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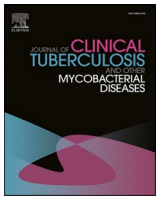

Negative effects of undernutrition on sputum smear conversion and treatment success among retreatment cases in Uganda: A quasi-experimental study

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ABSTRACT

Rationale: The causal relationship between undernutrition and response to anti-tuberculosis (TB) treatment and TB treatment outcomes among people with retreatment TB is understudied.
Objective: To evaluate the effect of undernutrition on treatment success and sputum smear conversion among people with retreatment drug-susceptible TB in Kampala, Uganda.
Methods: We conducted a quasi-experimental study utilizing propensity score weighting among people with retreatment drug-susceptible TB aged ≥ 15 years treated between 2012 and 2022 in Kampala. The primary exposure was undernutrition assessed using the mid-upper arm circumference at the time of TB diagnosis. The primary outcome was treatment success defined as cure or treatment completion at month 6. Sputum smear conversion was the secondary outcome and was measured as a change in sputum smear status from positive to negative at months 2, 5, and 6. We estimated the causal effect of undernutrition on the outcomes using a propensity-score weighted modified Poisson regression model with robust error variance.
Measurements and main results: Of the 605 participants, 432 (71.4 %) were male, 215 (35.5 %) were aged 25–34 years, 427 (70.6 %) had bacteriologically confirmed pulmonary TB, 133 (22.0 %) were undernourished and 398 (65.8 %) achieved treatment success. Of participants with bacteriologically confirmed pulmonary TB, 232 (59.0 %), 327 (59.3 %), and 360 (97.6 %) achieved sputum smear conversion at months 2, 5, and 6, respectively. Undernutrition reduced treatment success (RR 0.42, 95 % CI 0.32–0.55) as well as sputum smear conversion at months 2 (RR 0.45, 95 % CI 0.42–0.49) and 5 (RR 0.46, 95 % CI 0.43–0.51) but not month 6 (RR 0.99, 95 % CI 0.97–1.02).
Conclusion: Undernutrition negatively impacts treatment outcomes. Therefore, nutritional assessment should be an integral component of TB care, with nutritional counseling and support offered to those undernourished to optimize their TB treatment response and outcomes.

1. Introduction

Tuberculosis (TB) and malnutrition adversely affect each other via several pathways [1]. TB is associated with inadequate nutrient intake due to a loss of appetite thus leading to or exacerbating existing undernutrition [1]. Undernutrition causes immunodeficiency hence increasing susceptibility to TB disease, worsening TB disease severity, and increasing the risk of death among people with TB [2]. Undernutrition is generally prevalent among people with TB [3] but people with retreatment TB have a three-fold higher likelihood of being undernourished compared to those newly diagnosed with TB [4].

Evidence from a systematic review and *meta*-analysis of global observational data of people with TB who received treatment between 1990 and 2022 found a pooled prevalence of malnutrition of 48 % (95 % confidence interval 40.9–55.2) [5]. Furthermore, the review showed that undernutrition is more prevalent among males than females, among people with bacteriologically confirmed pulmonary TB (PTB), low-income status, and rural residents. The review reported a pooled

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prevalence for mild, moderate, and severe malnutrition at 21.4 %, 14.0 %, and 29.4 %, respectively [5]. Mortality among people with TB who have moderate or severe malnutrition (as measured by the body mass index—BMI) has been reported as 8.9 % and 16.3 % respectively, while that among those well-nourished is as low as 3.1 % [6]. Notable factors associated with an increased likelihood of undernutrition include low daily food frequency (food insecurity), HIV, diabetes mellitus, and age at the extremities (younger and older persons) per a study in Burkina Faso [7]. In Ethiopia, a large family size, younger age, and low dietary diversity have been reported as factors associated with an increased likelihood of undernutrition among people with TB [4].

While many studies have shown that undernutrition is associated with poor treatment outcomes, the evidence is largely for people with drug-resistant TB [8]. In Uganda, few studies have reported on malnutrition among people with TB [9–12]. Of the existing studies, none has focused primarily on malnutrition among people with retreatment TB despite their elevated risk for developing multi-drug resistant TB and mortality [13,14]. There is a need to examine the effect of undernutrition on response to TB treatment and treatment outcomes among people with retreatment TB. Therefore, we evaluated the effect of undernutrition on sputum smear conversion and treatment success among people with retreatment drug-susceptible TB treated with a 6-month anti-TB regimen in Kampala, Uganda.

Our evidence contributes to understanding the significance of malnutrition among people with retreatment drug-susceptible TB in Uganda and other settings with a high prevalence of malnutrition and TB co-morbidity.

2. Methods and materials

2.1. Description of data

The data were collected from six TB clinics in Kampala, the capital city of Uganda. Between January and February 2022, trained research assistants retrieved clinical and sociodemographic data from TB registers. The data retrieval targeted people with retreatment drug-susceptible TB aged $\geq$ 15 years and treated with either the 6-month anti-TB regimen comprising Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol for 2 months followed by Isoniazid and Rifampicin for 4 months—2RHZE/4RH, or the 8-month anti-TB regimen comprising HRZE and Streptomycin (S) for 2 months, then RHZE for 1 month, and lastly RHE for 5 months—2RHZES/1RHZE/5RHE. The patients received treatment between January 2012 and December 2021. We included all bacteriologically confirmed and clinically diagnosed PTB cases as well as people with extrapulmonary TB. People with TB meningitis and osteoarticular TB were excluded from the parent study as treatment is typically longer than eight months, including a possibility of extension depending on the response to treatment. All people with bacteriologically confirmed TB received Xpert MTB/RIF (Cepheid, USA) testing and were all confirmed as rifampicin sensitive before initiating TB treatment. People with confirmed or intermediate rifampicin resistance were excluded as they had drug-resistant TB and needed second-line TB treatment. We also excluded those transferred to other TB clinics as their treatment outcomes were not known. We described the study setting and data in our previous studies [15,16]. The data analyzed were collected to evaluate the effect of a six vs. eight-month anti-TB regimen on treatment outcomes in the anti-TB regimen (ATTIRE) study approved by the Clarke International University Research Ethics Committee (CLARKE-2021–101) and administratively cleared by the Kampala Capital City Authority (KCCA) Directorate of Public Health and Environment (DPHE/KCCA/1301). For this analysis, a waiver of informed consent was provided by the Ethics Committee as approval was granted in the past and data are secondary without identifiers.

2.2. Study design

We designed a quasi-experimental study from observational data as there was no randomization [17,18]. We used propensity score weighting, a statistical approach that enables the approximation of a randomized controlled trial by weighting the exposed and unexposed groups using propensity scores thereby achieving comparability on all observed factors [19,20]. Propensity score weighting reduces selection bias and confounding hence simulating a randomized controlled trial, allowing the estimation of the unbiased effect of an exposure on an outcome [21]. The propensity score is the probability of being in the exposed group conditional on observed characteristics [22] and it ranges from 0 to 1 [23].

2.3. Variables and measurements

2.3.1. Exposure

Undernutrition at the time of TB diagnosis was the exposure. People diagnosed with TB received nutrition assessment using age-specific color-coded mid-upper arm circumference (MUAC) tapes, usually taken by the attending clinician (TB focal person). Measurements were taken at the mid-upper arm, with the individual in standing up or sitting down position, the elbow bent at a 90-degree angle, and the upper arm held parallel to the side of the body. The MUAC measurements were reported as green (G), yellow (Y), or (R) to signify no malnutrition (well-nourished), moderate malnutrition, and severe malnutrition, respectively. The cut-offs for the R, Y, and G MUAC measurements were $<$ 11.5 cm (cm), 11.5 to 12.49 cm, and 12.5 to 26.5 cm, respectively. The exposed group comprised undernourished participants who had yellow or red MUAC measurements and the unexposed group comprised well-nourished participants who had green MUAC measurements. MUAC measurements are cheaper and simpler to perform than BMI [24] and studies show MUAC and BMI produce comparable estimates [24–27]. MUAC has been used to study undernutrition in people with TB in several settings [28–30].

2.3.2. Outcomes

TB treatment success is the primary outcome and was measured on a binary scale (successful vs. unsuccessful) at month 6. Successfully treated participants were those with TB treatment outcomes of cure or treatment completion and unsuccessfully treated participants were those with TB treatment outcomes of treatment failure, death, or loss to follow. The secondary outcome was sputum smear conversion, measured as a change in sputum smear status from positive to negative among participants with a bacteriologically confirmed PTB at months 2, 5, and 6.

2.3.3. Covariates

We included the following baseline covariates: the level of health facility, study sites, age as continuous and separately as a categorical variable, sex, and the type of TB disease classification namely extrapulmonary TB (EPTB), bacteriologically confirmed pulmonary TB (BC-PTB), and clinically diagnosed pulmonary TB (CD-PTB). We also include HIV status, the type of anti-TB regimen, the reason for retreatment of TB (relapse, treatment after failure, treatment after loss to follow-up, other previous treatment, and unknown previous treatment history), the type of directly observed therapy short-course, treatment supporter availability, and the year of TB treatment. These variables are known from the literature to be associated with the study outcomes.

2.4. Statistical analysis

We summarized categorical data as frequencies and percentages, and numerical data as mean and standard deviation if normally distributed or median and interquartile range if skewed. We stratified the baseline covariates by nutritional status and assessed covariate balance using

standardized mean differences (SMD) as p-values are sample size dependent, with an SMD < 0.1 taken indicative of covariate balance. We performed propensity score weighting using the"*PSW package*" in R [31]. First, we identified all baseline covariates known from the literature to influence the study outcome. We constructed a propensity score model using a logistic regression for the exposure (undernutrition) as a function of the baseline covariates. To improve the propensity score model, we included interaction terms and log-transformed variables for those with skewed distribution. We then generated propensity scores using the predicted coefficients of the covariates and used them to weigh both the exposed and unexposed groups. The exposure group was weighted using the reciprocal of the propensity scores (1/propensity score) while the unexposed group was weighted using the inverse of the propensity scores minus one (1/[1-propensity score]), creating a pseudopopulation with both groups balanced on the covariates. We assessed covariate balance across the exposed and unexposed groups using two approaches. First, we plotted a propensity score histogram and considered the distributional similarity of propensity score as suggestive of covariate balance. Second, we compared the standardized mean difference for each covariate across the exposed and unexposed groups and considered an SMD ≤ 0.1 as confirmatory of covariate balance [32–34]. Once we established that the exposed and unexposed groups were comparable on baseline covariates, we estimated the effect of the exposure on the outcomes using a modified Poisson regression analysis with robust standard errors to mitigate the violation of its assumptions, adjusted for the propensity score weights.

We reported the effect estimates as risk ratio (RR) and 95 % confidence interval. We assessed the specification of the propensity score model using a propensity score model specification test, with the null hypothesis as a correct model specification [32]. Furthermore, we assessed the robustness of the causal estimates by comparing them with estimates from non-causal analysis computed using unadjusted and adjusted Poisson regression models, and we reported the findings as supplementary.

We conducted a sensitivity analysis to check the robustness of the causal estimates to unmeasured confounding (hidden bias) in a matched sample. Here, we performed the Rosenbaum Wilcoxon signed rank test to compute the value of Gamma—the odds of treatment assignment hidden bias. We considered a larger change in the odds of the lower or upper bounds of the Gamma value to shift from a significant to non-significant (or vice-versa) value as suggestive of the findings being robust to unmeasured confounders (hidden bias). However, if a small change in the lower or upper bounds of the Gamma value to achieve statistical significance or non-significance from the point of no hidden bias was observed, we concluded that the findings are not robust due to several unmeasured confounders.

2.5. Reporting of findings

We reported the findings following the propensity score analysis guidelines [35] and the guidelines on Improving the Reporting Quality of Nonrandomized Evaluations of Behavioral and Public Health Interventions: The TREND statement [36]. The overall analysis was performed in R Statistical Software and Programming Language (R version 4.2.1).

3. Results

3.1. Participant characteristics

Overall, we studied 605 participants, of whom 432 (71.4 %) were males, 215 (35.5 %) were aged 25–34 years, and slightly more than 7 in 10 had bacteriologically confirmed PTB (Table 1). 133 (22.0 %) participants were undernourished and the majority of the participants were male (69.2 %), 25–44 (67.6 %) years old, and bacteriologically-confirmed PTB (56.4 %). The average age of all participants was 35.2

Table 1
Distribution of participant characteristics by undernutrition.

Variables	Level	All (n = 605)	Undernutrition		P-value
			No (n = 472)	Yes (n = 133)	
		No. (%)	No. (%)	No. (%)	
Health facility level	Health Center III	266 (44.0)	260 (55.1)	6 (4.5)	<0.001
	Health Centre IV	339 (56.0)	212 (44.9)	127 (95.5)	
Sex	Female	173 (28.6)	132 (28.0)	41 (30.8)	0.592
	Male	432 (71.4)	340 (72.0)	92 (69.2)	
Age group (years)	15–24	86 (14.2)	71 (15.0)	15 (11.3)	0.345
	25–34	215 (35.5)	168 (35.6)	47 (35.3)	
	35–44	186 (30.7)	143 (30.3)	43 (32.3)	
	45–54	90 (14.9)	72 (15.3)	18 (13.5)	
	55 and more	28 (4.6)	18 (3.8)	10 (7.5)	
	Mean (SD)	35.2 (10.9)	34.8 (10.1)	36.4 (13.2)	0.134
TB disease classification	EPTB	8 (1.3)	8 (1.7)	0 (0.0)	<0.001
	BC-PTB	427 (70.6)	352 (74.6)	75 (56.4)	
	CD-PTB	170 (28.1)	112 (23.7)	58 (43.6)	
Risk categories	Diabetic patient	1 (0.2)	1 (0.2)	0 (0.0)	<0.001
	Health worker	5 (0.8)	4 (0.8)	1 (0.8)	
	Mentally ill	1 (0.2)	1 (0.2)	0 (0.0)	
	Miner	19 (3.1)	19 (4.0)	0 (0.0)	
	TB contact	448 (74.0)	361 (76.5)	87 (65.4)	
	Tobacco user	76 (12.6)	76 (16.1)	0 (0.0)	
	Uniformed personnel	55 (9.1)	10 (2.1)	45 (33.8)	
Anti-TB regimen	6-month	213 (35.2)	168 (35.6)	45 (33.8)	0.785
	8-month	392 (64.8)	304 (64.4)	88 (66.2)	
Reason for retreatment of TB	Relapse	603 (99.7)	470 (99.6)	133 (100.0)	1.000
	Treatment after failure	2 (0.3)	2 (0.4)	0 (0.0)	
HIV status	Negative	209 (34.5)	181 (38.3)	28 (21.1)	<0.001
	Positive	206 (34.0)	162 (34.3)	44 (33.1)	
	Unknown	190 (31.4)	129 (27.3)	61 (45.9)	
Treatment model	Digital Community DOT	70 (11.6)	34 (7.2)	36 (27.1)	<0.001
	Health facility based	512 (84.6)	431 (91.3)	81 (60.9)	
	Non-digital Community DOT	23 (3.8)	7 (1.5)	16 (12.0)	
Treatment support	No	83 (13.7)	81 (17.2)	2 (1.5)	<0.001
	Yes	522 (86.3)	391 (82.8)	131 (98.5)	

Note: 1) BC-PTB: Bacteriologically confirmed pulmonary TB; 2) CD-PTB: Clinically diagnosed pulmonary TB; 3) DOT: Directly Observed Short Course Therapy; 4) EPTB: Extrapulmonary TB.

± 10.9 years, with those undernourished being slightly younger than those well-nourished (36.4 ± 13.2 vs. 34.8 ± 10.1, p = 0.13). The distribution of participant characteristics across nutritional status was systematically different according to the level of health facility (p < 0.001), TB disease classification (p < 0.001), risk categories, HIV status (p < 0.001), mode of TB treatment (p < 0.001), and TB treatment supporter availability (p < 0.001).

3.2. Covariate distribution before and after propensity score weighting

Table 2 shows covariate distribution before and after propensity score weighting. The participants with and without undernutrition were systematically different regarding the level of health facility, age, risk category, mode of TB treatment, treatment supporter availability, year of TB treatment, TB disease classification, study sites, and transfer-in status before propensity score weighting (all covariates showed an SMD > 0.1). However, after propensity score weighting, the covariate distribution became similar as all of them had an SMD < 0.1, suggesting participants with and without undernutrition were similar based on the covariates.

3.3. Treatment outcome and sputum smear conversion

Of 605 participants (Table 3), 249 (41.2 %) achieved TB cure (51.1 % well-nourished vs. 6.0 % undernourished), 49 (24.6 %) completed TB treatment (19.9 % well-nourished vs. 41.4 % undernourished), 150 (24.8 %) failed TB treatment (19.3 % well-nourished vs. 44.4 % undernourished), and 21 (3.5 %) died (2.1 % well-nourished vs. 8.3 % undernourished). Overall, 398 (65.8 %) participants had a successful TB treatment outcome, mainly among those who were well-nourished compared to those who were undernourished: 71 % vs. 47.4 %. The findings regarding sputum smear conversion were restricted to participants with bacteriologically confirmed PTB who had received sputum smear follow-up testing at specific time points. We observed statistically significant differences in sputum smear conversion between participants with and without undernutrition at months 2 and 5 as both showed a p < 0.001 but not at month 6 (p = 1.000). Of the 605 participants, 427 (70.6 %) had a BC-PTB of whom, 393 (92.0 %) had sputum smear testing at month 2, 383 (89.6 %) at month 5, and 369 (86.4 %) at month 6. Of those who received sputum smear testing, 232 (59.0 %) achieve sputum smear conversion at month 2, (70.3 % well-nourished vs. 9.6 % undernourished), 227 (59.3 %) at month 5 (70.6 % well-nourished vs. 11.0 % undernourished), and 360 (97.6 %) at month 6 (97.7 % well-nourished vs. 97.1 % undernourished).

Table 3
Treatment outcomes at month 6 and sputum smear conversion at months 2, 5, and 6 by undernutrition.

Variables	Level	All (n = 605)	Undernutrition		P-value
			No (n = 472)	Yes (n = 133)	
Treatment success	No	207 (34.2)	137 (29.0)	70 (52.6)	<0.001
	Yes	398 (65.8)	335 (71.0)	63 (47.4)	
Treatment outcomes	Cured	249 (41.2)	241 (51.1)	8 (6.0)	<0.001
	Treatment completed	149 (24.6)	94 (19.9)	55 (41.4)	
	Treatment failed	150 (24.8)	91 (19.3)	59 (44.4)	
	Dead	21 (3.5)	10 (2.1)	11 (8.3)	
	Lost to follow	36 (6.0)	36 (7.6)	0 (0.0)	
Sputum smear conversion					
Month 2 (n = 393)	Positive	161 (41.0)	95 (29.7)	66 (90.4)	<0.001
	Negative	232 (59.0)	225 (70.3)	7 (9.6)	
Month 5 (n = 383)	Positive	156 (40.7)	91 (29.4)	65 (89.0)	<0.001
	Negative	227 (59.3)	219 (70.6)	8 (11.0)	
Month 6 (n = 369)	Positive	9 (2.4)	7 (2.3)	2 (2.9)	1.000
	Negative	360 (97.6)	292 (97.7)	68 (97.1)	

3.4. Effect of undernutrition on treatment success and sputum smear conversion

In propensity-score weighted analysis (Table 4), undernutrition was significantly associated with a reduction in treatment success (RR 0.64, 95 % CI 0.54–0.75) and sputum smear conversion at months 2 (RR 0.45, 95 % CI 0.42–0.49), 5 (RR 0.46, 95 % CI 0.43–0.51), and 6 (RR 0.99, 95 % CI 0.97–1.02).

3.5. Robustness checks

In a non-causal (multivariable regression) analysis, similar findings emerged between undernutrition and treatment success (adjusted RR

Table 2
Covariate distribution before and after propensity score weighting.

	Before propensity score weighting (n = 605)					After propensity score weighting (n = 605)				
	Undernourished		Well-nourished			Undernourished		Well-nourished		
	Mean	SD	Mean	SD	SMD	Mean	SD	Mean	SD	SMD
Level of health facility	1.95	0.21	1.45	0.50	1.33	1.93	0.26	1.92	0.27	0.023
Sex	1.69	0.46	1.72	0.45	−0.06	1.69	0.46	1.70	0.46	−0.022
Age categories	2.71	1.08	2.57	1.04	0.13	2.65	1.09	2.72	1.04	−0.066
Age in years	36.43	13.23	34.83	10.09	0.14	35.44	12.86	36.17	10.78	−0.061
Risk factor	1.65	0.48	1.76	0.42	−0.25	1.74	0.44	1.75	0.43	−0.026
Treatment model	1.85	0.61	1.94	0.29	−0.20	1.93	0.59	1.95	0.32	−0.028
Treatment supporter availability	1.98	0.12	1.83	0.38	0.56	1.98	0.15	1.98	0.15	0.002
HIV status	2.25	0.78	1.89	0.80	0.45	2.37	0.76	2.37	0.83	−0.001
Anti-TB regimen	1.66	0.47	1.64	0.48	0.04	1.65	0.48	1.64	0.48	0.038
Year of TB treatment	7.61	0.00	7.61	0.00	−0.78	7.61	0.00	7.61	0.00	−0.005
Type of TB disease	2.44	0.50	2.22	0.45	0.45	2.39	0.49	2.39	0.50	−0.001
Study site	2.35	1.72	3.50	1.44	−0.73	2.71	1.76	2.81	1.09	−0.065
Transfer-in status	1.80	0.40	1.30	0.46	1.2	1.70	0.46	1.70	0.46	0.014
Sex*age categories	4.64	2.41	4.51	2.29	0.05	4.57	2.44	4.72	2.30	−0.063
Type of TB disease * HIV status	5.53	2.34	4.17	1.93	0.63	5.67	2.19	5.66	2.31	0.002

Note: 1) SMD: Standardized mean difference; 2) SMD < 0.1 suggests balanced covariate between participants with and without undernutrition and vice-versa; 3) SD: Standard deviation.

Table 4
The effect of undernutrition on treatment success at month 6 and sputum smear conversion at months 2, 5, and 6.

		Propensity score weighted analysis	Propensity score unweighted effect estimate (none causal analysis)	
Study Outcomes	**Level**	**RR (95 % CI)**	**aRR (95 % CI)**	**RR (95 % CI)**
Treatment success	No	1	1	1
	Yes	0.64*** (0.54–0.75)	0.89 (0.74, 1.06)	0.67*** (0.57, 0.78)
Month of sputum smear conversion				
Month 2	No	1	1	1
	Yes	0.45*** (0.42–0.49)	0.66*** (0.59–0.73)	0.52*** (0.45–0.55)
Month 5	No	1	1	1
	Yes	0.46*** (0.43–0.51)	0.68*** (0.61–0.76)	0.51*** (0.46–0.56)
Month 6	No	1	1	1
	Yes	0.99 (0.97–1.02)	1.00 (0.98–1.02)	1.00 (0.97–1.02)

Note: 1) Risk ratios are exponentiated coefficients at a 5 % significant level; 2) 95 % confidence intervals in brackets; 3) *$p < 0.05$, ***$p < 0.01$, ***$p < 0.001$; 4) RR: Risk ratio; 5) aRR: Adjusted risk ratio.

[aRR] 0.89, 95 % CI 0.74–1.06) and sputum smear conversion at months 2 (aRR 0.66, 95 % CI 0.59–0.73), 5 (aRR 0.68, 95 % CI 0.61–0.76), and 6 (aRR 1.00, 95 % CI 0.97–1.02). Our propensity score model specification was correct as the null hypothesis could not be rejected following a statistical test (t-test = 18.61, df = 15, p = 0.232). In sensitivity analysis, the lower bound estimate changed from a non-significant (0.5874) to a significant (0.0274) value when the gamma was 1.60 corresponding to a large change in the odds before a change in statistical significance was reached. This implied that our findings are robust to unmeasured confounders.

4. Discussion

Among people with retreatment TB, we found undernutrition adversely impacts treatment outcomes. Our findings of reduced treatment success and sputum smear conversion are supported by previous studies that show similar effects but people with multi-drug-resistant TB [8,9]. Our study among people with retreatment TB is one of the first few studies to demonstrate a potential causal link between undernutrition and treatment success and sputum smear conversion. Our findings might be explained in several ways. First, undernutrition weakens the immune system [37], leading to an increased susceptibility to infectious diseases, delayed immune restoration, slowed recovery from TB disease, and exacerbation of an existing undernutrition. Second, undernourished individuals with TB are less likely to adhere to TB medications as they experience more medication-related side effects [3] leading to suboptimal drug levels, delayed sputum smear non-conversion, and ultimately reduced treatment success. Lastly, sputum smear non-conversion reduces the proportion of people who achieve TB cure and this reflects suboptimal treatment success. Treatment success is reduced if sputum smear conversion status among people with bacteriologically confirmed PTB is suboptimal or even remains unknown [38]. Programmatically, people with TB who do not achieve sputum smear conversion at months 2 and 6 are considered cases of treatment failure and they constitute those with unsuccessful treatment. The effect of undernutrition on treatment success is reinforced by our data showing that 1 in 4 (25 %) participants had failed treatment and the majority were undernourished.

The lack of effect of undernutrition on sputum smear conversion at month 6 requires cautious interpretation. We attribute the finding to the higher proportion of people who had attained sputum smear conversion by month 6, which in our study was around 98 %. Hence, we had a small proportion of participants without sputum smear conversion at the time. Our interpretation is reinforced by findings from an Ethiopian study reporting that at month 5, around 85 % to 99 % of people with TB attain sputum smear conversion [39]. Furthermore, our previous study which compared the effect of anti-TB regimens (six vs. eight) on sputum smear conversions found no difference in sputum smear conversion at month 6 for the same reasons [16].

The implications of our findings for TB control programs are several. Our findings underscore the significance of routine nutritional assessment among people with TB in establishing malnutrition and providing early nutritional intervention (treatment, counseling, education, and support) for those undernourished. Such interventions would improve treatment outcomes among people with TB as a result of boosted immune recovery and better treatment response.

Furthermore, since undernutrition (largely macronutrient deficiencies) might combine with micronutrient deficiencies, early identification of undernutrition would enable micronutrient supplementation hence improving immune recovery, the TB treatment response, and TB treatment outcomes. Findings from a systematic review and *meta*-analysis that evaluated the effectiveness of zinc and Vitamin A (retinol) supplementation on TB treatment response showed that providing a combined zinc and vitamin A supplementation significantly improves early sputum smear conversion by nearly two-fold [40].

Macro and micronutrient supplementation appears important for better TB treatment outcomes. Nutritional support like food rations and micronutrient pills alongside TB treatment has been proven to improve treatment success and weight gain [41]. Additionally, monthly rations of rice and lentils reduce the risk of unfavorable treatment outcomes [42]. However, the overall effectiveness of macro and micronutrient supplementation in improving treatment outcomes in people with TB remains controversial as a review of a few randomized interventional studies shows inconclusive findings. For example, findings of a review published in 2016 show that macronutrient support such as providing free food and high-energy supplements has little or no effect on reducing mortality and improving cure and treatment completion [43]. However, there was modest weight gain and improvement in quality of life. Similarly, the review reported that micronutrient supplementation did not significantly improve cure, treatment completion, or sputum smear non-conversion in people with TB. However, the evidence is based on a few low-quality randomized interventional studies, and the quantity of nutritional supplementation needed remains unclear [43].

Evidence from a recent systematic review of studies published between January 1, 2000, and January 1, 2023 [44], shows that macronutrient supplementation improves TB treatment adherence, which in turn optimizes bactericidal activity, accelerates immune recovery, and combats concurrent infections that worsen malnutrition and TB disease. Overall, although the evidence for nutritional supplementation is mixed, we make a recommendation for macro and micronutrient nutritional support for undernourished individuals with TB given the absence of undesirable effects associated with them. However, more rigorous studies should be done to provide conclusive evidence. Lastly, since undernutrition negatively impacts the progression of TB disease and treatment outcomes, tackling it should be an important component of the End TB strategy [37].

The strengths of our study include utilizing a robust causal analytic approach to achieve comparability between participants with and without undernutrition on measured confounders hence emulating a randomized controlled trial. We correctly specified the propensity score model, both causal and non-causal estimates show the same direction of effect, and findings are robust to hidden bias (unmeasured confounders). Our sample size for the analytic approach was larger compared to those in previous studies, ranging from 90 to 240, ensuring credible estimates [45–47]. Our study has potential limitations and these include possible data inaccuracies in the TB registers due to recording errors although

data analyzed have been validated. There are also reliability concerns around MUAC for assessing malnutrition compared to methods considered robust such as hydrodensitometry, bioimpedance spectroscopy, electronic bioimpedance, and x-ray absorptiometry [48]. However, the robust methods are expensive and not affordable in low-income settings due to inadequate healthcare funding and MUAC has proven adequate for nutritional assessment as shown in previous studies [24–27]. The use of MUAC rather than BMI may have led to overestimation or underestimation of malnutrition in people with TB. We did not have BMI measures because height and weight are not routinely measured in practice. However, MUAC is a stable anthropometric measure in various populations, including children, adults, and pregnant women, making it unlikely to rapidly change over time [25]. Methodologically, our analytic approach does not control for unmeasured and unknown confounders although sensitivity analysis showed that the findings are robust to unmeasured confounders. In summary, our findings demonstrate that undernutrition reduces sputum smear conversion and treatment success among people with retreatment drug-susceptible TB. Therefore, people with TB should receive routine nutritional assessment along with nutritional counseling and support for those undernourished in order to optimize the TB treatment response and treatment success.

Ethical statement

The data analyzed were collected to evaluate the effect of a six vs. eight-month anti-TB regimen on treatment outcomes in the anti-TB regimen (ATTIRE) study approved by the Clarke International University Research Ethics Committee (CLARKE-2021–101) and administratively cleared by the Kampala Capital City Authority (KCCA) Directorate of Public Health and Environment (DPHE/KCCA/1301). For this analysis, a waiver of informed consent was provided by the Ethics Committee as approval was granted in the past and data are secondary without identifiers.

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CRediT authorship contribution statement

Jonathan Izudi: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Francis Bajunirwe:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Adithya Cattamanchi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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