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Causal effects on complex traits are similar for common variants across segments of different continental ancestries within admixed individuals

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Supplementary Information

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Supplementary Note

1 Alternative formulations of methods to estimate r_{admix}

Recall that we use the following model in deriving the default method

$$\mathbf{y} \sim \mathcal{N}(\mathbf{C}\boldsymbol{\alpha}, \sigma_g^2 \frac{\mathbf{G}_1\mathbf{G}_1^\top + \mathbf{G}_2\mathbf{G}_2^\top}{S} + \rho_g \frac{\mathbf{G}_1\mathbf{G}_2^\top + \mathbf{G}_2\mathbf{G}_1^\top}{S} + \sigma_e^2\mathbf{I}),$$

and we calculate profile likelihood of $r_{\text{admix}} = \frac{\rho_g}{\sigma_g^2} \in [-1, 1]$ to obtain the point estimate and credible interval (we omit the prior variance term $\mathcal{T}$ for simplicity). Here, we explore two alternative approaches to estimate r_{admix}:

- **Alternative method (1):** by directly optimizing and estimating σ_g^2 and ρ_g, without posing the constraint of $r_{\text{admix}} = \frac{\rho_g}{\sigma_g^2} \in [-1, 1]$. Parameter estimation can be performed by optimizing $\sigma_g^2, \rho_g, \sigma_e^2$ using the standard variance component estimation as implemented in GCTA.
- **Alternative method (2):** by relaxing the assumption that $\sigma_{g,1}^2 = \sigma_{g,2}^2$ across local ancestries, the above model becomes

  $$\mathbf{y} \sim \mathcal{N}(\mathbf{C}\boldsymbol{\alpha}, \sigma_{g,1}^2 \frac{\mathbf{G}_1\mathbf{G}_1^\top}{S} + \sigma_{g,2}^2 \frac{\mathbf{G}_2\mathbf{G}_2^\top}{S} + \rho_g \frac{\mathbf{G}_1\mathbf{G}_2^\top + \mathbf{G}_2\mathbf{G}_1^\top}{S} + \sigma_e^2\mathbf{I}).$$

  Here, r_{admix} can be defined as $r_{\text{admix}} = \frac{\rho_g}{\sqrt{\sigma_{g,1}^2\sigma_{g,2}^2}}$. Parameter estimation can be similarly performed by optimizing $\sigma_{g,1}^2, \sigma_{g,2}^2, \rho_g, \sigma_e^2$ using the standard variance component estimation.

We applied the alternative methods (1) and (2) to African-European admixed individuals in PAGE data and compared the results to our default method. First, comparing alternative method (1) and the default method, for traits with $r_{\text{admix}} < 1$ using the default method, results are consistent across method (1) and the default method; while for traits with $r_{\text{admix}} = 1$ using the default method, alternative method (1) produced estimated $r_{\text{admix}} > 1$ for some traits, which can be explained by sampling variance of r_{admix} (Extended Data Figure 5a). Second, results are overall consistent comparing alternative method (2) and the default method, while we note the estimates from alternative method (2) are consistently higher than those of the default method (Extended Data Figure 5b). In addition, we performed a likelihood ratio test of hypothesis of $H_0 : \sigma_{g,1}^2 = \sigma_{g,2}^2$ by comparing alternative method (1) and (2). Overall, we are unable to reject H_0 for any individual trait, indicating lack of the evidence for $\sigma_{g,1}^2 \neq \sigma_{g,2}^2$ for traits we analyzed, justifying the assumption of $\sigma_g^2 = \sigma_{g,1}^2 = \sigma_{g,2}^2$ in the default method (Supplementary Table 9).

2 Defining heritability in the model

Under the model described in Methods section, the heritability h_g^2 can be derived as a function of $\sigma_g^2, \rho_g, \sigma_e^2$ as general form of $h_g^2 := \frac{\text{Var}[\mathbf{G}_1\boldsymbol{\beta}_1+\mathbf{G}_2\boldsymbol{\beta}_2]}{\text{Var}[\mathbf{G}_1\boldsymbol{\beta}_1+\mathbf{G}_2\boldsymbol{\beta}_2]+\sigma_e^2}$. Assuming $r_{\text{admix}} = 1$, we have $\rho_g = \sigma_g^2$ and perfectly correlated $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$, we denote $\boldsymbol{\beta} = \boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$ as per-SNP effect sizes. Defining $\mathbf{G} = \mathbf{G}_1+\mathbf{G}_2$, h_g^2 can be written as $h_g^2 = \frac{\text{Var}[\mathbf{G}\boldsymbol{\beta}]}{\text{Var}[\mathbf{G}\boldsymbol{\beta}]+\sigma_e^2}$. Assuming genotype matrix $\mathbf{G}$ is centered for each SNP, $\text{Var}[\mathbf{G}\boldsymbol{\beta}] = \mathbb{E}[\frac{\boldsymbol{\beta}^\top\mathbf{G}^\top\mathbf{G}\boldsymbol{\beta}}{N}] = \mathbb{E}[\text{tr}[\frac{\boldsymbol{\beta}^\top\mathbf{G}^\top\mathbf{G}\boldsymbol{\beta}}{N}]] = \text{tr}[\mathbb{E}[\boldsymbol{\beta}\boldsymbol{\beta}^\top]\frac{\mathbf{G}^\top\mathbf{G}}{N}]$. Noting that s-th element of the diagonal matrix $\mathbb{E}[\boldsymbol{\beta}\boldsymbol{\beta}^\top]$ is $\frac{\tau_s^2\sigma_g^2}{S}$ and s-th element of $\frac{\mathbf{G}^\top\mathbf{G}}{N}$ diagonal is SNP variance $2f_s(1-f_s)$, $\text{Var}[\mathbf{G}\boldsymbol{\beta}]$ can be calculated with

$$\mathrm{Var}[\mathbf{G}\boldsymbol{\beta}] = \frac{\sigma_g^2}{S}\left[\sum_{s=1}^{S} 2f_s(1-f_s)\tau_s^2\right].$$

We have made the assumption of $r_{\text{admix}} = 1$ when deriving the heritability formula, and we have shown through simulations that this formula leads to accurate estimates of heritability in simulation even when this assumption is violated (with $r_{\text{admix}} = 0.9, 0.95, 1.0$; Supplementary Tables 5 and 6). Given the simplicity of this formula and that our real data analysis results indicate $r_{\text{admix}} > 0.9$ (Table 1), we used this formula throughout in this work. In our real data analysis, each trait can have heritability estimates from multiple studies. To obtain a single estimate of heritability for each trait, we performed random-effects meta-analysis using point estimates and standard error of the heritability obtained in each study (i.e. heritability estimates in Table 1 are per-trait meta-analysis results from heritability estimates in Supplementary Table 7).

3 Induced heterogeneity in marginal effects due to tagging

Here we describe the induced heterogeneity of estimated marginal effects at tagging variants, even when causal effects are identical by ancestry. We consider two variants s, t, with variant s as the causal variant and variant t as the tagging variant. For simplicity, we ignore the covariates and assume $\mathbf{y}, \mathbf{g}_{s,1}, \mathbf{g}_{s,2}$ have been centered (equivalent to including the all '1' covariate in the model); similar results can be derived for scenarios with covariates by projecting $\mathbf{y}, \mathbf{g}_{s,1}, \mathbf{g}_{s,2}$ out of the covariate space.

We first assume s as the only causal variant. Phenotype can be modeled as $\mathbf{y} = \mathbf{g}_{s,1}\beta_{s,1} + \mathbf{g}_{s,2}\beta_{s,2} + \boldsymbol{\epsilon}$, or for notation convenience as

$$\mathbf{y} = \mathbf{G}_s\boldsymbol{\beta}_s + \boldsymbol{\epsilon},$$

where we denote $\mathbf{G}_s := \begin{bmatrix} | & | \\ \mathbf{g}_{s,1} & \mathbf{g}_{s,2} \\ | & | \end{bmatrix} \in \mathbb{R}^{N\times 2}$, and $\boldsymbol{\beta}_s = \begin{bmatrix}\beta_{s,1}\\ \beta_{s,2}\end{bmatrix} \in \mathbb{R}^{2\times 1}$ (similarly for $\mathbf{G}_t, \boldsymbol{\beta}_t$). Using model $\mathbf{y} = \mathbf{G}_t\boldsymbol{\beta}_t + \boldsymbol{\epsilon}$, we can estimate the effect sizes of the tagging variant t with

$$\widehat{\boldsymbol{\beta}_t^{(m)}} = (\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\mathbf{y}$$

Expectation and variance of the estimated effects at variant t are

$$\mathbb{E}[\widehat{\boldsymbol{\beta}_t^{(m)}}] = (\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\mathbf{G}_s\boldsymbol{\beta}_s, \qquad \mathbb{V}[\widehat{\boldsymbol{\beta}_t}] = \sigma_\epsilon^2(\mathbf{G}_t^\top\mathbf{G}_t)^{-1}.$$

The derivation can be extended to multiple causal variants by replacing $(\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\mathbf{G}_s\boldsymbol{\beta}_s$ with $(\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\left(\sum_s \mathbf{G}_s\boldsymbol{\beta}_s\right)$, where the summation of s is over all causal variants.

To simplify the discussion, we further assume effects are the same across ancestries at causal variant s, $\beta_{s,1} = \beta_{s,2} = \beta_s$. Denoting $\mathbf{g}_s := \mathbf{g}_{s,1} + \mathbf{g}_{s,2}$, we have

$$\mathbb{E}[\widehat{\boldsymbol{\beta}_t^{(m)}}] = (\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\mathbf{g}_s\beta_s, \qquad \mathbb{V}[\widehat{\boldsymbol{\beta}_t^{(m)}}] = \sigma_\epsilon^2(\mathbf{G}_t^\top\mathbf{G}_t)^{-1}.$$

$(\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\mathbf{g}_s$ determines the expectation of the estimated effects at tagging variant t, and consequently differences in ancestry-specific taggability. Of note, $(\mathbf{G}_t^\top\mathbf{G}_t)^{-1}\mathbf{G}_t^\top\mathbf{g}_s$ is exactly the solution of least squares when regressing $\mathbf{g}_s$ against $\mathbf{G}_t$; and if $t = s$, $(\mathbf{G}_s^\top\mathbf{G}_s)^{-1}\mathbf{G}_s^\top\mathbf{g}_s = \begin{bmatrix}1\\1\end{bmatrix}$ (this can be verified by noting $\mathbf{g}_{s,1} + \mathbf{g}_{s,2} = \mathbf{g}_s$).

4 Heterogeneity by local ancestry in marginal effects in real data

We provide additional discussion of heterogeneity by local ancestry in marginal effects in real data analysis. Across 60 study-trait pairs, we detected a total of 217 GWAS significant clumped trait-SNP pairs and we estimated the ancestry-specific marginal effects for each of these SNPs at GWAS loci. 41 out of 217 trait-SNP pairs

had significant heterogeneity in marginal effects by ancestry (HET test $p_{\text{HET}} < 0.05/217$). 16 out of 41 SNPs with significant heterogeneity were from UKBB data and PAGE data: 14 MCH-associated SNPs at 16p13.3 in UKBB data had strongest heterogeneity with average $-\log_{10}(p_{\text{HET}}) = 13.0$. By performing statistical fine-mapping analyses (Methods), we determined there were multiple conditionally independent association signals (Extended Data Figure 6a; also reported in ref.[1]). Similarly, we determined there were multiple conditionally independent trait-associated variants nearby 1 RBC count-associated SNP at 16p13.3 in UKBB data (Extended Data Figure 6b; $-\log_{10}(p_{\text{HET}}) = 5.5$) and 1 CRP-associated SNPs at 1q23.2 in PAGE data (Extended Data Figure 6c; $-\log_{10}(p_{\text{HET}}) = 4.1$; also reported in ref.[2]) that exhibited heterogeneity in marginal effects. The rest 25 out of 41 SNPs with significant heterogeneity were from AoU data: 22 height-associated SNPs with $-\log_{10}(p_{\text{HET}}) = 6.8$, 2 total cholesterol-associated SNPs with $-\log_{10}(p_{\text{HET}}) = 5.8$, 1 LDL-associated SNPs with average $-\log_{10}(p_{\text{HET}}) = 6.8$. We did not perform statistical fine-mapping on AoU microarray data, because we were concerned that imperfect tagging of relatively low density of microarray SNPs may lead to error-prone inference for existence of multiple causal variants. We leave fine-mapping analysis on high density SNPs (such as whole genome sequencing or densely-imputed) of AoU data for future work. Overall, we detected abundant evidence of multiple causal SNPs for loci that exhibit heterogeneity in marginal effects (especially for MCH-associated SNPs with the strongest heterogeneity), which was consistent to our simulation study with $r_{\text{admix}} = 1$ (see Results).

5 Local ancestry adjustment in heterogeneity estimation

We discuss the use of local ancestry in the heterogeneity estimation. Recall that our main equation is

$$y = \ell_s \beta^{(m)}_{s,\text{lanc}} + g_{s,\text{eur}} \beta^{(m)}_{s,\text{eur}} + g_{s,\text{afr}} \beta^{(m)}_{s,\text{afr}} + \mathbf{c}^\top \boldsymbol{\alpha} + \epsilon,$$

and we evaluated three approaches: (1) ignoring local ancestry altogether ("w/o"); (2) including local ancestry as a covariate in the model ("lanc-included") ; (3) regressing out the local ancestry from phenotype ("lanc-regressed") followed by heterogeneity estimation on residuals. In null simulations, we have observed the inflation of HET test using "lanc-regressed". In power simulations, we have observed the reduced power of HET test using "lanc-included".

These results are explained by the induced correlation between the local ancestry and ancestry-specific genotypes $\ell_s, g_{s,\text{eur}}, g_{s,\text{afr}}$. Intuitively, each additional local ancestry from African ancestries ℓ_s, indicates an expected increase of risk allele counts from African ancestries $g_{s,\text{afr}}$, and an expected decrease of risk allele counts from European ancestries $g_{s,\text{eur}}$. Consequently, ℓ_s will be positively correlated with $g_{s,\text{afr}}$ and negatively correlated with $g_{s,\text{eur}}$. Indeed, the average correlation in a set of randomly sampled SNPs in PAGE data is 0.36 for $\ell_s \sim g_{s,\text{afr}}$ and -0.55 for $\ell_s \sim g_{s,\text{eur}}$ (Supplementary Table 17). Consequently, regressing out the local ancestry only from the phenotype is equivalent to adding a positive effect to $g_{s,\text{eur}}$ and a negative effect to $g_{s,\text{afr}}$; "lanc-regressed" leads to drastically inflated HET test (Figure 5a). On the other hand, a joint inference of $\beta_{s,\text{lanc}}, \beta_{s,\text{eur}}, \beta_{s,\text{afr}}$ in the presence of correlations among $\ell_s, g_{s,\text{eur}}, g_{s,\text{afr}}$ would lead to increased variance in the estimated effects, therefore a power loss in "lanc-included" (Figure 5b).

6 Pitfalls of using marginal effects at GWAS significant variants to estimate heterogeneity

We investigated four methods that use marginal effects as input: (1) HET test; (2) Deming regression slopes of the marginal effects across SNPs (Deming slope); (3) Ordinary least squares regression slopes of estimated ancestry-specific marginal effects across SNPs (OLS slope); (4) Pearson correlation of the marginal effects across SNPs (Pearson correlation). Except for HET test which can compare effects difference for each individual SNP, the other three methods evaluate the aggregated effects difference across multiple SNPs. We have performed simulations both with single causal variant and multiple causal variants. In the following, we describe more details on the performance of HET test and Deming slope (in addition to those in Results section). And we also describe the performance of OLS slope and Pearson correlation.

6.1 Simulation with single causal variant

When evaluated at causal variants, in contrast to HET test and Deming slope, Pearson correlation and OLS slope were severely mis-calibrated (Extended Data Figure 7 and supplementary Table 13). For example, when the simulated $h_g^2 = 0.6\%$, the false positive rate of HET test was 0.051 (SE 0.01), consistent with the expected level of 0.05 (Extended Data Figure 7a); the average Deming regression slope was 1.005 (SE 0.01) when regressing β_{eur} against β_{afr} ($\beta_{\text{eur}} \sim \beta_{\text{afr}}$) and 0.996 (SE 0.01) for $\beta_{\text{afr}} \sim \beta_{\text{eur}}$, consistent with the expected slope of 1 (Extended Data Figure 7bc). Pearson correlation significantly deviated from the expected level of 1: 0.964 (SE 0.005) (Extended Data Figure 7); OLS slope was consistently smaller than 1 for $\beta_{\text{afr}} \sim \beta_{\text{eur}}$ (0.943 (SE 0.017)) and for $\beta_{\text{eur}} \sim \beta_{\text{afr}}$ (0.985 (SE 0.017)) (Extended Data Figure 7ef). Interestingly, OLS slope's downward bias varied with the regression order ($\beta_{\text{afr}} \sim \beta_{\text{eur}}$ v.s. $\beta_{\text{eur}} \sim \beta_{\text{afr}}$). This is because the bias of OLS slope is a function of noise level in the independent variable, and estimated marginal effects in European ancestries and African ancestries were associated with different levels of standard errors (larger standard errors for β_{eur} because of smaller European ancestries proportion in PAGE African American individuals). Deming slope produced accurate results regardless of regression order as the differential standard errors are taken into consideration (Methods). Overall our results are consistent with mis-calibrations of Pearson correlation and OLS slopes due to their ignorance of the errors in the estimated effects[3].

When the causal SNPs were unknown and clumped SNP were used, as shown in Results section, HET test was increasingly mis-calibrated with larger h_g^2 while Deming slope remained relatively robust (Figure 6). Similar to HET test, Pearson correlation and OLS slope were less calibrated for clumped SNPs, likely due to increased standard errors of estimated effects (Extended Data Figure 7d-f). The mis-calibration induced by clumping arises from the inclusion of multiple SNPs in the clumped set (even though only 1 causal variant was simulated); the clumped SNPs included both index SNPs with the strongest associations, and secondary SNPs with weaker associations. These secondary SNPs were less correlated with the causal SNPs (average $r^2 = 0.072$) and were physically more distant from the causal SNPs (average distance 432.5kb) compared to those strongest associated SNPs in each region (average $r^2 = 0.973$, average distance 2.4kb) (in simulation with $h_g^2 = 1.0\%$), and therefore can induce heterogeneity by ancestry as indicated in Figure 1c. After restricting to SNPs with the strongest association after clumping (thus matching the simulation setup of a single simulated causal variant), both HET test and Deming slope resumed well-calibration (Supplementary Table 13). This indicates the efficiency of LD clumping in capturing causal variant (e.g., 63% of clumped variants were causal when the simulated $h_g^2 = 1.0\%$; Supplementary Table 16). However, we note OLS slope and Pearson correlation remained not calibrated (Supplementary Table 13).

6.2 Simulation with multiple causal variants

In contrast to simulation with a single causal variant, even evaluated at the causal variants, both HET test and Deming slope were biased in the presence of multiple causals within the same LD region; the mis-calibration/bias increased with polygenicity (Figure 6 and supplementary Table 14). For example, in simulation with 2 causal SNPs per Mb ($n_{\text{causal}} = 500$ on chromosome 1) and $h_g^2 = 10\%$, HET had inflated false positive rate (0.249 (SE 0.012) at the nominal 0.05 rate); average Deming slope of $\beta_{\text{eur}} \sim \beta_{\text{afr}}$ was 1.085 (SE 0.016). This is likely due to tagging among multiple causal variants whereby a causal SNP also tags effect of nearby causal SNPs in an ancestry-specific way (Methods). LD clumping did not alleviate the mis-calibration/bias (Figure 6 and supplementary Table 14); for example, the average FPR was 0.279 (SE 0.008) and the average Deming slope was 1.083 (SE 0.018) in simulations with 4 causal variants per Mb ($n_{\text{causal}} = 1,000$ on chromosome 1). Such mis-calibrations occurred irrespective of sample size (Extended Data Figure 8), or simulated heritability h_g^2 (Supplementary Table 14). For completeness, we also evaluated OLS regression slope and Pearson correlation showing mis-calibrations with a large magnitude (Supplementary Table 14). Finally, we note the upward/downward biases of Deming slope for $\beta_{\text{eur}} \sim \beta_{\text{afr}}$ / $\beta_{\text{afr}} \sim \beta_{\text{eur}}$, which were likely due to imbalanced ancestry proportions (~80% African and ~20% European ancestries) of admixed genotypes in PAGE data (Supplementary Table 18).

7 Identifying individuals with admixed African and European ancestries with principal component analysis

We seek to identify individuals with African-European admixed ancestries from a diverse population of genotyped individuals (sample data, e.g., AoU) together with a reference panel (reference data, e.g., 1,000 Genomes) using principal component analysis. First, we perform a principal component analysis jointly on the sample and reference data and obtain top principal components (PCs) $\mathbf{w}_i$ for each individual i. We calculate the averaged PCs for individuals with European and African continental ancestries in 1,000 Genomes:

$$\overline{\mathbf{w}_{\text{afr}}} = \frac{\sum_{i\in\text{afr}} \mathbf{w}_i}{|\text{afr}|}, \qquad \overline{\mathbf{w}_{\text{eur}}} = \frac{\sum_{i\in\text{eur}} \mathbf{w}_i}{|\text{eur}|}.$$

(In our analysis, for African continental ancestries in 1,000 Genomes, we did not include individuals with sup-population "ASW" (African Ancestry in Southwest US) or "ACB" (African Caribbean in Barbados), because some individuals in these sub-populations had admixed ancestries.) Second, we calculate the projected length and distance of each individual $\mathbf{w}_i$ to the line $(\overline{\mathbf{w}_{\text{afr}}}, \overline{\mathbf{w}_{\text{eur}}})$. We first define $\overline{\mathbf{w}_\Delta} = \overline{\mathbf{w}_{\text{afr}}} - \overline{\mathbf{w}_{\text{eur}}}$, and calculate the normalized projected length t_i and distance d_i as:

$$t_i = \frac{(\mathbf{w}_i - \overline{\mathbf{w}_{\text{eur}}})^\top \overline{\mathbf{w}_\Delta}}{\|\overline{\mathbf{w}_\Delta}\|_2^2}, \qquad \mathbf{n}_i = (\mathbf{w}_i - \overline{\mathbf{w}_{\text{eur}}}) - t_i \cdot \overline{\mathbf{w}_\Delta}, \qquad d_i = \|\mathbf{n}_i\|_2 .$$

Roughly speaking, $t_i \in [0, 1]$ if individual i locates in the PC space between European and African ancestries, and has the interpretation of global ancestry proportion: the closer t_i is to 1, the more African ancestries individual i has, and vice versa. Finally, we define the normalized distance $\tilde{d}_i$ with

$$\tilde{d}_i = \frac{d_i}{t \cdot \max_{i\in\text{afr}}\{d_i\} + (1-t) \cdot \max_{i\in\text{eur}}\{d_i\}}$$

to account for the different spread (in PC space) for individuals with European and African continental ancestries. In our analysis, we used the first two PCs when calculating these quantities, and the set of selected admixed individuals was robust to the number of PCs used. We selected individuals with admixed ancestries with at least both 10% European ancestries and 10% African ancestries ($t_i \in [0.1, 0.9]$), and who was within $2 \times$ normalized distance ($\tilde{d}_i < 2$) from the line connecting individuals of European ancestries and African ancestries in 1,000 Genomes reference panel.

8 Population-specific SNPs can induce downward bias of estimated genetic correlation

We explain reasons that ignoring rare population-specific SNPs can induce downward bias of estimated genetic correlation. We consider a following example with two SNPs (SNP 1 and SNP 2) and two populations (population A and population B). We analyze the expected marginal effects when one causal variant is very rare in one population to explain the potential bias in genetic correlation estimation. For population A, SNPs 1 and 2 are both common (MAF=30%) and in perfect LD (Cor[SNP 1, SNP 2] = 100%). While for population B, SNP 1 is common (MAF=30%) but SNP 2 is rare (MAF=0.01%). In population B, because SNP 2 is rare, LD between SNP A and B is close to zero. Furthermore, we assume same causal allelic effects for population A and B, with $\beta_1 = 0.5, \beta_2 = 2.0$. Causal effects and MAF are summarized in the following table (with MAF in parentheses).

	Population A	Population B
SNP 1 β_1	0.5 (30%)	0.5 (30%)
SNP 2 β_2	2.0 (30%)	2.0 (0.01%)

Causal effects and MAF in two-SNP example.

We then consider the expected marginal effects as a function of LD and causal effects (similar as Figure 4). For population A, because SNP 1 and 2 are in perfect LD and tag the causal effects from both SNPs, the marginal effects are expected to be the same as $\beta_1^{(m)} = \beta_2^{(m)} = 0.5 + 2.0 = 2.5$. While for population B, because of the near-zero LD, marginal effects are expected to be the same as causal effects, where $\beta_1^{(m)} = 0.5, \beta_2^{(m)} = 2.0$.

	Population A	Population B
SNP 1 $\beta_1^{(m)}$	2.5	0.5
SNP 2 $\beta_2^{(m)}$	2.5	2.0

Expected marginal effects in the two-SNP example. SNP 2 will be excluded when population-specific SNPs are excluded in the analysis.

When population-specific SNPs (SNP 2) are excluded in the analysis, only SNP 1 is observed with marginal effects of 2.5 in population A and 0.5 in population B; difference across ancestries is then induced. Therefore, exclusion of population-specific variants can induce downward bias in estimated genetic correlation.

9 Genetic correlation across African and European populations in UK Biobank

We performed genetic correlation analysis of 26 traits across African and European populations in UK Biobank. We used individuals of European ancestries (average N = 19K) and African ancestries (average N = 6K) in UK Biobank. European individuals were a subset of white British individuals[4] (we used a small subset of individuals for computational efficiency), and African individuals were identified using SCOPE analysis with African ancestry proportion > 90%. We retained 4.7M SNPs with MAF > 0.5% in both populations from imputed variants in UK Biobank. We used bivariate REML implemented in GCTA[5], a method that leverage individual-level data and therefore have improved precision[6] to quantify the correlation of causal effects between European and African populations. Bivariate REML requires building a genomic relationship matrix (GRM) among all individuals. We explored three approaches for standardizing genotypes when building the GRM.

- **Overall standardized.** Each individual i's genotype at s-th SNP $g_{i,s}$ is standardized using $\tilde{g}_{i,s} = \frac{(g_{i,s} - 2f_{s,\text{overall}})}{\sqrt{2f_{s,\text{overall}}(1-f_{s,\text{overall}})}}$ for all individuals regardless of genetic ancestries, where $f_{s,\text{overall}}$ is the overall allele frequencies calculated across all individuals.
- **Population-specific standardized.** Each individual i's genotype at s-th SNP $g_{i,s}$ is standardized using $\tilde{g}_{i,s} = \frac{(g_{i,s} - 2f_{s,\text{afr}})}{\sqrt{2f_{s,\text{afr}}(1-f_{s,\text{afr}})}}$ for individual i of African ancestries, where $f_{s,\text{afr}}$ is the allele frequency for s-th SNP in individuals of African ancestries. Similar standardization is performed for individuals with European ancestries.
- **Population-specific allelic.** Genotype $\tilde{g}_{i,s} = (g_{i,s} - 2f_{s,\text{afr}})$ for individual i of African ancestries. Similar standardization is performed for individuals with European ancestries.

With the standardized genotypes $\tilde{g}_{i,s}$, each entry of GRM matrix for individual i and j is then $\frac{\sum_{s=1}^{S} \tilde{g}_{i,s}\tilde{g}_{j,s}}{S}$. The standardization methods of "overall standardized" and "population-specific standardized" were explored in ref.[6] while the standardization method of "population-specific allelic" was explored in refs.[7,8]. We focused on the method of "population-specific allelic" where allelic effects were compared across genetic ancestries, because this is similar to our method of genetic correlation within admixed populations. In the analysis of each trait, we included age, sex, age*sex, and top 20 principal-components of GRM of all individuals as covariates. We performed quantile normalization of phenotype and covariate values. We performed bivariate REML using `gcta64 --reml-bivar`. We also determined that results are consistent with or without the flag of `--reml-bivar-no-constrain` that constrains the estimate between -1 and 1 in our analyses.

10 Additional Discussions

First, for Latino American populations, given the large noises in estimated African local ancestries because of their small proportion[9], it may be desired to alternatively estimate genetic correlation of Native American ancestries vs. other ancestries (including both European and African ancestries). In this case, the estimated genetic correlation can be interpreted as differences of causal effects in Native American local ancestries versus the average causal effects of European and African local ancestries. Second, we have focused on estimating a single global parameter r_{admix} which summarizes the overall genome-wide genetic correlation. Our modeling framework can be extended to stratified analyses of SNPs in different annotation categories (e.g., MAF bins or functional annotations[10]) to estimate the genetic correlation within each category. To obtain estimates with sufficient precision for each SNP category, such stratified analyses would require larger sample sizes compared to the overall analyses we performed here. We leave such stratified analyses for future work with access to larger sample sizes of admixed individuals. Third, in the analysis of AoU data, we analyzed microarray data instead of whole genome sequencing (WGS) data to reduce computational cost. However, our method is shown to be robust to untyped variants. We leave AoU WGS data analysis for future work. Fourth, methods described here can be readily applied to gene expression data of admixed individuals to investigate heterogeneity for gene expression; we leave this to future work because such data with large sample size is currently unavailable to us.

Supplementary Tables

r_{admix}	h_g^2	SNP set	Mode	95% credible interval	Pr[reject '$r_{\text{admix}} = 1'$]
0.90	0.10	hm3	0.900	[0.882, 0.916]	0.36
0.90	0.10	imputed	0.904	[0.885, 0.92]	0.31
0.90	0.25	hm3	0.890	[0.881, 0.899]	0.76
0.90	0.25	imputed	0.892	[0.883, 0.902]	0.67
0.90	0.50	hm3	0.888	[0.882, 0.894]	0.99
0.90	0.50	imputed	0.893	[0.887, 0.899]	0.94
0.95	0.10	hm3	0.931	[0.915, 0.946]	0.15
0.95	0.10	imputed	0.932	[0.915, 0.948]	0.13
0.95	0.25	hm3	0.938	[0.931, 0.945]	0.42
0.95	0.25	imputed	0.943	[0.935, 0.951]	0.28
0.95	0.50	hm3	0.943	[0.939, 0.948]	0.59
0.95	0.50	imputed	0.951	[0.946, 0.956]	0.43
1.00	0.10	hm3	0.994	[0.983, 1]	0.01
1.00	0.10	imputed	1.000	[0.989, 1]	0.01
1.00	0.25	hm3	0.991	[0.985, 0.998]	0.07
1.00	0.25	imputed	1.000	[0.996, 1]	0.06
1.00	0.50	hm3	0.989	[0.985, 0.994]	0.09
1.00	0.50	imputed	1.000	[0.998, 1]	0.03

Supplementary Table 1: **Numeric results of genetic correlation r_{admix} estimation in genome-wide simulations (with fixed $p_{\text{causal}} = 0.1\%$; Figure 2).** We fixed the proportion of causal variants $p_{\text{causal}} = 0.1\%$, and we varied genome-wide heritability $h_g^2 = 0.1, 0.25, 0.5$, genetic correlation $r_{\text{admix}} = 0.90, 0.95, 1.0$, and SNP set used in the estimation. For each simulated genetic architecture, we performed a meta-analysis of estimation across 100 simulations. We report the mode and 95% credible interval from the meta-analysis. We also report the empirical probability of rejecting the null hypothesis of $r_{\text{admix}} = 1$ (one-sided test).

r_{admix}	p_{causal}	SNP set	Mode	95% credible interval	Pr[reject '$r_{\text{admix}} = 1'$]
0.90	0.001%	hm3	0.909	[0.9, 0.917]	0.61
0.90	0.001%	imputed	0.911	[0.901, 0.919]	0.57
0.90	0.01%	hm3	0.900	[0.891, 0.909]	0.74
0.90	0.01%	imputed	0.903	[0.893, 0.912]	0.59
0.90	0.1%	hm3	0.890	[0.881, 0.899]	0.76
0.90	0.1%	imputed	0.892	[0.883, 0.902]	0.67
0.90	1%	hm3	0.902	[0.893, 0.911]	0.66
0.90	1%	imputed	0.904	[0.894, 0.913]	0.59
0.95	0.001%	hm3	0.923	[0.915, 0.931]	0.52
0.95	0.001%	imputed	0.930	[0.921, 0.938]	0.43
0.95	0.01%	hm3	0.944	[0.937, 0.951]	0.34
0.95	0.01%	imputed	0.952	[0.944, 0.959]	0.31
0.95	0.1%	hm3	0.938	[0.931, 0.945]	0.42
0.95	0.1%	imputed	0.943	[0.935, 0.951]	0.28
0.95	1%	hm3	0.939	[0.932, 0.946]	0.38
0.95	1%	imputed	0.946	[0.938, 0.954]	0.28
1.00	0.001%	hm3	0.994	[0.988, 0.999]	0.16
1.00	0.001%	imputed	1.000	[0.996, 1]	0.10
1.00	0.01%	hm3	0.988	[0.982, 0.995]	0.06
1.00	0.01%	imputed	1.000	[0.994, 1]	0.03
1.00	0.1%	hm3	0.991	[0.985, 0.998]	0.07
1.00	0.1%	imputed	1.000	[0.996, 1]	0.06
1.00	1%	hm3	0.994	[0.989, 1]	0.04
1.00	1%	imputed	1.000	[0.996, 1]	0.02

Supplementary Table 2: **Numeric results of genetic correlation r_{admix} estimation in genome-wide simulations (with fixed $h_g^2 = 0.25$).** We fixed genome-wide heritability $h_g^2 = 0.25$, and we varied the proportion of causal variants $p_{\text{causal}} = 0.001\%, 0.01\%, 0.1\%, 1\%$, genetic correlation $r_{\text{admix}} = 0.90, 0.95, 1.0$, and SNP set used in the estimation. For each simulated genetic architecture, we performed a meta-analysis of estimation across 100 simulations, we report the mode and 95% credible interval from the meta-analysis. We also report the empirical probability of rejecting the null hypothesis of $r_{\text{admix}} = 1$ (one-sided test).

r_{admix}	MAF threshold	Mode	95% credible interval	Pr[reject '$r_{\text{admix}} = 1'$]
0.90	0.5%	0.892	[0.883, 0.902]	0.67
0.90	1%	0.885	[0.876, 0.895]	0.73
0.90	5%	0.847	[0.837, 0.858]	0.89
0.95	0.5%	0.943	[0.935, 0.951]	0.28
0.95	1%	0.937	[0.929, 0.945]	0.35
0.95	5%	0.906	[0.896, 0.914]	0.63
1.00	0.5%	1.000	[0.996, 1]	0.06
1.00	1%	0.998	[0.991, 1]	0.06
1.00	5%	0.966	[0.959, 0.974]	0.14

Supplementary Table 3: **Numeric results of r_{admix} estimation in genome-wide simulations using other MAF thresholds in estimation stage.** We simulated phenotypes with fixed $h_g^2 = 0.25$, $p_{\text{causal}} = 0.1\%$, and imputed variants. We applied our methods using SNPs obtained from different population-specific MAF thresholds. We used SNPs that have MAF > 0.5% (default), MAF > 1%, MAF > 5% in both of the populations and we assessed the bias of the methods. We determined increased bias with more stringent MAF threshold. For each simulated genetic architecture, we performed a meta-analysis of estimation across 100 simulations, we report the mode and 95% credible interval from the meta-analysis. We also report the empirical probability of rejecting the null hypothesis of $r_{\text{admix}} = 1$ (one-sided test).

r_{admix}	Mode	95% credible interval	Pr[reject '$r_{\text{admix}} = 1'$]
1.00	1.000	[0.996, 1]	0.06
0.95	0.943	[0.935, 0.951]	0.28
0.90	0.892	[0.883, 0.902]	0.67
0.50	0.502	[0.482, 0.52]	1.00
0.00	0.009	[-0.023, 0.04]	1.00
-0.50	-0.486	[-0.532, -0.442]	1.00

Supplementary Table 4: **Numeric results of r_{admix} estimation in genome-wide simulations for additional range of r_{admix} (with fixed $h_g^2 = 0.25$, $p_{\text{causal}} = 0.1\%$, and imputed variants).** We varied genetic correlation $r_{\text{admix}} = -0.5, 0, 0.5, 0.90, 0.95, 1.0$. In these simulations, we assumed $-1 \leq r_{\text{admix}} \leq 1$ instead of $r_{\text{admix}} \geq 0$ as in our default method. For each simulated genetic architecture, we performed a meta-analysis of estimation across 100 simulations, we report the mode and 95% credible interval from the meta-analysis. We also report the empirical probability of rejecting the null hypothesis of $r_{\text{admix}} = 1$ (one-sided test).

h_g^2	r_{admix}	SNP set	Mean	SEM
0.10	0.90	hm3	0.104	0.00218
0.10	0.90	imputed	0.11	0.0021
0.10	0.95	hm3	0.0962	0.00203
0.10	0.95	imputed	0.101	0.00196
0.10	1.00	hm3	0.0918	0.00204
0.10	1.00	imputed	0.0972	0.00197
0.25	0.90	hm3	0.243	0.0025
0.25	0.90	imputed	0.259	0.0025
0.25	0.95	hm3	0.239	0.00211
0.25	0.95	imputed	0.255	0.00219
0.25	1.00	hm3	0.229	0.00199
0.25	1.00	imputed	0.247	0.00208
0.50	0.90	hm3	0.468	0.0023
0.50	0.90	imputed	0.502	0.00223
0.50	0.95	hm3	0.462	0.00221
0.50	0.95	imputed	0.498	0.00226
0.50	1.00	hm3	0.46	0.0024
0.50	1.00	imputed	0.498	0.0024

Supplementary Table 5: **Numeric results of h_g^2 estimation in genome-wide simulations (with fixed $p_{\text{causal}} = 0.1\%$).** We fixed the proportion of causal variants $p_{\text{causal}} = 0.1\%$, and we varied genome-wide heritability $h_g^2 = 0.1, 0.25, 0.5$, genetic correlation $r_{\text{admix}} = 0.90, 0.95, 1.0$, and SNP set used in the estimation. For each simulated genetic architecture, we report the mean and SEM of the estimates across 100 simulations.

p_{causal}	r_{admix}	SNP set	Mean	SEM
0.001%	0.90	hm3	0.24	0.0035
0.001%	0.90	imputed	0.256	0.00377
0.001%	0.95	hm3	0.234	0.00374
0.001%	0.95	imputed	0.252	0.00446
0.001%	1.00	hm3	0.235	0.00386
0.001%	1.00	imputed	0.252	0.00448
0.01%	0.90	hm3	0.244	0.00219
0.01%	0.90	imputed	0.261	0.00229
0.01%	0.95	hm3	0.239	0.00251
0.01%	0.95	imputed	0.256	0.00252
0.01%	1.00	hm3	0.231	0.00246
0.01%	1.00	imputed	0.249	0.00259
0.1%	0.90	hm3	0.243	0.0025
0.1%	0.90	imputed	0.259	0.0025
0.1%	0.95	hm3	0.239	0.00211
0.1%	0.95	imputed	0.255	0.00219
0.1%	1.00	hm3	0.229	0.00199
0.1%	1.00	imputed	0.247	0.00208
1%	0.90	hm3	0.242	0.0023
1%	0.90	imputed	0.257	0.0023
1%	0.95	hm3	0.238	0.00211
1%	0.95	imputed	0.256	0.00211
1%	1.00	hm3	0.232	0.00204
1%	1.00	imputed	0.248	0.00207

Supplementary Table 6: **Numeric results of h_g^2 estimation in genome-wide simulations (with fixed $h_g^2 = 0.25$).** We fixed genome-wide heritability $h_g^2 = 0.25$, and we varied the proportion of causal variants $p_{\text{causal}} = 0.001\%, 0.01\%, 0.1\%, 1\%$, genetic correlation $r_{\text{admix}} = 0.90, 0.95, 1.0$, and SNP set used in the estimation. For each simulated genetic architecture, we report the mean and SEM of the estimates across 100 simulations.

Study	Trait	N	Mode	95% credible interval(s)	p-value	h_g^2
UKBB	Asthma	4079	1.000	[0.15, 1.00]	1	0.21 ± 0.087
UKBB	BMD	1668	0.000	[0.00, 0.78]	0.012	0.34 ± 0.16
AoU	BMI	28747	0.996	[0.93, 1.00]	0.89	0.23 ± 0.017
PAGE	BMI	16684	0.929	[0.81, 1.00]	0.14	0.23 ± 0.024
UKBB	BMI	4090	1.000	[0.06, 1.00]	1	0.084 ± 0.082
PAGE	C-reactive protein	8321	0.995	[0.82, 1.00]	0.94	0.28 ± 0.046
PAGE	Cigarettes per day	6995	0.999	[0.08, 1.00]	1	0.097 ± 0.047
PAGE	Coffee consumption	11587	0.982	[0.10, 1.00]	0.9	0.074 ± 0.03
AoU	Diastolic blood pressure	28765	1.000	[0.88, 1.00]	1	0.094 ± 0.015
PAGE	Diastolic blood pressure	11005	1.000	[0.06, 1.00]	1	0.037 ± 0.028
UKBB	Diastolic blood pressure	4017	1.000	[0.07, 1.00]	1	0.14 ± 0.084
UKBB	Education years	3324	0.000	[0.00, 0.94]	0.4	0.055 ± 0.075
UKBB	Ever smoked	4083	0.764	[0.04, 0.98]	0.31	0.17 ± 0.082
PAGE	Fasting glucose	9646	0.695	[0.00, 0.93]	0.27	0.064 ± 0.035
PAGE	Fasting insulin	7753	1.000	[0.21, 1.00]	1	0.13 ± 0.044
AoU	HDL	8539	0.969	[0.65, 1.00]	0.66	0.24 ± 0.049
PAGE	HDL	9929	0.788	[0.10, 0.99]	0.1	0.13 ± 0.036
UKBB	HDL	3571	1.000	[0.66, 1.00]	1	0.35 ± 0.098
UKBB	HLR count	3852	1.000	[0.07, 1.00]	1	0.12 ± 0.086
PAGE	HbA1c	1740	1.000	[0.06, 1.00]	1	0.27 ± 0.2
UKBB	HbA1c	3613	0.883	[0.07, 1.00]	0.58	0.17 ± 0.085
AoU	Heart rate	28764	0.980	[0.82, 1.00]	0.74	0.099 ± 0.015
AoU	Height	28800	0.952	[0.90, 0.99]	0.03	0.41 ± 0.017
PAGE	Height	16705	0.902	[0.81, 0.97]	0.0042	0.39 ± 0.025
UKBB	Height	4100	0.911	[0.51, 1.00]	0.37	0.43 ± 0.089
PAGE	Hypertension	16617	0.910	[0.16, 1.00]	0.42	0.071 ± 0.021
UKBB	Hypertension	4127	0.983	[0.09, 1.00]	0.93	0.16 ± 0.082
UKBB	Hypothyroidism	4063	1.000	[0.05, 1.00]	1	0.046 ± 0.07
AoU	LDL	8513	0.835	[0.06, 1.00]	0.46	0.075 ± 0.04
PAGE	LDL	9574	0.967	[0.39, 1.00]	0.73	0.15 ± 0.037
UKBB	LDL	3892	0.991	[0.26, 1.00]	0.94	0.28 ± 0.088
UKBB	Lymphocyte count	3935	1.000	[0.00, 0.60] [0.66, 1.00]	1	0.13 ± 0.086
UKBB	MCH	3948	0.829	[0.07, 1.00]	0.36	0.2 ± 0.076
PAGE	MCHC	3650	0.228	[0.00, 0.87]	0.061	0.21 ± 0.092
UKBB	Monocyte count	3935	0.972	[0.26, 1.00]	0.82	0.3 ± 0.087
UKBB	Neuroticism	3044	1.000	[0.36, 1.00]	1	0.36 ± 0.11
PAGE	PR interval	4071	0.844	[0.08, 1.00]	0.36	0.22 ± 0.084
PAGE	Platelet count	8597	0.839	[0.20, 1.00]	0.12	0.18 ± 0.042
UKBB	Platelet count	3948	0.617	[0.00, 0.90]	0.083	0.21 ± 0.086
PAGE	QRS interval	4078	1.000	[0.07, 1.00]	1	0.12 ± 0.082
PAGE	QT interval	4089	0.920	[0.07, 1.00]	0.69	0.16 ± 0.083
UKBB	RBC count	3948	1.000	[0.37, 1.00]	1	0.31 ± 0.09
UKBB	RBC distribution width	3925	1.000	[0.27, 1.00]	1	0.28 ± 0.087
AoU	Systolic blood pressure	28765	1.000	[0.79, 1.00]	1	0.069 ± 0.014
PAGE	Systolic blood pressure	11006	1.000	[0.11, 1.00]	1	0.073 ± 0.032
UKBB	Systolic blood pressure	4017	1.000	[0.06, 1.00]	1	0.13 ± 0.086
AoU	Total cholesterol	8676	0.861	[0.10, 1.00]	0.28	0.13 ± 0.041
PAGE	Total cholesterol	9981	0.696	[0.10, 0.92]	0.0053	0.18 ± 0.036
UKBB	Total cholesterol	3898	0.972	[0.36, 1.00]	0.81	0.32 ± 0.089
AoU	Triglycerides	8698	0.891	[0.29, 1.00]	0.2	0.2 ± 0.043
PAGE	Triglycerides	9896	0.792	[0.17, 1.00]	0.062	0.15 ± 0.036
UKBB	Triglycerides	3900	0.822	[0.09, 1.00]	0.24	0.27 ± 0.082
UKBB	Type 1 diabetes	3767	0.381	[0.00, 0.95]	0.77	−0.033 ± 0.016
PAGE	Type 2 diabetes	14516	0.895	[0.47, 1.00]	0.24	0.12 ± 0.026
UKBB	Type 2 diabetes	4114	0.920	[0.06, 1.00]	0.82	0.09 ± 0.072
AoU	WHR	26689	0.989	[0.86, 1.00]	0.83	0.12 ± 0.017
PAGE	WHR	10067	0.903	[0.15, 1.00]	0.38	0.12 ± 0.035
PAGE	White blood cell count	8615	0.902	[0.61, 1.00]	0.17	0.25 ± 0.041
UKBB	White blood cell count	4140	1.000	[0.13, 1.00]	1	0.18 ± 0.074
PAGE	eGFR	7978	0.805	[0.16, 1.00]	0.09	0.19 ± 0.046

Supplementary Table 7: **Genome-wide genetic correlation across 38 complex traits (60 study-trait pairs) for African-European admixed individuals in PAGE, UKBB, AoU.** For each trait, we report number of individuals, posterior mode and 95% credible interval(s) for estimated r_{admix}, p-value for rejecting the null hypothesis of $H_0 : r_{\text{admix}} = 1$ (one-sided test), and estimated heritability and standard error. Meta analysis results are performed across 60 study-trait pairs. UKBB Lymphocyte count has two credible intervals because of the non-concave profile likelihood curve, likely as a result of small sample size.

See Supplementary Excel table.

Supplementary Table 8: **Genetic correlation estimation are robust to genetic architecture and SNP set.** We performed r_{admix} estimation under the assumption of alternative genetic architecture and SNP set on real trait analysis across PAGE and UKBB. We compared posterior mode, 95% credible intervals and p-values (for one-sided test of $H_0 : r_{\text{admix}} = 1$) of our default setting (using frequency-dependent genetic architecture and imputed SNPs; Table 1) to those obtained using GCTA genetic architecture and imputed SNPs, and to those obtained using frequency-dependent genetic architecture and HM3 SNPs. Study-trait pairs whose GCTA optimization failed to converge are indicated as 'NA'.

		2-component model				3-component model						
Trait	r (default)	σ_g^2	ρ_g	σ_e^2	r	σ_{g1}^2	σ_{g2}^2	ρ_g	σ_e^2	r	Loglik. diff.	p-value of same var.
C-reactive protein	0.996	0.27 (0.05)	0.26 (0.06)	0.70 (0.05)	0.99 (0.06)	0.30 (0.08)	0.25 (0.05)	0.28 (0.06)	0.70 (0.05)	1.00 (0.06)	0.185	0.667
White blood cell count	0.902	0.18 (0.04)	0.16 (0.05)	0.64 (0.04)	0.90 (0.09)	0.15 (0.06)	0.19 (0.04)	0.15 (0.05)	0.63 (0.04)	0.90 (0.09)	0.137	0.711
MCHC	0.228	0.08 (0.10)	0.02 (0.12)	0.83 (0.10)	0.21 (1.29)	-0.03 (0.14)	0.12 (0.11)	-0.02 (0.12)	0.82 (0.10)	-	-	-
Platelet count	0.84	0.14 (0.04)	0.11 (0.05)	0.81 (0.04)	0.84 (0.14)	-0.05 (0.07)	0.19 (0.05)	0.05 (0.05)	0.80 (0.04)	-	-	-
HDL	0.788	0.09 (0.04)	0.07 (0.04)	0.81 (0.04)	0.79 (0.19)	-0.02 (0.06)	0.13 (0.04)	0.03 (0.05)	0.81 (0.04)	-	-	-
LDL	0.968	0.12 (0.04)	0.12 (0.04)	0.75 (0.04)	0.97 (0.10)	0.18 (0.06)	0.10 (0.04)	0.14 (0.05)	0.75 (0.04)	1.01 (0.10)	0.665	0.415
Triglycerides	0.792	0.12 (0.04)	0.09 (0.05)	0.84 (0.04)	0.79 (0.16)	0.14 (0.06)	0.11 (0.04)	0.10 (0.05)	0.84 (0.04)	0.81 (0.16)	0.117	0.732
Total cholesterol	0.696	0.11 (0.04)	0.08 (0.04)	0.75 (0.03)	0.70 (0.18)	0.09 (0.06)	0.11 (0.04)	0.07 (0.04)	0.75 (0.03)	0.68 (0.20)	0.059	0.808
Cigarettes per day	1.0	0.09 (0.05)	0.09 (0.06)	0.84 (0.05)	1.00 (0.16)	0.04 (0.08)	0.11 (0.06)	0.08 (0.06)	0.84 (0.05)	1.07 (0.35)	0.365	0.546
Coffee consumption	0.982	0.05 (0.02)	0.05 (0.03)	0.65 (0.02)	0.98 (0.14)	0.15 (0.04)	0.02 (0.03)	0.08 (0.03)	0.65 (0.02)	1.56 (0.71)	4.08	0.043
HbA1c	1.0	0.30 (0.22)	0.32 (0.26)	0.69 (0.21)	1.07 (0.19)	0.19 (0.30)	0.31 (0.23)	0.27 (0.27)	0.69 (0.21)	1.10 (0.27)	0.115	0.735
Fasting insulin	1.0	0.14 (0.05)	0.14 (0.06)	0.84 (0.05)	1.02 (0.09)	0.09 (0.07)	0.15 (0.05)	0.12 (0.06)	0.84 (0.05)	1.05 (0.13)	0.309	0.578
Fasting glucose	0.694	0.04 (0.04)	0.02 (0.04)	0.86 (0.04)	0.70 (0.52)	-0.19 (0.05)	0.11 (0.04)	-0.06 (0.04)	0.86 (0.04)	-	-	-
Type 2 diabetes	0.896	0.05 (0.01)	0.04 (0.01)	0.37 (0.01)	0.89 (0.11)	0.01 (0.02)	0.06 (0.01)	0.03 (0.01)	0.37 (0.01)	1.16 (0.64)	2.739	0.098
QT interval	0.92	0.14 (0.09)	0.13 (0.11)	0.84 (0.09)	0.92 (0.23)	0.16 (0.13)	0.14 (0.10)	0.14 (0.11)	0.84 (0.09)	0.93 (0.22)	0.016	0.899
QRS interval	1.0	0.15 (0.09)	0.17 (0.10)	0.83 (0.09)	1.16 (0.13)	0.05 (0.12)	0.19 (0.10)	0.14 (0.11)	0.81 (0.09)	1.48 (1.07)	0.749	0.387
PR interval	0.844	0.17 (0.10)	0.14 (0.11)	0.80 (0.09)	0.84 (0.23)	0.04 (0.13)	0.21 (0.10)	0.10 (0.11)	0.80 (0.09)	1.01 (0.73)	0.876	0.349
Systolic blood pressure	1.0	0.08 (0.03)	0.09 (0.04)	0.86 (0.03)	1.07 (0.09)	-0.02 (0.06)	0.11 (0.04)	0.04 (0.04)	0.86 (0.03)	-	-	-
Diastolic blood pressure	1.0	0.04 (0.03)	0.04 (0.04)	0.94 (0.04)	1.01 (0.23)	-0.17 (0.03)	0.13 (0.04)	-0.02 (0.03)	0.91 (0.03)	-	-	-
Hypertension	0.91	0.02 (0.01)	0.02 (0.01)	0.38 (0.01)	0.91 (0.14)	0.05 (0.02)	0.02 (0.01)	0.03 (0.01)	0.38 (0.01)	1.13 (0.23)	1.951	0.162
WHR	0.902	0.08 (0.03)	0.08 (0.04)	0.73 (0.03)	0.90 (0.14)	0.13 (0.05)	0.07 (0.04)	0.09 (0.04)	0.73 (0.03)	0.97 (0.14)	0.525	0.469
Height	0.902	0.22 (0.02)	0.20 (0.02)	0.38 (0.02)	0.90 (0.04)	0.18 (0.03)	0.24 (0.02)	0.19 (0.02)	0.38 (0.02)	0.90 (0.04)	2.066	0.151
BMI	0.93	0.20 (0.02)	0.19 (0.03)	0.74 (0.02)	0.93 (0.05)	0.18 (0.04)	0.21 (0.03)	0.18 (0.03)	0.74 (0.02)	0.93 (0.06)	0.246	0.62
eGFR	0.806	0.11 (0.04)	0.09 (0.04)	0.63 (0.04)	0.81 (0.16)	-0.06 (0.05)	0.17 (0.04)	0.03 (0.04)	0.62 (0.04)	-	-	-

Supplementary Table 9: **Numerical results comparing estimated r_{admix} between alternative method formulations and default method (related to Extended Data Figure 5).** We compare results of (1) default method (2) directly optimizing and estimating σ_g^2, ρ_g (2-component) (3) directly optimizing and estimating $\sigma_{g,1}^2, \sigma_{g,2}^2$ and ρ_g (3-component). Results of 3-component method for some traits were not displayed because one of $\sigma_{g,1}^2, \sigma_{g,2}^2$ is estimated to be negative, causing the genetic correlation undefined. Standard errors are reported in parentheses. We also report the log-likelihood difference between 2-component model and 3-component model, and p-value for two-sided test of $H_0 : \sigma_{g,1}^2 = \sigma_{g,2}^2$. The observation that r_{admix} estimated via alternative methods without constraining $r_{\text{admix}} \leq 1$ were larger than those estimated via the default method suggests that estimates from the default method provided a lower bound of true r_{admix} in real data analysis. See Supplementary Notes for details.

Trait	N_{EUR}	N_{AFR}	Population-specific allelic	Population-specific standardized	Overall standardized
Hypothyroidism	19850	6092	0.667 (0.79)	0.192 (0.31)	1.00 (3.0)
Type 1 diabetes	19004	5516	-	-	-
Type 2 diabetes	19927	6140	1.00 (0.75)	0.668 (0.48)	0.944 (0.89)
Hypertension	19996	6176	0.131 (0.31)	-0.112 (0.33)	-0.184 (0.29)
Asthma	19570	6127	1.00 (2.4)	0.339 (0.38)	0.934 (2.0)
Total cholesterol	19051	5790	0.847 (0.22)	0.743 (0.21)	0.887 (0.24)
Diastolic blood pressure	18632	6043	0.238 (0.22)	0.145 (0.21)	0.0920 (0.25)
RBC distribution width	19375	5790	0.634 (0.24)	0.754 (0.25)	0.902 (0.33)
RBC count	19403	5837	0.501 (0.12)	0.484 (0.12)	0.530 (0.14)
Ever smoked	19924	6073	0.534 (0.24)	0.496 (0.22)	0.513 (0.25)
Height	19951	6079	0.547 (0.077)	0.507 (0.074)	0.510 (0.079)
LDL	19018	5779	0.878 (0.25)	0.806 (0.24)	0.926 (0.26)
BMI	19930	6071	0.663 (0.14)	0.552 (0.13)	0.686 (0.17)
HbA1c	19058	4853	0.571 (0.23)	0.681 (0.28)	0.784 (0.31)
HDL	17478	5368	0.473 (0.20)	0.297 (0.16)	0.392 (0.21)
BMD	11326	2197	0.214 (0.26)	0.313 (0.35)	0.250 (0.26)
HLR count	19030	5681	0.334 (0.13)	0.276 (0.13)	0.265 (0.14)
White blood cell count	19405	5839	0.466 (0.14)	0.427 (0.12)	0.571 (0.16)
Lymphocyte count	19366	5821	0.632 (0.19)	0.496 (0.16)	0.687 (0.25)
Monocyte count	19369	5818	0.206 (0.14)	0.177 (0.16)	0.198 (0.19)
Platelet count	19405	5839	0.604 (0.13)	0.578 (0.13)	0.650 (0.16)
Triglycerides	19039	5786	0.539 (0.14)	0.510 (0.14)	0.620 (0.17)
MCH	19397	5838	0.433 (0.13)	0.426 (0.11)	0.438 (0.14)
Neuroticism	16297	4002	0.811 (0.75)	0.623 (0.42)	1.00 (2.0)
Systolic blood pressure	18632	6043	0.468 (0.18)	0.472 (0.18)	0.535 (0.21)
Education years	16620	5118	0.337 (0.19)	0.408 (0.17)	0.560 (0.25)
Meta analysis			0.497 (0.034)	0.457 (0.032)	0.506 (0.041)

Supplementary Table 10: **Genome-wide genetic correlation across 26 complex traits for African and European ancestral populations in UK Biobank.** For each trait, we report number of individuals for European and African ancestral populations. We reported results of genetic correlation using three methods used to normalize the genotype matrix when calculating the GRM matrix: (1) population-specific allelic effects (default); (2) populations-specific standardized effects; (3) overall standardized effects (see Methods for details). We also report results of random-effects meta-analysis across traits. REML analysis for Type 1 diabetes did not converge and results are therefore not reported. We note that our results are overall consistent with the estimated correlation reported in recent works[6,11,12] (differences across these works can be explained by the different set of analyzed traits).

See Supplementary Excel table.

Supplementary Table 11: **Summary statistics of 217 genome-wide significant trait-associated SNPs.** We performed GWAS for each of 60 study-trait pairs in PAGE, UKBB, AoU. We report summary statistics for each of trait-associated SNPs that have two-sided association $p < 5 \times 10^{-8}$ and minor allele frequency > 0.5% in both European and African ancestries. For each pair of trait and SNP, we report two-sided association p-value, two-sided HET p-value, ancestry-specific allele frequencies calculated within PAGE, UKBB, AoU admixed individuals, estimated ancestry-specific effect sizes and standard errors. Across all 217 SNPs, Pearson's r = 0.73 (SE 0.04), OLS regression slope of $\beta_{afr} \sim \beta_{eur}$ = 0.84 (SE 0.06), OLS regression slope of $\beta_{eur} \sim \beta_{afr}$ = 0.64 (SE 0.06), Deming slope of $\beta_{afr} \sim \beta_{eur}$ = 1.22 (SE 0.09), Deming regression slope of $\beta_{eur} \sim \beta_{afr}$ = 0.82 (SE 0.06). Across 193 SNPs after excluding MCH-associated SNPs, Pearson's r = 0.85 (SE 0.03), OLS regression slope of $\beta_{afr} \sim \beta_{eur}$ = 0.92 (SE 0.05), OLS regression slope of $\beta_{eur} \sim \beta_{afr}$ = 0.80 (SE 0.06), Deming slope of $\beta_{afr} \sim \beta_{eur}$ = 1.08 (SE 0.05), Deming regression slope of $\beta_{eur} \sim \beta_{afr}$ = 0.93 (SE 0.04).

h_g^2	$\beta_{\text{eur}} : \beta_{\text{afr}}$	w/o	lanc included	lanc regressed
0.2%	1.00	0.0515 (0.012)	0.0509 (0.01)	0.0768 (0.013)
	1.05	0.0525 (0.011)	0.0514 (0.0096)	0.0791 (0.014)
	1.10	0.0598 (0.01)	0.0575 (0.0094)	0.0814 (0.014)
	1.15	0.0714 (0.011)	0.0613 (0.011)	0.0884 (0.014)
	1.20	0.0826 (0.011)	0.0675 (0.01)	0.0946 (0.014)
0.6%	1.00	0.0503 (0.01)	0.0509 (0.0094)	0.166 (0.014)
	1.05	0.0583 (0.011)	0.0557 (0.01)	0.174 (0.016)
	1.10	0.0841 (0.012)	0.0687 (0.013)	0.191 (0.015)
	1.15	0.113 (0.015)	0.0832 (0.013)	0.207 (0.018)
	1.20	0.153 (0.016)	0.104 (0.013)	0.22 (0.019)
1.0%	1.00	0.0524 (0.01)	0.0528 (0.0091)	0.228 (0.018)
	1.05	0.0631 (0.01)	0.0584 (0.0097)	0.242 (0.018)
	1.10	0.0989 (0.013)	0.0771 (0.012)	0.263 (0.021)
	1.15	0.158 (0.015)	0.106 (0.015)	0.283 (0.022)
	1.20	0.227 (0.017)	0.147 (0.017)	0.308 (0.02)

Supplementary Table 12: **Numerical results for pitfalls of including local ancestry in estimating heterogeneity (Figure 5).** We report the false positive rate (for null simulations) and power (for power simulations) for two-sided HET p-values. In each simulation, we selected a single causal variant and simulated quantitive phenotypes where causal variants had varying heritability $h_g^2 = 0.2\%, 0.6\%, 1.0\%$ and varying ratios of effects across ancestries $\beta_{\text{eur}} : \beta_{\text{afr}} = 1.0, 1.05, 1.1, 1.15, 1.2$. Standard errors (displayed in parentheses) were calculated based on 100 random sub-samplings with each sample consisting of 500 SNPs (Methods).

group	h_g^2	HET FPR	Deming (AFR~EUR)	Deming (EUR~AFR)	Pearson r	OLS (AFR~EUR)	OLS (EUR~AFR)
Causal	0.2%	0.051 (0.01)	0.999 (0.013)	1.001 (0.013)	0.914 (0.009)	0.878 (0.023)	0.952 (0.024)
	0.6%	0.051 (0.011)	0.996 (0.01)	1.005 (0.01)	0.964 (0.005)	0.943 (0.017)	0.985 (0.017)
	1.0%	0.048 (0.008)	0.999 (0.008)	1.001 (0.008)	0.978 (0.002)	0.967 (0.013)	0.989 (0.013)
Clumped (single)	0.2%	0.048 (0.008)	1.003 (0.014)	0.997 (0.014)	0.886 (0.048)	0.837 (0.08)	0.939 (0.032)
	0.6%	0.049 (0.009)	0.998 (0.009)	1.002 (0.009)	0.964 (0.004)	0.947 (0.017)	0.983 (0.017)
	1.0%	0.047 (0.009)	0.999 (0.007)	1.001 (0.007)	0.978 (0.002)	0.968 (0.013)	0.988 (0.013)
Clumped (all)	0.2%	0.048 (0.008)	1.002 (0.014)	0.998 (0.014)	0.87 (0.047)	0.823 (0.074)	0.921 (0.05)
	0.6%	0.064 (0.01)	0.996 (0.011)	1.004 (0.011)	0.859 (0.052)	0.797 (0.07)	0.927 (0.058)
	1.0%	0.14 (0.014)	0.984 (0.009)	1.016 (0.01)	0.709 (0.054)	0.562 (0.07)	0.898 (0.072)

Supplementary Table 13: **Numerical results for simulations with single causal variant (Figure 6).** We report the average and standard errors for each metric in simulations. Standard errors (displayed in parentheses) are based on 100 random sub-samplings with each sample consists of 500 SNPs. For clumped variants, we either retained only the SNP with strongest association within each region ("Clumped (single)"), or retained all the SNPs from clumping results ("Clumped (all)") (Methods).

n_{causal}	h_g^2	HET FPR	Deming (AFR~EUR)	Deming (EUR~AFR)	Pearson r	OLS (AFR~EUR)	OLS (EUR~AFR)
62	10%	0.181 (0.011)	0.985 (0.011)	1.015 (0.011)	0.916 (0.008)	0.858 (0.015)	0.978 (0.013)
	20%	0.25 (0.013)	0.995 (0.012)	1.005 (0.012)	0.926 (0.005)	0.885 (0.013)	0.969 (0.012)
125	10%	0.195 (0.013)	0.987 (0.012)	1.014 (0.012)	0.884 (0.01)	0.817 (0.018)	0.957 (0.014)
	20%	0.279 (0.015)	0.979 (0.014)	1.022 (0.015)	0.892 (0.007)	0.83 (0.015)	0.959 (0.015)
250	10%	0.203 (0.011)	0.975 (0.013)	1.025 (0.013)	0.874 (0.009)	0.804 (0.016)	0.95 (0.013)
	20%	0.304 (0.014)	0.958 (0.017)	1.044 (0.019)	0.852 (0.009)	0.773 (0.016)	0.94 (0.02)
500	10%	0.249 (0.012)	0.922 (0.013)	1.085 (0.016)	0.838 (0.011)	0.739 (0.016)	0.951 (0.015)
	20%	0.307 (0.015)	0.954 (0.019)	1.049 (0.021)	0.817 (0.011)	0.729 (0.018)	0.917 (0.019)
1000	10%	0.28 (0.011)	0.942 (0.012)	1.062 (0.014)	0.818 (0.009)	0.732 (0.014)	0.914 (0.014)
	20%	0.361 (0.015)	0.906 (0.022)	1.105 (0.026)	0.761 (0.014)	0.651 (0.017)	0.89 (0.026)

(a) Results for causal variants

n_{causal}	h_g^2	HET FPR	Deming (AFR~EUR)	Deming (EUR~AFR)	Pearson r	OLS (AFR~EUR)	OLS (EUR~AFR)
62	10%	0.234 (0.013)	0.963 (0.013)	1.038 (0.014)	0.548 (0.057)	0.383 (0.062)	0.789 (0.066)
	20%	0.354 (0.015)	0.923 (0.02)	1.084 (0.024)	0.426 (0.046)	0.275 (0.044)	0.662 (0.075)
125	10%	0.23 (0.012)	0.971 (0.015)	1.031 (0.016)	0.606 (0.082)	0.498 (0.095)	0.745 (0.101)
	20%	0.357 (0.013)	0.908 (0.021)	1.102 (0.026)	0.462 (0.047)	0.345 (0.054)	0.626 (0.083)
250	10%	0.217 (0.013)	0.97 (0.013)	1.031 (0.014)	0.669 (0.075)	0.567 (0.097)	0.798 (0.099)
	20%	0.355 (0.015)	0.921 (0.019)	1.087 (0.022)	0.514 (0.055)	0.395 (0.07)	0.679 (0.086)
500	10%	0.25 (0.013)	0.941 (0.018)	1.063 (0.02)	0.632 (0.057)	0.531 (0.087)	0.759 (0.08)
	20%	0.351 (0.014)	0.915 (0.02)	1.094 (0.024)	0.502 (0.061)	0.414 (0.083)	0.619 (0.089)
1000	10%	0.28 (0.012)	0.923 (0.016)	1.083 (0.018)	0.535 (0.067)	0.466 (0.088)	0.621 (0.071)
	20%	0.395 (0.017)	0.875 (0.024)	1.144 (0.031)	0.459 (0.064)	0.393 (0.081)	0.543 (0.076)

(b) Results for clumped variants

Supplementary Table 14: **Numerical results for simulations with multiple causal variants (Figure 6).** We report numerical results for the 4 metrics in simulations with varying number of causal variants 62, 125, 250, 500, 1000 causal variants (such that on average there were approximately 0.25, 0.5, 1.0, 2.0, 4.0 causal variants per Mb) and varying heritability explained by all causal variants $h_g^2 = 10\%, 20\%$. We specified heritability values that were larger than the chromosome 1 heritability of a typical complex trait because the limited sample size in our data produced only few clumped variants when h_g^2 was small. We report the average and standard errors for each metric in simulations. Standard errors (displayed in parentheses) were based on 100 random sub-samplings with each sample consists of 1,000 SNPs (Methods).

h_g^2	$\beta_{eur} : \beta_{afr}$	HET FPR / Power	Deming (EUR~AFR)	OLS (EUR~AFR)
0.2%	0.0	0.648 (0.022)	0.039 (0.011)	0.042 (0.016)
	0.5	0.337 (0.021)	0.537 (0.011)	0.512 (0.017)
	0.9	0.062 (0.012)	0.918 (0.014)	0.88 (0.027)
	1.0	0.052 (0.01)	1.004 (0.016)	0.948 (0.026)
	1.1	0.064 (0.012)	1.099 (0.018)	1.042 (0.026)
0.6%	0.0	0.905 (0.013)	0.001 (0.004)	0.0 (0.008)
	0.5	0.668 (0.02)	0.503 (0.007)	0.495 (0.011)
	0.9	0.085 (0.012)	0.906 (0.008)	0.892 (0.013)
	1.0	0.047 (0.01)	1.0 (0.009)	0.98 (0.018)
	1.1	0.078 (0.013)	1.102 (0.011)	1.079 (0.018)
1.0%	0.0	0.948 (0.01)	0.001 (0.003)	0.001 (0.007)
	0.5	0.79 (0.018)	0.503 (0.006)	0.497 (0.009)
	0.9	0.105 (0.014)	0.899 (0.007)	0.887 (0.013)
	1.0	0.047 (0.01)	0.999 (0.007)	0.985 (0.014)
	1.1	0.097 (0.012)	1.1 (0.008)	1.085 (0.014)
2.0%	0.0	0.982 (0.006)	0.001 (0.002)	-0.001 (0.004)
	0.5	0.893 (0.013)	0.501 (0.004)	0.5 (0.006)
	0.9	0.151 (0.016)	0.902 (0.005)	0.902 (0.008)
	1.0	0.048 (0.009)	0.998 (0.005)	0.995 (0.009)
	1.1	0.14 (0.015)	1.1 (0.006)	1.093 (0.009)
5.0%	0.0	0.999 (0.001)	0.001 (0.001)	-0.0 (0.002)
	0.5	0.96 (0.009)	0.499 (0.002)	0.499 (0.004)
	0.9	0.306 (0.021)	0.9 (0.003)	0.897 (0.005)
	1.0	0.052 (0.011)	1.0 (0.003)	0.999 (0.005)
	1.1	0.276 (0.02)	1.101 (0.004)	1.099 (0.006)

(a) Results for causal variants

h_g^2	$\beta_{eur} : \beta_{afr}$	HET FPR / Power	Deming (EUR~AFR)	OLS (EUR~AFR)
0.2%	0.0	0.452 (0.02)	0.248 (0.017)	0.235 (0.097)
	0.5	0.296 (0.023)	0.573 (0.013)	0.533 (0.026)
	0.9	0.057 (0.011)	0.923 (0.015)	0.873 (0.058)
	1.0	0.049 (0.009)	1.001 (0.014)	0.939 (0.047)
	1.1	0.058 (0.01)	1.085 (0.017)	0.972 (0.069)
0.6%	0.0	0.77 (0.018)	0.07 (0.016)	0.073 (0.053)
	0.5	0.648 (0.019)	0.515 (0.008)	0.505 (0.012)
	0.9	0.083 (0.011)	0.909 (0.009)	0.896 (0.014)
	1.0	0.047 (0.009)	0.998 (0.01)	0.975 (0.016)
	1.1	0.076 (0.012)	1.1 (0.01)	1.071 (0.024)
1.0%	0.0	0.836 (0.018)	0.041 (0.012)	0.04 (0.039)
	0.5	0.772 (0.019)	0.511 (0.006)	0.503 (0.009)
	0.9	0.105 (0.015)	0.901 (0.008)	0.887 (0.014)
	1.0	0.05 (0.01)	1.0 (0.007)	0.986 (0.014)
	1.1	0.094 (0.013)	1.098 (0.007)	1.081 (0.013)
2.0%	0.0	0.897 (0.012)	0.015 (0.007)	0.024 (0.029)
	0.5	0.88 (0.013)	0.506 (0.004)	0.505 (0.007)
	0.9	0.151 (0.015)	0.903 (0.005)	0.901 (0.01)
	1.0	0.05 (0.009)	0.998 (0.005)	0.995 (0.009)
	1.1	0.14 (0.013)	1.099 (0.005)	1.091 (0.01)
5.0%	0.0	0.932 (0.011)	0.005 (0.003)	0.015 (0.015)
	0.5	0.956 (0.01)	0.501 (0.003)	0.5 (0.005)
	0.9	0.305 (0.022)	0.9 (0.003)	0.898 (0.006)
	1.0	0.051 (0.009)	1.0 (0.003)	0.998 (0.006)
	1.1	0.275 (0.019)	1.101 (0.003)	1.099 (0.007)

(b) Results for clumped variants

Supplementary Table 15: **Numerical results for additional simulations with single causal variant with varying h_g^2 and $\beta_{eur} : \beta_{afr}$ (Figure 6).** We report the average and standard errors for each metric in simulations. Standard errors (displayed in parentheses) are based on 100 random sub-samplings with each sample consists of 500 SNPs. For clumped variants, we retained only the SNP with strongest association within each region. For causal variants at small h_g^2 simulation settings ($h_g^2 = 0.2\%$), we observed small upward bias for Deming regression when $\beta_{eur} : \beta_{afr} < 1$, which can result from that Deming regression ignores the correlation between estimated β_{eur} and β_{afr} (Methods); this bias diminishes as h_g^2 increases. For clumped variants at small h_g^2 simulation settings ($h_g^2 = 0.2\%$), we observed bias towards the null of $\beta_{eur} : \beta_{afr} = 1$, which can be explained by that variants with similar effects by ancestry are more likely to be prioritized in clumping procedure; this bias diminishes as h_g^2 increases.

h_g^2	Single	All
0.2%	0.45	0.45
0.6%	0.57	0.51
1.0%	0.63	0.36

Supplementary Table 16: **Probability for the clumped variants being causal in simulations with single causal variant (Figure 6).** We report the probability for the clumped variants to be causal in simulations. "Single" corresponds to retaining only the SNP with strongest association within each region and "All" corresponds to retaining all the SNPs from clumping results (Methods).

	EUR	AFR	lanc
EUR	1.00	-0.22 ± 0.0086	-0.55 ± 0.0098
AFR	-0.22 ± 0.0086	1.00	0.36 ± 0.0092
lanc	-0.55 ± 0.0098	0.36 ± 0.0092	1.00

Supplementary Table 17: **Correlation between ancestry-specific genotypes and local ancestry.** We report the pairwise Pearson correlation across ancestry-specific genotypes $g_{s,\text{eur}}, g_{s,\text{eur}}$ and local ancestry ℓ_s. For each SNP, we calculated the pairwise correlations across 17,299 individuals. We report the mean and SEM averaged across 500 random SNPs across chromosome 1.

Group	n_{causal}	HET FPR	Deming (AFR~EUR)	Deming (EUR~AFR)	Pearson r	OLS (AFR~EUR)	OLS (EUR~AFR)
PAGE	1	0.052 (0.01)	0.999 (0.008)	1.001 (0.008)	0.964 (0.004)	0.947 (0.016)	0.981 (0.016)
	41	0.623 (0.023)	0.888 (0.047)	1.129 (0.06)	0.748 (0.019)	0.651 (0.023)	0.86 (0.035)
Simu 20% EUR 80% AFR	1	0.048 (0.008)	0.995 (0.008)	1.005 (0.008)	0.968 (0.004)	0.946 (0.018)	0.99 (0.017)
	41	0.6 (0.021)	0.922 (0.038)	1.086 (0.045)	0.808 (0.014)	0.727 (0.022)	0.899 (0.028)
Simu 80% EUR 20% AFR	1	0.047 (0.008)	1.001 (0.008)	0.999 (0.008)	0.967 (0.004)	0.987 (0.017)	0.948 (0.016)
	41	0.581 (0.022)	1.067 (0.048)	0.939 (0.043)	0.817 (0.014)	0.899 (0.032)	0.743 (0.023)

(a) Results for causal variants

Group	n_{causal}	HET FPR	Deming (AFR~EUR)	Deming (EUR~AFR)	Pearson r	OLS (AFR~EUR)	OLS (EUR~AFR)
PAGE	1	0.114 (0.014)	0.989 (0.011)	1.011 (0.011)	0.857 (0.044)	0.792 (0.081)	0.931 (0.05)
	41	0.604 (0.022)	0.403 (0.181)	2.322 (0.34)	0.134 (0.052)	0.109 (0.048)	0.169 (0.064)
Simu 20% EUR 80% AFR	1	0.083 (0.013)	0.991 (0.009)	1.009 (0.009)	0.821 (0.056)	0.688 (0.091)	0.983 (0.027)
	41	0.566 (0.021)	0.593 (0.063)	1.705 (0.183)	0.331 (0.045)	0.188 (0.037)	0.586 (0.079)
Simu 80% EUR 20% AFR	1	0.069 (0.01)	1.004 (0.009)	0.996 (0.009)	0.871 (0.056)	0.893 (0.086)	0.855 (0.082)
	41	0.508 (0.024)	1.527 (0.147)	0.661 (0.063)	0.315 (0.051)	0.222 (0.045)	0.451 (0.083)

(b) Results for clumped variants

Supplementary Table 18: **Simulation results in PAGE data set and simulated genotype data sets with varying ancestry proportion.** We investigated the bias of Deming slope ($\beta_{\text{eur}}^{(m)} \sim \beta_{\text{afr}}^{(m)}$) observed in Figure 6 by performing simulations on 3 genotype data sets: **(a)** PAGE data set of 17,299 individuals with ~20% European and ~80% African ancestry proportions. **(b)** simulated genotype data set of 20000 individuals with 20% European and 80% African ancestry proportions. **(c)** simulated genotype data set of 20,000 individuals with 80% European and 20% African ancestry proportions. Simulated genotype data was generated as follows: first, we simulated the local ancestries for each SNP and individual using a Poisson process parametrized by the recombination rate and genetic distance; second, we used the phased genotype segment from a random individual in 1,000 Genomes with the corresponding ancestry (European / African) as the genotype for each simulated local ancestry segment. Such simulation method preserves the realistic local ancestry segment length distribution, MAF and LD structure for the generated genotypes. To simulate the phenotype, we randomly selected 100 regions each spanning 20 Mb on chromosome 1. For each region, we either simulated $n_{\text{causal}} = 1$ causal variant at the middle of the region, or simulated $n_{\text{causal}} = 41$ equally spaced across 20 Mb (on average 2 causal variant per Mb); these causal variants had same causal effects across local ancestries and *each* causal variant was expected to explain a fixed amount of heritability (0.6%) (we simulated a large heritability to better simulate the bias due to different ancestry proportions). We determined that biases from PAGE and simulated genotype data with 20% European / 80% African ancestries were both upward and biases from simulated genotype data with 80% European / 20% African ancestries were downward. Therefore, we determined the biases were due to imbalanced ancestry proportions (~20% European and ~80% African ancestries) in PAGE data. We report the mean and standard errors for each metric. Standard errors (displayed in parentheses) are based on 100 random sub-samplings with each sample consists of 500 SNPs.

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