Dear Dr Salem,  
  
I am writing to inform you that your manuscript entitled 'KDPS: a tool for phenotype-aware decoupling of related subjects' (BIB-25-0577) has now been peer-reviewed.  The comments of the reviewers follow at the end of this email.  
  
We should like to invite you to respond to the comments of the reviewers and revise your manuscript according to their suggestions.  
  
To revise your manuscript, log into [https://mc.manuscriptcentral.com/bib](https://urldefense.com/v3/__https:/mc.manuscriptcentral.com/bib__;!!LLK065n_VXAQ!kEoBn8A10281LeV4X7gqgBtUefraOGV8CLzv3BXw67Qs6C-lCGdbrGSs5gXWSUZA0KS1jL5dHsthRg7vWVGIyPKTbI27$) and enter your Author Center, where you will find your manuscript listed under "Manuscripts with Decisions."  Under "Actions," click on "Create a Revision."    
  
When creating your revision, you will be asked to provide a response to the reviewers' comments, point-by-point.  Where possible, please provide this response in the text box provided, rather than uploading your response as a document.  **Do not use the file type 'Response to Decision Letter' as this is for transferred papers ONLY.** Please ensure that any changes made to your manuscript are highlighted in colour, bold or underlining.  By doing this, you will help us to minimise the time needed to provide you with a decision.  
  
IMPORTANT:  Your original files are available to you when you upload your revised manuscript.  Please delete any redundant files before completing the submission.  
  
Because we are trying to facilitate timely publication of manuscripts submitted to Briefings in Bioinformatics, we request that you submit your revised manuscript within the next four weeks.    
  
Once again, thank you for submitting your manuscript to Briefings in Bioinformatics and I look forward to receiving your revised paper in due course.  
  
Yours sincerely,  
  
Dr. Shuangge Ma (Editor in Chief) and Dr. Zhenxia Chen (Deputy Editor), Briefings in Bioinformatics  
  
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.  
  
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).  
  
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..  
  
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.  
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.  
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.  
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.  
   
  
Editor's Comments to Author:  
Editor  
Comments to the Author:  
This manuscript cannot be accepted in its current form. It needs to be revised substantially to address the two reviewers' comments.