# Improved analyses of GWAS summary statistics by reducing data heterogeneity and errors

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## Abstract

Summary statistics from genome-wide association studies (GWAS) have facilitated the development of various summary data-based methods, which typically require a reference sample for linkage disequilibrium (LD) estimation. Analyses using these methods may be biased by errors in GWAS summary data and heterogeneity between GWAS and LD reference. Here we propose a quality control method, DENTIST, that leverages LD among genetic variants to detect and eliminate errors in GWAS or LD reference and heterogeneity between the two. Through simulations, we demonstrate that DENTIST substantially reduces false-positive rate (FPR) in detecting secondary signals in the summary-data-based conditional and joint (COJO) association analysis, especially for imputed rare variants (FPR reduced from >28% to <2% in the presence of ancestral difference between GWAS and LD reference). We further show that DENTIST can improve other summary-data-based analyses such as LD score regression analysis, and integrative analysis of GWAS and expression quantitative trait locus data.

## Introduction

Genome-wide association studies (GWASs) have been extraordinarily successful in uncovering genetic variants associated with complex human traits and diseases[1,2]. Summary statistics available from GWASs have facilitated the development of various summary-data-based methods[3] such as those for fine-mapping[4-9], imputing summary statistics at untyped variants[10,11], estimating SNP-based heritability[12-14], assessing causal or genetic relationship between traits[15-17], prioritizing candidate causal genes for a trait[18-21], and polygenetic risk prediction[8,22,23]. Most of the summary-data-based methods require linkage disequilibrium (LD) structure of the variants used, which are not available in the summary data but can be estimated from a reference cohort with individual-level genotypes assuming a homogeneous LD structure between the GWAS and reference cohorts. Hence, summary-data-based analyses can be affected by not only errors in the GWAS and LD reference data sets but also differences between them for the following reasons. First, there are often errors in GWAS summary statistics resulting from the data generation and analysis processes (e.g., genotyping/imputation errors and genetic variants with mis-specified effect alleles)[24,25], some of which are not easy to detect, even if individual-level data are available. Second, there is often heterogeneity between data sets (e.g., between the discovery GWAS and LD reference) because of differences in ancestry, and genotyping platform, analysis pipeline. Although the recommended practice is to use an ancestry-matched reference cohort, samples with similar ancestries, such as populations of European ancestry, can still have discernable differences in LD structure[26], and the effects of such differences on summary-data-based analyses are largely unexplored. To the best of our knowledge, there is no existing method specifically designed to detect data heterogeneity that affect summary data-based analyses.

In this study, we propose a quality control (QC) method to identify errors in GWAS summary data and heterogeneity between summary data and LD reference by testing the difference between the observed z-score of each variant and its predicted value from the surrounding variants. The method has been implemented in a software tool named DENTIST (detecting errors in analyses of summary statistics). We show by simulation that DENTIST can effectively detect simulated errors of several kinds. We then demonstrate the utility of DENTIST as a QC step for multiple, frequently-used, summary data-based methods, including the conditional and joint analysis (COJO)[6] of summary statistics, LD score regression[12], and heterogeneity in dependent instruments (HEIDI) test[21].

## Results

### Overview of the DENTIST method

Details of the methodology can be found in the Methods section. In brief, we first use a sliding window approach to divide the variants into 2Mb segments with a 500kb overlap between two adjacent segments. Within each segment, we randomly partition variants into two subsets, S1 and S2, with an equal number of variants, and apply the statistic below to test the difference between the observed z-score of a variant *i* ($z_i$) in S1 and its predicted value ($\tilde{z}_i$) based on z-scores of an array of variants $\boldsymbol{t}$ in S2 (**Methods**).

$$T_{d(i)} = \frac{(z_i - \tilde{z}_i)^2}{\mathbf{1} - \mathbf{R}_{it}\mathbf{R}_{tt}^{-1}\mathbf{R}_{it}'} \text{ with } \tilde{z}_i = \mathbf{R}_{it}\mathbf{R}_{tt}^{-1}\,\boldsymbol{z_t} \quad (1)$$

where $\boldsymbol{z_t}$ is a vector of z-scores of variants $\boldsymbol{t}$ in S2, and $\mathbf{R}$ is the LD correlation matrix calculated from a reference sample with $\mathbf{R}_{\boldsymbol{tt}}$ to denote the LD between variants $\boldsymbol{t}$ and $\mathbf{R}_{\boldsymbol{it}}$ to denote the LD between variant *i* and variants $\boldsymbol{t}$. $T_d$ follows approximately a $\chi^2$ distribution with 1 degree of freedom. Note that methods that leverage LD to predict GWAS test-statistic of a variant (i.e., $\tilde{z}_i$) from test-statistics of its adjacent variants (i.e., $\boldsymbol{z_t}$) have been developed in prior work[10,11]. A significant difference between the observed and predicted z-scores indicates errors in the discovery GWAS or LD reference, or heterogeneity between them. If the difference between $z_i$ and $\tilde{z}_i$ is due to error in $z_i$, the power of $T_d$ depends on how $z_i$ deviates from its true value and how well variant *i* is tagged by variants $\boldsymbol{t}$. We conduct a truncated singular value decomposition (SVD) on $\mathbf{R}_{\boldsymbol{tt}}$ to mitigate the sampling noise in LD estimated from the reference that is often independent from the discovery GWAS and to perform a pseudo inverse when $\mathbf{R}_{\boldsymbol{tt}}$ is singular[13] (see **Methods**).

One challenge for the DENTIST method is that errors can be present in both S1 and S2, and errors in S2 can inflate $T_d$ statistics of the variants in S1. To mitigate this issue, we propose an iterative partitioning approach. In each iteration, we partition the variants at random into two subsets (S1 and S2) and remove variants with $P_{DENTIST} < 5\times10^{-8}$ (capped at 0.5% variants with the smallest *P*-values). This step is to create a more reliable set of variants for the next iteration. The problematic variants are prioritized and filtered out in the first few iterations so that the prediction of $\tilde{z}_i$ (Equation 1) becomes more accurate in the following iterations. We set the number of iterations to 10 in practice. All variants with $P_{DENTIST} < 5\times10^{-8}$ are removed in the final step.

## Detecting simulated errors in GWAS data

To assess the performance of DENTIST in detecting errors, we simulated GWAS data with genotyping errors and allelic errors (i.e., variants with the effect allele mis-labelled) using whole genome sequence (WGS) data of chromosome 22 on 3,642 unrelated individuals from the UK10K project[27,28] (denoted by UK10K-WGS). A descriptive summary of all the data sets used in

this study can be found in **Supplementary Table 1** and the Methods section. We simulated a trait affected by 50 common, causal variants with effects drawn from $N(0,1)$, which together explained 20% of the phenotypic variation (proportion of variance explained by a causal variant, denoted by $q^2$, was 0.4%, on average). Prior to the simulations with errors, we showed by a simulation under the null (i.e., simulating a scenario without errors and applying DENTIST using the discovery GWAS as the reference) that the DENTIST test-statistics were well calibrated, meaning that DENTIST will only remove a very small proportion of variants if there are no errors and heterogeneity in the data (**Supplementary Figure 1**). We then simulated genotyping and allelic errors at 0.5% randomly selected variants respectively. Genotyping errors of each of these variants were simulated by altering the genotypes of a certain proportion ($f_{error}$ = 0.05, 0.1 or 0.15) of randomly selected individuals, and allelic error of each of the variants was introduced by swapping the effect allele by the other allele. The simulation was repeated 200 times with the causal and erroneous variants re-sampled in each simulation. We then ran DENTIST using UK10K-WGS or an independent sample (UKB-8K-1KGP) as the LD reference after standard QCs of the discovery GWAS: removing variants with a Hardy-Weinberg Equilibrium (HWE) P-value < $10^{-6}$ using the individual-level data or ΔAF > 0.1 with ΔAF being the difference in allele frequency (AF) between the summary data and reference sample. The independent sample UKB-8K-1KGP is referred to as a set of 8000 unrelated individuals from the UK Biobank[29] (UKB) with variants imputed from the 1000 Genomes Project (1KGP). The statistical power (sensitivity) was measured by the proportion of erroneous variants in the data that can be detected from QC. We also computed the fold enrichment in probability of an erroneous variant being detected from QC compared to a random guess (i.e., the ratio of the percentage of true erroneous variants in the variants detected by DENTIST to that in all variants).

When using UKB-8K-1KGP as the reference, ~45% of the genotyping and ~95% of the allelic errors could be removed by the standard QCs (**Supplementary Table 2**). However, the ΔAF approach performed poorly for the very common variants, e.g., the power was ~16% for variants with MAF > 0.45. After the standard QCs, DENTIST was able to detect ~42% of the remaining genotyping and ~78% of the remaining allelic errors (**Figure 1** and **Supplementary Table 3**), with only ~0.3% variants being removed in total (**Supplementary Table 4**). The fold enrichment was 212 for allelic errors and of 112 for genotyping errors (**Supplementary Table 5**), showing good specificity of DENTIST in detecting the simulated errors. Notably, the power to detect allelic errors was ~78% for variants with MAF > 0.45, compensating the low power of the ΔAF approach in this MAF range (note: another shortcoming of the ΔAF approach is that the threshold is heavily sample size dependent, and currently there is no consensus guidance on the choice of a ΔAF threshold in practice). When restricted to variants passing the genome-wide

significance level (i.e., $p < 5\times10^{-8}$), the DENTIST detection power increased to ~87% for the genotyping errors and ~84% for the allelic errors (**Supplementary Table 3**). The power also varied with the genotyping error rate ($f_{error}$), e.g., the power in the $f_{error}$=0.05 scenario was, on average, lower than that for $f_{error}$=0.15 (**Figure 1c** and **Supplementary Table 3**). When using UK10K-WGS as the reference (mimicking the application of DENTIST in a scenario where individual-level data of the discovery GWAS are available), the power remained similar, but the fold enrichment was much higher compared to that using UKB-8K-1KGP (**Supplementary Tables 5** and **6**). In addition, using this same simulation setting, we explored the choice of the parameter $\theta_k$ (i.e., the proportion of eigenvectors retained in SVD; see Methods for details) and reference sample size ($n_{\mathrm{ref}}$), and the results suggested a choice of $\theta_k$=0.5 and $n_{\mathrm{ref}} \geq 5000$ in practice (**Supplementary Figure 2**). Together, these results demonstrate the power of DENTIST to identify allelic and genotyping errors even after the standard QCs, suggesting that DENTIST can complement existing QC filters for either individual- or summary-level GWAS data. On the other hand, DENTIST was parsimonious in data filtering, with ~0.3% of the variants being removed in total across all the simulation scenarios (**Supplementary Table 4**). Nevertheless, we acknowledge that this simulation did not cover the full complexity of real case scenarios, which may involve multiple independent samples with heterogeneous LD structures caused by several factors, such as imputation errors or ancestry mismatches (**Supplementary Figure 3**). These cases are difficult to mimic in this simulation but will be assessed in the following analyses.

**Applying DENTIST to COJO with simulated phenotypes**

COJO[6] is a method that uses summary data from a GWAS or meta-analysis and LD data from a reference sample to run a conditional and joint multi-SNP regression analysis. We used simulations to assess the performance of COJO in the presence of heterogeneity between discovery GWAS and LD reference before and after DENTIST filtering. To mimic the reality that causal signals are often not perfectly captured by imputed variants, we simulated a phenotype affected by one or two sequenced variants using WGS data (i.e., UK10K-WGS) and performed association analyses using imputed data of the same individuals (imputing 312,264 variants, in common with those on an SNP array, to the 1KGP[28,30]; denoted by UK10K-1KG). More specifically, we first randomly selected one or two variants from two MAF bins as causal variants, i.e., variants with MAF≥0.01 (denoted by common-causal) and 0.01>MAF≥0.001 (denoted by rare-causal) to generate a phenotype (note: MAF > 0.001 is equivalent to minor allele count > 7 in this sample). The causal variant $q^2$ was set to 2% to achieve similar power to a scenario with $q^2$ = 0.03% and $n$ = 250,000 (note: the mean $q^2$ of 697 height variants discovered in Wood et al.[31] is 0.03%) because the power of GWAS is determined by $nq^2/(1-q^2)$. Then, we

168 ran a GWAS using UK10K-1KGP and performed COJO analyses using multiple LD references,
169 including the discovery GWAS sample, UKB-8K-1KGP, the Health Retirement Study (HRS)[32], and
170 the Atherosclerosis Risk In Communities (ARIC) study[33], with different degrees of ancestral
171 differences with UK10K-1KGP (**Supplementary Figure 4**). For a fair comparison, only the
172 variants shared between these reference samples were included. We repeated the simulation
173 100 times for each autosome and computed the false positive rate (FPR, i.e., the frequency of
174 observing two COJO signals in the scenario where there was only one causal variant) and power
175 (the frequency of observing two COJO signals in the scenario where there were two distinct
176 causal variants with LD $r^2$ <0.1 between them). It should be noted that the false positive COJO
177 signals defined here are not false associations but falsely claimed as jointly associated (also
178 known as quasi-independent) signals.
179
180 When using the discovery GWAS sample as the LD reference, the FPR of COJO was 0.1% for
181 common-causal and 0.2% for rare-causal (**Figure 2; Table 1**), which can be regarded as a
182 baseline for comparison as there was no data heterogeneity in this case. The FPRs were higher
183 than the expected values because the causal variants were not perfectly tagged by the imputed
184 variants (**Supplementary Table 7**). When using UKB-8K-1KGP (i.e., 1KGP-imputed data of 8000
185 UKB participants with similar ancestry to the UK10K participants as shown in **Supplementary**
186 **Figure 4**) as the LD reference, the FPR was close to the benchmark for common-causal (1%) and
187 slightly inflated for rare-causal (2.7%) (**Figure 2**). After DENTIST filtering (using UKB-8K-1KGP
188 as the LD reference), the FPR for rare-causal decreased to 1.3%. Moreover, when using LD
189 computed from European-American individuals in HRS or ARIC, the FPR of COJO was strongly
190 inflated in the whole MAF range: >7% for common-causal and >28% for rare-causal, likely
191 because of the difference in ancestry between HRS/ARIC and UK10K-1KGP. DENTIST can
192 effectively control the FPR of COJO to <1% for common-causal and <2% for rare-causal (**Figure**
193 **2**). Taken together, the FPR of COJO was reasonably well controlled for common variants but
194 substantially inflated for rare variants especially when there was a difference in ancestry
195 between the GWAS and LD reference samples, and most of the false positive COJO signals could
196 be removed by DENTIST.
197
198 The power of COJO (without DENTIST) using in-sample LD from UK10K-1KGP or out-of-sample
199 LD from the other references were similar: 77-81% for common-causal and 26-30% for rare-
200 causal (**Table 1**). The low power for rare-causal was because they were poorly captured by
201 imputation (**Supplementary Table 7**). DENTIST filtering caused a <2% loss of power for
202 common-causal, and 5-10% for rare-causal (**Table 1**). Hence, the control of FPR of COJO by

203 DENTIST was to some extent at the expense of power although the reduction in FPR was larger
204 than that in power.
205
206 We also examined the effect of imputation INFO score-based QC on the FPR and power of COJO.
207 Take the analysis with HRS as an example. By removing variants with INFO-scores < 0.9 from the
208 HRS data, the FPR of COJO decreased to 2.3% for common-causal and 6% for rare-causal
209 (**Supplementary Table 8**), both of which were higher than those using DENTIST (FPR = 0.5%
210 for common-causal and 1.7% for rare-causal) (**Table 1**). Meanwhile, the power of COJO after the
211 INFO score-based QC decreased to 70% for common-causal and 12% for rare-causal
212 (**Supplementary Table 8**), both of which were lower than those using DENTIST (power = 81%
213 for common-causal and 27% rare-causal). The other less stringent INFO-score threshold were
214 even less effective, and the results from analyses using the other references were similar
215 (**Supplementary Table 8**). These results suggest that filtering variants by imputation INFO is
216 less effectively than that by DENTIST.
217
218 **Applying DENTIST to COJO for real phenotypes**
219 Having assessed the performance of DENTIST in COJO analyses by simulation, we then applied it
220 to COJO analyses for height in the UKB. The height GWAS summary statistics (n = 328,577) were
221 generated from a GWAS analysis of all the unrelated individuals of European ancestry in the UKB
222 (denoted by UKBv3-329K) except 20,000 individuals (denoted by UKBv3-20K), which were used
223 as a non-overlapping LD reference. Genotype imputation of the UKB data was performed by the
224 UKB team with most of the variants imputed from the Haplotype Reference Consortium (HRC)[34].
225 We performed COJO analyses with a host of references: overlapping in-sample references with
226 sample sizes ($n_{\mathrm{ref}}$) varying from 10,000 to 150,000, non-overlapping in-sample references
227 including UKBv3-8K (n = 8,000) and UKBv3-20K (containing UKBv3-8k), and out-of-sample
228 references including ARIC and HRS (**Supplementary Table 1**). We excluded from the analysis
229 variants with MAF < 0.001 to ensure sufficient number of minor alleles for rare variants in
230 reference samples with $n_{\mathrm{ref}}$ < 10k. We first performed a COJO analysis using the actual GWAS
231 sample as the reference and identified 1,279 signals from variants with MAFs >0.01, and 1310
232 signals from variants with MAFs > 0.001 (**Table 2**). These results can be regarded as a
233 benchmark. When using the overlapping in-sample LD references, the number of COJO signals
234 first decreased as $n_{\mathrm{ref}}$ increased and then started to stabilize when $n_{\mathrm{ref}}$ exceeded 30,000
235 (**Supplementary Figure 5**). The results from using the two non-overlapping in-sample
236 references (UKBv3-8K and UKBv3-20K) were comparable to those from using the overlapping
237 in-sample references with similar sample sizes (**Table 2** and **Supplementary Table 9**) because
238 the non-overlapping in-sample references, despite being excluded from the GWAS, were

239 consistent with the GWAS sample with respect to ancestry, data collection, and analysis
240 procedures.
241
242 When using LD from an out-of-sample reference (either HRS or ARIC), there was substantial
243 inflation in the number of COJO signals compared to the benchmark (by 15.5-16.1% for common
244 variants and 18.7-25.6% for all variants), with a few variants in weak LD with those identified
245 from the benchmark analysis (**Supplementary Figure 6**). The results from using the two out-of-
246 sample references became more consistent with the benchmark after DENTIST filtering, with the
247 inflation reduced to 4.6-5.8% for common variants and 2.7-6.7% for all variants, comparable to
248 the results using an in-sample LD reference with a similar sample size (**Table 2**). Polygenic score
249 analysis shows that the reduction in the number of COJO signals owing to DENTIST QC had
250 almost no effect on the accuracy of using the COJO signals to predict height in HRS
251 (**Supplementary Table 10**), suggesting the redundancy of the COJO signals removed by
252 DENTIST. We further found that compared to using the imputed data from ARIC or HRS, using
253 UK10K-WGS (n=3,642) as the reference showed lower inflation (10% for common variants and
254 <12.4% for all variants) before DENTIST QC but larger inflation after DENTIST QC (**Table 2**),
255 suggesting a large reference sample size is essential even for WGS data. In all the DENTIST
256 analyses above, the total number of removed variants varied from 0.05% to 0.98%
257 (**Supplementary Table 11**). All these results are consistent with what we observed from
258 simulations, demonstrating the effectiveness of DENTIST in eliminating heterogeneity between
259 GWAS and LD reference samples.
260
261 We further applied DENTIST to Educational Attainment (EA), Coronary Artery Disease (CAD),
262 Type 2 Diabetes(T2D), Crohn's Disease (CD), Major Depressive Disorder (MDD), Schizophrenia
263 (SCZ), Ovarian Cancer (OC), Breast Cancer (BC), Height and Body Mass Index (BMI) using GWAS
264 summary data from the public domain[35-43] (**Supplementary Table 12**) and three LD reference
265 samples (i.e., ARIC, HRS, and UKBv3-8K). Since these published studies focus on common
266 variants (rare variants are not available in most of the data sets), we used a MAF threshold of
267 0.01 in this analysis. When using ARIC as the LD reference, the proportion of variants removed
268 by DENTIST QC ranged from 0.02% (BMI) to 0.94% (CAD) with a median of 0.28%
269 (**Supplementary Table 13**), and the reduction in the number of COJO signals for common
270 variants ranged from 0% (OC and MDD) to 11.9% (CAD) with a median of 1.5%
271 (**Supplementary Table 14**). The results from using the other two references are similar
272 (**Supplementary Table 13** and **14**).
273
274 **Improved HEIDI test with DENTIST**

275 The summary data-based Mendelian randomization (SMR) is a method that integrates summary-
276 level data from a GWAS and an expression quantitative trait loci (eQTL) study to test pleiotropic
277 associations between a trait and expression levels of genes[21]. It features the HEIDI test that
278 utilizes multiple cis-eQTL variants at a locus to distinguish pleiotropy (the trait and expression
279 level of a gene are affected by the same causal variants) from linkage (causal variants for the
280 trait are in LD with a distinct set of causal variants affecting gene expression). The HEIDI test
281 uses summary data from two studies and LD from a reference so that any errors in and
282 heterogeneity between the GWAS, eQTL and reference samples can cause inflated HEIDI test
283 statistics, giving rise to more SMR associations being rejected than expected by chance[21,44]. Here,
284 we performed simulations to assess the effect of data heterogeneity on HEIDI and sought to
285 mitigate it using DENTIST. We first generated a trait based on a causal variant ($q^2$ = 1%)
286 randomly sampled from the variants on chromosome 22 in the ARIC data. To simulate a
287 pleiotropic model, we used the same causal variant to simulate the expression level of a gene in a
288 subset of the HRS data (n = 3,000; denoted by HRS-3K) with $q^2$ for the gene expression level
289 randomly sampled from the eQTL $q^2$ distribution reported by the Consortium for the
290 Architecture of Gene Expression (CAGE)[45]. To simulate a linkage model, a second causal variant
291 in LD ($r^2 > 0.25$) with the trait causal variant was selected to generate the gene expression level,
292 again with the eQTL $q^2$ value sampled from the CAGE. In addition to the two-sample scenario
293 above, we also simulated a one-sample scenario in which both the trait and gene expression
294 level were generated in the HRS-3K sample. The UKB-8K-1KGP sample was used as the LD
295 reference for both the SMR-HEIDI and DENTIST analyses. For each scenario, the simulation was
296 repeated 4000 times with the causal variants re-sampled in each replicate. The FPR of the HEIDI
297 test was calculated as the proportion of pleiotropic models detected with $P_{\mathrm{HEIDI}} < 0.05$, and the
298 power was defined as the proportion of linkage models detected with $P_{\mathrm{HEIDI}} < 0.05$.
299
300 We found that the FPR of HEIDI was close to the expected value (5%) in the one-sample scenario
301 (5.8%) but inflated (9.8%) in the two-sample scenario (**Figures 3a** and **3b**, and **Supplementary**
302 **Table 15**). To mitigate the inflation, we performed DENTIST in both the GWAS and eQTL
303 summary data using UKB-8K-1KGP as the reference. After DENTIST filtering, the FPR of HEIDI in
304 the two-sample scenario decreased to 7.6%; the decrease was small but statistically significant
305 ($P_{difference}$ = 0.002). The results remained similar when the discovery GWAS sample (i.e., HRS-3K)
306 was used as the reference (**Supplementary Table 15)**. These results suggest that the HEIDI test
307 statistic was inflated in the two-sample scenario likely because of LD heterogeneity between the
308 GWAS and eQTL samples. The power of HEIDI to detect the linkage model remained almost the
309 same before and after DENTIST filtering (**Figure 3c** and **Supplementary Table 15**). To further
310 validate if the inflation of HEIDI FPR was due to heterogeneity between the GWAS and eQTL

311 samples, we increased the difference in ancestry between the two discovery samples by
312 simulating GWAS and eQTL data from UKB-8K-1KGP and HRS-3K, respectively, and performed
313 the HEIDI analysis using ARIC as the reference. In this case, the FPR of HEIDI increased to 12.0%
314 before and to 9.1% after DENTIST filtering (**Supplementary Table 15**). All these results suggest
315 that DENTIST slightly improved the FPR of HEIDI in the presence of data heterogeneity at almost
316 no expense of power and that in the presence of ancestry difference between the GWAS and
317 eQTL samples, HEIDI tends to be conservative (rejecting more SMR associations than expected
318 by chance) even after DENTIST filtering.
319
320 **Improved LD score regression analysis with DENTIST**
321 LD score regression (LDSC) is an approach which was originally developed to distinguish
322 polygenicity from population stratification in GWAS summary data set by a weighted regression
323 of GWAS $\chi^2$ statistics against LD scores computed from a reference[12] but has often been used to
324 estimate the SNP-based heritability ($h^2_{SNP}$). We investigated the impact of DENTIST on LDSC
325 using the height GWAS summary data generated using the UKBv3-329K sample along with
326 several reference samples including four imputation-based samples (i.e., the discovery GWAS
327 sample, HRS, ARIC and UKB-8K-1KGP) and two WGS-based samples (i.e., UK10K-WGS and the
328 European individuals from the 1KGP (1KGP-EUR)). We performed the one- and two-step LDSC
329 analyses using LD scores of the variants, in common with those in the HapMap3, computed from
330 each of the references before and after DENTIST-based QC. Note that DENTIST was performed
331 for all common variants but only those overlapped with HapMap3 were included in the LDSC
332 analyses.
333
334 Using the discovery GWAS sample as the reference, the estimates of $h^2_{SNP}$ and regression
335 intercept from the one-step LDSC were 46% (SE = 0.02) and 1.13 (SE = 0.04) respectively (**Table**
336 **3**). When using the other reference samples, the results were very close to the benchmark except
337 for a noticeably larger estimate of regression intercept using HRS (1.24, SE = 0.04). After
338 DENTIST filtering, the intercept estimate using HRS decreased to 1.15 (SE = 0.04) with little
339 difference in $\hat{h}^2_{SNP}$ (increased from 45% to 46%) (**Table 3**). To better understand the effect of
340 DENTIST QC on LDSC using HRS, we plotted the mean $\chi^2$-statistic against the mean LD score
341 across the LD score bins. We found that the GWAS mean $\chi^2$-statistic in the bin with the smallest
342 mean LD score deviated from the value expected from a linear relationship between the LD
343 score and $\chi^2$-statistic (**Figure 4a**), and the deviation was removed by filtering out a small
344 proportion of variants with very small LD scores but large $\chi^2$-statistic by DENTIST
345 (**Supplementary Figure 7**). These results show how the quality of LD reference can impact the
346 LDSC analysis, but such effect is typically unknown *a priori* and varied across different reference

347 samples. We also re-ran the analyses using the two-step LDSC, where the intercept was
348 estimated using the variants with $\chi^2$ values < 30 in the first step and constrained in the second
349 step to estimate $h^2_{SNP}$ using all the variants. Compared to the one-step approach, the two-step
350 approach provides larger estimates of the intercepts and smaller estimates of $h^2_{SNP}$ either before
351 or after DENTIST filtering. It is noteworthy that when using 1KGP-EUR as the LD reference,
352 DENTIST suggested many more variants for removal compared to that using the other
353 references, which caused a substantially smaller estimate of $h^2_{SNP}$ (**Table 3**). This is because LD
354 correlations computed from references of small sample size are noisy due to sampling variation,
355 which cause inflated test-statistic and thereby elevated FPR of DENTIST (**Supplementary**
356 **Figure 2**). This result cautions the use of DENTIST with LD references with small sample sizes
357 (e.g., $n < 5000$). In addition, we applied LDSC to the 10 published GWAS data sets mentioned
358 above (**Supplementary Table 12**) using ARIC and UKBv3-8K as the reference. The
359 improvement of LDSC by DENTIST QC was small particularly for traits whose LDSC intercepts
360 were close to 1 before DENTIST QC (**Supplementary Table 16**), demonstrating the robustness
361 of LDSC to data heterogeneity and errors.
362
363 **Discussion**
364 In this study, we developed DENTIST, an QC tool for summary data-based analyses, which
365 leverages LD from a reference sample to detect and filter out problematic variants by testing the
366 difference between the observed z-score of a variant and a predicted z-score from the
367 neighboring variants. From simulations and real data analyses, we show that some of the
368 commonly-used analyses including the COJO, SMR-HEIDI and LDSC, can be biased to various
369 extents in the presence of data heterogeneity, e.g., inflated number of COJO signals, elevated rate
370 of rejecting pleiotropic models for SMR-HEIDI, or biased estimates of regression intercept and
371 $h^2_{SNP}$ for LDSC. For most of these analyses, DENTIST-based QC can substantially mitigate the
372 biases.
373
374 Our results suggest that summary-data-based analyses are generally well calibrated in the
375 absence of data heterogeneity but biased otherwise. For example, we showed that the mismatch
376 in ancestry between the discovery GWAS and LD reference (e.g., European vs. British ancestry)
377 caused inflated FPRs of both COJO and SMR-HEIDI analyses (**Table 2** and **Supplementary Table**
378 **15**). Also, we found that the FPR of COJO for rare variants was much higher than that for
379 common variants likely because rare variants are more difficult to impute such that they are
380 more likely to have discrepancy in LD between two imputed data sets. It should be clarified that
381 the false-positive COJO signals as defined here are not false associations but falsely claimed as
382 jointly significant associations. DENTIST substantially reduced false-positive detections from

383 COJO analyses especially for rare variants even when there was a difference in ancestry between
384 the GWAS and LD reference samples. This extends the utility of COJO, which was originally
385 developed for common variants, to rare variants. This message is important for the field because
386 more and more GWASs and meta-analyses have started included rare variants from imputation.
387 The FPR of HEIDI was only marginally reduced by DENTIST but at almost no cost of power. It
388 should also be clarified again that the inflated HEIDI test-statistics would not lead to false
389 discoveries because higher HEIDI test-statistics correspond to higher probability of rejecting
390 SMR associations rather than tending to claim more significant associations. Among all the
391 methods tested, LDSC was least affected by errors or data heterogeneity, but in one case where
392 HRS was used as the LD reference for the analysis of the UKB height summary data, the
393 estimates were biased but could be corrected by DENTIST (**Figure 4a**). DENTIST has the unique
394 feature to detect heterogeneity between a GWAS summary data set and an LD reference. The
395 benefit of using DENTIST as a QC tool has been demonstrated in the three case studies above,
396 but we believe that it can potentially be applied to all GWAS summary data-based analyses that
397 require a LD reference such as fine mapping methods[7,9,46] and joint modeling of all variants for
398 polygenic risk prediction[22,23,47] . We have also shown by simulation that DENTIST can even add
399 value to the standard GWAS QC process in a single-cohort-based GWAS to detect
400 genotyping/imputation errors.
401
402 Given that a QC step can potentially remove true signals, we make sure that DENTIST is
403 conservative in filtering variants. We show by simulation that in the absence of errors and data
404 heterogeneity, the DENTIST test-statistics were not inflated, and on average, only <0.05%
405 variants were filtered out by DENTIST (**Supplementary Figure 1**). In practice, we implemented
406 two strategies to avoid widespread inflation of the DENTIST statistics in the presence of data
407 errors or heterogeneity: 1) we used the SVD truncation method to control for sampling variation
408 in LD estimated from the reference; 2) we applied an iterative approach to prioritize the
409 elimination of larger outliers in earlier iterations (Methods). We optimized the parameters
410 related to these two steps through simulations (**Supplementary Figure 2)**. Throughout all the
411 analyses performed in this study, we found in no cases DENTIST degraded the results, and
412 DENTIST often only needed to remove a very small proportion of the variants to correct or
413 alleviate the biases (**Table 3** and **Supplementary Tables 4, 11, 13**). To the contrary, filtering
414 variants based on imputation INFO score[48] caused significant loss of power in the COJO analysis
415 when a stringent INFO score threshold was used to achieve a similar level of FPR as that using
416 DENTIST.
417

418 Our method is an early attempt at QC for summary-data-based analyses. To avoid misuse, we
419 summarize the usages and limitations, in addition to the features mentioned above. Firstly,
420 DENTIST is a QC method for detecting not only errors in summary-data but also heterogeneity
421 between discovery and reference data. As shown from our simulation, DENTIST does not
422 guarantee the filtering of all the errors but most of them with large GWAS z-scores and a large
423 proportion of them with small z-scores. Secondly, DENTIST can identify errors that passed the
424 standard QC approaches (such as HWE test and allelic frequency checking), which makes it a
425 good complementary method to existing QC filters. We suggest that DENTIST-based QC should
426 be applied after the standard QC as DENTIST is more powerful when the proportion of errors is
427 smaller (**Supplementary Table 3**). DENTIST can also be used as a method for checking
428 summary data sanity by running it with a reliable LD reference sample. Thirdly, regarding the
429 choice of a reference sample, DENTIST expects unrelated individuals from a closely matched
430 ancestry, with a large sample size (n > 5,000). From simulations, we found that small reference
431 sample size biased the DENTIST test statistics leading to significantly elevated FPR
432 (**Supplementary Figure 2**). Lastly, DENTIST assumes the test statistics of different variants
433 have similar sample sizes; violation of this assumption will lead to variants with significantly
434 smaller or larger sample sizes being mistakenly recognized as problematic variants by DENTIST.
435
436 In summary, we have proposed a new QC approach to improve summary-data-based analyses
437 that are potentially affected by the errors in summary data or heterogeneity between data sets.
438 This method has been implemented in a user-friendly software tool DENTIST. The software tool
439 is multi-threaded so that it is computationally efficient when enough computing resources are
440 available. For example, when running each chromosome in parallel, it took <1h to run DENTIST
441 for all variants with MAF > 1% and <5h for all variants with MAF > 0.01% on each chromosome
442 (**Supplementary Table 16**).
443

## Methods

### The DENTIST test-statistic

Given an ancestrally homogeneous sample and a genotype matrix **X** consisting of *n* unrelated individuals genotyped/imputed at *m* variants, an association study is carried out at each variant by performing a linear regression between the variant and a phenotype of interest. This provides a set of summary data that include the estimate of variant effect, the corresponding standard error, and thereby the z-statistic. Under the null hypothesis of no association, the z-scores of *m* variants follow a multivariate normal distribution, $\boldsymbol{Z} \sim MVN(\mathbf{0}, \boldsymbol{\Sigma})$ with $\boldsymbol{Z} = (Z_1, Z_2, \dots, Z_m)$, with $\boldsymbol{\Sigma}$ a LD correlation matrix of the variants.

The aim of this method is to test the difference between the z-statistic of a variant and that predicted from adjacent variants. To do this, we use a sliding window approach to divide genome into 2Mb segments with a 500kb overlap between one another and randomly partition the variants in a segment into two subsets, S1 and S2, with similar numbers of variants. We then use variants in S2 to predict those in S1 and vice versa. According to previous studies[10,11] , the distribution of z-statistic of a variant *i* from S1, conditional on the observed z-scores of a set of variants from S2 is

$$Z_i|\mathbf{Z}_{\boldsymbol{t}} = \mathbf{z}_{\boldsymbol{t}} \sim N(\boldsymbol{\Sigma}_{\boldsymbol{it}}\boldsymbol{\Sigma}_{\boldsymbol{tt}}^{-1}\,\mathbf{z}_{\boldsymbol{t}},\ \Sigma_{ii} - \boldsymbol{\Sigma}_{\boldsymbol{it}}\boldsymbol{\Sigma}_{\boldsymbol{tt}}^{-1}\boldsymbol{\Sigma}_{\boldsymbol{it}}') \quad (1),$$

where $\boldsymbol{\Sigma}_{\boldsymbol{it}}$ denotes the correlation of z-scores between variant *i* from S1 and variants $\boldsymbol{t}$ from S2, and $\boldsymbol{\Sigma}_{\boldsymbol{tt}}$ is the correlation matrix of variants $\boldsymbol{t}$. We use the correlation matrix calculated from an ancestry-matched reference sample (denoted by **R**) to replace that in the discovery sample if individual-level genotypes of in the discovery GWAS are unavailable. In this case, **Equation 1** can be rewritten as

$$Z_i|\mathbf{z}_{\boldsymbol{t}} \sim N(\mathbf{R}_{\boldsymbol{it}}\mathbf{R}_{\boldsymbol{tt}}^{-1}\,\boldsymbol{z}_{\boldsymbol{t}}, \mathbf{1} - \mathbf{R}_{\boldsymbol{it}}\mathbf{R}_{\boldsymbol{tt}}^{-1}\mathbf{R}_{\boldsymbol{it}}') \quad (2).$$

We can use $E(Z_i|\mathbf{z}_{\boldsymbol{t}})$ as a predictor of $Z_i$, i.e., $\tilde{z}_i = \mathbf{R}_{\boldsymbol{it}}\mathbf{R}_{\boldsymbol{tt}}^{-1}\,\boldsymbol{z}_{\boldsymbol{t}}$, and can therefore use the test-statistic below to test the difference between the observed and predicted z-scores

$$T_{d(i)} = (z_i - \mathbf{R}_{\boldsymbol{it}}\mathbf{R}_{\boldsymbol{tt}}^{-1}\,\boldsymbol{z}_{\boldsymbol{t}})^2/(\mathbf{1} - \mathbf{R}_{\boldsymbol{it}}\mathbf{R}_{\boldsymbol{tt}}^{-1}\mathbf{R}_{\boldsymbol{it}}') \quad (3)$$

which approximately follows a $\chi^2$ distribution with 1 degree of freedom. A deviation of $T_{d(i)}$ from $\chi_1^2$ can be attributed to 1) errors in the summary data; 2) errors in the reference data; or 3) heterogeneity between the two data sets. Using **Equation 3**, the test statistic $T_d$ can be calculated for each variant in S1 given z-scores from S2. As in previous studies[10,11], the method is derived under the null hypothesis of no association, but the test-statistics are well calibrated in the presence of true association signals (**Supplementary Figure 2**).

### The iterative partitioning approach

One challenge of using **Equation 3** is that errors in $\mathbf{z}_t$ or discrepancy between $\mathbf{R}_{it}$ and $\mathbf{\Sigma}_{it}$ can affect the accuracy of predicting $\tilde{z}_i$. To mitigate this, we use an iterative partitioning approach. That is, in each iteration, we randomly partition the variants into two sets, S1 and S2, predict the z-statistic of each variant in S1 using its adjacent variants in S2 and vice versa, and run the $T_d$ test to remove a small fraction of variants with $P_{\text{DENTIST}} < 5\times10^{-8}$ (capped at 0.5% variants with the smallest $P_{\text{DENTIST}}$ if more than 0.5% of the variants exceeding this threshold). The default number of iterations is set to 10. In this iterative process, variants with very large errors or LD heterogeneity between the discovery and LD reference samples are prioritized for removal in the first few iterations so that the prediction accuracy increases in the following iterations. After the iterations are completed, any SNPs with $P_{\text{DENTIST}} < 5\times10^{-8}$ are removed in the final step.

**Accounting for sampling noise in LD**

A simple replacement of the LD correlation matrix $\mathbf{\Sigma}$ by $\mathbf{R}$ introduces additional noises, which can inflate $T_d$, because the sampling variations in $\mathbf{R}$ differ from those $\mathbf{\Sigma}$. Therefore, we adopt a truncated singular value decomposition (SVD) approach used in a previous study[13] to suppress the sampling noises. The essential idea was to remove variance components of $\mathbf{R}_{tt}$ that corresponded to the smallest singular values in SVD, as these variance components were likely to be induced by sampling noises. Given the equivalence between SVD and eigen decomposition of $\mathbf{R}_{tt}$, we perform pseudoinverse of $\mathbf{R}_{tt}$ using eigen decomposition, set small eigen values to 0, and retain only $k$ components with large eigen values.

$$\mathbf{R}_{it}\mathbf{R}_{tt}^{-1}\,\boldsymbol{z}_t = \mathbf{R}_{it}\mathbf{R}_{tt}^{+}\,\boldsymbol{z}_t = \textstyle\sum_{\mathbf{1..k}} 1/w_k(\mathbf{R}_{it}\boldsymbol{v}_k)(\boldsymbol{v}_k'\boldsymbol{z}_t) \quad (4)$$

$$\mathbf{R}_{it}\mathbf{R}_{tt}^{-1}\mathbf{R}_{it}' = \mathbf{R}_{it}\mathbf{R}_{tt}^{+}\mathbf{R}_{it}' = \textstyle\sum_{\mathbf{1..k}} 1/w_k(\mathbf{R}_{it}\boldsymbol{v}_k)^2 \quad (5)$$

$\mathbf{R}_{tt}^{+}$ denotes the pseudo inversion of $\mathbf{R}_{tt}$. The scalars $w_1,\ldots w_k$ correspond to the largest $k$ eigenvalues, and vectors $\boldsymbol{v}_1\ldots\boldsymbol{v}_k$ are the corresponding $k$ eigenvectors. Given $q$ = rank ($\mathbf{R}_{tt}$), the suggested value of $k$ is $k \ll q$. Let $\theta_k = k/q$. We show by simulation that $\theta_k = 0.5$ appears to be a good choice meanwhile a large reference sample size (e.g., $n_{\text{ref}} \geq 5000$) is need (**Supplementary Figure 2**). This pseudoinverse also prevents the problem of rank deficiency due to strongly correlated variants when computing $\mathbf{R}_{tt}^{-1}$.

According to the term $\mathbf{R}_{it}\mathbf{R}_{tt}^{-1}\,\boldsymbol{z}_t$ in **Equation 3**, which is a weighted sum of multiple z-scores, a variant displaying a strong correlation with $i$ can overrule the information from the rest of the variants in S2. This would affect the robustness of our method. Therefore, we prune the variants for LD with an $r^2$ threshold of 0.95 (note: we do not actually remove variants in this case). For a set of variants in high LD ($r^2 > 0.95$), variants pruned out by this pruning process are assigned with the same $T_d$ value as that of the variant retained.

515

516 **Genotype data sets**

517 This study is approved by the University of Queensland Human Research Ethics Committee
518 (approval number: 2011001173). A summary of the genotype data sets used in this study as well
519 as their relevant information can be found in **Supplementary Table 1**. These data are from four
520 GWAS cohorts of European descendants, including the Health Retirement Study (HRS)[32],
521 Atherosclerosis Risk in Communities (ARIC) study[33], UK10K[27], and UK Biobank (UKB)[29]. The
522 samples were genotyped using either WGS or SNP array technology (**Supplementary Table 1**).
523 Imputation of the UKB data had been performed in a previous study[49] using the Haplotype
524 Reference Consortium (HRC)[34] and UK10K reference panels[29,50]. We used different subsets of the
525 imputed UKB data as the LD reference in this study, denoted with the prefix "UKBv3", such as
526 UKBv3-unrel (all the unrelated individuals of European ancestry, n = 348,577), UKBv3-329K (a
527 subset of 328,577 individuals of UKBv3-unrel), UKBv3-20K (another subset of 20,000 individuals
528 of UKBv3-unrel, independent of UKBv3-392K) and UKBv3-8K (a subset of 8,000 individuals of
529 UKBv3-20K). HRS, ARIC and UK10K cohorts were imputed to the 1KGP reference panel in prior
530 studies[28,30], and a subset of 8000 unrelated individuals from UKB were imputed to the 1KGP
531 reference panel in this study (referred to as UKB-8K-1KGP). The UK10K variants in common with
532 those on an Illumina CoreExome array were used for 1KGP imputation[30]. The imputation dosage
533 values were converted to best-guess genotypes in all the data sets except for UKBv3-all, in which
534 the hard-called genotypes were converted from the imputation dosage values using PLINK2 --
535 hard-call-threshold 0.1 (Ref[51]). For all the data set, standard QCs were performed to remove
536 variants with HWE test *P*-value < $10^{-6}$, imputation INFO score <0.3, or MAF < 0.001. Since the hard-
537 called genotypes had missing values, in UKBv3 and its subsets, we further removed variants with
538 missingness rate > 0.05.

539

540 **Genome-wide association analysis for height using the UKB data**

541 We performed a genome-wide association analysis for height using the genotype data of UKBv3-
542 329K, i.e., all the unrelated individuals of European ancestry in the UKB (n=328,577) except for
543 20000 individuals randomly selected to create a non-overlapping reference sample (i.e., UKBv3-
544 20K). The height phenotype was pre-adjusted for sex and age. We conducted the association
545 analysis using the simple linear regression model in fastGWA[52] with the first 10 principle
546 components (PCs) fitted as covariates.

547

548 **Data availability**

549 All the data sets used in this study are available in the public domain (**Supplementary Table 12**).

550

551 **Code availability**

552 The software tool DENTIST was written in C++ as a command-line tool. The source code and
553 pre-compiled executable for 64-bit Linux distributions are available at https://github.com/Yves-
554 CHEN/DENTIST/.

555

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562

563 **Author Contributions**

564 JY conceived and supervised the study. WC, ZZh and JY developed the method. WC, YW, ZZh, and
565 JY designed the experiment. WC performed the simulations and data analyses under the
566 assistance and guidance from YW, ZZl, TQ, PMV, ZZh and JY. WC developed the software tool.
567 PMV and JY contributed funding and resources. WC and JY wrote the manuscript with the
568 participation of all authors. All authors reviewed and approved the final manuscript.

569

570 **Competing Interests**

571 The authors declare no competing interests.

572

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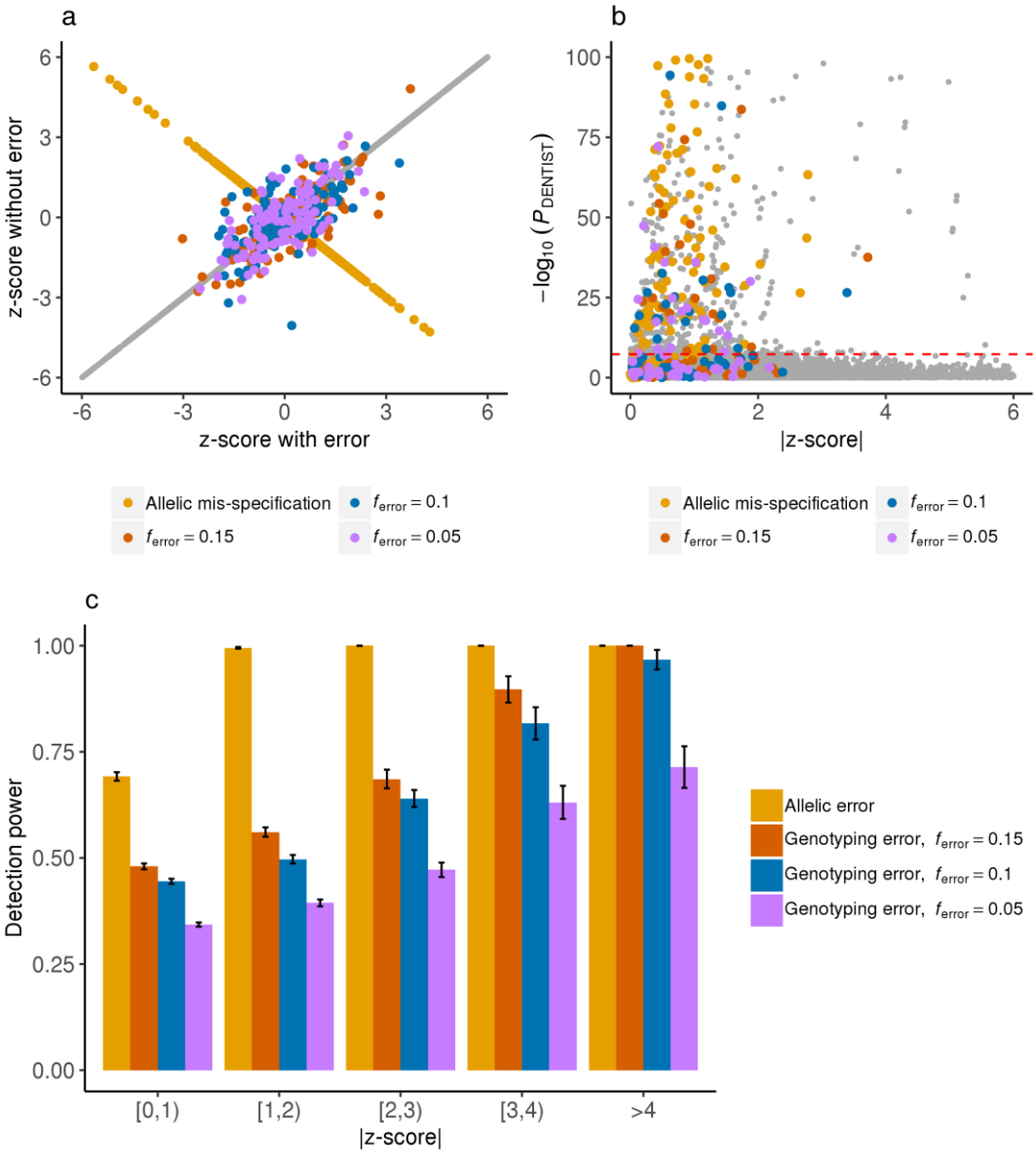


**Figure 1. Detecting simulated allelic and genotyping errors using DENTIST.** We assessed the power of DENTIST in detecting allelic and genotyping errors. There are three levels of genotyping error rate ($f_{error}$=0.15, 0.1 or 0.05), defined as the proportion of individuals with erroneous genotypes for a variant. Panel a) is a plot of the GWAS z-scores from data with simulated errors against those from data without such errors. The gray dots in the diagonal represents z-scores of variants without errors. In panel b), the DENTIST *P*-values are plotted against the absolute values of the GWAS z-scores for all the variants. The horizontal dashed line corresponds to $P = 5 \times 10^{-8}$. In panel c), to demonstrate the power in each |z-score| bin, we pooled the results from 200 simulations. Each bar plot (+/- s.e.) represents power computed from the pooled results.

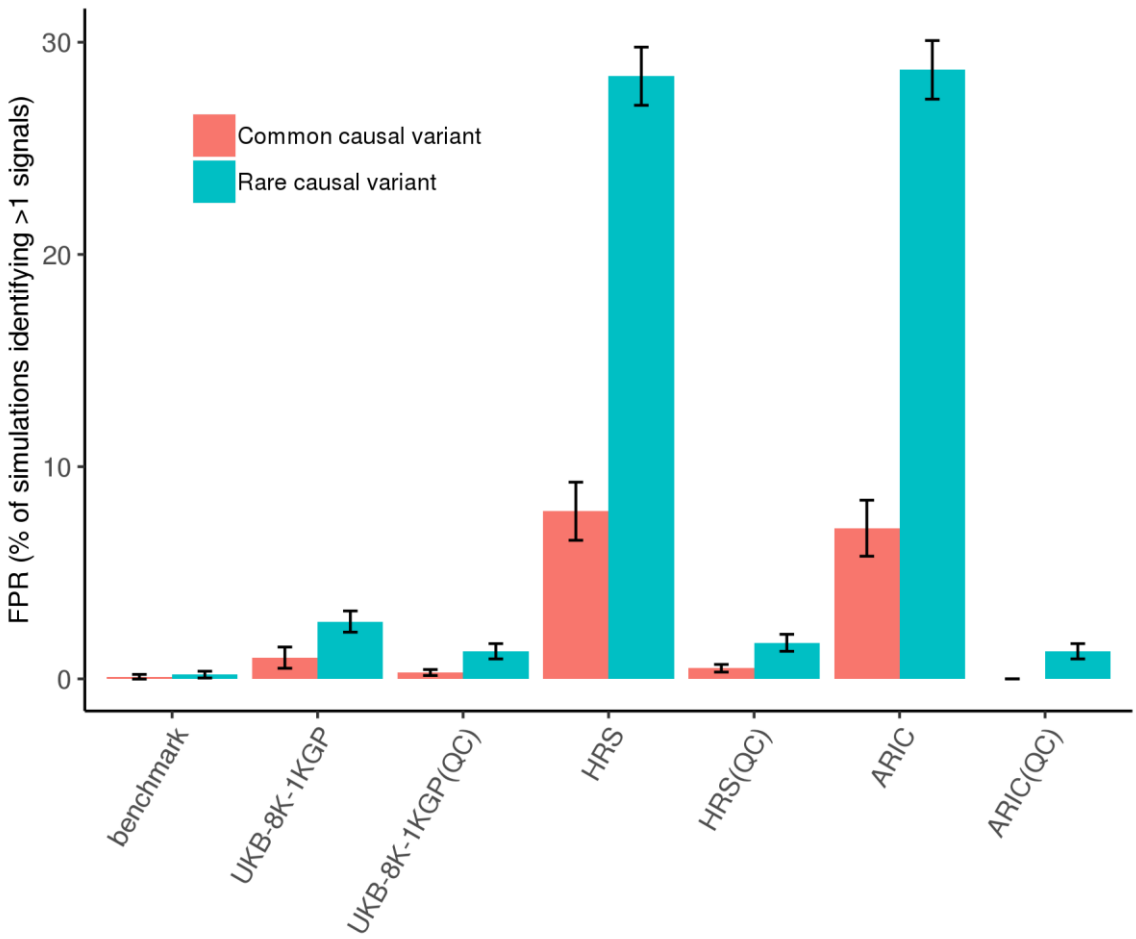


**Figure 2. FPRs of COJO with and without DENTIST.** Based on simulations with one causal signal, we assessed the FPRs of COJO analyses when performed with and without DENTIST-based QC (FPR is defined as the frequency of observing more than one COJO signals in the scenario in which only one causal variant was simulated). The x-axis labels indicate the LD reference samples used in the COJO analyses, and those performed after DENTIST QC are labeled with "QC" in the parentheses. The error bars correspond to the standard error of FPRs calculated from 2200 replications, each with a re-sampled causal variant.

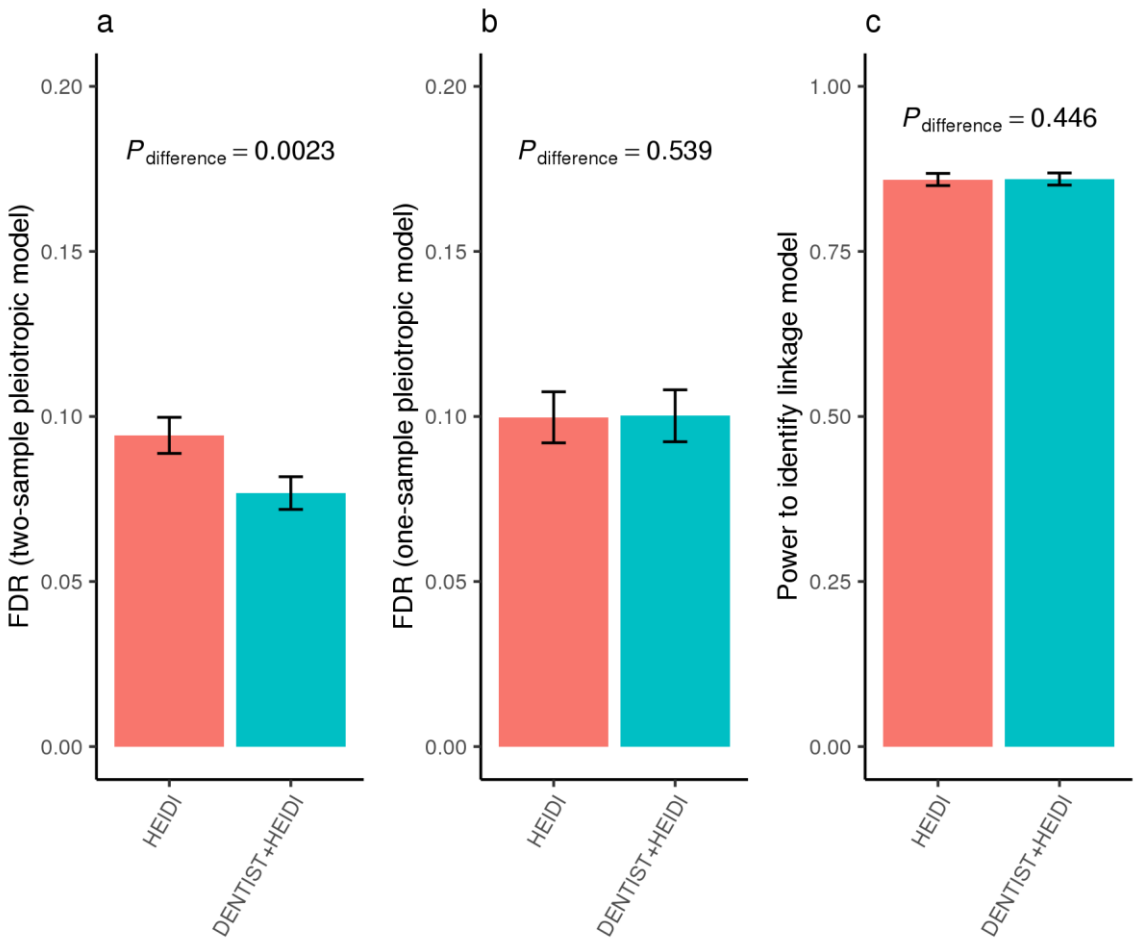


**Figure 3. FPRs and power of the HEIDI test with and without DENTIST**. Shown are the results from simulations to quantify the FPR of HEIDI under a pleiotropic model (panels **a** and **b**) and the power of HEIDI under a linkage model (panel **c**). The two-sample pleiotropic model in panel **a** refers to the scenario where the eQTL and GWAS summary data were simulated based on two different samples (HRS-3K and ARIC). The one-sample scenario in panel **b** refers to the scenario where the GWAS and eQTL data were simulated using the same sample (HRS-3K). In both scenarios, an independent sample (UK10K-1KGP) was used as the LD reference. $P_{\text{difference}}$ is to test if the FPR after QC is significantly different that without QC. $P_{\text{difference}}$ is calculated from a posterior distribution of $k_1 \sim$ Binomial $(n, p)$ with $p$ from a prior distribution of $p \sim Beta(k_2, n - k_2)$, where $n$ is the number of simulation replicates, and $k_1$ and $k_2$ are the numbers of simulation replicates in which the HEIDI test correctly identified the right model with and without the DENTIST-based QC, respectively. The error bars correspond to the standard errors of the correspond metrics calculated from 4000 replications with re-sampled causal variants.

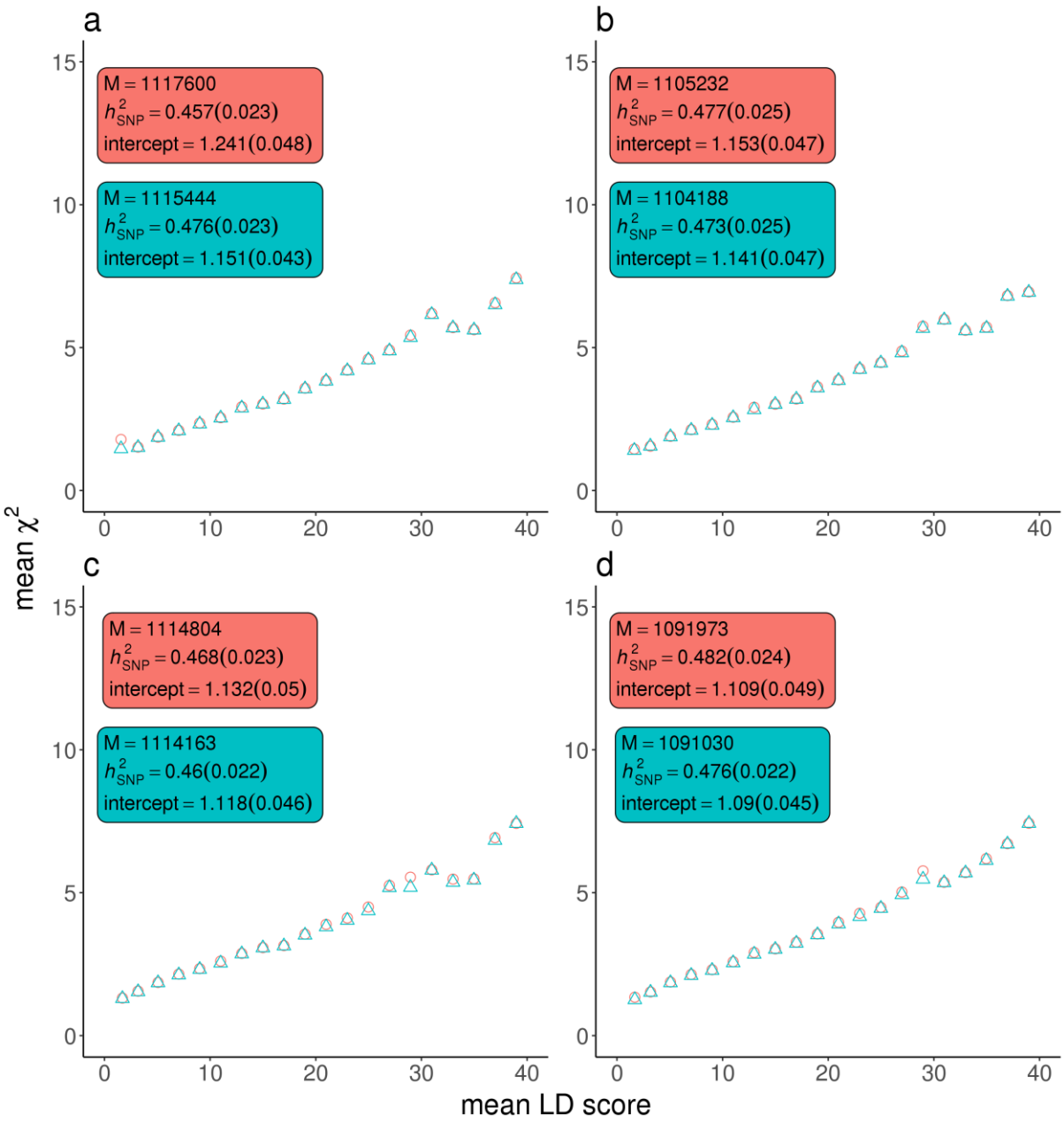


**Figure 4. The effect of DENTIST-based QC on LDSC analysis of the UKB height summary data.** We assessed the effect of DENTIST on LDSC when different LD references were used, including **a**) HRS, **b**) ARIC, **c**) UKB-8K-1KGP, and **d**) UK10K-WGS. For each reference sample, LDSC was performed before and after DENTIST-based QC, and the corresponding results are shown in the red and cyan text boxes, respectively, on each plot. The variants are binned by their LD scores. Each dot on the plots represents the mean LD score value of each bin on the x-axis and the mean $\chi^2$ value on the y-axis, with those before and after DENTIST-based QC in red and cyan colors respectively. In the textbox, "M" represents the number of variants, "$h^2_{SNP}$" represents the estimate of SNP-based heritability, and "intercept" represents the LDSC intercept, with the corresponding standard errors given the parentheses.

733 **Table 1.** FPRs and power of COJO before and after DENTIST-based QC in simulations.

| Analysis method (LD reference) | FPR (%) | | Power (%) | |
|---|---|---|---|---|
| | Common-causal | Rare-causal | Common-causal | Rare-causal |
| Benchmark | 0.1 ± 0.11 | 0.2 ± 0.16 | 78.8 ± 0.9 | 30.6±1.4 |
| COJO without DENTIST (UKB-8K-1KGP) | 1.0 ± 0.50 | 2.7 ± 0.50 | 79.0 ± 0.9 | 28.6±1.9 |
| COJO with DENTIST (UKB-8K-1KGP) | 0.3 ± 0.14 | 1.3 ± 0.36 | 77.3 ± 0.9 | 22.2±1.6 |
| COJO without DENTIST (HRS) | 7.9 ± 1.37 | 28.4 ± 1.37 | 81.8±3.9 | 27.7±1.4 |
| COJO with DENTIST (HRS) | 0.5 ± 0.18 | 1.7 ± 0.40 | 81.2±1.3 | 16.8±1.1 |
| COJO without DENTIST (ARIC) | 7.1 ± 1.32 | 28.7 ± 1.38 | 77.6±0.9 | 26.7±1.7 |
| COJO with DENTIST (ARIC) | 0 ± 0.00 | 1.3 ± 0.36 | 75.8 ± 0.9 | 17.1±1.4 |

734 Benchmark: COJO analysis using the discovery GWAS as the reference without DENTIST. Shown
735 are mean ± standard error.

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737

738 **Table 2.** Numbers of COJO signals from analyses of the UKB height summary data using different
739 LD reference samples with and without DENTIST-based QC.

| | **Benchmark** | **UKBv3-20K (n = 20,000)** | **UKBv3-8K (n = 8,000)** | **HRS (n = 8,557)** | **ARIC (n = 7,703)** | **UK10K-WGS (n = 3,642)** |
|---|---|---|---|---|---|---|
| MAF > 0.01 Without DENTIST | 1279 | 1296 (1.3%) | 1337 (4.5%) | 1477 (15.5%) | 1485 (16.1%) | 1417 (10.8%) |
| MAF > 0.01 With DENTIST | / | 1300 (1.6%) | 1319 (3.1%) | 1338 (4.6%) | 1353 (5.8%) | 1413 (10.5%) |
| MAF > 0.001 Without DENTIST | 1310 | 1313 (0.2%) | 1337 (2.0%) | 1555 (18.7%) | 1645 (25.6%) | 1473 (12.4%) |
| MAF > 0.001 With DENTIST | / | 1326 (1.2%) | 1326 (1.2%) | 1346 (2.7%) | 1398 (6.7%) | 1421 (8.5%) |

740 Benchmark: COJO analysis using the discovery GWAS (UKBv3-329K) as the reference without
741 DENTIST. The inflation rate as compared to the benchmark is shown in the parentheses.
742

743 **Table 3.** Estimates from LDSC analyses of the UKB height GWAS summary data with and without
744 DENTIST-based QC.

| | Number of variants | One-step approach | | Two-step approach | |
|---|---|---|---|---|---|
| | | $h^2_{SNP}$ | Intercept | $h^2_{SNP}$ | Intercept |
| **Reference = the discovery GWAS sample** | | | | | |
| Benchmark | 1114780 | 0.46 (0.023) | 1.13 (0.049) | 0.41(0.017) | 1.34 (0.030) |
| **Reference = HRS** | | | | | |
| Without DENTIST | 1117600 | 0.45 (0.022) | 1.24 (0.047) | 0.42 (0.018) | 1.36 (0.028) |
| With DENTIST | 1116249 | 0.46 (0.022) | 1.15 (0.040) | 0.41 (0.017) | 1.35 (0.027) |
| **Reference = ARIC** | | | | | |
| Without DENTIST | 1105232 | 0.47 (0.025) | 1.15 (0.047) | 0.42 (0.018) | 1.34 (0.030) |
| With DENTIST | 1102229 | 0.47 (0.024) | 1.14 (0.047) | 0.41 (0.018) | 1.34 (0.030) |
| **Reference = UKB-8K-1KGP** | | | | | |
| Without DENTIST | 1114804 | 0.46(0.023) | 1.13(0.050) | 0.41 (0.017) | 1.33 (0.030) |
| With DENTIST | 1113260 | 0.46(0.022) | 1.12(0.048) | 0.40 (0.016) | 1.33 (0.030) |
| **Reference = UK10K-WGS** | | | | | |
| Without DENTIST | 1091973 | 0.48 (0.023) | 1.10(0.048) | 0.42 (0.018) | 1.31 (0.029) |
| With DENTIST | 1074399 | 0.47 (0.022) | 1.07 (0.042) | 0.41 (0.016) | 1.30(0.028) |
| **Reference = 1KGP-EUR** | | | | | |
| Without DENTIST | 1133151 | 0.48 (0.024) | 1.15 (0.047) | 0.43 (0.018) | 1.33 (0.028) |
| With DENTIST | 1071447 | 0.40 (0.018) | 1.03 (0.030) | 0.35 (0.014) | 1.22 (0.024) |

745 Standard errors are given in the parentheses.