

An Open-Source "R-Package" and "R-Shiny" Application Designed to Integrate Single-Arm Observational Data and Bridge Gaps in Disconnected Evidence Networks

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CONCLUSIONS

- The development of the open-source R-package “**closedloop**” and its web application on the R-Shiny interface enables the simplification of methodology Schmitz et al., making it more accessible for users, including non-programmers
- The package streamlines the intricate tasks of data validation, weight assignment, and distance metric calculation, making it particularly valuable for conducting Network Meta-Analysis (NMA), especially when integrating observational studies with randomized controlled trials (RCTs).
- By providing users with tools to calculate distance metrics, adjust covariates, and perform scenario analyses, the package enhances the robustness of comparisons between single-arm trials, supporting evidence synthesis in fragmented networks.
- .The package's successful deployment on CRAN and GitHub, along with its web-based interface, promotes transparency, collaboration, and continuous improvement, fostering wider adoption and engagement within the research community.

INTRODUCTION

- Network Meta-Analysis (NMA) allows for the comparison of multiple treatments, even in the absence of direct, head-to-head trial data, offering a comprehensive view of relative treatment effects
- Establishing a connected evidence network is critical to deriving robust comparative insights; however, many disease areas, particularly rare or complex conditions, face challenges due to limited direct comparative data. This results in disconnected evidence networks, complicating efforts to draw valid and reliable conclusions in these therapeutic areas
- Schmitz et al. proposed a novel methodology to address gaps in disconnected evidence networks by integrating covariate information from single-arm observational studies, facilitating indirect treatment comparisons
- This method systematically assesses study similarity by incorporating patient characteristics, thereby strengthening connections within networks
- By constructing a distance matrix using baseline covariates, this approach identifies similarities across studies. This matrix is then used to refine the network by excluding studies that do not meet a defined similarity threshold, thereby enhancing the accuracy of indirect comparisons and the overall robustness of Network Meta-Analyses.

OBJECTIVE

- Develop an open-source R package based on Schmitz et al.'s methodology to standardize the integration of single-arm studies in Network Meta-Analysis (NMA), thereby enhancing the ability to conduct robust indirect treatment comparisons.
- Create an R Shiny interface to make the package accessible to non-programmers, allowing users to run analyses seamlessly without requiring extensive coding knowledge.

METHODS

- The open-source package, “**closedloop**,” was developed using R (v4.3.1), with its functions structured using the *roxygen2* documentation framework.
- The "closedloop" package includes the following core functions:
 - check_data**: Validates the dataset to ensure that all covariates are numeric and that there are no duplicates in study or treatment identifiers, leveraging pattern recognition (regex) techniques for accuracy.
 - is_prop**: Checks specific covariates designated as proportions by the user to confirm that the data values lie within the valid range of 0 to 1.
 - specify_weights**: Allows users to assign customized weights to different covariates, enabling nuanced analyses. For instance, if a study prioritizes sex over age, this function can adjust the weightings accordingly.
 - calc_dist**: Calculates the distance between single-arm studies using the weighted covariate data, providing a quantitative measure for matching studies based on covariate similarities.
- The distance metric between two studies is computed as the weighted average of differences in covariates, scaled between 0 and 1. A lower value signifies a higher degree of similarity. Following the methodology outlined by Schmitz et al., a threshold of 0.1 is set as the maximum allowable distance for considering study pairs to be comparable based on baseline characteristics.
- This methodology effectively detects and account for outliers, ensuring that similar studies are connected while minimizing mismatches
- The web-based interface was developed using R-shiny package, deployed on Amazon Web Services (AWS) server with Auth0 as user-based authentication management system

RESULTS

- The "closedloop" package was successfully developed and approved for publication on the Comprehensive R Archive Network (CRAN), meeting the stringent quality standards for R packages.
- A development version of the package has been committed to a publicly accessible GitHub repository, promoting transparency, collaboration, and user engagement.
- This open-access release allows the community to access the latest updates, report issues, and contribute to ongoing enhancements, fostering continuous improvement of the package.

Figure 1: CRAN and GitHub package screenshots

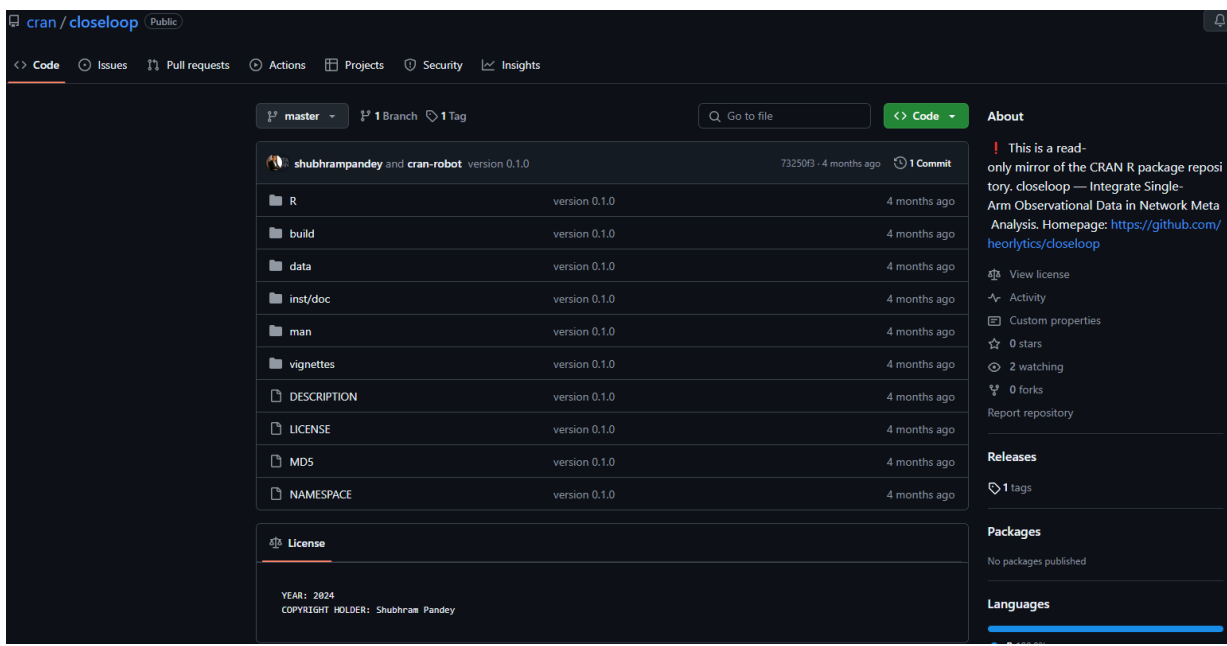
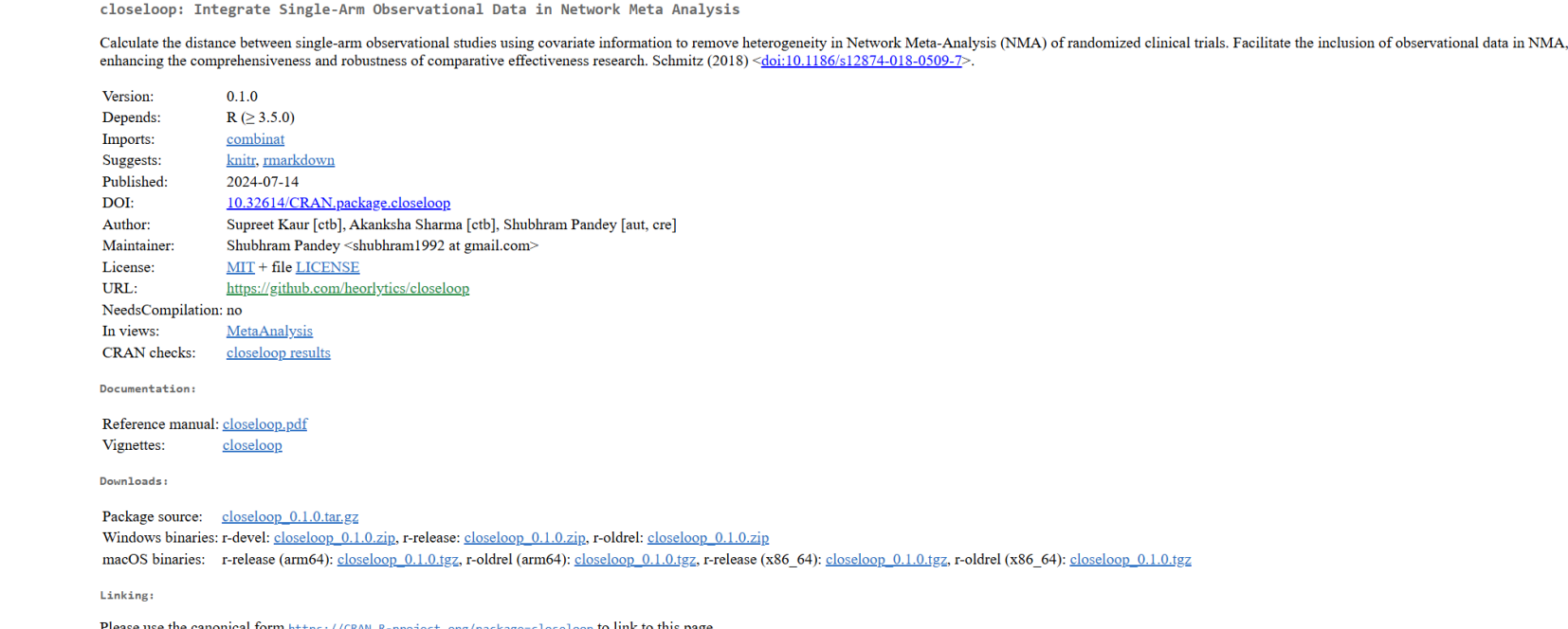
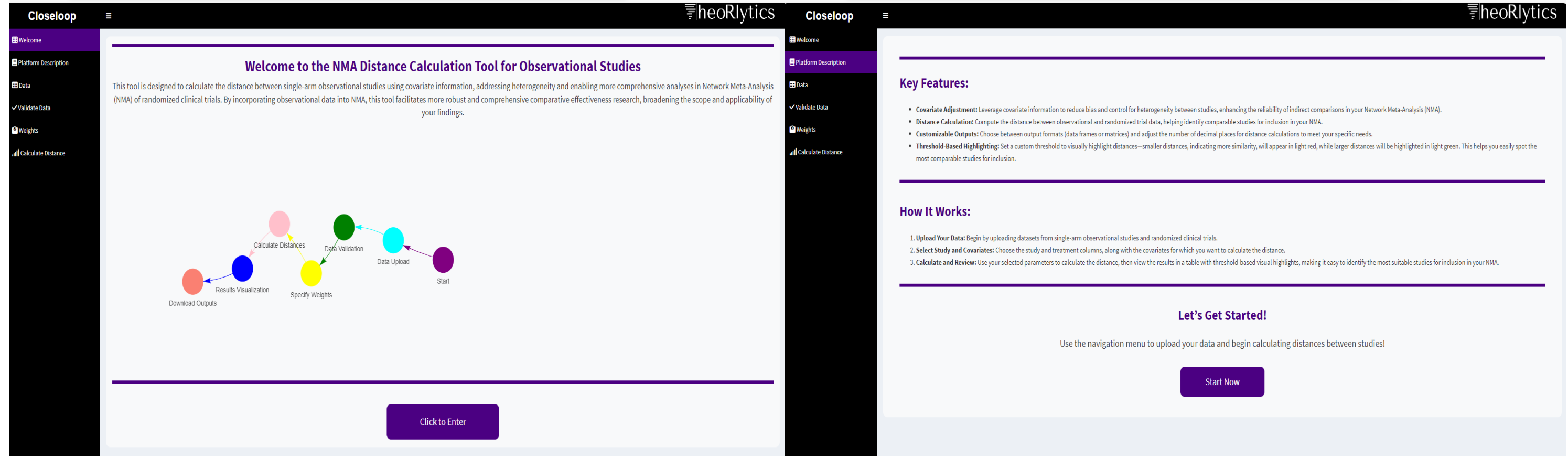
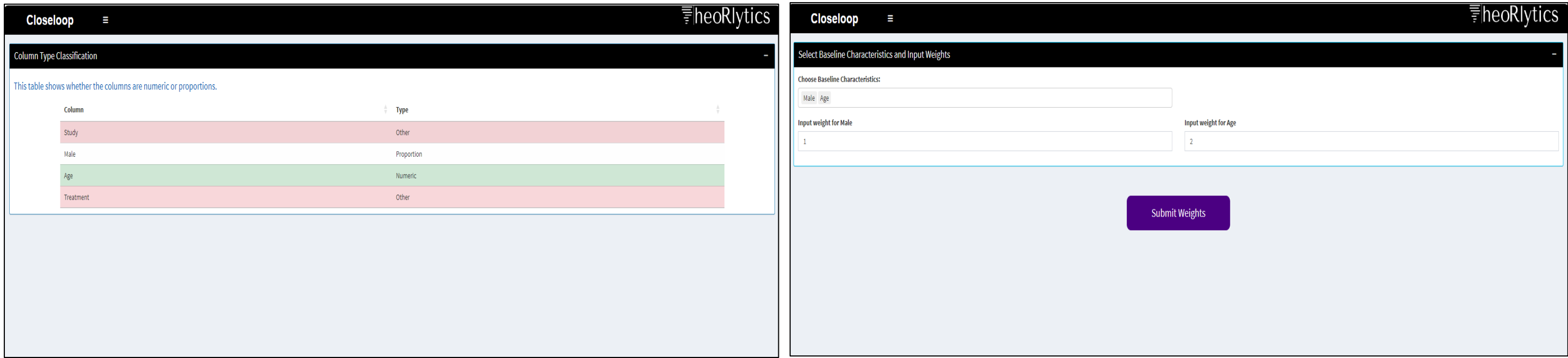


Figure 2: Home and description page of web-based interface



- Users can calculate distance metrics that reflect the degree of similarity between studies, enabling a more robust comparison of single-arm trials. This feature supports the identification of studies that are closely aligned based on baseline covariates.
- The package allows for covariate adjustments, providing users with the flexibility to adjust analyses for specific variables, thus refining the matching process based on their study design requirements.
- Scenario analyses can be conducted using customizable similarity thresholds, empowering users to explore how varying the thresholds impacts study matches and the robustness of the results.
- The outputs include comprehensive distance calculations, with options to export results as either a data frame or a matrix. Users can also specify decimal precision to tailor the level of detail in reporting.
- All analysis results are easily downloadable in Excel format, enabling straightforward documentation, further analysis, and integration into reporting workflows.

Figure 3: Data Validation and Weight Input Interface



- The "closedloop" application is deployed on an AWS-hosted R Shiny platform, leveraging cloud infrastructure for scalability and reliability. The platform ensures data security by implementing SSL certificates for encrypted data transmission and Auth0 authentication for secure user access.
- The application uses session-based data handling, where any uploaded data is treated as temporary and is not stored on the server. This design aligns with stringent data security protocols, ensuring that sensitive data remains protected and is not inadvertently retained.
- Users have the flexibility to adjust the similarity threshold to optimize study comparisons. A lower threshold may reduce the risk of overestimating similarity but might increase uncertainty, while a higher threshold could match studies that are too dissimilar, potentially impacting the validity of the results.
- The platform provides intuitive controls for adjusting thresholds, allowing users to refine their analyses based on specific study characteristics and desired levels of confidence in study matching. This capability ensures meaningful comparisons while maintaining the integrity of the analysis.

Figure4: Threshold Adjustment Feature, set Decimal Precision and Desired Output

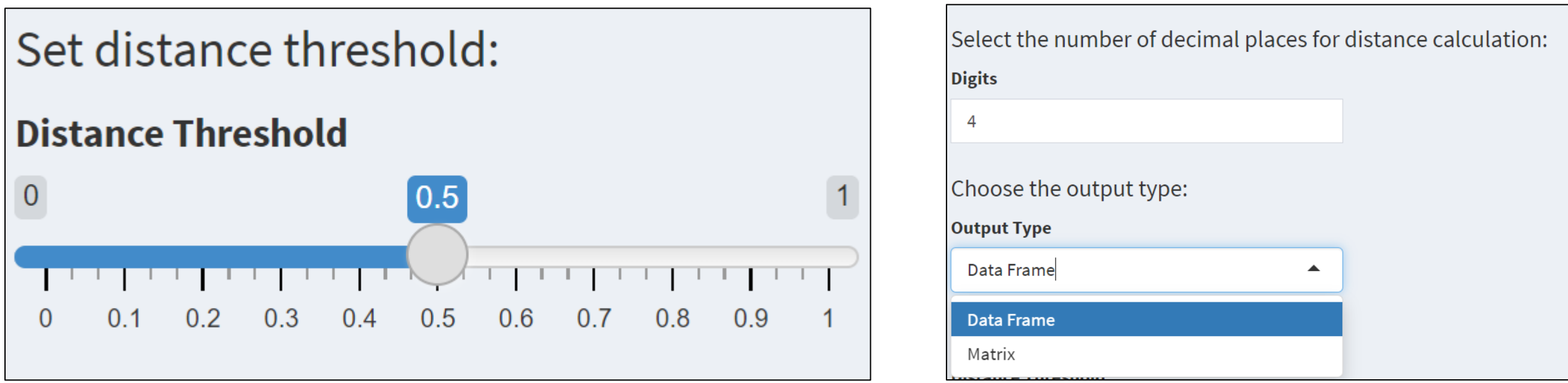


Figure 5: Output formats (Data frame and Matrix) generated by the R-shiny web application at a threshold value of 0.5

Study	Treatment	Distance	
1	Study 1 - Study 2	T1 - T2	0.2725
2	Study 1 - Study 3	T1 - T3	0.1451
3	Study 1 - Study 4	T1 - T4	0.2177
4	Study 1 - Study 5	T1 - T1	0.6608
5	Study 1 - Study 6	T1 - T2	0.7823
6	Study 1 - Study 7	T1 - T3	0.8
7	Study 1 - Study 8	T1 - T4	0.6314
8	Study 1 - Study 9	T1 - T1	0.2686
9	Study 1 - Study 10	T1 - T2	0.3961
10	Study 2 - Study 3	T2 - T3	0.2059

Study 1 (T1)	Study 2 (T2)	Study 3 (T3)	Study 4 (T4)	Study 5 (T1)	Study 6 (T2)	Study 7 (T3)	Study 8 (T4)	Study 9 (T1)	Study 10 (T2)	
Study 1 (T1)		0.2725	0.1451	0.2177	0.6608	0.7823	0.8	0.6314	0.2686	0.3961
Study 2 (T2)	0.2725		0.2059	0.2118	0.7883	0.5098	0.7275	0.4255	0.3961	0.5137
Study 3 (T3)	0.1451	0.2059		0.0726	0.5824	0.6373	0.6549	0.4863	0.1902	0.3079
Study 4 (T4)	0.2177	0.2118	0.0726		0.5765	0.5647	0.5823	0.4137	0.1843	0.3019
Study 5 (T1)	0.6608	0.7883	0.5824	0.5765		0.2785	0.1392	0.3627	0.3922	0.2745
Study 6 (T2)	0.7823	0.5098	0.6373	0.5647	0.2785		0.2177	0.1509	0.5137	0.3961
Study 7 (T3)	0.8	0.7275	0.6549	0.5823	0.1392	0.2177		0.3019	0.5314	0.4137
Study 8 (T4)	0.6314	0.4255	0.4863	0.4137	0.3627	0.1509	0.3019		0.3628	0.2451
Study 9 (T1)	0.2686	0.3961	0.1902	0.1843	0.3922	0.5137	0.5314	0.3628		0.1177
Study 10 (T2)	0.3961	0.5137	0.3079	0.3019	0.2745	0.3961	0.4137	0.2451	0.1177	

References

Susanne Schmitz, Áine Maguire, James Morris, Kai Ruggeri, Elisa Haller, Isla Kuhn, Joy Leahy, Natalia Homer, Ayesha Khan, Jack Bowden, Vanessa Buchanan, Michael O'Dwyer, Gordon Cook & Cathal Walsh. The use of single armed observational data to closing the gap in otherwise disconnected evidence networks: a network meta-analysis in multiple myeloma. <doi>10.1186/s12874-018-0509-7</doi>

Disclosures

SK, AS, PB, BS and SP are the authors, declare that they have no conflict of interest

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