

Analysis of Polygenic Score Usage and Performance across Diverse Human Populations

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Abstract

Studies of the relationship between genetic and phenotypic variation have historically been carried out on people of European ancestry. Efforts are underway to address this limitation, but until they succeed, the legacy of a Euro-centric bias in medical genetic studies will continue to hinder research, including the use of polygenic scores, which are individual-level metrics of genetic risk. Ongoing debate surrounds the generalizability of polygenic scores based on genome-wide association studies (GWAS) conducted in European ancestry samples, to non-European ancestry samples. We analyzed the first decade of polygenic scoring studies (2008-2017, inclusive), and found that 67% of studies included exclusively European ancestry participants and another 19% included only East Asian ancestry participants. Only 3.8% of studies were carried out on samples of African, Hispanic, or Indigenous peoples. We find that effect sizes for European ancestry-derived polygenic scores are only 36% as large in African ancestry samples, as in European ancestry samples ($t=-10.056$, $df=22$, $p=5.5 \times 10^{-10}$). Poorer performance was also observed in other non-European ancestry samples. Analysis of polygenic scores in the 1000Genomes samples revealed many strong correlations with global principal components, and relationships between height polygenic scores and height phenotypes that were highly variable depending on methodological choices in polygenic score construction. As polygenic score use increases in research, precision medicine, and direct-to-consumer testing, improved handling of linkage disequilibrium and variant frequencies (both of which currently reduce transferability of scores) across populations will improve polygenic score performance. These findings bolster the rationale for large-scale GWAS in diverse human populations.

Significance Statement

The modern genetics revolution enabled rough calculations of individuals' genetic liability for many phenotypes, including height, weight, and schizophrenia. Increasingly, polygenic scores, which are individual-level metrics of genetic liability, are available via direct-to-consumer testing, and they are already widely used in research. The performance of these scores depends on the availability of very large genetic studies, and consequently it is problematic that people of European ancestry are vastly over-represented in these studies. We quantify the magnitude of this problem on the performance of polygenic scores in global samples and also show ancestry-related properties of polygenic scores. These findings set benchmarks for future progress, and they demonstrate the need for large-scale genetic studies in diverse human populations.

Introduction

Awareness of the over-representation of participants of European ancestry in human genetics research has been broadly acknowledged¹⁻⁵, and increasing the representation of diverse populations has recently become a higher priority for the research community⁵⁻¹⁰. This has led funding agencies such as the National Institutes of Mental Health to make genetic studies of diverse populations a priority. Accordingly, representation of non-European ancestry participants in genome-wide association studies (GWAS) increased, from 4% in 2009¹ to 19% in 2016³. Most of the increase in non-European ancestry research is attributable to expansion of genetic studies of East Asian populations, as reported previously³ and as observed in our data (see below). As such, most populations are still severely underrepresented. This lack of

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representation, if not mitigated, will limit our understanding of etiological factors predisposing to disease risk, and will hinder efforts to develop precision medicine. It is also important to understand the implications of the European-centric bias of earlier genetic studies, for work that builds upon existing research. For example, researchers want to know how the limited diversity in early medical genetic studies impacts the use of polygenic risk scores in non-European ancestry populations.

The use of polygenic risk scores^{11,12} (PRS, also known as risk profile scoring, genetic scoring, and genetic risk scoring) has become widespread in biomedical and social science disciplines^{13–15}. Businesses have commercialized this technology, including direct-to-consumer testing from 23&Me and other companies. Perhaps most importantly, there is hope that polygenic risk scores can improve health outcomes by accelerating diagnosis and matching patients to tailored treatments¹⁶. Polygenic scoring studies have demonstrated reliable, though modest, prediction using straightforward scoring methods^{11,12} and genetic data alone, for many complex genetic phenotypes (e.g. blood pressure^{13,17}, height¹⁸, diabetes^{9,19}, depression^{7,20}, and schizophrenia¹⁴). Polygenic risk scores are calculated by summing risk alleles, which are weighted by effect sizes derived from GWAS results^{11,12,21}. Commonly used methods account for ancestry using principal components (calculated on pruned genetic data). In the parlance of polygenic scoring studies, the *training* GWAS is referred to as the “discovery” sample, and the *testing* dataset is referred to as the “target” sample. No overlap between discovery and target datasets is imperative, as is the removal of related individuals from analyses, as demonstrated by Wray and colleagues²¹. Methods of prediction that offer modest improvements on this basic framework are also available^{22–25}.

Polygenic scores can be constructed for any complex genetic phenotype for which appropriate GWAS (or other robust association) results are available. The challenges inherent in using polygenic scores – including modest predictive ability and considerations of statistical power in the interpretation of results – have been reviewed previously^{21,26}. Recent research has focused on the generalizability of polygenic scores to non-European ancestry populations²⁷. While there is good reason to anticipate reduced predictive power in non-European samples^{12,28} (due to differences in variant frequencies and linkage disequilibrium patterns), some have suggested that scores derived from European-ancestry samples should not be used in more diverse samples²⁹. Most researchers expect reduced power in non-European ancestry samples, rather than complete non-transferability of scores. However, the expected decrease in the performance of polygenic scores in target populations that differ from discovery populations is unknown. Further, previous findings may need to be re-evaluated in light of newer findings about relationships between ancestry and GWAS results^{29–31}. Few systematic studies of polygenic score performance across different ancestry groups are available, though see Hoffman and colleagues¹³ for a thorough investigation of blood pressure metrics. To date, all available information has been based on individual phenotypes or small numbers of empirical observations^{28,32}.

A second major area of inquiry concerns the degree to which distributions of polygenic scores differ across global populations^{27,30,31,33–39}. Multiple potential causes of observed distribution differences of polygenic scores have been reported, including drift²⁷, selection^{33,36–39}, artifactual

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differences due to uncorrected population stratification^{30,31} and different environmental effects^{40,41}. We investigate relationships between global principal components and polygenic scores, and assess relationships between polygenic scores and phenotypes for height, using 1000Genomes⁴² data and country-level height information. Using these data, the dependence of polygenic scores on methodological choices in score construction is shown. Further, we demonstrate why it is not straightforward to describe true differences in polygenic risk among global populations, using currently available data. These analyses will be helpful in calibrating researcher expectations about polygenic scores, as currently calculated, across diverse global populations.

Results

Usage and performance of polygenic scores in diverse human populations

How well different ancestry groups have been represented in the first decade of polygenic scoring research (2008-2017, inclusive) is shown in **Figure 1A**, which presents cumulative distributions of studies for specific ancestry groups across time. The field has been dominated by European ancestry studies. Across the 733 studies examined (see **Methods** for inclusion criteria and **Supplementary Table 1** for a list of studies), 67% included exclusively European ancestry participants. There have also been 140 studies conducted in exclusively Asian populations (19%), most commonly in East Asian countries (e.g., China and Japan). Only 3.8% of the polygenic studies from the first decade of polygenic scoring research concerned populations of African, Latino/Hispanic, or Indigenous peoples combined*. These results are similar to those reported by Popejoy and Fullerton³, who noted that non-European ancestry representation in GWASs was almost exclusively in Asian populations, and East Asian populations in particular.

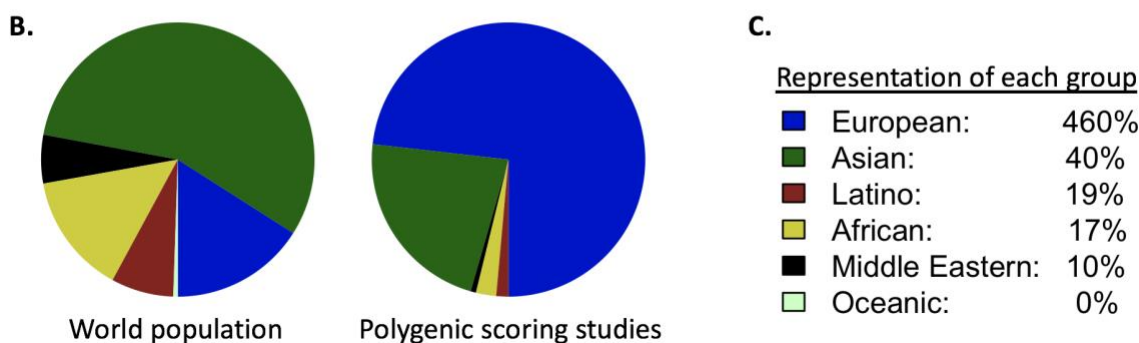
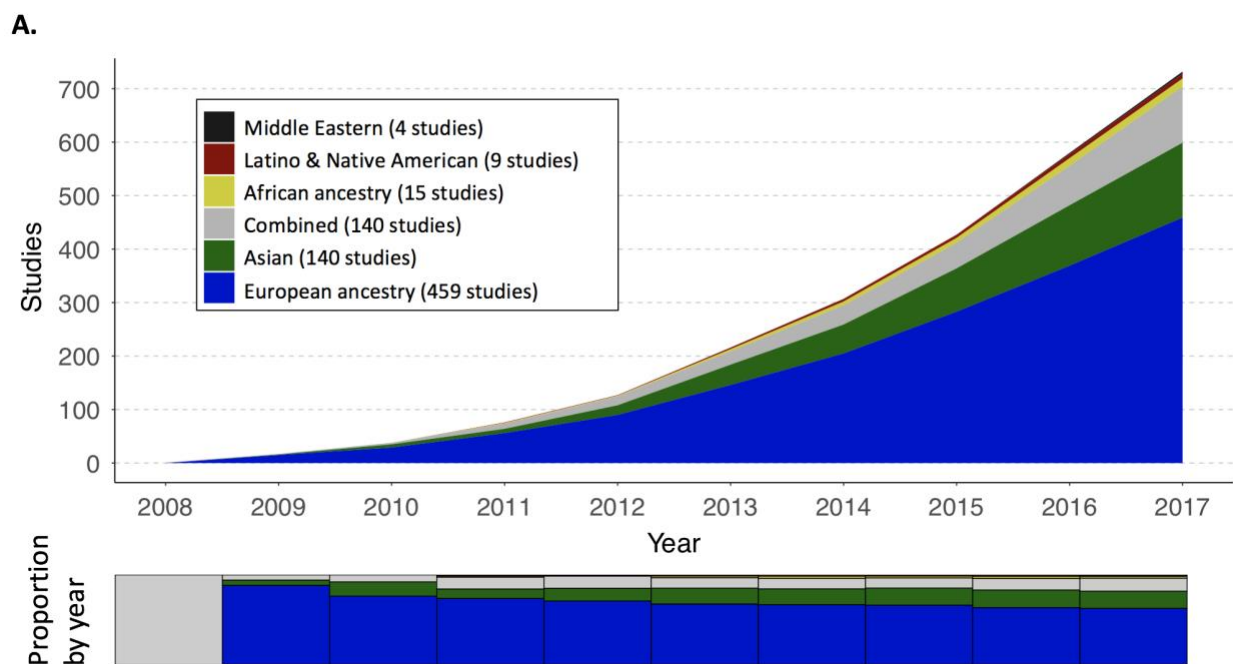
By comparing representation of particular ancestry groups with world population estimates for those groups (**Figure 1B**), it is possible to quantify the over- or under-representation of each major ancestry group. European ancestry representation was approximately 460% of what it would be if representation was proportional to world ancestry. In contrast, African ancestry (17%) and Latino samples (19%) were under-represented relative to world populations. East and South Asian samples are combined in this figure, but it should be noted that representation of East Asian samples is much higher than South Asian samples, which have been included in very few polygenic scoring studies to date. Middle Eastern and Oceanic populations have the lowest representation in polygenic scoring studies relative to world populations for these groups (10% and 0%, respectively).

Figure 1. The first decade of polygenic scoring studies (2008-2017) focused primarily on European ancestry samples (N=733 studies). **A.** Cumulative numbers of studies by year are denoted by color. The stacked bar graph below the cumulative distribution plot shows proportional ancestry by year. **B.** Pie charts depict world ancestry representation (left) and polygenic scoring study representation (right). **C.** The percentage representation for each

*Note that we retain populations names from the original reports (e.g. “Native American” and “Middle Eastern”) for Figure 1 in order to maintain consistency in terminology. “Combined” means that more than one ancestry group was included in the study (e.g. European ancestry and Asian ancestry participants).

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ancestry group is given, such that 100% would indicate equal representation in the world and in polygenic scoring studies. For example, European ancestry samples are over-represented (460%) whereas African ancestry samples are under-represented (17%).



Having analyzed the *use* of polygenic scores in different ancestry groups (above), we next assessed the *performance* of polygenic scores among ancestry groups. We assembled a comprehensive collection of polygenic scoring results (see **Methods**) and found that polygenic scores yield statistically significant predictions for numerous complex genetic phenotypes, across diverse populations. The transferability of polygenic scores across populations is consistent with evidence about shared risk loci^{6,43} and findings of positive, significant genetic correlations across ancestry for numerous complex genetic phenotypes⁴⁴. This means that concerns about complete non-transferability of polygenic scores to diverse populations are likely unwarranted.²⁹ Rather, empirical data and population genetic theory suggest that polygenic scores will not work as well in populations that differ from the discovery GWAS population^{28,44}. Thus, we sought to quantify *how well* polygenic scores performed across ancestry groups in published studies, for a variety of

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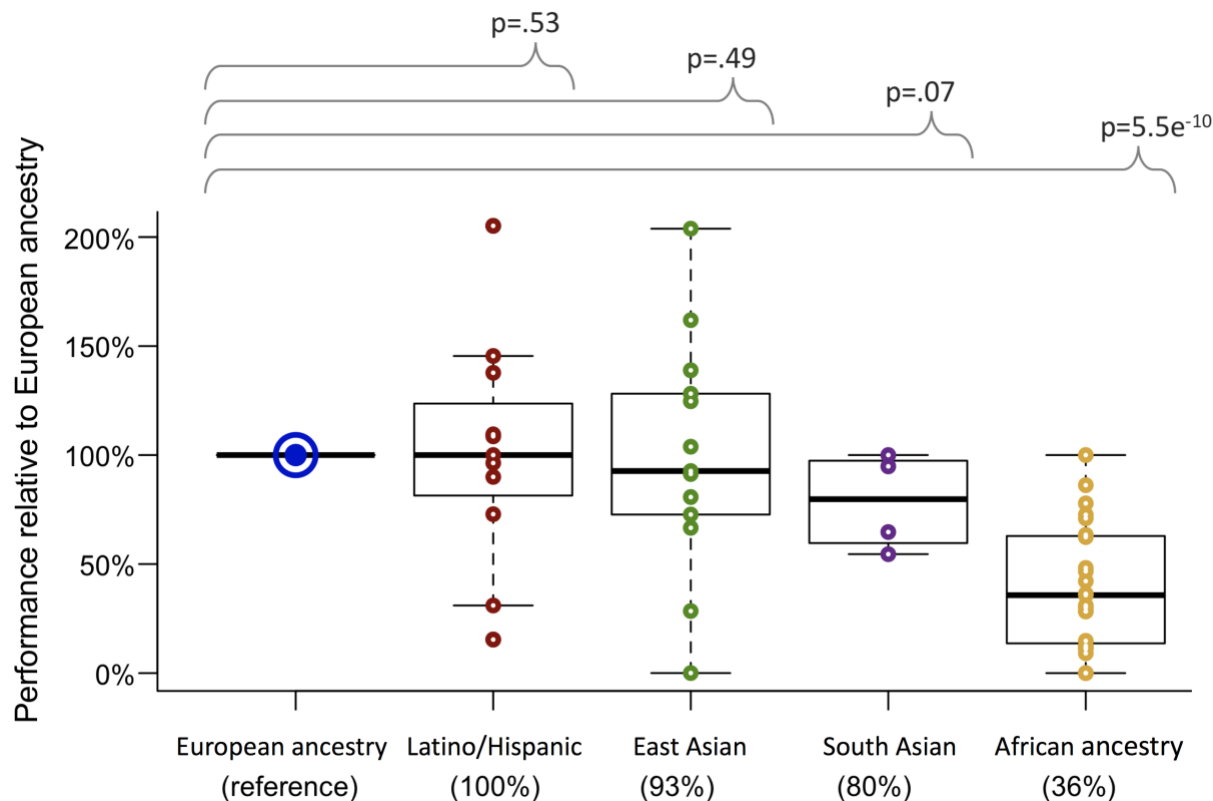
complex genetic phenotypes (e.g. blood pressure and schizophrenia). Since most large-scale GWAS have been conducted in primarily (or exclusively) European ancestry individuals our *a priori* hypothesis was that polygenic scores would perform best among European ancestry individuals, and less well for other populations.

Figure 2 provides an overview of polygenic score performance across ancestry groups. Results from all complex genetic phenotypes are analyzed together in order to increase the amount of data available for analysis. Data used for these analyses were extracted from 29 studies that met eligibility criteria (see **Methods**). Briefly, we extracted effect-size metrics for polygenic scores from every study that conducted polygenic scoring in at least two different ancestry groups, and we required that the same polygenic scoring procedures were used for all ancestry groups within each study (e.g. same genotyping chip, same discovery GWAS weights for all participants in a given study, etc.). We deemed these sets of analyses (within each study), “matched analyses”. For each of the 29 studies, polygenic score performance was normalized to performance in the European-ancestry sample in that study. For example, the first polygenic scoring study of schizophrenia¹² found that polygenic scores explained only 0.4% of phenotypic variance in an African ancestry sample, whereas 3.2% of phenotypic variance was explained in a matched European ancestry sample. Consequently, the value of 12.5% ($100 \times (0.004/0.032)$) is represented as one yellow point in **Figure 2**, among the African ancestry observations displayed on the right side of the **Figure 2**. Thus, each small point represents one comparison between a non-European ancestry sample and a matched European ancestry sample. European ancestry performance is standardized to 100% in all comparisons and is represented by the blue circle on the left side of the figure. By normalizing within-study effect sizes to European ancestry effect sizes, we were able to combine observations across phenotypes, and therefore to obtain general estimates of polygenic score performance across ancestry groups and complex genetic phenotypes. We only analyzed results from studies employing the “classical” polygenic scoring approach, which includes “pruning and thresholding”, and allele weights derived from an independent discovery GWAS^{11,12,21,26}.

Polygenic score performance, on average, was worst among African ancestry samples. The median effect size of polygenic scores in African ancestry samples was only 36% that of matched European ancestry samples ($t=-10.056$, $df=22$, $p=5.5 \times 10^{-10}$). Relative to matched European ancestry samples, performance was also lower in South (80%) and East Asian (93%) samples, but not significantly so. In sum, an expectation of poorer polygenic score performance in non-European ancestry populations seems reasonable given these data. Attenuation of predictive performances is likely to be most extreme in samples of African ancestry, consistent with, on average, greater genetic distance between European and African ancestry populations, than between European and other ancestry populations^{28,45}.

Figure 2 Performance of polygenic scores in Latino, East Asian, South Asian, and African ancestry samples, relative to performance in matched European ancestry samples (29 total studies). In order to make data comparable across studies, performance in each study was standardized to European ancestry performance, hence the single European ancestry y-axis value of 100%. Each point represents one pair of polygenic scoring analyses between a European ancestry sample and a matched sample from another ancestry (see text for details).

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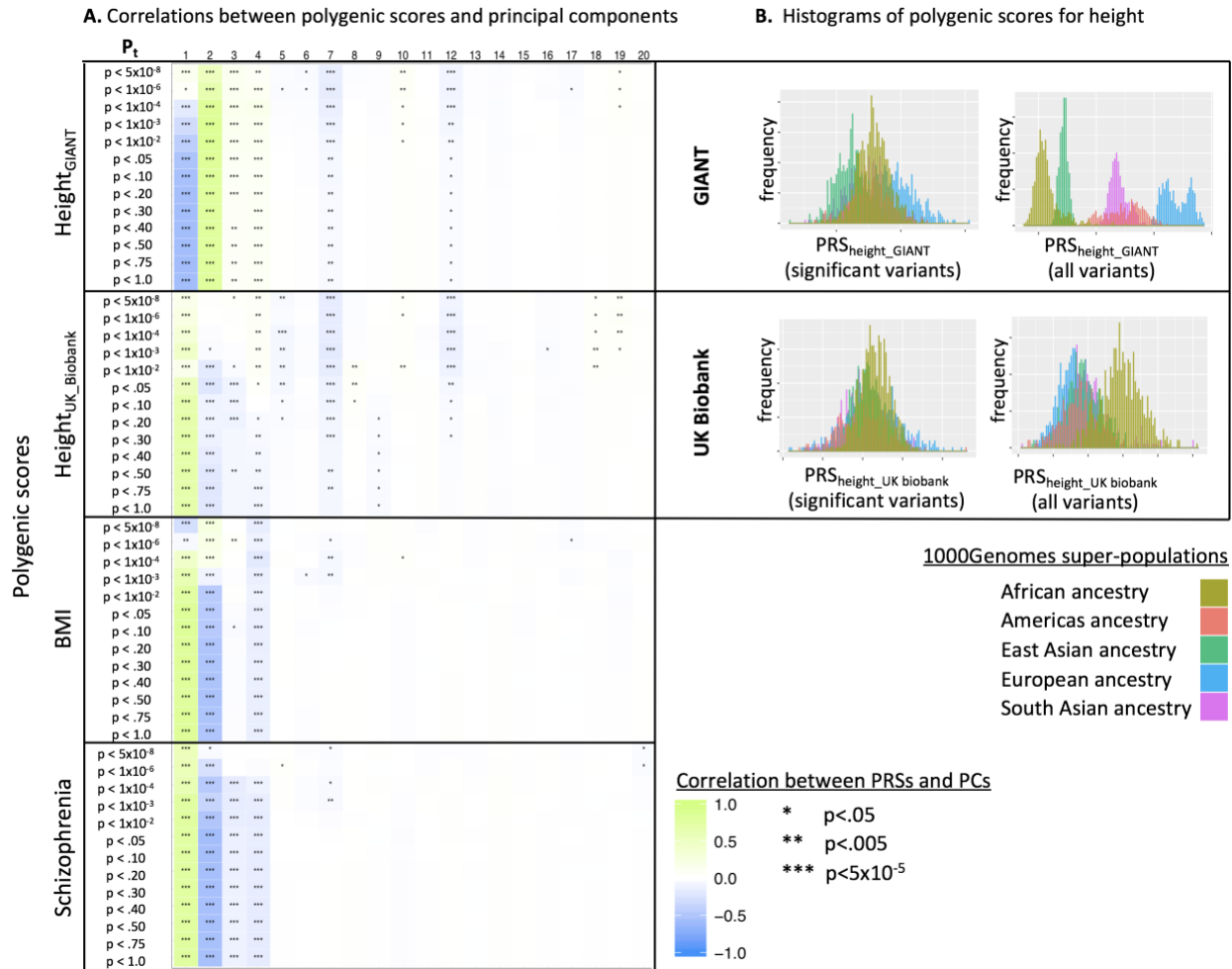
Correlations between global principal components (PCs) and polygenic scores, as currently calculated

We now consider questions about putative differences in polygenic scores across ancestral populations. Polygenic scores, as currently calculated, vary with ancestry. Indeed, polygenic scoring practices from as early as 2009 accounted for this¹². The method used by Purcell and colleagues in 2009 (and frequently since) includes two steps for mixed ancestry samples. First, samples are separated into more ancestrally homogeneous subgroups (using visual inspection of plots of principal components calculated on all genetic data from all samples). Second, principal components are calculated again within each ancestrally homogeneous subgroup, and are used as covariates in polygenic scoring analyses, which are conducted separately within each subgroup. **Figure 3** demonstrates why these ancestry analysis procedures have been used, given that many global PCs are strongly correlated with polygenic risk scores, as currently calculated.

Figure 3 Properties of polygenic scores for 1000Genomes participants, across phenotypes ($height_{GIANT}$, $height_{UK_Biobank}$, body mass index, and schizophrenia) and across a range of p-values thresholds used to construct polygenic scores. **A.** Polygenic scores are oftentimes correlated with global principal components. For each phenotype, polygenic scores were constructed using 13 different p-value thresholds as applied to the discovery GWAS (denoted in the left-most column). Twenty global principal components (PCs) were calculated on 1000Genomes participants and are denoted across the top. Within the plot, correlations between each PC and each polygenic score are color-coded to reflect magnitude and direction of correlations from sky blue=-1 to lime=1. Stars indicate statistical significance of each correlation as follows: * $p < 0.05$, ** $p < 0.005$, ***Bonferroni significant. **B.** Histograms of height polygenic scores for 1000Genomes participants are color-coded according to super-population. Two height GWAS were used to construct scores: GIANT (top) and UK biobank (bottom). Scores were constructed

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using two p-value thresholds: genome-wide significant variants (left) and using all variants (right). As can be seen for both GIANT and UK Biobank-based scores, the choice of p-value threshold applied to the discovery GWAS has a dramatic impact on score distributions among different populations. In general, inclusion of more variants in polygenic scores leads to greater differentiation in distributions of polygenic scores for global populations.



P_t=p-value threshold applied to discovery GWAS in order to construct polygenic scores, PRS=polygenic risk score, GIANT=Genetic Investigation of ANthropomorphic Traits, UK=United Kingdom, BMI=body mass index, PCs=principal components.

Figure 3 shows that polygenic risk scores for the complex genetic phenotypes of height, body mass index (BMI), and schizophrenia are all significantly correlated with various global PCs (**3A**) and also that distributions of scores, as currently calculated, vary across global populations (**3B**). In order to construct Figure 3, we calculated polygenic scores and global PCs on all 1000Genomes individuals. We applied standard procedures including pruning and weighting alleles based on discovery GWAS results (see **Methods** for additional details). The results show that multiple, sometimes non-consecutive, PCs are strongly correlated with polygenic risk scores, as currently calculated. Many significant correlations are higher than $r=.5$, and 17.3% of correlations in **Figure 3** are significant after Bonferroni correction for 1,040 tests (i.e. $0.05/1,040 = p < 5 \times 10^{-5}$; 20 PCs x 4 phenotypes x 13 p-value thresholds for each discovery GWAS

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= 1,040 tests). See **Supplementary Table 2** for correlations and corresponding p-values for **Figure 3A**.

In addition to showing the existence of significant correlations between global PCs and polygenic scores, as currently calculated, **Figure 3** also demonstrates that the choice of p-value threshold applied to the discovery GWAS (in the construction of polygenic scores) has a dramatic effect on score distributions across populations. The differences are so pronounced that the direction of the correlation between individuals' values for a given PC and their polygenic scores may reverse across the range of p-value thresholds used to construct polygenic scores. For example, 1000Genomes participants' scores for the first global principal component and their GIANT¹⁸-based polygenic scores for height are modestly positively correlated when only genome wide significant variants are used to construct scores ($r=.14$, $p=3.4 \times 10^{-12}$, faint green), whereas they are strongly negatively correlated when using all variants to construct polygenic scores ($r=-.59$, $p=1.9 \times 10^{-223}$, blue). In other words, there are many highly significant correlations, which vary not only in magnitude, but also in direction across the range of p-values used in the construction of polygenic scores. The effects of the methodological choice of p-value threshold on polygenic scores is further demonstrated on the right-hand side of **Figure 3B**, which shows the distributions of GIANT-based height polygenic scores for 1000Genomes participants, using two choices of p-value thresholds (top: genome-wide significant variants, bottom: all variants). Plots of distributions of UK Biobank-based⁴⁶ polygenic scores for height are also shown on the right (bottom two plots).

Figure 3 demonstrates key points relevant to the use of polygenic scores in diverse human populations. First, polygenic scores are often correlated with global PCs, and the correlated PCs are not necessarily consecutive (e.g. global PCs 1-4, 7, and 12 are correlated with height polygenic scores). Second, methodological choices of p-value threshold and discovery GWAS can have dramatic effects on polygenic scores, such that the magnitude and even the direction of observed relationships (e.g. between polygenic scores and PCs) may change across the range of commonly used parameters (e.g. across the range of p-value thresholds used to construct scores). These findings highlight the importance of treating ancestry properly in all analyses involving polygenic risk scores. Indeed, these findings suggest that a conservative approach that analyzes polygenic scores separately in each ancestry group may be warranted, at least until a better understanding of polygenic score differences across populations (and across different phenotypes) is achieved. As noted by Chen and colleagues, explicit modeling of ancestry may afford even greater predictive power with polygenic scores⁴⁷.

Assessing putative correlations between global phenotypes and polygenic scores

Finally, we turn to the most difficult question: what causes differences in polygenic scores, as currently calculated, among global populations (e.g. see Figure 3B)? Differences could be real or artifactual (i.e. due to bias in data and/or methods), and five categories of explanations are listed below.

- 1) True differences due to drift
- 2) True differences due to selection
- 3) True differences in genetic effects due to environmental differences (gene-environment interactions)

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- 4) Bias due to uncorrected population stratification in discovery and/or training samples
- 5) Bias due to discovery/training population data and/or polygenic scoring methods. Specifically, linkage disequilibrium (LD) structure and variant frequency are captured imperfectly with current methods (including genotyping and imputation), and they vary across populations, and currently available data resources are unequally representative of diverse global populations.

Drift has been implicated as an explanation for population differences in polygenic scores across populations²⁷, but others reported that drift is insufficient to explain such differences³³. Further, initial estimates of the strength of polygenic selection on height in European ancestry populations^{33,37} have recently been greatly reduced^{30,31}, based on findings of uncorrected population stratification in summary statistics from the GIANT Consortium^{30,31}. There is also disagreement about whether or not polygenic score differences across populations might contribute to phenotypic differences across populations (which could also be due to environmental variation). Some have noted apparent positive correlations between polygenic scores and phenotypes for BMI³⁴, lupus³⁵, and height as calculated using GIANT Consortium scores^{33,36,37} and one group argued that there is no such correlation for height based on GIANT Consortium scores²⁷. As described below, we include more data than used previously to address questions about putative correlations between global height polygenic scores and height phenotypes.

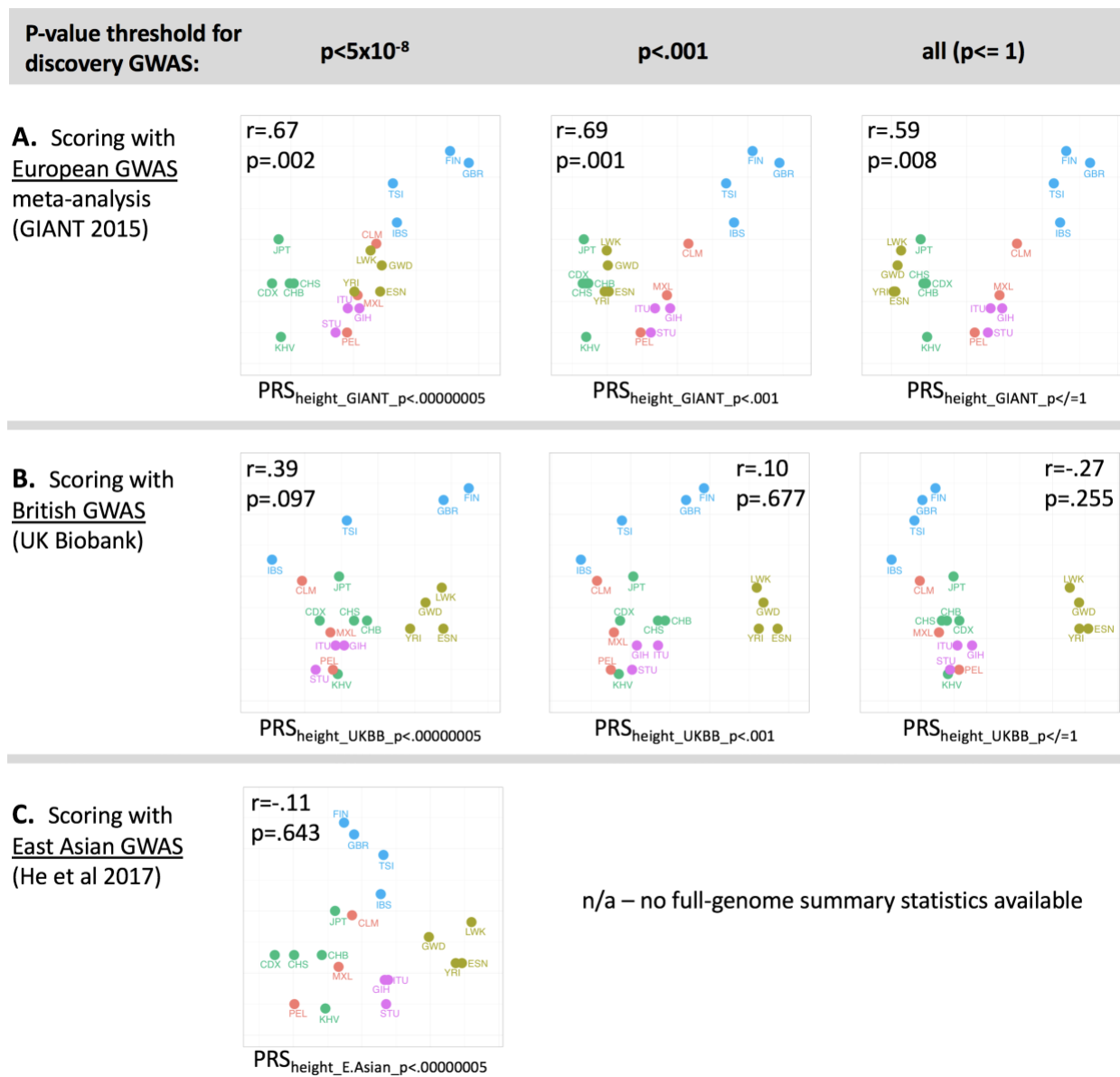
Briefly, using 1000Genomes data (as described in the **Methods**), we provide evidence consistent with artifacts contributing to differences in polygenic scores among global populations. In **Figure 4** we plot average polygenic scores for height of 1000Genomes populations on the x-axis, using three sources of weights for constructing scores (PRS=polygenic risk score):

- **4A** (top row) GIANT Consortium¹⁸ based scores: $PRS_{\text{height_GIANT}}$
- **4B** (middle row) UKBiobank⁴⁶ based scores from the NealeLab: $PRS_{\text{height_UKBiobank}}$
- **4C** (bottom row) East-Asian GWAS based scores⁴⁸ from He et al: $PRS_{\text{height_EastAsian}}$

On the y-axis, we plot average height for countries of origin for 1000Genomes populations, when available (see **Methods** for details and exclusions).

Figure 4 Scatterplots of height polygenic scores (x-axis) and phenotypic height (y-axis) show that correlations are not consistent across discovery GWAS. The y-values for phenotypic height are the same for each plot, and reflect average height of individuals in the country of origin or each population included. Three different GWAS of height were used to score populations (i.e. three rows), and three p-value thresholds (i.e. three columns) were used for polygenic score construction as applied to the relevant discovery GWAS. **A.** GIANT-based polygenic scores for height. **B.** UK Biobank-based scores for height. **C.** East-Asian-based polygenic scores for height. The last two plots are missing because only genome-wide significant variants were available for the East Asian GWAS of height⁴⁸.

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GWAS=genome-wide association study, GIANT=Genetic Investigation of ANthropomorphic Traits, PRS=polygenic risk score, UK=United Kingdom, PCs=principal components. Population abbreviations are standard abbreviations from the 1000Genomes project^{42,45} and are included in Supplementary Table 3.

As shown in **Figure 4A**, height phenotypes for global populations (y-axes) are positively correlated with GIANT-based¹⁸ polygenic scores for height (x-axes), but not with UK-Biobank-based polygenic scores (**4B**) or East-Asian GWAS based polygenic scores (**4C**). Polygenic scores constructed using only genome-wide significant variants from GIANT (top left) were positively correlated with height phenotypes ($r = .67$, $p = .002$), as were scores constructed using larger numbers of GIANT-based variants (e.g. all variants, top right, $r = .59$, $p = .008$). Results in **4B** and **4C** demonstrate that correlations (or lack of correlations) between height and polygenic scores for height are dependent on discovery GWAS. Recent findings suggest that correction for population stratification may not have been adequate in GIANT^{30,31}, and therefore the positive correlations observed in 4A may be partially due to uncorrected population stratification. The

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dependence of correlation estimates on discovery GWAS is further illustrated in **4C**, in which the point estimate for correlation between height and East Asian GWAS based polygenic scores for height is negative ($r=-.11$, $p=.643$). Power in discovery GWAS is also relevant, and greater confidence should be attributed to the results in **4A** and **4B** because both European ancestry discovery GWAS were adequately powered to detect hundreds of height loci, whereas the East Asian height GWAS was only adequately powered to detect 17 loci.

These results suggest that both the ancestry of the participants in the discovery GWAS (e.g. European^{18,46} vs. East Asian⁴⁸) and uncorrected population stratification^{30,31} contribute to observed positive correlations between GIANT-based polygenic scores for height and height phenotypes across global populations. UK Biobank-based polygenic scores provide no evidence of a positive correlation between global heights and mean height polygenic scores for global populations. eMore research is needed to better understand the exact causes of differences in score distributions across populations and their putative relationships to phenotypes. Future research must also account for environmental effects on phenotypes, as well as variability in measurement validity and reliability across populations. Even for the relatively simple example of height (which is easily measured and for which major environmental influences are relatively well-understood) our analyses suggest that a great deal of caution should be used in drawing conclusions about polygenic score differences underling global phenotypic differences, until data resources are significantly improved (i.e. well-powered GWAS in diverse populations), and until a deeper understanding of relevant population genetics principles has emerged. As discussed further below, even more caution will be required for other phenotypes such as psychiatric disorders.

Discussion

As the discussion about personalized medicine is making its way to the general public, it is important to recognize the need to include underrepresented populations in genetic studies. Among other concerns, the inclusion of participants representing diverse ancestries in research is imperative to ensure equitable benefit from scientific discoveries for diverse populations, and to prevent further increase long-standing health disparities. Relevant to these longer-term objectives, our findings provide foundational information about polygenic risk score usage among diverse populations, summarized in four key points. First, polygenic scoring studies have primarily been conducted in European and East Asian ancestry populations. Second, the performance of polygenic scores in non-European populations is generally poorer than performance in European ancestry samples. Third, polygenic scores for complex genetic phenotypes are often correlated with global principal components. Fourth, appropriate data resources are lacking to address most questions about putative differences in polygenic scores across global (non-European ancestry) populations. The straightforward, albeit expensive and time-consuming, solution to improving polygenic score performance across diverse populations is to create well-powered GWAS data resources for many different global populations. Perhaps the most tractable near-term goal is large-scale multi-population GWAS of an easily measurable trait such as height, and the GIANT Consortium is taking on this important goal.

Concerning expectations about polygenic score performance in diverse (non-European ancestry) samples we note that polygenic scores for many complex genetic phenotypes are strongly

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correlated with global PCs. The existence of such correlations highlights the critical importance of appropriate statistical methods for the analysis of genetic data from diverse ancestry populations, including analyst/statistical geneticist familiarity with multi-ethnic samples. Testing future polygenic scoring results for robustness to the inclusion of variable combinations of PCs can reduce chances for spurious results, that are actually due to ancestry. We also provide benchmarks for the relative performance of polygenic scores in diverse populations, as compared to performance in populations of European ancestry. This is important, because it not only informs power calculations for future research but also highlights relative differences in predictive utility across diverse populations. We find that currently available data resources are inadequate for polygenic scoring among African ancestry populations, as compared to data resources available for European ancestry samples. Furthermore, estimates of relative polygenic risk score effect sizes, provided here, can inform power calculations in future studies. In sum, the preponderance of genetic studies based on European ancestry samples has led to a situation in which polygenic scores are approximately one-third as informative for African ancestry individuals, as they are for European ancestry individuals. This is presumably true for commercially available tests as well, and consumers should be aware of the differential performance of tests across individuals.

Regarding scientific and public perception of polygenic scores, it is important to address apparent differences in polygenic score distributions across populations. Our findings suggest that it is currently not possible to know precisely the distribution of polygenic scores for diverse non-European populations, for any complex genetic phenotype, because data resources for most populations are currently inadequate. Further, as we have shown, the ordering of population distributions of polygenic scores varies across accepted methods of constructing polygenic scores (i.e. using different p-value thresholds for variant inclusion in scores and using alternative discovery GWAS). Explanations for these differences are currently incomplete. Until vastly superior data resources are available – including large scale GWAS in multiple global populations – scientists are unlikely to reach consensus regarding the existence, nature, and exact causes of polygenic score differences among populations.

We chose to examine the phenotype of height because it is easily measured across populations and because factors affecting height (e.g. nutrition) are also relatively easily quantified. In contrast, research on other variables such as weight, smoking status, psychological symptoms, and cognitive performance will require more careful control for environmental confounders, which may often be correlated with ancestry and thus global principal components and polygenic scores, as currently calculated. This means that confounding of environmental and genetic effects is likely. For example, social experiences such as being subjected to racism are prime candidates for confounding in genetic studies.

We specifically addressed the topic of potential ancestry-based differences in genetic contributions to complex genetic phenotypes because future findings could hold both promise for precision medicine, and peril if information is misused. Already it is known that certain Mendelian disorders vary, in part, with ancestry (e.g. cystic fibrosis⁴⁹ and sickle cell disease⁵⁰), and scientists should be aware that ancestry-based differences in polygenic influences might exist. However, given the sensitivity of certain complex genetic phenotypes such as cognitive and psychological variables – combined with the historical precedent for misuse of scientific

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claims (even those that proved to be false) by governments and racist groups⁵¹ – it is critical that scientists proceed with caution. For these reasons, our findings about the inadequacy of currently available data to assess putative correlations between polygenic scores and phenotypes across global populations are particularly important.

In closing, we emphasize the need to engage experts from other disciplines, such as social psychology and bioethicists, as geneticists attempt to characterize genetic effects on phenotypes such as cognitive variables. This is necessary because societal influences including socioeconomic status and discrimination can powerfully influence such phenotypes as cognitive performance⁵², and these causal social factors often co-vary with ancestry. In genetic research, there is potential for relative blindness to non-genetic influences on phenotypes. Consequently, experts must be consulted in order to properly account for non-genetic influences on many complex genetic phenotypes and gene-environment interplay (i.e. correlations and interactions). This precaution applies to psychiatric phenotypes as well, which may be differentially reported (and manifested) across cultures. Nevertheless, with cautious and broadly-informed research, potential medical benefits of correctly interpreting polygenic variation within and among populations can be realized.

Materials and Methods

This study has two major parts. First, we analyzed data extracted from previous polygenic scoring studies in order to describe trends in polygenic scoring research and to provide the most comprehensive analysis of polygenic scoring performance available to date. Second, we analyzed properties of polygenic scores as calculated for the 1000Genomes individuals. Relevant procedures for these two parts are described below. This work received a notice of determination that this was not human subjects research from Stanford University.

Part 1: Extracting and analyzing data from previous polygenic scoring studies. We first identified studies with data suitable for extraction, via PubMed on January 23rd, 2018 using the following search terms: (Genome-Wide Association Stud* OR GWAS OR Genome Wide Association Stud*) and (polygenic risk score OR genetic risk score OR polygenic risk scor* OR genetic risk scor* OR risk profile scor* OR “genomic profile”). We sought to identify all polygenic scoring studies, of any complex genetic phenotype, from the first decade of polygenic scoring research (note Purcell et al. 2009 was manually added). This yielded 1,226 studies, 733 of which were polygenic scoring studies (see **Figure 1**). From these 733 studies we extracted data about the ancestry of participants and methods of constructing polygenic scores. We then applied criteria to identify studies that contained valid comparisons of the performance of polygenic scores in European ancestry participants and at least one other ancestry. Specifically, matched analyses (from two or more ancestry groups, from any given publication) had to use the same genotyping chip for all samples, the same weights for variants, the same for constructing polygenic scores, and the same methods of measuring phenotypes across all participants. Data from 29 studies met inclusion criteria. From these studies we then extracted effect size metrics for each ancestry group and then normalized score performance for all ancestry groups to performance within the European ancestry participants, by dividing all effect sizes (within each study) by the effect size of the relevant European ancestry sample. We multiplied values by 100 so that performance for each non-European ancestry sample could be expressed as a percentage

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of European ancestry performance, which was standardized to 100%. This yielded the data in **Figure 2**, wherein each point represents one within-study comparison between a non-European ancestry sample and the matched (within-study) European ancestry sample.

Part 2: Examining polygenic scores in 1000Genomes individuals. For part 2, we used publicly available data from 1000Genomes⁴²; genotype data for 2,557 individuals was downloaded from <ftp-trace.ncbi.nih.gov/1000genomes/ftp/release/20130502/>. Weights for constructing polygenic scores came from multiple, publicly-available sources of GWAS results^{14,18,46,48}. Data about average human height, for countries of origin for 1000Genomes populations, was downloaded from a pre-compiled table with male and female heights by country: https://en.wikipedia.org/wiki/List_of_average_human_height_worldwide.

Data preparation and analysis included the following steps. The full 1000Genomes dataset was first filtered to include only bi-allelic single nucleotide polymorphisms (SNPs) with greater than .1% minor allele frequency. Prior to calculating principal components across 1000Genomes genotypes, we used second generation PLINK⁵³ to obtain variants in approximate linkage equilibrium, and we also removed the MHC region of chromosome 6 (25-35Mb) and the large inversion region on chromosome 8 (7-13Mb). We then calculated 20 PCs across all individuals. Summary statistics files (i.e. GWAS results) were pruned to include only variants in approximate linkage equilibrium, using second generation PLINK^{53,54} and the following thresholds: --clump-kb 500, --clump-p1 1, --clump-p2 1, --clump-r2 0.2. 1000Genomes European ancestry data was used as the source of linkage disequilibrium information for pruning all summary statistic files given the primarily European ancestry of discovery GWAS datasets. We could not use individual-level genotype data for linkage disequilibrium pruning of the GWAS results files because it was not available. Second generation PLINK⁵³ was used to construct polygenic scores for each phenotype for the 1000Genomes participants, using 13 thresholds for including pruned discovery GWAS variants in scores, as follows: $p < 5 \times 10^{-8}$, $p < 1 \times 10^{-6}$, $p < 1 \times 10^{-4}$, $p < 1 \times 10^{-3}$, $p < 1 \times 10^{-2}$, $p < .05$, $p < .1$, $p < .2$, $p < .3$, $p < .4$, $p < .5$, $p < .75$, $p < / = 1$. Plotting, t-tests, and correlations were conducted in R⁵⁵. Height phenotype data was downloaded from a compiled table of average heights, for males and females, by countries. Heights for males and females were averaged. Certain populations were excluded from the analysis of correlations between polygenic risk scores for height and height phenotypes for three reasons: Four populations were excluded due to lack of height phenotype data: Puerto Rican in Puerto Rico (PUR), Bengali in Bangladesh (BEB), Punjabi in Lahore, Pakistan (PJL), Mende in Sierra Leone (MSL). Two populations were excluded due to the combination of highly mixed country ancestry (impacting validity of height phenotype) and admixture of the 1000Genomes population (impacting variability in the polygenic scores for height): African Ancestry in Southwest US (ASW), African Caribbean in Barbados (ACB). One population was excluded due to the absence of a single European country of origin: Utah residents with Northern and Western European ancestry (CEU). Details are given in **Supplementary_Table_3_1000Genomes_countries_of_origin.xlsx**

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Figure Legends

For ease of review, figure legends are also supplied in the main text.

Figure 1. The first decade of polygenic scoring studies (2008-2017) focused primarily on European ancestry samples (N=733 studies). **A.** Cumulative numbers of studies by year are denoted by color. The stacked bar graph below the cumulative distribution plot shows proportional ancestry by year. **B.** Pie charts depict world ancestry representation (left) and polygenic scoring study representation (right). **C.** The percentage representation for each ancestry group is given, such that 100% would indicate equal representation in the world and in polygenic scoring studies. For example, European ancestry samples are over-represented (460%) whereas African ancestry samples are under-represented (17%).

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Figure 2 Performance of polygenic scores in Latino, East Asian, South Asian, and African ancestry samples, relative to performance in matched European ancestry samples (29 total studies). In order to make data comparable across studies, performance in each study was standardized to European ancestry performance, hence the single European ancestry y-axis value of 100%. Each point represents one pair of polygenic scoring analyses between a European ancestry sample and a matched sample from another ancestry (see text for details).

Figure 3 Properties of polygenic scores for 1000Genomes participants, across phenotypes (height_{GIANT}, height_{UK_Biobank}, body mass index, and schizophrenia) and across a range of p-values thresholds used to construct polygenic scores. **A.** Polygenic scores are oftentimes correlated with global principal components. For each phenotype, polygenic scores were constructed using 13 different p-value thresholds as applied to the discovery GWAS (denoted in the left-most column). Twenty global principal components (PCs) were calculated on 1000Genomes participants and are denoted across the top. Within the plot, correlations between each PC and each polygenic score are color-coded to reflect magnitude and direction of correlations from sky blue=-1 to lime=1. Stars indicate statistical significance of each correlation as follows: *p<0.05, **p<0.005, ***Bonferroni significant. **B.** Histograms of height polygenic scores for 1000Genomes participants are color-coded according to super-population. Two height GWAS were used to construct scores: GIANT (top) and UK biobank (bottom). Scores were constructed using two p-value thresholds: genome-wide significant variants (left) and using all variants (right). As can be seen for both GIANT and UK Biobank-based scores, the choice of p-value threshold applied to the discovery GWAS has a dramatic impact on score distributions among different populations. In general, inclusion of more variants in polygenic scores leads to greater differentiation in distributions of polygenic scores for global populations.

Figure 4 Scatterplots of height polygenic scores (x-axis) and phenotypic height (y-axis) show that correlations are not consistent across discovery GWAS. The y-values for phenotypic height are the same for each plot, and reflect average height of individuals in the country of origin or each population included. Three different GWAS of height were used to score populations (i.e. three rows), and three p-value thresholds (i.e. three columns) were used for polygenic score construction as applied to the relevant discovery GWAS. **A.** GIANT-based polygenic scores for height. **B.** UK Biobank-based scores for height. **C.** East-Asian-based polygenic scores for height. The last two plots are missing because only genome-wide significant variants were available for the East Asian GWAS of height⁴⁸.