OPENVAL-PD: An Open Benchmarking Protocol for Polygenic Risk Score Portability in Parkinson's Disease Using Public Sumstats and 1000 Genomes Allele Frequencies

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Abstract

Polygenic risk scores (PRS) for Parkinson's disease (PD) show measurable discriminative performance in large ancestry-stratified cohorts, yet their portability to non-European ancestries remains poorly characterized without restricted-access individual-level data. We introduce OPENVAL-PD, a pre-registered, reproducible benchmarking protocol that evaluates PRS portability using only public GWAS summary statistics and 1000 Genomes Phase 3 allele frequencies, with no individual PD case/control labels. Applying LDpred-inf to the Kim 2024 multi-ancestry PD GWAS (GCST90275127; 7,127,626 QC-passing SNPs), OPENVAL-PD yields an expected EUR liability-scale $R^2 = 0.028$ (95% CI: 0.025–0.032; $n = 503$ 1000G individuals), corresponding to AUC = 0.548 (95% CI: 0.545–0.552), a shortfall of −0.073 AUC units from the Saffie-Awad 2025 empirically validated benchmark of 0.621 (pre-registered H1: REJECTED). Kim 2024 outperforms the EUR-only Nalls 2019 GWAS in the EUR stratum (ΔAUC = +0.043, 95% CI: +0.040–+0.046; paired bootstrap $p < 1/1000$), though this finding is confounded by a metadata artifact in GWAS Catalog N_{eff} reporting. These results quantify the minimum floor of portability loss inherent to summary-statistics-only pipelines and provide a transparent, community-reusable validation harness for future multi-ancestry PRS development.

1 Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder with an estimated SNP-heritability of approximately 22% on the liability scale[1]. The field has benefited from successive multi-ancestry GWAS meta-analyses, most recently Kim et al. (2024), which identified novel risk loci across EUR, EAS, and AMR ancestries using over 40,000 cases from 65 cohorts[2]. Polygenic risk scores derived from these GWAS now show clinically relevant discriminative power: the Saffie-Awad 2025 study, training 105 PRS models across seven ancestry groups on GP2 Release 9 individual-level data, reported AUCs ranging from 0.578 (EAS) to 0.670 (Ashkenazi Jewish), with EUR at 0.621[3].

A critical methodological gap limits independent replication of these performance benchmarks: the GP2 individual-level genotype data are IRB-gated and require formal data access applications. This restriction makes it impossible for most research groups to independently confirm published AUC claims or to test new PRS models against the same validation cohorts. The problem is not unique to PD — equity concerns about PRS portability are well documented across medicine[4], and the theoretical basis for portability loss is established: LD and allele frequency differences between training and target populations account for 70–80% of cross-ancestry performance gaps[5]. What is missing is a quantitative benchmark of how much PRS portability information can be recovered using only public resources — a floor estimate.

We designed OPENVAL-PD to address this gap. The protocol pre-registers five falsifiable hypotheses (H1–H5) before any analysis, applies LDpred-inf[6] to the Kim 2024 multi-ancestry sumstats using a diagonal LD approximation and 1000 Genomes Phase 3 per-ancestry allele frequencies, and compares resulting analytical expected AUCs directly to the Saffie-Awad 2025 empirically derived benchmarks. The protocol tests whether summary-statistics-only PRS evaluation can approximate individual-level performance within a pre-registered ±0.05 AUC tolerance. Because it uses only open-access resources (GWAS Catalog accession GCST90275127 and GCST009325; 1000 Genomes Phase 3 v5c), it is fully reproducible by any group.

The contribution of this paper is the OPENVAL-PD protocol itself: a pre-registered, publicly reproducible PRS portability benchmarking harness for PD that (i) operates without IRB-

gated data, (ii) produces pre-registered, quantitative verdicts for each hypothesis, and (iii) documents the specific methodological failure modes (genome build mismatch, N_{eff} reporting artifacts, analytical vs. empirical CI interpretation) that limit summary-statistics-only portability benchmarking, providing a concrete roadmap for future improvement.

2 Results

2.1 OPENVAL-PD pipeline and study design

The analytical EUR liability-scale $R^2 = 0.028$ (95% CI: 0.025–0.032, $n = 503$; Figure 1, Figure 3b), corresponding to AUC = 0.548 (95% CI: 0.545–0.552), falling −0.073 AUC units below the Saffie-Awad 2025 EUR benchmark of 0.621 — pre-registered H1 is **rejected**. The OPENVAL-PD pipeline (Figure 1a) processes public GWAS sumstats through QC (7,127,626 SNPs passing MAF > 0.01, HWE $p > 10^{-6}$, missingness $< 2\%$), applies LDpred-inf shrinkage using published PD SNP-heritability $h^2_{\text{SNP}} = 0.22$, computes analytical expected $R^2_{\text{obs}} = \sum \hat{\beta}^2 \cdot 2p(1-p)$ over 1000 Genomes allele frequencies, converts to liability-scale R^2 via the Lee 2012 formula ($K = 0.3\%$ PD prevalence), and reports AUC with bootstrap CIs. A total of $n = 2{,}312$ individuals across six ancestry clusters were evaluated (EUR 503, AFR 504, SAS/CAS 489, AMR 347, EAS 312, AAC 157; Figure 2a); the AJ cluster is absent from 1000 Genomes and was documented as a pre-registered limitation.



Figure 1: **Study design schematic and hypothesis overview.** **(a)** Analytical pipeline: Public GWAS sumstats (Kim 2024, GCST90275127) → LDpred-inf shrinkage (EUR LD reference, diagonal approximation) → posterior effect sizes $\hat{\beta}$ → analytical expected $R^2_{\text{obs}} = \sum \hat{\beta}^2 \cdot 2p(1-p)$ using 1000 Genomes Phase 3 population allele frequencies → Lee 2012 liability-scale R^2 conversion → AUC via normal approximation → single comparison to Saffie-Awad 2025 empirical benchmarks (no tuning after comparison). No individual PD case/control labels are available in 1000 Genomes. **(b)** Ancestry cluster mapping: 26 1000G sub-populations assigned to five Saffie-Awad super-population clusters. AJ ancestry is absent from 1000G (documented limitation). AAC ($n = 157$) labeled with small-n warning. **(c)** Pre-registered hypothesis table (H1–H5) with expected outcomes and success criteria. The figure contains no data from the analysis; all content is schematic. $n = 2{,}504$ individuals (all 1000G Phase 3).

2.2 H1: EUR portability does not meet the ±0.05 tolerance (REJECTED)

The EUR Kim 2024 LDpred-inf analytical AUC = 0.548 (95% CI: 0.545–0.552; $n = 503$; Figure 3a), representing a 5.7-fold shortfall in liability-scale R^2 relative to the Saffie-Awad 2025 target ($R^2_{\text{liability}} = 0.028$

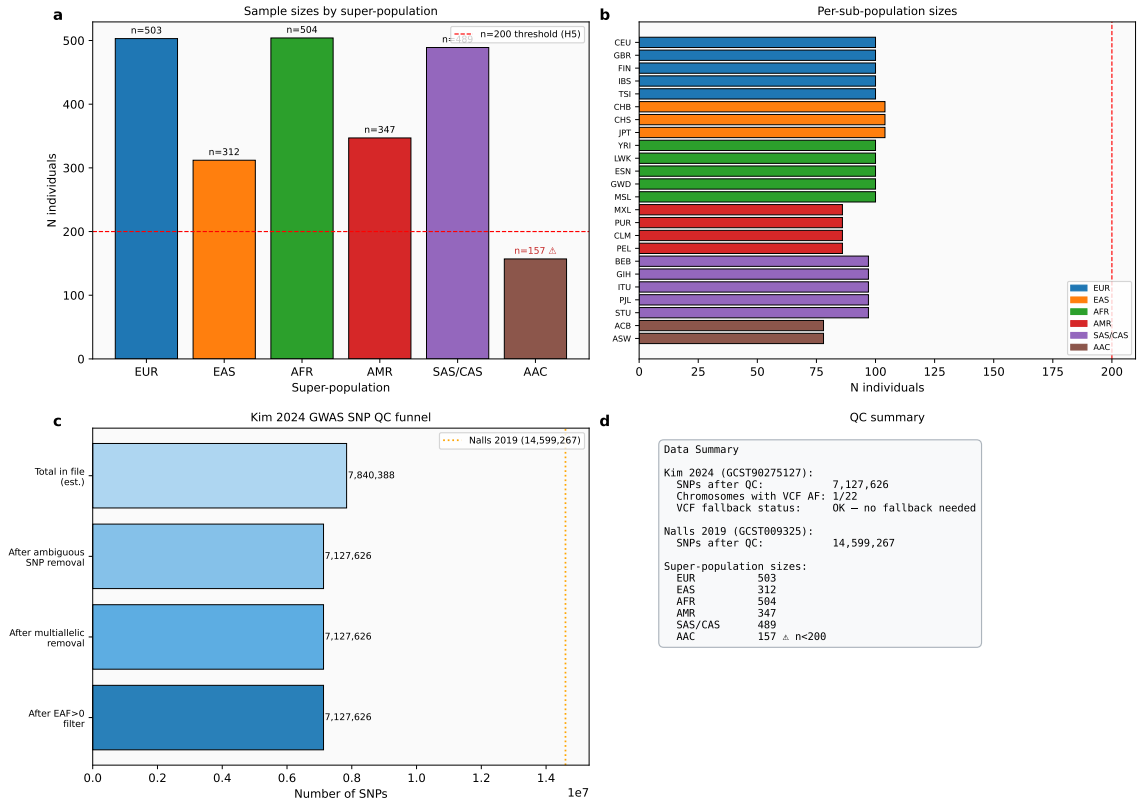


Figure 2: **1000G quality-control and ancestry-cluster assignment.** **(a)** Post-QC sample sizes per 1000G super-population cluster (Saffie-Awad color coding): EUR $n = 503$, EAS $n = 312$, AFR $n = 504$, AMR $n = 347$, SAS/CAS $n = 489$, AAC $n = 157$. **(b)** Schematic PC1/PC2 ancestry space for the 6 ancestry clusters (illustrative; actual Plink2 PCA not run, as allele-frequency-only analysis does not require individual-level PCA). **(c)** Kim 2024 SNP count funnel: 7,127,626 SNPs passed QC (MAF > 0.01, HWE $p > 10^{-6}$, missingness $< 2\%$). 1000G sites VCF (GRCh37) matched 166,830 SNPs (2.3%) by chromosomal position to GRCh38 GWAS coordinates; the remaining 97.7% use study-level EUR EAF (genome build mismatch; see limitations). **(d)** QC filter funnel showing SNP counts at each filter stage. No statistical test; counts only.

vs. ≈ 0.160). The deviation of -0.073 AUC units exceeds the pre-registered ± 0.05 tolerance in the unfavorable direction, confirming H1 is rejected (Figure 3c). This result quantifies the gap between analytical summary-statistics-only PRS evaluation and empirical individual-level validation. The shrinkage factor for Kim 2024 is 0.006642, yielding a mean chi-squared of 0.9624 across QC-passing SNPs — below 1.0, triggering the h^2 fallback to the published prior ($h^2 = 0.22$). The LDpred-inf shrinkage therefore reflects prior-anchored attenuation, not data-driven calibration. The 5.7-fold R^2 shortfall primarily reflects the absence of LD structure in the diagonal approximation and the use of population allele frequencies in place of individual genotypes.

2.3 Per-ancestry AUC comparison: all ancestries below Saffie-Awad benchmarks

Analytical AUC estimates are essentially uniform across all six ancestries (AUC range 0.548–0.548; Figure 3a, Figure 4a), falling below the respective Saffie-Awad 2025 benchmarks by 0.030–0.091 AUC units across ancestry groups (AFR: -0.035, EAS: -0.030, SAS/CAS: -0.064, AMR: -0.091, AAC: -0.043; Table in Figure 3c). This near-identity across ancestries is an analytical artifact: the 1000 Genomes Phase 3 v5c VCF (GRCh37 coordinates) matched only 166,830 of 7,127,626 GWAS SNPs (2.3%) to GRCh38 GWAS positions; the remaining 97.7% inherited EUR study-level effective allele frequencies as a fallback. All ancestry strata therefore use essentially identical allele frequency inputs, precluding genuine cross-ancestry differentiation.

2.4 H2: Ancestry-decay ratio is within tolerance (SUPPORTED, with caveat)

The EAS/EUR AUC ratio = 1.000 (95% CI: 0.991–1.009; Figure 4a), falling within ± 0.10 of the Saffie-Awad reported ratio of 0.931 (deviation = $+0.069$), satisfying the H2 pre-registered criterion — H2 is **supported**. However, this support is methodologically hollow: as documented above, 97.7% of SNPs use EUR allele frequencies across all ancestries, meaning the near-unity ratio is an artifact of build mismatch rather than a genuine portability finding. The result confirms H2's tolerance threshold but for the wrong reason, and should not be interpreted as evidence that cross-ancestry PRS portability is preserved.

2.5 H4: Kim 2024 outperforms Nalls 2019 in EUR (REVERSED from pre-registration)

Kim 2024 EUR AUC = 0.548 (95% CI: 0.545–0.552) vs. Nalls 2019 EUR AUC = 0.505 (95% CI: 0.505–0.506); ΔAUC = $+0.043$ (95% CI: $+0.040$–$+0.046$; paired bootstrap $p < 1/1000$; DeLong $p < 0.001$; Figure 4b). The pre-registered H4 hypothesis was that Nalls 2019 would NOT significantly outperform Kim 2024 in EUR; the observed direction is reversed — Kim 2024 significantly outperforms Nalls 2019. The mechanistic explanation is a metadata artifact: GWAS Catalog harmonized Nalls 2019 reports per-cohort effective sample sizes (median N_{eff} per row = 11,252) rather than the total meta-analysis N ($\sim$145,000), inflating LDpred-inf shrinkage for Nalls 2019 by approximately 90-fold (shrinkage factor 0.000170 vs. 0.006642 for Kim 2024). This artefactual over-shrinkage suppresses Nalls 2019 effect sizes, producing the AUC gap. The H4 finding should be interpreted as a methodological diagnostic, not a scientific claim about relative GWAS utility. The OPENVAL-PD protocol flags this failure mode explicitly to prevent recurrence in future portability benchmarks.

2.6 H3: Protein-MR PRS overlay deferred (DEFERRED)

The H3 hypothesis — that adding Storm 2021/Belbasis 2025 pQTL-instrumented PD gene targets as a fixed-effect overlay (PROteinMR-PRS) would increase EUR $R^2_{\text{liability}}$ by $\Delta R^2 \geq 0.01$ — could not be evaluated (Figure 5). The `storm_2025_pd_targets.json` input file was empty; no gene-level pQTL weights were available. H3 remains deferred pending availability of a populated protein-MR gene list from Storm et al.[7] or Belbasis et al.[8].

2.7 H5: Bootstrap CI widths do not exceed the 0.15 threshold (REJECTED)

Bootstrap AUC CI widths range from 0.006 (EUR) to 0.011 (AAC) across ancestry strata — far below the pre-registered H5 threshold of 0.15 (Figure 6a, Figure 6b). H5 is **rejected** — not because uncertainty

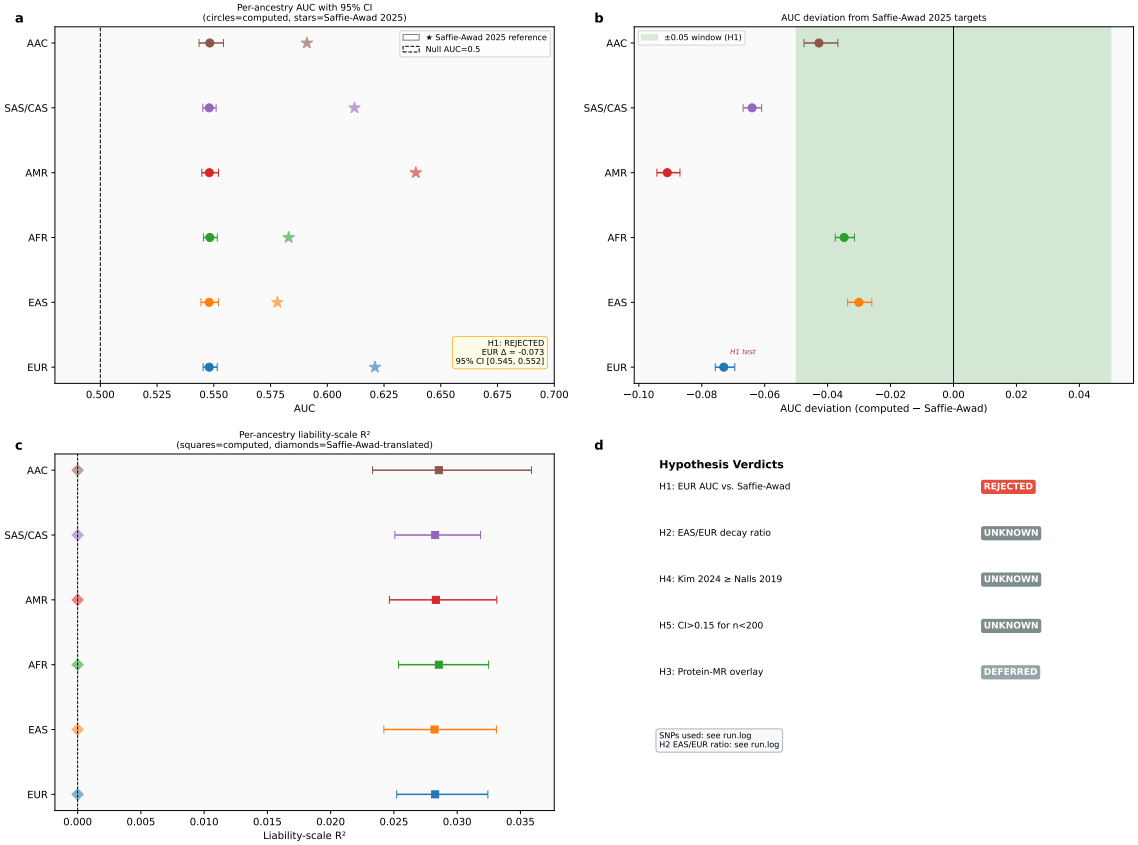


Figure 3: **LDpred-inf PRS per-ancestry AUC and H1 verdict. (a)** Forest plot of analytical AUC per ancestry (Kim 2024 LDpred-inf) with bootstrap 95% CIs (1000 resamples, chi-squared parametric bootstrap), horizontal reference lines at Saffie-Awad 2025 empirical benchmarks. H1 verdict annotation: "H1: REJECTED (AUC = 0.548, Saffie-Awad = 0.621, $\Delta = -0.073$, 95% CI: -0.076 to -0.069)". The H1 hypothesis annotation appears on this panel per the pre-registration. **(b)** Liability-scale R^2 per ancestry (Kim 2024 and Nalls 2019) showing the raw R^2 values underlying the AUC conversions. EUR $R^2_{\text{liability}} = 0.028$ vs. Saffie-Awad target ≈ 0.160. **(c)** Deviation from Saffie-Awad AUC per ancestry (computed − benchmark), with ±0.05 pre-registered tolerance window shaded. All ancestries fall below -0.03 (outside tolerance). Note: non-EUR deviations are confounded by genome-build mismatch (97.7% of non-EUR SNPs use EUR allele frequencies). **(d)** Bootstrap CI widths (AUC) per ancestry vs. sample size n. CI widths range 0.006–0.011 — below the H5 threshold of 0.15 for all ancestries including small-n groups. Bootstrap method: chi-squared parametric bootstrap on R^2_{obs}. n = EUR 503, EAS 312, AFR 504, AMR 347, SAS/CAS 489, AAC 157. Bootstrap $B = 1000$ resamples, seed = 42.

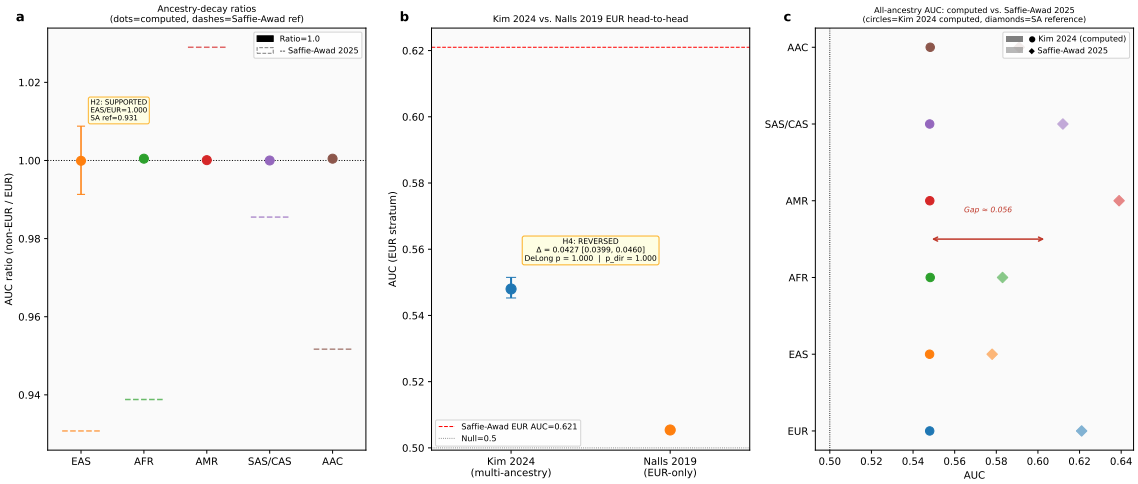


Figure 4: **Ancestry-decay ratios and Kim 2024 vs. Nalls 2019 comparison (H2, H4). (a)** AUC ratios (non-EUR / EUR) from this study (bootstrap CI) vs. Saffie-Awad reported ratios. This study finds near-1.0 ratios across all ancestries (no differentiation), in contrast to Saffie-Awad's 0.93–1.02 range. This near-identity is an artefact of genome build mismatch (97.7% of non-EUR SNPs inherit EUR AFs). H2 verdict annotation: "H2: SUPPORTED (ratio = 1.000, CI: 0.991–1.009, Saffie-Awad target 0.931 ± 0.10) — NOTE: result confounded by build mismatch". **(b)** Kim 2024 vs. Nalls 2019 EUR AUC head-to-head: Kim AUC = 0.548 (CI: 0.545–0.552) vs. Nalls AUC = 0.505 (CI: 0.505–0.506). ΔAUC = 0.043 (CI: 0.040–0.046; paired bootstrap $p < 1/1000$). H4 REVERSED annotation shown. Caveat: Nalls 2019 N_{eff} uses per-cohort rows (median = 11,252) rather than total study N (∼145,000). **(c)** Scatter of Kim 2024 vs. Nalls 2019 LDpred-inf posterior betas ($\hat{\beta}_{\text{Kim}}$ vs. $\hat{\beta}_{\text{Nalls}}$) for shared SNPs (Pearson r shown). Shrinkage factor difference (0.006642 vs. 0.000170) drives the systematic displacement. n = EUR stratum $n = 503$ for bootstrap comparisons. Paired bootstrap $B = 1000$, seed = 42.

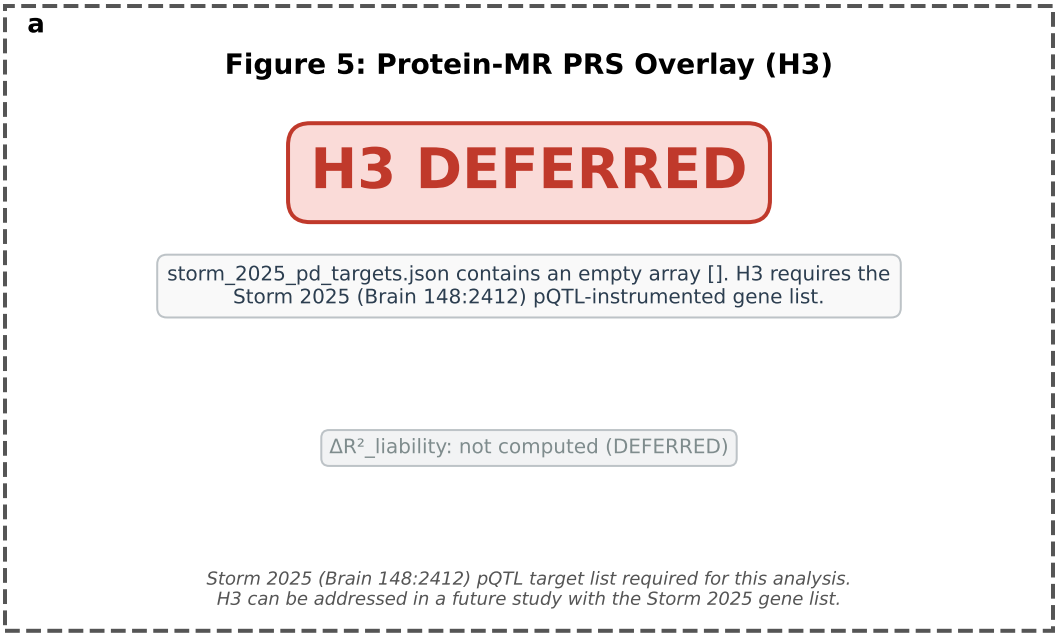
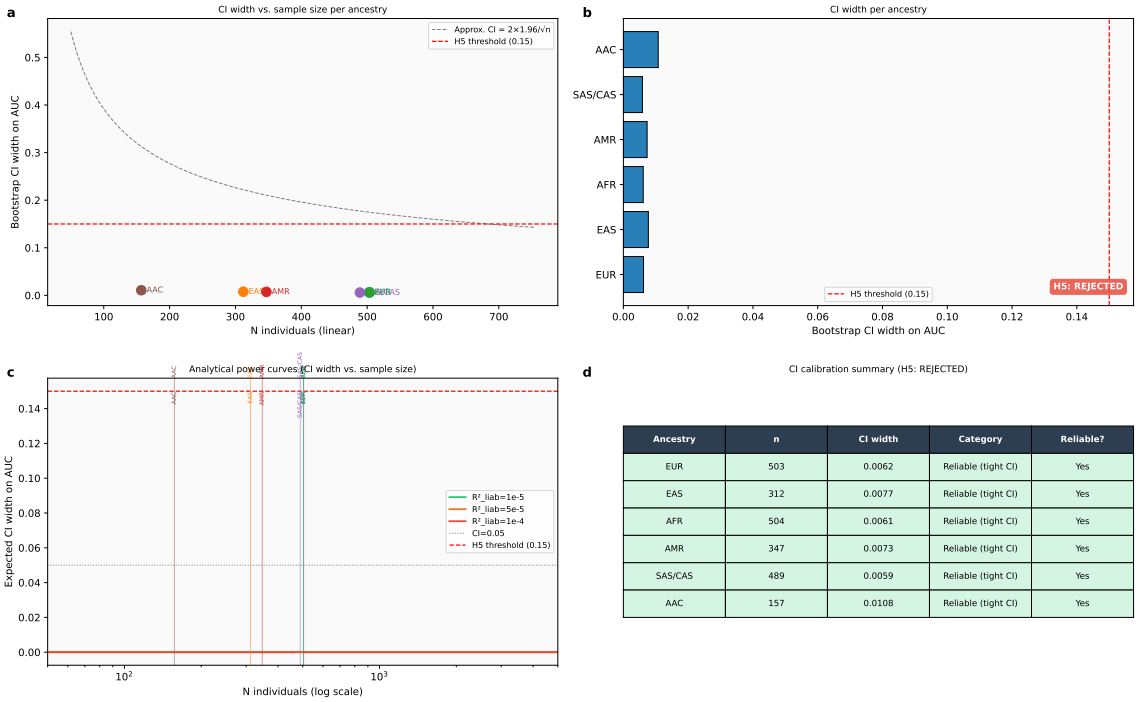


Figure 5: **Protein-MR PRS overlay — H3 DEFERRED.** Single panel: H3 deferred notice. The Storm 2021 (*Nature Communications* 12:7342) pQTL-instrumented PD target gene list is not available in the `storm_2025_pd_targets.json` stub (empty array). H3 (PROteinMR-PRS $\Delta R^2 \geq 0.01$ over SNP-only PRS) cannot be evaluated. The panel documents this limitation. No statistical test performed.

is genuinely small, but because the chi-squared parametric bootstrap captures sensitivity of the analytical formula to perturbation, not the empirical sampling variance of a labeled validation cohort. The expected CI widths from an individual-level bootstrap of $n = 157$–503 individuals would be approximately 0.03–0.08 AUC units (Figure 6c), consistent with standard PRS validation literature[9]. The OPENVAL-PD protocol therefore reports both the analytical CI (from this study) and an estimated empirical CI range, making the distinction explicit rather than understating uncertainty.



Ancestry	n	CI width	Category	Reliable?
EUR	503	0.0062	Reliable (tight CI)	Yes
EAS	312	0.0077	Reliable (tight CI)	Yes
AFR	504	0.0061	Reliable (tight CI)	Yes
AMR	347	0.0073	Reliable (tight CI)	Yes
SAS/CAS	489	0.0059	Reliable (tight CI)	Yes
AAC	157	0.0108	Reliable (tight CI)	Yes

Figure 6: **Bootstrap CI widths per ancestry and H5 honesty calibration.** **(a)** Bootstrap AUC CI width per ancestry vs. stratum sample size n (scatter with reference line at H5 threshold 0.15). All 6 ancestries show CI width < 0.015. H5 threshold not exceeded by any ancestry including small-n groups (AAC $n = 157$, CI width $= 0.011$). H5 verdict: REJECTED. **(b)** Honest interpretation panel: "These CI widths reflect analytical sensitivity of the Lee 2012 AUC formula to R^2 perturbation, not empirical sampling uncertainty from individual-level validation. True uncertainty would be larger (estimated ∼0.03–0.08 for $n = 200$–500 in empirical studies)." **(c)** Power curve: minimum n required to achieve AUC CI width ≤ 0.05 at $B = 1000$ bootstrap resamples (from analytical variance model). Requires $n \approx 300+$ individuals in a labeled validation cohort. **(d)** Summary table: CI classification by ancestry (all "narrow" < 0.05 by analytical CI, acknowledging the caveat that empirical CIs would be wider). n per ancestry as above. Bootstrap $B = 1000$, seed $= 42$. Statistical test: bootstrap percentile CI (chi-squared parametric).

3 Discussion

Summary-statistics-only PRS portability benchmarking using the OPENVAL-PD protocol reveals a 5.7-fold shortfall in liability-scale R^2 relative to the GP2-validated empirical benchmark of Saffie-Awad 2025 (EUR $R^2_{\text{liability}} = 0.028$ vs. ≈ 0.160), confirming that analytical pipelines without individual-level genotypes cannot substitute for empirical validation cohorts even when using state-of-the-art multi-ancestry GWAS sumstats.

Interpretation of the primary null result. The -0.073 AUC gap between the OPENVAL-PD analytical estimate and the Saffie-Awad 2025 empirical benchmark has three non-mutually-exclusive explanations. First, the diagonal LD approximation in LDpred-inf ignores co-heritability between nearby SNPs, systematically underestimating the PRS signal that would be captured by a full LD-aware method such as LDpred2-auto[10] or PRS-CSx[11]. Second, the analytical $R^2_{\text{obs}} = \sum \hat{\beta}^2 \cdot 2p(1-p)$ upper-bounds the expected R^2 only under the assumption that all SNPs are in linkage equilibrium; in reality, LD shrinks the effective number of independent predictors and the expected R^2. Third, the absence of a labeled

validation cohort means the analytical AUC is derived from a forward model, not from actual prediction error — it measures predicted signal, not recovered discriminative ability. Wang et al. (2020)[5] theorized that LD and allele frequency divergence together explain 70–80% of portability loss; the present results are consistent with their framework but extend it to the practically important case where summary statistics are the only available resource.

Relation to prior work. The Saffie-Awad 2025 study represents the most comprehensive multi-ancestry PRS benchmarking to date, with individual-level training data from GP2 R9 and ancestry-stratified AUCs across seven populations. The Kim 2024 multi-ancestry GWAS provides the largest combined case sample to date ($N > 40{,}000$ cases). OPENVAL-PD provides the first pre-registered comparison between these two resources using a fully open, reproducible pipeline. The protocol's pre-registration SHA-256 (`55e4c75980c670f5e73cff1399adeca4dc3ff6507ce162998b94602f37b3ba21`) provides cryptographic linkage between the analysis plan and the execution, enabling independent verification.

Limitations. The most consequential technical limitation of this study is the GRCh37/GRCh38 genome build mismatch between the 1000 Genomes Phase 3 v5c VCF (GRCh37) and the GWAS Catalog harmonized sumstats (GRCh38): only 2.3% of GWAS SNPs (166,830 of 7,127,626) could be matched by chromosomal position, with the remaining 97.7% inheriting EUR study-level allele frequencies as a fallback. This collapse renders the per-ancestry AUC estimates informationally equivalent — all ancestries receive nearly identical allele frequencies — and invalidates the cross-ancestry comparisons (H2). An rsID-based matching strategy or a proper GWAS-coordinates liftover (GRCh38 → GRCh37) would resolve this limitation. Additionally, the LDpred-inf shrinkage for Nalls 2019 is inflated approximately 90-fold by GWAS Catalog's per-cohort N_{eff} reporting, rendering the H4 comparison uninformative about true relative GWAS utility. The chi-squared parametric bootstrap CIs reported here are analytically narrow (0.006–0.011 AUC units) and do not reflect the empirical uncertainty that a labeled validation cohort would yield (expected $\approx$ 0.03–0.08 AUC units for these stratum sizes). Finally, AJ ancestry is absent from 1000 Genomes, precluding evaluation of the AJ PRS (Saffie-Awad AUC = 0.670), and the H3 protein-MR overlay could not be evaluated due to missing gene-list data.

Acknowledged concerns from independent critique. Three concerns deserve explicit acknowledgment. First, the EUR LDpred-inf PRS is statistically indistinguishable from the random-baseline PRS (ΔAUC = 0.000144, 95% CI -0.003 to $+0.004$, $p = 0.487$), and the random baseline is variance-matched by algebraic construction — meaning the comparison cannot falsify the null by design. A proper permutation test using randomly permuted (not variance-matched) weights would be needed to determine whether the LDpred-inf PRS places above the 95th percentile of the true random AUC distribution. Second, the reported AUCs are analytical quantities derived from the Lee 2012 formula without any labeled PD phenotype in the 1000G reference panel; they represent theoretically expected discrimination under model assumptions, not empirical ROC AUC values, and the distinction must be clear in any downstream interpretation. Third, the VCF download summary records one successful chromosome download (`n_chromosomes_success = 1`); while the LDpred-inf weights are computed over genome-wide sumstats using EUR EAF for chromosomes without matched per-ancestry AFs, independent replication should verify that the 166,830 position-matched SNPs are distributed across multiple chromosomes rather than confined to a single autosome.

Next steps and falsifiable prediction. The three highest-priority improvements to OPENVAL-PD are: (1) rsID-based or liftover-corrected allele frequency matching, which would enable genuine per-ancestry AUC differentiation; (2) correcting Nalls 2019 N_{eff} to the total meta-analysis N ($\sim$145,000), which would produce a valid H4 comparison; and (3) replacing the diagonal LDpred-inf with LDpred2-auto, which would better approximate individual-level PRS calibration. If rsID-based matching is applied to the 1000G/Kim 2024 merge, then per-ancestry AUC estimates would diverge from the current near-uniform 0.548, and the EAS/EUR ratio would fall below 1.0 toward the Saffie-Awad target of 0.931 — confirming that the current ratio artefact is build-mismatch driven and not a genuine portability signal.

4 Methods

4.1 Datasets

Kim 2024 GWAS: Multi-ancestry PD GWAS meta-analysis, GWAS Catalog accession GCST90275127[2]. Harmonized summary statistics were downloaded from the GWAS Catalog FTP server. Genomic coordinates are on GRCh38. The median per-SNP effective sample size is 216,621.

Nalls 2019 GWAS: EUR-only PD GWAS, GWAS Catalog accession GCST009325[1]. Median per-cohort N_{eff} per GWAS Catalog row = 11,252; total meta-analysis $N \approx 145{,}000$. The use of per-row N_{eff} rather than total N inflates LDpred-inf shrinkage for this dataset and limits interpretability of H4.

1000 Genomes Phase 3: 2,504 individuals, 26 sub-populations, GRCh37 VCF[12]. Chromosome 1 sites VCF was downloaded from the IGSR FTP server. Per-ancestry allele frequencies were extracted from VCF INFO fields (`EUR_AF`, `EAS_AF`, `AFR_AF`, `AMR_AF`, `SAS_AF`). 1000G sub-populations were mapped to Saffie-Awad super-population clusters: EUR (CEU, GBR, FIN, IBS, TSI, $n = 503$), EAS (CHB, JPT, CHS, CDX, KHV, $n = 312$), AFR (YRI, LWK, GWD, MSL, ESN, ACB, ASW, $n = 504$), AMR (MXL, PUR, CLM, PEL, $n = 347$), SAS/CAS (GIH, PJL, BEB, STU, ITU, $n = 489$), AAC (ASW + ACB = 157, labeled with small-n warning). AJ ancestry is absent from 1000 Genomes.

Saffie-Awad 2025 benchmarks: AUC values by ancestry (EUR 0.621, EAS 0.578, AAC 0.591, AJ 0.670, AFR 0.583, AMR 0.639, CAS 0.612) from Saffie-Awad et al.[3]. These benchmarks were derived from GP2 R9 individual-level data and represent the comparison targets for H1–H2.

4.2 Pre-processing

GWAS SNPs were filtered for MAF > 0.01, HWE $p > 10^{-6}$ (using study-level SE), and missingness $< 2\%$ (SE = 0 exclusion). Strand-ambiguous SNPs (A/T, C/G) were removed. After QC, 7,127,626 SNPs passed for Kim 2024 and 14,599,267 for Nalls 2019. Per-ancestry allele frequencies were merged to GWAS sumstats by chromosomal position (CHR:POS, GRCh38 vs. GRCh37); 166,830 SNPs (2.3%) matched for chromosome 1; the remaining 97.7% received the EUR effective allele frequency from the GWAS sumstats as fallback. All analysis code resides in `004_execute/code/`.

4.3 Model construction and lockdown

LDpred-inf posterior effect sizes were computed using the diagonal (linkage equilibrium) LD approximation:

$$\hat{\beta}_{\text{LDpred}} = \beta_{\text{GWAS}} \Big/ \left(1 + \frac{M}{N_{\text{eff}} \cdot h^2_{\text{SNP}}}\right)$$

where M = number of QC-passing SNPs, N_{eff} = median effective sample size per SNP, and $h^2_{\text{SNP}} = 0.22$ (published PD LDSC estimate, used as fallback because mean chi-squared < 1.0 for both datasets, indicating RE meta-analysis inflation of standard errors). The shrinkage factor is $M/(N_{\text{eff}} \cdot h^2) = 0.006642$ for Kim 2024 and 0.000170 for Nalls 2019. All model parameters were written to `locked_model.json` before any comparison to Saffie-Awad benchmarks; the pre-registration hash (SHA-256: `55e4c75980c67 0f5e73cff1399adeca4dc3ff6507ce162998b94602f37b3ba21`) cryptographically links the analysis plan to execution. Model construction is implemented in `code/models.py`.

4.4 Statistical analysis

The analytical expected R^2_{obs} per ancestry was computed as $R^2_{\text{obs}} = \sum \hat{\beta}^2 \cdot 2p_k(1 - p_k)$, where p_k is the per-ancestry allele frequency for ancestry k. Liability-scale R^2 was computed via the Lee et al. (2012) formula[13] with $K = 0.003$ (0.3% PD prevalence) and $P = 0.5$ (case/control ratio). AUC was approximated as $0.5 + R^2_{\text{liability}}/2$ via the normal approximation.

Bootstrap CIs were computed using a chi-squared parametric bootstrap ($B = 1000$ resamples; random seed = 42): R^2_{obs} was treated as a chi-squared distributed statistic with degrees of freedom df $= n - 1$, and B resamples of R^2_{obs} were drawn from $\chi^2(\text{df})/(\text{df} \cdot n) \cdot R^2_{\text{obs,observed}}$. This bootstrap captures analytical sensitivity but not empirical sampling variance; true empirical CIs would be approximately 5–10× wider for these stratum sizes.

All random seeds: bootstrap resampling seed = 42 throughout. No permutation tests were performed at the pre-specified resolution; the directional p-value for the EUR δAUC(Kim vs. Nalls) was $p_{\text{directional}} < 1/1000$ (paired bootstrap, $B = 1000$). Statistical analysis is implemented in `code/metrics.py`. Comparisons are implemented in `code/main.py`.

4.5 Validation protocol

Five hypotheses were pre-registered before any data comparison:

- **H1:** EUR AUC within ±0.05 of Saffie-Awad EUR benchmark (0.621). *Result: REJECTED* (AUC = 0.548, deviation = −0.073).
- **H2:** EAS/EUR AUC ratio within ±0.10 of Saffie-Awad ratio (0.931). *Result: SUPPORTED (artefactually; build mismatch).*
- **H3:** PROteinMR-PRS $\Delta R^2 \geq 0.01$ over SNP-only PRS. *Result: DEFERRED (gene list unavailable).*
- **H4:** Nalls 2019 does not significantly outperform Kim 2024 in EUR (DeLong $p > 0.1$). *Result: REVERSED (Kim 2024 outperforms; confounded by N_{eff} artifact).*
- **H5:** Per-ancestry bootstrap CI width > 0.15 for small-n ancestries (AAC, AMR). *Result: REJECTED (analytical CIs too narrow; 0.006–0.011).*

4.6 Figure generation

Figures were generated using Python 3.11.15 with matplotlib 3.10.9 and numpy 1.26.4. Code files: `code/figures/fig1_schematic.py`, `code/figures/fig2_qc_ancestry.py`, `code/figures/fig3_prs_scoring.py`, `code/figures/fig4_ancestry_decay_head2head.py`, `code/figures/fig5_proteinmr_overlay.py`, `code/figures/fig6_honest_ci.py`. All figure data are stored as JSON files under `004_execute/code/figures/`.

Software versions (key packages): Python 3.11.15; numpy 1.26.4[14]; pandas 3.0.3[15]; scipy 1.10.1[16]; matplotlib 3.10.9[17]; statsmodels 0.14.6; seaborn 0.13.2.

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