1 **Signals of polygenic adaptation on height have been overestimated due**
2 **to uncorrected population structure in genome-wide association studies**
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## Abstract

Genetic predictions of height differ among human populations and these differences are too large to be explained by genetic drift. This observation has been interpreted as evidence of polygenic adaptation. Differences across populations were detected using SNPs genome-wide significantly associated with height, and many studies also found that the signals grew stronger when large numbers of sub-significant SNPs were analyzed. This has led to excitement about the prospect of analyzing large fractions of the genome to detect subtle signals of selection and claims of polygenic adaptation for multiple traits. Polygenic adaptation studies of height have been based on SNP effect size measurements in the GIANT Consortium meta-analysis. Here we repeat the height analyses in the UK Biobank, a much more homogeneously designed study. Our results show that polygenic adaptation signals based on large numbers of SNPs below genome-wide significance are extremely sensitive to biases due to uncorrected population structure.

## Introduction

Most human complex traits are highly polygenic.[1,2] For example, height has been estimated to be modulated by as much as 4% of human allelic variation.[2],[3] Polygenic traits are expected to evolve differently from monogenic ones, through slight but coordinated shifts in the frequencies of a large number of alleles, each with mostly small effect. In recent years, multiple methods have sought to detect selection on polygenic traits by evaluating whether shifts in the frequency of trait-associated alleles are correlated with the signed effects of the alleles estimated by genome-wide association studies (GWAS).[4–10]

Here we focus on a series of recent studies—some involving co-authors of the present manuscript—that have reported evidence of polygenic adaptation at alleles associated with height in Europeans. One set of studies observed that height-increasing alleles are systematically elevated in frequency in northern compared to southern European populations, a result that has subsequently been extended to ancient DNA.[4–11]Another study using a very different methodology (singleton density scores, SDS) found that height-increasing alleles have systematically more recent coalescent times in the United Kingdom (UK) consistent with selection for increased height over the last few thousand years.[12]

All of these studies have been based on SNP associations, in most cases with effect sizes discovered by the GIANT Consortium, which most recently combined 79 individual GWAS through meta-analysis, encompassing a total of 253,288 individuals.[13,14] Here, we show that the selection effects described in these studies are severely attenuated and in some cases no longer significant when using summary statistics derived from the UK Biobank, an independent and larger single study that includes 336,474 genetically unrelated individuals who derive their ancestry almost entirely from British Isles (identified as "white British ancestry" by the UK Biobank) (**Supplementary Table S1**). The UK Biobank analysis is based on a single cohort drawn from a relatively homogeneous population enabling excellent control of potential population stratification. Our analysis of the UK Biobank data confirms that almost all genome-wide significant loci discovered by the GIANT

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93  consortium are real associations, and that the two datasets have high concordance
94  for low P value SNPs which do not reach genome-wide significance
95  (**Supplementary Figure S1**; genetic correlation between the two height studies is
96  0.94 [se=0.0078]). However, our analysis yields qualitatively different conclusions
97  with respect to signals of polygenic adaptation.
98
99  **Results**
100
101  We began by estimating "polygenic height scores"—sums of allele
102  frequencies at independent SNPs from GIANT weighted by their effect sizes—to
103  study population level differences among ancient and present-day European
104  samples. We used a set of different significance thresholds and strategies to correct
105  for linkage disequilibrium as employed by previous studies, and replicated their
106  signals for significant differences in genetic height across populations.[4–11]
107  (**Figure 1a, Supplementary Figure S2**). We then repeated the analysis using
108  summary statistics from a GWAS for height in the UK Biobank restricting to
109  individuals of British Isles ancestry and correcting for population stratification
110  based on the first ten principal components (UKB).[15] This analysis resulted in a
111  dramatic attenuation of differences in polygenic height scores (**Figure 1a,**
112  **Supplementary Figures S2-S4**). The differences between ancient European
113  populations also greatly attenuated (**Figure 1a, Supplementary Figure S5**).
114  Strikingly, the ordering of the scores for populations also changed depending on
115  which GWAS was used to estimate genetic height both within Europe (**Figure 1a,**
116  **Supplementary Figures S2-S5**) and globally (**Supplementary Figure S6**),
117  consistent with reports from a recent simulation study.[16] The height scores were
118  qualitatively similar only when we restricted to independent genome-wide
119  significant SNPs in GIANT and the UK Biobank (P < 5x10$^{-8}$) (**Supplementary Figure**
120  **S2b**). This replicates the originally reported significant north-south difference in the
121  allele frequency of the height-increasing allele[4] or in genetic height[5] across
122  Europe, as well as the finding of greater genetic height in ancient European steppe
123  pastoralists than in ancient European farmers,[6] although the signals are
124  attenuated even here. This suggests that tests of polygenic adaptation based on
125  genome-wide significant SNPs may be relatively insensitive to confounding
126  (**Supplementary Figure S2b**), and that confounding due to stratification is a
127  particular danger for sub-significant SNPs (**Figure 1a, Supplementary Figure S2a**).
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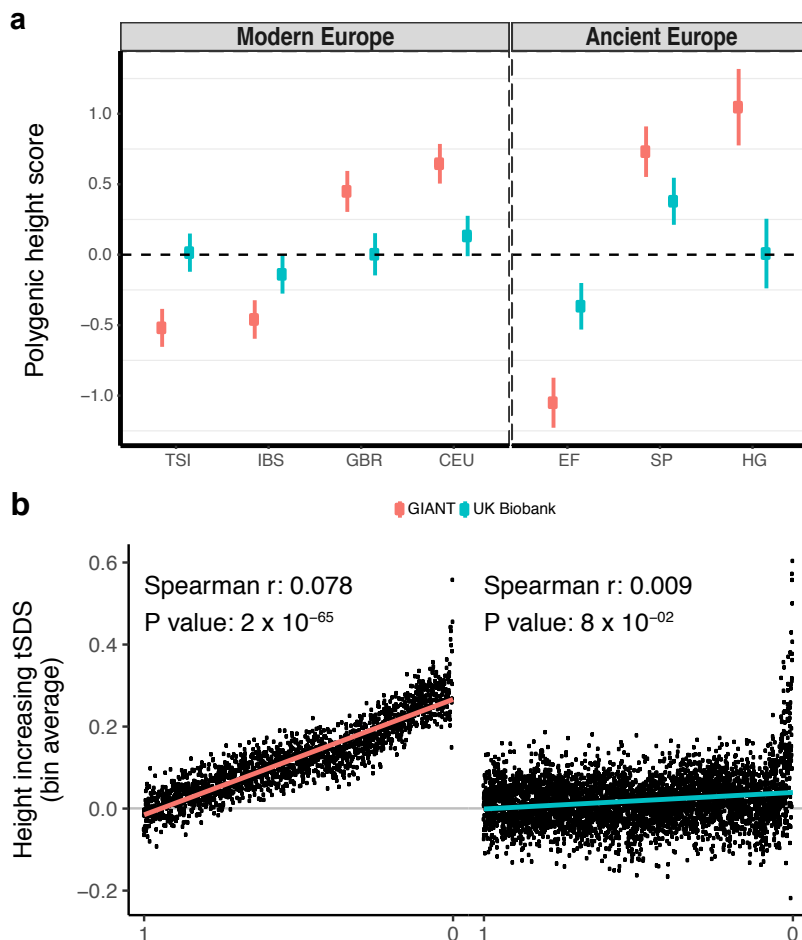
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**Figure 1**. **Polygenic height scores and tSDS scores based on GIANT and UK Biobank GWAS.**
Polygenic scores in present-day and ancient European populations are shown, centered by the average score across populations and standardized by the square root of the additive variance. Independent SNPs for the polygenic score from both GIANT (*red*) and the UK Biobank (*blue*) were selected by picking the SNP with the lowest P value in each of 1700 independent LD blocks similarly to refs [8,9] (see methods). Present-day populations are shown from Northern Europe (CEU, GBR) and Southern Europe (IBS, TSI) from the 1000 genomes project; Ancient populations are shown in three meta-populations (HG = Hunter-Gatherer (n=162 individuals), EF = Early Farmer (n=485 individuals), and SP = Steppe Ancestry (n=465 individuals)) (see **Supplementary Table S2**). Error bars are drawn at 95% credible intervals. See **Supplementary figures S2-S6** for polygenic height scores computed using other linkage disequilibrium pruning procedures, significance thresholds, summary statistics and populations. (b) tSDS for height-increasing allele in GIANT (left) and UK Biobank (right).  The tSDS method was applied using pre-computed Singleton Density Scores for 4,451,435 autosomal SNPs obtained from 3,195 individuals from the UK10K project[12]·[17] for SNPs associated with height in GIANT and the UK biobank. SNPs were ordered by GWAS P value and grouped into bins of 1000 SNPs each. The mean tSDS score within each P value bin is shown on the y-axis. The Spearman correlation coefficient between the tSDS scores and GWAS P values, as well as the correlation standard errors and P values, were computed on the un-binned data. The gray line indicates the null-expectation, and the colored lines are the linear regression fit. The correlation is significant for GIANT (Spearman r = 0.078, P = 1.55 x 10$^{-65}$) but not for UK Biobank (Spearman r = -0.009, P = 0.077).

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153     Next, we looked at polygenic adaptation within the UK using the "singleton
154  density score" (SDS)—an independent measure that uses the local density of alleles
155  that occur only once in the sample as a proxy for coalescent branch lengths.[12,17]
156  SDS can be combined with GWAS effect sizes estimates by aligning the SDS sign to
157  the trait-increasing allele, after which the score is referred to as tSDS. A tSDS score
158  larger than zero implies that height-increasing alleles have been increasing in
159  frequency over time due to natural selection. We replicate the finding that tSDS
160  computed in the UK10K is positively rank-correlated with GIANT[12] height P
161  values (Spearman's $\rho$ = 0.078, P = 1.55 x $10^{-65}$, **Figure 1b**). However, this signal of
162  polygenic adaptation in the UK attenuated when we used UK Biobank height effect
163  size estimates and P values and became formally non-significant ($\rho$ = 0.009, P =
164  0.077, **Figure 1b**).
165     We propose that the qualitative difference between the polygenic adaptation
166  signals in GIANT and the UK Biobank is the cumulative effect of subtle biases in each
167  of the contributing SNPs in GIANT. This bias can arise due to incomplete control of
168  the population structure in GWAS.[18] For example, if height were differentiated
169  along a north-south axis because of differences in environment, any variant that is
170  differentiated in frequency along the same axis would have an artifactually large
171  effect size estimated in the GWAS.  Population structure is substantially less well
172  controlled for in the GIANT study than in the UK Biobank study, both because the
173  GIANT study population is more heterogeneous than that in the UK Biobank, and
174  because the population structure in GIANT may not have been well controlled in
175  some component cohorts of GIANT due to the relatively small size of individual
176  studies (i.e., the ability to detect and correct population structure is dependent on
177  sample size[19,20]). The GIANT meta-analysis also found that such stratification
178  effects worsen as SNPs below genome-wide significance are used to estimate height
179  scores,[14] consistent with our finding that the differences in genetic height
180  increase when including these SNPs.
181     To obtain further insight into our observed discrepancy between polygenic
182  adaptation signals in GIANT vs the UK Biobank, we repeated our analyses using
183  estimates of height effect sizes computed using different methods, and then
184  interrogated each of these for signs of population structure. Repeating our analysis
185  with family-based effect size estimates from an independent study (NG2015
186  sibs),[7] we found evidence for significant differences in polygenic scores between
187  northern and southern Europeans that were qualitatively similar to those obtained
188  using GIANT effect size estimates (**Supplementary Figure S4-S5**). Inclusion of
189  individuals from the UK Biobank who were not of British Isles ancestry without
190  controlling for population structure (UKB all no PCs) in the measurements of effect
191  sizes also produced this pattern (**Supplementary Figure S3-S5**). Thus, UK Biobank
192  estimates that retain population structure show similar patterns to GIANT and
193  previously published family-based estimates (NG 2015 sibs).  In contrast, no
194  significant signals of genetic stratification of height or a strong tSDS signal are
195  present across populations from: 1) a genetically homogeneous sample of UK
196  Biobank with entirely British Isles ancestry without controlling for population
197  structure (UKB WB no PCs), or 2) effect size estimates based on UK Biobank families

198  (UKB sibs, UKB sibs WB) (**Supplementary Figures S3-S5, S7-S8**). These analyses
199  provide further evidence that the lack of signal in the UK Biobank analysis is
200  unlikely to be simply due to over-correction for structure in the original UKB
201  estimates.
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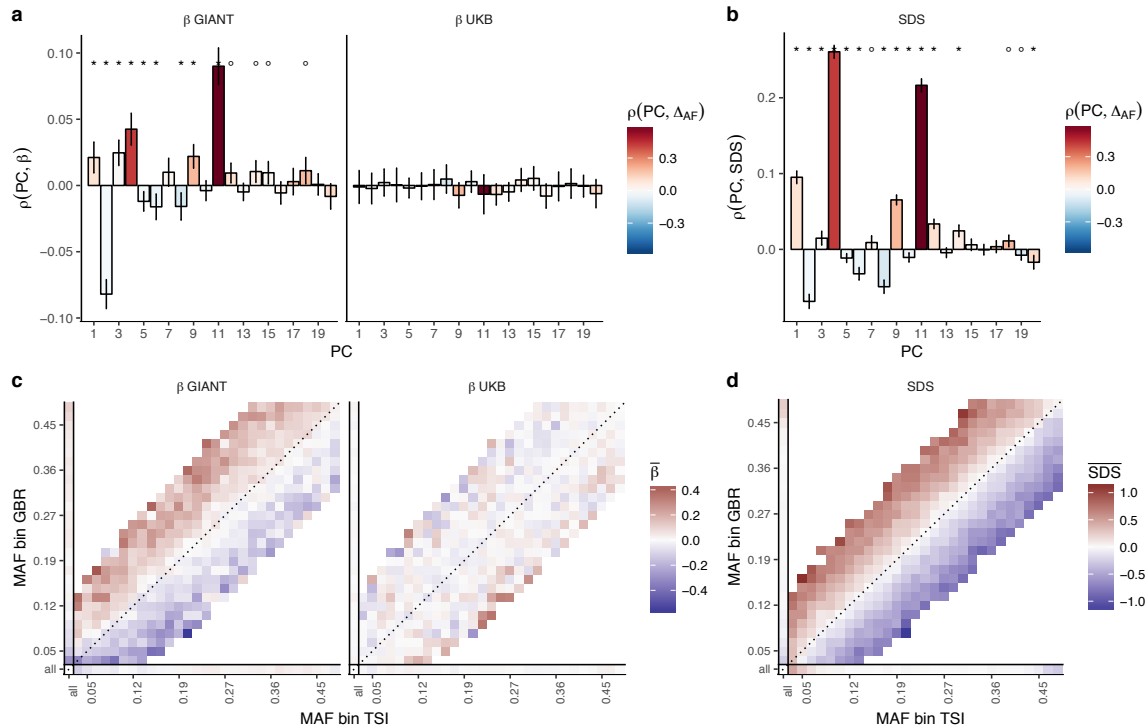


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205  **Figure 2. Evidence of stratification in height summary statistics.**
206  Top row: Pearson Correlation coefficients of (a) PC loadings and height beta coefficients
207  from GIANT and UKB, and (b) PC loadings and SDS (pre-computed in the UK10K) across all
208  SNPs. PCs were computed in all 1000 genomes phase 1 samples. Colors indicate the
209  correlation of each PC loading with the allele frequency difference between GBR and TSI, a
210  proxy for the European North-South genetic differentiation. PC 4 and 11 are most highly
211  correlated with the GBR - TSI allele frequency difference. Confidence intervals and P values
212  are based on Jackknife standard errors (1000 blocks). Open circles indicate correlations
213  significant at alpha = 0.05, stars indicate correlations significant after Bonferroni correction
214  in 20 PCs (P < 0.0025).
215  Bottom row: Heat map after binning all SNPs by GBR and TSI minor allele frequency of (c)
216  mean beta coefficients from GIANT and UKB, and (d) SDS scores for all SNPs. Only bins with
217  at least 300 SNPs are shown. While the stratification effect in SDS is not unexpected, it can
218  lead to false conclusions when applied to summary statistics that exhibit similar
219  stratification effects. UKB height betas exhibit stratification effects that are weaker, and in
220  the opposite direction of the stratification effects in GIANT (see **Supplementary Figure S9**
221  for a possible explanation).
222
223      We obtained direct confirmation that population structure is more correlated
224  with effect size estimates in GIANT than to those in the UK Biobank. **Figure 2a**
225  shows that the effect sizes estimated in GIANT are highly correlated with the SNP
226  loadings of several principal components of population structure (PC loadings).

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227 Previously published family-based effect size estimates[7] (NG 2015 sibs) are
228 similarly correlated with the PC loadings showing that they are also affected  by
229 population structure despite being computed within families; in other words, these
230 empirical analyses show that even previously published family-based effect size
231 estimates are not free from concerns about population structure. The within-family
232 strategy for eliminating concerns about population stratification is not problematic
233 on its own as our UK Biobank family estimates (UKB sibs, UKB sibs WB) computed
234 using the same method do not show any stratification effects (**Supplementary
235 Figures S10-S12**). We also do not see a strong correlation with PC loadings in our
236 UK Biobank estimates computed using unrelated individuals (UKB)(**Figure 2a**).
237 However, the UK Biobank estimates including individuals not of British Isles
238 ancestry and not correcting for population structure (UKB all no PCs) show the
239 same stratification effects as GIANT and NG2015 sibs (**Supplementary Figure S10-
240 S12**). Similarly, we find that alleles that are more common in the Great Britain
241 population (GBR) than in the Tuscan population from Italy (TSI) tend to be
242 preferentially height-increasing according to the GIANT and NG2015 sibs estimates
243 but not according to the UKB estimates (**Figure 2c, Supplementary Figures S11,
244 S12**).
245       The tSDS analysis should be robust to the type of population structure
246 discussed above.[12] However, there is a north-south cline in singleton density in
247 Europe due to the lower genetic diversity in northern than in southern Europeans,
248 with singleton density being lower in northern than in southern regions.[21] As a
249 consequence, SDS tends to be higher in alleles more common in GBR than in TSI
250 (**Figure 2d**). This cline in singleton density coincidentally parallels the phenotypic
251 cline in height and the major axis of genome-wide genetic variation. Therefore,
252 when we perform the tSDS test using GIANT-estimated effect sizes and P values, we
253 find fewer singletons (corresponding to higher SDS) around the inferred height-
254 increasing alleles which tend, due to the uncontrolled population stratification in
255 GIANT, to be at high frequency in northern Europe (**Figures 2c**). This effect does not
256 appear when we use UK Biobank summary statistics because of the much lower
257 level of population stratification and more modest variation in height. We find that
258 SDS is not only correlated with GBR-TSI allele frequency differences, but with
259 several principal component loadings across all SNPs (**Figure 2b**), and that these
260 SDS-PC correlations often coincide with correlations between GIANT-estimated
261 effect sizes and PC loadings (**Figure 2a**).
262       We further find that the tSDS signal which is observed across the whole
263 range of P values in some summary statistics can be mimicked by replacing SDS
264 with GBR-TSI allele frequency differences (**Figures 3a, 3c, Supplementary Figures
265 S7-S8, S13-S14**), suggesting that the tSDS signal at non-significant SNPs may be
266 driven in part by residual population stratification. As with the polygenic score
267 analysis, a small but significant effect is observed when we restrict to genome-wide
268 significant SNPs ($P < 5 \times 10^{-8}$). This effect persists when using UK Biobank family-
269 based estimates for genome-wide significant SNPs (**Figure 3b**), and is not driven by
270 allele frequency differences between GBR and TSI (**Figure 3d**), suggesting a true but
271 attenuated signal of polygenic adaptation in the UK that is driven by a much smaller
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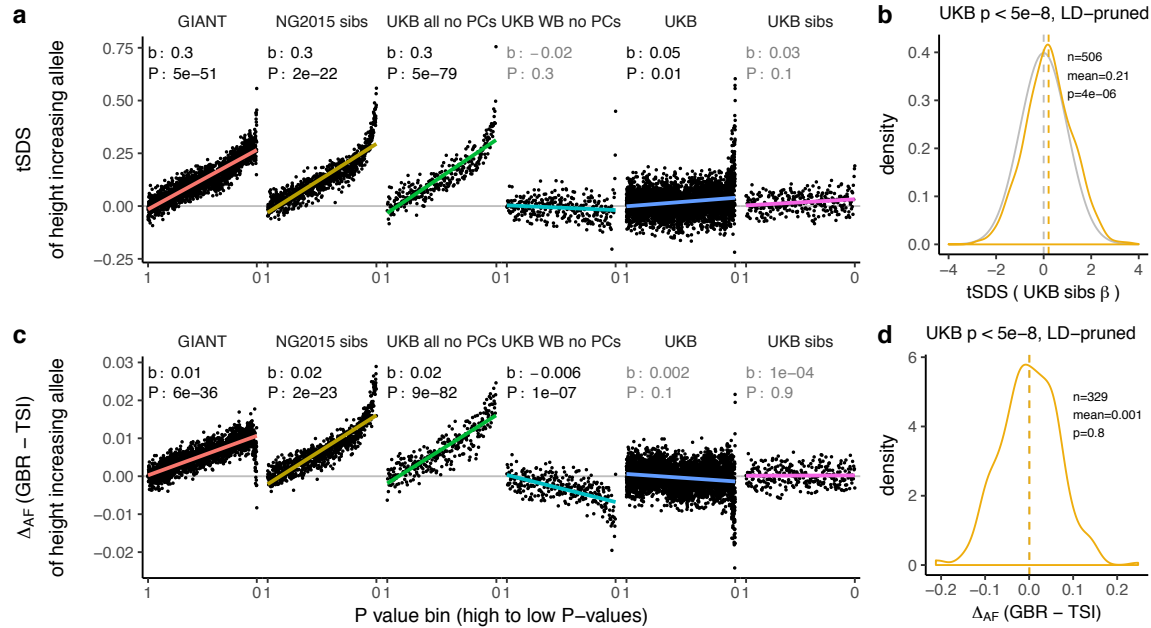
**Figure 3. Height tSDS results for different summary statistics.**
(a) Mean tSDS of the height increasing allele in each P value bin for six different summary statistics. The first two panels are computed analogously to Figure 4A and Figure S22 in Field et al. In contrast to those Figures and to **Figure 1b**, the displayed betas and P values correspond to the slope and P value of the linear regression across all un-binned SNPs (rather than the Spearman correlation coefficient and Jackknife P values). The y-axis has been truncated at 0.75, and does not show the top bin for UKB all no PCs, which has a mean tSDS of 1.5. See **Supplementary Figure S7** for other GWAS summary statistics (b) tSDS distribution of the height increasing allele in 506 LD-independent SNPs which are genome-wide significant in a UKB height GWAS, where the beta coefficient is taken from a within sibling analysis in the UKB. The gray curve represents the standard normal null distribution, and we observe a significant shift providing confirmation of a real SDS signal of polygenic adaptation for height. (c) Allele frequency difference between GBR and TSI of the height increasing allele in each P value bin for six different summary statistics. Betas and P values correspond to the slope and P value of the linear regression across all un-binned SNPs. The lowest P value bin in UKB all no PCs with a y-axis value of 0.06 has been omitted. See **Supplementary Figure S13** for other GWAS summary statistics. (d) Allele frequency difference between GBR and TSI of the height increasing allele in 329 LD-independent SNPs which are genome-wide significant in a UKB height GWAS and were intersecting with our set of 1000 genomes SNPs. There is no significant difference in frequency in these two populations, suggesting that tSDS shift at the gw-significant SNPs is not driven by population stratification.
The patterns shown here suggest that the positive tSDS values across the whole range of P values is a consequence of residual stratification. At the same time, the increase in tSDS at genome-wide significant, LD-independent SNPs in (b) cannot be explained by GBR - TSI allele frequency differences as shown in (d). Binning SNPs by P value without LD-pruning can lead to unpredictable patterns at the low P value end, as the SNPs at the low P value end are less independent of each other than higher P value SNPs (**Supplementary Figure S15**). **Supplementary Figures S8 and S14** therefore show the same data for a set of LD-pruned SNPs.

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305
306  number of SNPs than previously thought. Indeed, a tSDS signal which is driven by
307  natural selection is not expected to lead to an almost linear increase over the whole
308  P value range in a well-powered GWAS. Instead, we would expect to see a greater
309  difference between highly significant SNPs and non-significant SNPs, similar to the
310  pattern observed in the UK Biobank (**Figure 3a**).
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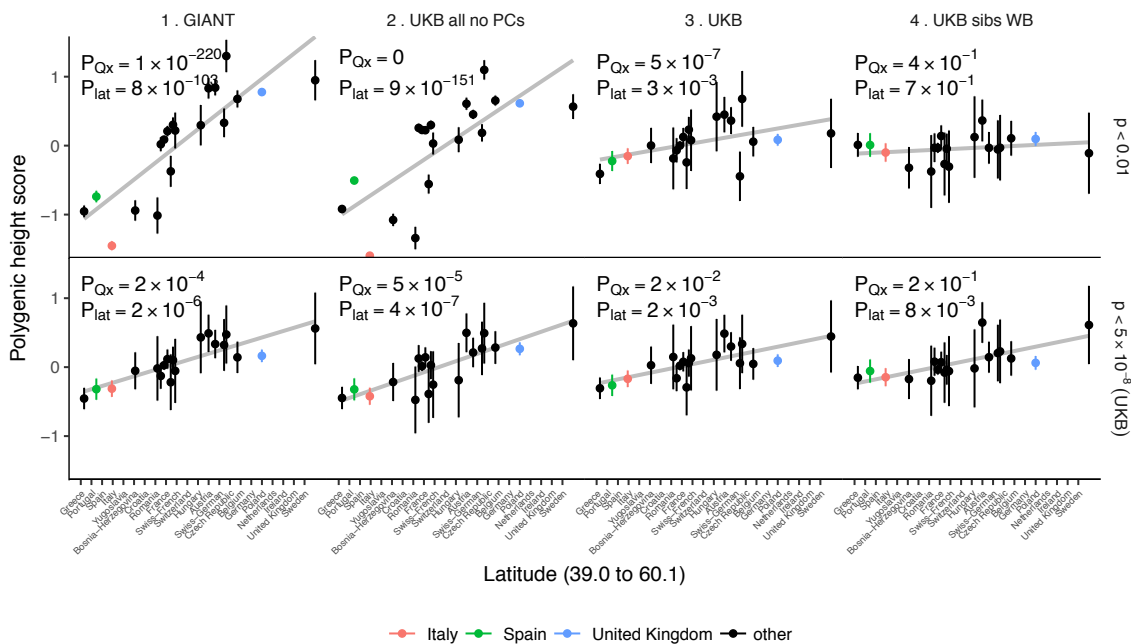


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**Figure 4. Polygenic height scores in POPRES populations show a residual albeit attenuated signal of polygenic adaptation for height.**
316  Standardized polygenic height scores from six summary statistics for 19 POPRES
317  populations with at least 10 samples per population, ordered by latitude (see
318  **Supplementary Table S3**). The grey line is the linear regression fit to the mean polygenic
319  scores per population. Error bars represent 95% confidence intervals and are calculated in
320  the same way as in **Figure 1**.
321  SNPs which were overlapping between each set of the summary statistics and the POPRES
322  SNPs were clumped using PLINK 1.9 with parameters $r^2 < 0.1$, 1 Mb distance, $P < 1$.
323  (Top) A number of independent SNPs was chosen for each summary statistic to match the
324  number of SNPs which remained when clumping UKB at $P < 0.01$.
325  (Bottom) A set of independent SNPs with $P < 5 \times 10^{-8}$ in the UK Biobank was selected and
326  used to compute polygenic scores along with effect size estimates from each of the different
327  summary statistics. SNP numbers for each panel ($P < 0.01$ / $P < 5 \times 10^{-8}$): GIANT: 9463 /
328  869; UKB all no PCs: 9341 / 359; UKB: 9341 / 1034; UKB sibs WB: 9391 / 380. The
329  numbers on each plot show the $Q_x$ P value and the latitude covariance P value respectively
330  for each summary statistic. See **Supplementary Figures S16-S18** for other clumping
331  strategies and GWAS summary statistics.
332
333          Lastly, we asked whether any remaining differences in polygenic height
334  scores among populations are driven by polygenic selection by using the $Q_x$

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335  framework to test against a null model of genetic drift.[5] We re-computed
336  polygenic height scores in the POPRES dataset for this analysis as it has larger
337  sample sizes of northern and southern Europeans than the 1000 Genomes
338  project.[22] We computed height scores using independent SNPs that are 1)
339  genome-wide significant in the UK Biobank ("gw-sig", $P < 5$ x $10^{-8}$) and 2) sub-
340  significantly associated with height ("sub-sig", $P < 0.01$) in different GWAS datasets.
341  For each of these, we tested if population differences were significant due to an
342  overall overdispersion ($P_{Qx}$), and if they were significant along a north-south cline
343  ($P_{lat}$) (**Figure 4, Supplementary Figure S16-S17**). Both gw-sig and sub-sig SNP-
344  based scores computed using GIANT effect sizes showed significant overdispersion
345  of height scores overall and along a latitude cline, consistent with previous results
346  (**Figure 4, Supplementary Figure S16-S17**). However, the signal attenuated
347  dramatically between sub-sig ($Q_x = 1100$, $P_{Qx} = 1$ x $10^{-220}$) and gw-sig ($Q_x = 48$, $P_{Qx} =$
348  $2$ x $10^{-4}$) height scores. In comparison, scores that were computed using the UK
349  Biobank  (UKB) effect sizes showed substantially attenuated differences using both
350  sub-sig ($Q_x = 64$, $P_{Qx} = $ 5 x $10^{-7}$) and gw-sig ($Q_x = 33$, $P_{Qx} = 0.02$) SNPs, and a smaller
351  difference between the two scores. This suggests that the attenuation of the signal in
352  GIANT is not only driven by a loss of power when using fewer gw-sig SNPs, but also
353  reflects a decrease in stratification effects. The overdispersion signal disappeared
354  entirely when the UK Biobank family based effect sizes were used (**Figure 4,**
355  **Supplementary Figure S16-S17**). Moreover, $Q_x$ P values based on randomly
356  ascertained SNPs and UK Biobank summary statistics are not uniformly distributed
357  as would be expected if the theoretical null model is valid and if population
358  structure is absent (**Supplementary Figure S19**). The possibility of residual
359  stratification effects even in the UK Biobank is also supported by a recent study [23].
360  Therefore, we remain cautious about interpreting any residual signals as "real"
361  signals of polygenic adaptation.
362
363  **Discussion**
364
365      We have shown that estimates of population differences in polygenic height
366  scores are strikingly attenuated with the UK Biobank GWAS data relative to
367  previous analyses.  We find some evidence for population-level differences in
368  genetic height, but it can only be robustly seen at highly significant SNPs, because
369  any signal at less significant P values is dominated by the effect of residual
370  population structure. Even genome-wide significant SNPs in these analyses may be
371  subtly affected by population structure, leading to continued overestimation of the
372  effect.  Thus, it is difficult to arrive at any quantitative conclusion regarding the
373  proportion of the population differences that are due to statistical biases vs.
374  population stratification of genetic height. It is equally challenging to test whether
375  differences in genetic height are due to adaptation in response to environmental
376  differences, migration and admixture (e.g. fraction of Steppe pastoralist ancestry),
377  or relaxation of negative selection. Further, estimates of the number of independent
378  genetic loci contributing to height variation are sensitive to and likely confounded
379  by residual population stratification.

380    We conclude that while effect estimates are highly concordant between
381 GIANT and the UK Biobank when measured individually (**Supplementary Tables**
382 **S4-S6, Supplementary Figure S1**), they are also influenced by residual population
383 stratification that can mislead inferences about polygenic selection across
384 populations in aggregate. Although these biases are subtle, in the context of tests for
385 polygenic adaptation, which are driven by small systematic shifts in allele
386 frequency, they can create highly significant artificial signals especially when SNPs
387 that are not genome-wide significant are used to estimate genetic height. In no way
388 do our results question the reliability of the genome-wide significant associations
389 discovered in the GIANT cohort or the validity of the statistical methodology used in
390 previously reported polygenic tests for adaptation. However, we urge caution in the
391 interpretation of genome-wide signals of polygenic adaption that are based on large
392 number of sub-significant SNPs–particularly when using effect sizes derived from
393 meta-analysis of heterogeneous cohorts which may be unable to fully control for
394 population structure.
395
396
397 **Materials and Methods**
398
399 **Genome-wide association studies (GWAS)**
400    We analyzed height using publicly available summary statistics that were
401 obtained either by meta-analysis of multiple GWAS or by a GWAS performed on a
402 single large population. We used results from the GIANT Consortium
403 (N=253,288)[14] and a GWAS performed on individuals of the UK Biobank  (UKB
404 Neale" or simply "UK Biobank (UKB)", N=336,474)[15] who derive their ancestry
405 almost entirely from the British Isles (identified as "white British ancestry" by the
406 UK Biobank). We also used an independent GWAS that included all UK Biobank
407 individuals irrespective of ancestry and relatedness ("UKB Loh", N=459,327)[24].
408 The Neale lab's GWAS uses a linear model with sex and 10 principal components as
409 covariates.  Loh *et al.*'s GWAS uses a BOLT-LMM Bayesian mixed model. Association
410 signals from the three studies are generally correlated for SNPs that are genome-
411 wide significant in GIANT (see [[25]]).
412
413    We also used previously published family-based effect size estimates[7]
414 ("NG2015 sibs") as well as a number of test summary statistics on the UK Biobank
415 that we generated to study the effects of population stratification. These are: "UKB
416 Neale new" (Similar to UKB Neale, with less stringent ancestry definition and 20 PCs
417 calculated within sample), "UKB all no PCs" (All UK Biobank samples included in the
418 GWAS without correction by principal components), "UKB all 10 PCs" (All UK
419 Biobank samples included in the GWAS with correction by 10 principal
420 components), "UK WB no PCs" (Only "white British ancestry" samples included in
421 the GWAS without correction by principal components), "UKB WB 10 PCs" (Only
422 "white British ancestry" samples included in the GWAS with correction by 10
423 principal components), "UKB sibs all" (All UK Biobank siblings included in the
424 GWAS),  "UKB sibs WB" (Only UK Biobank "white British ancestry" siblings included

11

425 in the GWAS) (Please see **Supplementary Table S1** for sample sizes and other
426 details).
427
428 **Population genetic data for ancient and modern samples**
429 　　We analyzed ancient and modern populations for which genotype data are
430 publicly available. For ancient samples[26,27], we computed scores after dividing
431 populations into three previously described broad ancestry labels (HG = Hunter-
432 Gatherer (n=162 individuals), EF = Early Farmer (n=485 individuals), and SP =
433 Steppe Ancestry (n=465 individuals)). For modern samples available through the
434 1000 genomes phase 3 release[28], we computed scores in 2 populations each from
435 Northern Europe (GBR, CEU), Southern Europe (IBS, TSI), Africa (YRI, LWK), South
436 Asia (PJL, BEB) and East Asia (CHB, JPT) (**Figure 1a**, **Supplementary Figures S2-**
437 **S6**). In total, we analyzed 1112 ancient individuals, and 1005 modern individuals
438 from 10 different populations in the 1000 genomes project (**Supplementary Table**
439 **S2**). We used the allele frequency differences between the GBR and TSI populations
440 for a number of analyses to study population stratification (**Figures 3c**, **3d**,
441 **Supplementary Figures S11-S14**). We also analyzed 19 European populations
442 from the POPRES[22] dataset with at least 10 samples per population (**Figure 4**,
443 **Supplementary Table S3, Supplementary Figures S16-S18**).
444
445 　　All ancient samples had 'pseudo-haploid' genotype calls at 1240k sites
446 generated by selecting a single sequence randomly for each individual at each SNP[9].
447 Thus, there is only a single allele from each individual at each site, but adjacent
448 alleles might come from either of the two haplotypes of the individual. We also re-
449 computed scores in present-day 1000 genomes individuals using only pseudo-
450 haploid calls at 1240k sites to allow for a fair comparison between ancient and
451 modern samples (**Supplementary Figure S6**).
452
453 **Polygenic scores**
454 　　The polygenic scores, confidence intervals and test statistics (against the null
455 model of genetic drift) were computed based on the methodology developed in refs
456 ([5],[29]). We computed the polygenic score (Z) for a trait in a population by taking
457 the sum of allele frequencies across L sites associated with the trait, weighting each
458 allele's frequency by its effect on the trait ($\beta_l$).
459

$$Z = \sum_l^L \beta_l p_l$$

460
461 Al polygenic scores are plotted in centered standardized form ($\frac{Z-\mu}{\sqrt{V_A}}$), where
462 $\mu = \sum_l \beta_l \overline{p_l}, V_A = \sum_l \beta_l^2 \overline{p_l}(1 - \overline{p_l})$, and $\overline{p_l}$ is the mean allele frequency across all
463 populations analyzed.
464
465 　　Polygenic scores were computed using independent GWAS SNPs associated
466 with height in three main ways: (1) The genome was divided into ~1700 non-

12

467 overlapping linkage disequilibrium (LD) blocks[30], and the SNP with the lowest P
468 value within each block was picked to give a set of ~1700 independent SNPs for
469 each height GWAS used (all SNPs for which effect sizes are available were
470 considered) similarly to ref. [29]. In (2) and (3), Plink's[31,32] clumping procedure
471 was used to make independent "clumps" of SNPs for each GWAS at different P value
472 thresholds. This procedure selects SNPs below a given P value threshold as index
473 SNPs to start clumps around, and then reduces all SNPs (P < 0.01) that are in LD
474 with these index SNPs (above an $r^2$ threshold, 0.1) and within a physical distance of
475 them (1 Mb) into clumps with them. Clumps are preferentially formed around index
476 SNPs with the lowest P value in a greedy manner. The index SNP from each clump is
477 then picked for further polygenic score analyses. The algorithm is also greedy such
478 that each SNP will only appear in one clump if at all. We clumped each GWAS to
479 obtain (2) a set of independent sub-significant SNPs associated with height (P <
480 0.01) similarly to ref. [7], and (3) a set of genome-wide significant SNPs associated
481 with height (P < 5 x $10^{-8}$). The 1000 genomes phase 3 dataset was used as the
482 reference panel for computing LD for the clumping procedure.
483
484     The estimated effect sizes for these three sets of SNPs from each GWAS was
485 used to compute scores. Only autosomal SNPs were used for all analyses to avoid
486 creating artificial mean differences between populations with different numbers of
487 males and females.
488
489     The 95% credible intervals were constructed by assuming that the posterior
490 of the underlying population allele frequency is independent across loci and
491 populations and follows a beta distribution. We updated a Uniform prior
492 distribution with allele counts from ancient and modern populations to obtain the
493 posterior distribution at each locus in each population. We estimated the variance of
494 the polygenic score $V_Z$ using the variance of the posterior distribution at each locus,
495 and computed the width of 95% credible intervals as $1.96\sqrt{V_Z}$ for each population.
496
497     The $Q_X$ test statistic measures the degree of overdispersion of the mean
498 population polygenic score compared to a null model of genetic drift. It assumes that
499 the vector of mean centered mean population polygenic score follows a multivariate
500 normal distribution: $Z \sim MVN(0, 2 V_A F)$, where $V_A$ is the additive genetic variance of
501 the ancestral population and F is a square matrix describing the population
502 structure. This is equivalent to the univariate case of the test statistic used in ref .
503 [7]. The latitude test statistic assumes that $Y'Z \sim N(0, 2 V_A Y'FY)$, where Y is a mean
504 centered vector of latitudes for each population.[33]
505
506 **tSDS analysis**
507     The Singleton Density Score (SDS) method identifies signatures of recent
508 positive selection based on a maximum likelihood estimate of the log-ratio of the
509 mean tip-branch length of the derived vs. the ancestral allele at a given SNP. The tip-
510 branch lengths are inferred from the average distance of each allele to the nearest
511 singleton SNP across all individuals in a sequencing panel. When the sign of the SDS

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512 scores is aligned with the trait-increasing or trait-decreasing allele in the effect
513 estimates of a GWAS, the Spearman correlation between the resulting tSDS scores
514 and the GWAS P values has been proposed as an estimate of recent positive
515 selection on polygenic traits.
516
517       Here, we applied the tSDS method using pre-computed Singleton Density
518 Scores for 4,451,435 autosomal SNPs obtained from 3,195 individuals from the
519 UK10K project [12,17] for SNPs associated with height in GIANT and the UK biobank
520 (**Figure 1b**) and in different summary statistics (**Figure 3, Supplementary Figures
521 S7-S8**). After normalizing SDS scores in each 1% allele frequency bin to mean zero
522 and unit variance, excluding SNPs from the MHC region on chromosome 6 and
523 aligning the sign of the SDS scores to the height increasing alleles (resulting in tSDS
524 scores), we computed the Spearman correlation coefficient between the tSDS score
525 and the GWAS P value. The tSDS Spearman correlation standard errors and P values
526 were computed using a block-jackknife approach, where each block of 1% of all
527 SNPs ordered by genomic location was left out and the Spearman correlation
528 coefficient was computed on the remaining SNPs. We also compared the tSDS score
529 distributions for only genome-wide significant SNPs (**Figure 3b**).
530
531 **Population structure analysis**
532       To compute SNP loadings of the principal components of population
533 structure (PC loadings) in the 1000 genomes data (**Figure 2, Supplementary
534 Figure S10**), we first computed PC scores for each individual. We used SNPs that
535 had matching alleles in 1000 genomes, GIANT and UK Biobank, that had minor allele
536 frequency > 5% in 1000 genomes, and that were not located in the MHC locus, the
537 chromosome 8 inversion region, or regions of long LD. After LD pruning to SNPs
538 with $r^2 < 0.2$ relative to each other, PCA was performed in PLINK on the 187,160
539 remaining SNPs. In order to get SNP PC loadings for more SNPs than those that were
540 used to compute PC scores, we performed linear regressions of the PC scores on the
541 genotype allele count of each SNP (after controlling for sex) and used the resulting
542 regression coefficients as the SNP PC loading estimates.
543
544
545 **Acknowledgements**
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**Competing interests**

The authors declare no competing interests.

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**Supplementary Note**


**Characterization of stratification effects in GIANT and UK Biobank**

To better understand how stratification influences the differences observed between GIANT and UK Biobank, we grouped SNPs by their P value in GIANT and by their P value in UK Biobank (**Supplementary Figure S1**). First, we observe that SNPs with low GIANT P values, but not SNPs with low UK Biobank P values, show greater differences in estimated effect size (**Supplementary Figure S1a**). However, the relative difference in beta values decreases for lower P values, and the correlation among betas approaches one at the most significant SNPs (**Supplementary Figure S1b,c**). In GIANT, more significant SNPs exhibit a greater correlation between effect estimates and GBR-TSI allele frequency differences, while this is not observed in the UK Biobank (**Supplementary Figure S1d**). Consequently, the difference in UK Biobank and GIANT effect size estimates is more correlated to GBR-TSI allele frequency differences at more significant SNPs (**Supplementary Figure S1e**). This suggests that while stratification effects are larger at more significant SNPs, the magnitude of stratification-independent effects is even larger, which may be why polygenic score results converge when using only the most significant SNPs.

Next, we investigated how P value inflation as measured by $\lambda_{GC}$ is influenced by stratification, by grouping SNPs into deciles based on their GBR-TSI allele frequency difference (**Supplementary Figure S12**). To guard against the effect of observing lower P values at more differentiated SNPs simply because those SNPs are more common on average, we restrict this analysis to SNPs with mean MAF > 20%. We find that $\lambda_{GC}$ is not much increased for SNPs that are more differentiated between populations. However, in the presence of stratification, there is a large difference between $\lambda_{GC}$ of height increasing alleles and $\lambda_{GC}$ of height decreasing alleles (**Supplementary Figure S12b**). Similarly, there are large effects on the frequency with which a SNP is estimated to be height increasing or height decreasing. In GIANT, SNPs in the highest decile of GBR-TSI allele frequency differences are 52% more often estimated to be height increasing than height decreasing, while these rates are close to even in the UK Biobank (**Supplementary Figure S12a**).

696 **Supplementary figures**

697

698 **Figure S1. Beta concordance between GIANT and UK Biobank by P value bin.**



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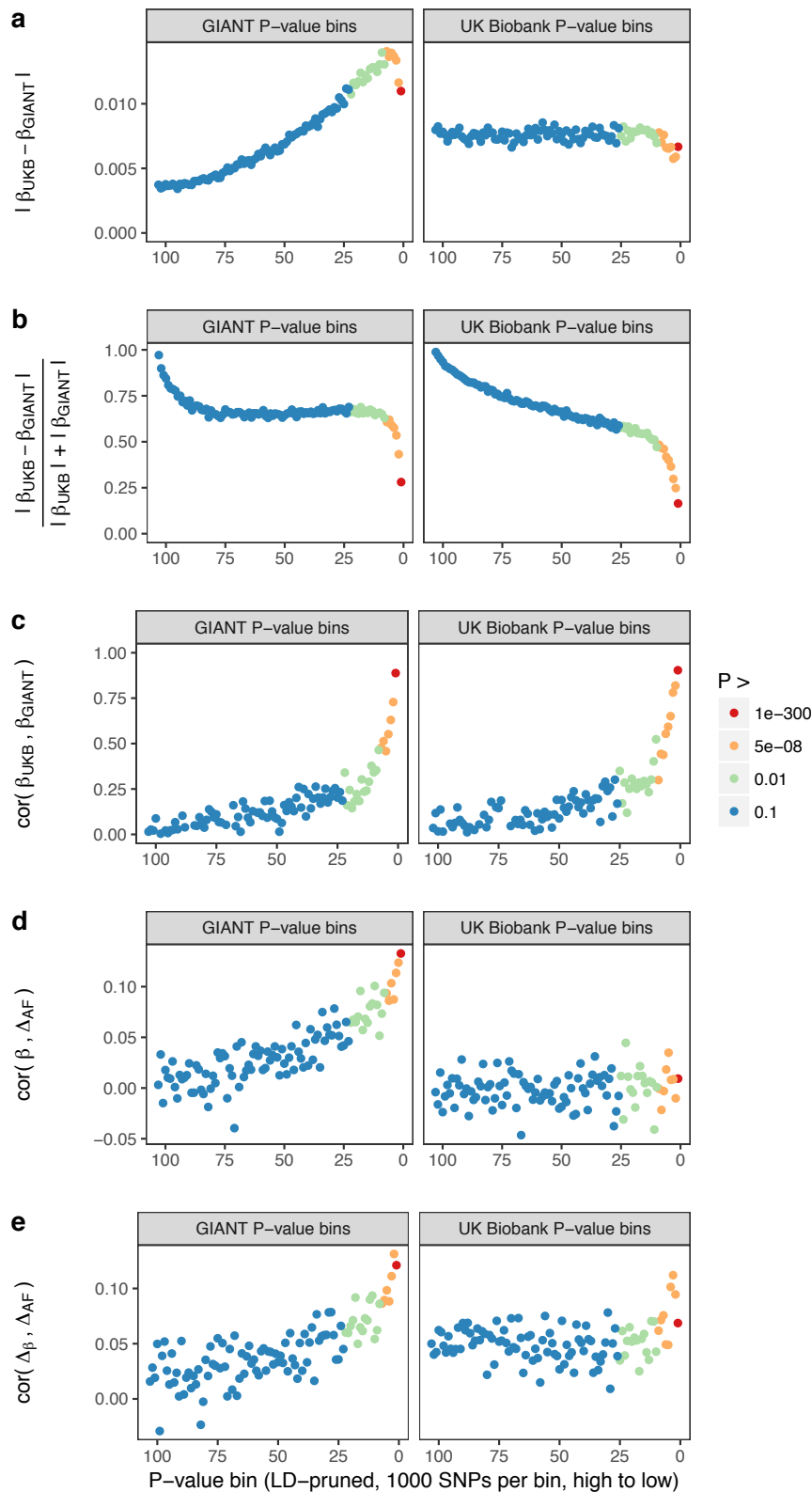
**Figure S1 (Continued). Beta concordance between GIANT and UK Biobank by P value bin.**

SNPs intersecting between GIANT and UKB were LD-pruned (using PLINK 1.9 with parameters r^2 = 0.1, window size = 1 Mb, step size 5) and grouped into P value bins of 500 SNPs each, for P values from GIANT (left) and UKB (right). Color is based on the smallest P value in each bin.

(a) Absolute beta difference. As expected, absolute beta and thus the absolute beta difference increases across P value bins.

(b) Absolute beta difference, scaled by the sum of absolute betas. The relative difference of absolute betas decreases for lower P values.

(c) Pearson correlation among betas approaches one for the lowest P values.

(d) Correlation between beta (left GIANT, right UK Biobank) and GBR-TSI allele frequency difference.

(e) Correlation between the GIANT - UK Biobank beta difference and GBR-TSI allele frequency difference.

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717

a. clumped, $r^2 < 0.1$, 1Mb, P < 0.01
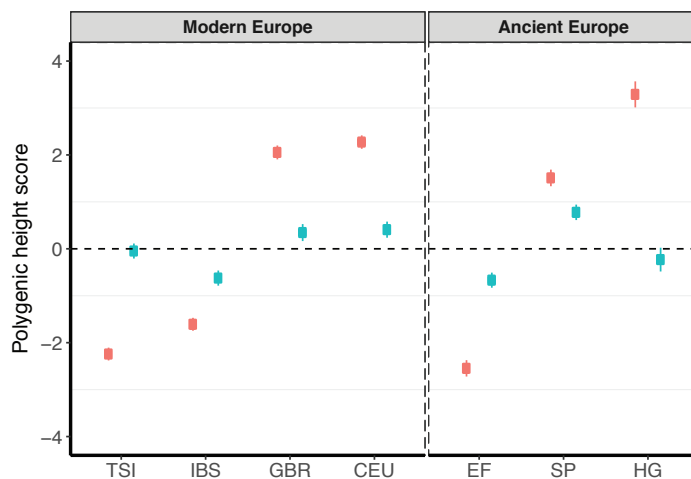


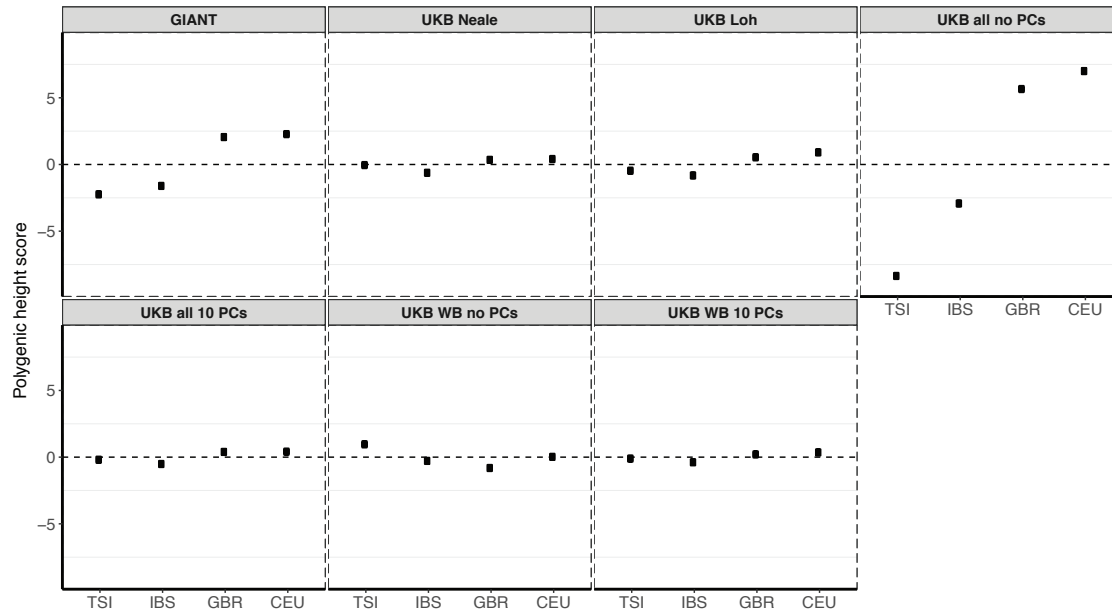b. clumped, $r^2 < 0.1$, 1Mb, P < $5 \times 10^{-8}$
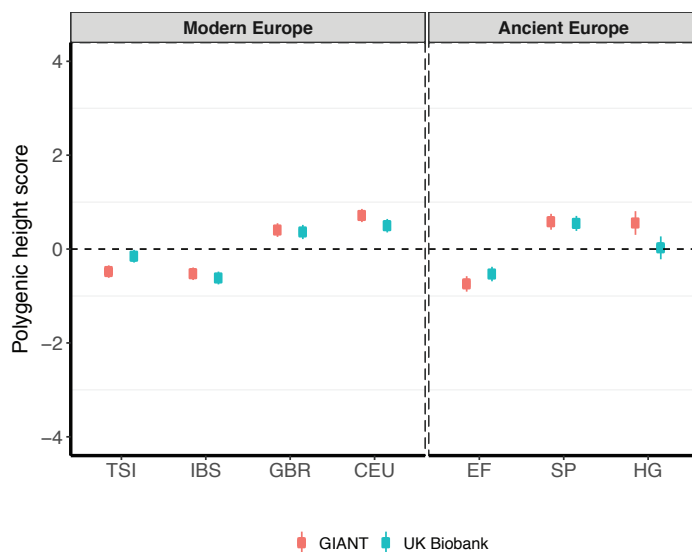


GIANT ▪ UK Biobank

**Figure S2**. **Polygenic scores using height-associated SNPs from GIANT- and UK Biobank-based GWA studies for clumped SNPs in present-day and ancient Europeans.** Scores are shown, centered by the average score across modern and ancient populations respectively and standardized by the square root of the additive variance. SNPs were LD-pruned with plink's clumping procedure for parameters: (a) $r^2 < 0.1$, 1Mb, P < 0.01 (81,941 SNPs in UKB, 22,561 SNPs in GIANT), and (b) $r^2 < 0.1$, 1Mb, P < $5 \times 10^{-8}$ (4478 SNPs in UKB, 1442 SNPs in GIANT). Modern populations are shown from Northern Europe (CEU, GBR) and Southern Europe (IBS, TSI) from the 1000 genomes project. Ancient populations are shown in three meta-populations, hunter-gatherers (HG), early farmers (EF) and Steppe Ancestry (SP). Error bars are drawn at 95% credible intervals.

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a. clumped, $r^2 < 0.1$, 1Mb, P < 0.01
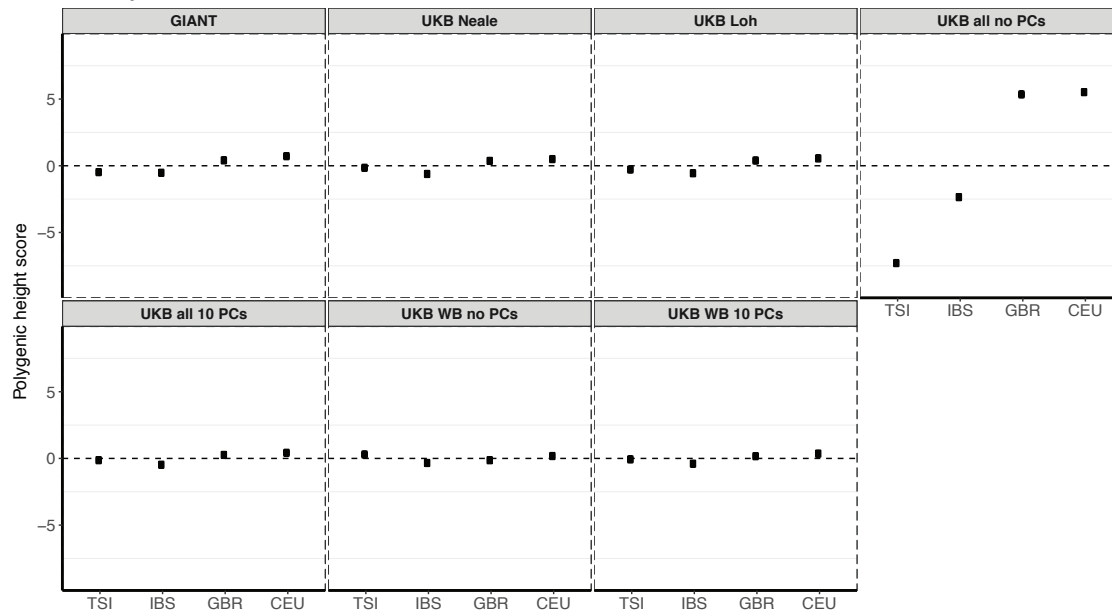


b. clumped, $r^2 < 0.1$, 1Mb, P < $5 \times 10^{-8}$



**Figure S3. Polygenic height scores in 1000 genomes European populations using clumped SNPs and effect sizes from different summary statistics.**
Polygenic scores in modern European populations are shown using SNPs LD-pruned with PLINK's clumping procedure with parameters: (a) $r^2 < 0.1$, 1Mb, P < 0.01, and (b) $r^2 < 0.1$, 1Mb, P < $5 \times 10^{-8}$. Scores are centered by the average score across populations and standardized by the square root of the additive variance. Modern populations are shown from Northern Europe (CEU, GBR) and Southern Europe (IBS, TSI) from the 1000 Genomes Project. Error bars are drawn at 95% credible intervals.

22
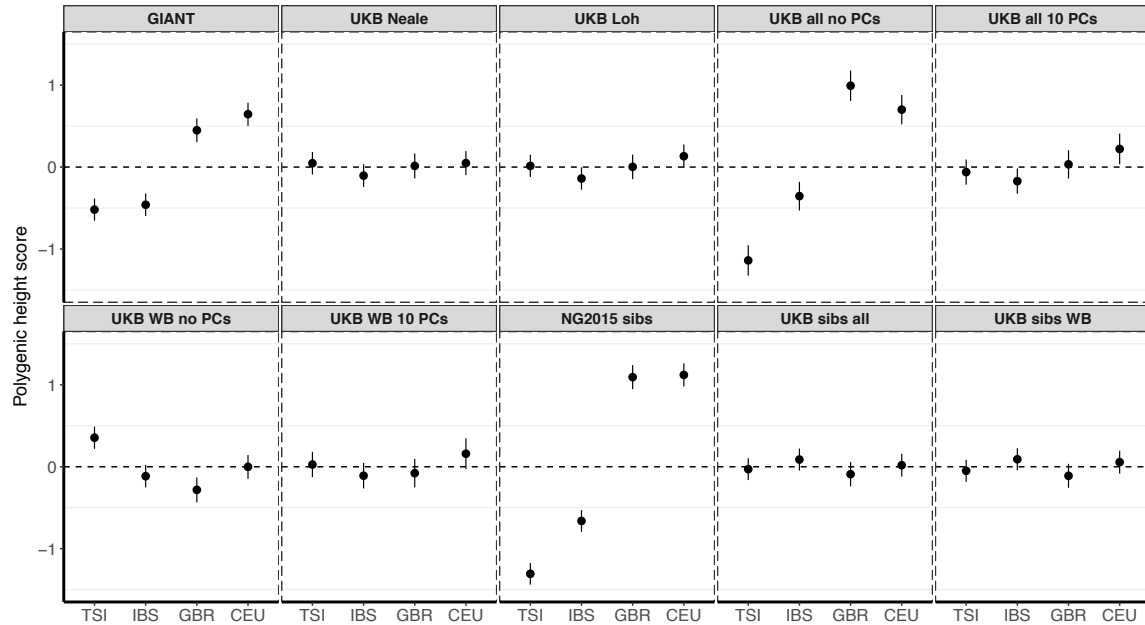
**Figure S4. Polygenic height scores in 1000 Genomes Project European populations using ~1700 independent SNPs and effect sizes from different summary statistics.**
Polygenic scores in modern European populations are shown using SNPs LD-pruned by picking the SNP with the lowest P value in each of ~1700 LD-independent blocks genome-wide. Scores are centered by the average score across populations and standardized by the square root of the additive variance. Modern populations are shown from Northern Europe (CEU, GBR) and Southern Europe (IBS, TSI) from the 1000 Genomes Project. Error bars are drawn at 95% credible intervals.
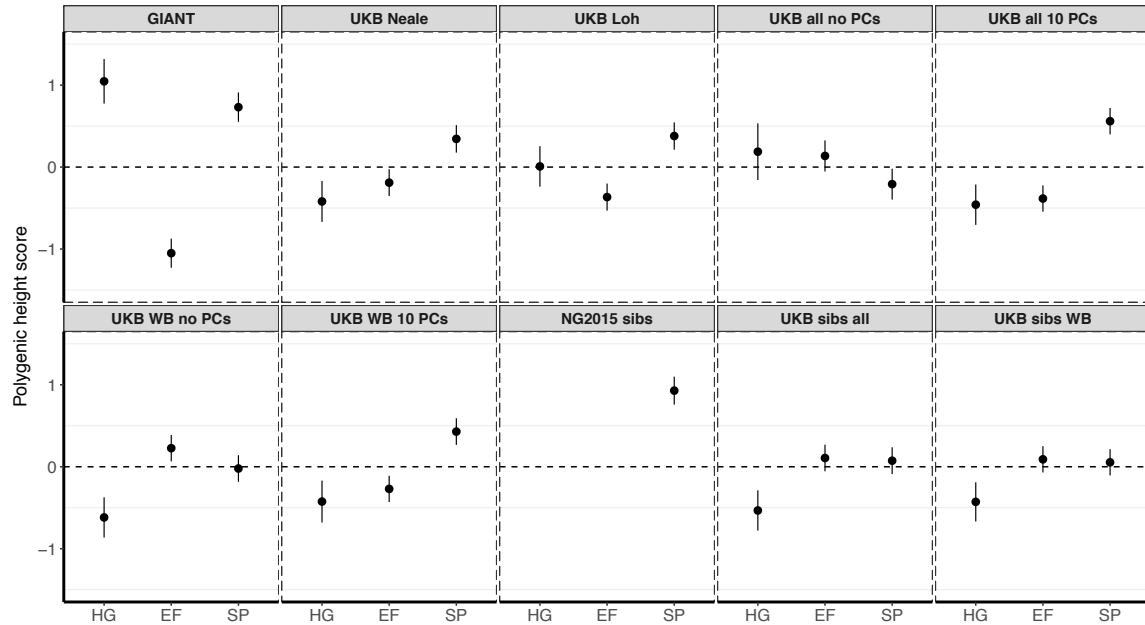
**Figure S5. Polygenic height scores in ancient populations using ~1700 independent SNPs and effect sizes from different summary statistics.**
Polygenic scores in ancient meta-populations are shown using SNPs LD-pruned by picking the SNP with the lowest P value in each of ~1700 LD-independent blocks genome-wide. Scores are centered by the average score across populations and standardized by the square root of the additive variance. Error bars are drawn at 95% credible intervals. . Ancient populations are shown in three meta-populations (HG = Hunter-Gatherer (n=162 individuals), EF = Early Farmer (n=485 individuals), and SP = Steppe Ancestry (n=465 individuals)). The y-axis is truncated at (-1.5, 1.5) for all panels – this omits two points in the NG2015 sibs panel: HG [3.86 (CI: 3.60, 4.12)], EF [-2.18(CI: -2.34, -2.02)].

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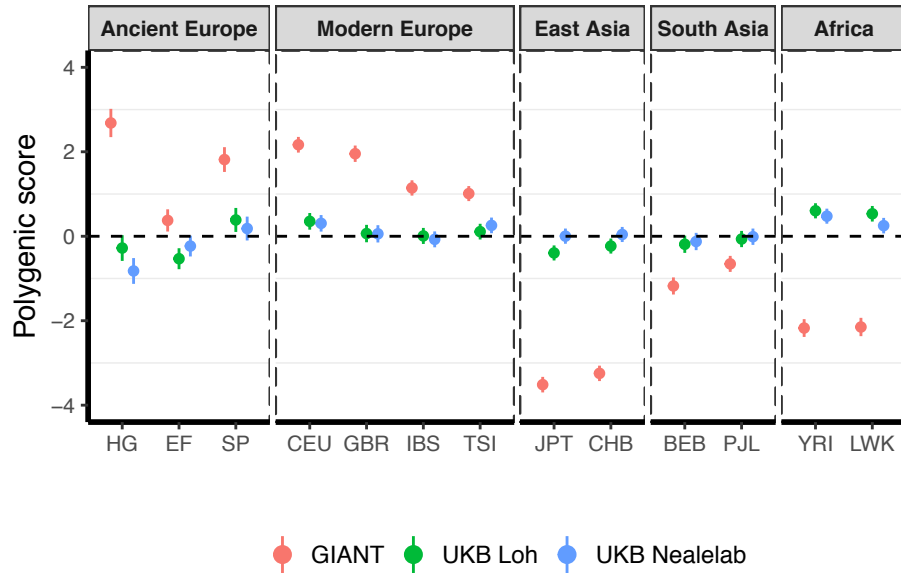
762
763
764 **Figure S6. Polygenic height scores in ancient and global modern populations using**
765 **three different GWAS.**
766 All scores are centered by the average score across all populations ($\mu_{GIANT} = 0.645, \mu_{LOH} =$
767 $-0.219, \mu_{NEALELAB} = -0.259$) and standardized by the square root of the additive variance.
768 Error bars are drawn at 95% credible intervals. Modern populations are shown from
769 Northern Europe (CEU, GBR), Southern Europe (IBS, TSI), South Asia (PJL, BEB), East Asia
770 (CHB, JPT) and Africa (YRI, LWK). Ancient populations are shown in three meta-
771 populations, hunter-gatherers (HG), early farmers (EF) and Steppe Ancestry (SP). Pseudo-
772 haploid genotype calls were made for modern populations before computing polygenic
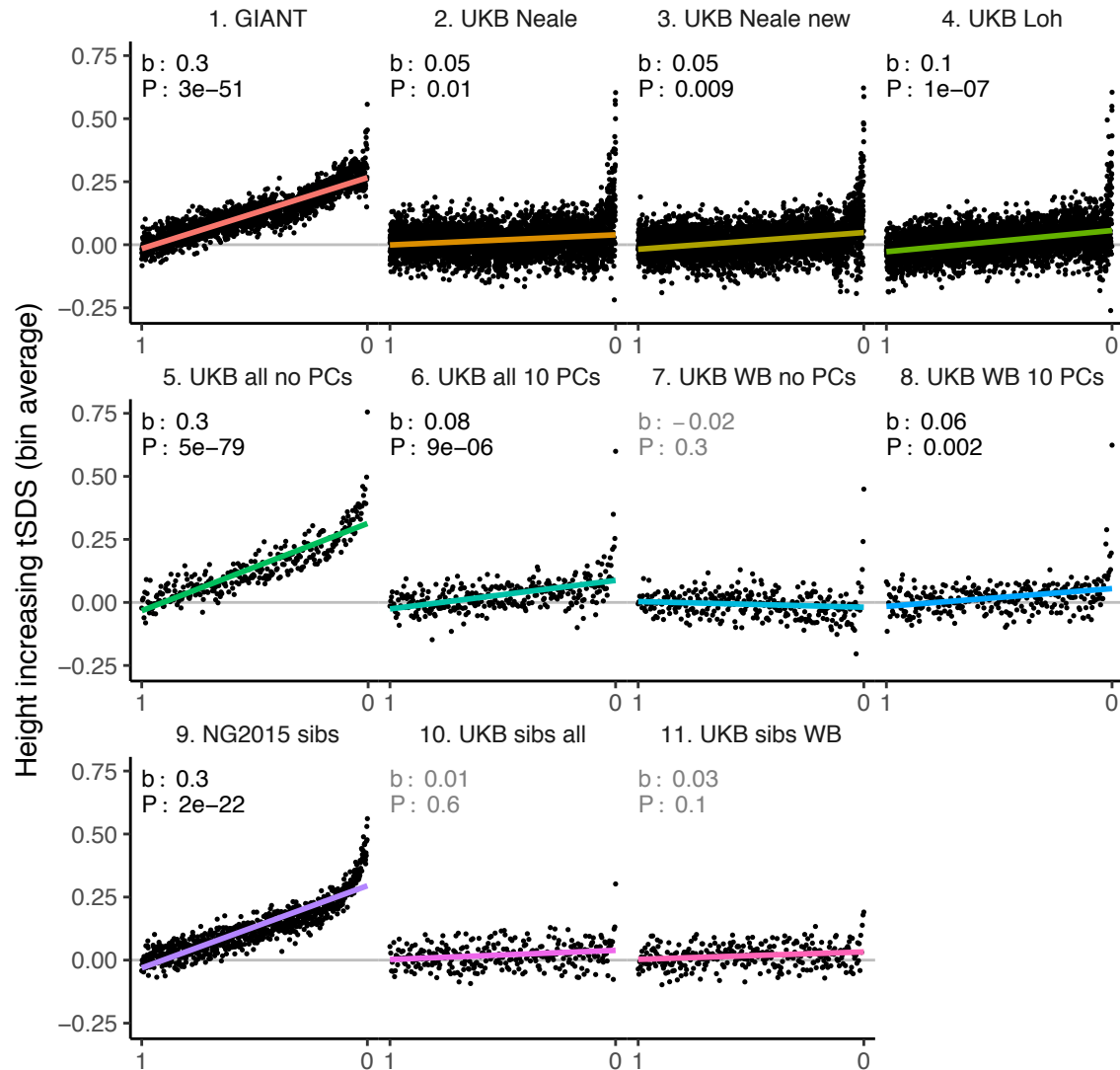773 scores to allow fair comparison with ancient DNA. SNPs were LD-pruned by picking the SNP
774 with the lowest P value in each of ~1700 LD-independent blocks genome-wide.
775

**Figure S7. tSDS for height-increasing alleles using effect sizes from different summary statistics.**

SNPs were ordered by GWAS P value and grouped into bins of 1000 SNPs each. The mean tSDS score within each P value bin is shown on the y-axis. In contrast to Figure 3, where Spearman correlation co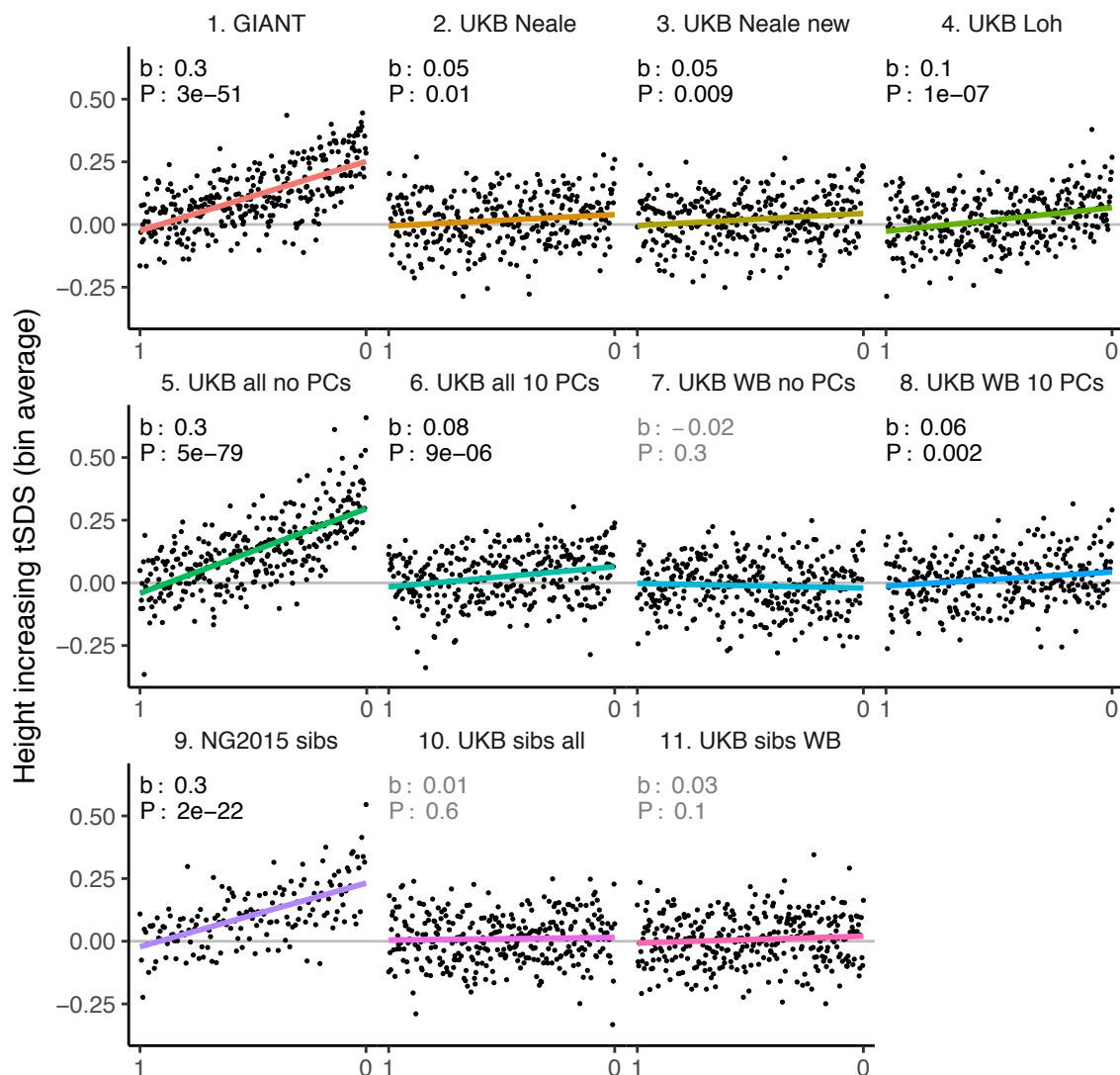efficients and Jackknife standard errors were computed, here we show the regression slope and P value, which were computed on the un-binned data. The gray line indicates the null-expectation, and the colored lines are the linear regression fit. The lowest P value bin in panel 5 with a y-axis value of 1.5 has been omitted.

26

**Figure S8. tSDS for LD-pruned height-increasing alleles using effect sizes from different summary statistics.**

Binning SNPs by P value can lead to spurious results at the low P value bins when SNPs are in LD (**Figure S15**). Here, LD-pruned SNPs were ordered by GWAS P value and grouped into bins of 100 SNPs each. The mean tSDS score within each P value bin is shown on the y-axis. In contrast to **Figure 3**, where Spearman correlation coefficients and Jackknife standard errors were computed, here we show the regression slope and P value, which were computed on the un-binned data. The gray line indicates the null-expectation, and the colored lines are the linear regression fit.

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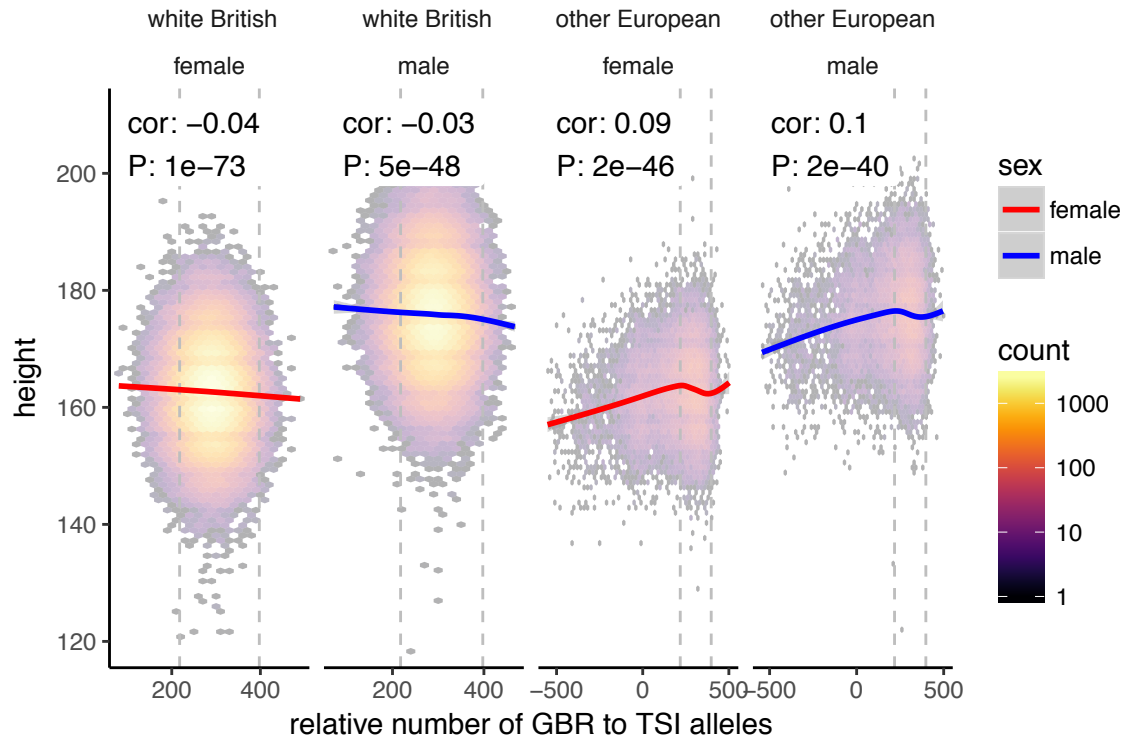
**Figure S9. Height (cm) in the UKB as a function of GBR-TSI score.**
We computed the relative number of GBR to TSI related alleles in each sample by multiplying the allele frequency difference by the number of alternative alleles in each sample in the UKB (GBR-TSI score). Vertical lines indicate 5th and 95th percentile of among-white British samples, showing that there is a significant negative relationship between the GBR-TSI allele sharing score and height (in cm). Among all other broadly European samples, this relationship is significantly positive across the whole range, but again significantly negative in the white British range. This can explain why stratification effects go in opposite directions in a UKB height GWAS of white British samples and a UKB height GWAS of all samples. Here, other European samples were defined as those that lie within the mean +/- 24 standard deviations along the first six principal components.

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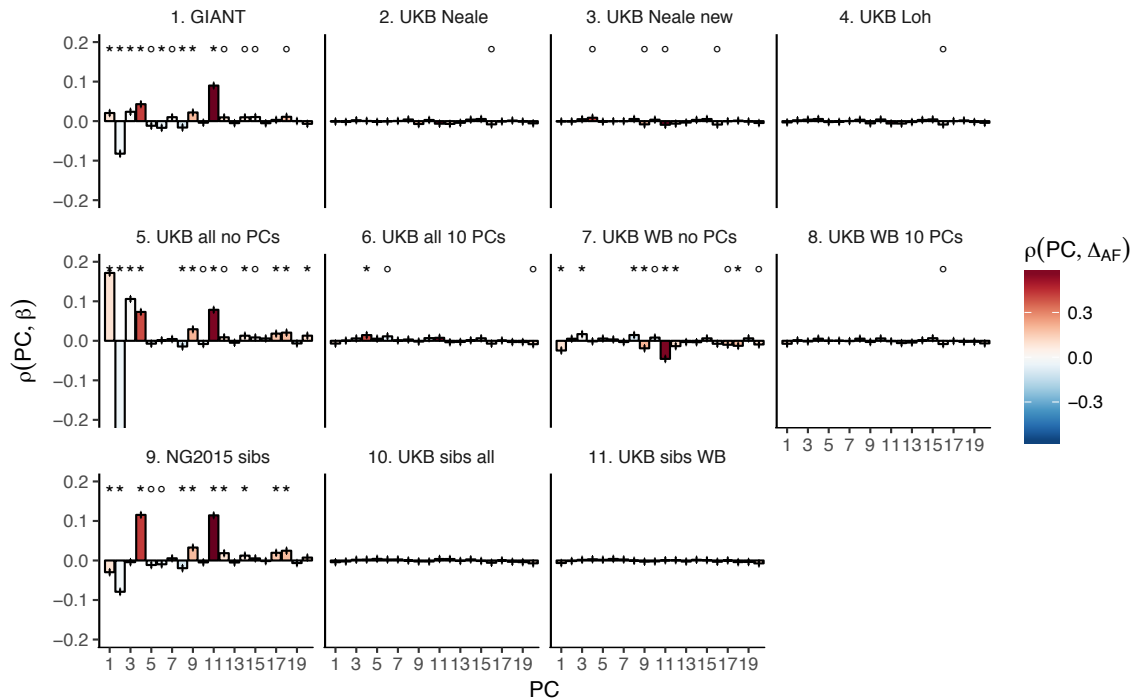


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**Figure S10. Pearson Correlation coefficients of PC loadings and height beta coefficients for different summary statistics.**
PCs were computed in all 1000 genomes phase 1 samples. Colors indicate the correlation of each PC loading with the allele frequency difference between GBR and TSI, a proxy for the European North-South genetic differentiation. PC 4 and 11 are most highly correlated with the GBR - TSI allele frequency difference. Error bars indicate 95% confidence interval of the correlation coefficient, assuming 60,000 independent genetic markers. We confirmed that the resulting errors are similar to block jackknife standard errors. Open circles indicate correlations significant at alpha = 0.05, stars indicate correlations significant after Bonferroni correction in 20 PCs (P < 0.0025).

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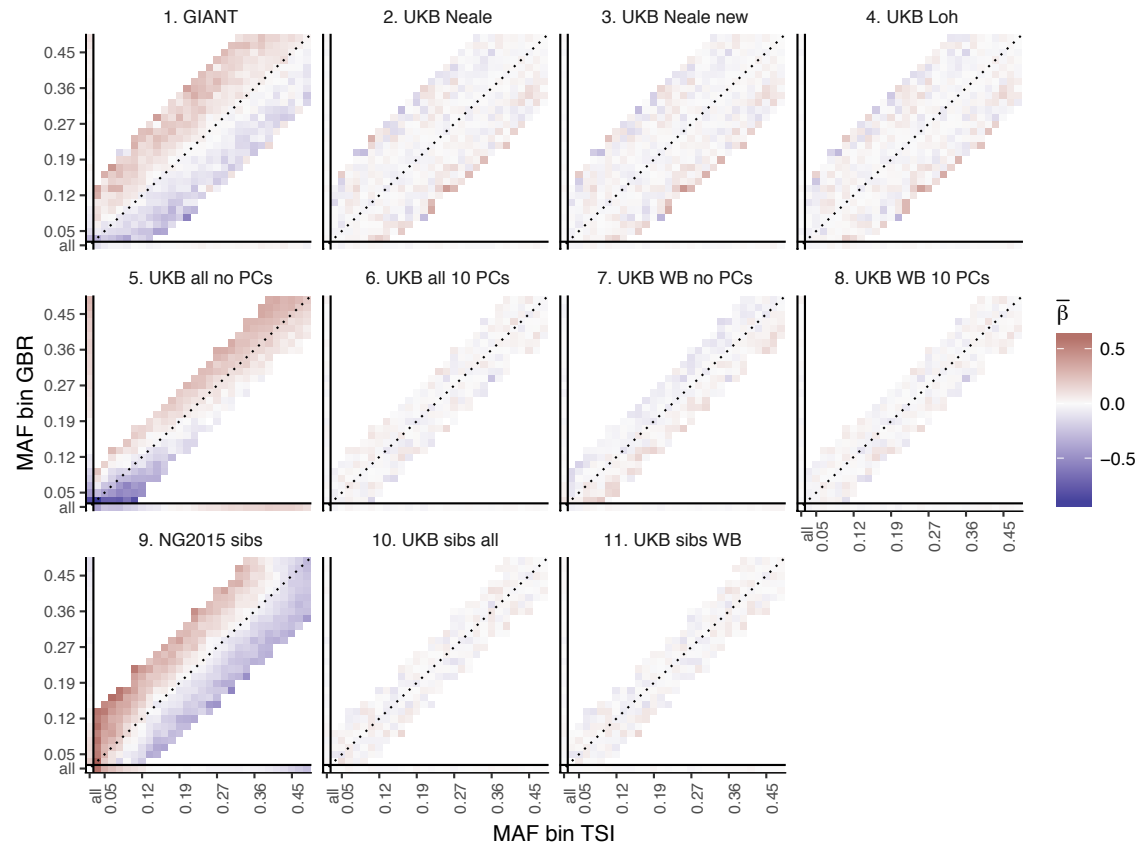
**Figure S11. Heat map of mean beta coefficients for different summary statistics.**
All SNPs are binned by GBR and TSI minor allele frequency. Only bins with at least 300 SNPs are shown. Panel 7 (as well as 2, 3 and 4) shows stratification effects in opposite direction to those in GIANT. **Figure S9** illustrates how these opposite-direction stratification effects can arise.
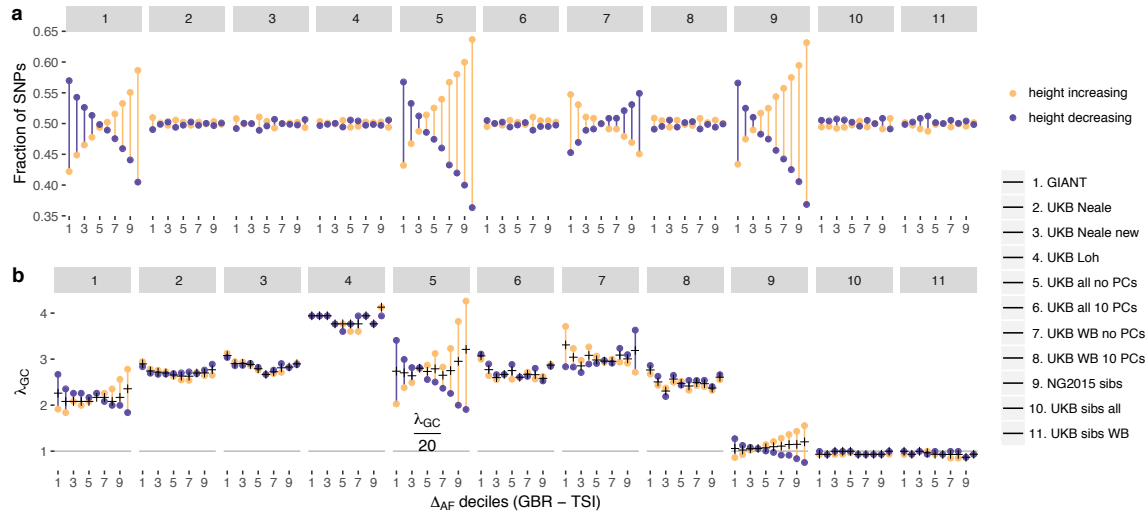
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**Figure S12. Effect of GBR-TSI allele frequency difference on beta estimates and P values.**

SNPs with MAF > 0.2 (based on mean between TSI and GBR) were grouped into GBR-TSI allele frequency difference deciles, with the first decile representing SNPs less common in GBR and the last decile representing SNPs more common in GBR.

(a) Fraction of height-increasing (yellow dots) vs. height-decreasing SNPs (purple dots) in each decile. In GIANT, 59% of SNPs in the highest decile are estimated to be height-increasing, and 41% are estimated to be height-decreasing. In the UK Biobank, this ratio is close to 50-50.

(b) Lambda-GC in each decile for height-increasing (yellow dots) vs. height-decreasing SNPs (purple dots). In GIANT, the median P value of SNPs in the highest decile is 2.78 for SNPs estimated to be height-increasing and 1.83 for SNPs estimated to be height-decreasing (a difference of 52%). In the UK Biobank, the median P value of SNPs in the highest decile is 2.65 for SNPs estimated to be height-increasing and 2.89 for SNPs estimated to be height-decreasing (a difference of only 9%, going in the opposite direction).

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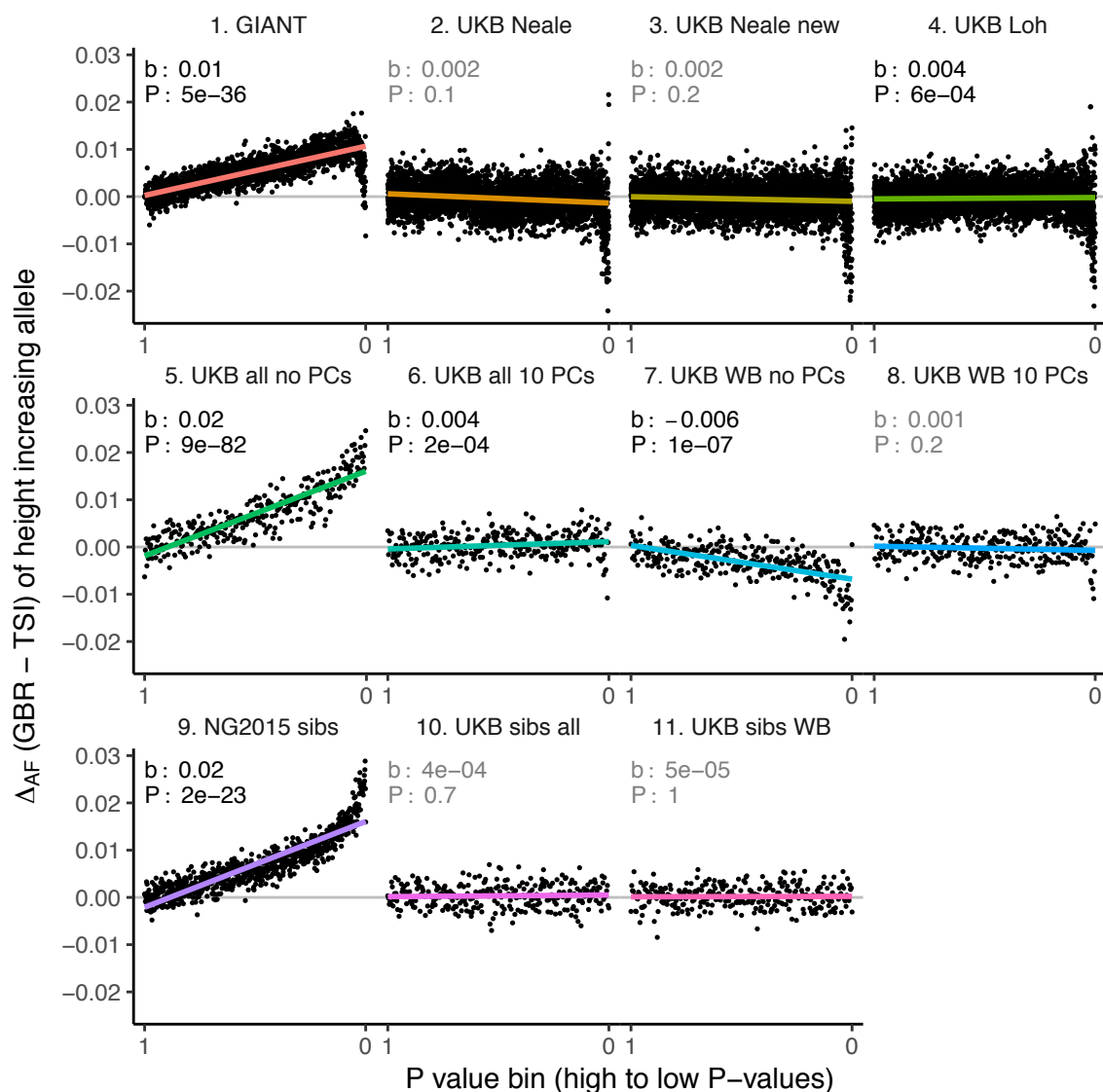
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853 **Figure S13. Allele frequency difference for height-increasing alleles using different**
854 **summary statistics**.
855 SNPs were ordered by GWAS P value and grouped into bins of 1000 SNPs each. The gray
856 line indicates the null-expectation, and the colored lines are the linear regression fit. The
857 lowest P value bin in panel 5 with a y-axis value of 0.06 has been omitted.
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**Figure S14. Allele frequency difference for LD-pruned height-increasing alleles using different summary statistics**.

Binning SNPs by P value can lead to spurious results at the low P value bins when SNPs are in LD (**Figure S15**). Here, LD-pruned SNPs were ordered by GWAS P value and grouped into bins of 100 SNPs each. The gray line indicates the null-expectation, and the colored lines are the linear regression fit.

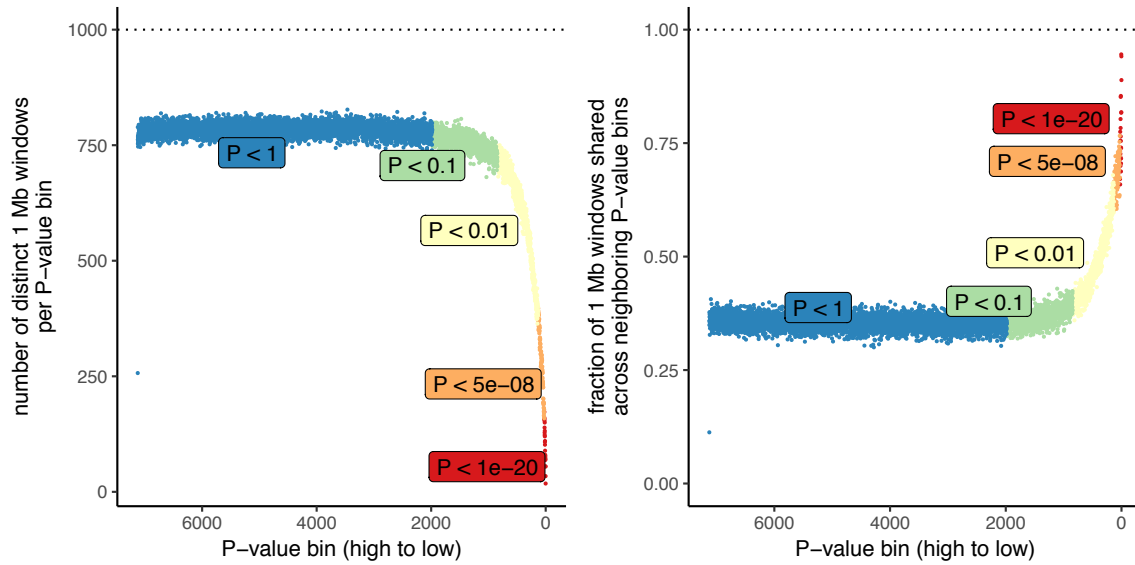**Figure S15. Number of independent regions per GWAS P value bin in the UK Biobank.** SDS results in Field et al. as well as in **Figure 3** in this article are visualized by grouping non-independent SNPs into bins according to their P value. This may lead to unpredictable patterns at the low end of the P value distribution, because the lowest P value bins do not represent independent signals. This is demonstrated here, by grouping all UKB SNPs into bins of 1000 SNPs each, as in the SDS plots in **Figure 1b** and **Figure 3**. Left: The number of independent SNPs per P value bin is much lower at lower P values. Right: Neighboring P value bins share a large fraction of 1Mb regions at lower P values. This demonstrates that the lowest P value bins do not represent independent signals if SNPs are not LD-pruned and can exhibit patterns that are dominated by one or a few LD-regions.

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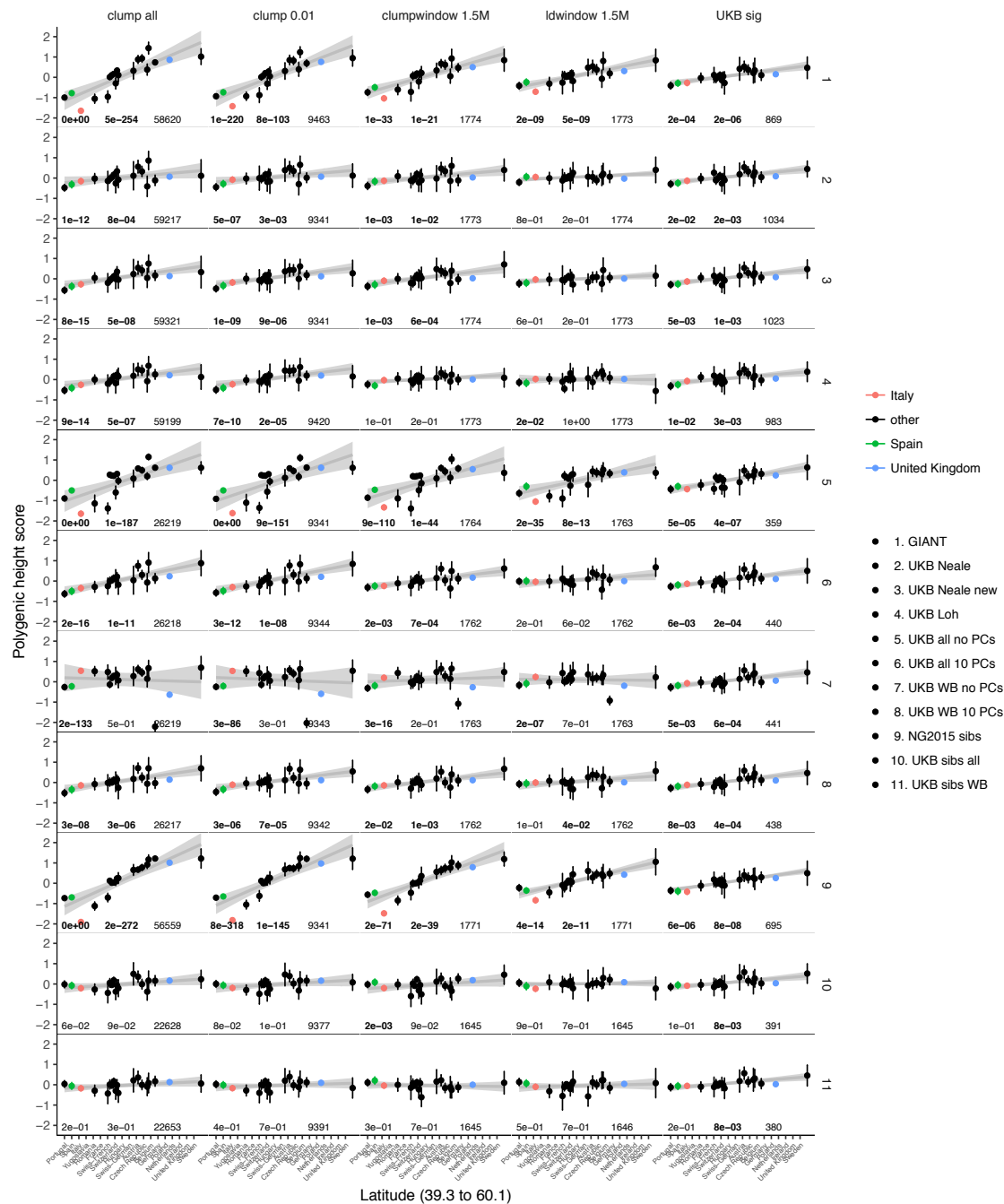


**Figure S16. Polygenic height scores in POPRES for different summary statistics.**
Standardized polygenic height score from diverse summary statistics for 19 POPRES populations with at least 10 samples per population, ordered by latitude (see **Table S3**). Confidence intervals and clumping procedure are the same as in (a). The gray line is the linear regression fit to the mean polygenic height score per population. The numbers on each plot show the $Q_x$ P value, the latitude covariance P value and the number of SNPs respectively for each summary statistic. Each column shows a different selection of SNPs. clump all: clumped SNPs with no P value threshold; clump 0.01: clumped SNPs with P < 0.01 in UKB and the same number of SNPs in other summary statistics (same as **Figure 4**); clumpwindow 1.5M: genome was split into blocks of 1.5 Mb, lowest P-value SNP was picked in each bin, similar to the 1700 blocks; ldwindow 1.5Mb: genome was split into blocks of 1.5 Mb, random SNP was picked in each bin; UKB sig: LD-pruned SNPs with P < 5x10⁻⁸ in UKB.

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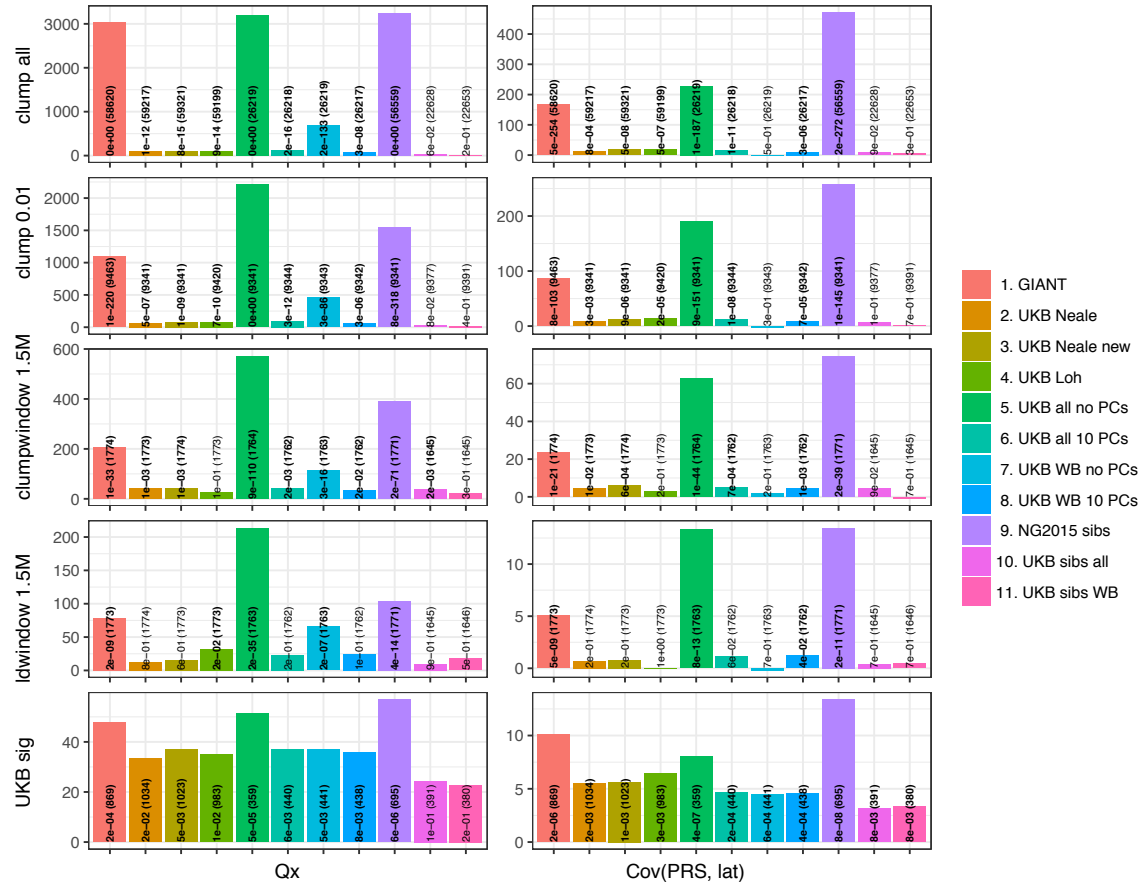
**Figure S17. Test statistics for $Q_x$ (left) and latitude correlation (right) in the POPRES dataset for different summary statistics.**

The numbers indicate P values and the number of SNPs, and numbers in bold highlight nominal significance ($p < 0.05$).
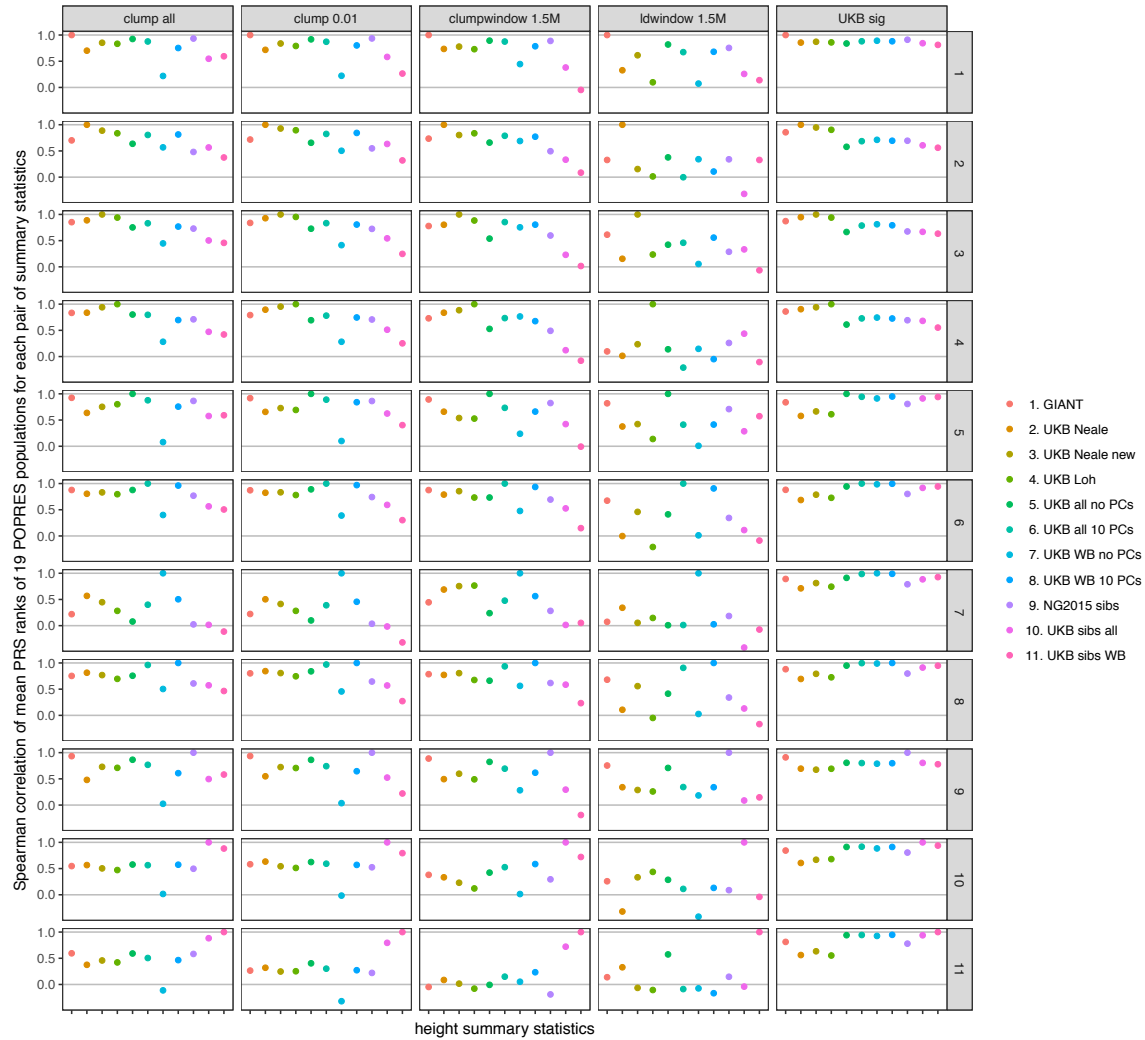
**Figure S18. Spearman correlations between polygenic height scores in the POPRES dataset computed from different summary statistics.**

Spearman correlation coefficients of mean population polygenic score ranking for all pairs of summary statistics at different SNP selections. Polygenic scores from independent SNPs which are genome-wide significant in UKB lead to more consistent rankings than PRS from other sets of SNPs, despite having lower prediction power. Each column shows a different selection of SNPs. clump all: clumped SNPs with no P value threshold; clump 0.01: clumped SNPs with P < 0.01 in UKB and the same number of SNPs in other summary statistics (same as **Figure 4**); clumpwindow 1.5M: genome was split into blocks of 1.5 Mb, lowest P-value SNP was picked in each bin, similar to the 1700 blocks; ldwindow 1.5Mb: genome was split into blocks of 1.5 Mb, random SNP was picked in each bin; UKB sig: LD-pruned SNPs with P < 5x10$^{-8}$ in UKB.

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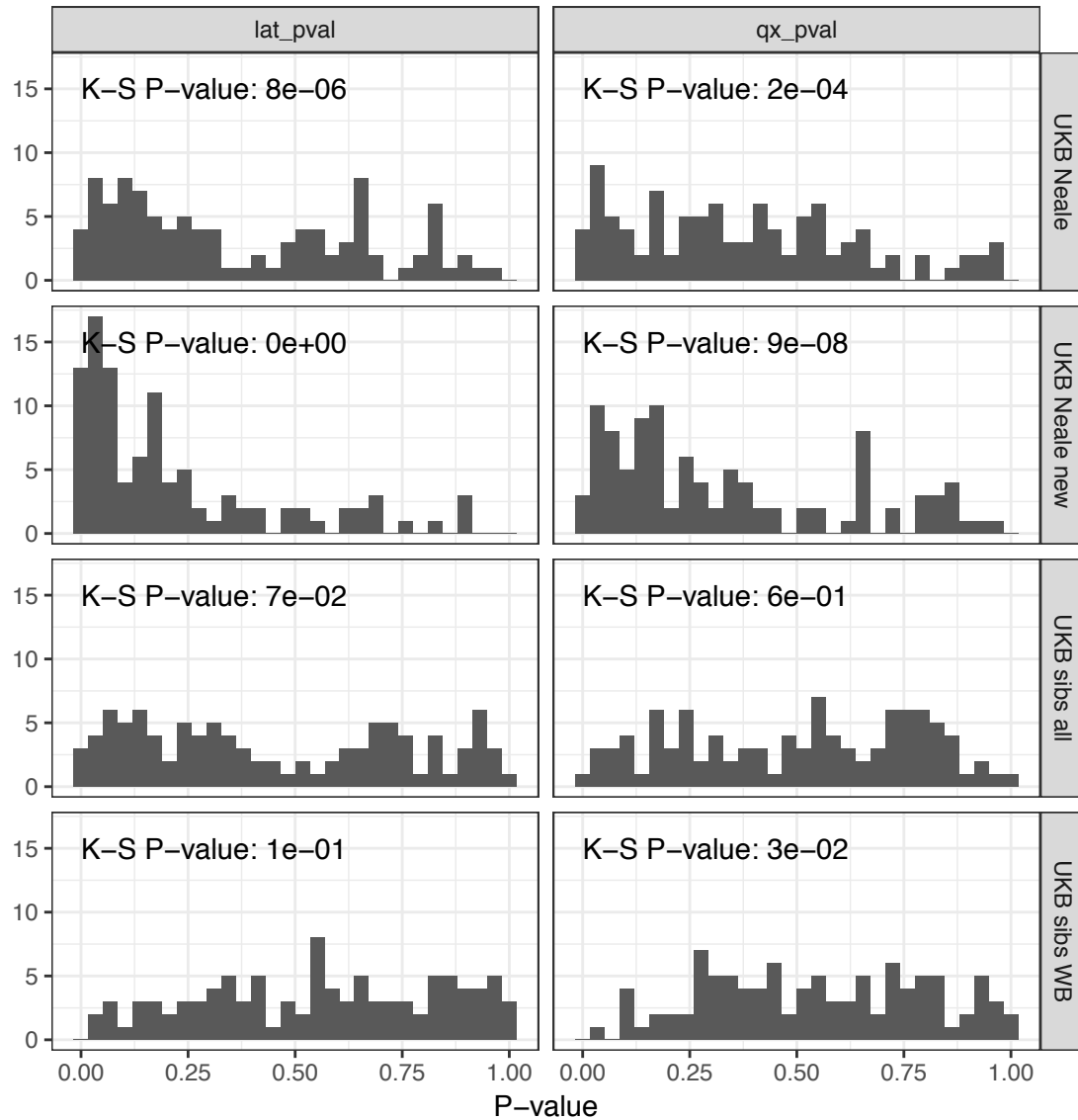
**Figure S19. P value calibration in the POPRES dataset for $Q_x$ and latitude covariance tests.** Random sets of around 1700 independent markers were drawn in 100 repetitions for four summary statistics and $Q_x$ and latitude P values were computed. In UK Biobank sibling estimates this resulted in a uniform P value distribution (non-significant Kolmogorov–Smirnov test), while an inflation was observed for UK Biobank GWAS summary statistics.

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922 **Supplementary tables**
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| name | sample size | number of SNPs (before intersecting) | type | comments | used in figures | PMID | URL |
|---|---|---|---|---|---|---|---|
| GIANT | 253288 | 2550858 | GWAS (OLS, meta-analysis) | | 1, 2, 3, 4 | 25282103 | https://portals.broadinstitute.org/collaboration/giant/images/0/01/GIANT_HEIGHT_Wood_et_al_2014_publicrelease_HapMapCeuFreq.txt.gz |
| UKB Neale (UKB) | 336474 | 10894596 | GWAS (OLS) | | 1, 2, 3, 4 | | https://www.dropbox.com/s/sbfgb6qd5i4cxku/50.assoc.tsv.gz |
| UKB Neale new | 360388 | 13791467 | GWAS (OLS) | soon be available on http://www.nealelab.is/ | supp only | | https://storage.googleapis.com/ukbb-robert/height_ukb_giant/robert1/50.imputed_v3.results.both_sexes.tsv.gz |
| UKB Loh | 458303 | 12007535 | BOLT-LMM | | supp only | 25642633 | https://data.broadinstitute.org/alkesgroup/UKBB/body_HEIGHTz.sumstats.gz |
| UKB all no PCs | 406825 | 729339 | GWAS (OLS) | genotyped SNPs | 3, 4 | | |
| UKB all 10 PCs | 406825 | 729339 | GWAS (OLS) | genotyped SNPs | supp only | | |
| UKB WB no PCs | 337208 | 729339 | GWAS (OLS) | genotyped SNPs | 3 | | |
| UKB WB 10 PCs | 337208 | 729339 | GWAS (OLS) | genotyped SNPs | supp only | | |
| NG2015 sibs | 17500 | 1006257 | within-family (QFAM) | | 3 | 26366552 | http://cnsgenomics.com/data/robinson_et_al_2015_ng/withinfam_summary_ht_bmi_release_March2016.tar.gz |
| UKB sibs all | 20166 | 729339 | within-family (QFAM) | genotyped SNPs | supp only | | |
| UKB sibs WB | 17358 | 729339 | within-family (QFAM) | genotyped SNPs | 3, 4 | | |

924
925 **Table S1. Description of 11 GWAS summary statistics.**
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| Population label | Population description | Meta-population | N |
|---|---|---|---|
| GBR | British in England & Scotland | Northern Europe | 92 |
| CEU | Utah residents with Northern & Western European Ancestry | Northern Europe | 99 |
| TSI | Toscani in Italia | Southern Europe | 108 |
| IBS | Iberian population in Spain | Southern Europe | 107 |
| PJL | Punjabi from Lahore, Pakistan | South Asia | 96 |
| BEB | Bengali from Bangladesh | South Asia | 86 |
| YRI | Yoruba in Ibadan, Nigeria | Africa | 109 |
| LWK | Luhya in Webuye, Kenya | Africa | 101 |
| JPT | Japanese in Tokyo, Japan | East Asia | 104 |
| CHB | Han Chinese in Beijing, China | East Asia | 103 |
| EF | Ancient | Early farmer | 485 |
| HG | Ancient | Hunter-gatherer | 162 |
| STP | Ancient | Steppe ancestry | 465 |

929
930 **Table S2. Table of ancient and 1000 genomes modern populations used with sample**
931 **sizes.**
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| Population | N | Latitude | Comments |
|---|---|---|---|
| Austria | 14 | 47.5 | |
| Belgium | 43 | 50.5 | |
| Czech Republic | 11 | 49.8 | |
| France | 92 | 46.2 | |
| Germany | 75 | 51.1 | |
| Hungary | 19 | 47.1 | |
| Ireland | 62 | 53.1 | |
| Italy | 225 | 41.8 | |
| Netherlands | 17 | 52.1 | |
| Poland | 22 | 51.9 | |
| Portugal | 135 | 39.3 | |
| Romania | 14 | 45.9 | |
| Spain | 137 | 40.4 | |
| Sweden | 11 | 60.1 | |
| Swiss-French | 760 | 46.5 | Lausanne |
| Swiss-German | 84 | 47.3 | Zurich |
| Switzerland | 168 | 46.8 | |
| United Kingdom | 390 | 55.3 | |
| Yugoslavia | 44 | 43.9 | |

935 **Table S3. Table of POPRES populations used with sample sizes and latitude.**
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| Name | h2 | h2 SE | lambda GC | mean chisq | intercept | intercept SE | ratio | n |
|---|---|---|---|---|---|---|---|---|
| GIANT | 0.31 | 0.01 | 2.00 | 2.92 | 1.28 | 0.02 | 0.15 | 253288 |
| UKB Neale (UKB) | 0.40 | 0.02 | 2.39 | 4.32 | 1.40 | 0.03 | 0.12 | 336474 |
| UKB Neale new | 0.42 | 0.02 | 2.48 | 4.69 | 1.43 | 0.03 | 0.12 | 360388 |
| UKB Loh | 0.60 | 0.03 | 3.31 | 7.66 | 1.75 | 0.04 | 0.11 | 458303 |
| UKB all no PCs | 13.76 | 0.22 | 55.97 | 65.24 | 9.42 | 0.08 | 0.13 | 406825 |
| UKB all 10 PCs | 0.48 | 0.02 | 2.37 | 4.69 | 1.39 | 0.04 | 0.11 | 406825 |
| UKB WB no PCs | 0.54 | 0.03 | 2.67 | 4.66 | 1.66 | 0.04 | 0.18 | 337208 |
| UKB WB 10 PCs | 0.51 | 0.03 | 2.17 | 4.19 | 1.30 | 0.04 | 0.09 | 337208 |
| NG2015 sibs | 0.49 | 0.03 | 1.07 | 1.08 | 0.90 | 0.01 | -1.21 | 17500 |
| UKB sibs all | 0.45 | 0.05 | 0.93 | 1.08 | 0.93 | 0.01 | -0.85 | 20166 |
| UKB sibs WB | 0.47 | 0.06 | 0.93 | 1.06 | 0.93 | 0.01 | -1.18 | 17358 |

937 **Table S4. LD Score regression estimates for 11 different summary statistics.**
938 LD score regression can be used to detect residual stratification effects in summary
939 statistics, and so we tested whether LDSC confirms our hypothesis of residual stratification.
940 We detect a greatly inflated intercept estimate of 9.42 in UKB all no PCs, but only a
941 moderately increased intercept value in GIANT and an intercept less than one in NG2015
942 sibs. The relatively small GIANT intercept can be explained by cohort-wise lambda-GC
943 correction, while the low intercept in NG2015 sibs is possibly caused by the adaptive
944 permutation procedure which does not compute precise p-values for non-significant
945 associations. In both cases LDSC cannot be expected to pick up stratification effects, since
946 the generation of summary statistics is not in line with the LDSC model.
947

| | GIANT | UKB Neale (UKB) | UKB Neale new | UKB Loh | UKB all no PCs | UKB all 10 PCs | UKB WB no PCs | UKB WB 10 PCs | NG2015 sibs | UKB sibs all | UKB sibs WB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GIANT | 1.000 | | | | | | | | | | |
| UKB Neale (UKB) | 0.660 | 1.000 | | | | | | | | | |
| UKB Neale new | 0.670 | 0.982 | 1.000 | | | | | | | | |
| UKB Loh | 0.691 | 0.912 | 0.924 | 1.000 | | | | | | | |
| UKB all no PCs | 0.332 | 0.276 | 0.274 | 0.251 | 1.000 | | | | | | |
| UKB all 10 PCs | 0.673 | 0.973 | 0.971 | 0.916 | 0.290 | 1.000 | | | | | |
| UKB WB no PCs | 0.635 | 0.952 | 0.933 | 0.865 | 0.270 | 0.929 | 1.000 | | | | |
| UKB WB 10 PCs | 0.660 | 0.998 | 0.981 | 0.911 | 0.276 | 0.975 | 0.953 | 1.000 | | | |
| NG2015 sibs | 0.368 | 0.261 | 0.265 | 0.276 | 0.151 | 0.271 | 0.238 | 0.261 | 1.000 | | |
| UKB sibs all | 0.264 | 0.325 | 0.326 | 0.351 | 0.095 | 0.328 | 0.307 | 0.324 | 0.114 | 1.000 | |
| UKB sibs WB | 0.250 | 0.312 | 0.312 | 0.336 | 0.088 | 0.311 | 0.296 | 0.311 | 0.108 | 0.928 | 1.000 |

948 **Table S5. Correlation of beta estimates at all 86,153 shared SNPs.**
949

|  | GIANT | UKB Neale (UKB) | UKB Neale new | UKB Loh | UKB all no PCs | UKB all 10 PCs | UKB WB no PCs | UKB WB 10 PCs | NG2015 sibs | UKB sibs all | UKB sibs WB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GIANT | 1.000 | | | | | | | | | | |
| UKB Neale (UKB) | 0.975 | 1.000 | | | | | | | | | |
| UKB Neale new | 0.976 | 0.999 | 1.000 | | | | | | | | |
| UKB Loh | 0.972 | 0.986 | 0.986 | 1.000 | | | | | | | |
| UKB all no PCs | 0.798 | 0.789 | 0.788 | 0.785 | 1.000 | | | | | | |
| UKB all 10 PCs | 0.976 | 0.998 | 0.998 | 0.988 | 0.791 | 1.000 | | | | | |
| UKB WB no PCs | 0.971 | 0.996 | 0.995 | 0.984 | 0.788 | 0.995 | 1.000 | | | | |
| UKB WB 10 PCs | 0.975 | 1.000 | 0.999 | 0.986 | 0.789 | 0.999 | 0.997 | 1.000 | | | |
| NG2015 sibs | 0.847 | 0.828 | 0.829 | 0.840 | 0.675 | 0.829 | 0.822 | 0.828 | 1.000 | | |
| UKB sibs all | 0.865 | 0.877 | 0.875 | 0.874 | 0.706 | 0.878 | 0.872 | 0.877 | 0.727 | 1.000 | |
| UKB sibs WB | 0.860 | 0.872 | 0.870 | 0.866 | 0.700 | 0.872 | 0.867 | 0.872 | 0.712 | 0.980 | 1.000 |

**Table S6. Correlation of beta estimates at 2,251 shared SNPs which are significant in the UK Biobank.**

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