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How robust are cross-population signatures of polygenic adaptation in humans?

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Abstract

Over the past decade, summary statistics from genome-wide association studies (GWASs) have been used to detect and quantify polygenic adaptation in humans. Several studies have reported signatures of natural selection at sets of SNPs associated with complex traits, like height and body mass index. However, more recent studies suggest that some of these signals may be caused by biases from uncorrected population stratification in the GWAS data with which these tests are performed. Moreover, past studies have predominantly relied on SNP effect size estimates obtained from GWAS panels of European ancestries, which are known to be poor predictors of phenotypes in non-European populations. Here, we collated GWAS data from multiple anthropometric and metabolic traits that have been measured in more than one cohort around the world, including the UK Biobank, FINRISK, Chinese NIPT, Biobank Japan, APCDR and PAGE. We then evaluated how robust signals of polygenic score overdispersion (which have been interpreted as suggesting polygenic adaptation) are to the choice of GWAS cohort used to identify associated variants and their effect size estimates. We did so while using the same panel to obtain population allele frequencies (The 1000 Genomes Project). We observe many discrepancies across tests performed on the same phenotype and find that association studies performed using multiple different cohorts, like meta-analyses and mega-analyses, tend to produce polygenic scores with strong overdispersion across populations. This results in apparent signatures of polygenic adaptation which are not observed when using effect size estimates from biobank-based GWASs of homogeneous ancestries. Indeed, we were able to artificially create score overdispersion when taking the UK Biobank cohort and simulating a meta-analysis on multiple subsets of the cohort. Finally, we show that the amount of overdispersion in scores for educational attainment - a trait with strong social implications and high potential for misinterpretation - is also strongly dependent on the specific GWAS used to build them. This suggests that extreme caution should be taken in the execution and interpretation of future tests of polygenic score overdispersion based on population differentiation, especially when using summary statistics from a GWAS that combines multiple cohorts.

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Introduction

Most human phenotypes are polygenic: the genetic component of trait variation across individuals is caused by differences in genotypes at a large number of variants, each with a relatively small contribution to a given trait (Fisher et al., 1918; Turelli, 2017). This applies to phenotypes as diverse as a person's height, their risk of schizophrenia or their risk of developing arthritis. The study of differences in complex traits spans more than a century but only in the last two decades has it become possible to systematically explore the underlying genetic architecture underlying these differences (Sella and N Barton, 2019). The advent of genome-wide association studies has led to the identification of thousands of variants that are associated with polygenic traits, either due to true biological mechanisms or because of linkage with causal variants (Visscher et al., 2012).

However, most research into the genetic aetiology of complex traits is based on GWAS data from populations of European ancestries (Popejoy and Fullerton, 2016). This bias in representation contributes to existing disparities in medical genetics and healthcare around the world (AR Martin, Kanai, et al., 2019). The low portability of European GWAS results - and, in particular, polygenic scores - to non-European populations is particularly concerning (AR Martin, Gignoux, et al., 2017; AR Martin, Kanai, et al., 2019) (but see Ragsdale et al., 2020). For example, the predictive accuracy of polygenic scores for height constructed using European effect size estimates has been shown to decrease with decreasing European ancestry in admixed populations (Bitarello and Mathieson, 2020). Recent studies have shown that ancestry deconvolution can be used to improve accuracy (Marnetto et al., 2020; M Wang et al., 2020), but important trait-associated variants in non-European populations may be missed if they have low frequencies or are absent in European populations. Moreover, effect size estimates for an associated variant derived from a European-ancestry GWAS may not accurately reflect the effect of the same variant on the trait in other populations (Wojcik et al., 2019). This could be due to differences in epistasis, differences in linkage disequilibrium between causal and ascertained variants, or gene-by-environment interactions, to name a few causes (Guo et al., 2018). Additionally, negative selection and demographic history may cause differences in genetic architectures between populations (Durvasula and Lohmueller, 2019).

During the last decade, GWAS summary statistics have also been used to look for evidence of directional selection towards a trait to a new phenotypic optimum, via allele-frequency shifts occurring across a large number of associated variants - a phenomenon known as polygenic adaptation (Hayward and Guy Sella, 2019; Pritchard et al., 2010). For example, several studies have consistently found evidence for polygenic adaptation operating on height-associated variants in Europe, mainly across a south-to-north gradient (Berg and Coop, 2014; Berg, Zhang, et al., 2017; Mathieson et al., 2015; Racimo et al., 2018; MR Robinson, Hemani, et al., 2015; Turchin et al., 2012). To test for selection, these studies primarily relied on summary statistics from the GIANT consortium dataset, which is a meta-analysis of anthropometric GWAS from multiple European cohorts (Allen et al., 2010; Wood et al., 2014). They looked for overdispersion and/or directional changes in the frequencies of trait-associated variants across populations, relative to a neutral null model. To account for potential confounding due to population stratification, some have tried to replicate this signal using family-based association studies (Allison et al., 1999; MR Robinson, Hemani, et al., 2015). Berg, Harpak, et al., 2019 and Sohail et al., 2019 showed that this signal of polygenic score overdispersion on height-associated variants in Europe (and possibly on other trait-associated variants) is attenuated and in some cases no longer significant when using effect size estimates from a GWAS performed on the UK Biobank - a large cohort composed primarily of individuals of British ancestry (Bycroft et al., 2018). There is no single explanation yet for these contradictory findings, but the most plausible one is that previous studies were impacted by very subtle confounding due to uncorrected population stratification in GIANT, and that data from family-based studies was not analyzed properly (Berg, Harpak, et al., 2019; Sohail et al., 2019). Another recent study has shown that other sources of stratification (based on age, sex and/or socioeconomic factors) might even lead to variation in the accuracy of polygenic scores when analyzing individuals from the same ancestry group Mostafavi et al. (2020).

It is as yet unclear how the choice of GWAS cohort affects tests of polygenic score overdispersion based on allele frequency differences between populations. Each cohort differs in ancestries of participants, inclusion criteria of individuals, SNP ascertainment scheme and association method. Given the poor portability of polygenic scores across populations, is it also true that GWASs performed on different cohorts will result in inconsistent signals of selection? Can we narrow down on the reason for the inconsistencies in previous studies of polygenic adaptation by looking at a larger number of cohorts? Here, we collated GWAS summary statistics from multiple complex traits that have been measured in more than one cohort around the world. We then evaluated how robust signals of polygenic score overdispersion are to the choice of cohort used to obtain effect size estimates. Across all comparisons, we used the same population genomic panel to obtain population allele frequency estimates: The 1000 Genomes Project phase 3 (The 1000 Genomes Project Consortium, 2015). We observe many discrepancies across tests performed on the same phenotype and attempt to understand what may be causing these discrepancies. We compare results for several traits and pay special attention to height, as it is the most well-characterized and studied complex trait in the human genetics literature, as well as a trait for which we have summary statistics from the largest number of GWAS cohorts. Finally, we perform an analogous analysis on educational attainment - a trait that has also been highlighted in recent studies of polygenic adaptation in humans (Racimo et al., 2018; Stern et al., 2021; Uricchio et al., 2019), and that is especially prone to be misinterpreted or misappropriated (Harmon, 2018; Novembre and Nicholas H Barton, 2018). We show that overdispersion signals for this trait are also highly sensitive to the choice of GWAS cohort.

Methods

GWAS summary statistics.

We obtained GWAS summary statistics from five large-scale biobanks, a GWAS meta-analysis and a mega-analysis (Figure 1). Since we aim to make comparisons among them, our interest is focused on traits that were measured in at least two different cohorts. This resulted in a total of 30 traits being included in our analysis.

Below, we provide a brief summary of each of the GWASs we focused on. For an overview of the type of arrays and association methods used in each of these, see Table 1.

- **UKBB**: Summary statistics from the GWAS performed on all UK Biobank traits (Bycroft et al., 2018). These were released by the Neale lab (round 2: http://www.nealelab.is/uk-biobank/), after filtering for individuals with European ancestries. The UK Biobank includes genetic and phenotypic data from participants from across the United Kingdom, aged between 40 and 69. The traits measured include a wide range of lifestyle factors, physical measurements, and other phenotypic information gained from blood, urine and saliva samples. The Neale lab performed association testing in $\sim$ 340,000 unrelated individuals.
- **FINRISK**: Summary statistics from GWASs carried out using the National FINRISK 1992-2012 collection from Finland (https://thl.fi/en/web/thl-biobank ; http://personal.broadinstitute.org/armartin/sumstats/finland/). The FINRISK study is coordinated by the National Institute for Health and Welfare (THL) in Finland and its target population is sampled from six different geographical areas in Northern Finland. The FINRISK cohort was conducted as a cross-sectional population survey every 5 years from 1972 to assess the risk factors of chronic diseases and health behavior in the working age population. Blood samples were collected from 1992 to 2012. Anthropometric measures and other lifestyle information were also collected. The number of samples used for the GWAS results varies among the different traits ($\sim$25,000 to $\sim$5,000) (Borodulin et al., 2018).
- **PAGE**: Summary statistics from a multi-ethnic GWAS mega-analysis performed by the PAGE (Population Architecture using Genomics and Epidemiology) consortium (http://www.pagestudy.org/). This is a project developed by the National Human Genome Research Institute and the National Institute on Minority Health and Health Disparities in the US, to characterize population-level disease risks in various populations from the

Americas (Carlson, 2016; Matise et al., 2011). The association analysis was assembled from four different cohorts: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the Women's Health Initiative (WHI), the Multiethnic Cohort (MEC) and the Icahn School of Medicine at Mount Sinai BioMe biobank in New York City (BioMe). The authors performed GWAS on 26 clinical and behavioural phenotypes. The study includes samples from 49,839 non-European-descent individuals. Genotyped individuals self-reported as Hispanic/Latino (n = 22,216), African American (n = 17,299), Asian (n = 4,680), Native Hawaiian (n = 3,940), Native American (n = 652) or Other (n = 1,052). The number of variants analyzed varies from 22 to 25 million for continuous phenotypes and 11 to 28 million for case/control traits. Sample sizes ranged from 9,066 to 49,796 individuals (Wojcik et al., 2019).

- **BBJ**: Summary statistics from GWASs performed using the Biobank Japan Project, which enrolled 200,000 patients from 12 medical institutions located throughout Japan between 2003-2008 (http://jenger.riken.jp/en/result). The authors collected biological samples and other clinical information related to 47 diseases and self-reported anthropometric measures. GWASs were then conducted on approximately 162,000 individuals to identify genetic variants associated with disease susceptibility and drug responses. Around 6 million variants were included for association testing (Hirata et al., 2017; Kanai et al., 2018; Nagai et al., 2017).
- **Chinese NIPT**: Summary statistics from an association study in China performed via non-invasive prenatal testing (NIPT) on 141,431 pregnant women (https://db.cngb.org/cmdb). The participants were recruited from 31 administrative divisions across the country. The study aimed to investigate genetic associations with maternal and infectious traits, as well as two anthropometric traits: height and BMI (S Liu et al. (2018)). The summary statistics for BMI and height were obtained from GWASs performed on a filtered set of $\sim 60,000$ individuals. The number of imputed variants used was around 2 million.
- **APCDR**: Summary statistics performed using the African Partnership for Chronic Disease Research cohort, which was assembled to conduct epidemiological and genomic research of non-communicable diseases across sub-Saharan Africa (https://personal.broadinstitute.org/armartin/sumstats/apcdr/). The dataset includes 4,956 samples from Uganda (Baganda, Banyarwanda, Burundi, and others). The authors performed GWAS on 34 phenotypes, including anthropometric traits, blood factors, glycemic control, blood pressure, lipid tests, and liver function tests (Heckerman et al., 2016).
- **GIANT**: Summary statistics published by the Genetic Investigation of Anthropometric Traits consortium (2012-2015 version, before including UK Biobank individuals) (Locke et al., 2015; Wood et al., 2014) (https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files). GIANT is a meta-analysis of summary association statistics for various anthropometric traits, and includes information from more than 250,000 individuals of European descent. The meta-analysis was performed on 2.5 million autosomal SNPs, after imputation.

Population genomic panel.

We used the 1000 Genomes Project phase 3 release data (The 1000 Genomes Project Consortium, 2015) to retrieve the allele frequencies of trait-associated variants in different population panels sampled from around the world (Figure 1). We used these to compute polygenic scores for each panel, using autosomal SNPs only. The dataset contains samples from 2,504 people from 26 present-day population panels, whose abbreviations and descriptions are listed in Table 6.

Identifying trait-associated SNPs.

We used summary statistics for a set of 30 traits that were measured in at least two of the previously-listed GWAS datasets. Table 7 shows the full list of the traits included in this analysis and the number of variants and individuals per trait. For each trait, we excluded triallelic variants, variants with a minor allele frequency lower than 0.01 across all samples and those classified as

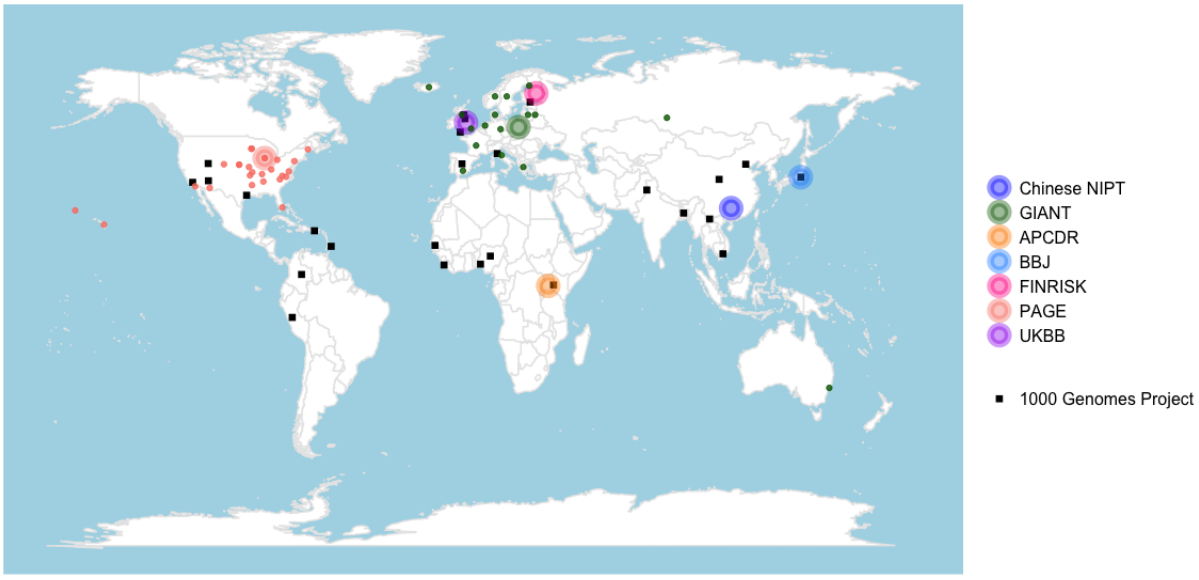

Figure 1 – Map containing the geographic provenance of the panels of each association study we examined (large circles), as well as the 26 population panels from the 1000 Genomes Project (black squares). Small colored dots denote the provenance of the individual GWAS cohorts that were used in GIANT and in PAGE.

Table 1 – Information on genotyping, imputation and association methods for each GWAS analyzed in this study. LM+PCs = linear model with principal components as covariates. LMM = linear mixed model.

GWAS cohort	No. individuals	No. genotyped SNPs	No. imputed SNPs	Association method	GWAS array or sequencing method	Filters
UKBB	360388	820967	10,800,000	LM+PCs	UK Biobank Axiom Array	INFO > 0.8 MAF > 1e−4 HWE P > 1e−10
GIANT	253288	[meta-analysis]	2,834,208	LM+PCs	Affymetrix 500K platform, Illumina genotyping arrays and custom Perlegen arrays	Removed low quality SNPs
BBJ	159,095	958,497	27,896,057	LM+PCs	Illumina HumanOmniExpressExome	INFO ≥ 0.4 MAF > 1.0% HWE P ≥ 1e−6
Chinese NIPT	61,321	NA	2,130,000	LM+PCs	Ultra low depth shotgun sequencing	INFO > 0.4 HWE P > 1e−6
PAGE	49,781	1,748,250	39,723,562	LMM	Illumina Multi-Ethnic Genotyping Array (MEGA)	INFO > 0.4
FINRISK	24,725	551,004	11,670,715	LM+PCs	Illumina CoreExome	INFO > 0.7 MAF > 1.0% HWE P > 1e−6
APCDR	4,778	2,382,209	16,477,797	LMM	Illumina Omni2.5	INFO ≥ 0.3 MAF > 0.5%

low confident variants whenever this information was available in the summary statistics file. We selected a set of trait-associated SNPs based on a P-value threshold, and the effect size estimates of these variants were used to construct a set of polygenic scores. To only include approximately independent trait-associated variants in our scores, we use a published set of 1,703 non-overlapping and approximately independent linkage-disequilibrium (LD) blocks to divide the genome (Berisa and Pickrell, 2016). We extracted the SNP within each block with the lowest association P-value. To investigate the robustness of signals to different filtering schemes, we used two P-value thresholds to extract significantly associated variants: 1) $P < 1e{-}5$ and 2) the standard genome-wide significant cutoff, $P < 5e{-}8$. Blocks that only contain variants that do not meet the chosen threshold were filtered out. As an example, Figure 9.A shows the distribution of effect size estimates of height-associated SNPs with $P < 1e{-}5$. In turn, Figure 9.B shows the distribution of the product of the effect size estimates and the square root of the study's sample size (N). This serves as a fairer comparison among studies, as the standard error of the effect

size estimate is approximately proportional to the inverse of $\sqrt{N}$ (see Casella and Berger, 2002; Edge, 2019; Holland et al., 2016). In order to build an empirical genome-wide covariance matrix (F-matrix) with non-associated SNPs, we extracted all SNPs with a P-value larger than $5e{-}8$ and then sampled every 20th of these SNPs across the autosomal genome.

We also used the LD score regression approach (Heckerman et al., 2016) to obtain an LD score regression intercept, LD score regression ratio, and a SNP heritability estimate for each GWAS that we looked at. The LD score intercept is an estimate of the contribution of population stratification to test statistic inflation in a GWAS analysis. The LD score regression ratio measures the proportion of the inflation in the mean χ^2 statistic that the LD Score regression intercept ascribes to causes other than polygenic heritability. Finally, an estimate of trait heritability can be obtained from the LD score regression slope (B Bulik-Sullivan et al., 2015; BK Bulik-Sullivan et al., 2015). We note, however, that Berg, Harpak, et al. (2019) showed that some of the assumptions of LD score regression - which allow one to separate estimates of stratification confounding from heritability - may be violated in the presence of background selection. Thus, these estimates may not accurately reflect the amount of stratification truly present in a GWAS.

Neutrality test for polygenic scores.

Polygenic risk scores are used to predict the genetic risk of a disease, or the genetic value of a trait, by combining the additive effect of a large number of trait-associated loci across the genome. For each trait, we obtained polygenic scores by computing the sum of allele frequencies at each of the top trait-associated SNPs from each block, weighted by their effect size estimates for that trait. The allele frequencies for these SNPs were retrieved from The 1000 Genomes Project population panels using *glactools* (Renaud, 2017). We then built a polygenic score vector for a given trait, $\vec{Z}$, that contains the polygenic scores of all populations for that trait. Let $\vec{p_l} \in [0,1]^M$ be the vector of derived allele frequencies at locus l, where $p_{l,m}$ is the derived allele frequency at locus l in population m, while α_l is the effect size estimate of the derived allele at locus l. Then, the vector of the polygenic scores, $\vec{Z}$, has length M equal to the number of populations (M = 26) and each element Z_m is the polygenic score for population m

$$Z_m = \sum_{l=1}^{L} 2\alpha_l p_{l,m} \tag{1}$$

Here, L is the total number of trait-associated loci. For each polygenic score we built, we also obtained 95% credible intervals, constructed using the method in Sohail et al. (2019), assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs, and that it follows a beta distribution.

Berg and Coop, 2014 introduced a model designed for comparing polygenic scores across populations, in order to test for deviations from neutrality, which could perhaps be driven by adaptive divergence between populations. The test works by looking for overdispersion from a multivariate normal distribution, which would fit the distribution of scores if this was determined purely by genetic drift.

Under neutral genetic drift, Berg and Coop, 2014 showed that the joint distribution of $\vec{Z}$ across closely-related populations should be approximately multivariate normal under a purely neutral model:

$$\vec{Z} \sim MVN(\mu\vec{1}, 2V_A\mathbf{F}) \tag{2}$$

where $\vec{1}$ is a vector of ones and:

$$\mu = 2\sum_{l=1}^{L} \alpha_l \overline{p}_l, \tag{3}$$

$$V_A = 2\sum_{l=1}^{L} \alpha_l^2 \bar{p}_l (1 - \bar{p}_l) \tag{4}$$

and $\bar{p}_l$ is the average allele frequency of locus l across all populations. The matrix **F** is a genome-wide covariance matrix that captures the co-ancestry among each pair of populations (Berg and Coop, 2014). Based on this null model, we can measure the Mahalanobis distance of the observed distribution of $\vec{Z}$ from the distribution under neutral genetic drift by computing Q_X

$$Q_X = \frac{(\vec{Z} - \mu)^T \mathbf{F}^{-1} (\vec{Z} - \mu)}{2V_A} \tag{5}$$

Under neutrality, the Q_X statistic is expected to follow a chi-squared distribution with M -1 degrees of freedom, χ^2_{M-1} (Berg and Coop, 2014). A significantly large value of Q_X indicates that there is an excess of variance in $\vec{Z}$ that cannot be explained by drift alone.

P-values via randomization schemes.

To avoid relying on the assumption that $\vec{Z}$ follows a multivariate normal distribution under neutrality, we also obtained P-values via two alternative methods (Berg and Coop, 2014; Berg, Zhang, et al., 2017; Racimo et al., 2018). The first one relies on obtaining neutral pseudo-samples by randomizing the sign (but not the magnitude) of the effect size estimates of all trait-associated SNPs, and then recomputing Q_X. The second one involves obtaining pseudo-samples by sampling random SNPs across the genome with the same allele frequency distribution in a particular (target) population as the SNPs used to computed Q_X. For each trait-associated SNP, we thus sampled a new SNP from a subset of the non-associated SNPs whose frequencies lie in the range $[0.01 - p, p + 0.01]$ where p is the derived allele frequency of the trait-associated SNP. Then, we obtained a new P-value by computing the Q_X statistic on each of the pseudo-samples i:

$$P = \frac{1 + \sum_i^S I(Q_X^i > Q_X^A)}{1 + S} \tag{6}$$

Here, Q_X^i is the Q_X statistic computed on pseudo-sample i, Q_X^A is the Q_X statistic computed on the true set of trait-associated SNPs, $I()$ is an indicator function and S is the number of pseudo-samples used, which was set to 1,000. We tested the effect of using different population panels as our 'target' population for the frequency-matching scheme. Since we are utilizing seven GWAS cohorts that are composed of Latin American individuals, Asian (Japanese and Chinese), sub-Saharan African and European (Finnish and British) individuals, we decided to use population panels from the 1000 Genomes that roughly matched the ancestry of the GWAS cohorts: CHB for Chinese NIPT, JPT for BBJ, LWK for APCDR, FIN for FINRISK and GBR for UKBB. While PAGE is a very heterogeneous cohort, we find that PUR is the panel with the lowest amount of differentiation to PAGE, among all 1000G panels (Table 8), so we used PUR as the closest match to PAGE.

Evaluating population structure.

To look for population stratification along different axes of population variation Sohail et al., 2019, we first selected those variants that were present in the 1000 Genomes Project, the UKBB height GWAS and another non-UKBB height GWAS used for comparison against UKBB. We filtered out variants that had minor allele frequency $< 5\%$ in the 1000 Genomes Project, or that were located in the MHC locus (chr6:28477797-33448354) or in the chromosome eight inversion region (chr8:7643092-11528113). We then performed LD pruning on the resulting set of variants (using the –indep-pairwise 200 100 0.2 option). The remaining SNPs were used to perform a PCA on a matrix of genotypes from all the 1000 Genomes Project individuals, from which we obtained the first 20 PC loadings of population structure, using plink. Then, we performed linear regression of the PC scores on the genotypes of each SNP that was previously removed

due to the pruning procedure. Finally, we plotted the correlations between each of the PCs and the effect size estimates from one of the two GWASs: UKBB or non-UKBB.

Assessing different association methods.

We were also interested in evaluating the effects of different types of association methods on the significance of the Q_X statistic. We used the UKBB cohort to perform different types of association studies on height. Starting from 805,426 genotyped variants across the genome, we restricted to SNPs with a minor allele frequency (MAF) $> 5\%$ globally, and performed associations on three different sets of individuals from the UKBB cohort: 1) self-reported white British individuals ("British"), 2) self-reported "white" individuals, and 3) "all ethnicities", i.e. a UKBB set including all self-reported ethnicity categories. We applied the following quality filters in each of the resulting sets: 1) removed variants with $P < 1e{-}10$ from the Hardy-Weinberg equilibrium test, 2) removed variants with $MAF < 0.1\%$ in the set, 3) removed variants with an INFO score less than 0.8, 4) removed variants outside the autosomes, and 5) removed individuals that were 7 standard deviations away from the first six PCs in a PCA of the set (following the Neale lab's procedure for defining British ancestry after performing PCA on the UKBB dataset). We then performed a GWAS via a linear model (LM) using PLINK v1.9 (Chang et al., 2015) and a GWAS via a linear mixed model (LMM) using BOLT-LMM (Loh et al., 2018), on each of the three sets (Table 2). We used sex, age, age^2, sex*age, sex*age^2 and the first 20 PCs as covariates.

We also aimed to test whether a meta-analysis approach could lead to overdispersion of polygenic scores, and consequently, an inflated Q_X statistic. Therefore, we created a set of artificial meta-analyses on the entire UKBB cohort, approximately emulating the number of individual sub-cohorts that were included in GIANT. We used both the "all ethnicities" and the "white British" UKBB cohorts to compare the results of a meta-analysis on a homogeneous vs. a diverse cohort of individuals. For each of the two cohorts, we divided the corresponding set of individuals into 75 subsets, using two different approaches. In one approach, we obtained 75 clusters from a K-means clustering of the first three principal components from a PCA of the individuals. Under this approach, different cohorts have different sample sizes (though they do not exactly match the cohort size distribution observed in GIANT). In the other approach, we created 75 groups of equal size, randomly assigning individuals to each group, regardless of their placement in the PCA.

We used PLINK 1.9 to perform a linear association model in each of the 75 clusters or groups. As before, we used sex, age, age^2, sex*age, sex*age^2 and the first 20 PCs as covariates. These covariates were included in the analysis of each cohort before the meta-analysis. We explored how PC correction affected the meta-analyses. As the first 20 PCs, we used either the components from a PCA performed on each of the 75 sub-cohorts or the components from a PCA performed on all individuals together, before they were split. We note that the latter PCA would not be available to a researcher performing a meta-analysis in practice, but we carried it out to check whether lack of power to correctly model population structure via the cohort-specific PCAs was somehow misleading us. Afterwards, we integrated all summary statistics into a meta-analysis, using two different methods (Table 2): an inverse variance method and a sample size-based method, both implemented in METAL (Willer et al., 2010). This led to a total of 16 different types of meta-analyses artificially performed on the UKBB data.

Educational attainment GWAS.

We also performed an assessment of robustness in the distribution of population-wide polygenic scores for educational attainment. In this case, together with effect size estimates from the UK Biobank, we also obtained estimates from three studies carried out by the Social Science Genetic Association Consortium (SSGAC) (ttps://www.thessgac.org):

- A meta-analysis of 126,559 individuals (42 discovery cohorts and 12 replication cohorts) (Rietveld et al., 2013)
- A meta-analysis of 293,723 individuals (64 cohorts) (Okbay et al., 2016).

Table 2 – Description of types of methods used to obtain SNP associations from UKBB.

Code	Cohort composition	Description of association method
british linear-model	Self-reported "British" individuals from UKBB	linear model implemented in PLINK 1.9
british mixed-model	Self-reported "British" individuals from UKBB	linear mixed model implemented in BOLT-LMM
white linear-model	Self-reported "White" individuals from UKBB	linear model implemented in PLINK 1.9
white mixed-model	Self-reported "White" individuals from UKBB	linear mixed model implemented in BOLT-LMM
all ethnicities linear-model	All self-reported ethnicities from UKBB	linear model implemented in PLINK 1.9
all ethnicities mixed-model	All self-reported ethnicities from UKBB	linear mixed model implemented in BOLT-LMM
meta-analysis.inverseSE.random	75 sub-cohorts of equal size, composed of randomly sampled individuals from UKBB (all ethnicities)	inverse-variance-based meta-analysis implemented in METAL
meta-analysis.inverseSE.kmeans	75 sub-cohorts obtained from K-means clustering using 1st 3 PCs of UKBB individuals (all ethnicities)	inverse-variance-based meta-analysis implemented in METAL
meta-analysis.samplesize.random	75 sub-cohorts of equal size, composed of randomly sampled individuals from UKBB (all ethnicities)	sample-size-based meta-analysis implemented in METAL
meta-analysis.samplesize.kmeans	75 sub-cohorts obtained from K-means clustering using 1st 3 PCs of UKBB individuals (all ethnicities)	sample-size-based meta-analysis implemented in METAL

- A meta-analysis of 1,131,881 individuals (Lee et al., 2018) (71 cohorts in total). Note that this study includes the samples from the Okbay et al., 2016 study and the UK Biobank as well.

We took the summary statistics of each educational attainment GWAS "as is", without modeling sample overlap between cohorts.

Results

Robustness of signal of selection and population-level differences.

We obtained sets of trait-associated SNPs for GWASs performed on seven different cohorts: UK Biobank, FINRISK, Chinese NIPT, Biobank Japan, APCDR and PAGE. Using the effect size estimates from each GWAS, we calculated population-wide polygenic scores for each of the 26 population panels from the 1000 Genome Project (The 1000 Genomes Project Consortium, 2015), using allele frequencies from each population panel. We then tested for overdispersion of these scores using the Q_X statistic, which was designed to detect deviations from neutral genetic drift affecting a set of trait-associated SNPs (Berg and Coop, 2014). We focused on 30 traits that were phenotyped in two or more cohorts, so that we could compare the P-value of this statistic using effect size estimates from at least two different cohorts (see Methods).

We applied the Q_X statistic to each of the 30 traits by selecting SNPs we deemed to be significantly associated with each trait . We used two different P-value cutoffs to select these SNPs: 1) a lenient cutoff, $P < 1e{-}5$ and 2) the standard genome-wide significance cutoff $P < 5e{-}8$. To verify that significant P-values of the Q_X statistics were not due to violations of the chi-squared distributional assumption, we also computed P-values using two randomization schemes: one is based on randomizing the sign of the effect size estimates of the trait-associated SNPs (but not their magnitude), while the other is based on using frequency-matched non-associated SNPs (see Methods). In general, P-values obtained from the three schemes are broadly similar across the various approaches used. However, we observe a few inconsistencies in the sign-randomization scheme, when compared to the other two approaches (Figures 10 and 11). The number of significant SNPs for each of the traits under the two cutoffs is shown in Figures 12 and 13.

We used two types of multiple-testing Bonferroni corrections: one that applies to us - correcting for both the number of traits assessed and the number of cohorts on which each of those traits were tested (we call this number m) - and another that would apply to a person that was blind to the other cohorts - and so would only correct for the n traits tested within their available

cohort (Figures 2, 10). We only find few traits with significant overdispersion in Q_X. Under the $P < 1e{-}5$ SNP-association cutoff, the only traits with significant overdispersion in at least one cohort are height and white blood cells (WBC) (Figures 2, 10). Potassium levels in urine and mean corpuscular hemoglobin (MCH) also result in significant values of Q_X when using the $P < 5e{-}8$ SNP-association cutoff (Figures 11, 14).

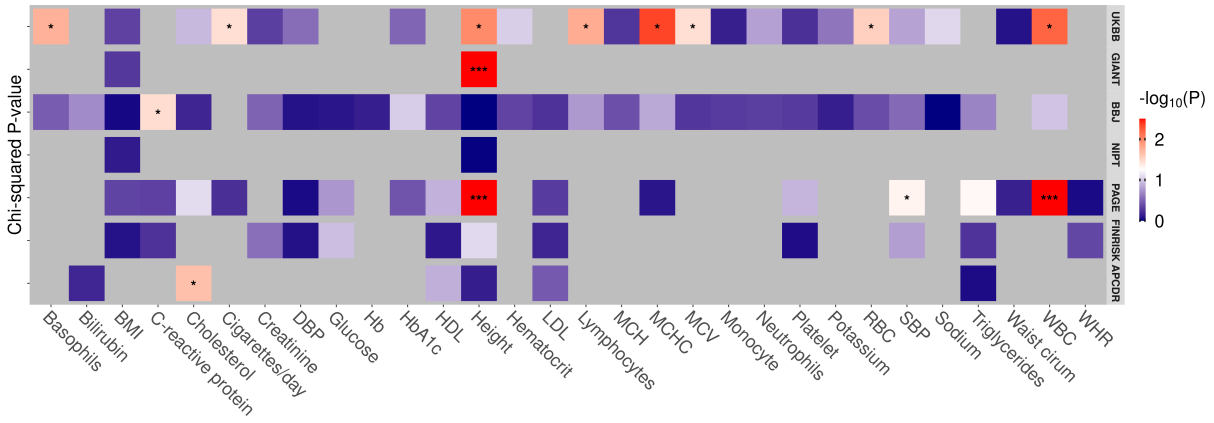

Figure 2 – Each cell of this heatmap is the $-log_{10}$(P-value) of a Q_X test using SNPs associated with different traits and effect size estimates obtained from different GWASs (grey-coloured cells indicate that no data is available for the corresponding trait). Each row corresponds to one of the six GWASs we are evaluating and the columns correspond to the different traits for each GWAS that have SNPs with $P < 1e{-}5$. BMI, body mass index; DBP, Diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell count; SBP, systolic blood pressure; WBC, white blood cell count; WHR, waist-to-hip ratio. Significance thresholds after Bonferroni correction: *** < 0.05/m, ** < 0.05/n, * < 0.05, where *n* is the number of traits in each GWAS (row-dependent) and *m* is the total number of tests calculated, across all GWASs.

Figure 3 shows polygenic scores computed for each of the 1000 Genomes populations for height. In agreement with previous studies (Berg, Harpak, et al., 2019; Sohail et al., 2019), we observe that differences in polygenic height scores when using effect size estimates from the UKBB are greatly attenuated relative to differences in scores built when using estimates from GIANT. Extending this analysis across all datasets, we observe that PAGE polygenic scores are also over-dispersed, though in different directions than GIANT scores (Figure 3). Additionally, the observation that Europeans have very high polygenic scores when using GIANT effect size estimates cannot be replicated using any of the other GWAS estimates. After multiple testing correction (for both association P-value threshold schemes), we only obtain significant Q_X P-values when using summary statistics from PAGE and GIANT. The number of SNPs used for polygenic scores are shown in Table 3. The LD score regression ratio is substantially higher for PAGE and FINRISK than for the other cohorts (Tables 4, 9).

We also tested how the choice of the SNP association P-value threshold influenced the results. Sohail et al., 2019 showed that between-population differences in polygenic height scores grow stronger when using more lenient SNP association P-value cutoffs. However, one then runs the risk of including more variants that may be significantly associated due to uncorrected population stratification. We see there is a smaller score overdispersion when using the genome-wide significant SNPs, than when using the more lenient P-value cutoff (right column, Table 3 and Figure 15).

Finally, we computed polygenic scores on a single set of candidate SNPs ascertained in the largest biobank (UKBB) but using effect size estimates from each of the other GWAS in turn. Signals of overdispersion in height polygenic scores are greatly attenuated in each of the non-UKBB GWAS, and are much more similar to the patterns observed in UKBB (Figure 16 and Figure

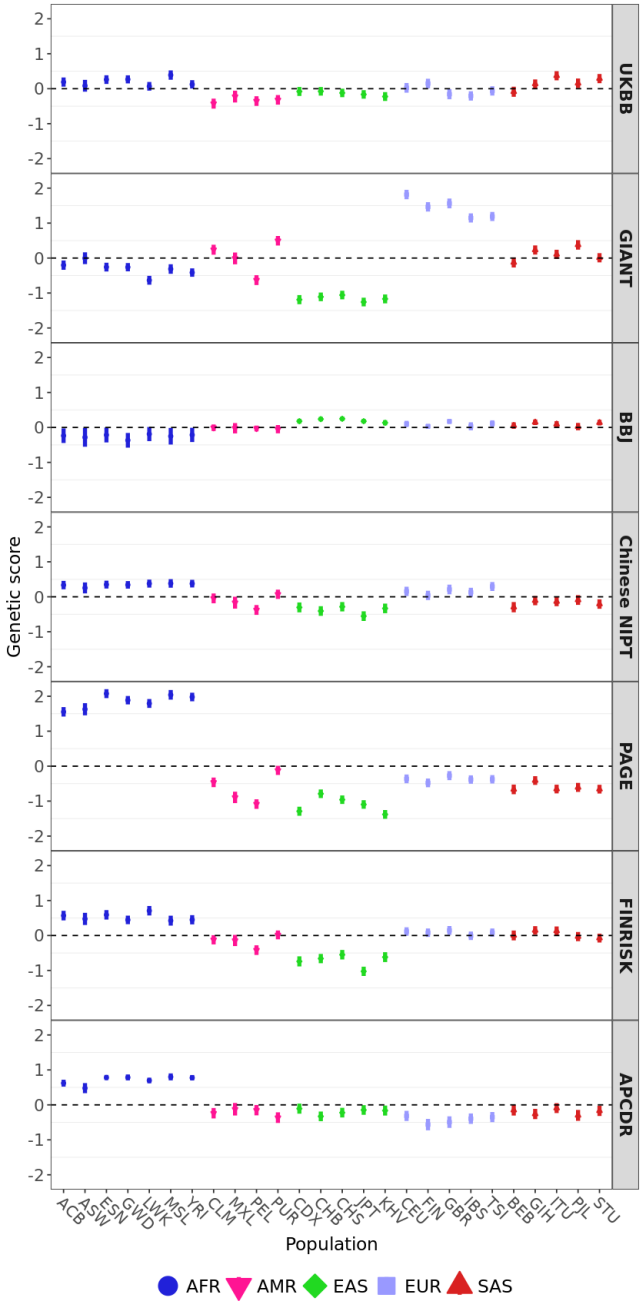

Figure 3 – Polygenic scores for height using candidate SNPs with $P < 1e{-}5$. The 1000 Genomes Project populations colored by their super-population code. The corresponding number of trait-associated SNPs and the Q_X P-value for each GWAS are shown in Table 3. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

17). This suggests an important reason for the observed overdispersion patterns in these other GWAS is the choice of significant SNPs recovered from each study.

We also looked in closer detail at other traits with evidence for significant overdispersion via the Q_X test. White blood cell counts (WBC), for example, shows strong overdispersion when using PAGE, but not when using the UKBB or BBJ effect size estimates (Figure 18). We also observe a similar pattern when looking at mean corpuscular hemoglobin (MCH) scores (Figure 19). In the case of potassium levels in urine, larger between-population differences are found in UKBB than in BBJ, when we use the stringent threshold (Figures 20). In general, we observe that

Table 3 – Height Q_X scores and P-values, assuming a chi-squared distribution for the scores. The number of trait-associated SNPs used to compute the scores are shown for both cutoffs.

	Lenient association threshold ($P < 1e{-}5$)		Strict association threshold ($P < 5e{-}8$)	
GWAS cohort	Num. trait associated SNPs	Q_X	Num. trait associated SNPs	Q_X
UKBB	1140	45.57 (P = 0.01)	810	39.72(P = 0.04)
GIANT	739	102.73 (P = 4e-3)	468	69.18 (P = 8e-8)
BBJ	759	9.255 (P = 0.99)	431	35.00 (P = 0.11)
Chinese NIPT	164	12.82 (P = 0.99)	60	24.68(P = 0.54)
PAGE	528	77.31 (P = 5e-7)	84	49.52 (P = 4e-3)
FINRISK	209	36.43 (P = 0.08)	47	41.48 (P = 0.03)
APCDR	61	21.15 (P = 0.73)	0	NA

Table 4 – SNP-based heritability and LD Score regression ratio and intercept estimates (with standard errors in parentheses) for height measured in different cohorts. LD scores were computed for the super-population panels in the 1000 Genomes Project. The APCDR heritability estimate is not shown because it was estimated to be negative, due to the small sample size of the cohort.

GWAS cohort	Genome-wide significant SNPs (P < 5e−8)	Observed scale heritability (SE)	LD regression ratio (SE)	LD regression intercept (SE)	Super Population
UKBB	30891	0.4205 (0.0183)	0.1184 (0.0098)	1.4384 (0.0362)	EUR
GIANT	11625	0.3159 (0.0146)	0.1419 (0.0094)	1.2727 (0.0181)	EUR
BBJ	9976	0.4168 (0.019)	0.1142 (0.0128)	1.1829 (0.0204)	EAS
Chinese NIPT	1573	0.329 (0.0201)	0.0746 (0.0353)	1.0425 (0.0201)	EAS
PAGE	564	0.2578 (0.0237)	0.371 (0.0336)	1.1762 (0.016)	AMR
FINRISK	415	0.4557 (0.0446)	0.3775 (0.035)	1.1358 (0.0126)	EUR
APCDR	0	NA	NA	NA	AFR

between-population differences in polygenic scores tend to be more similar between studies when using the stricter SNP-association P-value threshold, than when using the more lenient threshold.

Relationship between GWAS effect size estimates.

To better understand where the differences in overdispersion of Q_X could stem from, we performed pairwise comparisons of the effect size estimates from the different GWAS. Since the UKBB GWAS is the GWAS with the largest number of individuals, we decided to compare the estimates from each of the other studies to the UKBB estimates. Here, we only focused on the 1,703 approximately-independent SNPs (the best tag SNP within each LD block). We began by only using SNPs that were classified as significant in UKBB using the lenient cutoff ($P < 1e{-}5$) (Figure 4). We observe that effect size estimates are correlated, as expected, but the strength of this correlation varies strongly across comparisons. UKBB vs. GIANT shows the highest correlation, while UKBB vs. APCDR shows the lowest. Those SNPs that also have a significant P-value in the non-UKBB GWAS in each comparison (colored in red in Figure 4) show a higher correlation than the rest of the SNPs: a pattern expected due to the winner's curse, and exacerbated by differences in sample sizes and LD patterns between GWAS cohorts (Berg, Harpak, et al., 2019).

The same analysis was carried out with SNPs classified as significant in each of the non-UKBB studies. The correlation of effect size estimates is generally lower (Figure 21), and a high percentage of SNPs deemed to be significant in the non-UKBB GWAS have effect size estimates approximately equal to zero in the UKBB GWAS (Figure 21). This pattern is stronger when we do not filter the 1,703 approximately independent SNPs by a particular SNP-association P-value cutoff (Figures 22 and 23).

We computed pairwise Pearson correlation coefficients between estimated effect sizes in the UKBB GWAS and each of the other GWAS (Table 10 when using SNPs that are significant in UKBB and Table 11 when using SNPs that are significant in the other GWAS). We observe that

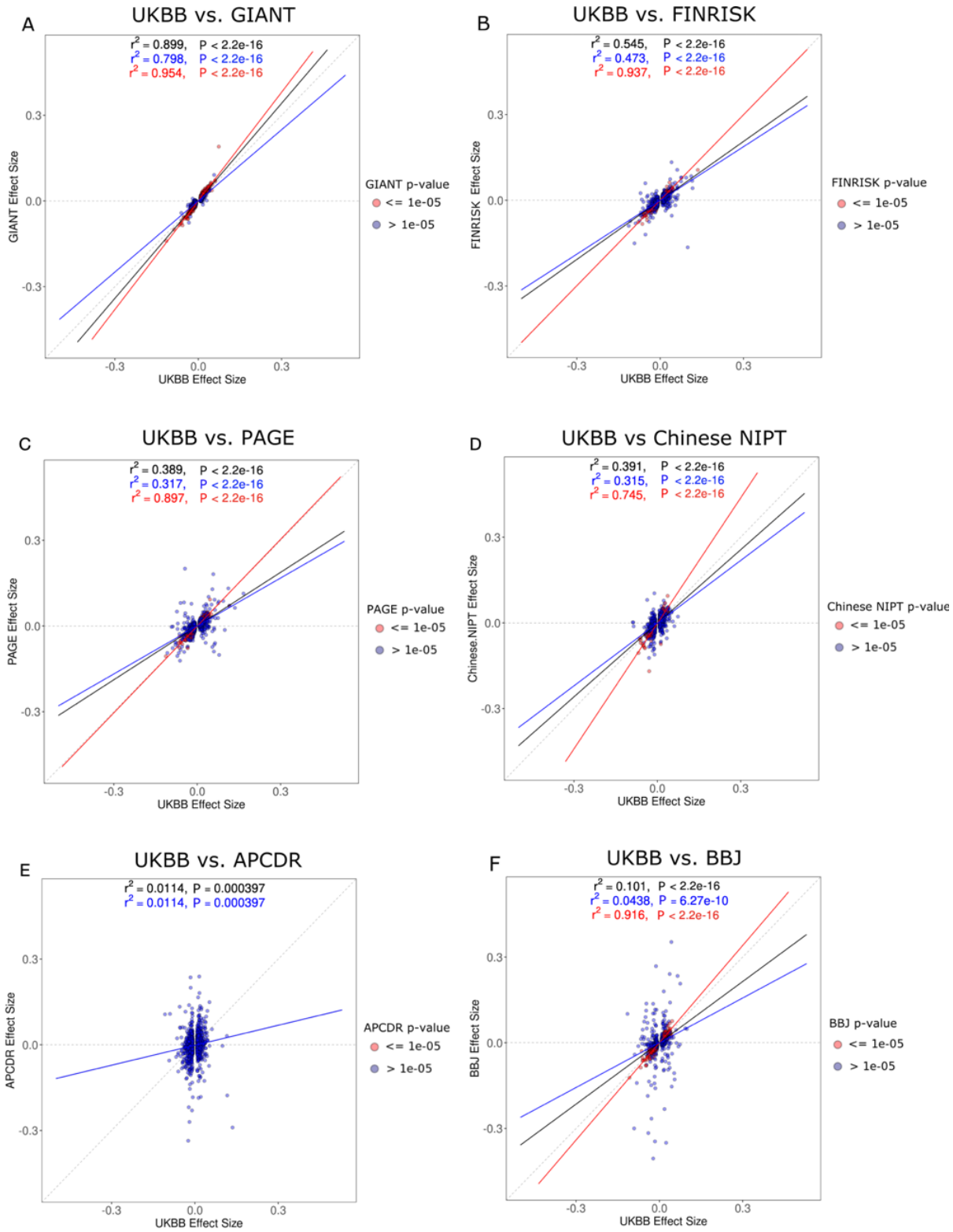

Figure 4 – Regression of UKBB effect size estimates against non-UKBB effect size estimates, after filtering for SNPs with $P < 1e{-}5$ in the UKBB GWAS. The SNPs are colored based on their P-value in the non-UKBB GWAS, as are the corresponding regression lines (red: $P < 1e{-}5$; blue: $P > 1e{-}5$). The black regression line was obtained using all SNPs, regardless of their P-value in the non-UKBB GWAS.

GWAS performed on individuals living geographically close to Britain have higher correlations to UKBB estimates than those that are performed on distant individuals. For instance, GIANT

and FINRISK (both European-based GWAS), show high correlation in effect size estimates with UKBB (0.9958 and 0.790, respectively). In contrast, the GWAS carried out on an African cohort - APCDR - shows an extremely low correlation in effect size estimates with UKBB (correlation coefficient = 0.087). This cohort has by far the smallest sample size of all the cohorts we analyzed (n = 4,778), which may explain the low correlation. We also observe higher correlations when filtering for significantly associated SNPs using either of the two SNP significance thresholds ($P < 1e{-}5$ and $P < 5e{-}8$) from the 1703 LD blocks.

The sample size of the GWAS might also affect the correlation in effect size estimates. We can see in Figure 24 that there is a positive relationship between the log_{10} of the number of samples included in the non-UKBB GWAS and the Pearson correlation coefficients between the estimated effects in the non-UKBB GWAS and those estimated in the UKBB GWAS (which has the largest sample size). We note, however, that the slope of a linear regression between these variables is only significantly different from zero when ascertaining SNPs in the non-UKBB study, and filtering for SNPs with P $< 1e{-}5$.

Most of our results stem from using LD block partitions derived from a European panel of the 1000 Genomes Project (Berisa and Pickrell, 2016; The 1000 Genomes Project Consortium, 2012). To investigate the sensitivity of our results to the choice of LD blocks (particularly when querying non-European GWASs), we also show results under an LD blocking scheme obtained from a population panel that was close to the GWAS from which we obtained effect size estimates (Berisa and Pickrell, 2016). For BBJ and Chinese NIPT, we use a set of 1,445 LD blocks constructed using LD patterns in the East Asian panels of the 1000 Genomes Project. For APCDR, we use a set of 2,582 LD blocks constructed using LD patterns in the African panels of the 1000 Genomes Project (Table 12). In the case of PAGE, we do not have a Latin-American-specific LD block partitioning scheme. However, when we use European LD blocks, we can detect a significant residual population structure pattern in PAGE, but this pattern is no longer significant when we use African LD blocks (Figure 25), so we show PAGE results using African LD blocks in Table 12-

Evidence for population stratification.

Berg, Harpak, et al., 2019 looked for latent population stratification by studying the relation between allele frequency differences in two populations and the difference in effect size estimates in two GWAS. Presumably, if neither GWAS is affected by population stratification, there should not be a correlation between these two variables. We plotted SNP differences in allele frequency between northern European and East Asian, African, and southern European samples (GBR, CHB, LWK and TSI subsets of 1000 Genomes, respectively) against the difference in height effect size between a pair of GWAS. When comparing the UKBB and GIANT, we replicate the signal of correlation in differences between northern and southern European from Berg, Harpak, et al., 2019 ($P < 1e{-}5$, see Figure 26). This pattern is also observed in the GBR vs. CHB and GBR vs. LWK comparisons (Figures 27 and 28, panel A and B). However, these differences are not observed for any other pairwise GWAS comparisons (Figures 26, 29, 30 and 31). We can see SNPs with large effect size differences tend to be low-frequency SNPs, as the standard error of the effect size estimate for a SNP in a GWAS is a function of the SNP's expected heterozygosity (Holland et al., 2016).

We also followed Sohail et al., 2019's approach to look for GWAS stratification along different PCA axes of population structure. We first performed a PCA on a matrix of genotypes from all 1000 Genomes Project individuals. Then, we computed the correlation between the first 20 loadings of that PCA and the effect size estimates obtained from the UKBB height GWAS, as well as the correlation between the same PC loadings and the effect size estimates from a different (non-UKBB) height GWAS, on the same set of sites (see Methods). We plotted each of these PC-specific correlations and colored them by the correlation between the corresponding PC and the allele frequency differences between two population panels: GBR vs. TSI (Figure 5); and GBR vs. CHB (Figure 32). This allows us to compare patterns of stratification between two GWASs (UKBB and non-UKBB) along particular axes of genetic variation. We observe large correlations between axes of population structure and effect size estimates in GIANT and PAGE,

and to a lesser degree in FINRISK, but not in the other GWAS we queried. Overall, this suggests GIANT and PAGE might be more strongly confounded by stratification than the other GWASs under study.

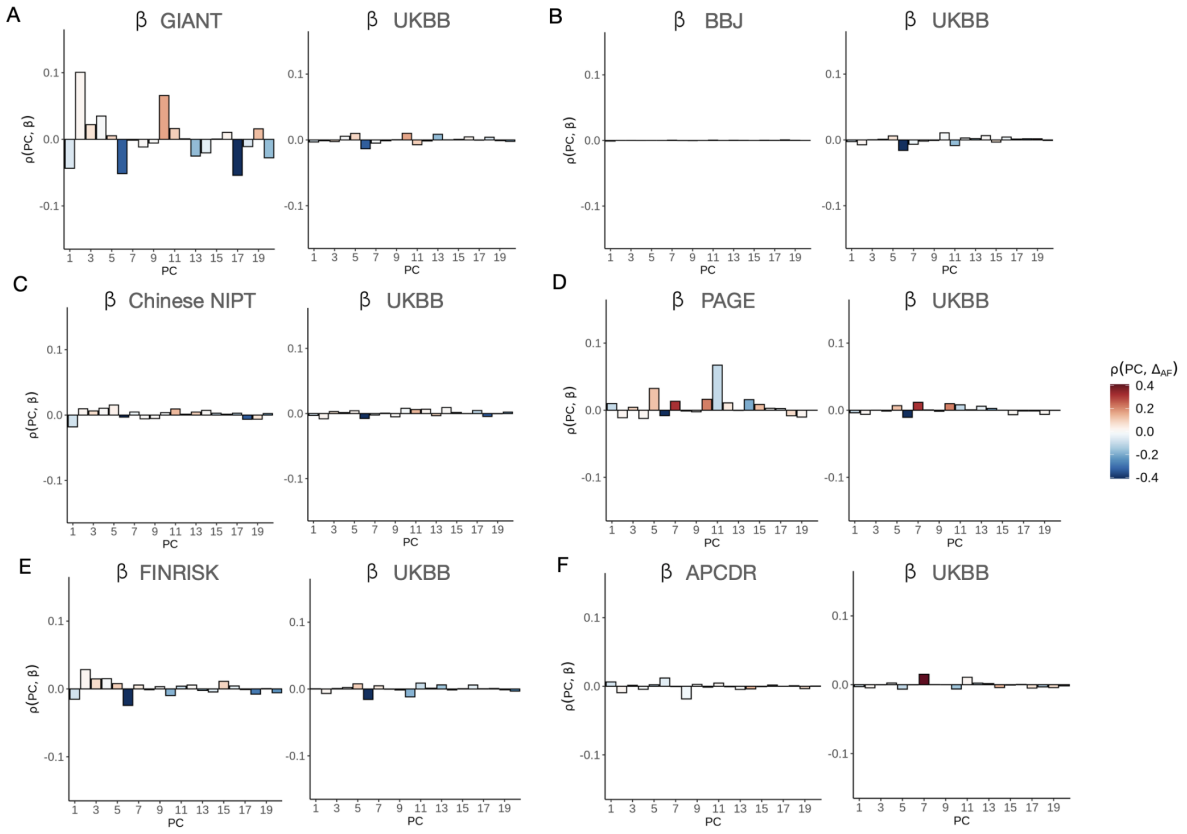

Figure 5 – Pearson correlations between 20 PC loadings and height effect size estimates from a non-UKBB GWASs, compared to the same correlation using effect size estimates from the UKBB GWAS, for different choices of non-UKBB GWAS. The correlations were computed using SNPs that are present in both the UKBB and non-UKBB GWAS cohorts, and in the 1000 Genomes Project. The barplots are coloured by the correlation between each loading and the allele frequency difference between GBR and TSI. A) GIANT vs. UKBB. B) BBJ vs. UKBB. C) Chinese NIPT vs. UKBB. D) PAGE vs. UKBB. E) FINRISK vs. UKBB. F) APCDR vs. UKBB.

Assessing different association methods.

We find strong differences in the amount of polygenic score overdispersion across GWASs, but the GWASs we assessed were carried out using different association methods. We wanted to evaluate the effect of different association methods on the overdispersion of polygenic scores, while using the same underlying association cohort. We chose the UKBB cohort for this assessment, as it is the largest cohort among the ones we tested. We first split the UKBB cohort into three increasingly more expansive sets: 1) "British", 2) "White", and 3) "all ethnicities", based on a self-identified ethnicity classification carried out by the UKBB consortium. We then performed linear model (LM) and linear mixed model (LMM) association methods on each of the three sets of individuals (Table 2, see Methods). We also wanted to see if we could replicate the strong overdispersion in polygenic scores we saw in GIANT, by partitioning the entire UKBB cohort into 75 cohorts (approximately emulating the number of cohorts in GIANT), and then performing a meta-analysis on the summary statistics obtained from individual GWASs performed separately on each of these cohorts (Table 2, see Methods).

The population-wide polygenic scores and the Q_X scores obtained using effect size estimates from each of these different methods are in Figures 6 and 7, respectively. We have more power to detect height-associated SNPs when we used the mixed model, and the distribution of polygenic scores differs quite markedly between the linear model and the mixed model approaches. For example, African polygenic scores tend to be higher when using the mixed model approach. Regardless of whether one uses a linear or a mixed model, GWASs performed on a more expansive category of people ("all-ethnicities") lead to increased overdispersion of polygenic scores than when using more restrictive categories ("British" or "White"). Additionally, our artificial meta-analysis on the UKBB data resulted in even stronger overdispersion of the scores and, consequently, an even more strongly inflated Q_X statistic, regardless of the set used. However, polygenic scores dispersion is slightly attenuated when we use the "British" set. The most extreme Q_X-derived P-values across settings were those from the meta-analyses in the "all ethnicities" set (Figure 33). This increased overdispersion is particularly evident when looking at the scores of European (FIN, CEU, GBR) and Latin American (PEL, CLM, MXL) populations in the meta-analysis setting (Figure 6). The choice of method for PC correction against population stratification does not lead to notably different results (Figure 34).

The case of educational attainment.

Previous studies have also found evidence for strong score overdispersion in variants associated with educational attainment (Racimo et al., 2018; Uricchio et al., 2019) - a trait consisting in the number of school years an individual has received. This trait has received considerable attention in both the media and the scientific literature, due to its potential for misappropriation and misuse by far-right groups (Harmon, 2018; Novembre and Nicholas H Barton, 2018). Though associated variants have been shown to be disproportionally located in genes involved in brain development, this trait is also highly affected by the environment (Lee et al., 2018; Okbay et al., 2016), and potentially likely to be confounded by unaccounted factors, such as cultural and socioeconomic background, and parental salary and education. Like height, the genetic value of this trait has also been shown to be significantly similar among spouses, due to assortative mating (Abdellaoui et al., 2015; Hugh-Jones et al., 2016; MR Robinson, Kleinman, et al., 2017; Yengo et al., 2018), which could, in turn, affect the interpretation of population genetic tests that assume individuals are not segregating on the basis of trait preferences. The robustness of previously reported signals of overdispersion thus warrants some attention, and we therefore set out to assess how consistent patterns of overdispersion were across available GWAS cohorts.

Though educational attainment is only available in one of the cohorts we had access to (UKBB), there are also 3 publicly available GWAS on this trait that were carried out in individuals of European ancestry by the SSGAC consortium: Lee et al. (2018), Okbay et al. (2016), and Rietveld et al. (2013). The SSGAC consortium used increasingly larger meta-analyses to test for genetic associations with this trait (Lee et al., 2018 included both the Okbay et al., 2016 cohorts and the UK Biobank cohort in its meta-analysis). To be able to replicate the results of Racimo et al., 2018, we also computed polygenic scores on the Okbay et al., 2016 GWAS estimates using the posterior-probability approach (PPA) used in that study, and compared them to the P-value approach used throughout this manuscript.

As with height, we find strong inconsistencies in patterns of score dispersion, depending on the P-value cutoff used to include SNPs in the polygenic score, and on which cohort we use for deriving effect size estimates (Figure 8 and Table 5). For example, when using genome-wide significant SNPs to build scores, the strongest pattern of overdispersion is found when utilizing estimates from Okbay et al., 2016 with the PPA method (Q_X-derived $P = 0.0037$). When including SNPs into the score via the more lenient SNP association P-value cutoff ($1e{-}5$), the strongest pattern of ovedispersion is found when using estimates from Lee et al., 2018 (Q_X-derived $P = 1.397e{-}5$). Importantly though, the patterns of dispersion are different under these two conditions: European polygenic scores are highest in the latter, but East Asian scores are highest in the former. The UKBB score pattern when using genome-wide significant SNPs resembles the Okbay et al., 2016 pattern (as noted in Racimo et al., 2018) but is very different from the Lee et al., 2018 pattern, and is also different from scores derived from the same (UKBB) cohort

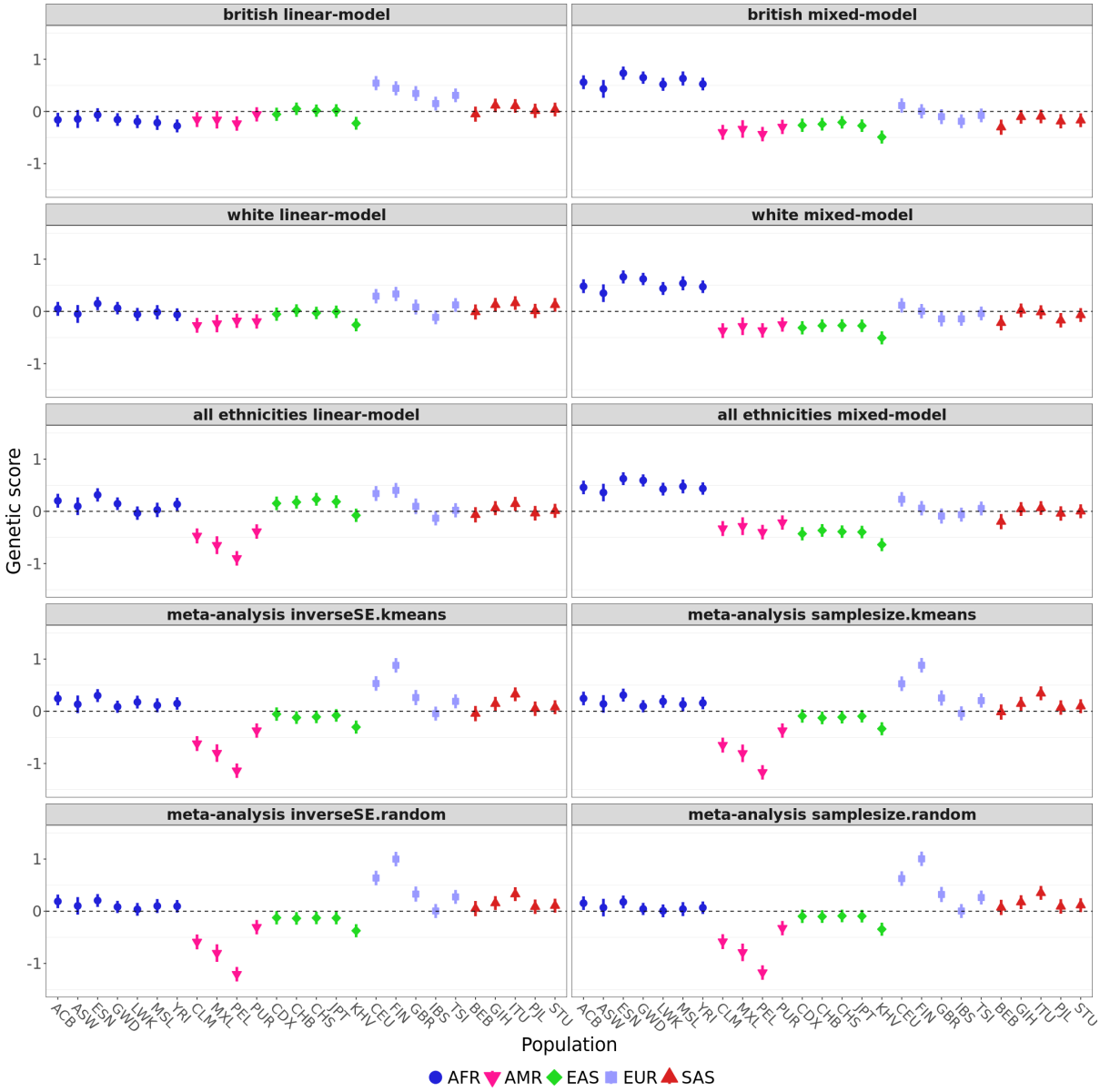

Figure 6 – Polygenic scores for height in each of the 1000 Genomes population panels, using effect size estimates from UKBB, obtained via different types of association methods. The types of GWAS methods used are described in Table 2. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

under the more lenient association P-value scheme. Even though evidence for population stratification is weaker in these meta-analyses than in the height GWAS meta- and mega-analyses (Figure 35), the axes of stratification still differ across studies, which might help to explain the differences in score distributions.

Discussion

When looking at patterns of polygenic score overdispersion across populations, we observe highly inconsistent signals depending on the GWAS cohort from which we obtained effect size estimates. Because we are using the exact same population panels to obtain population allele frequencies in all tests, the source of the inconsistencies must necessarily come from differences

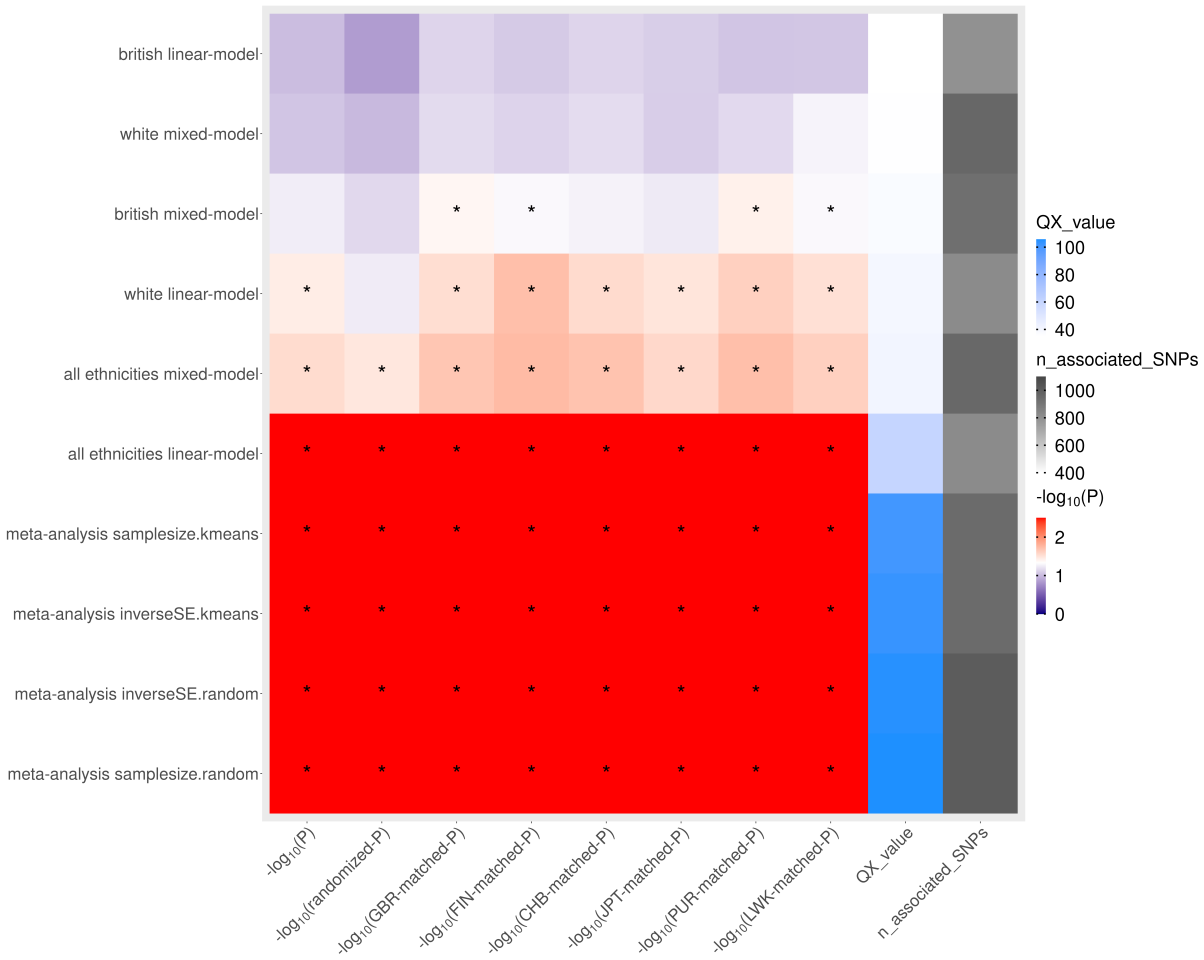

Figure 7 – Q_X statistics and P-values for the trait height, obtained by using different types of association methods on the UKBB data. The asterisk denotes a significance cutoff for Q_X of $P < 0.05$. "-log10(Chi squared P)" = -log10(P), obtained assuming a chi-squared distribution for the Q_X statistic. "-log10(randomized P)" = -log10(P-value), obtained using the effect sign-randomization scheme. All other P-values were obtained by sampling random SNPs from the genome using the allele frequency matching scheme in different populations, as described in the Methods section. The different types of GWAS methods along the y-axis are described in Table 2.

Table 5 – Educational attainment Q_X scores, assuming a chi-squared distribution for the scores. The number of trait-associated SNPs used to compute the scores are shown for both SNP P-value cutoffs.

	Lenient association threshold ($P < 1e{-}5$)		Strict association threshold ($P < 5e{-}8$)	
GWAS cohort	Num. trait associated SNPs	Q_X	Num. trait associated SNPs	Q_X
UKBB	746	40.087 (P = 0.038)	246	42.859 (P = 0.02)
Leeetal.2018	907	67.761 (P = 1.4e-5)	416	51.62 (P = 0.002)
Okbayetal.2016	319	36.814 (P = 0.08)	74	35.175 (P = 0.1)
Rietveldetal.2013	54	35.444 (P = 0.102)	4	29.005 (P = 0.311)

in the effect size estimates in the different GWAS, or be due to different SNPs passing the significance threshold in different GWAS. These inconsistencies are not limited to tests involving height-associated SNPs: they also appear in tests involving SNPs associated with other phenotypes, like white blood cell count, mean corpuscular hemoglobin, potassium levels in urine, and educational attainment.

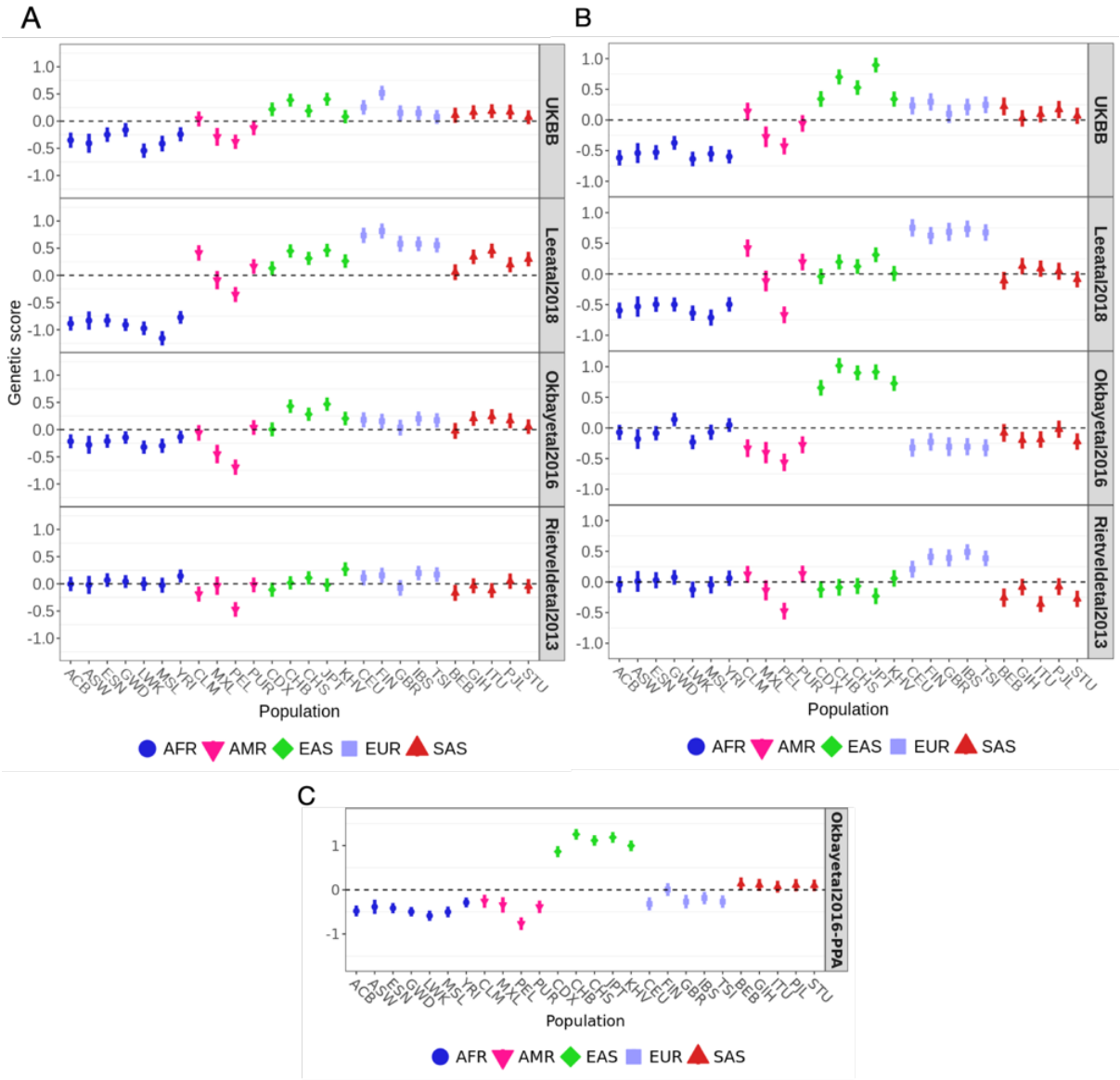

Figure 8 – Polygenic scores for educational attainment in each of the 1000 Genomes population panels, using effect size estimates from three SSGAC consortium GWAS studies (Lee et al., 2018; Okbay et al., 2016; Rietveld et al., 2013) and the UKBB Neale lab effect size estimates (round 2: http://www.nealelab.is/uk-biobank/). A. Polygenic scores for variants with $P < 1e{-}5$. B. Polygenic scores for variants with $P < 5e{-}8$. C. Variants selection using a posterior-probability approach (PPA) on the Okbay et al., 2016 summary statistics, emulating Racimo et al., 2018. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

For those phenotypes for which we have effect size estimates from more than two different sources, we find that the GWASs performed using multiple cohorts of diverse ancestries - GIANT and PAGE - show stronger overdispersion in genetic scores via the Q_X statistic and stronger evidence of population stratification (Figures 4 and 5). In biobank-based GWAS conducted using panels with relatively homogeneous ancestries, the signals of selection are generally (but not always) more attenuated, and signals of stratification are much weaker. This suggests differences in scores are perhaps not driven by a biological signal and are instead driven by population stratification in GIANT and/or PAGE. An alternative explanation is that the overdispersion in PAGE

or GIANT-derived scores is truly biological, and perhaps the GWAS performed in more homogeneous biobank studies are overcorrecting for population stratification, increasing the false negative rate of the Q_X statistic. Moreover, our power to find signals of polygenic adaptation might stem from SNPs with large contributions to phenotypic variance in non-European populations (e.g. African populations) and thus we might only be able to see these signals when we include individuals of African ancestry in a GWAS, as is done in PAGE.

Though plausible, alternative explanations seem less likely than stratification, but we cannot discard them at the moment, at least until a more extensive simulation study can allow us to compare these scenarios and their resulting score dispersion patterns. Another possible cause for these inconsistencies could be differences in the number of SNPs or individuals included in each GWAS, leading to differences in power to detect score overdispersion on trait-associated variants. Indeed, in some of the smaller cohorts (FINRISK and APCDR) we observe little to no evidence for strong deviations from neutrality in the distribution of genetic scores across populations.

We find that the type of test performed to obtain Q_X P-values does not yield strong differences in such P-values, at least not of the magnitude observed when using effect size estimates from different GWAS cohorts. Those phenotypes and GWAS cohorts for which we find significant overdispersion via the chi-squared distributional assumption for the Q_X statistic also tend to be the ones for which we find significant overdispersion when not relying on it. This suggests that this assumption - while not entirely accurate (Berg and Coop, 2014) - is still reasonably valid, across all the phenotypes we looked at, assuming the effect size estimates are not affected by stratification.

We were able to replicate the finding by Berg, Harpak, et al. (2019): there is a significant relationship between the differences in allele frequencies between GBR and other worldwide populations and the differences in effect size estimates between UKBB and GIANT. We note that a similar relationship was found by Uricchio et al. (2019), who showed an increase in the magnitude of allele frequency differences between GBR and TSI when ordering SNPs by their P-value in GIANT - an increase not observed when ordering them by their P-value in UKBB. We note, however, that this relationship is relatively absent in comparisons of UKBB and other GWAS, again suggesting that population stratification in GIANT, rather than over-correction of effect size estimates in UKBB, may be the culprit. In any case, Haworth et al. (2019), Novembre and Nicholas H Barton (2018), Coop (2019) and Rosenberg, Edge, et al. (2019) encourage caution about the interpretation of signals of polygenic adaptation due to the presence of residual stratification even in GWAS panels with no clear evidence for stratification, as these signals may be subtle enough to escape notice, yet still affect this type of tests.

Furthermore, when we performed an artificial meta-analysis on the UKBB data, emulating the methodology of GIANT, we observed more dispersion of polygenic scores among populations than when using a single GWAS cohort, echoing findings by Kerminen et al. (2019) at a more localized geographic scale. As we previously observed in the vanilla (single-cohort) UKBB analysis, the less homogeneous the ancestries of the individuals in the cohort ("all ethnicities" vs. "white British"), the more dispersion is observed, which in turn causes a more inflated Q_X statistic. Nevertheless, both meta-analyses ("all ethnicities" and "white British") show higher Q_X statistics than their single-cohort counterparts, regardless of the meta-analysis method deployed. This is also observed regardless of whether one uses cohort-specific PCs to correct for stratification in the meta-analysis or global PCs from a PCA including all individuals. Overall, this adds weight to the hypothesis that a failure of GWAS meta-analyses to control for population stratification may affect polygenic score tests against a neutral null hypothesis. We note that several of the component GWAS amalgamated in GIANT were not corrected via PCA or other standard methods of correction in common use today (Wood et al., 2014), so it is likely that we are being over-conservative in our simulations.

It is important to keep in mind that each particular GWAS used imposes strong conditions on the set of SNPs that are included in the Q_X analysis. We expect SNPs associated with a phenotype in a given cohort to explain more variance in the population from which that cohort was obtained than in other populations, simply because the significant SNPs need to have high

enough allele frequencies in the study cohort for them to be recovered in the first place. It is unclear how this will affect false positive and false negative rates of tests of score overdispersion performed in different cohorts. For example, if we see a score overdispersion signal when using a GWAS from cohort 1 but not when using a GWAS from cohort 2, this could be due to a true positive and a lack of power in cohort 2, or due to an artefact caused by cohort 1. It is also possible that, if negative selection acts on some of the trait-related variation, it might affect statistical power by constraining large-effect alleles to be kept at lower frequencies, thus making large-effect alleles more population-specific.

Ultimately, the set of SNPs used in each analysis and their influence on the score depends on a complex combination of factors including allele frequencies, linkage disequilibrium with causal variants, statistical power for detection and effect size inflation due to the winner's curse, together with the underlying evolutionary genetic process that "generates" the observed data. While modeling the individual effect of each of these factors on the inflation of the Q_X statistic is beyond the scope of this study, we note that all of these factors may be influencing the differences we observe among score sets. Indeed, when controlling for the set of SNPs included in the score, we see an attenuation of differences between scores (Figures 16 and 17).

In future studies of polygenic adaptation, we recommend the use of large homogeneous data sets and the verification of signals of polygenic score overdispersion in multiple GWAS cohorts (e.g. M Chen et al. (2019)). We also recommend caution even when finding that statistics testing against neutrality are significant in multiple GWAS cohorts: it is still possible that all the GWAS cohorts may be affected by subtle stratification or other confounding issues, possibly affecting different axes of population structure in different ways. To try to avoid stratification issues, recent studies have proposed to look for evidence for polygenic adaptation within the same panel that was used to obtain SNP effect size estimates, i.e. avoiding comparisons between populations that might be made up of individuals outside of the GWAS used to obtain effect size estimates (e.g. X Liu et al. (2018)). The argument favored by these studies is that, by ensuring that the population on which the GWAS was performed and from which allele frequencies are obtained matches exactly, one need not be confounded by differences in estimates between these populations (for example, due to gene-by-environment interactions). However, Mostafavi et al. (2020) recently showed that the accuracy of polygenic scores often depends on the age and sex composition of the GWAS study participants, even when studying individuals of roughly similar ancestries within a single cohort, due to heritability differences along these axes of variation. This implies that ancestry-based stratification is not the only confounder that researchers should be aware of when trying to detect polygenic adaptation.

Approaches based on tree sequence reconstructions along the genome (Hubisz and Siepel, 2020; Kelleher et al., 2016; Rasmussen et al., 2014; Speidel et al., 2019) appear to be a fruitful avenue of research towards the development of methods that can properly control for some of these confounders. These methods can model local genealogical relationships among individuals, which can in turn serve to track the segregation of trait-associated alleles backwards in time. For example, Stern et al. (2021) recently showed that a method for detecting polygenic adaptation based on tree sequences is highly robust to GWAS stratification, ascertainment bias in SNP effects and negative selection, among other potential confounders. They were also able to show that the signal of polygenic adaptation previously found at educational attainment-associated variants may be due to indirect selection on other, correlated, traits.

Overall, we generally urge caution in the interpretation of signals of polygenic score overdispersion based on human GWAS data, at least until we have robust generative models that can explain how stratification is creeping into these tests (Young et al., 2019). This is especially important when working with socially-charged traits like educational attainment, which are rife for misuse and misinterpretation, and potentially affected by unaccounted socioeconomic and cultural confounding factors. Due to the high risk of misappropriation of this type of results by hate groups (Harmon, 2018), we also recommend that researchers make an effort to explain the caveats and problems associated with these tests in their publications (Coop, 2019; Novembre and Nicholas H Barton, 2018; Rosenberg, Edge, et al., 2019), as well as the strong sensitivity of their performance to the input datasets that we choose to feed into them.

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Conflicts of interest disclosure

The authors of this article declare that they have no financial conflict of interest with the content of this article. Fernando Racimo is a PCI EvolBiol recommender.

Supplementary material

The code used to perform the analyses in this manuscript is available at: https://github.com/albarema/GWAS_choice/.

Supplementary Figures.

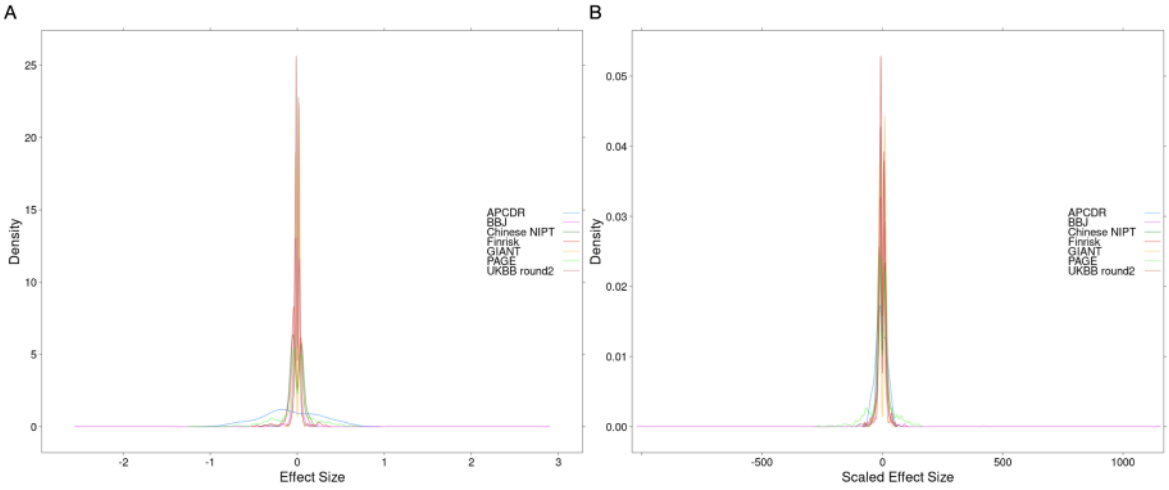

Figure 9 – A. Distribution of effect size estimates (with respect to the derived allele) for approximately independent height-associated SNPs with $P < 1e{-}5$. B. Distribution of the product of the effect size estimates and the square root of the sample size of the study from which they were obtained, for the same set of SNPs as in panel A.

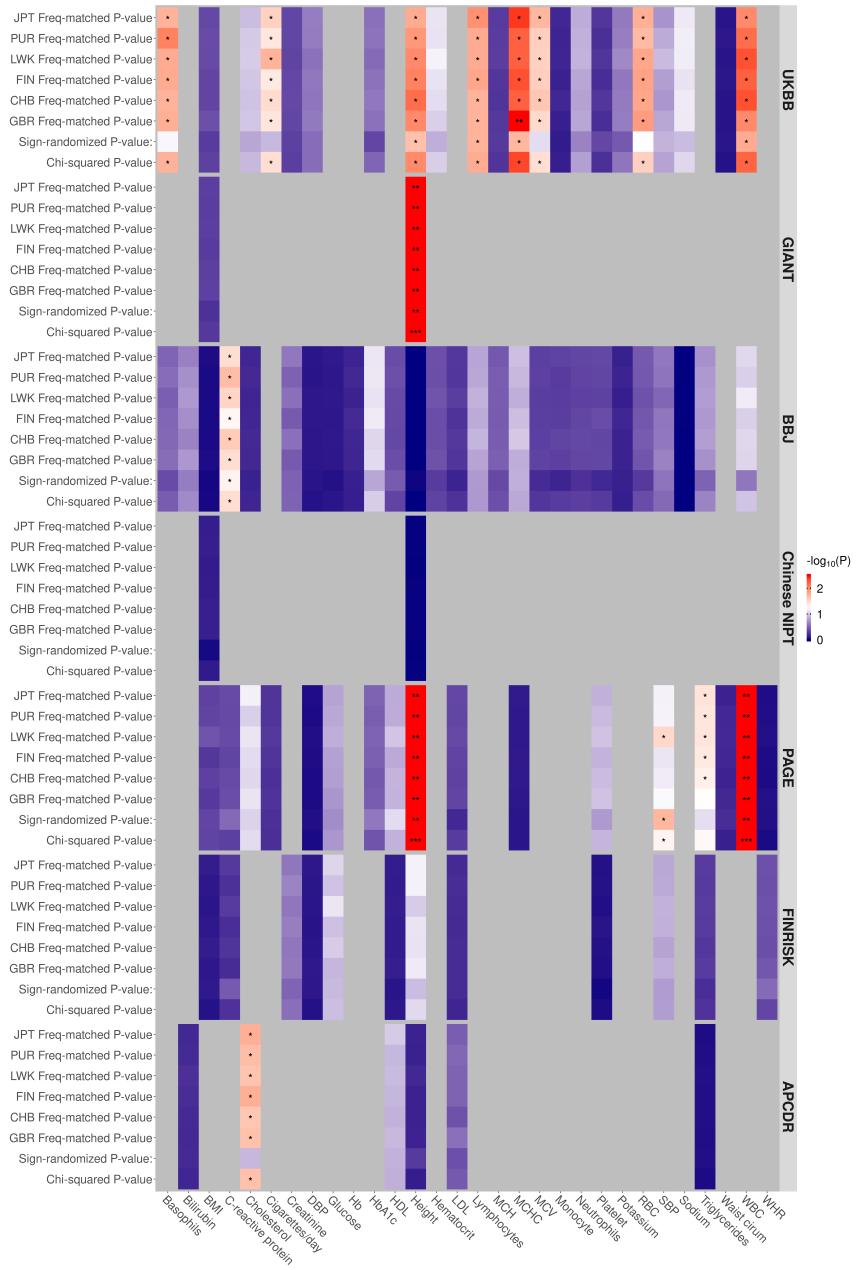

Figure 10 – Evidence for polygenic score overdispersion on trait-associated SNPs ($-log_{10}$(P-value)), using the Q_X test statistic. Each row in the heatmap corresponds to a specific GWAS cohort and a specific type of scheme to determine the significance of the Q_X statistic. The columns correspond to the different traits for each GWAS cohort that have SNPs with a P-value lower than $1e{-}5$. "Freq-matched P-value" = P-value obtained by sampling SNPs with matching frequencies to the trait-associated SNPs in a particular cohort. "Sign-randomized P-value" = P-value obtained by randomizing the signs of the effect size estimates. "Chi-squared P-value" = P-value obtained by assuming the Q_X statistics has a chi-squared distribution.

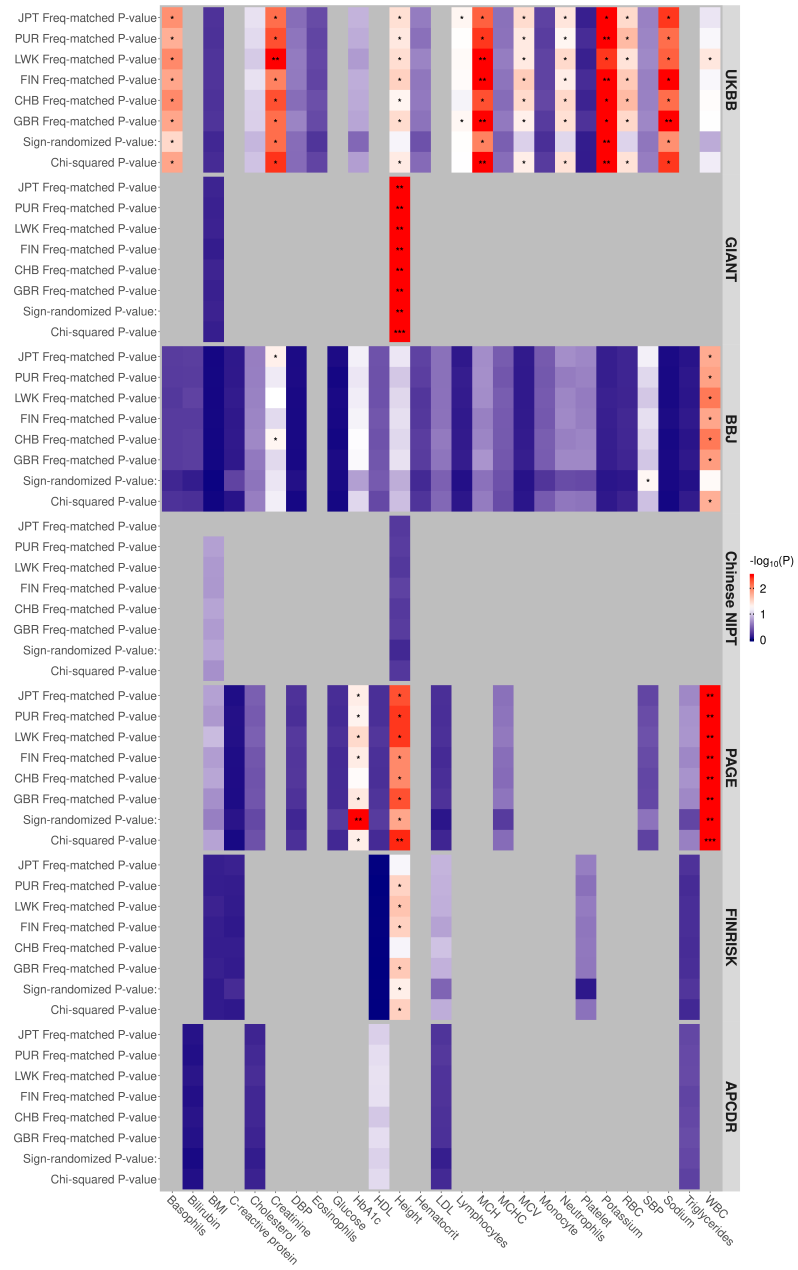

Figure 11 – Evidence for polygenic score overdispersion on trait-associated SNPs ($-log_{10}$(P-value)), using the Q_X test statistic. Each row in the heatmap corresponds to a specific GWAS cohort and a specific type of scheme to determine the significance of the Q_X statistic. The columns correspond to the different traits for each GWAS cohort that have SNPs with a P-value lower than $5e{-}8$. "Freq-matched P-value" = P-value obtained by sampling SNPs with matching frequencies to the trait-associated SNPs in a particular cohort. "Sign-randomized P-value" = P-value obtained by randomizing the signs of the effect size estimates. "Chi-squared P-value" = P-value obtained by assuming the Q_X statistics has a chi-squared distribution.

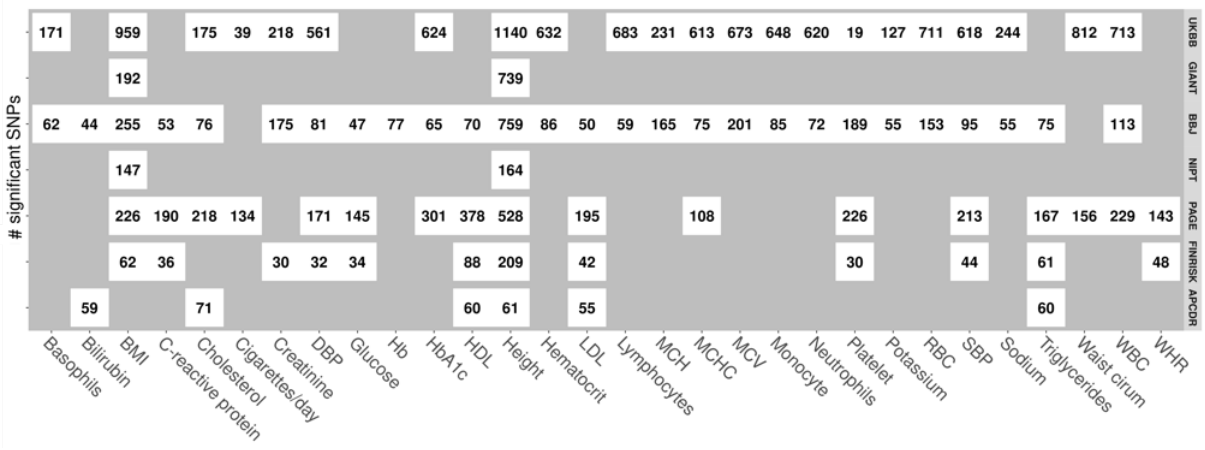

Figure 12 – Number of significant SNPs used to compute the Q_X statistics for each cell of Figure 2. $P < 1e{-}5$.

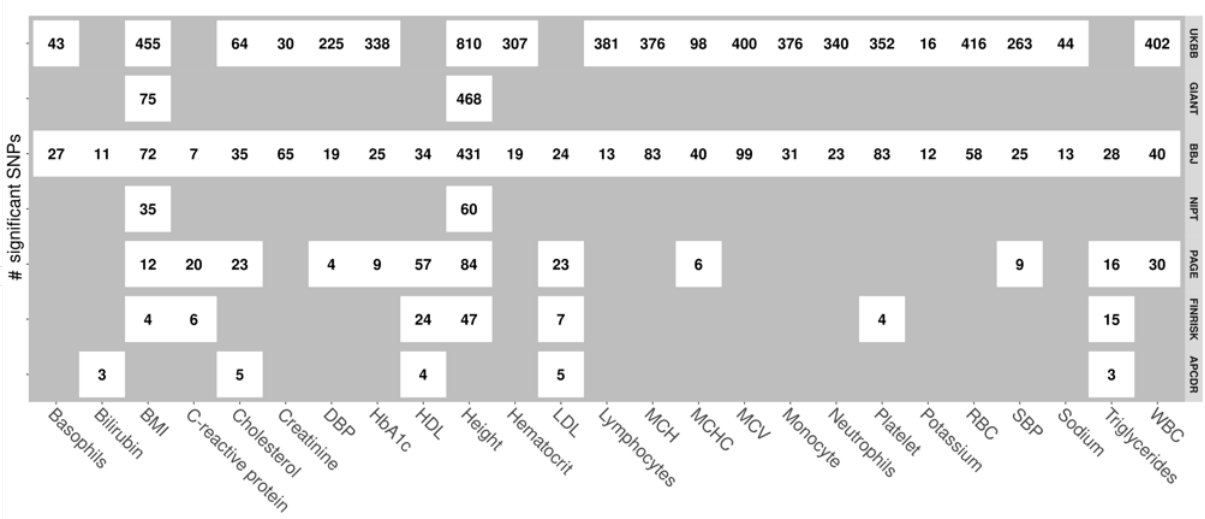

Figure 13 – Number of significant SNPs for each trait in each GWAS with $P < 5e{-}8$.

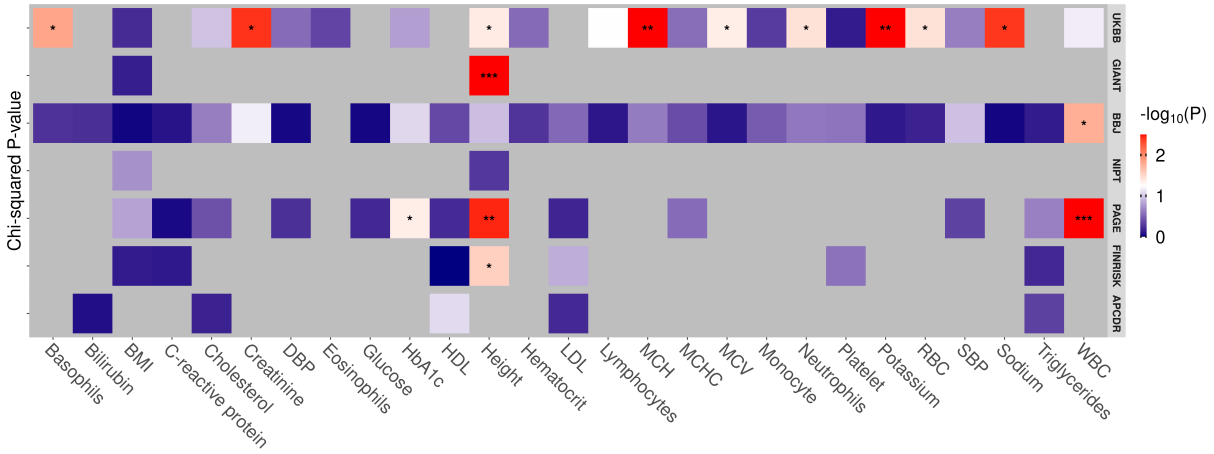

Figure 14 – Evidence for polygenic score overdispersion on trait-associated SNPs ($-log_{10}$(P-value)), using the Q_X test statistic. Each row in the heatmap corresponds to one of the six GWAS cohorts we are evaluating and the columns correspond to the different traits for each GWAS cohort that have SNPs with a P-value lower than $5e{-}8$. BMI, body mass index; DBP, Diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell count; SBP, systolic blood pressure; WBC, white blood cell count; WHR, waist-to-hip ratio. Significance thresholds after Bonferroni corrections: *** denotes P < 0.05/m, ** denotes P < 0.05/n, * denotes P < 0.05 where *n* is the number of traits measured in each GWAS (row-dependent) and *m* is the total number of tests calculated, across all GWAS.

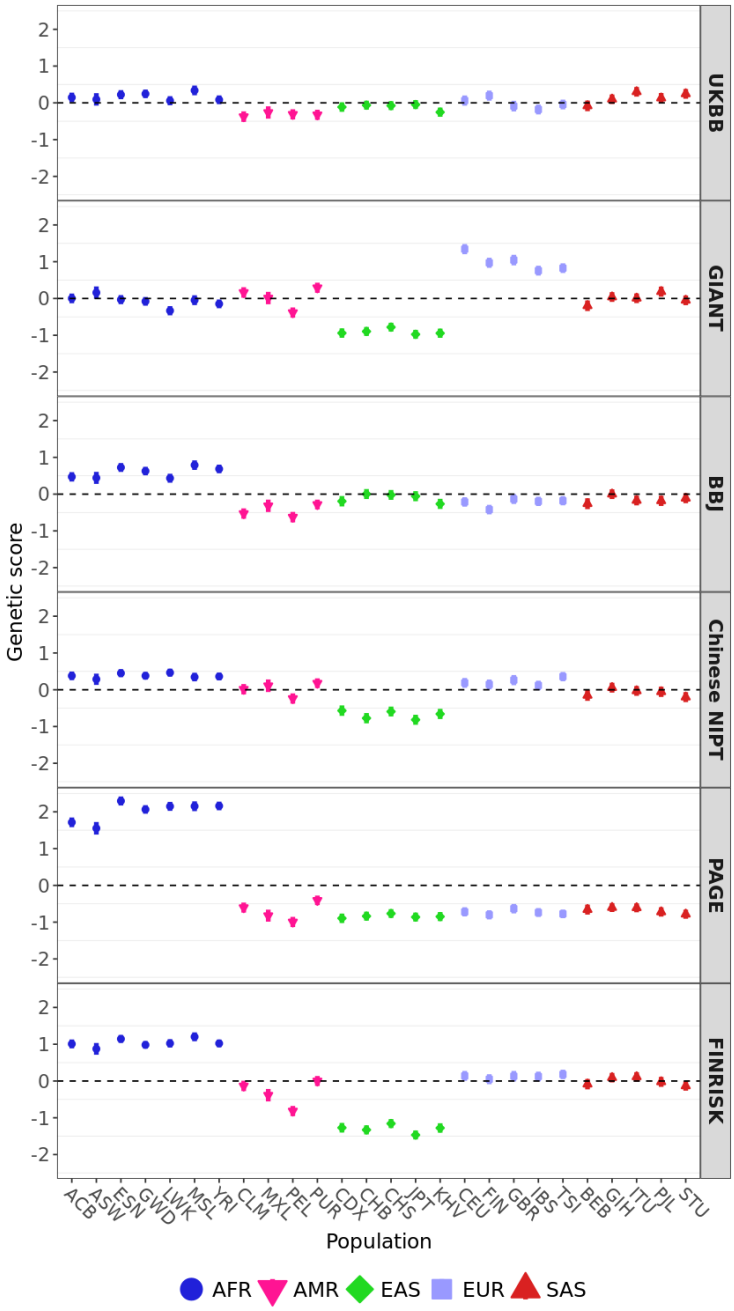

Figure 15 – Polygenic scores for height using candidate SNPs with $P < 5e{-}8$ in 1000 Genome populations colored by their super-population code. The corresponding number of trait-associated SNPs and the Q_X P-value for each GWAS are shown in the bottom row of Table 3. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

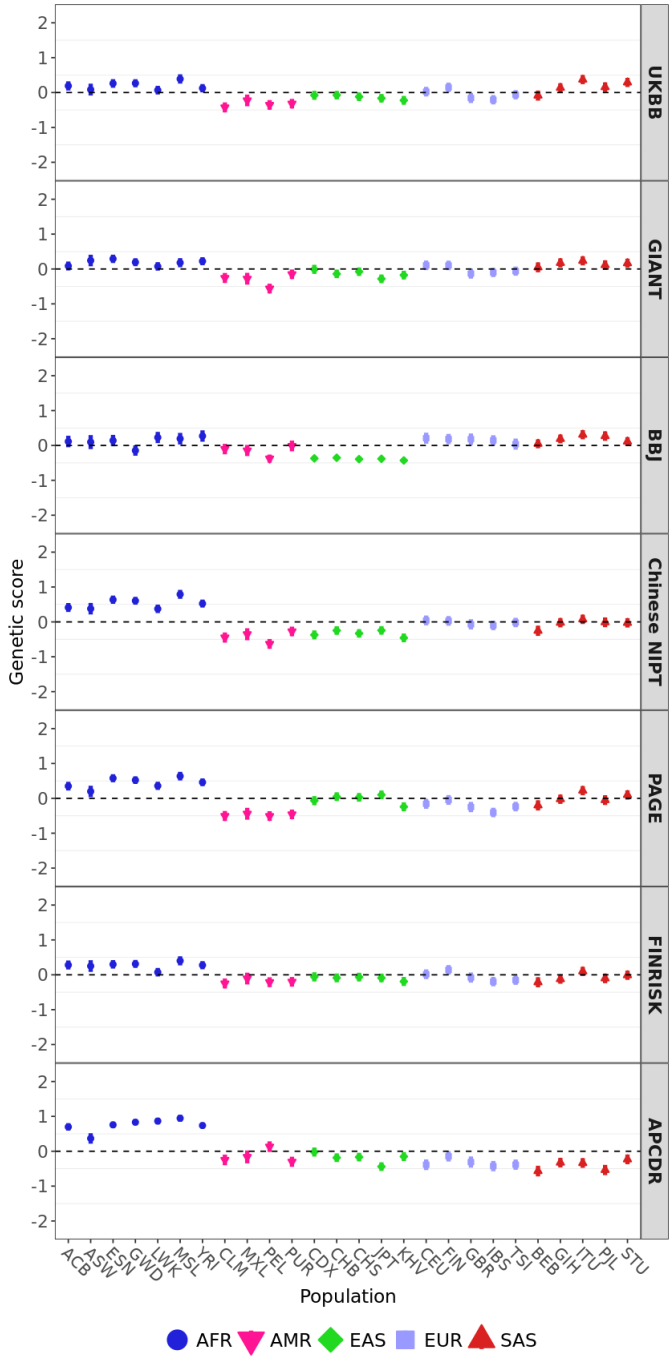

Figure 16 – Polygenic scores for height 1000 Genome populations colored by their super-population code. Candidate SNPs were ascertained in the UKBB using the cutoff of $P < 1e{-}5$. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

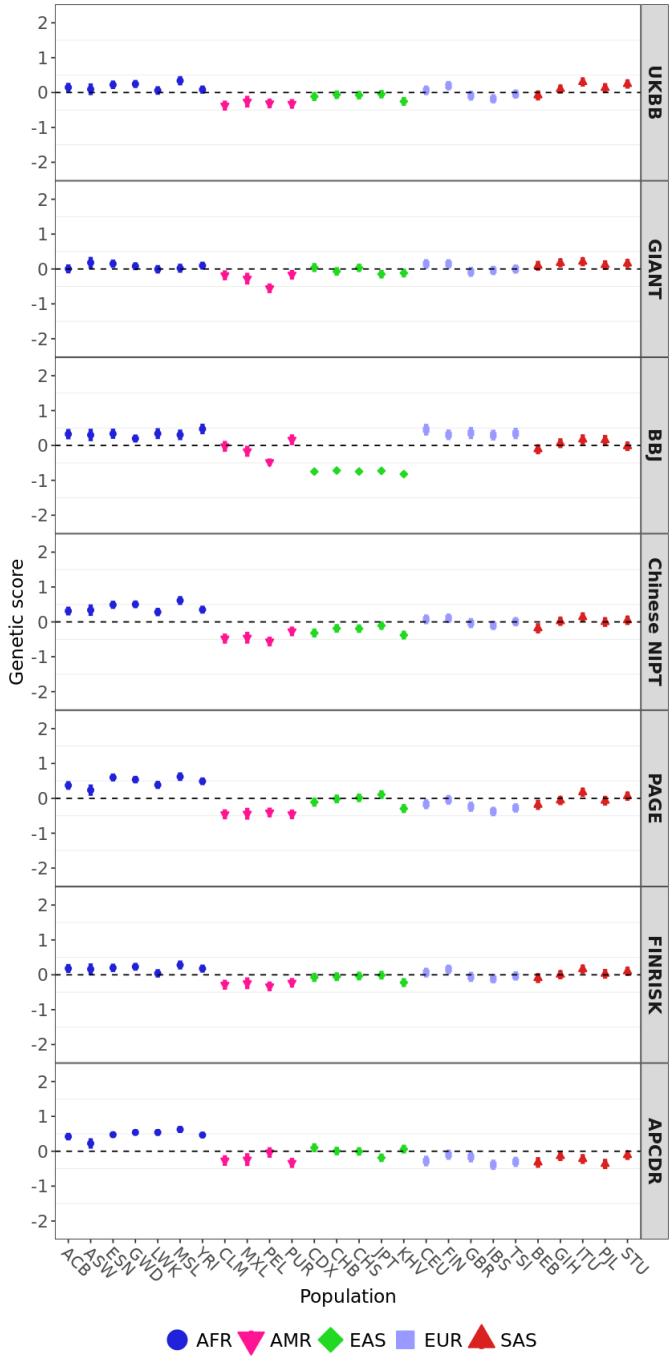

Figure 17 – Polygenic scores for height 1000 Genome populations colored by their super-population code. Candidate SNPs were ascertained in the UKBB using the cutoff of $P < 5e{-}8$. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

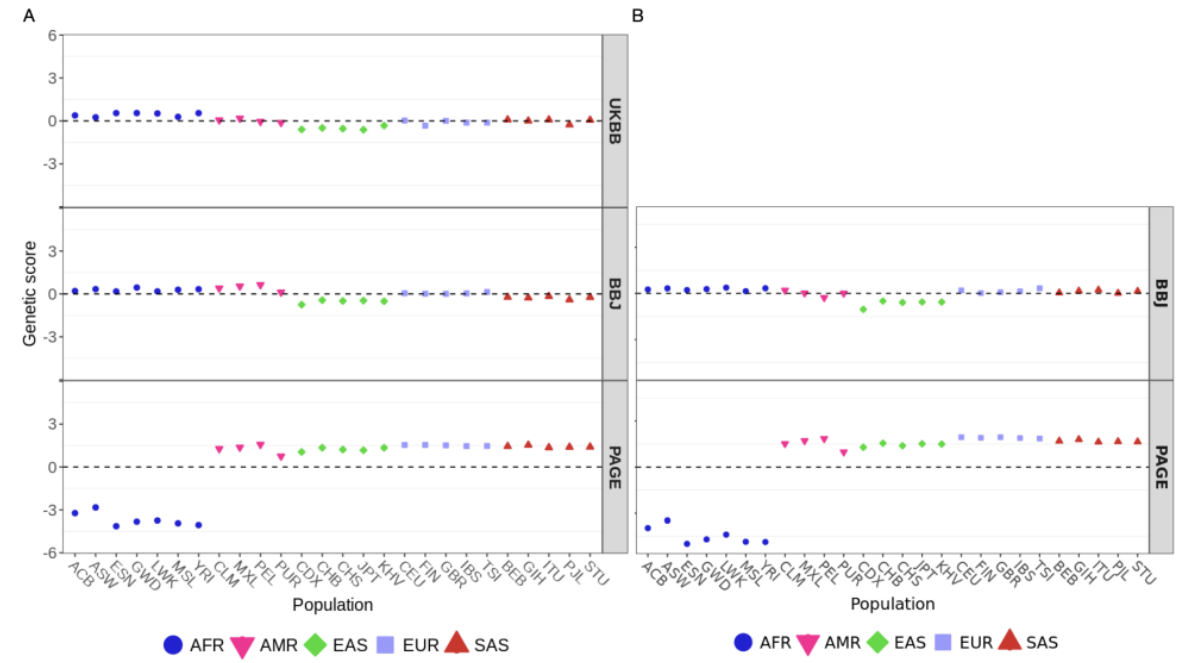

Figure 18 – Polygenic scores for white blood cell counts using candidate SNPs with A. $P < 1e{-}5$ and B. $P < 5e{-}8$ in the 1000 Genomes Project populations colored by their super-population code. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

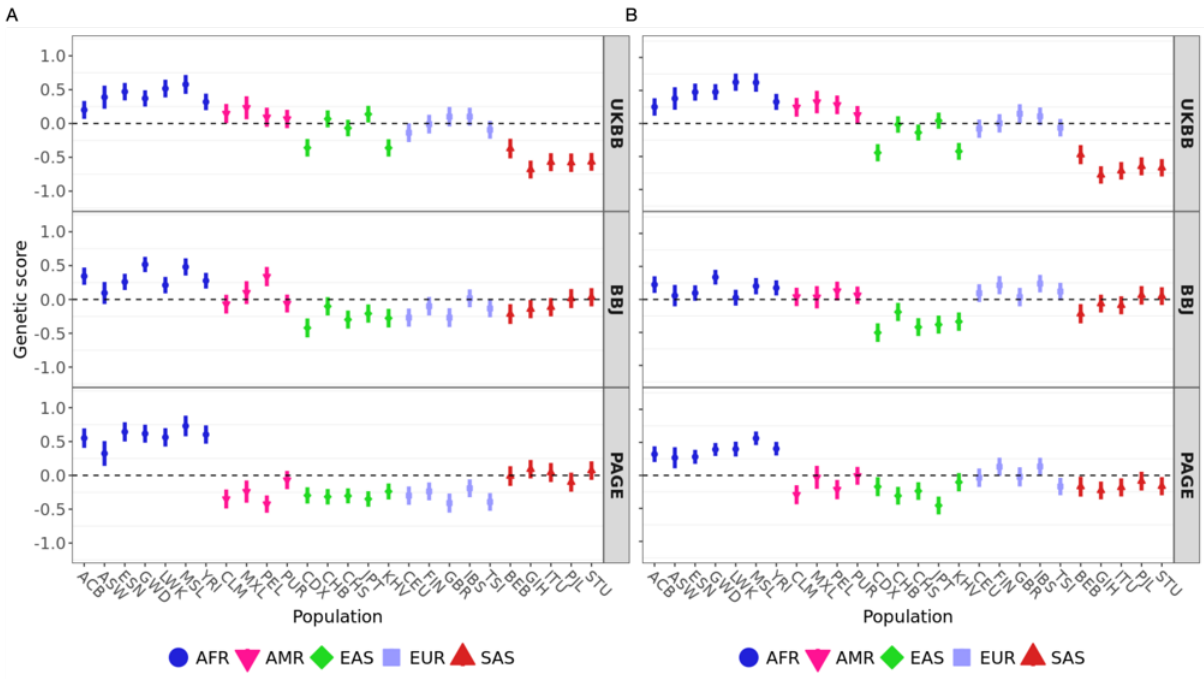

Figure 19 – Polygenic scores for mean corpuscular hemoglobin using candidate SNPs with A. $P < 1e{-}5$ and B. $P < 5e{-}8$ in 1000 Genome populations colored by their super-population code. X trait-associated SNPs. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

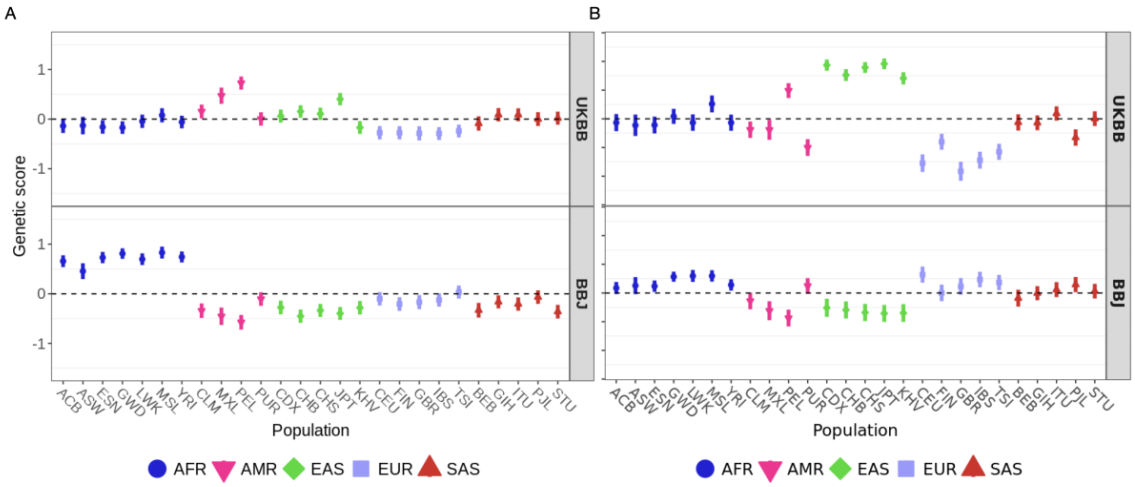

Figure 20 – Polygenic scores for potassium level using candidate SNPs with A. $P < 1e{-}5$ and B. $P < 5e{-}8$ in 1000 Genome populations colored by their super-population code. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

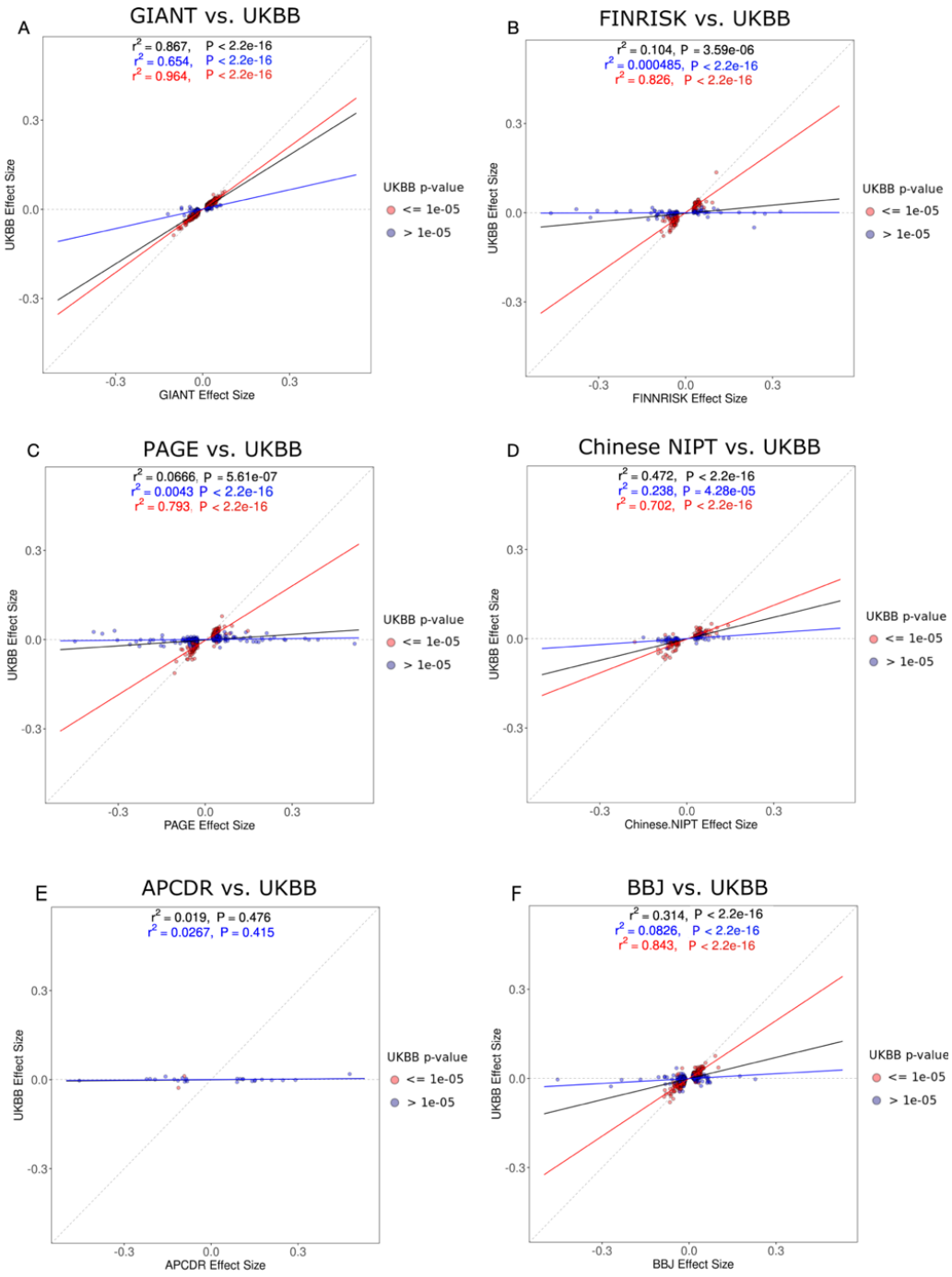

Figure 21 – Regression of UKBB height effect size estimates against non-UKBB height effect size estimates, after filtering for SNPs with $P < 1e{-}5$ in the non-UKBB GWAS. The SNPs are colored based on their P-value in the UKBB, as are the corresponding regression lines (red: $P < 1e{-}5$; blue: $P > 1e{-}5$). The black regression line was obtained using all SNPs, regardless of their P-value in the UKBB GWAS.

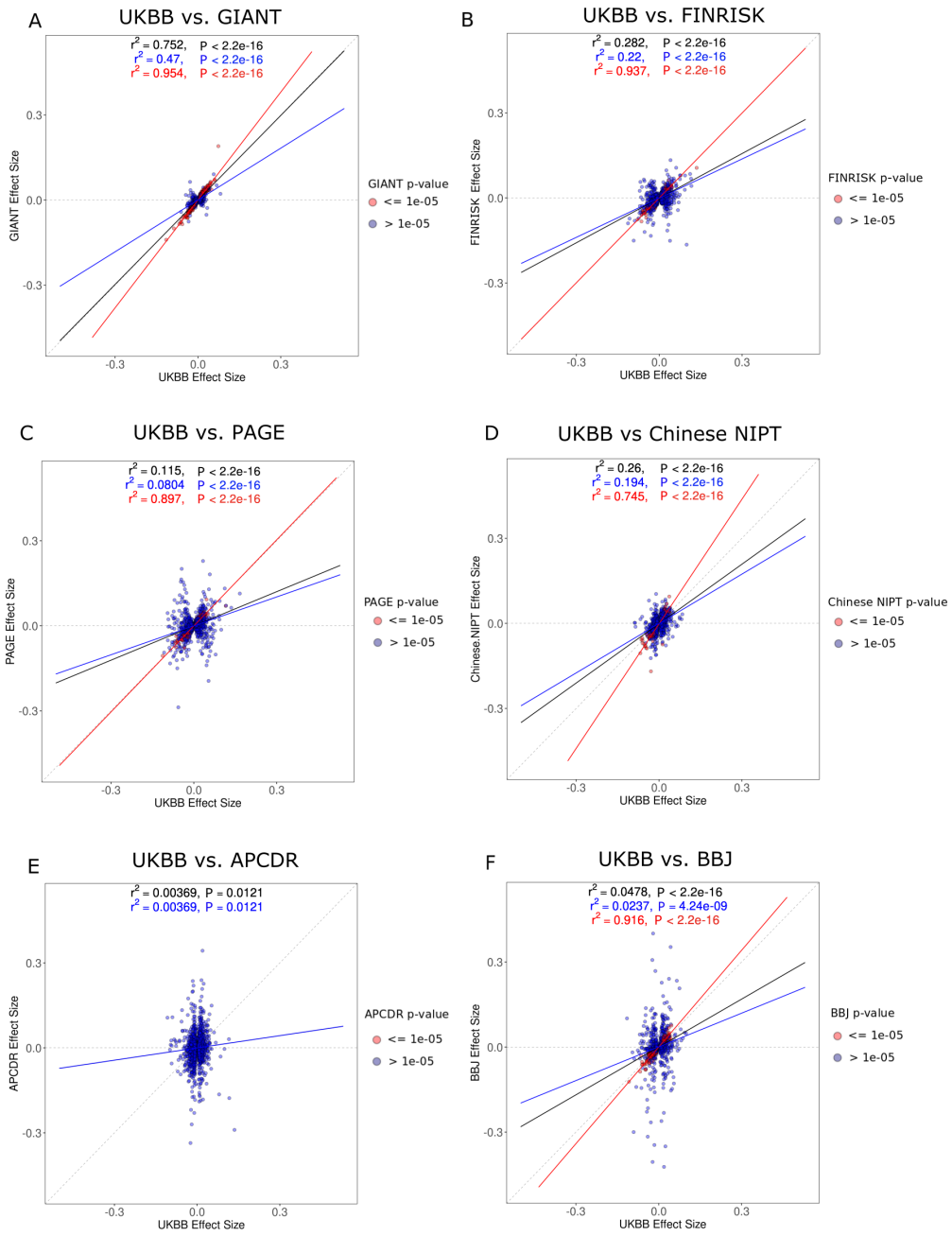

Figure 22 – Regression of non-UKBB height effect size estimates against UKBB height effect size estimates, after filtering for the SNPs with the lowest UKBB P-values in 1,703 approximately-independent LD blocks. The SNPs are colored based on their P-value in the non-UKBB GWAS, as are the corresponding regression lines (red: $P < 1e{-}5$; blue: $P > 1e{-}5$). The black regression line was obtained using all SNPs, regardless of their P-value in the non-UKBB GWAS.

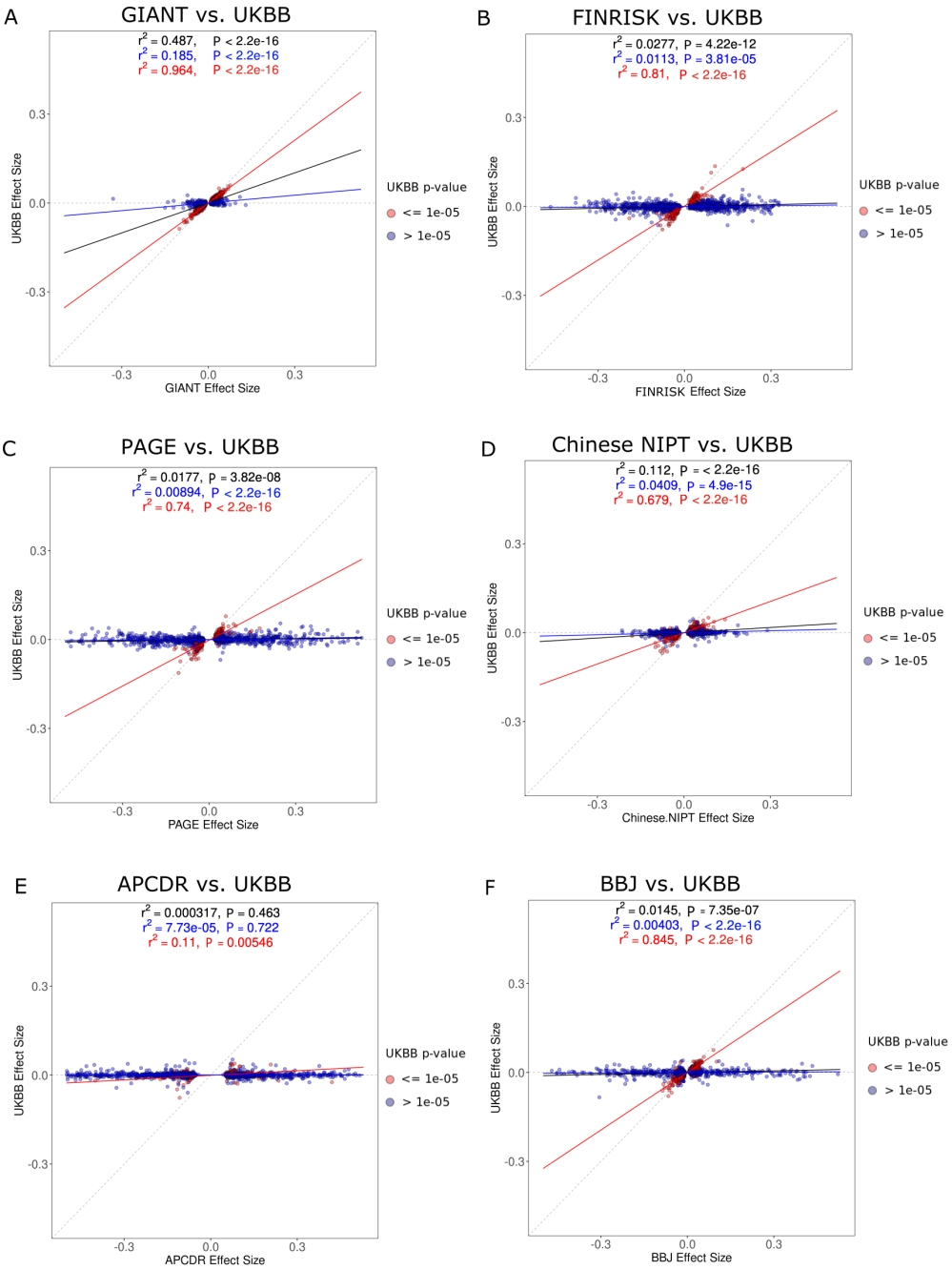

Figure 23 – Regression of UKBB height effect size estimates against non-UKBB height effect size estimates, after filtering for the SNPs with the lowest non-UKBB P-values in 1,703 approximately-independent LD blocks. The SNPs are colored based on their P-value in the UKBB GWAS, as are the corresponding regression lines (red: $P < 1e{-}5$; blue: $P > 1e{-}5$). The black regression line was obtained using all SNPs, regardless of their P-value in the UKBB GWAS.

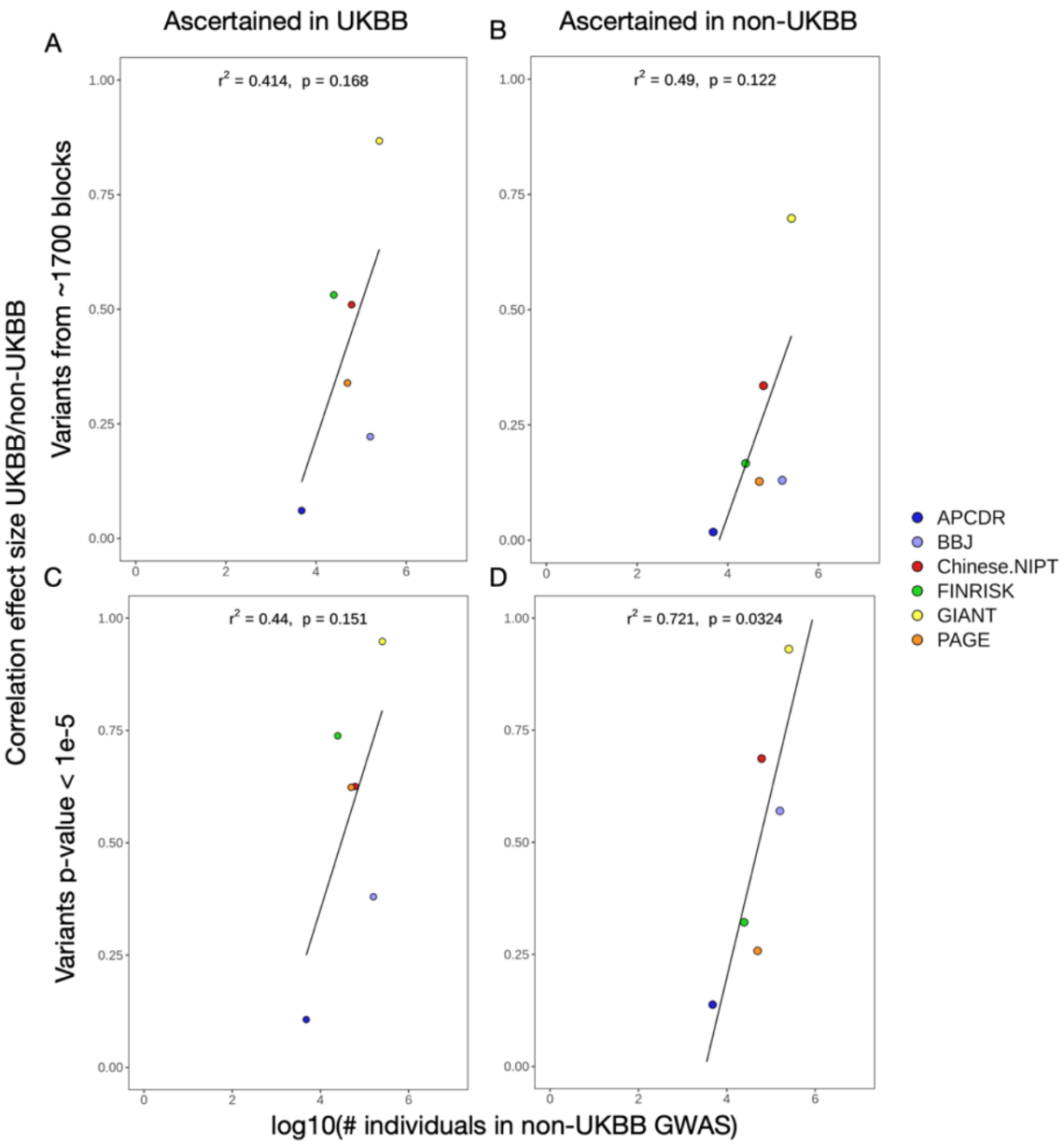

Figure 24 – Correlation between the number of individuals in a GWAS and the correlation of effect size estimates between two different GWAS. In all panels, we compare UKBB against one of the other studies. **A and B**. Coefficients obtained when we include the SNPs from the 1,703 LD blocks. **C and D**. Coefficients obtained when we filter out those SNPs with a P-value above the threshold ($P > 1e{-}5$).

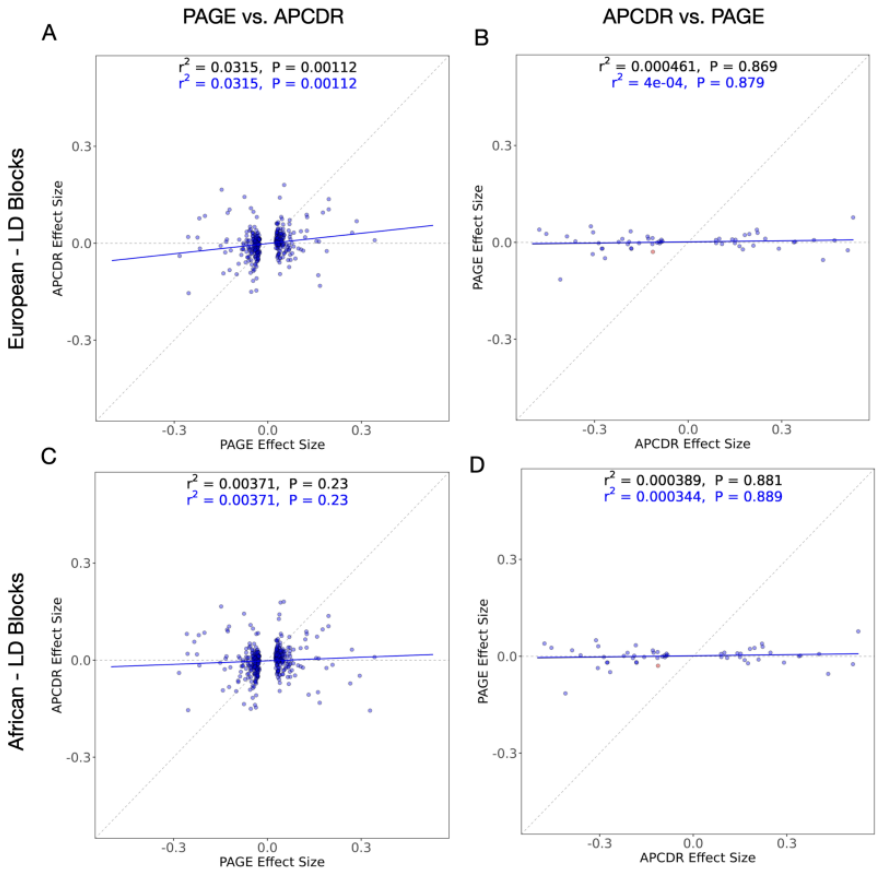

Figure 25 – Regression of effect size estimates obtained from PAGE and APCDR. In the top panels (A and B), we used European LD blocks and in the lower panels (C and D) we used African LD blocks. In the left panel (A and C) we ascertained significant SNPs based on their P-values in the PAGE GWAS ($P < 1e{-}5$). In the right panel (B and D), we ascertained significant SNPs based on their P-values in the APCDR GWAS ($P < 1e{-}5$). The SNPs are colored based on their P-value in the non-ascertained GWAS, as are the corresponding regression lines (red: $P < 1e{-}5$; blue: $P > 1e{-}5$). The black regression line was obtained using all SNPs, regardless of their P-value in the non-ascertained GWAS.

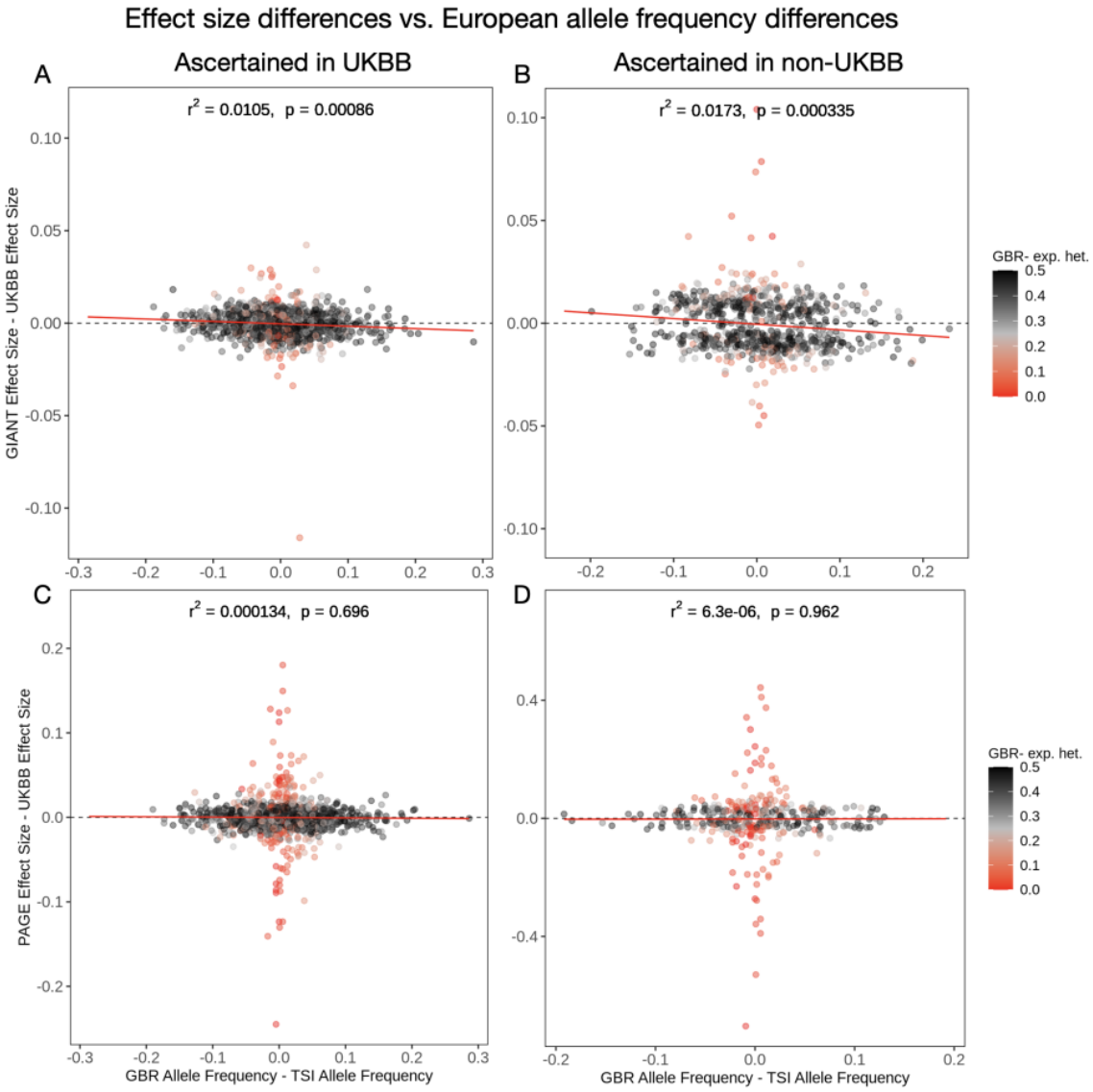

Figure 26 – Regression of GWAS height effect size differences against allele frequency differences between northern and southern European population panels (GBR and TSI). We selected SNPs for this analysis that had P $<$ 1e$-$5. SNPs are colored by their expected heterozygosity (2p(1-p)) in the GBR population.

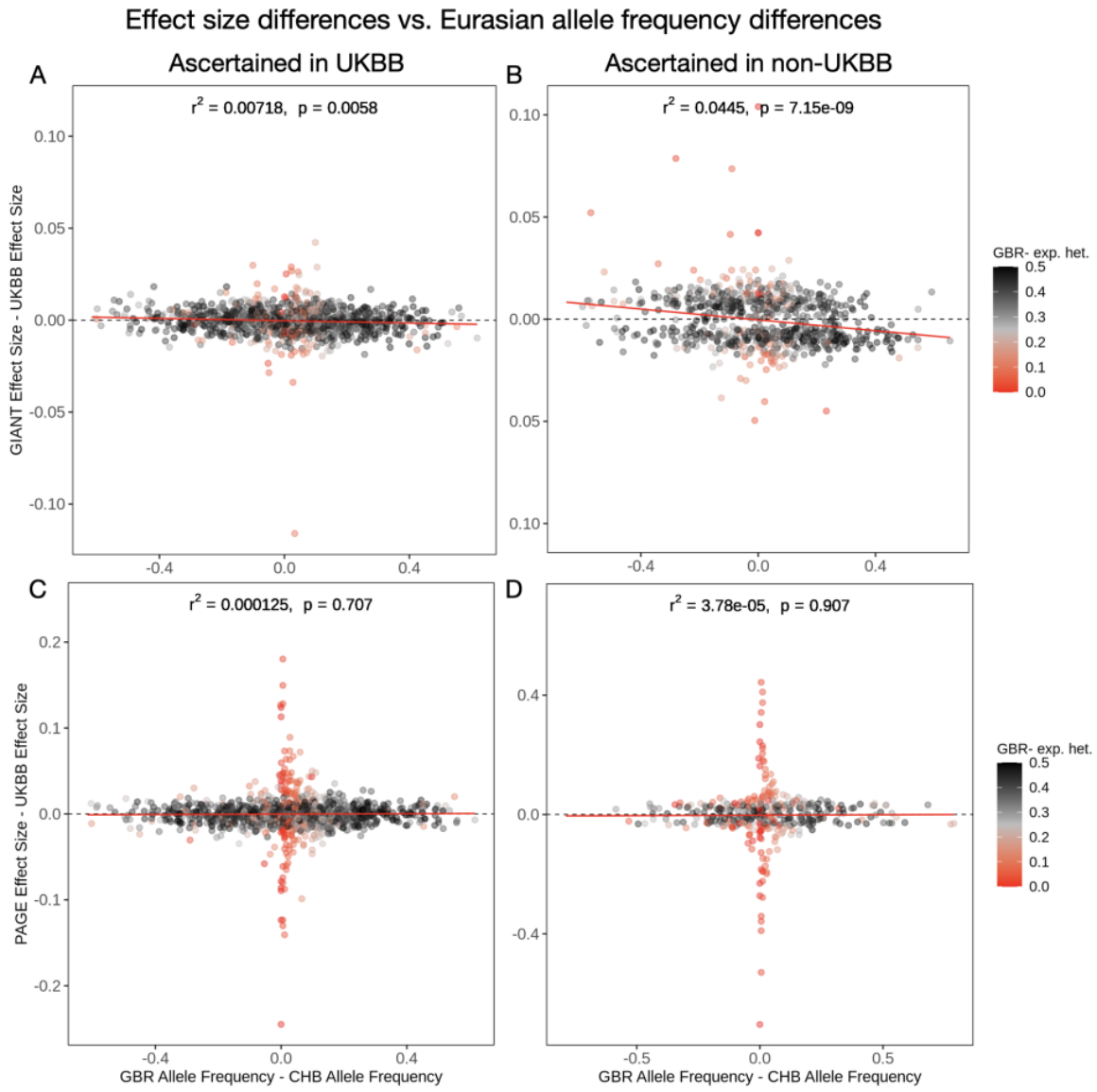

Figure 27 – Each panel in this figure shows the same regressions as Figure 26, except that the difference in allele frequency is between a European and Asian population panels (GBR and CHB). SNPs are colored by their expected heterozygosity (2p(1-p)) in the GBR population.

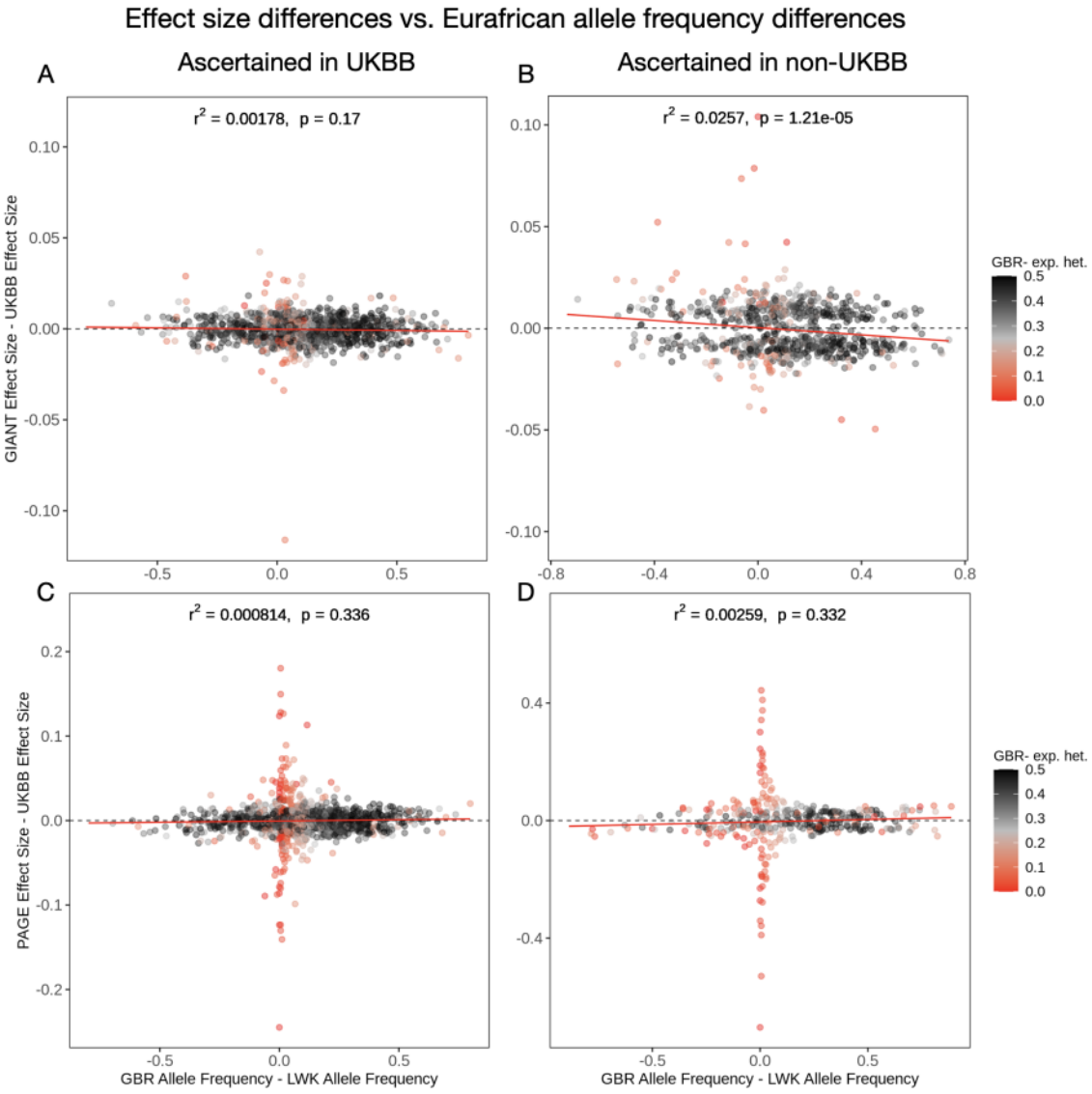

Figure 28 – Each panel in this figure shows the same regressions as Figure 26, except that the difference in allele frequency is between the European and African populations panels (GBR and LWK).SNPs are colored by their expected heterozygosity (2p(1-p)) in the GBR population.

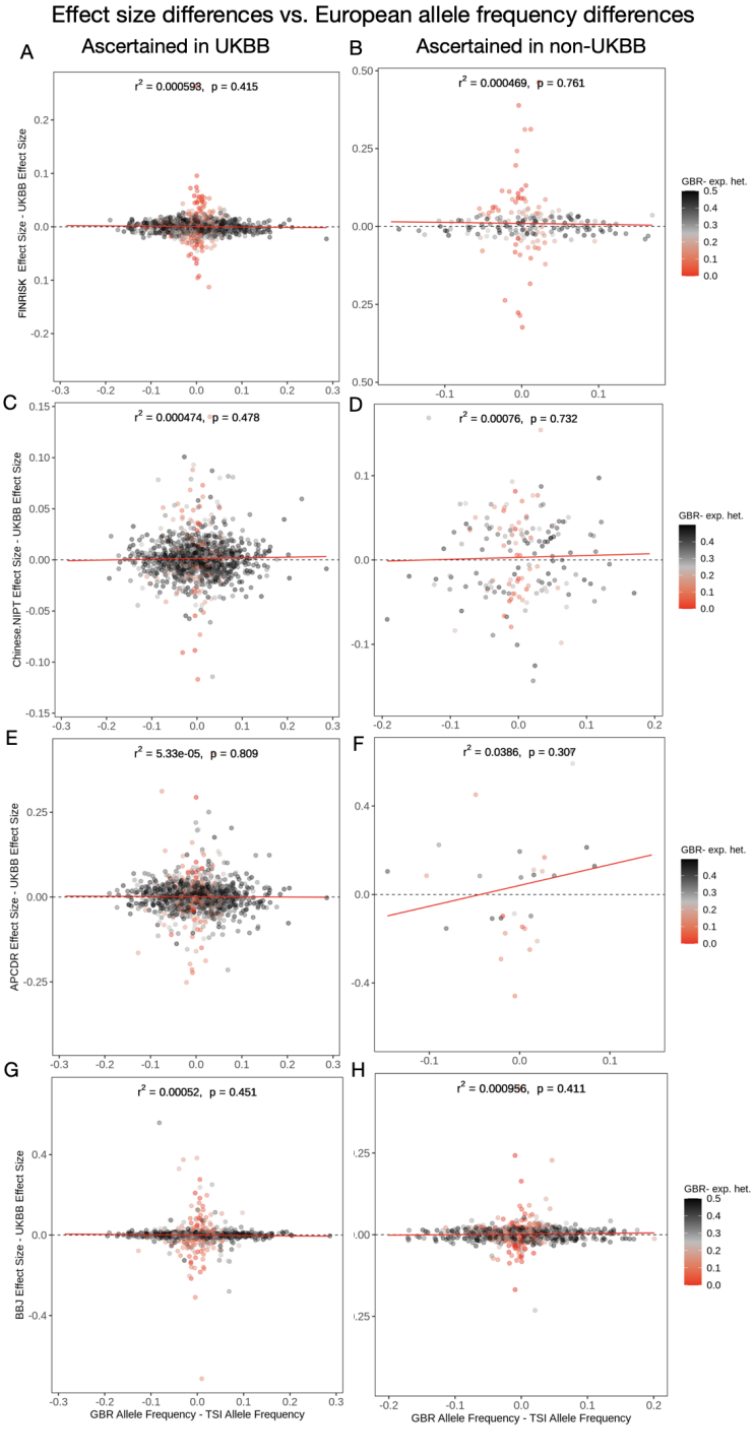

Figure 29 – Regression of GWAS height effect size differences against allele frequency differences between the northern and southern European populations (GBR and TSI). **A,B**. We selected SNPs for this analysis that had P $<$ 1e$-$5. SNPs are colored by their expected heterozygosity (2p(1-p)) in the GBR population.

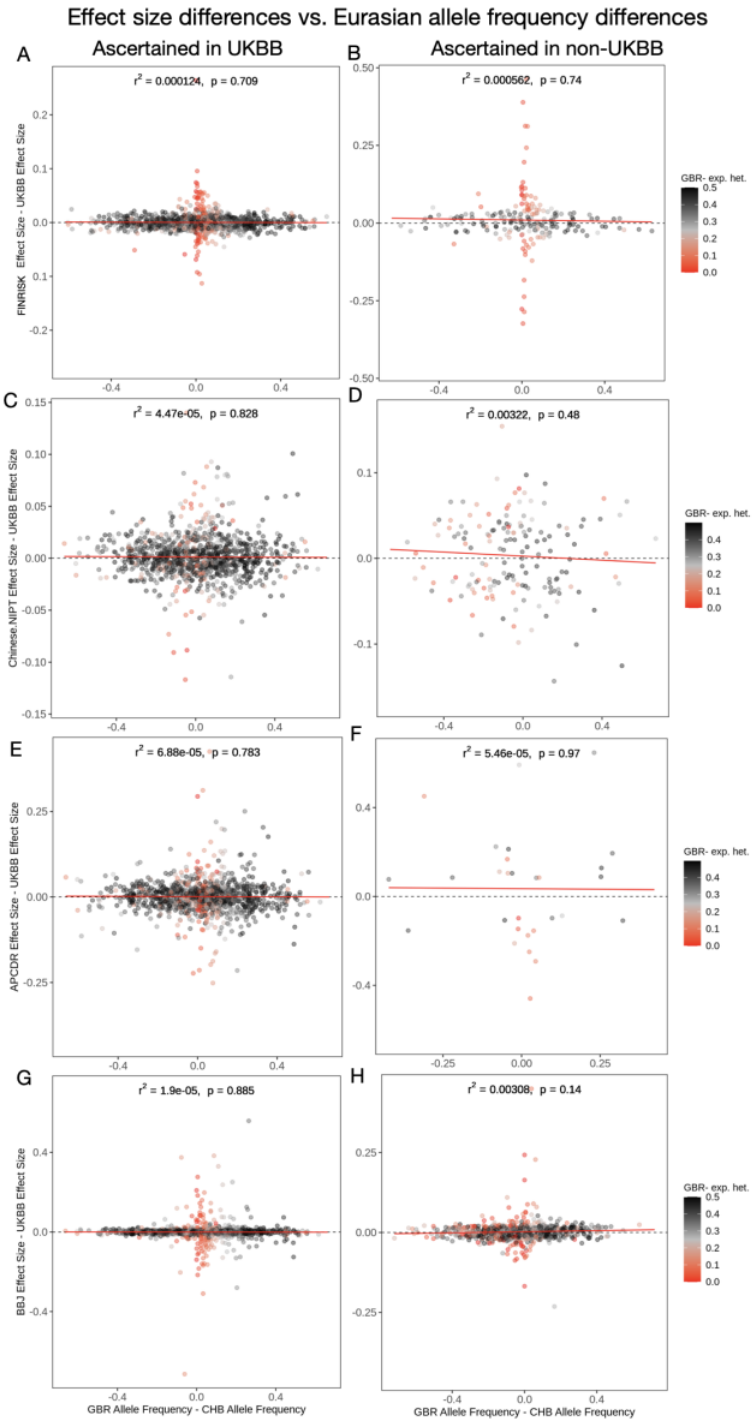

Figure 30 – Each panel in this figure shows the same regressions as Figure 29, except that the difference in allele frequency is between the European and Asian population panels (GBR and CHB). SNPs are colored by their expected heterozygosity (2p(1-p)) in the GBR population.

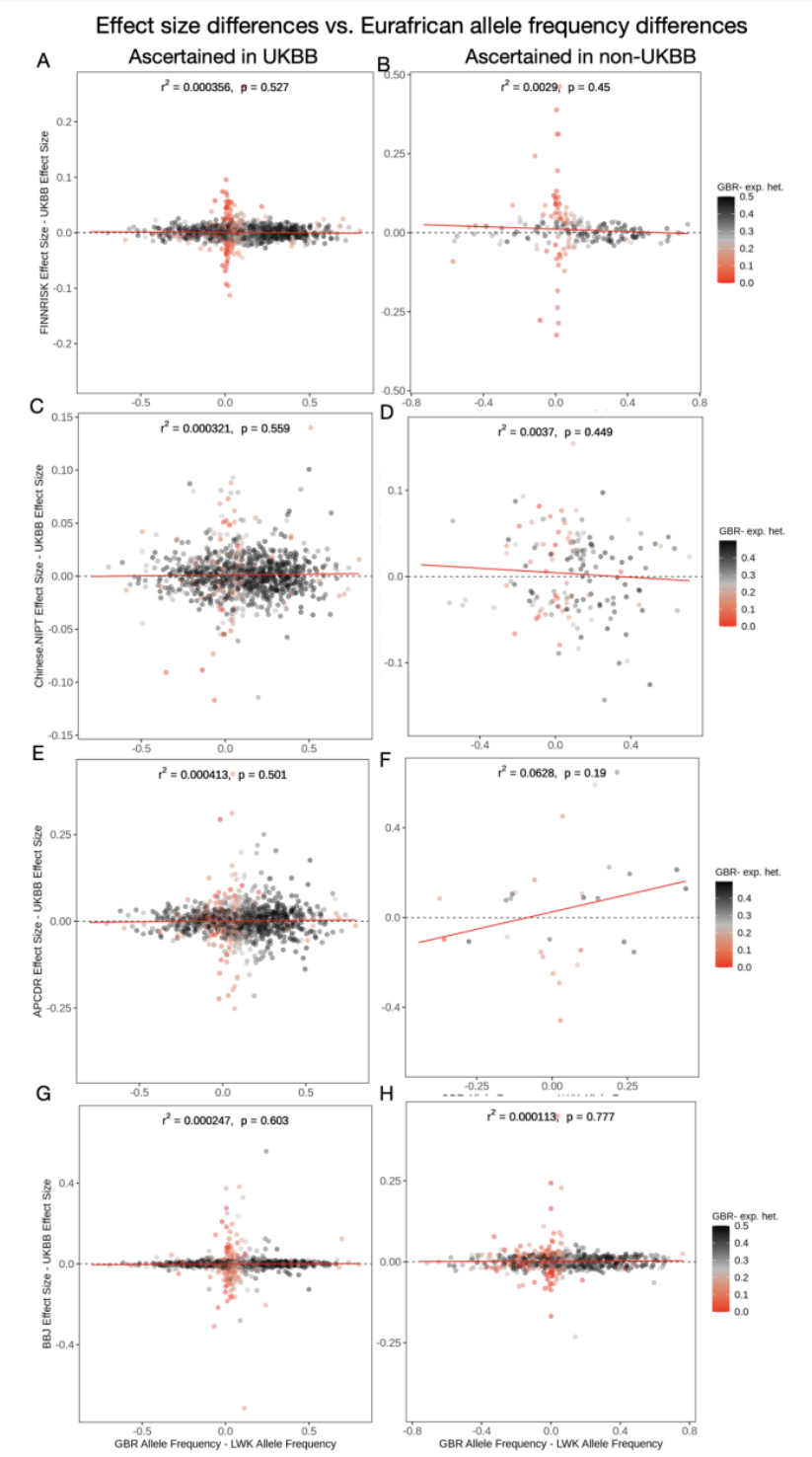

Figure 31 – Each panel in this figure shows the same regressions as Figure 29, except that the difference in allele frequency is between the European and African population panels (GBR and LWK). SNPs are colored by their expected heterozygosity (2p(1-p)) in the GBR population.

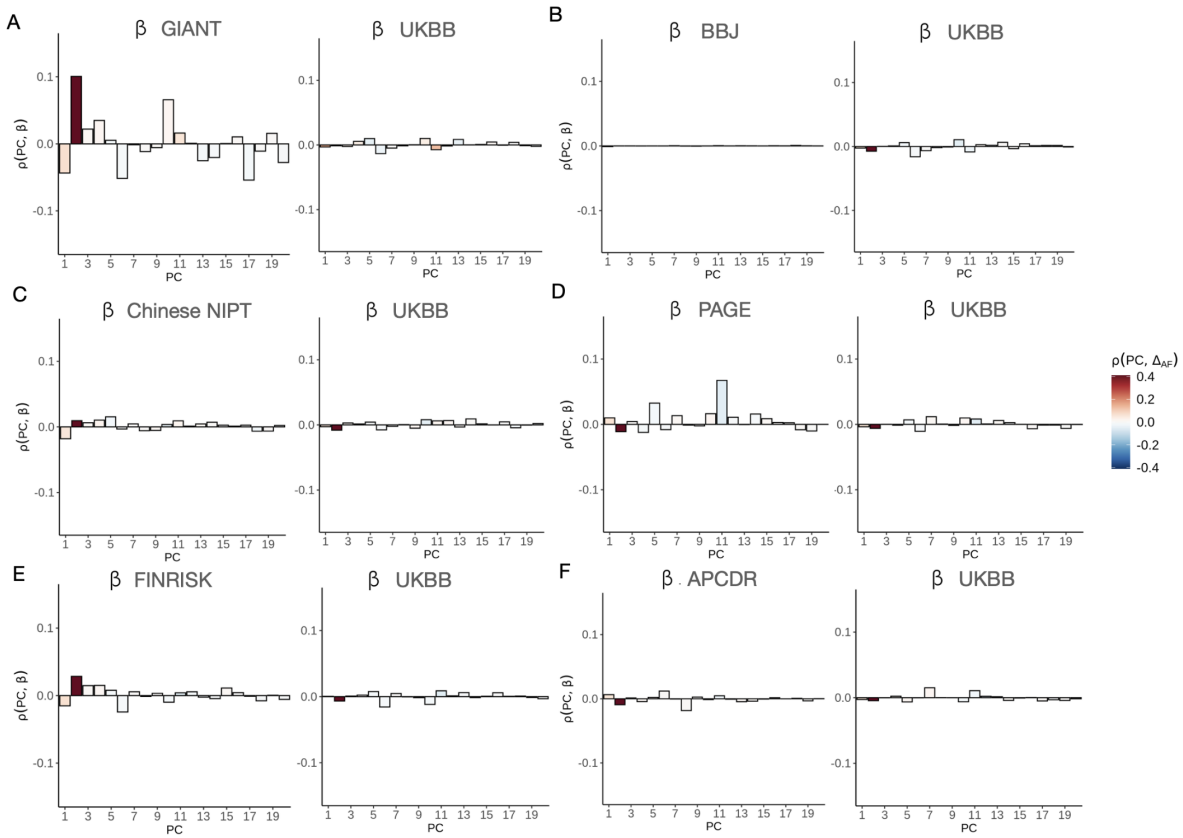

Figure 32 – Pearson correlations between 20 PC loadings and height effect size estimates from a non-UKBB GWASs, compared to the same correlation using effect size estimates from the UKBB GWAS, for different choices of non-UKBB GWAS. The correlations were computed using SNPs that are present in both the UKBB and non-UKBB GWAS cohorts, and in the 1000 Genomes Project. The barplots are coloured by the correlation between each loading and the allele frequency difference between GBR and CHB. A) GIANT vs. UKBB. B) BBJ vs. UKBB. C) Chinese NIPT vs. UKBB. D) PAGE vs. UKBB. E) FINRISK vs. UKBB. F) APCDR vs. UKBB.

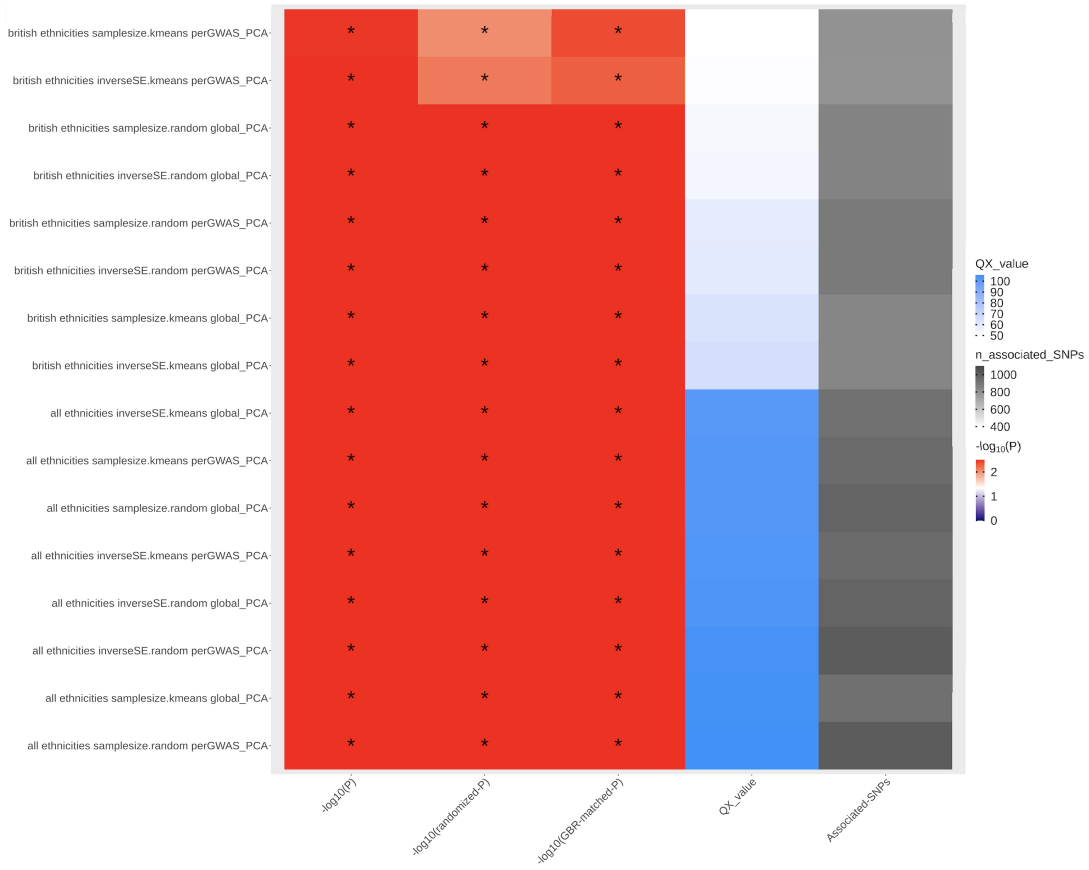

Figure 33 – Q_X statistics and P-values for the trait height, obtained by using different types of meta-analysis methods on the UKBB data (inverse variance and sample size based) and two PCA correction approaches (global vs. per-GWAS). The meta-analyses were performed in "all ethnicities" as well as "White-British" set of individuals. The asterisk denotes a significance cutoff for Q_X of $P < 0.05$. "-log10(Chi squared P)" = -log10(P-value), obtained assuming a chi-squared distribution for the Q_X statistic. "-log10(randomized P)" = -log10(P-value), obtained using the effect sign-randomization scheme. All other P-values were obtained by sampling random SNPs from the genome using the allele frequency matching scheme in different populations, as described in the Methods section.

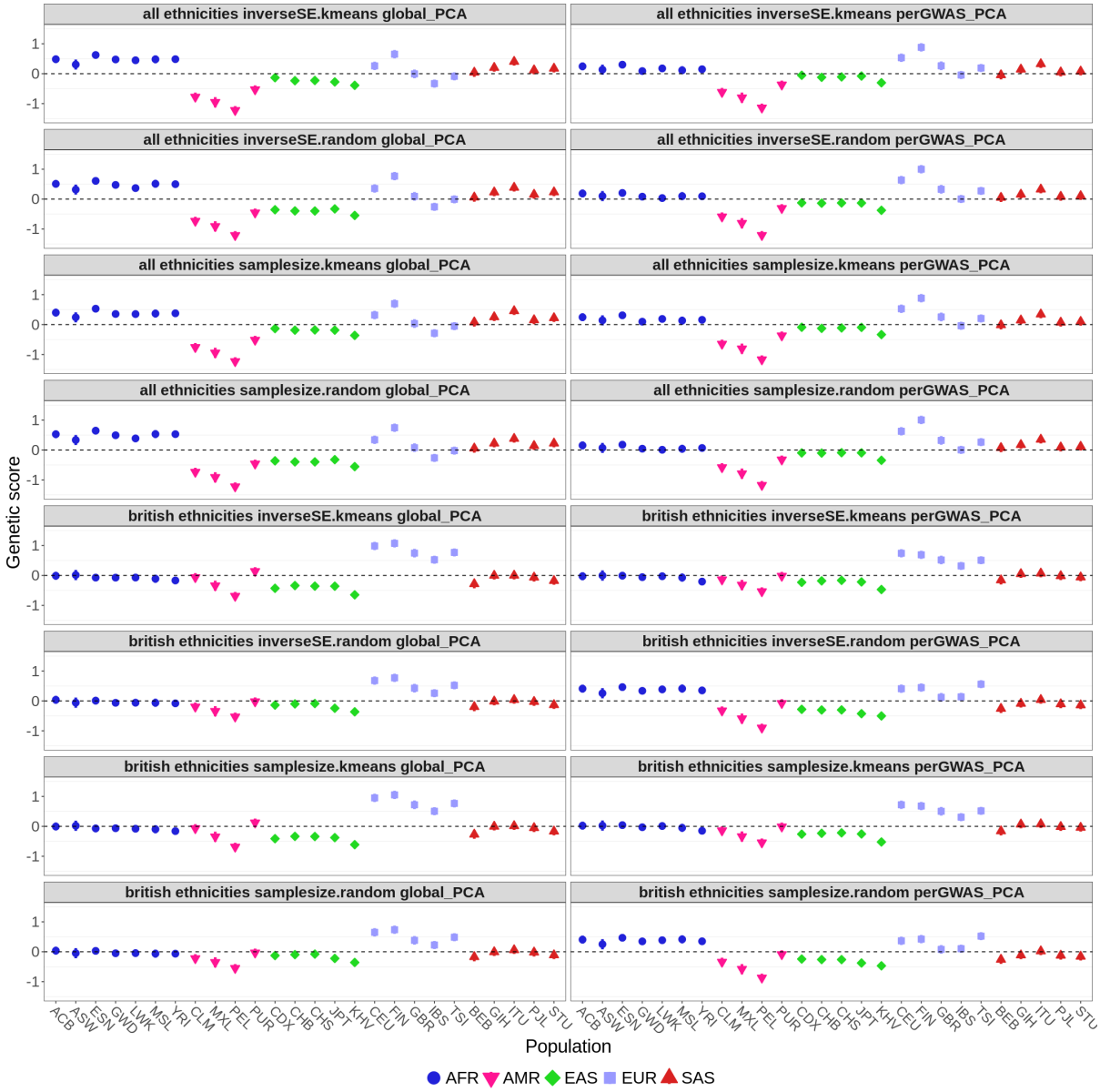

Figure 34 – Polygenic scores for height in each of the 1000 Genomes population panels, using effect size estimates from UKBB, obtained via different types of meta-analysis methods (inverse variance and sample size based) and two PCA correction approaches (global vs. per-GWAS). The meta-analyses were performed in the "all ethnicities" as well as in the "White-British" set of UKBB individuals. Error bars denote 95% credible intervals, constructed using the method in Sohail et al., 2019, assuming that the posterior distribution of the underlying population allele frequency is independent across populations and SNPs.

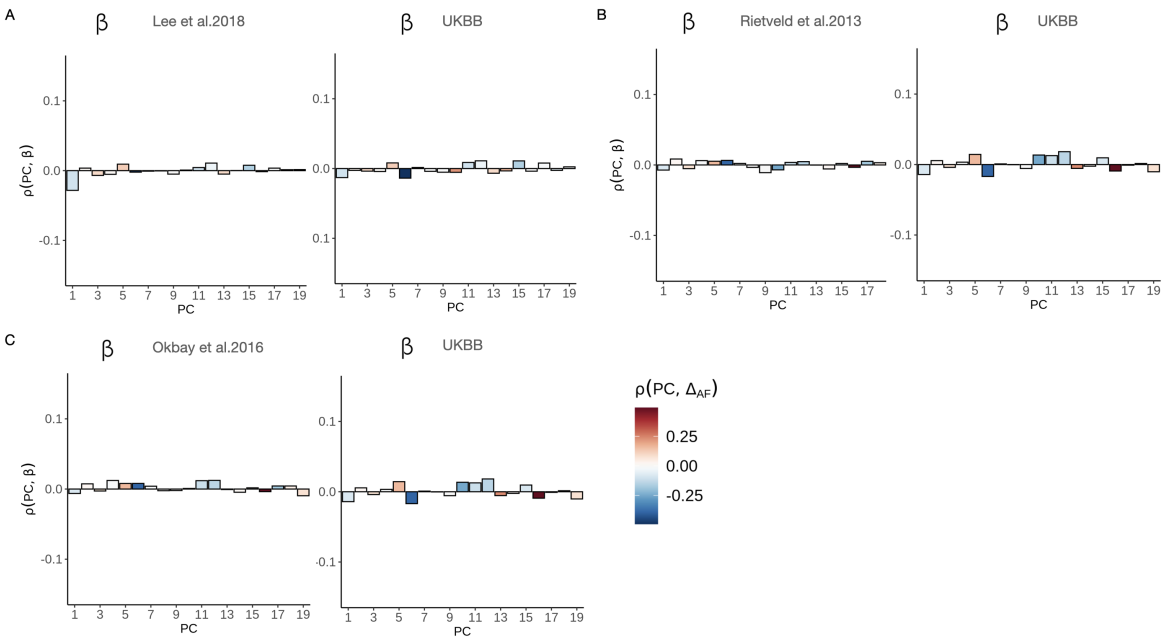

Figure 35 – Pearson correlations between 20 PC loadings and educational attainment effect size estimates from a non-UKBB GWAS, compared to the same correlation using effect size estimates from the UKBB GWAS, for different choices of the non-UKBB GWAS. The correlations were computed using SNPs that are present in both the UKBB and non-UKBB GWAS cohorts, and in the 1000 Genomes Project. The barplots are coloured by the correlation between each loading and the allele frequency difference between GBR and TSI. A) Lee et al. 2016 vs. UKBB. B) Rietveld et al. 2018 vs. UKBB. C) Okbay et al. 2016 vs. UKBB.

Supplementary Tables.

Table 6 – Full population descriptions of 1000 Genomes Project panels used in our analysis.

Population code	Description	Super population
CHB	Han Chinese in Beijing, China	EAS
JPT	Japanese in Tokyo, Japan	EAS
CHB	Southern Han Chinese	EAS
CDX	Chinese Dai in Xishuangbanna, China	EAS
KHV	Kinh in Ho Chi Minh City, Vietnam	EAS
CEU	Utah Residents with Northern and Western European Ancestries	EUR
TSI	Toscani in Italia	EUR
FIN	Finnish in Finland	EUR
GBR	British in England and Scotland	EUR
IBS	Iberian Population in Spain	EUR
YRI	Yoruba in Ibadan, Nigeria	AFR
LWK	Luhya in Webuye, Kenya	AFR
GWD	Gambian in Western Divisions in the Gambia	AFR
MSL	Mende in Sierra Leone	AFR
ESN	Esan in Nigeria	AFR
ASW	Americans of African Ancestry in SW USA	AFR
ACB	African Caribbeans in Barbados	AFR
MXL	Mexican Ancestry from Los Angeles USA	AMR
PUR	Puerto Ricans from,Puerto Rico	AMR
CLM	Colombians from Medellin, Colombia	AMR
PEL	Peruvians from Lima, Peru	AMR
GIB	Gujarati Indian from Houston, Texas	SAS
PJL	Punjabi from Lahore, Pakistan	SAS
BEB	Bengali from Bangladesh	SAS
STU	Sri Lankan Tamil from the UK	SAS
ITU	Indian Telugu from the UK	SAS

Table 7 – Full list of all traits tested and the total number of individuals (N) is shown for the GWAS in which this data was available. For GWAS summary statistics with variable N across positions, we list the maximum N for that study.

Traits		UKBB	BBJ	FINRISK	PAGE	APCDR	Chinese NIPT	GIANT
Anthropometric	BMI	359,983	158,284	24,722	49,335	-	60,652	231,410
	Height	360,388	159,095	24,725	49,781	4,778	61,321	253,288
	Waist circumference	360,564	-	-	33,942	-	-	-
	Waist hip ratio (WHR)	-	-	24,671	33,904	-	-	-
Blood pressure	diastolic blood pressure (DBP)	340,162	136,615	21,588	35,433	-	-	-
	Systolic blood pressure (SBP)	340,159	136,597	21,591	35,433	-	-	-
Inflammatory	Platelet	361,141	108,208	6,404	29,328	-	-	-
	Monocyte	349,856	62,076	-	-	-	-	-
	C-reactive protein (CRP)	-	75,391	16,529	28,537	-	-	-
	Hemoglobin (HbA1c)	350,474	42,790	-	11,178	-	-	-
	Mean corpuscular hemoglobin concentration (MCHC)	350,468	108,728	-	19,803	-	-	-
	Mean corpuscular hemoglobin (MCH)	350,472	108,054	-	-	-	-	-
	Mean corpuscular volume (MCV)	350,473	108,256	-	-	-	-	-
	Basophil count	349,856	62,076	-	-	-	-	-
	Hematocrit count	350,475	108,757	-	-	-	-	-
	White blood cell count (WBC)	350,470	107,964	-	28,534	-	-	-
	Red blood cell count (RBC)	350,475	108,794	-	-	-	-	-
	Lymphocyte count	349,856	62,076	-	-	-	-	-
	Monocyte count	349,856	62,076	-	-	-	-	-
	Neutrophil count	349,856	62,076	-	-	-	-	-
Kidney-related	Creatinine	350,812	142,097	6,376	-	-	-	-
Liver-related	Billirubin	-	110,207	-	-	4,778	-	-
Metabolic	Cholesterol	361,141	128,305	-		4,778	-	-
	High density lipoprotein (HDL)	-	70,657	21,620	33,063	4,778	-	-
	Low density lipoprotein (LDL)	-	72,866	21,250	32,221	4,778	-	-
	Triglycerides	-	105,597	21,619	33,096	4,778	-	-
	Glucose	-	93,146	4,418	23,923	-	-	-
Electrolits	Potassium	350,053	132,938	-	-	-	-	-
	Sodium	350,061	127,304	-	-	-	-	-
Lifestyle	Cigarettes per day	25,348	-	-	15,862	-	-	-

Table 8 – Pairwise Fst computed using SNPs present in PAGE, to estimate population differentiation between PAGE and each of the 1000 Genomes Project panels.

Population panel	Super-population	Fst against PAGE
PUR	AMR	0.013
CLM	AMR	0.017
MXL	AMR	0.023
ASW	AFR	0.026
PJL	SAS	0.029
BEB	SAS	0.03
GIH	SAS	0.033
ITU	SAS	0.033
STU	SAS	0.033
IBS	EUR	0.034
TSI	EUR	0.035
CEU	EUR	0.036
FIN	EUR	0.036
GBR	EUR	0.036
ACB	AFR	0.045
PEL	AMR	0.054
LWK	AFR	0.058
CHB	EAS	0.062
JPT	EAS	0.062
KHV	EAS	0.062
GWD	AFR	0.063
CHS	EAS	0.064
YRI	AFR	0.064
ESN	AFR	0.065
MSL	AFR	0.065
CDX	EAS	0.066

Table 9 – SNP-based heritability and LD Score regression ratio and intercept estimates (with standard errors in parentheses) for height measured in different cohorts. LD scores were computed using the closest population in the 1000 Genomes Project to each GWAS cohort (meta-analyses of multiple populations were not included here, but see Table 4). The APCDR heritability estimate is not shown because it was estimated to be negative, due to the small sample size of the cohort. For Chinese NIPT GWAS, we filtered out all the sites with INFO scores less than 0.4.

GWAS cohort	Genome-wide significant SNPs (P < 5e−8)	Observed scale heritability (SE)	LD regression ratio (SE)	LD regression intercept (SE)	Population
UKBB	30891	0.3911 (0.0211)	0.1887 (0.0099)	1.7056 (0.0371)	GBR
BBJ	9976	0.4168 (0.019)	0.1142 (0.0128)	1.1829 (0.0204)	JPT
Chinese NIPT	1573	0.2594 (0.0298)	0.2878 (0.0452)	1.1641 (0.0257)	CHB
FINRISK	415	0.4042 (0.0401)	0.3609 (0.0389)	1.1305 (0.0141)	FIN
APCDR	0	NA	14.8323 (9.7253)	1.0156 (0.0102)	LWK

Table 10 – Pairwise Pearson correlation coefficient between height effect size estimates from the UKBB GWAS and from another GWAS. The SNPs used were determined based on their P-value in the UKBB. n = number of SNPs used to compute the correlation.

	GIANT	FINRISK	PAGE	Chinese NIPT	BBJ	APCDR	SNP filtering scheme
Filtering based on UKBB P-values	0.867 (n = 1703)	0.531 (n = 1703)	0.339 (n = 1703)	0.510 (n = 1703)	0.219 (n = 1703)	0.061 (n = 1703)	SNP with lowest P-value in block
	0.948 (n = 1059)	0.738 (n = 1124)	0.624 (n = 1139)	0.625 (n = 1064)	0.317 (n = 1097)	0.107 (n = 1100)	SNP with lowest P-value in block, if P <1e−5
	0.958 (n = 809)	0.790 (n = 870)	0.615 (n = 881)	0.654 (n = 814)	0.359 (n = 783)	0.087 (n = 856)	SNP with lowest P-value in block, if P <5e−8

Table 11 – Pairwise Pearson correlation coefficient between height effect size estimates from the UKBB GWAS and from another GWAS. The SNPs used were determine based on their P-value in the non-UKBB study. n = number of SNPs used to compute the correlation.

	GIANT	FINRISK	PAGE	Chinese NIPT	BBJ	APCDR	SNP filtering scheme
Filtering based on non-UKBB P-values	0.698 (n = 1703)	0.167 (n = 1703)	0.128 (n = 1703)	0.335 (n = 1703)	0.018 (n = 1703)	0.121 (n = 1703)	SNP with lowest P-value in block
	0.931 (n = 738)	0.322 (n = 199)	0.258 (n = 366)	0.687 (n = 157)	0.561 (n = 709)	0.138 (n = 29)	SNP with lowest P-value in block if P <1e−5
	0.938 (n = 570)	0.334 (n = 136)	0.260 (n = 257)	0.654 (n = 112)	0.732 (n = 412)	0.087 (n = 15)	SNP with lowest P-value in block if P <5e−8

Table 12 – Height Q_X scores when using LD blocks derived from closely related populations. In the case of BBJ and the Chinese biobank, we used the ASN-specific LD blocks. In the case of APCDR, we used the AFR-specific blocks. In the case of PAGE, we used the AFR-specific blocks. The left columns show scores obtained when we used a $P < 1e{-}5$ threshold to include SNPs in the polygenic scores. The right columns show scores obtained using the genome-wide significant threshold ($P < 5e{-}8$). The number of trait-associated SNPs used to compute the scores are shown for both cutoffs.

	Lenient P-value threshold (1e−5)		Strict P-value threshold (5e−8)	
GWAS cohort	Num. trait-associated SNPs	Qx	Num. trait-associated SNPs	Qx
BBJ	693	9.701 (P = 0.99)	401	36.00 (P = 9e-2)
Chinese NIPT	160	13.05 (P = 0.98)	59	26.41 (P = 0.44)
PAGE	592	97.23 (P = 4e-10)	94	65.86 (P = 3e-5)
APCDR	60	21.15 (P = 0.73)	0	NA

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