

structure at the individual level is ignored, which to some extent reduces both the efficiency of information utilization and the precision of estimation (Bulik-Sullivan et al., 2015).

From an interpretative standpoint, therefore, the estimates provided by LDSC are more appropriately understood as an LD-weighted average level of genetic effects, rather than a direct characterization of the total genetic variance.

### 3.3.3 SumHer captures additional variance through flexible modeling

Compared with the two aforementioned methods, SumHer introduces a more flexible weighting scheme within its model specification and therefore tends to yield heritability estimates that are slightly higher than those from GREML (on average about 5% higher), with substantial increases observed for certain traits (up to approximately 38%) (Speed and Balding, 2019). This difference primarily arises from its more realistic modeling of the distribution of SNP effects.

Specifically, SumHer no longer assumes that SNP effects are uniform; instead, it allows them to vary as a function of factors such as minor allele frequency (MAF), linkage disequilibrium (LD) structure, and variant quality. This modeling strategy is consistent with empirical observations of genetic architectures, where low-frequency variants often exhibit larger effect sizes and regions with lower LD are more likely to harbor causal variants. On this basis, SumHer assigns differential weights to different classes of SNPs, thereby improving the overall ability to capture genetic variance.

Taken together, SumHer partially addresses the limitations of traditional GREML and LDSC frameworks in characterizing genetic heterogeneity, enabling it to capture components of genetic variation that were previously underexplained.

### 3.4 Sensitivity to genetic architecture and LD structure

Further analyses based on UK Biobank (UKB) data indicate that SNP heritability is not stable with respect to the genomic background, but instead shows pronounced sensitivity to features of the genetic architecture, particularly patterns of linkage disequilibrium (LD). In practical terms, when researchers deliberately remove regions characterized by strong LD—such as the major histocompatibility complex (MHC)—a substantial decrease in heritability estimates can be observed for certain traits, with reductions exceeding 0.2 in some cases (Ge et al., 2017). This phenomenon suggests that genetic variance is not uniformly distributed across the genome, but is instead concentrated within specific structural regions.

More fundamentally, the estimation of SNP heritability depends on the combined influence of multiple factors, including the extent to which LD enables tagging of causal variants, the density and distribution of genetic markers, and the contribution of variants across different allele frequency spectra. Together, these elements determine the degree to which the observed set of SNPs can “capture” the underlying genetic signal. Accordingly, rather than viewing SNP heritability as an intrinsic and fixed biological parameter, it is more appropriately interpreted as a statistical quantity contingent upon both data structure and methodological assumptions, with its value fundamentally governed by the level of capturability. This perspective is crucial for understanding the inconsistencies in heritability estimates reported across different studies.

### 3.5 Robustness to sampling and participation bias

At the level of sample structure, studies based on the UK Biobank (UKB) have systematically evaluated the impact of participation bias. The results indicate that such bias exerts a relatively substantial influence on downstream statistical measures such as genetic correlation, whereas its effect on SNP heritability itself is comparatively limited, generally remaining within 5% (Schoeler et al., 2023). This contrast suggests that, as a variance decomposition metric, SNP heritability exhibits a certain degree of robustness to sample selection bias at the population level.

However, this robustness does not imply that issues related to sample structure can be disregarded. On the contrary, when the focus shifts to genetic correlation, causal inference, or multi-trait analyses, the systematic