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Application of Propensity Score Methods to Address Missing Data in a Trial on the Effect of Energy Protein Supplementation Among Pulmonary TB-HIV Patients in Mwanza, Tanzania

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Abstract

Background

Missing data is common in research and can reduce statistical power and introduce bias. In the Pulmonary Tuberculosis – HIV coinfected patients (PTB-HIV) supplementation trial, patients' attrition rates from the trial were 12.2% at two months and 19.1% at five months. This study evaluated the performance of propensity score (PS) and multiple imputation (MI), -based approaches versus case analysis (CCA) a traditional methods

Methods

This study utilized data from a randomized controlled trial in assessing the impact of energy-protein supplementation on weight, body composition, and handgrip strength among PTB-HIV co-infected patients. The pattern of missing data were obtained, using the Little's Missing Completely at Random (MCAR) test and logistic regression in Stata Version X. Complete Case analysis (CCA) and Multiple Imputation (MI) analysis were conducted assuming data is MCAR and/or Missing at Random (MAR) respectively, Propensity Score Inverse probability Weighting (PS-IPW) was applied to create a weighted dataset. The effectiveness of PS-IPW was compared to CCA and MI using, mean squared error, relative efficiency, and bias. To assess possibility of data Missing Not At Random (MNAR), sensitivity analysis was conducted.

Results

The missingness in the data followed a monotonic pattern. The mechanism of missing data was MAR with little evidence of MNAR. The CCA, MI, and PS-IPW showed no statistically significant treatment effects. MI generally produced slightly larger effect estimates compared to CCA and PS-IPW, but without improved significance. Generally, MI and PS-IPW outperformed CCA in bias and efficiency.

Conclusion

There was a monotonic pattern of missingness with evidence of data being MAR. Different approaches to missingness showed no significant improvements in the assessment of outcomes. The MI and PS-IPW outperformed CCA, emphasizing the importance of robust missing data handling to ensure valid conclusion.

BACKGROUND

Malnutrition remains a critical determinant of morbidity and mortality among PTB-HIV co-infected patients, particularly in sub-Saharan Africa, where food insecurity and chronic infections intersect. In

Tanzania, undernutrition is highly prevalent among TB–HIV patients, with significant proportions presenting with low body mass index (BMI) and wasting at the time of diagnosis (1, 2). Energy supplementation has been proposed as an adjunct intervention to support nutritional recovery, improve immune competence, and enhance tolerance to anti-tuberculosis and antiretroviral therapies (3, 4). Adequate energy and protein intake are essential for maintaining lean body mass and restoring metabolic reserves depleted by chronic inflammation and catabolic states associated with TB and HIV infection.

Clinical trials conducted in Tanzania, including the Mwanza region, have explored the role of nutritional supplementation in this population, showing modest improvements in functional outcomes such as handgrip strength but limited effects on overall weight gain or treatment success (5). Despite these mixed findings, supplementation remains biologically plausible and contextually relevant, given its potential to mitigate the synergistic effects of malnutrition and infection. Current Tanzanian and WHO guidelines recommend integrating targeted nutritional support within TB–HIV treatment programs to address both clinical and socioeconomic determinants of undernutrition (6, 7).

Missing data remains a critical concern in clinical trials, threatening the validity and reliability of treatment effect estimates. When not adequately addressed, missing data can introduce bias and compromise the internal validity of randomized controlled trials, particularly in studies with high patient attrition rates or conducted in resource-limited settings (8, 9). Although the issue is well recognized, its methodological treatment in clinical research is often inconsistent and underdeveloped (8, 10). Missingness can result from a range of factors, including participant dropout, equipment failure, or administrative challenges.

Missing data commonly follow distinct patterns that influence both bias and statistical handling. These include monotone missingness where once a participant drops out and all subsequent measurements are missing, univariate missingness where missing values occurs across one variable only, multivariate where missing values occurs across multiple variables, and non-monotone where drop out does not follow a specific order. These patterns are often linked to different mechanisms, including missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR)(10, 11). Each of these mechanisms require different analytic strategies to avoid biased conclusions (5, 10, 11).

In resource-constrained environments, high levels of missing data are common and can severely distort estimates of treatment efficacy, particularly when the missingness is related to patient characteristics(12). Conventional methods like CCA or single imputation approaches, mean substitution or last observation carried forward (LOCF) are still widely used in such trials due to their simplicity but rest on assumptions that rarely hold in real-world clinical settings (13–15). Multiple Imputation (MI) improves on these methods by incorporating imputation uncertainty across multiple datasets and is valid under the MAR assumption (14, 16) yet it too can yield biased estimates under MNAR. In recent years, propensity score (PS) methods, particularly inverse probability weighting (IPW), have gained traction as alternatives for handling missing data. These methods estimate the probability of

missingness using observed baseline covariates and apply weights to account for systematic differences between those with and without observed outcomes, offering a promising solution when traditional methods fall short (8, 17–19).

Despite the increasing application of PS-based methods, few empirical studies have compared their performance against traditional missing data techniques in the context of clinical trials where MNAR is suspected. This study seeks to address that gap by evaluating PS based approaches using data from a randomized controlled trial of energy-protein supplementation in PTB-HIV co-infected patients. Specifically, we aim to describe the patterns and mechanisms of missingness at baseline, two months, and five months; apply propensity score-based methods to estimate the effect of supplementation on body weight; and compare their performance against CCA and MI. By doing so, this study contributes to the growing body of work aimed at improving the methodological rigor of missing data handling in clinical trials, particularly in high-attrition, high risk populations common in global health research.

METHODS

Study population:

This secondary data analysis draws on a previously published randomized controlled trial (RCT) that assessed the effects of energy–protein supplementation on body weight, arm fat and muscle areas, and handgrip strength in individuals co-infected with pulmonary tuberculosis (PTB) and HIV(5). It was conducted from April 2006 to March 2009 across four TB clinics in Mwanza City, Tanzania. Participants were HIV-positive individuals aged 15 years or older, residing in Mwanza City, and diagnosed with PTB; written informed consent was a prerequisite for inclusion. Those with extrapulmonary TB, pregnant women, and patients with terminal illnesses were excluded. A total of 354 eligible co-infected individuals were included in this analysis. The original study employed a consecutive sampling approach, whereby all eligible patients presenting at the participating clinics during the study period were invited to join. This non-probability method helped minimize selection bias and allowed for the inclusion of a diverse patient population, thereby enhancing the study's external validity and reflecting real-world clinical settings.

Randomization/Arm allocation

All eligible participants were randomized into intervention and control groups using a computer-generated sequence with permuted blocks of ten, created via http://www.randomization.com. A staff member not involved in recruitment or assessment managed the sequence, and the supplement packs were pre-labelled with identity numbers (1–500). To ensure allocation concealment, the sequence was securely stored and accessible only to the designated staff. TB clinic staff, blinded to the allocation, enrolled participants, after which the next sequential number and corresponding supplement pack were assigned. Although the study was not blinded due to the visible differences between supplements, rigorous randomization and concealment procedures minimized selection bias and strengthened methodological integrity.

Participants in the intervention group received six energy–protein biscuit bars daily for the first 60 days of TB treatment, providing a total of 3690 kJ of energy and 27 g of protein per day. One of the six bars also included added micronutrients such as vitamins A, B-complex, C, D3, E, and minerals like selenium, zinc, and copper, at levels known to benefit TB patients. In comparison, the control group received one biscuit bar per day over the same period, delivering 615 kJ of energy and 4.5 g of protein, along with basic minerals like phosphorus, calcium, magnesium, sodium, potassium, and trace iron and zinc.

Outcome measures

The primary outcomes were changes in weight at 2 and 5 months, i.e. at the end of the supplementation period and 3 months after. Secondary outcomes were arm circumference and handgrip strength at 2 and 5 months.

Data collection procedure:

Participant demographic data, along with smoking and alcohol use, were collected using standardized questionnaires. Blood samples were taken between 08:00am and 12:00 using a 10 mL plain vacutainer for HIV testing and a 5 mL EDTA vacutainer for CD4 count analysis. HIV status was determined using both the Capillus and Determine HIV-1/2 tests; concordant positive results confirmed HIV infection, while discordant or indeterminate results were resolved using the ELISA-Organon Uniform II assay. CD4 counts were measured using a Partec Cyflow Counter. Anthropometric assessments included weight, height, mid-upper arm circumference, triceps skinfold thickness, and handgrip strength, each measured with precise instruments and duplicated for accuracy. BMI, arm circumference and grip strength were calculated using standard formulas. Measurements were taken at enrollment, and again at 2 and 5 months, with trained staff ensuring consistency across all assessments.

Supplement intake was initially monitored directly by TB clinic staff as patients consumed their nutritional bars under supervision. After October 2006, participants choosing to take supplements home were given logbooks to track daily consumption. These were reviewed and updated at each clinic visit when patients collected new supplies. Compliance was defined as consumption of at least 80% of the supplements provided. Staff training and regular supervision were implemented throughout the study to maintain strict adherence to protocols and data quality.

Data analysis

Exploratory missing data analysis:

An exploratory analysis was conducted to examine the extent and patterns of missing data using summary statistics and visual tools such as histograms and missing data maps. Little’s MCAR test and binary logistic regression models were used to assess the missing data mechanism. Binary indicators of

missingness for key outcomes were analyzed against baseline characteristics. Significant associations ($p < 0.05$) suggested the data were likely MAR or MNAR, rather than MCAR.

Main analysis:

A CCA with linear regression to evaluate changes in weight, handgrip strength, and arm circumference at 2 and 5 months, assuming data were MCAR, was performed. To address potential bias from missing data, multiple imputations by chained equations (MICE) with 20 imputations was conducted using predictive mean matching, incorporating the outcomes and predictors to reflect the analysis model. Each imputed dataset was analyzed and results were combined using Rubin's rules to estimate treatment effects with associated standard errors, confidence intervals, and p-values. Additionally, PS Analysis was performed by modelling the probability of having observed data through logistic regression adjusting for baseline values and covariates..Stabilized IPWs applied were then generated and weighted regression models for each outcome.

Sensitivity Analysis to assess departure from MAR mechanism

Data are said to be missing at randomif we can use the observed covariates to explain the missing data. by. However, to assess robustness to violations of the MAR assumption, to the possibility of MNAR, that missingness can depend on unobserved covariates and the missingness itself a sensitivity analysis was done. A delta-based analysis using a pattern-mixture model was conducted under MNAR. Fixed delta values (0, − 0.5, − 1, − 2) were applied in MNAR sensitivity analyses to represent progressively worse unobserved outcomes relative to MAR, with − 0.5, − 1, and − 2 reflecting mild, moderate, and severe departures from MAR, respectively, thereby assessing the robustness of results under increasingly pessimistic assumptions. Treatment effects and confidence intervals were recalculated to assess the stability of results across plausible MNAR scenarios.

Assessment of the effectiveness of the propensity score method with CCA and MI

To evaluate the performance of different methods for handling missing data, we compared effect estimates and variances from Inverse Probability Weighting (IPW) and Multiple Imputation (MI) with those from Complete Case Analysis (CCA), which served as the reference. Bias was calculated as the difference between each method's estimate and the CCA estimate, with values near zero indicating data are missing completely at random (MCAR). Mean Squared Error (MSE), combining bias and variance, was used to assess overall accuracy, where a lower MSE indicates more reliable estimates. Relative efficiency (RE), defined as the ratio of MSE for CCA to that of the alternative method, measured efficiency gains; RE values above 1 signified better performance of IPW or MI compared to CCA. These metrics were applied across multiple outcomes to determine the consistency and robustness of each method.

Software and tools

The statistical analysis was conducted using R version 4.3.3.

RESULTS

Descriptive Analysis

A total of 354 participants were enrolled (183 intervention, 171 control), with a mean age of 35.1 years and balanced gender distribution (49.4% female). Most were non-smokers 84.7%, 44.4% used alcohol, and nearly half were married (48.6%). Occupations varied, with 38.4% in business or employed and 35.6% as farmers/fishermen. Baseline characteristics were similar between groups. Improvements were seen at 2 and 5 months in all outcomes, with weight reaching 57.0 kg, arm circumference 25.1 cm, and grip strength 30.3 kg (Table 1).

Table 1
Baseline characteristics of 354 pulmonary tuberculosis patients randomized to either the energy–protein or control group

Variable	Control (n = 171)	Intervention (n = 183)	Total (n = 354)
Age (years), t = 0			
Mean (SD)	35.4 (8.72)	34.8 (10.3)	35.1 (9.55)
Sex			
Female	82 (48.0%)	93 (50.8%)	175 (49.4%)
Male	89 (52.0%)	90 (49.2%)	179 (50.6%)
Marital Status			
Married	89 (52.0%)	83 (45.4%)	172 (48.6%)
Separated	45 (26.3%)	51 (27.9%)	96 (27.1%)
Single	36 (21.1%)	47 (25.7%)	83 (23.4%)
Missing	1 (0.6%)	2 (1.1%)	3 (0.8%)
Occupation			
Business/Employed	68 (39.8%)	68 (37.2%)	136 (38.4%)
Farmer/Fisherman	60 (35.1%)	66 (36.1%)	126 (35.6%)
Housewife	28 (16.4%)	24 (13.1%)	52 (14.7%)
Unemployed	7 (4.1%)	14 (7.7%)	21 (5.9%)
Missing	8 (4.7%)	11 (6.0%)	19 (5.4%)
Smoking Status			
No	144 (84.2%)	156 (85.2%)	300 (84.7%)
Yes	27 (15.8%)	27 (14.8%)	54 (15.3%)
BMI			
Normal	67 (39.2%)	71 (38.8%)	138 (39.0%)
Obese	1 (0.6%)	2 (1.1%)	3 (0.8%)
Overweight	3 (1.8%)	4 (2.2%)	7 (2.0%)
Underweight	100 (58.5%)	105 (57.4%)	205 (57.9%)
Missing	0 (0%)	1 (0.5%)	1 (0.3%)
Alcohol Status			

Variable	Control (n = 171)	Intervention (n = 183)	Total (n = 354)
Age (years), t = 0			
No	91 (53.2%)	106 (57.9%)	197 (55.6%)
Yes	80 (46.8%)	77 (42.1%)	157 (44.4%)
CD4			
Low CD4	138 (80.7%)	150 (82.0%)	288 (81.4%)
Normal CD4	33 (19.3%)	32 (17.5%)	65 (18.4%)
Missing	0 (0%)	1 (0.5%)	1 (0.3%)

[Table 1 near here]

Figure 1a and Fig. 1b show similar temporal patterns for weight, arm circumference, and grip strength in both the control and intervention groups across all time points. Mean values increased from baseline to endline with substantial overlap between study arms, and the inclusion of missing data after MI did not materially change the observed trends or between-group comparisons.

Evaluation of missing data.

Missing data were low at baseline (≤ 0.6%) but increased at follow-up: weight was missing in 9.3% at 2 months and 15.3% in 5 months; arm circumference in 9.0% and 15.3%; and grip strength in 9.0% and 15.5%. Missingness was similarly distributed across intervention and control groups, with no significant differences. The pattern followed a monotonic trend, likely due to participant dropout over time. The UpSet plot (Fig. 2) showed both isolated and overlapping missing data, with the highest individual missingness in 5-month outcomes and the largest intersection (n = 30) missing only arm circumference at 2 months. Smaller clusters, such as those missing all three outcomes at 5 months (n = 8), support a mixture of MAR and potential MNAR mechanisms, rather than MCAR.

Mechanism of Missingness

Little's MCAR test indicated that the data were not Missing Completely At Random ($p < 0.001$). Binary logistic regression analyses revealed significant associations between missingness in several outcomes and observed variables specifically, missing weight, arm circumference, and grip strength at 5 months were associated to their corresponding values at 2 months, while missing grip strength at 2 months was associated to baseline grip strength. These findings support the assumption that the data are likely Missing At Random (MAR).

Complete Case Analysis

The energy–protein supplementation showed no statistically significant effects on the outcomes. At 5 months, the intervention group had a non-significant weight reduction of 0.75 kg ($p = 0.145$) and small

negative differences in arm circumference. Grip strength declined at 2 months but improved by 0.83 kg at 5 months (p = 0.213). The findings indicate a modest, non-significant effect of supplementation on physical and functional recovery. Excluding participants with missing data may have introduced bias or reduced the precision of the estimates.

Multiple Imputation

Under the MAR assumption with multiple imputation, energy-protein supplementation showed non-significant effects. Wight increased by 0.11 kg at 2 months (p = 0.827) but declined by 0.78 kg at 5 months (p = 0.107). Arm circumference decreased by 0.28 cm at 5 months (p = 0.204), and grip strength rose by 0.64 kg (p = 0.315). Overall, no significant impact was observed.

Propensity Score- Inverse Probability Weighting

Alongside complete-case and multiple-imputation analyses, inverse probability weighting using propensity scores was applied to handle missing data. Adjusted PS-IPW results showed no significant effects, with the intervention group weighing 0.70 kg less at 5 months (p = 0.181) and grip strength increasing by 0.85 kg (p = 0.206). Similar non-significant findings were seen at 2 months. Overall, the supplementation had no significant impact on weight, arm circumference, or grip strength, though PS-IPW suggested slightly larger effects, particularly for weight at 5 months.(Table 2)

Table 2
The mean treatment effect of protein supplementation among PTB-HIV patients with CCA, MI and PS-IPW

Outcome	Timepoint	Analysis Method	Mean Treatment Effect (95% CI)	95% CI	p-value
Weight	2 months	CCA	-0.101	-1.05 to 0.84	0.834
		MI	-0.630	-2.59 to 1.33	0.526
		PS-IPW	-0.024	-1.00 to 0.95	0.961
	5 months	CCA	-0.748	-1.75 to 0.25	0.143
		MI	-1.167	-3.16 to 0.82	0.249
		PS-IPW	-0.722	-1.71 to 0.27	0.154
Arm Circumference	2 months	CCA	-0.198	-0.57 to 0.18	0.298
		MI	0.018	-0.68 to 0.72	0.959
		PS-IPW	-0.093	-0.48 to 0.30	0.641
	5 months	CCA	-0.242	-0.68 to 0.19	0.275
		MI	-0.142	-0.81 to 0.53	0.677
		PS-IPW	-0.259	-0.69 to 0.17	0.240
Grip Strength	2 months	CCA	-0.519	-1.62 to 0.58	0.353
		MI	0.119	-1.81 to 2.05	0.904
		PS-IPW	-0.009	-1.06 to 1.04	0.986
	5 months	CCA	0.843	-0.47 to 2.16	0.207
		MI	0.627	-1.28 to 2.54	0.519

Outcome	Timepoint	Analysis Method	Mean Treatment Effect (95% CI)	95% CI	p-value
		PS-IPW	0.822	-0.48 to 2.13	0.218

Assessment of effectiveness of the PS-IPW with CCA and MI.

The comparative analysis of PS-IPW and MI, using CCA as a reference, reveals that neither MI nor IPW is universally superior across all metrics. IPW generally shows lower bias for AC2, Grip5, Wt2, and Wt5, while MI has lower bias for AC5 and Grip2. Regarding MSE, IPW tends to have lower or similar values except for AC5 and Grip5 where MI performs slightly better. Relative efficiency is consistently higher for MI across most outcomes, except for Grip5 where both methods are comparable. These results indicate that MI may offer greater precision overall, but IPW provides more stable bias control for several key outcomes under potential missing data mechanisms as observed in Fig. 3.

Sensitivity analysis

The MNAR sensitivity analysis (delta = − 2) showed stable intervention effects at 2 months for weight, arm circumference, and grip strength, all remaining near zero. At 5 months, weight effects became more negative, and arm circumference shifted from − 0.3 to − 0.4, indicating a slightly greater negative impact. Grip strength at 5 months remained consistently positive across all assumptions. These results suggest minimal bias from missing data and support MNAR as a defensible assumption for handling missing data in this study. (Fig. 4)

DISCUSSION

Missing data increased over time, particularly at the 5-month follow-up, raising concerns about informative loss to follow-up, an issue common in vulnerable populations such as those with PTB-HIV co-infection. The non-monotone, clustered patterns suggest data are not MCAR. Instead, observed associations support MAR or MNAR mechanisms, under which methods like MI and PS-IPW are appropriate for valid inference (24). Sensitivity analyses under MNAR conditions yielded similar results across outcomes, strengthening the robustness of the findings (20–22). Across all methods, no statistically significant intervention effects were observed for weight, arm circumference, or grip strength at either 2 or 5 months, consistent with results reported by PrayGod et al. (5). At 5 months, the treatment effect on weight was − 0.72 kg with PS-IPW, − 0.75 kg with CCA, and − 1.17 kg with MI variations consistent with findings by Sterne et al. and Seaman & White, who reported that MI and PS-IPW tend to yield larger or more stable estimates under MAR assumptions (20, 23). Arm circumference similarly showed small, negative shifts (e.g., − 0.3 to − 0.4 cm). Notably, grip strength estimates at 5 months remained consistently positive across all methods, suggesting potential functional benefit despite a lack of statistical significance (24, 25).

Although the intervention did not achieve statistically significant effects, the direction and consistency of estimates, especially for grip strength, indicate possible clinical relevance in this metabolically stressed population. PS-IPW often produced more stable and favorable estimates, consistent with prior findings from Seaman and White, Molenberghs et al., and Nguyen et al., which highlight its strengths in adjusting for dropout and confounding under MAR and MNAR assumptions (21, 23, 26). Given the moderate, non-monotone missingness and empirical support for MAR, MI and PS-IPW outperformed CCA by improving precision and reducing potential bias.

Overall, the concordant findings across CCA, MI, and PS-IPW indicate that energy–protein supplementation had no clinically meaningful effect on weight, arm circumference, or grip strength in this population, regardless of how missing data were handled. The similarity of effect estimates suggests that missingness was unlikely to have substantially biased the main conclusions and that the true intervention effect, if present, is small. MI provided greater efficiency and precision, while PS-IPW offered improved bias control for some outcomes, highlighting the value of using complementary methods rather than relying on a single approach. As emphasized in epidemiologic research, lack of statistical significance does not imply absence of effect but reflects effect size, direction, and confidence interval width (27, 28). The modest observed effects likely result from the short intervention period and persistent catabolic stressors, underscoring the need for sustained nutritional and health interventions, particularly in settings like Tanzania and sub-Saharan Africa (29, 30).

Our study's finding that energy–protein supplementation led to only modest, non-significant improvements in weight, arm circumference, and grip strength mirrors recent evidence indicating that nutritional support alone often yields limited or mixed effects on key clinical outcomes in TB and TB–HIV populations. A 2024 systematic review reported that while some forms of nutritional support including food baskets or macronutrient enriched food may improve adherence and patient outcomes, the evidence remains inconsistent and highlights the need for more well powered trials to demonstrate clinical benefit in TB care overall(31). Likewise, broader systematic evidence suggests that macronutrient and food based interventions can improve weight gain and treatment success in some settings, but effects vary by context and study design(32, 33). The robust use of multiple missing data methods (CCA, MI, PS-IPW) strengthens confidence in these findings by demonstrating consistency across analytic approaches recommended in recent methodological literature on handling missingness in clinical studies. Additionally, recent health policy guidance has emphasized the importance of integrated nutritional assessment and support throughout TB care, reflecting recognition of the complex role of nutrition in recovery beyond simple supplementation(34–36). Taken together, these comparisons support our conclusion that, while nutritional interventions are important components of TB care strategies, energy–protein supplementation by itself may not produce large or consistent improvements in anthropometric and functional outcomes among PTB–HIV co infected patients.

This study is strengthened by the use of multiple complementary methods (CCA, MI, and PS-IPW) to address missing data, with consistent findings across the different statistical methods, supporting the robustness and internal validity of the results. Evaluating Bias, MSE, and relative efficiency further

enhances credibility by demonstrating transparent assessment of methodological performance. Additionally, reporting effect sizes with confidence intervals rather than relying solely on p-values aligns with current best practices and strengthens the interpretability of the findings.

Limitation of the Study.

One key limitation of the IPW approach used in this analysis is that it addresses missingness only in the outcome variable, while observations with missing covariate data are excluded from the sample. This results in a reduction in sample size, which may introduce bias if the excluded data are not missing completely at random, hence more precision using MI compared to IPW. Additionally, the small study period of five-month poses is small because this group of patients are affected by the medications that they use despite the disease itself. This approach assumes that the data are MAR, conditional on the observed variables.

Conclusion and Recommendation

This study found no statistically significant effects of short-term energy-protein supplementation on weight, arm circumference, or grip strength at 2 or 5 months, though consistent positive trends in grip strength at 5 months suggest potential functional benefits. Missing data, which increased over time and correlated with observed characteristics, supported a MAR assumption, under which multiple imputation (MI) and propensity score inverse probability weighting (PS-IPW) outperformed complete case analysis (CCA) by reducing bias and improving efficiency. These findings underscore the importance of avoiding CCA and adopting robust missing data strategies in RCTs, particularly in vulnerable populations. Future research should incorporate longer-term interventions, predefined missing data plans, and integrated social support to address the complex nutritional and clinical needs of TB-HIV co-infected individuals.

Declarations

Ethics approval and consent to participate

The study was approved by the Joint CUHAS-BMC Research and Ethics Committee (CREC/960/2025). As for the original study, ethical approvals were granted by NIMR, Tanzania and Danish National Committee on Biomedical Research Ethics, Denmark.

Consent for publication

“Not applicable”

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

AM, JK, EK, BK and NM; led the study from conception through proposal development, data analysis, report writing, and manuscript preparation. BK, JT, NM, FI contributed to the study design, interpretation of findings, and provided critical revisions to the manuscript. NM guided the statistical analysis, contributed to the methodology, interpretation of the findings, and supported the writing of the discussion and overall manuscript review.

JK facilitated access to the original trial data, reviewed the original trial protocol, and ensured the integrity of the secondary data use. All authors read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

References

1. Endalkachew K, Mulu Y, Derso T, Kebede A. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases Prevalence and associated factors of undernutrition among adult TB patients attending Amhara National Regional State hospitals, Northwest Ethiopia. J Clin Tuberc Other Mycobact Dis [Internet]. 2022;26(December 2021):100291. Available from: https://doi.org/10.1016/j.jctube.2021.100291
2. Mackenzie T, Lukmanji Z, Neke NM, Waddell R, Matee M, Pallangyo K et al. Nutritional status of HIV-infected women with tuberculosis in Dar es Salaam, Tanzania. 2013;(April 2018).

3. Rezazadeh L, Ostadrahimi A, Tutunchi H, Kermanshahi MN. Nutrition interventions to address nutritional problems in HIV – positive patients: translating knowledge into practice. J Heal Popul Nutr [Internet]. 2023;1–8. Available from: https://doi.org/10.1186/s41043-023-00440-z
4. Guideline. Nutritional care and support for patients with tuberculosis.
5. Praygod G, Range N, Faurholt-Jepsen D, Jeremiah K, Faurholt-Jepsen M, Aabye MG, et al. The effect of energy-protein supplementation on weight, body composition and handgrip strength among pulmonary tuberculosis HIV-co-infected patients: Randomised controlled trial in Mwanza, Tanzania. Br J Nutr. 2012;107(2):263–71.
6. United THE, Of R. THE UNITED REPUBLIC OF TANZANIA MANUAL FOR MANAGEMENT OF TUBERCULOSIS AND LEPROSY IN. 2020.
7. Guidelines N, Care N. THE UNITED REPUBLIC OF TANZANIA.
8. Shiba K, Kawahara T. Using Propensity Scores for Causal Inference: Pitfalls and Tips. J Epidemiol [Internet]. 2021;31(8):JE20210145. Available from: https://www.jstage.jst.go.jp/article/jea/31/8/31_JE20210145/_article
9. Little RJA, Rubin DB. Statistical Analysis with Missing Data [Internet]. Wiley; 2002. (Wiley Series in Probability and Statistics). Available from: https://onlinelibrary.wiley.com/doi/book/10.1002/9781119013563
10. Kang H. The prevention and handling of the missing data. Korean J Anesthesiol [Internet]. 2013;64(5):402. Available from: http://ekja.org/journal/view.php?doi=10.4097/kjae.2013.64.5.402
11. Emmanuel T, Maupong T, Mpoeleng D, Semong T, Mphago B, Tabona O. A survey on missing data in machine learning. J Big Data [Internet]. 2021;8(1):140. Available from: https://journalofbigdata.springeropen.com/articles/10.1186/s40537-021-00516-9
12. Mack C, Su Z, Westreich D. Managing Missing Data in Patient Registries. Agency Healthc Res Qual [Internet]. 2018;1–22. Available from: https://doi.org/10.23970/AHRQREGISTRIESMISSDATA
13. Greenland S, Finkle WD. A Critical Look at Methods for Handling Missing Covariates in Epidemiologic Regression Analyses. Am J Epidemiol [Internet]. 1995;142(12):1255–64. Available from: https://academic.oup.com/aje/article/59569/A
14. Dong Y, Peng C, ying J. Principled missing data methods for researchers. 2013;2004:1–17.
15. Chen YC, Zhang J. Guideline on missing data in confirmatory clinical trials. Chin J New Drugs. 2012;21(7):1–12.
16. White IR, Pandis N, Pham TM. Missing data, part 8. Reporting analyses with missing data. Am J Orthod Dentofac Orthop [Internet]. 2023;163(1):139–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0889540622006321
17. Xu X, Xia L, Zhang Q, Wu S, Wu M, Liu H. The ability of different imputation methods for missing values in mental measurement questionnaires. BMC Med Res Methodol [Internet]. 2020;20(1):42. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-020-00932-0

18. Austin PC, White IR, Lee DS, van Buuren S. Missing Data in Clinical Research: A Tutorial on Multiple Imputation. Can J Cardiol [Internet]. 2021;37(9):1322–31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0828282X20311119
19. Liu X. Methods and Applications of Longitudinal Data Analysis [Internet]. Elsevier; 2016. Available from: https://linkinghub.elsevier.com/retrieve/pii/C20130130826
20. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ [Internet]. 2009;338(jun29 1):b2393–b2393. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.b2393
21. Nguyen CD, Carlin JB, Lee KJ. Model checking in multiple imputation: an overview and case study. Emerg Themes Epidemiol [Internet]. 2017;14(1):8. Available from: https://ete-online.biomedcentral.com/articles/10.1186/s12982-017-0062-6
22. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Stat Med [Internet]. 2010;29(28):2920–31. Available from: https://onlinelibrary.wiley.com/doi/10.1002/sim.3944
23. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res [Internet]. 2013;22(3):278–95. Available from: https://journals.sagepub.com/doi/10.1177/0962280210395740
24. Selker HP, Eichler H, Stockbridge NL, McElwee NE, Dere WH, Cohen T et al. Efficacy and Effectiveness Too Trials: Clinical Trial Designs to Generate Evidence on Efficacy and on Effectiveness in Wide Practice. Clin Pharmacol Ther [Internet]. 2019;105(4):857–66. Available from: https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1347
25. Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: Outcome predictor and marker of nutritional status. Clin Nutr [Internet]. 2011;30(2):135–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0261561410001834
26. Molenberghs G, Fitzmaurice G, Kenward MG, Tsiatis A, Verbeke G, editors. Handbook of Missing Data Methodology [Internet]. Chapman and Hall/CRC; 2014. Available from: https://www.taylorfrancis.com/books/9781439854624
27. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond p < 0.05. Am Stat [Internet]. 2019;73(sup1):1–19. Available from: https://www.tandfonline.com/doi/full/10.1080/00031305.2019.1583913
28. Di Leo G, Sardanelli F. Statistical significance: p value, 0.05 threshold, and applications to radiomics—reasons for a conservative approach. Eur Radiol Exp [Internet]. 2020;4(1):18. Available from: https://eurradiolexp.springeropen.com/articles/10.1186/s41747-020-0145-y
29. Yang JY, Webster-Clark M, Lund JL, Sandler RS, Dellon ES, Stürmer T. Propensity score methods to control for confounding in observational cohort studies: a statistical primer and application to endoscopy research. Gastrointest Endosc [Internet]. 2019;90(3):360–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31051156

30. Chukwuma Ernest E, David Chinaecherem I, Uchechukwu Madukaku C, Uzochukwu Godswill E, John Chigozie E, Ugonma Winnie D, et al. The effectiveness of interventions for improving the uptake of Intermittent Preventive Treatment (IPT) for malaria control among pregnant women in sub-saharan Africa: A systematic literature review. Arch Prev Med. 2023;8(1):008–19.
31. Wagnew F, Gray D, Tsheten T, Kelly M, Clements ACA, Alene KA. Effectiveness of nutritional support to improve treatment adherence in patients with tuberculosis: a systematic review. Nutr Rev [Internet]. 2024;82(9):1216–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/37759339
32. Howell E, Dammala RR, Pandey P, Strouse D, Sharma A, Rao N et al. Evaluation of a results-based financing nutrition intervention for tuberculosis patients in Madhya Pradesh, India, implemented during the COVID-19 pandemic. BMC Glob Public Heal [Internet]. 2023;1(1):13. Available from: https://bmcglobalpublichealth.biomedcentral.com/articles/10.1186/s44263-023-00013-6
33. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM et al. WHO's new End TB Strategy. Lancet [Internet]. 2015;385(9979):1799–801. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673615605700
34. Sinha P, Bhargava M, Carwile ME, Dauphinais MR, Tisile P, Cintron C et al. A roadmap for integrating nutritional assessment, counselling, and support into the care of people with tuberculosis. Lancet Glob Heal [Internet]. 2025;13(5):e967–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214109X2500021X
35. Izudi J, Engoru S, Bajunirwe F. Malnutrition is a risk factor for tuberculosis disease among household contacts: A case-control study in Uganda. IJID Reg [Internet]. 2024;12:100409. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39224535
36. Sinha P, Lakshminarayanan SL, Cintron C, Narasimhan PB, Locks LM, Kulatilaka N et al. Nutritional Supplementation Would Be Cost-Effective for Reducing Tuberculosis Incidence and Mortality in India: The Ration Optimization to Impede Tuberculosis (ROTI-TB) Model. Clin Infect Dis [Internet]. 2022;75(4):577–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34910141

Figures

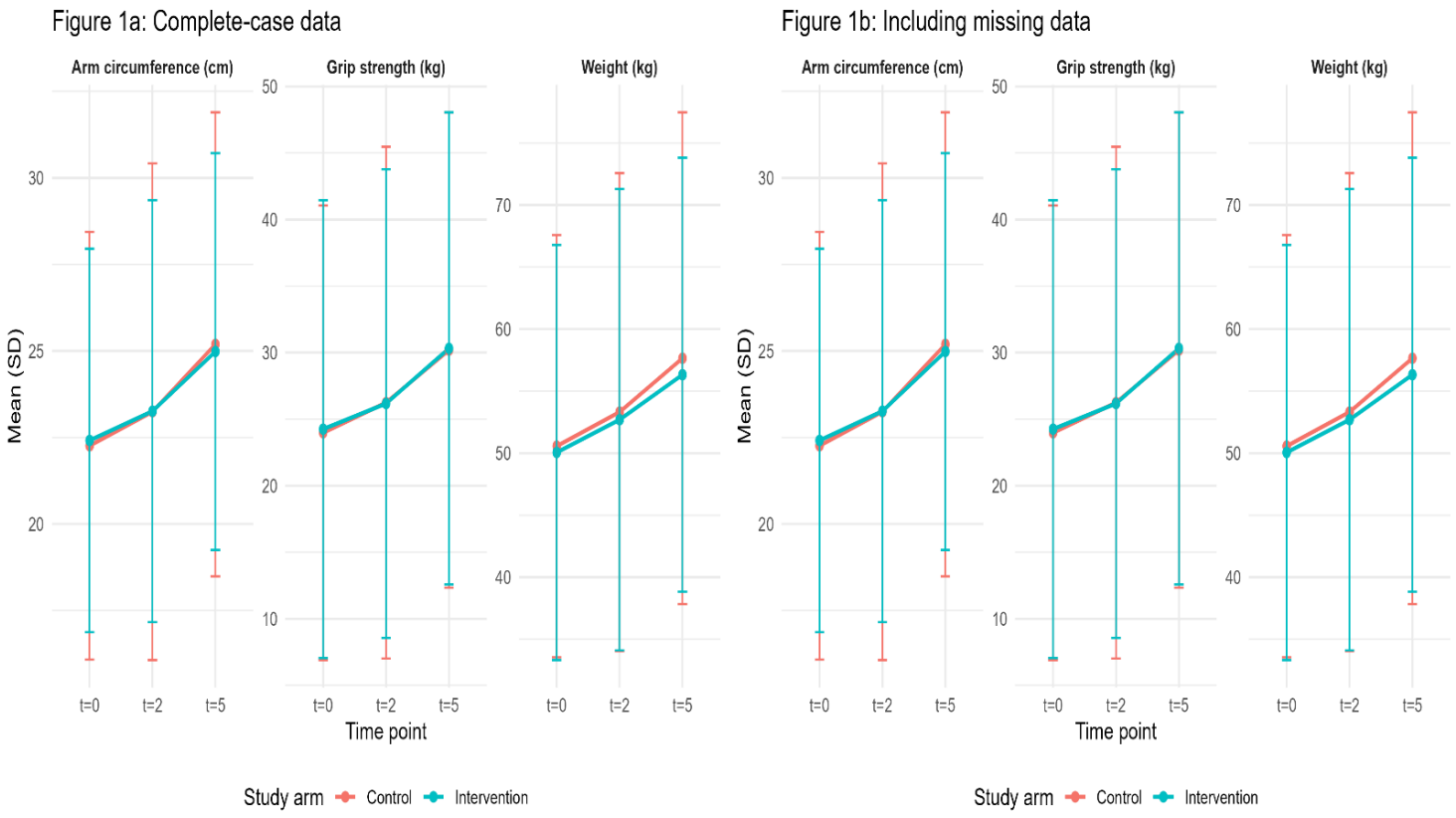


Figure 1

The mean outcome estimates and corresponding error bars by treatment arm over time.,

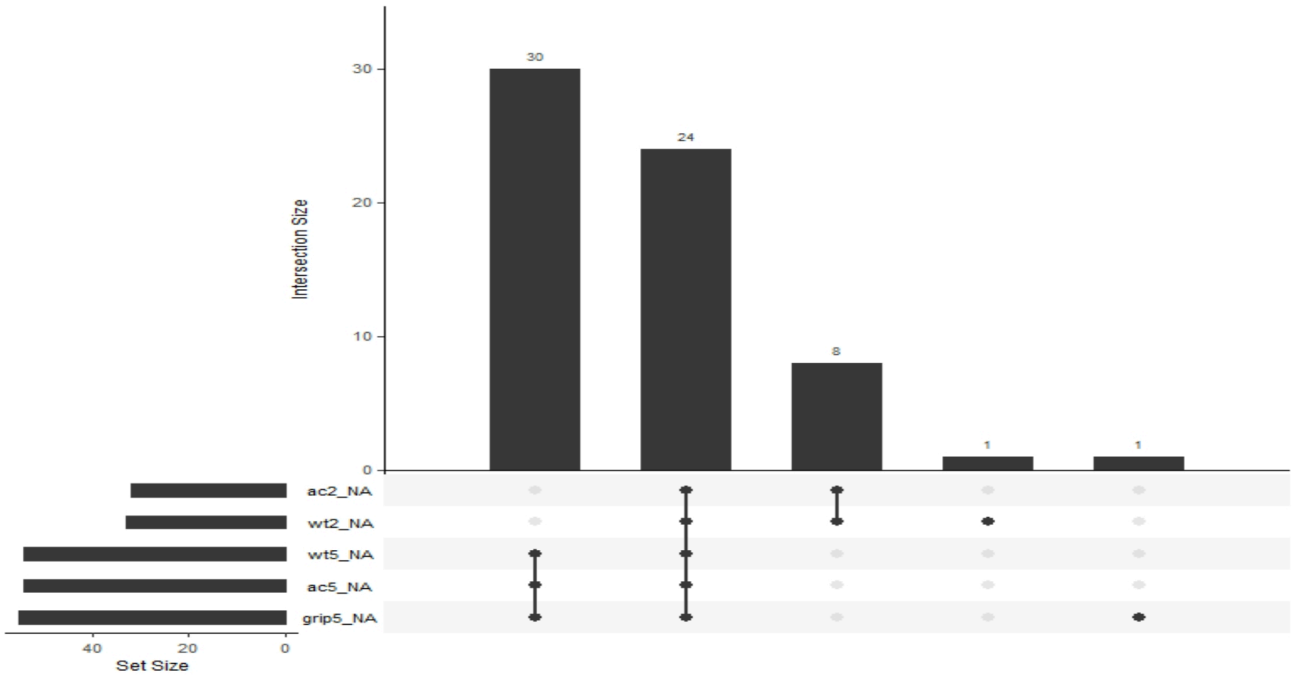


Figure 2

The UpSet plot to visualize the distribution and overlap of missing data among five follow-up outcome variables

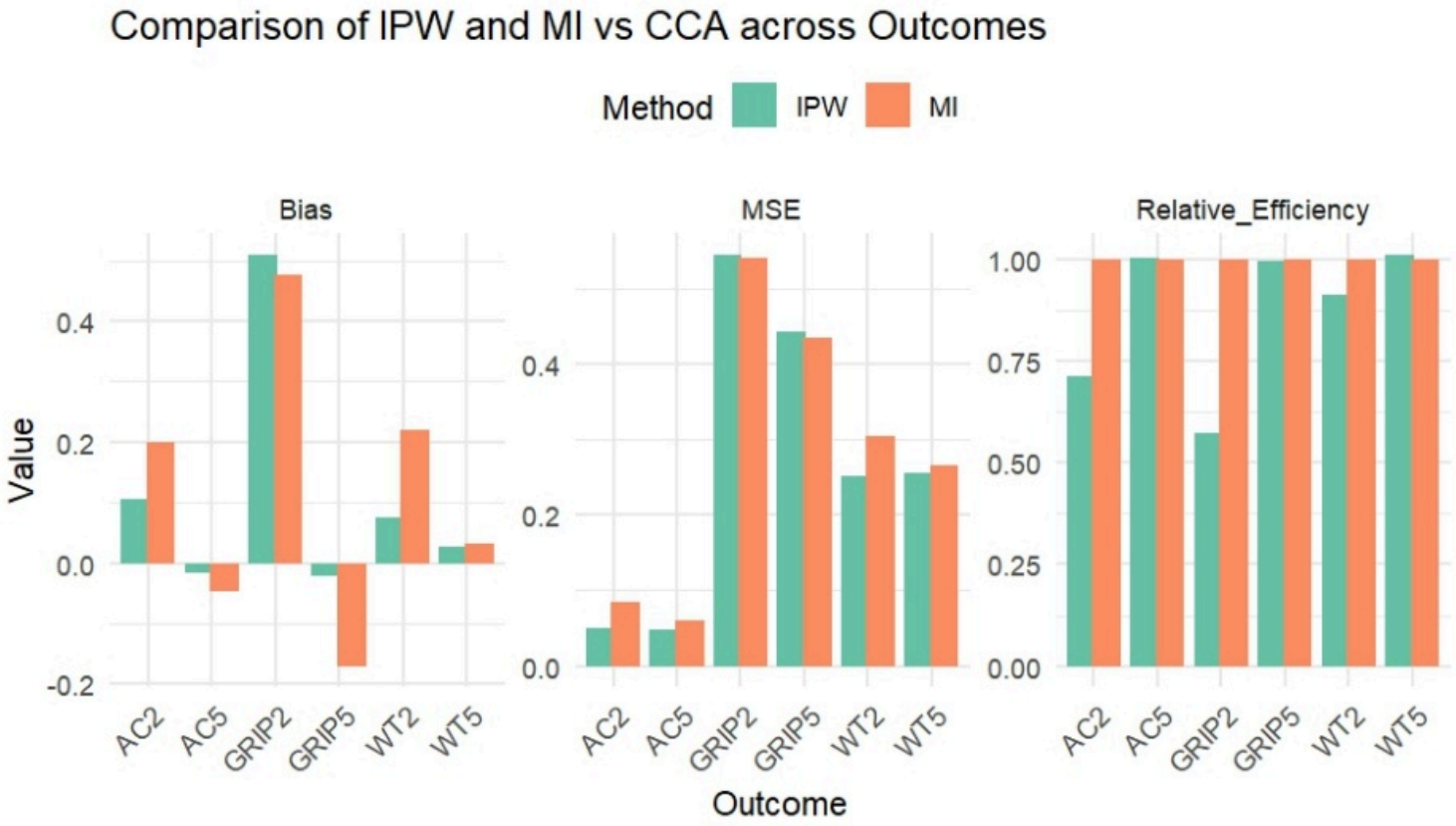


Figure 3

Comparison of CCA and MI against PS-IPW methods across outcomes

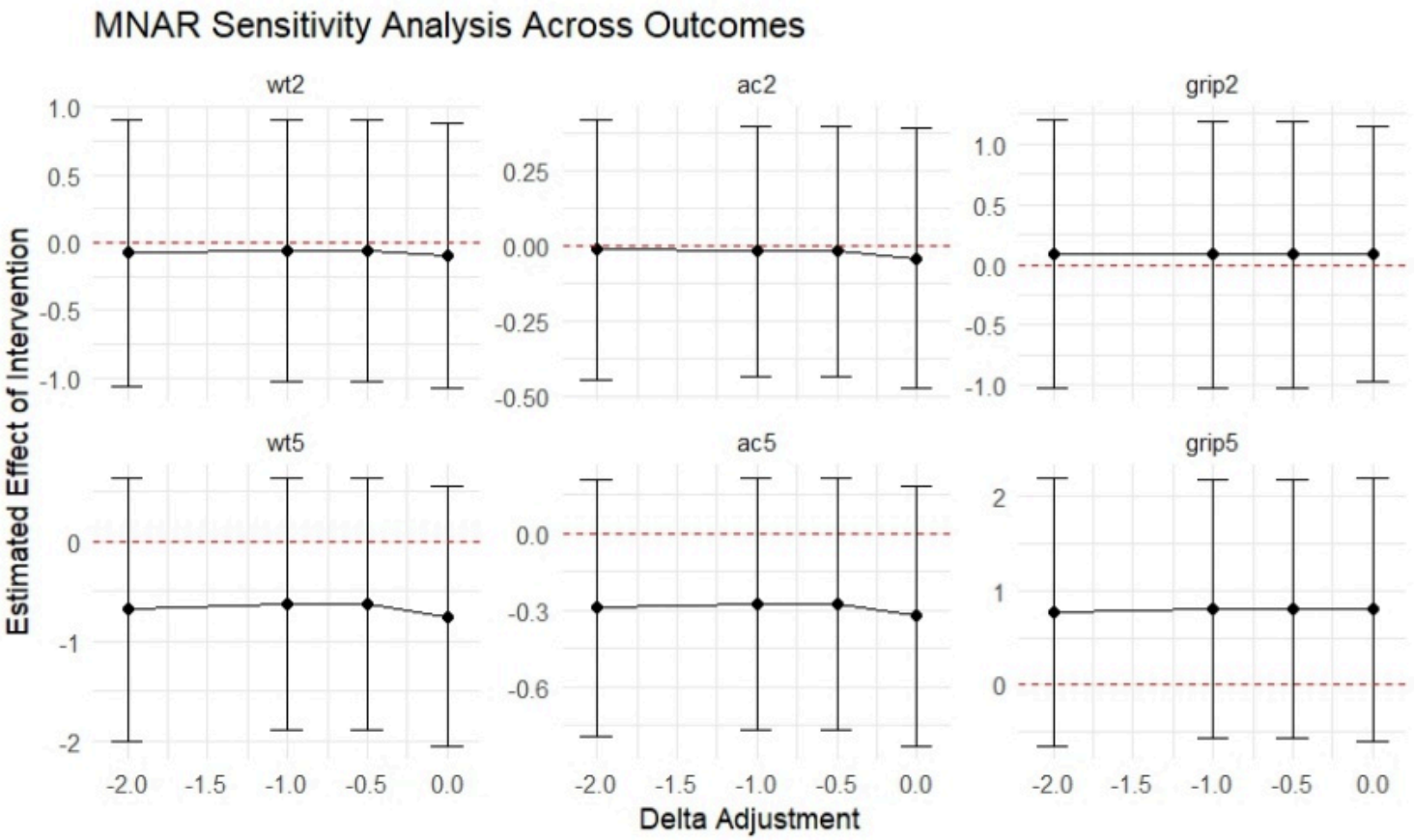


Figure 4

MNAR Sensitivity analysis with bars showing confidence intervals