

2.2.3 SumHer (LDAK framework)

The SumHer method, based on the LDAK (Linkage Disequilibrium Adjusted Kinship) framework, extends both GREML and LDSC by incorporating more realistic assumptions about genetic architecture (Speed and Balding, 2019). Its key principle is that SNP contributions to genetic variance depend on: Minor allele frequency (MAF), linkage disequilibrium (LD) structure, and genotype certainty.

Specifically, the SumHer model reflects a more refined characterization of heterogeneity in genetic architecture through its parameterization. Compared with traditional models that assume approximately uniform effect sizes across all loci, SumHer tends to assign greater effect weights to low-frequency variants. In terms of linkage disequilibrium (LD) structure, the model does not treat all SNPs equally; instead, it applies differential weighting based on the local LD environment. In addition, SumHer incorporates uncertainty in genotype calling into its weighting scheme. By introducing genotype certainty, the model can to some extent correct for the influence of sequencing errors or imputation biases, thereby making the estimation of genetic effects more robust.

This modeling framework better reflects empirical genetic architectures and can substantially increase heritability estimates when MAF- or LD-dependent effects are present. For example, in UKB analyses across multiple traits, SumHer estimates are on average ~25% higher than standard GREML and ~38% higher than LDSC (Speed et al., 2017; Speed and Balding, 2019).

2.3 Method comparison design

To enable a more rigorous comparison of the performance differences among various methods in estimating SNP heritability, this study first emphasizes the consistency of the underlying data. All analyses are conducted based on the same sample source and set of genetic variants, specifically using the European ancestry subset from the UK Biobank and restricting SNP selection to those with a minor allele frequency (MAF) greater than 0.01. This approach minimizes external sources of variation during method comparison and enhances the interpretability of differences observed across models (Hou et al., 2019).

On this basis, the study further performs a horizontal methodological comparison, encompassing both individual-level data approaches, such as GREML and GRE, and summary-statistics-based methods, including LDSC, stratified LDSC (S-LDSC), and the extended model SumHer. By integrating these representative methods within a unified analytical framework, it becomes possible to systematically evaluate their differences in heritability estimation from the perspectives of data utilization and model assumptions.

To more intuitively characterize the discrepancies among methods, this study introduces relative difference as a core metric to quantitatively compare the heritability estimates obtained from each approach. This standardized measure of deviation not only mitigates the issue of incomparability at the level of absolute values but also allows systematic biases between methods to be clearly identified. The formula for measuring inter-method deviation based on relative difference is as follows:

$$\text{Relative Difference} = \frac{h_{\text{method}}^2 - h_{\text{reference}}^2}{h_{\text{reference}}^2}$$

At the same time, the study also assessed the robustness of the results through multidimensional sensitivity analyses. Specifically, this included evaluating the impact of different LD reference panels, comparing various SNP selection strategies, and analyzing changes in the estimates after excluding regions with particularly high linkage disequilibrium (such as the major histocompatibility complex, MHC region). These high-LD regions contribute substantially to heritability estimation, and their removal often leads to a marked decrease in the estimated values, thereby indirectly highlighting the important role of local genetic structure in explaining overall genetic variation (Ge et al., 2017).

2.4 Statistical interpretation

The SNP heritability estimates obtained from different methods do not, in essence, correspond to the same statistical parameter; rather, they are constrained by their respective model specifications and data structures,