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Accounting for Missing Data in Clinical Research

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To the Editor

Drs Newgard and Lewis¹ provided an overview of many important issues to consider when dealing with missing data in clinical research. In particular, they summarized the limitations of traditional imputation methods – failure to account for uncertainty in imputed values, failure to make full use of observed values, possibilities for bias, and artificially low variance.

One imputation method in use for many years involves the K-Nearest Neighbors (KNN) approach,² which was not included in the JAMA Guide to Statistics and Methods article. In the KNN method, a variable's missing value for a participant is imputed by taking a weighted average of fully observed variable values for several participants that are the most similar (in terms of other covariates) to the person in question. KNN has been widely applied with considerable effectiveness, including in “-omics” clinical research.³

At the same time, KNN is one of the methods that “replaces a missing value with a single number ... and can threaten the validity of study results.”¹ Newgard and Lewis may have excluded KNN from their review for this reason, leading to their concluding statement that “In general, multiple imputation is the best approach for modeling the effects of missing data in studies.”

However, a recent modification⁴ to the KNN method efficiently resolves these limitations, as demonstrated in a colorectal cancer study. This modification quantifies the dependence induced by imputation, particularly between imputed values and the fully observed values on which they are based. This dependence can be accounted for in subsequent statistical tests, effectively accounting for uncertainty (or chance variability) in the imputed values, making full use of observed values, avoiding systematic bias, and appropriately adjusting variance estimates.

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Using this approach has been shown to achieve greater accuracy than the multiple imputation method, as well as better sensitivity than doing no imputation at all. Compared to this KNN-dependent method, the multiple imputation method preferred by Newgard and Lewis does have greater sensitivity, but also lower specificity (and in fact can fail to control the type I error rate entirely).⁴

As data collection methods in clinical research become more comprehensive, the nature of missing data will continue to evolve, and statistical methods for missing data will need to be updated accordingly.

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