5 Assessment and implications of disease-related malnutrition in adult tuberculosis patients: a scoping review

Submitted

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ABSTRACT

Prevalence of malnutrition in patients with tuberculosis (TB) is estimated at 70%. In this population, malnutrition is associated with a doubled risk of dying. Malnutrition is established as the most important risk factor for re-activation of TB, with a reported 27% attributable risk. This scoping review provides insight in how malnutrition is assessed in studies with TB patients, and the TB-specific implications of malnutrition. Furthermore, we aimed to explore which nutritional interventions are studied in TB patients.

Only 6% of the studies used nutritional assessment methods that attribute to the three domains of the conceptual definition of malnutrition. Functionality is understudied in TB patients. Nevertheless, studies on physical function in TB patients indicate a significant decrease in functionality. Cognitive function as a determinant of mental health has rarely been assessed in adult TB patients. Several studies have reported on mental health problems in TB patients, revealing moderate to strong associations between psychosocial or emotional distress, or (risk for) depression, or anxiety with 24 different factors in patients with TB. Malabsorption may be an underappreciated aspect of malnutrition with regard to TB treatment, as a decreased bioavailability of anti-TB drugs may result in low drug exposure. Changes in body composition may contribute to toxicity of TB drugs in patients with malnutrition. Thirty-five percent of the studies on nutritional interventions did not assess nutritional status at baseline. Primary outcome measures of nutritional intervention studies were mainly other than nutritional parameters. Only two studies referred to national guidelines regarding treatment of malnutrition.

INTRODUCTION

In 2016, tuberculosis (TB) was the infectious disease with the highest number of new patients, i.e., 10.4 million, and the infectious disease with the highest mortality, i.e., 1.7 million that died from TB.[1] The World Health Organization (WHO) 'End TB Strategy' requires a 90% reduction of TB deaths and an 80% reduction in the TB incidence rate by 2030.[2] In recent years, the annual decline in TB incidence worldwide has been very small, i.e., 2%. This annual decline in TB incidence therefore needs to accelerate to a 4–5% by the year of 2020, to reach the first milestones of the WHO's End TB Strategy.[1] TB is highly prevalent among people living in resource limited areas.[1] Hunger-related malnutrition caused by food-insecurity impacts the immune system of these people.[1,3,4] People living in these areas are more likely to be infected with TB because of an impaired immune system and frequent exposure to the bacteria from other infected patients.[1]

Malnutrition is defined as 'a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease' by the European Society for Clinical Nutrition and Metabolism (ESPEN).[3] Prevalence of malnutrition in patients with TB is estimated at 70%, and in this population, malnutrition is associated with a doubled risk of dying.[5] Malnutrition is established as the most important risk factor for re-activation of TB, with a reported 27% attributable risk.[6] Other risk factors include: indoor air pollution (22%), smoking (16%), HIV (11%), alcohol abuse (10%), and diabetes (8%).[6]

In patients with TB, two different types of malnutrition can be present: hunger-related malnutrition before being actively infected and disease-related malnutrition after the active infection, often due to loss of appetite, malabsorption, and/or inflammation-driven catabolism.[3,4] A low body mass index (BMI) is a characteristic of chronic malnutrition such as hunger-related malnutrition.[7] However, disease-related malnutrition leads to loss of fat-free mass, in all individuals including those who are overweight or obese.[3] Therefore, even TB patients with either a normal or high BMI may be malnourished.

A better understanding of the concept of malnutrition and its relation to TB may contribute to the WHO goal of ending the TB epidemic.[2] Malnutrition is considered an important potentially reversible risk factor for TB treatment failure.[8] Throughout the history of European civilisation, nutritional care has been an important, if not the dominant, component of TB treatment. Lacking adequate drugs, Hippocrates' TB treatment consisted of resting, praying, drinking milk, exercise, and avoiding of extreme weather conditions.[9] At the end of the nineteenth century, in the first sanatorium for TB patients, a more specific nutritional regimen was implemented in TB treatment: this diet was 'a mix of meat with plenty of vegetables'.[10] Patients had frequent, smaller meals as this was considered better for their delicate stomachs and wine was important in the diet. Furthermore, to treat symptoms

Table 1. Operationalisation of malnutrition as assessed in studies in patients with TB

Study	Year of publication	Country	Reported type of study [A]	Number of TB patients assessed for malnutrition [B]
Frediani JK, et al.[86]	2015	Georgia	(Prospective cohort)	191
Wondwossen A, et al.[87]	2015	Ethiopia	Prospective cohort	124 (including children)
Medellin-Garibay SE, et al.[88]	2015	Mexico	Longitudinal prospective	48
Bacelo AC, et al.[62]	2015	Brazil	Observational prospective follow-up	68
Ezeamama AE, et al.[89]	2015	Uganda	Longitudinal	208 (including children)
Golemba AS, et al.[90]	2015	Argentina	observational and descriptive	118 (including children)
Brake te LHM, et al. [91]	2015	Indonesia	descriptive	36
Maeda S, et al. [92]	2014	Vietnam	Cohort	464 [C]
Tian PW, et al. [93]	2014	China	Retrospective case control	480
Yuan K, et al.[22]	2013	China	(Prospective)	29
Nyendak MR, et al. [94]	2013	Uganda	Prospective cohort	50
Miyata S, et al. [18]	2013	Japan	(Retrospective)	53
Bhargava A, et al.[5]	2013	India	Retrospective cohort study	1523 [C]
Piva SG, et al.[95]	2013	Brazil	cross sectional descriptive study	72 (including children)
Rudolph M, et al. [75]	2013	South Africa	(pilot intervention)	87
Gupta S, et al. [96]	2012	India	Cross-sectional observational	45 (including children)
Lins TB, et al.[21]	2012	Brazil	Retrospective cohort	115
Kawai K, et al. [97]	2011	Tanzania	Observational	887
Schön T, et al. [98]	2011	Ethiopia	Controlled randomized clinical trial	179 [C] (including children)
Miyata S, et al. [19]	2011	Japan	(Prospective)	39 (including children)

	Percentage of HIV/ AIDS infected TB patients	Type of TB	Method used to assess malnutrition	Prevalence of malnutrition among TB patients [E]
	Not specified	Pulmonary	BMI<18.5 kg/m^2	24%
	Not specified	Pulmonary and extrapulmonary	BMI<18.5 kg/m^2	3.2% [F]
	0% (were excluded from study)	Various locations, including pulmonary	BMI<18.49 kg/m^2	21.7%
	32.4%	Pulmonary, extrapulmonary & disseminated	biomarkers (4 anthropometric, 4 haematological, 2 biochemical and 5 micronutrients)	100%
	100%	Pulmonary	BMI<18.5 kg/m^2	33.2% [F]
	5.1%	Various types, including pulmonary	BMI≤20 kg/m^2	6.1% [F]
	0% (were excluded from study)	Pulmonary	BMI<18.5 kg/m^2	30.6%
	8.2% [D]	Pulmonary	BMI<18.5 kg/m^2	55.2% [F]
	25.3% [D]	Pulmonary	BMI<18.5 kg/m^2 and/or serum albumin < 30 g/L	28.5%
	0%	Spinal	serum total protein: <50 g/L	17.2%
	0% (were excluded from study)	Pulmonary	BMI≤17 kg/m^2	30.0%
	Not specified	Pulmonary	Full Mini Nutritional Assessment	73.6%
	2.3%%	Pulmonary	BMI<18.5 kg/m^2	89.2%
	Not specified	Pulmonary	BMI<18.5 kg/m^2	50.0%
	67.0%	Not specified	Examination of hair, eyes, lips, gums, tongue, skin and nails.	50.0%
	Not specified	Pulmonary	BMI<18.5 kg/m^2	73.3% [F]
	53.0%	Pulmonary, disseminated, pleuropulmonary, lymph node, central nervous system, intestinal, osseous	Albumin <3.4 g/dL	70.0%
	53.1%	Pulmonary	BMI<18.5 kg/m^2	43.3%
	38.3%	Pulmonary	BMI<18.5 kg/m^2	Not given
	Not specified	Pulmonary	Subjective Global Assessment	69.2% [F]

Table 1. Operationalisation of malnutrition as assessed in studies in patients with TB (*continued*)

Study	Year of publication	Country	Reported type of study [A]	Number of TB patients assessed for malnutrition [B]
Podewils LJ, et al.[99]	2011	Latvia	Retrospective	995
Ollé-Goig JE [100]	2010	Uganda	Observational	576 [C] (including children)
Kim JH, et al.[101]	2010	South Korea	(Prospective)	23
Mupere E, et al. [102]	2010	Uganda	Cross-sectional	445
Jong de BC, et al.[103]	2009	Gambia	(Prospective)	214 [C] (including children)
Martins N, et al.[104]	2009	Timor-Leste	Parallel group randomised controlled trial	268 [C]
Pakasi TA, et al. [105]	2009	Indonesia	cross-sectional	300 (including children)
Pakasi TA, et al.[106]	2009	Timor & Indonesia	case-control	121
Ulasli SS, et al. [107]	2009	Turkey	Retrospective cohort	24
Ramakrishnan K, et al. [108]	2008	India	Cross-sectional	40
Dodor EA [109]	2008	Ghana	Interventional	570
Bose K, et al.[110]	2007	India	comparative	282 (including children)
Warmelink G, et al. [111]	2007	The Netherlands	Retrospective	32
Oosterhout van JJ, et al.[112]	2007	Malawi	(Prospective)	27
Karyadi E, et al.[113]	2007	Indonesia	Case control	41 (including children)

[A] When no informative description was given by the authors on the type of study, the authors put their interpretation between parentheses.
[B] If children (people <18 years of age) were included, this was mentioned between parentheses. If data on children and adults was separated in studies that included both adults and children, data from the child group was not included in this table.
[C] Not every TB patient in this study was assessed for malnutrition.
[D] Not every TB patient in this study was assessed for HIV/AIDS.
[E] If there were several groups of TB patients that were compared, the prevalence of malnutrition was calculated by the authors of this review
[F] Prevalence among adults not clear as there was no distinction made between children and adults.

	Percentage of HIV/ AIDS infected TB patients	Type of TB	Method used to assess malnutrition	Prevalence of malnutrition among TB patients [E]
	3.9% [D]	Pulmonary	BMI<18.5 kg/m^2	20.0%
	66.7% [D]	Not specified	BMI≤18.4 kg/m^2	54.3% [F]
	0% (were excluded from study)	Pulmonary	2 anthropometric markers and 4 lab values	34.8%
	44.0%	Pulmonary	BMI<18.5 kg/m^2	39.6%
	9.2% [D]	Pulmonary	BMI<16 kg/m^2 for adults >20 years of age, BMI-for-age-Z-score <3 for participants <20 years of age	17.3%
	Not specified	Pulmonary	BMI<18.5 kg/m^2	79.5%
	Not specified	Pulmonary	BMI<18.5 kg/m^2	83% [F]
	Not specified	Pulmonary	BMI≤18.5 kg/m^2	86.8%
	Not specified	Various locations	BMI<20 kg/m^2	50.0%
	50.0%	Pulmonary	BMI<18.5 kg/m^2	52.5%
	0% (were excluded from study)	Pulmonary	BMI<18.5 kg/m^2	51.0%
	Not specified	Not specified	BMI<18.5 kg/m^2	54.3% [F]
	28.1%	Not specified	weight loss >5% within 1 month and/or BMI<18.5 kg/m^2	62.5%
	100%	Pulmonary	BMI<18.5 kg/m^2	78.0%
	Not specified	Pulmonary	BMI<18.5 kg/m^2	65.9% [F]

like night sweats, cognac was used.[10] Finally, in the first randomized trial testing the potential of streptomycin injections, the control-standard care consisted of nutrition and bed rest.[11] These historical nutritional advices were at best experience-based or worst case-based on assumptions only, and as to the best of our knowledge, their effectiveness has not been studied.

It was not until 2013 that the WHO presented their first guideline on nutritional care and support specifically for TB patients. In this guideline, to prevent failure of the treatment, the WHO stressed that all patients with active TB should receive individualized nutritional assessment and management, including dietary counselling and nutritional interventions.[12] However, currently no nutritional assessment tool validated in TB patients is available. Moreover, little is known on how malnutrition impacts patients on TB, and consensus on which nutritional interventions are effective is lacking. This scoping review provides insight in how malnutrition is operationalized in studies with TB patients, and describes the TB-specific implications of malnutrition. Furthermore, we aimed to explore which nutritional interventions are studied in TB patients, after the WHO guideline on nutritional care and support for patients with TB was published.

Operationalization of malnutrition as assessed in studies in patients with TB

The consensus definition of malnutrition by ESPEN is merely a conceptual definition; due the absence of a gold standard for diagnosing malnutrition, it is still debated how malnutrition should be operationalized.[13] In 2015, ESPEN published their first consensus on diagnostic criteria for malnutrition, [14] but these criteria are subject to discussion.[15]

To report on how malnutrition is assessed in studies on TB, we determined the extent of content validity of the nutritional assessment methods used, by evaluating the attribution of these methods to the three domains of the ESPEN definition of malnutrition. These domains are: uptake or intake of nutrition (Domain A), body composition (Domain B), and physical and mental function (Domain C).[16,17]

On March 24th 2017, PubMed, CINAHL, and Cochrane Central one author searched for studies written in the English or Dutch language and published from 2007, to provide a time frame of the most recent decade. A broad search strategy was performed. Details on the search strategy, criteria, study selection, and data collection are presented in **Annex 1**. The search identified a total of 321 studie, sfrom which 62 duplicates were removed. The remaining 259 studies were screened by title and abstract (see **Annex 2** for details on criteria), which resulted in the removal of 156 inappropriate studies. Based on their full-text, 103 studies were assessed, from which 68 studies were removed, which resulted in the inclusion of 35 publications, as shown in **Table 1. Figure 1** shows a flow chart of the selection process.

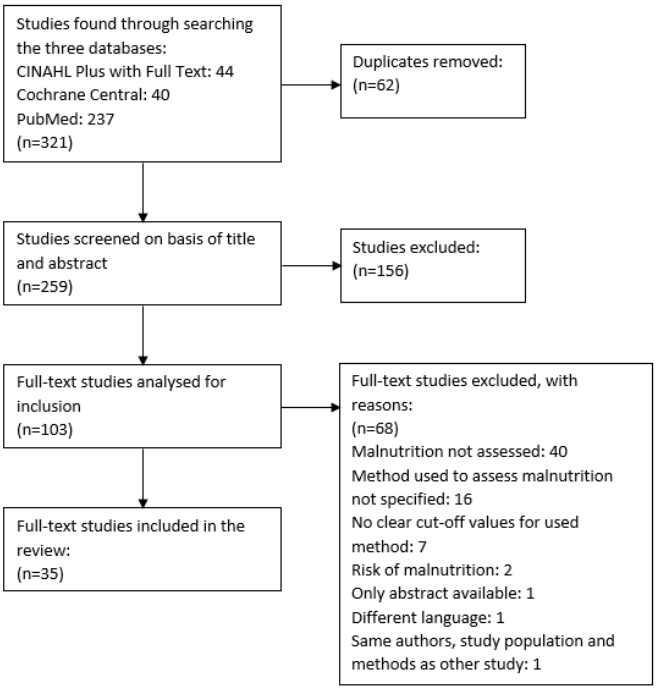

Figure 1: Flow chart of the selection process

Among these 35 studies, four were RCTs or non-randomized interventional studies, three case control studies, and 28 observational studies. Ten different methods to operationalize malnutrition were found. The sole use of BMI (with various cut-off points) was counted as one, two other methods included BMI optionally combined with other parameters. **Table 2** gives an overview of these methods, their frequency of use and their coverage of three domains of the definition of malnutrition. Eighty-six percent (30/35) of the studies used a unidimensional tool, i.e. assessing solely one domain. In only 2/35 (6%) of the studies a method was used that attributed to all three domains: the full Mini Nutritional Assessment (MNA) and the Subjective Global Assessment (SGA).[18,19] Three methods attributed to none of the three domains: Examination of hair, eyes, lips, gums, tongue, skin and nails, albumin <3.4 g/dL and serum total protein: <50 g/L.[20-22] BMI, with different cut-off values, was used to assess malnutrition in 74% (26/35) of the studies.

Implications of malnutrition in patients with TB

In disease in general, malnutrition is reported to have a huge impact on patients' outcomes and healthcare costs.[23] Postoperative complications, risk of injury from falling, hospital-acquired infections, risk of death, and costs of care are significantly higher in malnourished patients.[24-28] The specific implications of malnutrition with regard to patients with TB will be discussed here.

Table 2: Nutritional assessment methods and their coverage of the domains of the definition of malnutrition [3]

Nutritional assessment method	Frequency of use	Coverage of the domains of definition of malnutrition		
		Intake or uptake of nutrients	Body composition	Function
BMI <18.5 kg/m^2	19		✓	
BMI ≤18.5 kg/m^2	1		✓	
BMI <18.49 kg/m^2	1		✓	
BMI ≤18.4 kg/m^2	1		✓	
BMI ≤20 kg/m^2	1		✓	
BMI <20 kg/m^2	1		✓	
BMI ≤17 kg/m^2	1		✓	
BMI < 16 kg/m^2 for adults over 20 years of age BMI-for-age-Z-score <3 for participants under 20 years of age	1		✓	
weight loss >5% within 1 month and/or BMI <18.5 kg/m^2	1		✓	
biomarkers (4 anthropometric, 4 haematological, 2 biochemical and 5 micronutrients) [5]	1		✓	
2 anthropometric markers and 4 lab values [6]	1		✓	
BMI <18.5 and/or serum albumin < 30 g/L	1		✓	
Albumin <3.4 g/dL	1			
serum total protein: <50 g/L	1			
Full Mini Nutritional Assessment	1	✓	✓	✓
Subjective Global Assessment	1	✓	✓	✓
Examination of hair, eyes, lips, gums, tongue, skin and nails. [7]	1			

5,6,7: see Annex 5,6,7

Physical function

In general, disease-related malnutrition is associated with a decline in several physical functions, such as muscle, cardiovascular, renal, respiratory, gastrointestinal, thermo-regulation, and immune function, and wound healing.[4,29-39] Physical function, in combination with functional capacity or 'fitness', is the individual's capacity to undertake everyday tasks.[40] Being able to perform everyday tasks is crucial for living independently and for participating in society, as regaining of physical function shortens the time needed for recovery and enables TB patients to resume work.[41]

In three case-control studies proxy measures of physical function were evaluated. One study, in which physical function was operationalized as six-minute walk distance, found significantly lowered distances in patients newly diagnosed with TB.[42] Another study using accelerometry and heart rate monitoring reported a reduced level of activity in patients with

TB.[43] A third study reported severe decrease in handgrip strength in TB patients prior to treatment.[44]

Mental function

Otherwise healthy adults with an insufficient diet may have severe emotional distress and depression.[45] We defined mental function as 'mental health' according to the WHO definition: 'Mental health is defined as a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community'.[46] Assessment of cognitive function, as a determinant of mental health, is uncommon in the somatic adult population, except for elderly patients.[4]

To our knowledge, no studies reporting in the English language have been carried out to explore cognitive function in adult TB patients, except for patients with TB meningitis. Apart from cognitive function, mental health in TB patients may be determined by either psychosocial or emotional distress, or (risk for) depression, or anxiety. The prevalence of depression and anxiety in patients with TB has been reported to be 43% and 42% respectively in one study.[47]

Observational cohort studies reporting on psychosocial or emotional distress, or (risk for) depression, or anxiety in patients with TB found associations between these determinants of mental health and: male gender, and in another study female gender, older age, lower education, marital status, disease duration, extra-pulmonary TB, multi-drug resistant-TB (MDR-TB), previous treatment for TB, HIV coinfection, low BMI, dyspnoea, drug toxicity, poverty, unemployment, comorbidities, presence of ≥4 symptoms, pain, night sweats, and low perceived social support, perceived stigma, substance abuse, being in intensive phase of treatment, undergoing treatment longer than 6 months, and a family history of mental illness.[47-56]

Malnutrition-related clinical outcomes

Malabsorption

In general, malnutrition may be associated with malabsorption of nutrients, both as an effect and as a cause.[4] Malnutrition may cause malabsorption of drugs as well, by decreasing the gastro-intestinal function. As bioavailability of oral drugs largely depends on the absorption capacity of the digestive tract, malabsorption of drugs due to malnutrition may influence bioavailability of drugs.[57] Malabsorption may be an underappreciated aspect of malnutrition with regard to TB treatment, as a decreased bioavailability of anti-TB drugs may result in low drug exposure. The latter causes treatment failure and development of drug resistance.[6]

Toxicity

To estimate the dose required to achieve adequate plasma concentration of anti TB drugs, the volume of distribution, a proportionality factor, of a drug is used. The volume of distribution varies with body composition.[58] Fat-free mass determines the volume of distribution of many hydrophilic TB drugs. A lowered volume of distribution and impaired capacity of liver and kidney for drug elimination as a result of malnutrition may result in higher exposure to hydrophilic first line anti-TB drugs, such as isoniazid and pyrazinamid.[59] Such a change in body composition may therefore contribute to toxicity of TB drugs in patients with malnutrition. Malnutrition in obese patients (i.e. low fat-free mass with high total body weight) was reported to result in overdosing of ethambutol if dosing is calculated based on the total body weight.[60]

NUTRITIONAL INTERVENTION STUDIES IN PATIENTS WITH TB

In addition to the recommendation that all TB patients are entitled to adequate nutritional care, the WHO states that nutritional management of malnutrition in TB patients should be no different than in other patients, and should be aimed at restoration of nutritional status.[12] Nevertheless, malnutrition remains highly prevalent in TB patients.[5]

To explore which nutritional interventions in TB patients have been conducted since the publication of the WHO guideline, a literature search was performed. On June 23rd 2017, CINAHL, Cochrane Central and PubMed one author searched for studies on nutritional interventions in adult TB patients. Studies in the English or Dutch language that were published in or after 2013 were included. A broad search strategy that was adjusted to each database was performed. For details on the search strategy, see **Annex 3.** The search identified 116 studies, 86 of which remained after removal of 30 duplicates. In addition, we added 6 studies that were published in 2013 or later not identified through this search, but cited in the systematic review 'Nutritional supplements for people being treated for active tuberculosis (2016)'.[61] In total, 92 studies were screened by title and abstract (see **Annex 4** for details on criteria), after which 62 studies were removed. Thus, 30 studies were assessed based on their full-text, from which 13 studies were removed, which resulted in the inclusion of 17 publications, as shown in **Table 3A**. Two studies were performed in the same study population but with a different primary outcome parameter.[62,63] **Figure 2** shows a flow chart of the selection process.

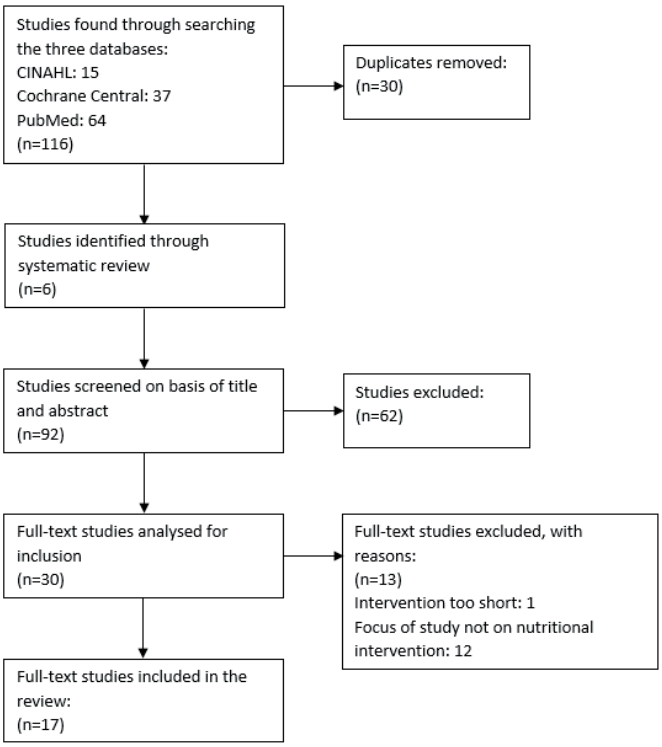

Figure 2: Flow diagram of selection process

As shown in **Table 3A**, 2/17 (12%) studies provided individual dietary counselling,[62,63] whereas 15/17 (88%) provided a supplementation.[64-78] Five studies provided a protein/amino acid or energy supplementation, four of which combined this with micronutrient supplementation. Furthermore, eight studies provided solely micronutrient supplementation: vitamin A, D, and/or zinc, and two studies provided solely a food extract supplement, ginger extract and channa striatus.

Five studies reported significantly positive results with regard to a nutritional parameter such as weight gain, or handgrip strength. Three of these five studies included protein/amino acid or energy supplementation, the other two studies solely provided micronutrients. Six studies reported significantly positive results with regard to primary outcome parameters, such as resolution of chest radiograph abnormalities or rifampin exposure. In four of these six studies only micronutrients, and in two protein/amino acid or energy, combined with micronutrients were supplemented.

Fifteen out of 17 studies were RCT/interventional studies, the other two were observational studies. As shown in **Table 3B**, in 65% of the studies (11/17), a nutritional parameter was assessed at baseline. In 59% of the studies (10/17) a nutritional parameter was assessed at the end of the study. Studies that did not assess a nutritional parameter at baseline (35%,

Table 3A. General details of nutritional intervention studies (n=17)

First author, year of publication and country	Reported type of study	Nutritional intervention
Bacelo AC, *et al.* (2017) Brazil [63]	Observational prospective follow-up study	Dietary counseling according to the Brazilian Ministry of Health
Bacelo AC, *et al.* (2015) Brazil [62]	Observational prospective follow-up study	Dietary counseling according to the Brazilian Ministry of Health
Kulkarni RA, *et al.* (2016) India [64]	Randomized, placebo-controlled trial	250 mg. of ginger extract, twice a day after a meal
Tukvadze N, *et al.* (2015) Georgia [65]	Bouble-blind, randomized, placebo-controlled, intent-to-treat trial	50,000 IU (1.25 mg) vitamin D_3 orally 3 times weekly for 8 consecutive weeks followed by 50,000 IU vitamin D_3 orally every 2 wk for an additional 8 wk.
Mily A, *et al.* (2015) Bangladesh [66]	Randomized, double-blind, placebo-controlled trial	(1) placebo PBA and placebo vitD3 or (2) 500 mg twice daily of PBA and placebo vitD3 or (3) placebo PBA and 5000 IU of vitD3 once daily or (4) PBA+vitD3.
Daley P, *et al.* (2015) India [67]	Randomized, double-blind, placebo-controlled, superiority trial	four doses of tasteless, odorless 2·5 mg vitamin D3 oil (100 000 IU per dose) orally, once every 2 weeks for 8 weeks
Denti P, *et al.* (2015) Tanzania [68]	Open-label randomized clinical trial	Biscuit containing 1000 kcal and vitamins and minerals
Farazi A, *et al.* (2015) Iran [69]	Randomized placebo-controlled trial	L-arginine (1000 mg pure L-arginine hydrochloride) or placebo (1000 mg sugar), twice daily administered orally
Kawai K, *et al.* (2014) Tanzania [70]	Randomized, double-blind, placebo-controlled trial	micronutrients (5000 IU retinol, 20 mg vitamin B1, 20 mg vitamin B2, 100 mg niacin, 25 mg vitamin B6, 50 μg vitamin B12, 500 mg vitamin C, 200 mg vitamin E, 0·8 mg folic acid, 100 μg selenium)
Jeremiah K, *et al.* (2014) Tanzania [71]	open-label, randomized, controlled clinical trial	high-energy and vitamin/mineral-enriched biscuits
Guzman-Rivero M, *et al.* (2014) Bolivia [72]	(randomized clinical trial)	315 mg of zinc gluconate
Salahuddin, *et al.* (2013) Pakistan [73]	randomized double blinded, multi-center, placebo-controlled clinical trial	600,000 IU of intramuscular vitamin D3 (cholecalciferol) for 2 doses one month apart

	Duration of nutritional intervention	Number of TB patients who received intervention/number of control subjects	Percentage of TB patients infected with HIV	Primary outcome measure
	180 days	68/no controls	67.6%	Self-reported adherence to the counseling
	180 days	68/no controls	67.6%	Recovery from nutritional impairment
	30 days	34/35	0%	Anti-inflammatory effects, as measured by serum TNF alpha, serum Ferritin and serum MDA
	16 weeks	100/99 (placebo)	2.0% (not all TB patients were tested for HIV)	Time to sputum culture conversion
	2 months	72 PBA + vit D, 72 vit D, 72 PBA/72 (placebo)	0% (were excluded from study)	Proportion of TB patients to become culture negative at week 4 and assessment of clinical endpoints at week 8
	8 weeks	121/126 (placebo)	0% (were excluded from study)	Time to sputum culture conversion
	2 months	51/49 (no biscuits)	50.0%	Exposure of isoniazid, pyrazinamide, or ethambutol.
	30 days	32/31 (placebo)	0% (were excluded from study)	Clinical outcome from disease
	8 months	200/223 (placebo)	36.9%	T cell-mediated immune responses as measured by lymphocyte proliferative responses to T-cell mitogens or mycobacterial antigens
	2 months	51/49 (no biscuits)	50%	Rifampin exposure
	3 months	10/11 (placebo)	0% (were excluded from study)	Immune function as measured by PBMC proliferation, production of INF-$_{y}$ and the CD4+/CD8+ ratio
	12 weeks	132/127 (placebo)	0% (were excluded from study)	Weight gain and resolution of chest radiograph abnormalities.

Table 3A. General details of nutritional intervention studies (n=17) (*continued*)

First author, year of publication and country	Reported type of study	Nutritional intervention
Ginawi I, *et al.* (2013) India [74]	randomized, double-blind, placebo-controlled trial	placebo or vitamin A or zinc or vitamin & zinc both. Each micronutrient capsule contained 1500 retinol equivalents (5000 IU) vitamin A (as retinyl acetate) and 15 mg Zn (as zinc sulfate).
Rudolph M, *et al.* (2013) South Africa [75]	(Pilot intervention study)	'e'Pap' 100 g daily, mixed with cool or warm water, or sprinkled over cooked food
Paliliewu N, *et al.* (2013) Indonesia [76]	Randomized, placebo-controlled, double-blind pilot study	Channa striatus capsules 2 g. 3 times a day
Singh AK, *et al.* (2013) India [77]	Randomized clinical trial	Group 1: only anti TB treatment Group 2: 500 mg. calcium and 250IU vitamin D, once every day for the first 10 days, then three times a week for the remaining time plus anti TB treatment.Group 3: zinc 50 mg. and vitamin A 25000 IU, once every day for the first week, then three times a week for the remaining time plus anti TB treatment.
Ralph AP, *et al.* (2013) Indonesia [78]	4-arm randomized, double-blind, placebo-controlled factorial trial	(A) active L-arginine 6 g. daily, plus active cholecalciferol 50,000 IU (1250 mcg) at baseline and on day 28; (B) active L-arginine plus placebo cholecalciferol (dosing regimen as above); (C) placebo L-arginine plus active cholecalciferol; (D) placebo L-arginine plus placebo cholecalciferol

	Duration of nutritional intervention	Number of TB patients who received intervention/number of control subjects	Percentage of TB patients infected with HIV	Primary outcome measure
	6 months	Vit.A-47, Zinc-49 and Vit A & Zinc-41/41 (placebo)	Not specified	Tuberculosis treatment
	2 months	87/no controls	67.0% of	Nutritional status
	12 weeks	18/18 (placebo)	0% (were excluded from study)	Cytokine response and sputum smear conversion
	6 months	11 received calcium + vitamin D, 13 received zinc + vitamin A, 13 received no micronutrients	Not specified	Sputum conversion during the first two months of anti TB treatment
	8 weeks	50 in group A, 49 in group B, 51 in group C, 50 in group D.	13.1% (not all patients were tested)	Proportion of participants with negative sputum culture on liquid medium at week 4, and a composite clinical severity score at week 8.

6/17) monitored other clinical parameters, such as sputum smear microscopy, serum vitamin D levels, and lymphocyte proliferative responses. In 53% (9/17) studies, results of the nutritional intervention with regard to a nutritional parameter were reported. One study reported monitoring of dietary intake during the intervention period.[63] No studies reported calculations of patients' individual nutritional needs. One study reported monitoring of nutrition impact symptoms.[63] Two studies referred to international or national guidelines regarding treatment of malnutrition.[62,63]

CONCLUSIONS

The current review shows that only 6% of the studies used assessment methods that attribute to all domains of the conceptual definition of malnutrition.[3] BMI < 18.5 kg/m^2 as an operationalization of malnutrition was used by more than half of the studies. The criterion of BMI < 18.5 kg/m^2 may be justified at a public health population level, since a low BMI is a characteristic of chronic malnutrition that involves loss of both fat and muscle tissue.[7] However, in clinical settings, using only BMI is of questionable relevance for assessing malnutrition, since in disease-related malnutrition predominantly muscle tissue is lost and even a small loss of muscle tissue has significant negative implications.[7] With the current overweight and obesity epidemic around the world, patients with catabolic diseases such as TB may lose more than 20% of their weight and muscle mass within 3 to 6 months, and still have BMI values at or above normal ranges.[79] For example: a patient with a length of 1.73 m and a weight of 90 kg has a BMI 30 kg/m^2. With 20% weight loss, BMI is still 25 kg/m^2 and not even close to the criterion of 18.5 kg/m^2.

The current review also identified that functionality is understudied in TB patients. Isolation regulations during initial treatment period may impede studying physical function in TB patients.[80] Nevertheless, studies on physical function in TB patients indicate a significant decrease in functionality. Cognitive function as a determinant of mental health has rarely been assessed in adult TB patients. Several studies have reported on mental health problems in TB patients, revealing moderate to strong associations between psychosocial or emotional distress, or (risk for) depression, or anxiety with 24 different factors in patients with TB. This finding implies that mental health in patients with TB may be considered multifactorial. Prevalence rates of depression and anxiety reported in TB patients, 43% and 42% respectively, are markedly increased compared to those in the general population, 4.4% and 3.6% respectively.[81] At this time, we have too little knowledge on physical and mental function in TB patients to know to which extent any decrease in physical and mental function is associated with nutritional status.

As fat-free mass represents the volume of distribution of many hydrophilic TB drugs, drug distribution in the body may be increased by loss of fat-free mass due malnutrition.

Table 3B. Details of nutritional intervention studies with regard to assessment of nutritional parameters and reported results (n=17)

First author, year of publication and country	Assessment of nutritional parameter* at start of study	Monitoring total dietary intake during study	Assessment of individual nutritional needs	Monitoring of Nutrition Impact Symptoms	Referring to (inter) national guidelines	Assessment of nutritional parameter* at end of study	Significant positive results with regard to nutritional parameter*	Significant positive results with regard to primary outcome
Bacelo AC, *et al.* (2017) Brazil	✓	✓	X	✓	✓	✓		X
Bacelo AC, *et al.* (2015) Brazil	✓	X	X	X	✓	✓	X	X
Kulkarni RA, *et al.* (2016) India	X	X	X	X	X	X	X	X**
Tukvadze N, *et al.* (2015) Georgia	✓	X	X	X	X	X		X
Mily A, *et al.* (2015) Bangladesh	X	X	X	X	X	X		✓
Daley P, *et al.* (2015) India	✓	X	X	X	X	✓	X	X
Denti P, *et al.* (2015) Tanzania	✓	X	X	X	X	✓		X
Farazi A, *et al.* (2015) Iran	✓	X	X	X	X	✓	✓	X
Kawai K, *et al.* (2014) Tanzania	X	X	X	X	X	X		X
Jeremiah K, *et al.* (2014) Tanzania	✓	X	X	X	X	✓	✓	✓
Guzman-Rivero M, *et al.* (2014) Bolivia	X	X	X	X	X	X		X
Salahuddin, *et al.* (2013) Pakistan	✓	X	X	X	X	✓	✓	✓
Ginawi I, *et al.* (2013) India	X	X	X	X	X	X		✓
Rudolph M, *et al.* (2013) South Africa	✓	X	X	X	X	✓	X/✓	X/✓
Paliliewu N, *et al.* (2013) Indonesia	X	X	X	X	X	X		X
Singh AK, *et al.* (2013) India	✓	X	X	X	X	✓	✓	✓
Ralph AP, *et al.* (2013) Indonesia	✓	X	X	X	X	✓	X	X

*attributing to at least one of the domains of the conceptual definition of malnutrition or consensus diagnostic criteria by ESPEN, ü=YES, X=NO, empty= not reported

**reported significant results in the placebo group as well, therefore not considered to be significant

However, malabsorption due to malnutrition on the other hand may reduce drug exposure. Therapeutic drug monitoring (TDM) could therefore be helpful in adequate dosing, to prevent low or toxic drug exposure.[8,82] There is a paucity of data to appreciate the role of malnutrition-related factors of clinical outcome, both in the context of pharmacotherapy as well as all other health-related aspects of nutritional status.[8] Increased knowledge may provide new pathways to improve outcomes in TB.

Only 65% of the studies on nutritional interventions assessed nutritional status at baseline. So, one third of studies that investigated a nutritional intervention did not perform baseline nutritional assessment. Interventions are thus applied to a group of patients whether malnourished or not, which makes it difficult to draw clear conclusions with regard to the effect of the intervention, since the intervention may have been performed on non-malnourished patients as well.

Primary outcome measures of most of nutritional intervention studies were mainly other than nutritional parameters, such as resolution of chest radiograph abnormalities or rifampin exposure, and 53% of the studies reported any results with regard to a nutritional parameter. These findings suggest that half of the studies on nutritional interventions do not consider nutritional status relevant for the interpretation of the results of their nutritional interventions, or do not have the skills to evaluate nutritional status.

A possible confounding factor in the study design of the studies reviewed was the absence of estimation or calculation of individual nutritional needs compared to monitoring of their current dietary intake. Thus, patients were given an intervention regardless of their individual nutritional requirements, and it is unknown to what extent the intervention may have replaced certain elements of a patient's diet instead of increasing total daily intake. Furthermore, only one study addressed nutrition impact symptoms such as nausea, pain, and anorexia. Patients experiencing these symptoms are obviously less likely to benefit from oral supplemental nutrition if these symptoms are not addressed appropriately.

Only two studies referred to national guidelines regarding treatment of malnutrition. The overall absence of reference to (inter)national guidelines on treatment of malnutrition implies there may be a gap between nutritional science and clinical practice. Overall, the study design of studies on nutritional interventions reflected ignorance or neglect of scientific and operational nutritional definitions and/or a conceptual framework.

In conclusion, awareness of the concept of malnutrition and nutritional assessment in health care professionals working with TB patients may need improvement. Nutritional assessment tools that attribute to the three domains of malnutrition should be validated in TB patients. The Scored Patient-Generated Subjective Global Assessment (PG-SGA© FD Ottery 2005, 2006, 2015) is a commonly used instrument for nutritional assessment and has first been validated in the oncology setting, and later in other patient populations.[83,84] In addition, the original English PG-SGA has been translated and culturally adapted for various other settings. The PG-SGA is one of the few nutritional assessment instruments

covering all domains of the definition of malnutrition.[85] The PG-SGA displays the specific components of nutritional status by scoring, and its simple questions give guidance to the required interdisciplinary interventions, depending on the components that generate the scores. This means that the healthcare professional can easily identify which problems need to be focused on, to improve nutritional status.

In addition, physical and mental function with regard to nutritional status in TB patients should be studied to explore the impact of malnutrition in these domains. Exploration of a TDM program for malnourished TB patients may be helpful to assess the relationship between malnutrition and bio-availability of TB drugs. Future nutritional intervention studies should be carefully designed as to truly study effects of nutritional interventions.

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Annex 1: Details of the search strategy, title abstract selection, data extraction and results

Studies that focused on and assessed malnutrition or undernutrition in adult, microbiological confirmed TB patients were included. Studies that included both adults and children were included as well. Because the assessment methods are the focus of this review, rather than the outcome, varying types of articles were considered, including randomized clinical trials, short communications, observational studies and quasi-experimental studies. Reviews were excluded, because the aim of this review is to give an overview of the assessment methods used in original studies. Case reports were excluded. Abstracts were excluded as well. All types of TB were included, as well as patients who also suffered from comorbidities such as HIV. No distinction was made between the varying degrees of malnutrition such as mild, moderate or severe malnutrition. Studies with all types of assessment methods were included. Studies were excluded if they assessed risk for malnutrition.

Excluded were all studies published before 2007.

For a full list of inclusion and exclusion criteria, see **Annex 2**. Duplicates were removed. Selection based on title was made by one author (RB), who consulted a second author (LtB) in case of doubt regarding eligibility. The process was repeated for the abstract and full-text articles until consensus was reached.

PubMed

("Malnutrition"[Mesh] OR "Malnutrition"[All Fields] OR Malnourishment[All Fields] OR Malnourished [All Fields] OR "Nutritional Deficiency"[All Fields] OR "Nutritional Deficiencies"[All Fields] OR Undernutrition[All Fields] OR Undernourished[All Fields] OR Undernourishment[All Fields] OR "Nutritional Status"[Mesh] OR "Nutritional Status"[All Fields] OR "Nutrition Status"[All Fields]) AND ("Tuberculosis"[Mesh] OR "Tuberculosis"[Title] OR TB[Title]) AND ("Adult"[Mesh] OR "Adult"[All Fields] OR "Adults"[All Fields]) AND (English[lang] OR Dutch[lang]) NOT (animals NOT humans)

Cochrane Central

#1 MeSH descriptor: [Malnutrition] explode all trees
#2 Malnutrition
#3 Malnourishment
#4 Malnourished
#5 Nutritional deficiency
#6 Nutritional deficiencies
#7 Undernutrition
#8 Undernourished
#9 Undernourishment
#10 MeSH descriptor: [Nutritional Status] explode all trees

#11	Nutritional status
#12	Nutrition status
#13	MeSH descriptor: [Tuberculosis] explode all trees
#14	Tuberculosis:ti
#15	TB:ti
#16	MeSH descriptor: [Adult] explode all trees
#17	Adult
#18	Adults
#19	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12) and (#13 or #14 or #15) and (#16 or #17 or #18)

CINAHL Plus with Full Text

S1	MH Malnutrition OR MH "Nutritional Status"
S2	malnutrition OR malnourishment OR malnourished OR "nutritional deficiency" OR "nutritional deficiencies" OR undernutrition OR undernourishment OR undernourished OR nutritional status OR nutrition status
S3	S1 OR S2
S4	MH tuberculosis
S5	TI tuberculosis OR TI TB
S6	S4 OR S5
S7	MH Adult+
S8	adult OR adults
S9	S7 OR S8
S10	S3 AND S6 AND S9
S11	S3 AND S6 AND S9 **Limiters** - Published Date: 20070101-20161231

Domain A was considered covered if an assessment method addressed nutritional intake or uptake. For domain B, anthropometric measurement, such as weight, BMI or skinfold measurements or measurement of body cell mass were considered covering domain B. Domain C was considered to be covered if functionality was addressed in any way, such as physical function tests or questions about activities of daily living. Laboratory tests in serum were not considered to attribute to any of the domains. Micronutriënt or trace elements in serum are not representative for intake or uptake of protein or energy.[3] Serum values of albumine or CRP are parameters for inflammation but are not related to parameters of protein/energy intake or functionality, nor do they represent body composition: "there are no good biochemical markers of the nutritional status. Plasma albumin and transthyretin/prealbumin concentrations may be used mainly to indicate and monitor catabolic activity. Their validity as nutrition indicators is low in view of their perturbation by inflammation". [3]

Annex 2: Details of inclusion and exclusion criteria

Exclusion criteria title/abstract

- "Tuberculosis" or related terms not in title
- Children or infants are the only subject
- Study is a review
- Study is a case report
- Study is a correspondence not including patients
- Focus of the study is not on TB patients
- Focus of the study is latent TB
- Study focused on risk of TB or whole population was at risk/assessed
- Study focused on the period after recovery from TB
- No mention of nutritional status or related terms, anthropometric measurements or any terms relating to dietary intake that imply any type of operationalization of malnutrition
- Nutritional status is mentioned, but refers only to a specific micronutrient
- Study protocols

Exclusion criteria for full text

- Malnutrition not assessed
- Method used to assess malnutrition not specified
- No clear cut-off values or scoring system for used method, if it were a method that allowed for numerical scoring such as anthropometric measurements or lab values. If a study differentiated between varying degrees of malnutrition (moderate, severe etc.) and only provided cut-off values for the severe case, it was excluded as well.
- Risk of malnutrition was assessed
- Only abstract available
- Other language than English or Dutch
- Same authors, study population and methods as other study

Annex 3: Details of the search strategy, title abstract selection, data extraction and results

The focus of this search was any nutritional intervention that was used for adults TB patients. This included clinical trials and prospective studies. Studies that included both adults and children were included as well. No distinction was made between the types of TB. Studies that focused on TB patients with various comorbidities, such as HIV, were included as well. All types of nutritional interventions were included, including protein-energy supplementation, micronutrient supplementation and sole dietary counselling. Studies were excluded if there was no nutritional intervention or dietary counselling. Reviews were excluded as well since the focus of this review is on the original articles so that new conclusions can be drawn. For a full list of inclusion -and exclusion criteria, see **Annex 7**. Duplicates were removed. Selection based on title was made by one author

(RB), who consulted a second author (LtB) in case of doubt regarding eligibility. The process was repeated for the abstract and full-text articles until consensus was reached. To assess the effectiveness of each nutritional intervention on nutritional status, nutritional parameters were evaluated. If no nutritional assessment tool was used, BMI or weight were evaluated if present. If the study provided no information regarding the nutritional status in terms of nutritional assessment tools, BMI or weight, or only provided in weight and length without any qualification or follow-up, nutritional status was considered to be not assessed.

Excluded were all studies published before 2013.

PubMed

("Nutrition therapy"[Mesh] OR "Nutrition therapy"[All Fields] OR "Nutritional therapy"[All Fields] OR "Nutrition support"[All Fields] OR "Nutritional support"[All Fields] OR "Nutrition intervention"[All Fields] OR "Nutritional intervention"[All Fields] OR "Nutritional supplement"[All Fields] OR "Nutrition supplement"[All Fields] OR "Nutritional Care"[All Fields] OR "Dietary Supplements"[Mesh] OR "Dietary Supplements"[All Fields] OR "Diet therapy"[Mesh] or "Diet therapy"[All Fields] OR "Diet intervention"[All Fields] OR "Dietary intervention"[All Fields] OR "Dietary proteins"[Mesh] Or "Dietary proteins"[All Fields] OR "Dietary care"[All Fields] OR "Food, fortified"[Mesh] OR "Fortified Food"[All Fields] OR "Protein supplementation"[All Fields] OR "Energy supplementation"[All Fields] OR Diet[Mesh] OR Diet[All Fields] OR "Dietary counseling"[All Fields]) AND ("Tuberculosis"[Mesh] OR "Tuberculosis"[Title] OR TB[Title]) AND ("Adult"[Mesh] OR "Adult"[All Fields] OR "Adults"[All Fields]) AND (English[lang] OR Dutch[lang]) NOT (animals NOT humans)

Cochrane Central

#1 MeSH descriptor: [Nutrition Therapy] explode all trees
#2 nutrition therapy
#3 Nutritional therapy
#4 Nutrition support
#5 Nutritional support
#6 Nutrition intervention
#7 Nutritional intervention
#8 Nutritional supplement
#9 Nutrition supplement
#10 Nutritional Care
#11 MeSH descriptor: [Dietary Supplements] explode all trees
#12 dietary supplements
#13 MeSH descriptor: [Diet Therapy] explode all trees
#14 Diet therapy

#15 Diet intervention
#16 Dietary intervention
#17 MeSH descriptor: [Dietary Proteins] explode all trees
#18 Dietary proteins
#19 Dietary care
#20 MeSH descriptor: [Food, Fortified] explode all trees
#21 Fortified Food
#22 Protein supplementation
#23 Energy supplementation
#24 MeSH descriptor: [Diet] explode all trees
#25 diet
#26 dietary counseling
#27 MeSH descriptor: [Tuberculosis] explode all trees
#28 Tuberculosis:ti
#29 TB:ti
#30 MeSH descriptor: [Adult] explode all trees
#31 Adult
#32 Adults
#33 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26) and (#27 or #28 or #29) and (#30 or #31 or #32)

CINAHL

S1 MH nutrition therapy OR MH Dietary supplements OR MH diet therapy OR MH dietary proteins OR MH food, fortified OR MH diet
S2 nutrition therapy OR nutritional therapy OR nutrition support OR nutritional support OR nutrition intervention OR nutritional intervention OR nutritional supplement OR nutrition supplement OR nutritional care OR dietary supplements OR diet therapy OR diet intervention
S3 dietary intervention OR dietary proteins OR dietary care OR fortified food OR protein supplementation OR energy supplementation OR diet OR dietary counseling
S4 S1 OR S2 OR S3
S5 MH Tuberculosis
S6 TI Tuberculosis or TI TB
S7 S5 OR S6
S8 MH Adult+
S9 Adult OR Adults
S10 S8 OR S9

S11 S4 AND S7 AND S10
S12 S4 AND S7 AND S10 Limiters - Published Date: 20120101-20161231

Annex 4: Details of inclusion and exclusion criteria

Exclusion criteria for title/abstract

- "Tuberculosis" or related terms not in title
- Study is a case report
- Children or infants are the only subject
- Focus not on TB patients
- Study is a review
- No mention of any type of nutritional assessment

Exclusion criteria for full text

- No nutritional intervention
- Nutritional intervention was shorter than 7 days

Annex 5: Details of assessment method

biomarkers (anthropometric, hematological, biochemical and micronutrients)
BMI 18.5-24.9 Kg/m^2
MUAC 28.5-29.3 cm
TSF 11.4-18.2 mm
MAMC 21.0-27.8 cm
Hemoglobin 11.0-18.0 g/dl
Hematocrit 34.0-54.0 %
Globulin 2.5-4.0 g/dl
Albumin 3.4-5.0 g/dl
TIBC 250.0-450.0 mcg/dl
Tranferrin 250-300 mg/dl
Retinol >0.7 mcg/dl
Tocopherol >5.0 mg/l
Zinc >70.0 mg/dl
Selenium 70.0-90.0 mcg/l
Iron 50.0-170.0 mcg/dl
If one or more of the biomarkers were out of the reverence values, the person was considered to be malnourished

Annex 6: Details of assessment method

2 anthropometric markers and 4 blood values.
PIBW <90
BMI <18.5

serum albumin <3.5 g/dL
total lymphocyte count (TLC) <1.800
total cholesterol <90 mg/dL
hemoglobin <12 g/dL women, <14g/dL men
Each factor was assigned a value of 1 if present or 0 if absent and the malnutrition score (0–6) was obtained by summation of the number of abnormal parameters for each patient. Patients with TB were further divided into 2 groups based on the malnutrition score: well-nourished (score < 3) and malnourished (score ≥ 3).

Annex 7: Details of assessment method

Examination of hair, eyes, lips, gums, tongue, skin and nails.

Trained nursing staff examined the participants for signs of malnutrition in the hair (lack of shine, thin, sparse, loose, flag sign), eyes (dry, foamy spots, night blindness, redness), lips (cheilosis, angular stomatitis), gums (spongy, bleeding), tongue (sore, smooth), skin (dry, scaling) and nails (spoon shaped, brittle, ridged, pale).