Reviewers' Comments to Author:

Reviewer: 1

Comments to the Author

This study introduced a novel tool, Kinship Decouple and Phenotype Selection (KDPS), designed to address statistical biases arising from genetic relatedness in genomic studies. Notably, KDPS innovated by incorporating phenotype prioritization during the removal of related individuals, aiming to maximize the retention of subjects with target phenotypes (e.g., rare diseases or specific exposures) and thereby enhance statistical power. Overall, this research contributes valuable knowledge to the field, but addressing these concerns will strengthen its impact.

1.The manuscript states: “...sequentially eliminating subjects with the lowest phenotypic weight who are related to more than m−f subjects, where m is the number of related pairs of the subject in the cohort who is related to the most people...” (Page 4, Lines 51–55). However, it remains unclear whether m refers to the initial maximum connectivity or is dynamically updated after each iteration. If m is calculated once from the initial network, the algorithm may fail to adapt to evolving network structures during iterative pruning. If m is dynamically updated (e.g., recalculated after each iteration), the frequency of updates and computational overhead must be explicitly described.

We thank the reviewer for their careful reading and insightful question. We acknowledge that this point was not sufficiently clear in the original manuscript. As suggested, we have clarified that the parameter \*m\* is recalculated dynamically after each iteration, enabling the algorithm to adaptively respond to changes in the evolving network topology. We have revised the manuscript text accordingly to improve clarity: (After each iteration, the algorithm recalculates … as the network is refined).

2.While the study mentions that the fuzziness score (f) is user-configurable and tested values f = 0,1,2,5,10, it did not provide practical guidelines for selecting f based on network density (e.g., sparse vs. dense kinship networks) or phenotype distribution (e.g., rare vs. common phenotypes).

We sincerely appreciate the reviewer’s valuable suggestion. We have now expanded our explanation of the fuzziness score, including practical guidelines for its use. Specifically, we provide examples of typical use cases informed by the distribution of relatedness observed in population-scale datasets. Supplementary Figure S1 introduces the concept of fuzziness score, while Supplementary Figure S2 illustrates empirical statistics of relatedness from a representative biobank-scale cohort. We also added corresponding discussion in the main text: (In most general-purpose large-genome study … prioritize phenotype over topology.)

3.The manuscript mentions that KDPS supports composite scores to handle scenarios with “multiple phenotypes and exposures of interest” but provides no validation in simulated or real-world datasets. This omission undermines the reliability of this feature. To ensure robustness, validation of composite scores should be added.

We thank the reviewer for highlighting this important point. In response, we have added a simulation evaluating the performance of KDPS using a composite phenotype defined from two independent binary traits. The simulation demonstrates KDPS’s ability to prioritize individuals who meet multiple criteria by leveraging composite weights. These results are now reported in the Results and Discussion sections and summarized in Supplementary Table S2: (In more complex scenarios where multiple phenotypes of interest … compared to equal-weight pruning).

Reviewer: 2

Comments to the Author

This study (BIB-25-0577) introduces the Kinship Decouple and Phenotype Selection (KDPS) tool, designed to improve subject selection in genetic and epidemiological research by incorporating phenotype prioritization. While the tool demonstrates promising capabilities, several aspects require further clarification and investigation:

1. Fuzziness Score Selection: The performance of KDPS is influenced by the fuzziness score, but the manuscript does not provide empirical guidance on how to select an optimal value for this score in practice.

We thank the reviewer for their thoughtful observation. We have added detailed explanation of the fuzziness score concept and provided practical guidelines for its application. These additions are supported by Supplementary Figure S1, which illustrates how fuzziness affects network topology, and Supplementary Figure S2, which summarizes population-level relatedness patterns. The revised manuscript text reflects this context: (In most general-purpose large-genome study … prioritize phenotype over topology.)

2. Simplistic Simulation Framework:

The simulation process lacks detail, particularly regarding the generation of simulated phenotypes. Key parameters—such as the distribution of genetic effects and heritability—are not described, raising concerns about the robustness of the benchmarking results.

We thank the reviewer for this important feedback. To address this, we have expanded the description of the simulation framework in both the Methods and Results sections. We now include greater detail on how the kinship matrix was derived (by anonymizing and adapting the real UK Biobank kinship structure) and how phenotypes were simulated. Furthermore, Table 1 has been revised to detail the parameters used in phenotype simulations. Simulation results evaluating KDPS on binary, categorical, and continuous traits have been added: (For simulations, a complex relatedness network … can be found in Table 1). (In the evaluation of the performance of KDPS … and the mean by 0.09%)

3. Impact of Phenotype Heritability:

The manuscript does not address how the heritability of a phenotype influences KDPS's performance. Since heritability affects the detectability of genetic associations, this is a critical factor to evaluate.

We appreciate the reviewer’s thoughtful suggestion. In the real-world application of KDPS, we have specifically included phenotypes with a broad range of heritability estimates: schizophrenia (~80%), multiple sclerosis (~30%), acute myocardial infarction (~40–50%), and alcohol consumption (~20–30%). These choices were intended to demonstrate KDPS's generalizability across varying genetic architectures. We have clarified this design in the manuscript to highlight that KDPS performs consistently across phenotypes with different levels of heritability: (In the real-world examples, KDPS … with varying genetic contributions).

4. Generalizability to Underrepresented Populations:

The UK Biobank (UKB) and many genetic studies suffer from significant underrepresentation of non-European populations. It remains unclear whether KDPS performs equally well in diverse ancestry groups, which is essential for ensuring broad applicability.

We thank the reviewer for this insightful point. While KDPS is designed to be agnostic to the ancestry of the input data, its performance depends on the accuracy of the underlying kinship or relatedness matrix. We agree that ancestry diversity and admixture may pose challenges for IBD estimation. Therefore, we have added a note of caution in the Discussion, advising users to use appropriate admixture-aware methods when generating kinship matrices in ancestrally diverse or admixed populations: (We fully acknowledge that this is a very good point … advocate the usage of admixture-aware kinship inference methods.).