.73e-06	3.73e-06	5.46e-06	4.25	0
rs7163757	4.76e-06 (1.00)	6.51e-06 (1.00)	4.14e-06	4.14e-06	6.04e-06	4.11	0
rs10842994	4.76e-06 (0.25)	6.92e-06 (1.00)	6.75e-06	6.75e-06	9.84e-06	3.93	0
rs8108269	4.98e-06 (1.00)	6.86e-06 (1.00)	4.60e-06	1.97e-03	6.71e-06	3.90	0.43
rs7041847	5.31e-06 (1.00)	7.21e-06 (1.00)	4.03e-06	4.12e-06	5.88e-06	4.20	0
rs11634397	6.29e-06 (0.00)	7.85e-06 (0.25)	1.60e-05	2.58e-03	2.16e-05	3.62	0.31
rs1359790	9.61e-06 (0.25)	2.46e-06 (0.25)	1.08e-05	8.73e-03	1.07e-05	3.60	0.47
rs780094	1.45e-05 (1.00)	1.62e-05 (1.00)	1.29e-05	2.76e-02	5.34e-06	3.81	0.75
rs10203174	3.29e-05 (0.00)	7.11e-06 (0.09)	7.28e-05	1.64e-01	4.99e-05	2.59	0.65
rs7955901	3.11e-05 (0.00)	1.62e-05 (0.00)	1.86e-03	3.68e-01	1.79e-04	2.15	0.76
rs6795735	3.59e-05 (0.00)	1.41e-04 (0.25)	2.00e-04	4.65e-03	2.80e-04	2.60	0.27
rs7593730	3.6e-05 (0.00)	1.13e-05 (0.00)	4.74e-04	1.89e-01	1.34e-04	2.41	0.68
rs7202877	4.32e-05 (0.00)	2.28e-04 (0.09)	5.53e-04	6.23e-02	2.09e-04	2.43	0.72
rs13233731	1.11e-04 (0.00)	1.97e-06 (0.00)	4.08e-03	3.42e-01	1.35e-05	3.90	0.85
rs16861329	2.68e-04 (0.00)	1.46e-05 (0.00)	5.06e-02	6.95e-01	1.01e-04	2.45	0.90
rs11063069	3.33e-04 (0.00)	4.02e-04 (0.25)	9.97e-04	3.87e-02	1.40e-03	1.78	0.25
rs3786897	3.83e-04 (1.00)	3.20e-04 (0.25)	3.34e-04	2.22e-01	1.45e-05	3.84	0.83
rs9470794	3.95e-04 (0.00)	2.61e-04 (0.09)	1.75e-03	3.48e-01	1.53e-03	1.81	0.68
rs6815464	4.39e-04 (0.00)	4.39e-04 (0.00)	NA	NA	NA	2.13	0
rs6878122	5.81e-04 (0.25)	3.23e-04 (0.25)	5.75e-04	1.36e-01	4.64e-05	2.23	0.82
rs1802295	6.97e-04 (0.00)	1.22e-03 (0.25)	1.10e-03	1.56e-01	1.95e-04	1.97	0.81
rs831571	6.84e-04 (1.00)	3.99e-04 (0.25)	5.26e-04	2.10e-01	4.56e-04	2.25	0.73
rs459193	1.06e-03 (1.00)	1.51e-03 (1.00)	8.20e-04	8.20e-04	1.15e-03	1.84	0
rs2334499	1.61e-03 (1.00)	1.64e-03 (0.25)	1.38e-03	1.38e-03	1.93e-03	1.69	0
rs10923931	3.03e-03 (0.00)	1.01e-03 (0.00)	7.10e-03	3.55e-01	8.61e-03	0.95	0.46
rs10401969	3.91e-03 (0.00)	3.35e-03 (0.09)	7.18e-03	1.62e-01	6.19e-03	1.15	0.68
rs6467136	6.72e-02 (0.00)	5.93e-02 (0.00)	2.14e-01	4.63e-01	1.80e-02	0.80	0.76
rs10278336	1.08e-01 (0.00)	1.21e-01 (0.09)	1.11e-01	1.73e-01	1.33e-01	0.11	0.16
rs7403531	1.54e-01 (0.25)	3.78e-02 (0.00)	1.28e-01	7.23e-01	6.81e-02	0.20	0.68
rs6723108	3.49e-01 (1.00)	4.30e-01 (1.00)	3.17e-01	3.17e-01	3.64e-01	-0.21	0
rs17584499	4.98e-01 (0.00)	4.63e-01 (0.00)	5.20e-01	5.62e-01	5.60e-01	-1.18	0.52
rs7560163	5.76e-01 (1.00)	6.06e-01 (1.00)	4.72e-01	4.72e-01	5.08e-01	-0.37	0
rs10886471	5.86e-01 (0.00)	6.45e-01 (0.00)	6.46e-01	6.46e-01	7.05e-01	-0.45	0
rs391300	8.42e-01 (1.00)	8.78e-01 (1.00)	7.40e-01	7.40e-01	7.90e-01	-0.55	0

Supplementary Table 5: Summary Table of the I^2 statistic for each of the 2000 SNPs in the five power comparison scenarios. In each cell of the table, we first present the median of the I^2 statistic for all the SNPs (out of 2000) whose optimal ρ value from TransMeta.Fst is as specified at beginning of the row, then we present the corresponding inter-quartile range (IQR) in the parenthesis.

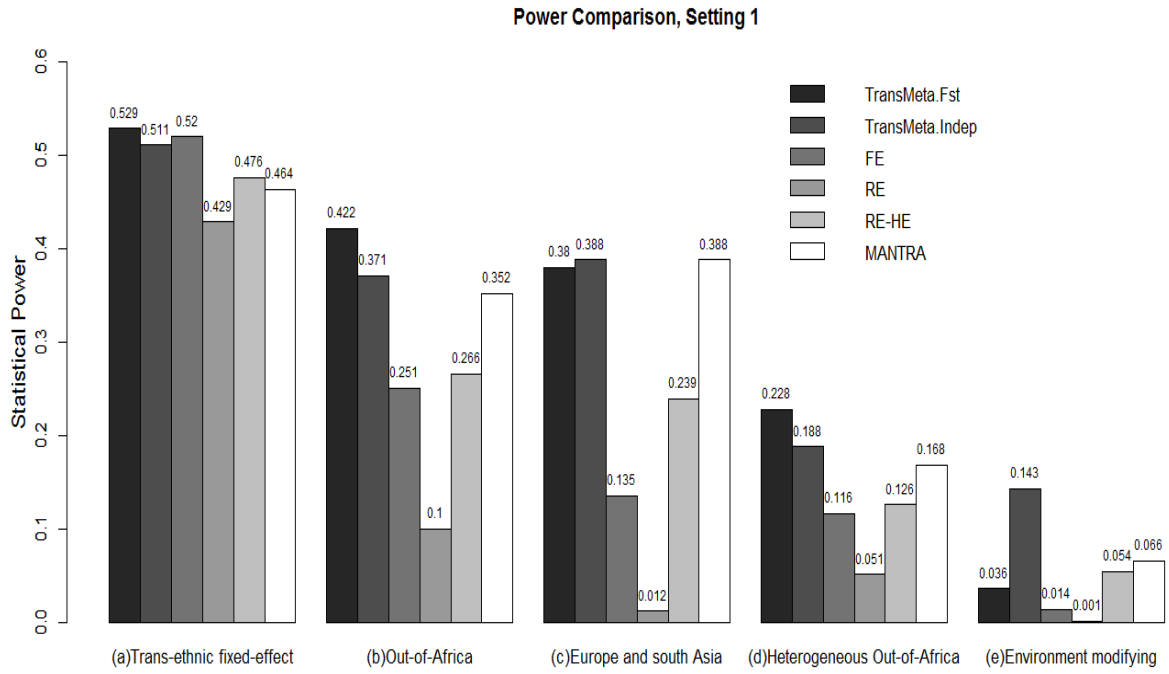
The optimal ρ value	Scenario (a)	Scenario (b)	Scenario (c)	Scenario (d)	Scenario (e)
$\rho = 0$	0.05 (0.28)	0.55 (0.27)	0.69 (0.17)	0.50 (0.29)	0.70 (0.17)
$\rho = 0.09$	0 (0.17)	0.39 (0.45)	0.65 (0.33)	0.21 (0.45)	0.64 (0.18)
$\rho = 0.25$	0 (0.11)	0.20 (0.51)	0.36 (0.38)	0.11 (0.36)	0.63 (0.23)
$\rho = 1$	0 (0.18)	0.03 (0.32)	0.27 (0.36)	0.12 (0.33)	0.53 (0.32)
Overall median (IQR)	0 (0.21)	0.52 (0.33)	0.68 (0.19)	0.45 (0.38)	0.67 (0.20)

Supplementary Table 6: Contingency Table of the selected optimal ρ value from TransMeta.Fst for each of the 2000 SNPs in the five power comparison scenarios. In each cell of the table, the entry represents the total number of SNPs (out of 2000) which has the selected optimal ρ value as listed at the beginning of the row under the scenario specified at the top of the column.

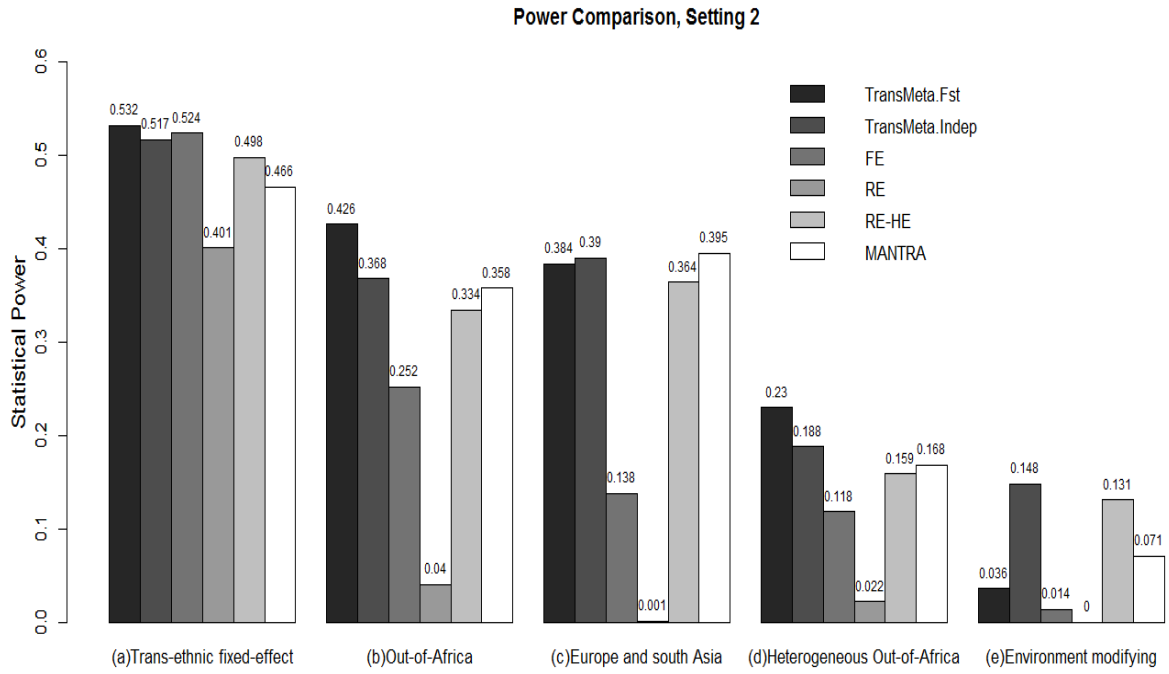
The optimal ρ value	Scenario (a)	Scenario (b)	Scenario (c)	Scenario (d)	Scenario (e)
$\rho = 0$	480	**1674**	**1864**	**1573**	**1385**
$\rho = 0.09$	309	136	58	120	109
$\rho = 0.25$	276	77	36	122	143
$\rho = 1$	**935**	113	142	185	363
Total counts	2000	2000	2000	2000	2000



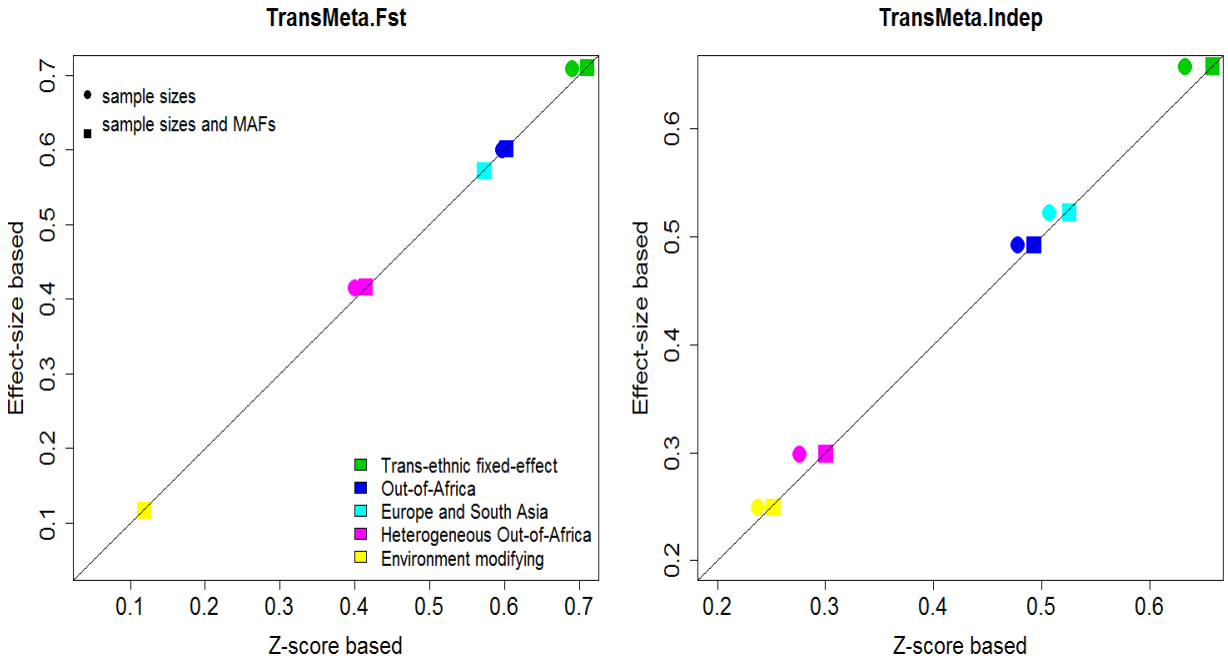
Supplementary Figure 1: Calibration of the Bayes' factor to the empirical type I error rate. The vertical axis measures the empirical type I error rate on a -log10 scale, the horizontal axis measures the Bayes' factor on a log10 scale. The blue straight represents the fitted regression line -log10(empirical type I error rate) = 1.08577 + 0.98106 $\times$ log10(Bayes' factor).



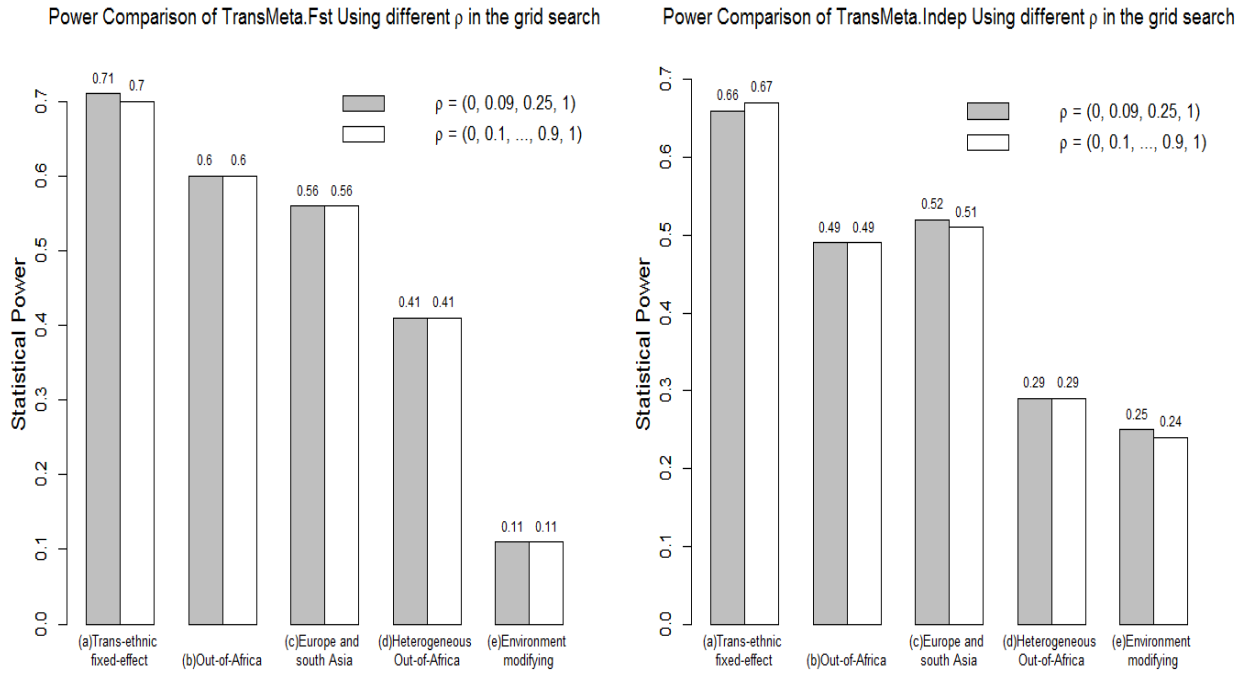
Supplementary Figure 2: Empirical power for TransMeta and existing methods under the five effect size scenarios. Three studies were simulated per ancestry group, each with 500 cases and 500 controls. The empirical power was obtained based on 2000 replicates with the level of significance defined as a p-value less than 5×10^{-8} or as a log10 Bayes' factor larger than 6.34. The five effect size scenarios are (a) 'Trans-ethnic fixed-effect', where no heterogeneity exists in allelic effects at the causal SNP between populations; (b) 'Out-of-Africa effect', where only studies from the non-African populations carry the causal variant; (c) 'Europe and south Asia effect', where only studies from the European and south Asian populations carry the causal variant; (d) 'Heterogeneous Out-of-Africa effect', where the causal variant has genetic effects only in non-African populations, but the effect size in the east Asian populations is different from that in the European and south Asian populations; (e) 'Environment modifying effect', where the causal variant has genetic effect only in the populations living in Europe and USA.



Supplementary Figure 3: Empirical power for TransMeta and existing methods under the five effect size scenarios. One integrated study was simulated per ancestry group, each with 1500 cases and 1500 controls. The empirical power was obtained based on 2000 replicates with the level of significance defined as a p-value less than 5×10^{-8} or as a log10 Bayes' factor larger than 6.34. The five effect size scenarios are (a) 'Trans-ethnic fixed-effect', where no heterogeneity exists in allelic effects at the causal SNP between populations; (b) 'Out-of-Africa effect', where only studies from the non-African populations carry the causal variant; (c) 'Europe and south Asia effect', where only studies from the European and south Asian populations carry the causal variant; (d) 'Heterogeneous Out-of-Africa effect', where the causal variant has genetic effects only in non-African populations, but the effect size in the east Asian populations is different from that in the European and south Asian populations; (e) 'Environment modifying effect', where the causal variant has genetic effect only in the populations living in Europe and USA.



Supplementary Figure 4: Power comparison of the effect-size and Z-score based TransMeta under the five effect size scenarios. One integrated study was simulated per ancestry group, each with 1500 cases and 1500 controls. The empirical power was obtained based on 2000 replicates with the level of significance defined as a p-value less than 1.8×10^{-6}. The left panel is based on TransMeta.Fst and the right panel is based on TransMeta.Indep. In each plot, the x-axis denotes empirical power of the Z-score based TransMeta and the y-axis denotes empirical power of the effect-size based TransMeta. The solid dots represent the power of transformed Z-scores using only sample sizes, and the solid squares represent transformed Z-scores using both sample sizes and MAFs.



Supplementary Figure 5: Comparison of the empirical power for TransMeta under the five effect size scenarios, using different grid searches for ρ . Three studies were simulated per ancestry group, each with 500 cases and 500 controls. The empirical power was obtained based on 2000 replicates with the level of significance defined as a p-value less than 1.8×10^{-6}. The two grids being compared are: $\rho = (0, 0.09, 0.25, 1)$ v.s $\rho = (0, 0.1, 0.2, \ldots, 0.8, 0.9, 1)$. The left panel is based on TransMeta.Fst and the right panel is based on TransMeta.Indep. The five effect size scenarios are (a) 'Trans-ethnic fixed-effect', where no heterogeneity exists in allelic effects at the causal SNP between populations; (b) 'Out-of-Africa effect', where only studies from the non-African populations carry the causal variant; (c) 'Europe and south Asia effect', where only studies from the European and south Asian populations carry the causal variant; (d) 'Heterogeneous Out-of-Africa effect', where the causal variant has genetic effects only in non-African populations, but the effect size in the east Asian populations is different from that in the European and south Asian populations; (e) 'Environment modifying effect', where the causal variant has genetic effect only in the populations living in Europe and USA.