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Nutritional supplements for people being treated for active tuberculosis (Review)

Grobler L, Nagpal S, Sudarsanam TD, Sinclair D

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[Intervention Review]

Nutritional supplements for people being treated for active tuberculosis

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ABSTRACT

Background

Tuberculosis and malnutrition are linked in a complex relationship. Tuberculosis may cause undernutrition through increased metabolic demands and decreased intake, and nutritional deficiencies may worsen the disease, or delay recovery by depressing important immune functions. At present, there is no evidence-based nutritional guidance for adults and children being treated for tuberculosis.

Objectives

To assess the effects of oral nutritional supplements in people being treated with antituberculous drug therapy for active tuberculosis.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2016), MEDLINE (from 1946 to 4 February 2016), EMBASE (from 1980 to 4 February 2016), LILACS (from 1982 to 4 February 2016), the *meta*Register of Controlled Trials (*m*RCT), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the *Indian Journal of Tuberculosis* up to 4 February 2016, and checked the reference lists of all included studies.

Selection criteria

Randomized controlled trials that compared any oral nutritional supplement given for at least four weeks with no nutritional intervention, placebo, or dietary advice only for people being treated for active tuberculosis. The primary outcomes of interest were all-cause death, and cure at six and 12 months.

Data collection and analysis

Two review authors independently selected trials for inclusion, and extracted data and assessed the risk of bias in the included trials. We presented the results as risk ratios (RR) for dichotomous variables, and mean differences (MD) for continuous variables, with 95% confidence intervals (CIs). Where appropriate, we pooled data from trials with similar interventions and outcomes. We assessed the quality of the evidence using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.

Main results

Thirty-five trials, including 8283 participants, met the inclusion criteria of this review.

Macronutrient supplementation

Six trials assessed the provision of free food, or high-energy supplements. Only two trials measured total dietary intake, and in both trials the intervention increased calorie consumption compared to controls.

The available trials were too small to reliably prove or exclude clinically important benefits on mortality (RR 0.34, 95% CI 0.10 to 1.20; four trials, 567 participants, *very low quality evidence*), cure (RR 0.91, 95% CI 0.59 to 1.41; one trial, 102 participants, *very low quality evidence*), or treatment completion (data not pooled; two trials, 365 participants, *very low quality evidence*).

Supplementation probably produces a modest increase in weight gain during treatment for active tuberculosis, although this was not seen consistently across all trials (data not pooled; five trials, 883 participants, *moderate quality evidence*). Two small studies provide some evidence that quality of life may also be improved but the trials were too small to have much confidence in the result (data not pooled; two trials, 134 participants, *low quality evidence*).

Micronutrient supplementation

Six trials assessed multi-micronutrient supplementation in doses up to 10 times the dietary reference intake, and 18 trials assessed single or dual micronutrient supplementation.

Routine multi-micronutrient supplementation may have little or no effect on mortality in HIV-negative people with tuberculosis (RR 0.86, 95% CI 0.46 to 1.6; four trials, 1219 participants, *low quality evidence*), or HIV-positive people who are not taking antiretroviral therapy (RR 0.92, 95% CI 0.69 to 1.23; three trials, 1429 participants, *moderate quality evidence*). There is insufficient evidence to know if supplementation improves cure (no trials), treatment completion (RR 0.99, 95% CI 0.95 to 1.04; one trial, 302 participants, *very low quality evidence*), or the proportion of people who remain sputum positive during the first eight weeks (RR 0.92, 95% CI 0.63 to 1.35; two trials, 1020 participants, *very low quality evidence*). However, supplementation may have little or no effect on weight gain during treatment (data not pooled; five trials, 2940 participants, *low quality evidence*), and no studies have assessed the effect on quality of life.

Plasma levels of vitamin A appear to increase following initiation of tuberculosis treatment regardless of supplementation. In contrast, supplementation probably does improve plasma levels of zinc, vitamin D, vitamin E, and selenium, but this has not been shown to have clinically important benefits. Of note, despite multiple studies of vitamin D supplementation in different doses, statistically significant benefits on sputum conversion have not been demonstrated.

Authors' conclusions

There is currently insufficient research to know whether routinely providing free food, or energy supplements improves tuberculosis treatment outcomes, but it probably improves weight gain in some settings.

Although blood levels of some vitamins may be low in people starting treatment for active tuberculosis, there is currently no reliable evidence that routinely supplementing above recommended daily amounts has clinical benefits.

17 April 2019

Update pending

Studies awaiting assessment

The CIDG is currently examining a new search conducted in April 2019 for potentially relevant studies. These studies have not yet been incorporated into this Cochrane Review.

PLAIN LANGUAGE SUMMARY

Nutritional supplements for people being treated for active tuberculosis

Cochrane researchers conducted a review of the effects of nutritional supplements for people being treated for tuberculosis. After searching for relevant studies up to 4 February 2016, they included 35 relevant studies with 8283 participants. Their findings are summarized below.

What is active tuberculosis and how might nutritional supplements work?

Tuberculosis is a bacterial infection which most commonly affects the lungs. Most people who get infected never develop symptoms as their immune system manages to control the bacteria. Active tuberculosis occurs when the infection is no longer contained by the immune system, and typical symptoms are cough, chest pain, fever, night sweats, weight loss, and sometimes coughing up blood. Treatment is with a combination of antibiotic drugs, which must be taken for at least six months.

People with tuberculosis are often malnourished, and malnourished people are at higher risk of developing tuberculosis as their immune system is weakened. Nutritional supplements could help people recover from the illness by strengthening their immune system, and

by improving weight gain, and muscle strength, allowing them to return to an active life. Good nutrition requires a daily intake of macronutrients (carbohydrate, protein, and fat), and micronutrients (essential vitamins and minerals).

What the research says

Effect of providing nutritional supplements to people being treated for tuberculosis

We currently don't know if providing free food to tuberculosis patients, as hot meals or ration parcels, reduces death or improves cure (*very low quality evidence*). However, it probably does improve weight gain in some settings (*moderate quality evidence*), and may improve quality of life (*low quality evidence*).

Routinely providing multi-micronutrient supplements may have little or no effect on deaths in HIV-negative people with tuberculosis (*low quality evidence*), or HIV-positive people who are not taking anti-retroviral therapy (*moderate quality evidence*). We currently don't know if micronutrient supplements have any effect on tuberculosis treatment outcomes (*very low quality evidence*), but they may have no effect on weight gain (*low quality evidence*). No studies have assessed the effect on quality of life.

Plasma levels of vitamin A appear to increase after starting tuberculosis treatment regardless of supplementation. In contrast, supplementation probably does improve plasma levels of zinc, vitamin D, vitamin E, and selenium, but this has not been shown to have clinically important benefits. Despite multiple studies of vitamin D supplementation in different doses, statistically significant benefits on sputum conversion have not been demonstrated.

Authors' conclusions

Food or energy supplements may improve weight gain during recovery from tuberculosis in some settings, but there is currently no evidence that they improve tuberculosis treatment outcomes. There is also currently no reliable evidence that routinely supplementing above recommended daily amounts has clinical benefits.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. 'Summary of findings' table 1

Food provision compared with nutritional advice or no intervention for patients with active tuberculosis

Patient or population: adults and children with active tuberculosis

Settings: low- and middle-income countries

Intervention: calorie supplementation as food or energy dense supplements

Comparison: nutritional advice, micronutrient supplement, or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	Increased calorie intake				
Death (at 6 months)	**3 per 100**	**1 per 100** (0 to 4)	**RR 0.34** (0.10 to 1.20)	567 (4 trials)	⊕⊝⊝⊝ **very low** [1,2,3]	We don't know if food supplementation reduces mortality from tuberculosis in food-insecure settings
Cured (at 6 months)	**48 per 100**	**44 per 100** (28 to 68)	**RR 0.91** (0.59 to 1.41)	102 (1 trial)	⊕⊝⊝⊝ **very low** [2,3,4]	We don't know if food supplementation increases cure in tuberculosis patients
Treatment completion (at 6 months)	**79 per 100**	**85 per 100** (70 to 100)	Not pooled	365 (2 trials)	⊕⊝⊝⊝ **very low** [3,5,6]	We don't know if food supplementation increases treatment completion in tuberculosis patients
Sputum negative (at 8 weeks)	**76 per 100**	**82 per 100** (65 to 100)	**RR 1.08** (0.86 to 1.37)	222 (3 trials)	⊕⊝⊝⊝ **very low** [3,5,6]	We don't know if food supplementation reduces the duration of sputum positivity in tuberculosis patients
Mean weight gain (At 8 weeks)	—	—	Not pooled	883 (5 trials)	⊕⊕⊕⊝ **moderate** [7,8]	Supplementation probably increases weight gain during treatment

Quality of life (At 8 weeks)	—	—	Not pooled	134 (2 trials)	⊕⊕⊖⊖ **low** [9,10]	Supplementation may increase quality of life scores during the first 2 months of treatment

*The **assumed risk** is taken from the mean risk in the control groups in the included studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI = confidence interval; RR = risk ratio; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Three trials reported some deaths during the 6 months of treatment (Jahnavi 2010 IND; Jeremiah 2014 TZA; Sudarsanam 2010 IND), and 1 reported that no deaths occurred (Martins 2009 TLS). The trials were conducted in Tanzania, Timor-Leste, and India in participants with signs of undernutrition. Martins 2009 TLS gave a daily hot meal, Sudarsanam 2010 IND gave monthly ration packs, Jahnavi 2010 IND gave daily locally appropriate supplements, and Jeremiah 2014 TZA gave high energy multivitamin enriched biscuits.
[2]Downgraded by 1 for indirectness: trials are only available from limited settings. Food supplementation would plausibly have its biggest effect in highly food-insecure or emergency settings which are not reflected in these trials.
[3]Downgraded by 2 for imprecision: the trials and meta-analysis are significantly underpowered to either detect or exclude an effect if it exists.
[4]Data on successful cure at 6 months is only available from Sudarsanam 2010 IND which randomized tuberculosis patients in India to monthly ration packs or advice only.
[5]Two trials report on tuberculosis treatment completion at 6 months (Jahnavi 2010 IND; Martins 2009 TLS). One trial was conducted in India and 1 in Timor-Leste in participants with signs of undernutrition. Both trials gave daily locally appropriate supplements.
[6]Downgraded by 1 for inconsistency. Jahnavi 2010 IND found a statistically significant benefit while the larger trial, Martins 2009 TLS, did not.
[7]Five studies reported measures of weight gain but at different time-points, which prevented meta-analysis.
[8]Downgraded by 1 for inconsistency. Praygod 2011b TZA included only HIV-positive patients and although the trend was towards a benefit this did not reach statistical significance. Jeremiah 2014 TZA noted a greater increase in mean weight gain in the supplemented group compared to the non-supplemented group after 8 weeks; however the difference was not appreciable (1.09 kg, P < 0.6, authors' own figures). The 3 other trials all demonstrated clinically important benefits.
[9]Downgraded by 1 for indirectness. Only 2 small trials, 1 from Singapore (Paton 2004 SGP) and 1 from India (Jahnavi 2010 IND) report quality of life scores. The results can not be generalized to other populations or settings with any certainty.
[10]Downgraded by 1 for imprecision. The presented data appear highly skewed and could not be pooled.

Summary of findings 2. 'Summary of findings' table 2

Multi-micronutrient supplementation compared with placebo for patients with active tuberculosis

Patient or population: adults and children with active tuberculosis

Settings: low- and middle-income countries

Intervention: multi-micronutrient supplements

Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Multi-micronutrients				
Death	**HIV-negative participants**		**RR 0.86** (0.46 to 1.6)	1219 (4 trials)	⊕⊕⊝⊝ **low** [1,2,3]	Multi-micronutrient supplements may have little or no effect on mortality in HIV-negative tuberculosis patients
	40 per 1000	**34 per 1000** (18 to 64)				
	HIV-positive participants		**RR 0.92** (0.69 to 1.23)	1429 (3 trials)	⊕⊕⊕⊝ **moderate** [4,5]	Multi-micronutrients probably have little or no effect on mortality in HIV-positive tuberculosis patients not on ARV therapy
	357 per 1000	**328 per 1000** (246 to 439)				
Cure rate	—	—	—	(0 trials)	—	We don't know if multi-micronutrients improve cure in tuberculosis patients
Treatment completion	**970 per 1000**	**960 per 1000** (920 to 101)	**RR 0.99** (0.95 to 1.04)	302 (1 trial)	⊕⊝⊝⊝ **very low** [6,7]	We don't know if multi-micronutrients improve treatment completion in tuberculosis patients
Remaining sputum positive (at 4 weeks)	**309 per 1000**	**312 per 1000** (263 to 371)	**RR 0.92** (0.63 to 1.35)	1020 (2 studies)	⊕⊝⊝⊝ **very low** [8,9,10]	We don't know if multi-micronutrients reduce the proportion of patients still sputum positive at 4 weeks
Weight gain	—	—	Not pooled	2940 (5 trials)	⊕⊕⊝⊝ **low** [11]	Multi-micronutrient supplements may not improve weight gain in tuberculosis patients
Quality of life	—	—	—	(0 trials)	—	We don't know if multi-micronutrients improve quality of life in tuberculosis patients

*The **assumed risk** is taken from the risk in the control groups of the included studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI = confidence interval; RR = risk ratio; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

[1]Five RCTs comparing multi-micronutrient supplementation with placebo in adults (Range 2005 TZA; Semba 2007 MWI; Villamor 2008 TZA) and children (Lodha 2014 IND; Mehta 2011 TZA), reported deaths during treatment. The exact composition of nutrients varied from 1 to 10 times the DRI. Three studies are from Tanzania, 1 from Malawi, and 1 from India. There is evidence of participants being significantly undernourished at baseline.

[2]No serious inconsistency: statistical heterogeneity was low. Although the estimate of effect is trending towards a benefit this is due to 1 trial (Villamor 2008 TZA), the remaining trials found non significant trends in the opposite direction. Not downgraded.

[3]Downgraded by 2 for imprecision: the 95% CI of the pooled effect crosses 1 and includes a 2% absolute reduction in death which might be considered beneficial given the low cost of the intervention. The optimal information size to reliably detect a clinically beneficial effect if there is 1 is greater than 2000.

[4]Downgraded by 1 for indirectness: none of the participants in these trials were receiving antiretroviral therapy (Range 2005 TZA; Semba 2007 MWI; Villamor 2008 TZA). The exact composition of nutrients varied from 1 to 10 times the DRI. Two studies are from Tanzania and 1 in Malawi. There is evidence of participants being significantly undernourished at baseline.

[5]No serious imprecision: the 95% CI of the pooled effect crosses 1 and does includes a 5% absolute reduction in death which might be considered beneficial given the low cost of the intervention. However, the effect estimate is of no difference between the treatments and the optimal information size to reliably detect a clinically beneficial effect is met.

[6]Downgraded by 2 for indirectness: current evidence is limited to 1 small trial (Lodha 2014 IND) conducted in moderately undernourished, HIV-negative children in India, where treatment completion was very high in both groups. The result is not easily generalized to other settings.

[7]Downgraded by 1 for imprecision: although this trial approaches adequate power to detect a result, the fact that treatment completion was so high in both arm renders the result irrelevant to settings where treatment completion is lower.

[8]Downgraded by 1 for inconsistency. Statistical heterogeneity is high; 1 study found a non-significant trend in favour of supplementation, and 1 study in favour of placebo.

[9]Downgraded by 1 for indirectness. Both studies were conducted in Tanzania. Different populations may differ in their micronutrient deficiency or requirement.

[10]Downgraded by 1 for imprecision. The 95% CI is wide and includes what may be clinically important effects.

[11]Downgraded by 2 for inconsistency: Statistical heterogeneity is very high. Four studies from Tanzania and India found no evidence of improved weight gain with supplements, while 1 study from Tanzania found large increases in weight with micronutrients at 8 months.

BACKGROUND

Description of the condition

Tuberculosis is an infection caused by the bacterium *Mycobacterium tuberculosis,* which is spread from person to person by inhalation of respiratory droplets (Harries 2006). In 2013, the World Health Organization (WHO) estimated that there were nine million new cases of active tuberculosis worldwide, and 1.5 million deaths (WHO 2014).

Most people who are infected with *M. tuberculosis* develop what is known as latent tuberculosis. People with latent tuberculosis are infected with the bacterium *Mycobacterium tuberculosis*, but the infection is contained by their immune system. These people remain well and do not exhibit any clinical signs or symptoms of illness (Barry 2009). The immune response to infection is complex, it initially involves the uptake of the bacterium into macrophage cells as part of the non-specific 'innate' immune response, and later recruitment of both B- and T-lymphocytes of the cellular immune response (Schluger 1998). These cells isolate the bacterium as a granuloma, typically in the lung (Saunders 2007).

Active tuberculosis occurs when the infection is no longer contained by the immune system, and can occur at any time following infection. The lifetime risk of conversion from latent to active tuberculosis is around 5% to 10% in an otherwise healthy population (Harries 2006), but this can rise to around 50% in people with severe impairment of their immune system, such as occurs with human immunodeficiency virus (HIV) infection (Zumla 2000; Aaron 2004).

Tuberculosis most commonly affects the lungs (pulmonary tuberculosis), but can also spread to affect the central nervous system, lymphatic system, circulatory system, genitourinary system, and bones and joints. The symptoms of active pulmonary tuberculosis include cough, chest pain, fever, night sweats, weight loss, and sometimes coughing up blood (Harries 2006).

Tuberculosis is treated with a combination of antibiotic drugs (antituberculous therapy), which must be taken for a period of at least six months to ensure success (WHO 2010). If left untreated, around half of those with active tuberculosis will die of the disease (Corbett 2003). With adequate treatment the mortality is around 5% globally (WHO 2009), although this may be higher in HIV-positive people (Aaron 2004). The WHO target for successful cure in national tuberculosis control programmes is 85% (WHO 2009).

Throughout the world, poor nutritional status is more common in people with active tuberculosis than in people without tuberculosis (van Lettow 2003), and weight loss, including loss of lean body mass, is a well-recognized symptom of the disease. Cohort and cross-sectional studies have suggested that active tuberculosis is commonly associated with low serum levels of important micronutrients such as zinc (Taneja 1990), and vitamins A, C, D, and E (Davies 1985; Plit 1998; Nnoaham 2008). However, the measurement of serum vitamin levels during an acute infection, such as tuberculosis, is known to be unreliable, as transient abnormalities can occur (Louw 1992).

The daily nutritional requirements for healthy individuals of all age groups are well described (Meyers 2006), and it is unlikely that people with active tuberculosis would require less than these recommended amounts. The two important questions are therefore whether tuberculosis patients require more, and whether these increased requirements should be provided as part of routine health care.

The effects of supplementation in people with HIV (but without tuberculosis) is covered in two other Cochrane Reviews (Irlam 2010; Grobler 2013).

Description of the intervention

Nutritional requirements can be broadly divided into macronutrients (carbohydrate, protein, and fat) and micronutrients (essential vitamins and trace elements).

Macronutrients

Each day the average 70 kg male requires approximately 2500 kilocalories (kcal) of energy to maintain body weight and composition; ideally consumed as 55% carbohydrate, 15% protein, and 30% fat (Meyers 2006).

If it was shown that patients with active tuberculosis required additional macronutrients; these could be purchased and consumed by the patient simply following nutritional advice. However, in many situations, especially in low- and middle-income countries, the patient may not be able to acquire this additional food due to economic hardship through illness and loss of work, or due to local food insecurity (Kamolratanakul 1999; Wyss 2001). In these situations healthcare services might provide increased nutrients through free provision of meals, take home rations, or specific high energy supplements. In many crisis or low-income settings this already happens and the World Food Programme (WFP) in particular is involved in many food support programmes for tuberculosis patients (WFP 2007).

Micronutrients

The daily micronutrient requirements for an adult male are given in Appendix 1. These are usually expressed as the 'dietary reference intake' (DRI), and this is different for each individual micronutrient (Meyers 2006).

These requirements can be gained from the consumption of a healthy, and varied diet, or through pharmaceutical supplementation as tablets, capsules, or powders. Any additional requirements could be gained through increased consumption following dietary advice, or through pharmaceutical provision via the health service or tuberculosis programme.

In trials of macronutrient and micronutrient interventions two important factors should be noted.

- The intervention is a supplement and does not represent the total daily intake of that nutrient.
- Any benefit derived from the intervention is likely to be dependant on the initial nutritional status of the patient.

In order to accurately interpret data it is therefore essential to consider both the baseline nutritional status, and the overall nutritional intake of the patients.

How the intervention might work

Tuberculosis and undernutrition interact in a two-way process. Tuberculosis can lead to weight loss and micronutrient deficiencies by increasing nutritional requirements, by changing metabolic processes, or by decreasing appetite and causing a reduction in food intake (Macallan 1999). Alternatively, low body mass index (BMI; a measure of weight for height that is indicative of nutritional status) and some micronutrient deficiencies can depress cell-mediated immunity, the key host defence against tuberculosis, increasing the susceptibility to active tuberculosis and delaying recovery (Chandra 1996; Zachariah 2002; Cegielski 2004).

The micronutrients which have received the most attention are the following.

- Vitamin A, which is involved in both T- and B-lymphocyte function, macrophage activity and the generation of antibody responses (Semba 1998; Stephensen 2001).
- Vitamin D, which is involved in the function of macrophages, a key component of the immune response to tuberculosis (Wintergerst 2007).
- Vitamin E, which has anti-oxidant properties and may protect against T-lympocyte failure due to oxidative stress (Wintergerst 2007).
- Zinc, which is necessary for adequate functioning of many aspects of human immunity (Shankar 1998).
- Selenium; which is essential for both cell-mediated and humoral immunity (Arthur 2003).

Nutritional interventions, in people with active tuberculosis, therefore have the potential to do the following.

- Improve tuberculosis treatment outcomes; through restoration of cell-mediated immunity, increasing the individuals' ability to fight the infection and hastening recovery from the illness.
- Promote nutritional recovery; with improved weight gain, restoration of muscle strength, function, and quality of life. Nutritional recovery is of great importance in tuberculosis treatment, allowing the patient to return to work, and recover economically as well as physically.

Food may also be given to people with tuberculosis for quite different reasons, such as; to promote adherence to treatment, or to mitigate the financial consequences of prolonged illness. Another Cochrane Review is addressing the use of food to promote adherence (Lutge 2009).

In addition, it is important to note that pathogens such as tuberculosis also require certain micronutrients for their own metabolism, and greater availability of these nutrients through supplementation could encourage their growth. There is some evidence for this in the case of iron (Lounis 2001), and so nutritional interventions cannot be considered entirely benign.

Why it is important to do this review

There is currently no evidence-based guidance on food provision or supplementation for adults or children being treated for tuberculosis, with or without concurrent HIV infection. This Cochrane Review seeks to assess the evidence for the effectiveness of different food and nutritional supplements in helping people to gain weight and recover from tuberculosis, and highlight where more research might be needed.

OBJECTIVES

To assess the effects of oral nutritional supplements in people being treated with antituberculous drug therapy for active tuberculosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Children or adults being treated for active tuberculosis with or without concurrent HIV infection, and with or without a diagnosis of being underweight, malnourished, or nutrient deficient.

Types of interventions

Intervention

Any oral macro or micronutrient supplement given for at least four weeks.

We excluded trials that assessed tube feeding or parenteral nutrition, and trials that assessed dietary advice alone without the actual provision of supplements.

Control

No nutritional intervention, placebo, or dietary advice alone.

Types of outcome measures

Primary outcomes

- All-cause death.
- Cure (completed treatment and sputum-smear or sputum-culture negative) at six and 12 months.

Secondary outcomes

- Completion of treatment.
- Sputum positive at follow-up.
- Self-reported recovery from illness or resolution of symptoms.
- Change in weight, skinfold thickness, or other measure of lean or total mass.
- Any measure of growth in children.
- Any measures of physical functioning, quality of life, or ability to return to work.
- Total calorie intake.
- Micronutrient levels before and after supplementation.

We intended to include cure assessed at six and 12 months, as is customary. For other outcome measures, we accepted data presented at any time point.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published or unpublished, in press, or in progress).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 2.

- Cochrane Infectious Disease Group Specialized Register.
- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2016).
- MEDLINE (from 1946 to 4 February 2016).
- EMBASE (from 1980 to 4 February 2016).
- LILACS (from 1982 to 4 February 2016).

We checked the *meta*Register of Controlled Trials (*m*RCT) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) up to 4 February 2016, using 'tuberculosis' and 'supplementation' as search terms.

In addition we searched the *Indian Journal of Tuberculosis* using the keywords given in the search strategy (Appendix 2) on 4 February 2016.

Searching other resources

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (Liesl Grobler (LG) and Sukrti Nagpal (SN)/ Thambu Sudarsanam (TS)) independently screened all citations and abstracts identified in the search for potentially eligible studies. Full reports of potentially eligible studies were obtained and assessed for inclusion in the review by the same authors using a pre-designed eligibility form based on the inclusion criteria. Where it was unclear whether a study was eligible for the review, we attempted to contact the authors for clarification. We resolved differences in opinion by discussion and, where necessary, by discussion with a fourth author (David Sinclair). We screened all papers for multiple publications. We excluded studies that did not meet the criteria and documented the reasons for their exclusion.

Data extraction and management

Two review authors (LG and SN) independently extracted data using a tailored data extraction form. We extracted data on study design, participant characteristics, interventions, and outcomes.

For dichotomous data, we extracted the number of participants with the outcome and the total number analysed. For continuous data, we extracted the arithmetic mean and standard deviation (SD) for each group. If medians were used, we also extracted the ranges where possible. If there was skewed continuous data, we planned to extract geometric means where presented by the trial author(s). We resolved any discrepancies regarding extracted data by discussion between the review authors.

Assessment of risk of bias in included studies

Two review authors (LG and SN) independently assessed components of risk of bias of the included trials using the Cochrane 'Risk of bias' assessment tool (RevMan 2014), and discussed any differences of opinion. We followed the guidance to assess whether adequate steps were taken to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. We categorized our judgements as either 'low', 'high', or 'unclear' risk of bias. Where our judgment was 'unclear', we attempted to contact the trial authors for clarification.

Measures of treatment effect

We compared interventions using risk ratios (RR) for dichotomous data, and mean difference (MD) values for continuous data. We presented all results with 95% confidence intervals (CIs).

Unit of analysis issues

We split trials that included more than two comparison groups and analysed them as individual pair-wise comparisons. When we conducted meta-analysis we ensured that we did not count participants and cases in the placebo group more than once, by dividing the placebo cases and participants evenly between the intervention groups.

Dealing with missing data

If data from the trial reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information.

Assessment of heterogeneity

We assessed heterogeneity amongst trials by inspection of the forest plots (to detect overlapping CIs), the I^2 statistic with a level of 50% to denote moderate levels of heterogeneity, and application of the Chi^2 test with a P value of 0.10 to indicate appreciable heterogeneity.

Assessment of reporting biases

We planned to assess the likelihood of publication bias by examining the funnel plots for asymmetry. However, there were too few trials to make this assessment meaningful.

Data synthesis

We analysed the data using Review Manager (RevMan) (RevMan 2014). Using pair-wise meta-analyses we compared the treatments. We stratified meta-analyses by time-point or HIV status where appropriate.

When there was no statistically significant heterogeneity we used the fixed-effect meta-analysis model. When we observed moderate statistically significant heterogeneity within groups that we could not explain by subgroup or sensitivity analyses we used a random-effects meta-analysis model to synthesize the data. When a pooled meta-analysis result was considered to be meaningless because of clinical or substantial statistical heterogeneity the results are presented in a forest plot without a pooled estimate of effect.

Data presented as medians and ranges are presented in tables and described in the narrative. Highly skewed continuous data (where the SDs were larger than the means) are only presented in tables.

Subgroup analysis and investigation of heterogeneity

Due to the small number of included trials or each comparison, the investigation of heterogeneity was not necessary or possible. In

future updates of this Cochrane review we may perform subgroup analyses by: HIV status, nutritional status at baseline, presence of co-morbidities, and specific micronutrient level at baseline.

Sensitivity analysis

We have planned to perform a sensitivity analysis to investigate the robustness of the results to the 'Risk of bias' components. However, there were too few included trials for each comparison for this to be possible.

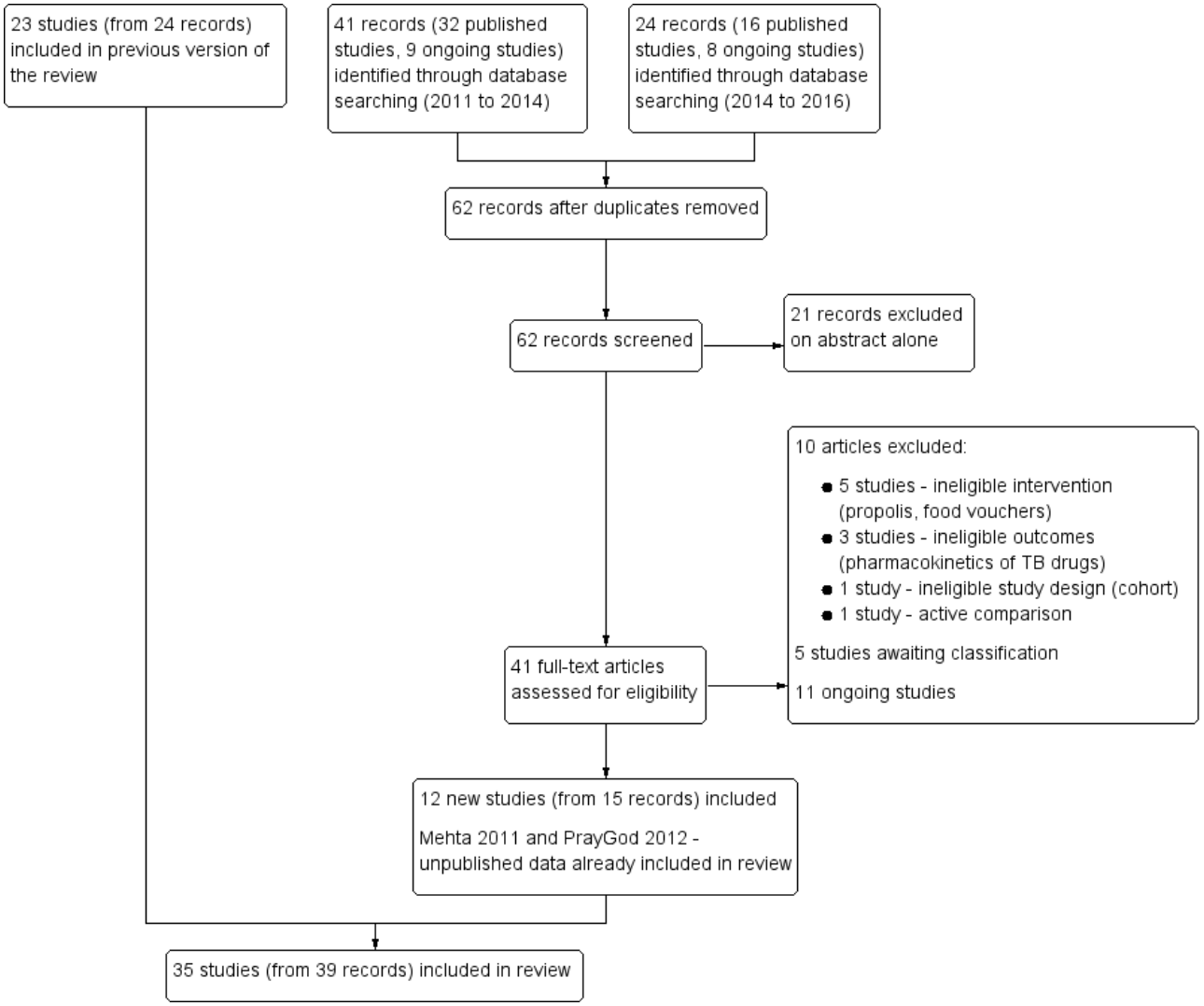
RESULTS

Description of studies

Results of the search

The original search (June 2008) identified 47 articles, and the updated search (July 2011) identified a further 17 articles. The searches conducted in December 2014 and updated in February 2016 identified 48 published articles and 16 ongoing studies. In total the current review includes data from 39 reports, covering 35 individually randomized controlled trials (RCTs) (see Figure 1).

Figure 1. Study flow diagram.



Included studies

Participants

The 35 trials included 8285 participants. Twenty-eight trials included only adults being treated for pulmonary tuberculosis, and three trials also included adults with extrapulmonary tuberculosis (Wejse 2008 GNB; Jahnavi 2010 IND; Sudarsanam 2010 IND). Likewise of four studies in children, one included only pulmonary tuberculosis (Hanekom 1997 ZAF), and three also included extrapulmonary tuberculosis (Morcos 1998 EGY; Mehta 2011 TZA; Lodha 2014 IND).

HIV status

Eleven trials specifically included people with HIV, and presented some results separately for HIV positive and HIV negative participants (Schön 2003 ETH; Range 2005 TZA; Semba 2007 MWI; Villamor 2008 TZA; Wejse 2008 GNB; Lawson 2010 NGA; Mehta 2011 TZA; Sudarsanam 2010 IND; Schön 2011 ETH; Ralph 2013 IDN;

Jeremiah 2014 TZA). Four of the trials that presented results for HIV-positive and HIV-negative participants separately used stratified randomization (Villamor 2008 TZA; Wejse 2008 GNB; Sudarsanam 2010 IND; Jeremiah 2014 TZA), but six tested participants for HIV following randomization (Schön 2003 ETH; Range 2005 TZA; Semba 2007 MWI; Lawson 2010 NGA; Mehta 2011 TZA; Schön 2011 ETH), and therefore the subgroup analyses by HIV status cannot be said to be truly randomized. Four trials included both HIV-positive and HIV-negative individuals and reported on numbers but did not present results separately (Martineau 2011 GBR; Praygod 2011a TZA; Visser 2011 ZAF; Tukvadze 2015 GEO). One trial included only HIV-positive participants (Praygod 2011b TZA). None of the HIV-positive participants were receiving antiretroviral treatment. One trial was stopped early when antiretrovirals became locally available (Semba 2007 MWI). Eleven trials excluded people with HIV infection (Hanekom 1997 ZAF; Paton 2004 SGP; Pérez-Guzmán 2005 MEX; Nursyam 2006 IDN; Armijos 2010 MEX; Jahnavi 2010 IND; Paliliewu 2013 IDN; Lodha 2014 IND; Daley 2015 IND; Farazi 2015 IRN; Mily 2015 BGD), and eight trials did not mention HIV infection (Morcos 1998 EGY; Karyadi 2002 IDN; Seyedrezazadeh 2006 IRN; Martins 2009 TLS; Pakasi 2010 IDN; Kota 2011 IND; Ginawi 2013 IND; Singh 2013 IND).

Study site

Trials were undertaken in the following locations.

- Africa: Egypt (Morcos 1998 EGY), Guinnea-Bissau (Wejse 2008 GNB), Ethiopia (Schön 2003 ETH; Schön 2011 ETH), Tanzania (Range 2005 TZA; Villamor 2008 TZA; Mehta 2011 TZA; Praygod 2011b TZA; Praygod 2011a TZA; Jeremiah 2014 TZA), Malawi (Semba 2007 MWI), Nigeria (Lawson 2010 NGA), and South Africa (Hanekom 1997 ZAF; Visser 2011 ZAF).
- Asia: Singapore (Paton 2004 SGP), Indonesia (Karyadi 2002 IDN; Nursyam 2006 IDN; Pakasi 2010 IDN; Paliliewu 2013 IDN; Ralph 2013 IDN), Iran (Seyedrezazadeh 2006 IRN; Farazi 2015 IRN), Bangladesh (Mily 2015 BGD), and India (Jahnavi 2010 IND; Sudarsanam 2010 IND; Kota 2011 IND; Ginawi 2013 IND; Singh 2013 IND; Lodha 2014 IND; Daley 2015 IND).
- Oceania: Timor Leste (Martins 2009 TLS).
- North America: Mexico (Pérez-Guzmán 2005 MEX; Armijos 2010 MEX).
- Europe: UK (Martineau 2011 GBR) and Georgia (Tukvadze 2015 GEO).

Interventions

Seven trials assessed macronutrient supplementation (Paton 2004 SGP; Pérez-Guzmán 2005 MEX; Martins 2009 TLS; Jahnavi 2010 IND; Sudarsanam 2010 IND; Praygod 2011b TZA; Jeremiah 2014 TZA), six trials assessed multi-micronutrient supplementation (Range 2005 TZA; Semba 2007 MWI; Villamor 2008 TZA; Mehta 2011 TZA; Praygod 2011a TZA; Lodha 2014 IND), and 21 trials assessed single or dual micronutrient supplementation. The remaining trial assessed the effect of supplementation with *Channa striata* capsules (Paliliewu 2013 IDN). *C. striata* is a fresh-water fish found in most tropical and subtropical countries.

Sample size

Eleven of the 35 trials included less than 100 participants in their final analysis. To aid interpretation and inform future research we have calculated the optimal sample size to reliably demonstrate some suggested clinically important results (Appendix 3; Appendix 4).

As micronutrients are a cheap and easily administered intervention, even a small effect on tuberculosis treatment outcomes might be considered clinically important. For example, to demonstrate a reduction in death from the worldwide average of 5% to just 4% (a relative risk reduction of 20%); a sample size of over 13,000 participants would be necessary. This is far above the data included in this Cochrane Review. Similarly an increase in successful cure rate from 80% to 84% would require almost 3000 participants.

For full details of the included trials see the 'Characteristics of included studies' table.

Excluded studies

We excluded 17 studies that we had thought were eligible after initial screening for the reasons we have given in the 'Characteristics of excluded studies' table. Five trials are currently awaiting classification pending further information from the author (Chandra 2004; Guzman-Rivero 2013; Nagrale 2013; Nawas 2013; Al Mamun 2014). In addition we are aware of 17 potentially relevant ongoing or unpublished trials; see the 'Characteristics of ongoing studies' table.

Risk of bias in included studies

We have displayed the 'Risk of bias' assessments in a table and summarised these results in Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

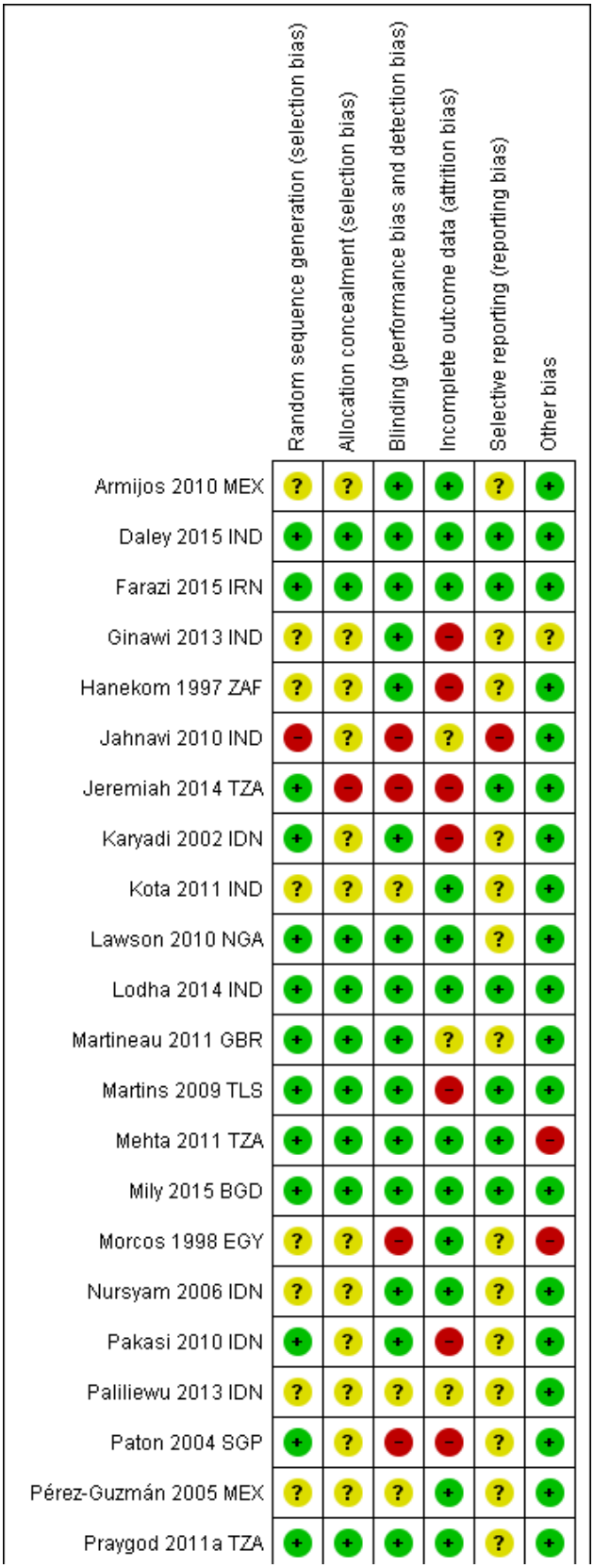
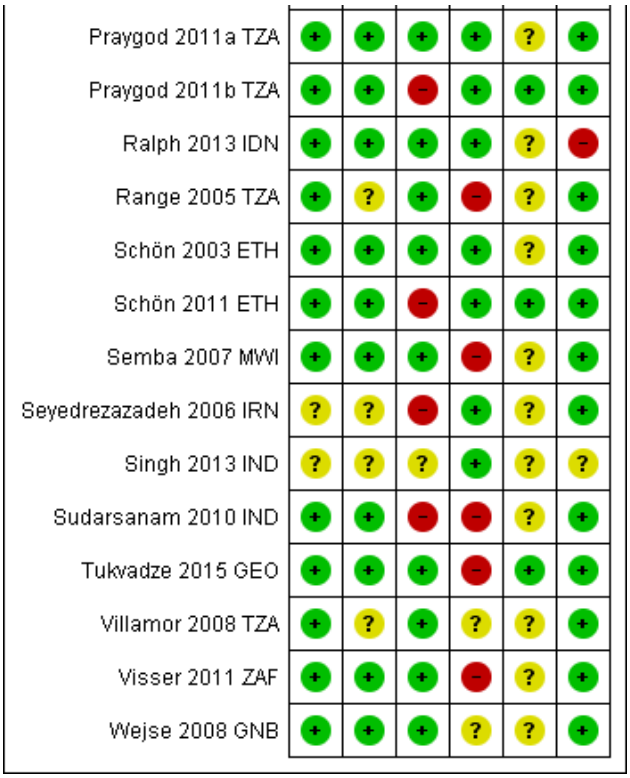


Figure 2. (Continued)



Allocation

Twenty-four trials described an adequate method of generating a truly random allocation sequence (Karyadi 2002 IDN; Schön 2003 ETH; Paton 2004 SGP; Range 2005 TZA; Semba 2007 MWI; Villamor 2008 TZA; Wejse 2008 GNB; Martins 2009 TLS; Lawson 2010 NGA; Pakasi 2010 IDN; Sudarsanam 2010 IND; Martineau 2011 GBR; Mehta 2011 TZA; Praygod 2011a TZA; Praygod 2011b TZA; Schön 2011 ETH; Visser 2011 ZAF; Ralph 2013 IDN; Jeremiah 2014 TZA; Lodha 2014 IND; Daley 2015 IND; Farazi 2015 IRN; Mily 2015 BGD; Tukvadze 2015 GEO). The other trials did not report how the random sequences were generated although all were described as "randomized".

Eighteen trials described an adequate method of ensuring allocation concealment (Schön 2003 ETH; Semba 2007 MWI; Wejse 2008 GNB; Martins 2009 TLS; Lawson 2010 NGA; Sudarsanam 2010 IND; Martineau 2011 GBR; Mehta 2011 TZA; Praygod 2011a TZA; Praygod 2011b TZA; Schön 2011 ETH; Visser 2011 ZAF; Ralph 2013 IDN; Lodha 2014 IND; Daley 2015 IND; Farazi 2015 IRN; Mily 2015 BGD; Tukvadze 2015 GEO). The other trials did not provide sufficient information to determine if the allocation sequence was truly concealed from the person allocating participants to the treatment groups.

Blinding

It is generally not possible to blind patients to macronutrient supplementation. However, it is possible to blind the outcome assessors but only one of the six studies reports an attempt to do this (Martins 2009 TLS).

Twenty-one of the 27 trials assessing micronutrients used placebos and adequately blinded participants and study staff to be considered at low risk of bias.

Incomplete outcome data

We considered 12 studies at high risk of bias for some outcomes due to high losses to follow-up (that is, loss to follow-up > 10% overall, between groups or within a group (Hanekom 1997 ZAF; Karyadi 2002 IDN; Paton 2004 SGP; Range 2005 TZA; Semba 2007 MWI; Martins 2009 TLS; Pakasi 2010 IDN; Sudarsanam 2010 IND; Visser 2011 ZAF; Ginawi 2013 IND; Jeremiah 2014 TZA; Tukvadze 2015 GEO).

Selective reporting

Although treatment outcomes in tuberculosis such as cure, and treatment completion are well established in tuberculosis programmes only one trial reported cure (Sudarsanam 2010 IND), and five reported treatment completion (Martins 2009 TLS; Jahnavi 2010 IND; Pakasi 2010 IDN; Sudarsanam 2010 IND; Farazi 2015 IRN). We were unable to retrieve trial protocols.

Other potential sources of bias

One trial did not adequately describe baseline nutritional status (Morcos 1998 EGY), one trial had a large imbalance in HIV status at baseline (Mehta 2011 TZA), and one trial had appreciable difference in both HIV status and severity of chest X-ray at baseline (Ralph 2013 IDN).

Effects of interventions

See: **Summary of findings for the main comparison** 'Summary of findings' table 1; **Summary of findings 2** 'Summary of findings' table 2

1. Macronutrients

1.1 Increased energy supplementation (average daily requirement for a male adult: 2500 kcal)

Six trials examined the effects of providing macronutrient supplements through the health service.

- In Timor Leste, adults with pulmonary tuberculosis and a mean weight of 43.3 kg (31% of participants had a BMI of less than 16 kg/m^2) were randomized to nutritional advice plus a daily cooked meal or nutritional advice alone (Martins 2009 TLS). The daily midday meal (administered for two months during the intensive phase) consisted of a bowl of meat, kidney beans, and vegetable stew with rice. During the continuation phase participants in the supplement group also received a weekly food parcel containing unprepared red kidney beans, rice, and oil adequate for one meal per day.
- In India, adults with pulmonary tuberculosis and a BMI of less than 19 kg/m^2 were randomized to receive a macronutrient and micronutrient supplement plus standard care versus standard care alone (Sudarsanam 2010 IND). The supplement consisted of three daily servings of a cereal and lentil mixture (providing 930 kcal and 31.5 g protein) and a once-a-day multivitamin tablet. Participants were given a month's supply of supplement at a time.
- The remaining four trials compared daily high energy supplements with: nutritional advice alone (Paton 2004 SGP; Jahnavi 2010 IND); a single multi-micronutrient biscuit (Praygod 2011b TZA); or no supplement (Jeremiah 2014 TZA). The supplements were described as 'sweetballs' (made from wheat flour, caramel, ground nuts, and vegetable ghee) (Jahnavi 2010 IND), high energy 'packets' (Paton 2004 SGP), and high energy 'biscuits' (Praygod 2011b TZA; Jeremiah 2014 TZA) (see Appendix 5). None of the studies estimated the total daily energy intake, but the supplement provided between 600 and 3690 kcal per day on top of the regular diet. All four studies recruited people with mean BMI below 20 kg/m^2.

Only two trials measured total dietary intake. Both trials confirmed that supplementation had increased nutritional intake compared to dietary advice alone, and not simply substituted food that patients might have obtained elsewhere (Paton 2004 SGP; Sudarsanam 2010 IND).

Tuberculosis treatment outcomes

The number of deaths reported from these trials was very low, and trials were too small to reliably detect or exclude important differences in mortality (risk ratio (RR) 0.34, 95% confidence interval (CI) 0.10 to 1.20; four trials, 567 participants; Analysis 1.1), or cure (RR 0.91, 95% CI 0.59 to 1.41; one trial, 102 participants; Analysis 1.2). Jahnavi 2010 IND found a statistically significant difference in treatment completion in favour of supplementation, but this was not seen in the larger trial conducted in Timor Leste (two trials, 365 participants, Analysis 1.3).

Jahnavi 2010 IND also found that more participants given supplements were smear negative at eight weeks, while Martins 2009 TLS and Jeremiah 2014 TZA found no statistically significant difference (RR 1.08, 95% CI 0.86 to 1.37; three trials, 222 participants; Analysis 1.4).

Nutritional recovery and quality of life

Effects on weight gain were mixed (five trials, 689 participants, Analysis 1.5). The daily hot meal was associated with an extra 1.7 kg weight gain at eight weeks (95% CI 0.1 to 3.2; P = 0.04; authors' own figures), and 2.6 kg at eight months (95% CI 0.1 to 5.2; P = 0.04; authors' own figures; Martins 2009 TLS), whereas the monthly ration pack was not associated with important differences (change in lean body mass, and percentage body fat were not significantly different between groups; P = 0.479 and P = 0.573 respectively; authors' own figures; Sudarsanam 2010 IND).

Of the trials evaluating high energy supplements, the two smaller trials in HIV-negative participants found that supplementation resulted in significantly more weight gain than advice alone at six weeks (MD 1.73 kg, 95% CI 0.81 to 2.65; one trial, 34 participants; Analysis 1.5) and 12 weeks, respectively (MD 2.6 kg, 95% CI 1.74 to 3.46; one trial, 100 participants; Analysis 1.5). Paton 2004 SGP further quantified this as an increase in lean body mass (MD 1.13 kg, 95% CI 0.37 to 1.89; one trial, 34 participants), with no significant difference in total fat mass. However, in Tanzania Praygod 2011b TZA found no significant difference in weight gain with supplementation in HIV-positive participants at eight or 20 weeks (one trial, 332 participants, Analysis 1.5). Similarly, Jeremiah 2014 TZA found no difference in final mean weight between the supplement and no supplement group after two months of supplementation (one trial, 92 participants, Analysis 1.5).

Three trials of high energy supplements (Paton 2004 SGP; Jahnavi 2010 IND; Praygod 2011b TZA) report changes in maximum grip strength, and again a statistically significant benefit was seen in the small trials of HIV-negative participants but not the larger trial of HIV-positive participants although the data appear skewed (three trials, 466 participants, Analysis 1.6).

Jahnavi 2010 IND and Paton 2004 SGP also reported that the benefits on weight gain and grip strength were accompanied by improvements in some quality of life scores. It was not possible to assess whether these difference were statistically significant because the data appeared highly skewed (the SDs were larger than the means for most outcomes); see Analysis 1.7 and Appendix 6.

1.2 Altered dietary composition

One very small trial of 21 participants compared a high cholesterol diet (2500 kcal per day with 800 mg cholesterol per day) with a diet with a similar nutritional profile but lower in cholesterol (2500 kcal per day with 250 mg cholesterol per day) for eight weeks in adults being treated for sputum-culture positive pulmonary tuberculosis (Pérez-Guzmán 2005 MEX).

Tuberculosis treatment outcomes

This trial did not report on death, cure, or treatment completion.

Fewer participants in the high cholesterol group were still sputum-culture positive at two weeks compared with those in the normal cholesterol group (RR of remaining sputum positive at two weeks 0.22, 95% CI 0.06 to 0.77; one trial, 20 participants, Analysis 2.1),

the difference was not significant at four weeks, and at eight weeks all participants in both groups were sputum-culture negative. Self reported cough and dyspnoea are reported to have decreased at the same rate in both groups (figures not given).

Nutritional recovery and quality of life

This trial did not report on any aspect of the participant's nutritional recovery or quality of life.

2. Micronutrients

2.1 Multivitamins and trace elements

Four trials in adults being treated for sputum test positive or negative pulmonary tuberculosis (Range 2005 TZA; Semba 2007 MWI; Villamor 2008 TZA; Praygod 2011a TZA) and two trials in children (Mehta 2011 TZA; Lodha 2014 IND) compared daily multiple micronutrient supplements (containing a range of vitamins and trace elements), with placebo. The exact doses of the individual constituents ranged from one to 10 times the dietary reference intake (DRI), and are given in Appendix 1. In summary: vitamin A (1 to 3 x DRI), B vitamins (1 to 10 x DRI), vitamin C (1 to 5 x DRI), vitamin D (approximately 1 x DRI), vitamin E (1 to 10 x DRI), zinc (1 to 5 x DRI), and selenium (1 to 4 x DRI).

In two trials participants received daily supplements for two months (Mehta 2011 TZA; Praygod 2011a TZA), one trial for six months (Lodha 2014 IND), one trial for eight months (Range 2005 TZA), and in two trials they received daily supplements for 24 months (Semba 2007 MWI; Villamor 2008 TZA).

Tuberculosis treatment outcomes

In trials with HIV negative people the number of deaths from tuberculosis was low and the trials substantially underpowered to demonstrate an effect, Consequently, the 95% CI is wide and includes clinically important benefit and harm (RR 0.86, 95% CI 0.46 to 1.60, four trials, 1219 participants, Analysis 3.1). Deaths were more common in trials with HIV positive people not taking antiretroviral therapy, but again no differences between micronutrients and placebo were demonstrated (RR 0.92, 95% CI 0.69 to 1.23, three trials, 1429 participants, Analysis 3.1).

Lodha 2014 IND reported no difference in tuberculosis treatment completion at six months between micronutrients (with and without zinc) and placebo (one trial, 302 participants, Analysis 3.2).

There was no statistically significant difference between the supplement and control groups in the numbers of participants who remained sputum-culture or sputum-smear positive at one month (two trials, 1020 participants, Analysis 3.3) or two months (two trials, 731 participants, Analysis 3.4).

Lodha 2014 IND and Mehta 2011 TZA reported no appreciable difference in chest x-ray clearance (after two or six months of supplementation) between the supplemented children and the placebo children at follow-up (two trials, 497 participants, Analysis 3.5).

Nutritional recovery and quality of life

Five trials reported changes in weight or body mass using a variety of parameters, and only Range 2005 TZA reported statistically significant effects (see Table 1).

Range 2005 TZA found that participants receiving multiple micronutrients had gained significantly more weight at seven months than those in the placebo group. This was a 2 x 2 factorial study and the difference in weight was appreciable in both treatment groups compared to placebo. In the treatment arm that received both high dose multivitamins and high dose zinc, the weight gain appeared clinically important (MD 2.37 kg, 95% CI 2.21 to 2.53; one trial, 192 participants, Analysis 3.6). However, in the treatment arm that received high-dose multivitamins alone, the weight gain was minimal (MD 0.30 kg, 95% CI 0.17 to 0.43; one trial, 198 participants, Analysis 3.6). In Lodha 2014 IND, multi-micronutrient supplementation with or without zinc did not consistently alter children's weight, BMI-for-age z score or height-for-age z score (one trial, 198 participants; Analysis 3.7).

One study, Praygod 2011a TZA, found an appreciable improvement in mean handgrip strength at two months but not five months (mean difference (change in handgrip strength) 1.22 kg, 95% CI 0.49 to 1.95; one trial, 771 participants; Analysis 3.8). The clinical importance of this difference is unclear. Consistent with the change in weight, this increase was only present in HIV-negative participants.

2.2 Individual micronutrients

Vitamin A (DRI: 900 µg/3000 IU per day)

Supplement dosing regimes

Three trials directly compared vitamin A given alone versus placebo (Ginawi 2013 IND: vitamin A 5000 IU; Hanekom 1997 ZAF: vitamin A 200,000 IU on Day 0 and Day 1; Pakasi 2010 IDN: vitamin A 5000 IU daily). In addition, seven trials combined vitamin A with zinc (see Comparison 6: Zinc plus vitamin A versus placebo), and five studies gave vitamin A as part of a multi-micronutrient supplement (see Comparison 3: Multivitamin and trace element tablets versus placebo).

Serum vitamin A concentrations at baseline and follow-up

Seven studies report on measures of vitamin A status, but Pakasi 2010 IDN and Visser 2011 ZAF reported data as median plasma levels so could not be included in the meta-analysis, and Semba 2007 MWI only presented data graphically (see Table 2). Only Semba 2007 MWI reports a difference that was statistically significant in favour of supplements, but this difference (at eight months) is unlikely to be of clinical significance.

In four trials in adults and one in children, mean serum vitamin A level substantially increased in both intervention and control arms regardless of supplementation, and there was no statistically significant difference between the groups (one trial, 85 participants; Analysis 4.1; three trials, 242 participants; Analysis 4.2; Table 2).

Tuberculosis treatment outcomes

Supplementation with vitamin A alone or in combination with other micronutrients appears to have little or no effect on mortality (eight trials, 3308 participants; Analysis 4.3), but these trials, even the larger ones, were significantly underpowered to rule out a clinically important effect.

Only Pakasi 2010 IDN reported on treatment completion and found no statistically significant effect (one trial, 158 participants, Analysis 4.4). Hanekom 1997 ZAF reported that more children in

the supplement group remained symptomatic after six weeks of tuberculosis treatment than in the control group, but this was not statistically significant (one trial, 76 participants, Analysis 4.5). The trial authors also reported no statistically significant differences in respiratory symptoms at three months, or in chest x-ray resolution; but specific data on these outcomes were not provided.

Supplementation with vitamin A alone had no effect on the number of participants who were sputum smear negative after two weeks, one month, or two months (two trials, 224 participants, Analysis 4.6). Pakasi 2010 IDN reported that all participants in the vitamin A and placebo arm were smear negative at two months.

Nutritional recovery and quality of life

Hanekom 1997 ZAF reported that the mean weight z score at baseline was −1.41 (SD 1.41) in the supplement group, and −1.44 (SD 1.34) in the placebo group (it is unclear whether this is weight for age or weight for height). The trial authors also reported that no statistically significant differences in change-in-weight z scores were recorded at any time-point, but the specific data for this outcome was not provided.

Pakasi 2010 IDN reports that the mean BMI at baseline was 16.5 kg/m^2 (SD 2.2) in the supplement group and 16.4 kg/m^2 (SD 2.5) in the placebo group. There was no statistically significant difference in mean BMI between groups at two or six months (one trial, 158 participants, Analysis 4.7). Pakasi 2010 IDN also reported that there were no statistically significant differences in mid upper arm circumference (MUAC) or percentage body fat (Analysis 4.8).

Zinc (DRI: 11 mg/day)

Supplement dosing regimes

Five trials directly compared daily zinc given alone versus placebo (Ginawi 2013 IND: 15 mg zinc sulphate; Lodha 2014 IND: 20 mg elemental zinc; Range 2005 TZA: zinc 45 mg daily; Lawson 2010 NGA: 90 mg elemental zinc weekly; Pakasi 2010 IDN: 15 mg zinc sulphate daily). In addition, seven trials combined vitamin A with zinc (see Comparison 6: zinc plus vitamin A versus placebo), and four trials gave zinc as part of a multi-micronutrient supplement (see comparison 3: Multivitamin and trace element tablets versus placebo).

Serum zinc concentrations at baseline and follow-up

Five studies report mean plasma zinc levels at baseline and during follow-up (see Table 3). Pakasi 2010 IDN and Armijos 2010 MEX report mean zinc levels within the normal range at baseline. Ginawi 2013 IND and Karyadi 2002 IDN reported that 30% of the participants had low zinc levels (less than 10.7 µmol/L) and in Lodha 2014 IND approximately 50% of the participants had zinc levels greater than 65 µg/dL.

Overall, daily supplementation with zinc sulphate increased serum zinc concentrations after two months and six months compared to placebo (four trials, 472 participants, Analysis 5.1; Table 3), with more consistent effects at six months.

Tuberculosis treatment outcomes

No effect on mortality has been seen with zinc alone or in combination with other micronutrients (seven trials, 2862 participants, Analysis 5.2, Analysis 5.3). These trials, even the larger ones, are significantly underpowered to rule out a clinically important effect.

There was no appreciable differences in treatment completion between the zinc alone and placebo groups (two trials, 353 participants, Analysis 5.4), and there were no differences between the groups in the numbers who remained sputum-culture positive at four weeks (three trials, 783 participants, Analysis 5.5) or eight weeks (five trials, 1076 participants, Analysis 5.5). Furthermore, Lodha 2014 IND reports no difference in chest X-ray clearance after six months between the zinc and placebo groups (one trial, 201 participants, Analysis 5.6).

Nutritional recovery and quality of life

One trial in children in India found no difference in mean weight (kg), weight-for-age z score, BMI-for-age z score or height-for-age z score after two months or six months supplementation with zinc alone (one trial, 201 participants, Analysis 5.7; Analysis 5.10; Analysis 5.11; Analysis 5.12). Similarly, Pakasi 2010 IDN found no difference in BMI or body fat (%) in adults at two or six months (one trial, 162 participants, Analysis 5.8 and Analysis 5.9; Pakasi 2010 IDN), and Lawson 2010 NGA presented data on changes in BMI graphically, and BMI appeared to improve at the same rate in all groups (Lawson 2010 NGA).

Range 2005 TZA reported a very small but statistically significant decrease in weight gain with supplementation compared to placebo (MD −0.21 kg, 95% CI −0.36 to −0.06; one trial 183 participants; Analysis 5.7).

Vitamin A plus zinc (DRI: vitamin A 900 µg/3000 IU, zinc 11 mg per day)

Supplement dosing regimes

Seven studies in adults with sputum positive pulmonary tuberculosis compared the combination of vitamin A and zinc versus placebo (Ginawi 2013 IND: vitamin A 5000 IU and 15 mg zinc sulphate; Singh 2013 IND: 25000 IU vitamin A and 50 mg zinc sulphate, once daily for 10 days and then thrice weekly until six months; Karyadi 2002 IDN: vitamin A 5000 IU and zinc 15 mg daily for six months; Armijos 2010 MEX: vitamin A 5000 IU plus zinc 50 mg daily for four months; Lawson 2010 NGA: vitamin A 5000 IU/day plus 90 mg elemental zinc/week for six months; Pakasi 2010 IDN: vitamin A 5000 IU plus 15 mg zinc sulphate daily for six months; Visser 2011 ZAF: vitamin A 100,000 IU at baseline plus zinc 15 mg for five days per week for two months).

Tuberculosis treatment outcomes

Four trials reported on deaths that occurred during the trial. In HIV negative participants there were no statistically significant differences in risk of death between those who received zinc and vitamin A or placebo (four trials, 430 participants, Analysis 6.1), but in HIV-positive participants the effect did reach statistical significance (RR 5.94, 95% CI 1.07 to 32.96; two trials, 136 participants; Analysis 6.1). However, both of these analyses are substantially underpowered to have confidence in these effects.

Only Pakasi 2010 IDN reported on treatment completion and found no statistically significant difference between the groups (one trial, 152 participants; Analysis 6.2). Overall, there is no statistically significant difference between supplementation and placebo in the number of participants who remain sputum-smear positive at one month or two months (seven trials, 726 participants,

Analysis 6.3). One study, Armijos 2010 MEX, did find a statistically significant difference in sputum positivity at three months in favour of supplementation (RR 0.12, 95% CI 0.02 to 0.84; one trial, 33 participants; Analysis 6.3), but the difference was not significant at two or four months. Visser 2011 ZAF found no statistically significant difference in time to smear or culture conversion (one trial, 154 participants; P = 0.15 and P = 0.38 respectively, authors' own figures).

Nutritional recovery and quality of life

Karyadi 2002 IDN reported a statistically significant increase in mean body weight at six months (MD 3.10 kg, 95% CI 0.74 to 5.46; one trial, 80 participants; Analysis 6.4), but there were no differences in any other nutritional parameters (see Table 4 and Analysis 6.5; Analysis 6.6; Analysis 6.7; Analysis 6.8; Analysis 6.9; Analysis 6.10; Analysis 6.11; Analysis 6.12). There was no statistically significant differences between intervention and control arms in any of the other three trials that reported changes in BMI or weight.

Two trials reported on changes in Karnofsy score, a rating scale of a person's ability to perform activities of daily living ranging from 0 (dead) to 100 (normal). Karyadi 2002 IDN reported that supplementation resulted in a small but statistically significant difference in Karnofsky score at six months (MD 2.5%, 95% CI 0.91 to 4.09; one trial 80 participants; Analysis 6.13), while Lawson 2010 NGA found no difference at two or six months but only presented data graphically (one trial, 233 participants). A difference in Karnofsky score of 2.5% is unlikely to be of clinical significance.

Vitamin D (DRI for adults: 5 to 15 µg/200 to 600 IU per day)

Supplement dosing regimes

Eight trials evaluated vitamin D supplementation versus placebo: Morcos 1998 EGY: 1000 IU daily for eight weeks; Nursyam 2006 IDN: 250 µg daily for six weeks; Ralph 2013 IDN: 50,000 IU daily for eight weeks; Mily 2015 BGD: 5000 IU daily for eight weeks; Tukvadze 2015 GEO: 50000 IU three times a week for eight weeks, then every two weeks for eight weeks; Wejse 2008 GNB: 100,000 IU at 0, 5, and 8 months; Daley 2015 IND and Martineau 2011 GBR: 2.5 mg on days 0, 14, 28, and 42).

In addition, one trial evaluated vitamin D combined with arginine (Ralph 2013 IDN: 50,000 IU plus arginine 6 g daily for eight weeks), two trials evaluated vitamin D combined with calcium (Singh 2013 IND: 250 IU plus calcium 500 mg daily for 10 days then three times a week; Kota 2011 IND: 60,000 IU per week plus calcium 1000 mg per day for 3 months), and four trials of multi-micronutrients included vitamin D in standard daily doses (see comparison 3).

Vitamin D levels at baseline and follow-up (deficient ≤ 50 nmol/L, and insufficient ≤ 75 nmol/L)

Seven trials reported vitamin D status at baseline and during follow-up, although only four trials provided data that we could include in a meta-analysis of the effect of Vitamin D supplementation on Vitamin D levels at follow-up (see Analysis 7.1; Table 5).

In four studies where the mean serum vitamin D levels were in the deficient range at baseline, there were large improvements at eight weeks with vitamin D compared to placebo (Martineau 2011 GBR: MD 78.60, 95% CI 54.17 to 103.03; Kota 2011 IND: MD 28.00, 95% CI 20.29 to 35.71; Mily 2015 BGD and Tukvadze 2015 GEO presented graphically, see Table 5). In two additional studies where the mean serum vitamin D levels were in the normal or insufficient range at baseline, there were no statistically significant differences at eight weeks (Wejse 2008 GNB: MD 2.00, 95% CI −7.76 to 11.76), or six months (Daley 2015 IND: MD 8.60, 95%CI −6.29 to 23.49).

Tuberculosis treatment outcomes

There were no statistically significant differences in the number of deaths between those receiving vitamin D (any formulation) or placebo regardless of HIV status (seven trials, 2649 participants, Analysis 7.2; Analysis 7.3).

Only Ralph 2013 IDN reported on cure, for which there was no statistically significant difference between the vitamin D and the placebo groups (one trial, 76 participants, Analysis 7.4). Wejse 2008 GNB also found no statistically significant difference in recovery, as defined by a newly developed tuberculosis scoring system (one trial, 348 participants, Analysis 7.5). This system rates the patient's condition on a scale of zero to 13, based on signs and symptoms and anthropometric measurements (Wesje 2008).

Overall, there were no statistically significant differences in the proportion of people that remained sputum positive at any time point from four weeks to eight months (seven trials, 1197 participants, Analysis 7.6). One trial of daily supplementation, Nursyam 2006 IDN, showed a statistically significant difference in the proportion of participants who remained sputum positive at six weeks (RR 0.06, 95% CI 0.00 to 0.95; one trial, 67 participants, Analysis 7.6); but the difference was not significant two weeks later. One additional trial, Kota 2011 IND, also reported finding a statistically significant difference but only presented the P value (P = 0.067).

Nutritional *recovery and quality of life*

There were no statistically significant differences in mean BMI after six to eight weeks of supplementation (four trials, 430 participants, Analysis 7.7), or in mean body weight (two trials, 150 participants, Analysis 7.8). Wejse 2008 GNB also reported no statistically significant difference in weight gain at eight months but only reported the P value (one trial, 359 participants, P = 0.9, authors' own figures), and Ralph 2013 IDN reported no statistically significant difference in the proportions gaining less than 5%, 5% to 9.9%, or greater than 10% weight.

Daley 2015 IND reported that mean Karnofsky score increased in both groups, with no statistically significant difference at eight weeks (one trial, 212 participants, Analysis 7.9).

Adverse events

Five trials reported adverse events, which we have summarized in Table 6. There were no important differences in reported adverse events between the supplemented and the placebo groups.

Vitamin E and selenium capsules (DRI: vitamin E 15 mg, selenium 55 µg per day)

One trial compared a daily vitamin E (140 mg) and selenium (200 µg) supplement with placebo in adults being treated for sputum-smear positive pulmonary tuberculosis (Seyedrezazadeh 2006 IRN).

The trial authors reported the median plasma vitamin E and selenium levels at baseline and at eight weeks. They reported that the median level of both micronutrients rose in the supplement group and decreased in the placebo group. We were unable to

assess whether these differences between groups were statistically significant (Appendix 8). In addition, one study that gave multi-micronutrients, including vitamin E (133 mg) and selenium (65 µg), measured the vitamin E and selenium levels at baseline and during follow-up (Semba 2007 MWI). The trial authors reported that both vitamin E and selenium levels were "significantly higher" in the supplement group after eight months, but only presented the data graphically.

Tuberculosis treatment outcomes

No deaths were reported and this trial did not report cure or treatment completion.

There was no statistically significant difference between the supplement and placebo groups in the numbers of participants who were sputum-smear positive at 15, 30, 45, and 60 days after the start of antituberculous treatment (one trial, 35 participants, Analysis 9.1).

Nutritional *recovery and quality of life*

The trial authors reported a 'constant increment' in BMI for the two months of treatment with no statistically significant differences between the groups, but did not present these data.

Arginine (currently considered a conditionally essential amino acid, depending on the developmental stage and health status of the individual)

Four trials compared daily supplementation with arginine (1 mg daily: Schön 2003 ETH and Schön 2011 ETH; 1000 mg twice daily for 30 days: Farazi 2015 IRN; and 6 mg daily for eight weeks: Ralph 2013 IDN) with either placebo (Schön 2003 ETH; Ralph 2013 IDN; Farazi 2015 IRN) or a biscuit that contained trace amounts of arginine (0.1 mg arginine, Schön 2011 ETH). The trials were all conducted in adults being treated for smear-positive pulmonary tuberculosis. Farazi 2015 IRN only included HIV-negative participants. The percentage of HIV-positive participants in the other three trials ranged from 13% (Ralph 2013 IDN) to 52% (Schön 2003 ETH).

Tuberculosis treatment outcomes

The included trials reported a total of 12 deaths. There was no significant difference in the risk of death between the arginine supplemented group and the placebo group (three trials, 394 participants, Analysis 8.1). There was also no significant difference in the proportion of participants who were cured (two trials, 279 participants, Analysis 8.2), or sputum smear or culture positive at four or eight weeks of follow-up (four trials, 464 participants, Analysis 8.3). Schön 2003 ETH reported a statistically significant increase in sputum-smear conversion in HIV-negative participants receiving arginine; however, our analysis of the data showed a non-significant difference between groups in the numbers of participants still sputum-smear positive at eight weeks (one trial, 56 participants, Analysis 8.3).

At two weeks Schön 2003 ETH reported that compared to the placebo group, fewer HIV-negative participants in the arginine group reported cough (RR 0.71, 95% CI 0.53 to 0.96; one trial, 56 participants, Analysis 8.4). Similarly, at eight weeks significantly fewer participants in the arginine group reported cough compared to those in the placebo group (RR 0.78, 95% CI 0.61 to 0.99; three trials, 348 participants, Analysis 8.4); this difference should be viewed with caution as only Farazi 2015 IRN provided baseline data that showed no difference in cough symptoms between groups.

Nutritional recovery and quality of life

In two studies there was no significant difference in weight gain (Schön 2003 ETH only presented the data graphically) or the proportion of participants with weight gain greater than 10% (Schön 2011 ETH; one trial, 170 participants, Analysis 8.5) between the arginine and placebo or low arginine groups. In a recent study, arginine supplementation significantly reduced the number of participants with a BMI of less than 18.5 after one (P = 0.032) and two (P = 0.04) months of antituberculous treatment compared to placebo (Farazi 2015 IRN).

3. Other trials

One small trial compared supplementation with *C. striata* capsules (6 g per day), for four months, with organoleptically-matched placebo on sputum and cytokine conversion in 36 HIV-negative participants with sputum smear positive pulmonary tuberculosis (Paliliewu 2013 IDN).

Tuberculosis treatment outcomes

This trial did not report on death, cure, or treatment completion. The rate of sputum smear conversion was greater in the supplemented group compared to placebo group. However, these differences were not statistically significant at any of the time points measured.

Nutritional recovery and quality of life

This outcome was not reported.

DISCUSSION

Summary of main results

Macronutrient supplementation

The included trials were too small to reliably prove or exclude clinically important benefits on mortality, cure, or treatment completion (*very low quality evidence*). One small trial from India did find a statistically significant benefit on treatment completion, and clearance of the bacteria from the sputum, but these findings have not been confirmed in larger trials elsewhere.

The provision of free food or high-energy nutritional products probably does produce a modest increase in weight gain during treatment for active tuberculosis, although this was not consistent across all included trials (*moderate quality evidence*). Two small studies provide some evidence that quality of life may also be improved but the trials were too small to have much confidence in the result (*low quality evidence*).

Micronutrient supplementation

Multi-micronutrients may have little or no effect on mortality in HIV-negative people with tuberculosis (*low quality evidence*), and probably have little or no effect on mortality in HIV-positive patients who are not taking anti-retroviral therapy (*moderate quality evidence*). There is insufficient evidence to know if multi-micronutrients improve cure, treatment completion, or the proportion of tuberculosis patients remaining sputum positive during the first eight weeks (*very low quality evidence*).

Multi-micronutrients may have little or no effect on weight gain during treatment (*low quality evidence*), although one of the three studies did find a substantial benefit in one study arm. No studies

assessed the effect of multi-micronutrient supplementation on quality of life.

Individual micronutrients

Although low vitamin A levels are common in tuberculosis, plasma levels probably increase following initiation of tuberculosis treatment regardless of supplementation. There is no evidence that supplementation in doses up to three times the DRI has a beneficial effect on tuberculosis treatment outcomes, or nutritional recovery.

B vitamins have been given in doses up to 10 times the DRI as part of multi-micronutrient supplementation. There is no evidence of an effect on mortality from tuberculosis. Due to the paucity of trials we cannot make any further conclusions about the effect of this vitamin on other tuberculosis outcomes.

Vitamin C has only been evaluated as part of multi-micronutrient supplements. Doses of vitamin C up to five times the DRI had no effect on tuberculosis mortality. Due to the paucity of trials we cannot make any further conclusions about the effect of this vitamin on other tuberculosis outcomes.

Vitamin D supplementation appears to improve plasma levels compared to placebo when participants are deficient at the start of supplementation, but may not have any clinically important effects on early sputum conversion.

Vitamin E has only been assessed in combination with other vitamins or selenium. The dose used was up to 10 times the DRI. None of these trials show any significant benefit or harm with supplementation, but supplementation probably does improve blood levels of both vitamin E and selenium.

There is some evidence that plasma zinc levels increase during the first six months of supplementation, but no convincing evidence of other benefits.

Overall completeness and applicability of evidence

The included studies were generally too small and too limited to make broad conclusions on the presence or absence of clinically important benefits of nutritional supplementation on tuberculosis treatment outcomes.

Although the included studies are from low- and middle-income countries, they may not reflect the food-insecure settings where most supplementation programmes take place, and where the benefit may plausibly be greatest.

Where a supplement has so far not shown any benefit, this may also be an issue relating to the dose used as people recovering from tuberculosis may have micronutrient requirements which are higher than healthy people, however there is currently no evidence to support this.

In addition, it should be noted that most of the HIV-positive participants in these trials were not taking antiretroviral therapy.

Quality of the evidence

We assessed the quality of evidence using the GRADE methodology, and displayed the results in two 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2). 'Moderate' quality evidence implies we can have some confidence in the result, but further research evidence would still be helpful. 'Low' and 'very low' quality reflect decreasing levels of confidence in the result.

The quality of evidence was mainly downgraded under 'directness' and 'precision'. Directness is an assessment of how well the evidence matches the PICO question being asked (population, intervention, control, outcome). Because nutritional deficiencies are likely to differ widely among populations, it is difficult to generalize the results of one or two trials to other settings or subgroups. Precision involves an assessment of the statistical and clinical significance of the result, and also whether the sample size of the trials is adequate to reliably detect an effect. Most of these trials were small and well below the optimal information size for the outcomes that were being measured.

Potential biases in the review process

We minimized biases in the review process by performing a comprehensive search of the literature for relevant published, unpublished, and ongoing trials and by independently selecting and appraising the studies, and extracting the data in duplicate. Where data was missing, we sought additional information and data directly from the study authors where this was possible to do so. We did not conduct an extensive hand-search for grey literature. Therefore, the review is at risk of publication bias from less prominent trials. We attempted to reduce this risk by identifying relevant conference abstracts and registered ongoing trials. The search of the trials registry to identify trial protocols and ongoing trials yielded 16 potentially relevant trial protocols. These will require further assessment and exploration to either: 1) link them to trials already included in the review; or 2) if not included, to attempt to obtain the completed trial reports. This task is time-consuming and has to be balanced against feasibility and time constraints.

Agreements and disagreements with other studies or reviews

Nutritional supplementation in HIV-positive patients without tuberculosis has been assessed by two further Cochrane reviews (Irlam 2010; Grobler 2013).

Grobler 2013 found 14 small trials that compared macronutrient supplementation with no supplementation and concluded that although there was evidence that supplementation increased both energy and protein intake, there was no evidence of a clinical benefit on either nutritional- or HIV-related outcomes.

Irlam 2010 assessed 30 trials that compared micronutrients with placebo from both developed and developing countries. The authors concluded that multi-micronutrient supplements have significant benefits in HIV-positive pregnant women and children. In children there was also evidence of a reduction in mortality with vitamin A, and a reduction in diarrhoeal morbidity with zinc.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient research to know whether routinely providing free food or energy supplements results in better tuberculosis treatment outcomes, but limited evidence suggests it probably improves weight gain.

Although blood levels of some vitamins may be low in patients starting treatment for active tuberculosis, there is currently no reliable evidence that routinely supplementing above recommended daily amounts has clinical benefits.

Implications for research

High quality studies of food provision to tuberculosis patients in food-insecure settings are urgently needed to support the continued expenditure on food support to tuberculosis programmes. In designing these studies, researchers, and programme managers need to be clear about the aim of food provision. Whilst an effect on mortality would provide strong advocacy for continued financial support, if the primary aim is to promote adherence, or to mitigate the catastrophic financial consequences of the illness, then these are the outcomes that should be measured, and appropriate comparison interventions should be selected. If the primary aim is to reduce mortality, then future trials must be large enough to reliably detect or exclude an effect.

The failure to demonstrate a beneficial effect with micronutrient supplementation does not imply that one does not exist. Further studies, perhaps using higher doses, would still be beneficial but should have adequate sample sizes to reliably detect or exclude clinically important benefits. It would also be useful if some standardization of outcome measurements could be made.

For nutritional recovery it seems important to assess changes in weight and lean body mass during the first two months of treatment rather than as a single measure at the end of treatment. It is also essential that measures of how this translates into improved quality of life and physical functioning are made, as weight gain on its own is of little interest.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Armijos 2010 MEX

Methods	Study design: randomized controlled trial (RCT). Study dates and duration: recruited August 2005 to July 2006, follow-up 6 months. Standard care: all participants received directly observed antituberculous therapy, per Instituto Mexicano del Seguro Social (IMSS) guidelines: 2 months of isoniazid/rifampin/pyrazinamide/ethambutol followed by 4 months of isoniazid and rifampin.
Participants	Number: 39 enrolled; 33 analysed. Inclusion criteria: adults aged 18 to 65 years, smear positive pulmonary tuberculosis, informed consent. Exclusion criteria: pregnancy, breast feeding, used corticosteroids, human immunodeficiency virus (HIV), diabetes, or another serious co-morbidity. Baseline characteristics • Nutritional status: mean body mass index (BMI) (standard deviation (SD)): 20.4 kg/m^2 (5.0) treatment group versus 22.6 kg/m^2 (4.2) control group. • HIV status: all negative. • Multidrug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB): not described. • Vitamin A status µg/dL (SD): 29.4 (13.3) supplement group versus 29.8 (13.8) placebo group; normal range. • Zinc status µg/L (SD): 738 (168) supplement group versus 764 (137) placebo group; normal range.
Interventions	Group 1: vitamin A 5000 IU/day (as retinyl acetate) plus zinc 50 mg/day (as zinc chelate) for 4 months. Group 2: placebo with identical appearance.
Outcomes	• Deaths during study. • Percentage remaining smear positive at 1, 2, 3, 4, and 5 months. • Mean zinc, retinol, and albumin levels at 0, 2, and 6 months. Not included in review: mean monthly intake of zinc and vitamin A, measures of immune response at 0, 2, and 6 months.
Notes	Location: Ciudad Juárez, México. Setting: IMSS outpatient services. Funding: Center for Border Health Research, UTEP-UTSPH Hispanic Health Disparities Research Center.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors described it as "randomised", but gave no further details.
Allocation concealment (selection bias)	Unclear risk	"A co-investigator not involved in data collection or analysis maintained the study codes and allocated the supplements".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo group subjects received organoleptically identical, matched placebo...Subject codes remained sealed until after data analysis".

Armijos 2010 MEX *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The analysis included 33/39 (85%) randomized participants. The trial authors clearly stated the reasons for drop-out.
Selective reporting (reporting bias)	Unclear risk	We could not retrieve the trial protocol. Trial participants were followed-up to 6 months but treatment completion and cure were not reported.
Other bias	Low risk	We did not identify any other sources of bias.

Daley 2015 IND

Methods	Study design: RCT. Study dates and duration: January 2010 to August 2011 (enrolment), follow-up completed by February 2012. Standard care: both groups received standard category 1 tuberculosis treatment according to Indian national guidelines.
Participants	Number: 247 randomized (121 to vitamin D group, 126 to placebo). Vitamin D group: 101/121 included in primary analysis. Placebo group: 110/126 included in primary analysis. Inclusion: HIV-negative participants aged 18 to 75 years with pulmonary tuberculosis (at least 1 documented positive sputum smear) who had received 1 dose or less of tuberculosis treatment Exclusion: participants with multidrug-resistant tuberculosis, pre-existing liver or kidney disease, concurrent steroid or cytotoxic drug treatment, metastatic malignant disease, pregnancy or lactation, active diarrhoea, hyper-calcaemia (corrected serum calcium > 2.62 mmol/L), or those who were not expected to survive for 180 days. Baseline characteristics • Nutritional status: mean BMI ± SD: 18.2 ± 2.9 kg/m^2 vitamin D group versus 17.8 ± 3.0 kg/m^2 placebo. • HIV status: all negative. • MDR/XDR-TB: excluded. • Mean vitamin D status ± SD (mmol/L): 63.1 ± 46.6 vitamin D group versus 62.2 ± 51.0 placebo group.
Interventions	Both groups received antituberculous treatment and were not provided with any advice about changing their diet or sun exposure. Vitamin D group: 4 doses of tasteless, odourless 2.5 mg vitamin D3 oil (100,000 IU per dose) orally once every 2 weeks for 8 weeks. Placebo group: identical Miglyol (the dosing regime is not clearly stated but we assume that it was identical to that of the vitamin D).
Outcomes	Primary outcome: time to sputum culture conversion (time to first negative culture). Secondary outcome: time to sputum culture conversion (time to first of 2 consecutive negative cultures), time to smear conversion (time to first negative smear and time to first of 2 consecutive negative smears), proportion of participants who had positive cultures at 56 days, Karnofsky performance status and body mass index (BMI) at 56 days, rate of rise in time to detection in culture and 25-hydroxyvitamin-D concentration at day 180. Primary safety outcome: incidence of hypercalcaemia (corrected serum calcium > 2.62 mmol/L).

Daley 2015 IND *(Continued)*

	Secondary safety outcome: rate of serious adverse events (death, admission to hospital, life-threatening illness, persistent disability, congenital anomaly, or predefined disease-related complications of tuberculosis infection), and adverse events (any untoward medical occurrence after study drug).
Notes	Baseline characteristics: mostly similar between groups, but the placebo group had slightly more men than the vitamin D group, and there were slightly more participants with isoniazid monoresistance in the vitamin D group (14/121; 12%) compared to the placebo group (8/126; 6%). It is unclear whether these differences were appreciably different or not. Setting: 13 clinics in Vellore and Krishnagiri districts of Tamil Nadu, India. Funding: Dalhousie University and Infectious Diseases Training and Research Centre. Trial registration: NCT00366470.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Bottles containing vitamin D or placebo were randomized by computer into permuted blocks of 4 without stratification, then labelled with serial study numbers in their randomized order. The randomization code was maintained in Canada and only after the database was locked was the code broken.
Allocation concealment (selection bias)	Low risk	The trial authors stated that neither the participant nor the clinical and laboratory investigators and personnel in India were aware of treatment assignment. As each participant was recruited, the next serially numbered bottle was assigned to the participant by study personnel. Both treatments were stored in identical dark glass dropper bottles at room temperature and protected from light.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors state that neither the patient nor the clinical and laboratory investigators and personnel in India were aware of treatment assignment. The randomization code was maintained in Canada by 1 investigator. After the database was locked, the code was broken and analysis was done with knowledge of assignment. Both treatments were stored in identical dark glass dropper bottles at room temperature and protected from light. Both treatments were oil-based and were tasteless and odourless.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants receiving 1 dose of intervention and with at least 2 sputum culture results were included in the primary analysis. Participants with only 1 culture result were excluded: Vitamin D group = 8/121 (7%) and placebo group = 5/126 (4%).
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported in the publication match those set out in the protocol.
Other bias	Low risk	Baseline and demographic characteristics were mostly similar between groups, but the placebo group had slightly more men than the vitamin D group, and there were slightly more participants with isoniazid mono-resistance in the vitamin D group. Funding source: Dalhousie University and Infectious Diseases Research and Training Center. Conflict of interest: Reinhold Vieth co-owns Ddrops a company that promotes and sells Vitamin D. All other trial authors declared no conflicts of interest.

Farazi 2015 IRN

Methods	Study design: RCT. Study dates and duration: recruited December 2012 to May 2014, follow-up 4 weeks. Standard care: all participants received directly observed antituberculous therapy (isoniazid, pyrazinamide, rifampicin, and ethambutol for 2 months followed by isoniazid and ethambutol for 6 months).
Participants	Number: 63 randomized (32 in arginine group, 31 in placebo group). Sex: arginine group 46.9% male; placebo group 51.6% male. Inclusion: new cases smear-positive pulmonary TB 15 years or older. Exclusion: hospitalization, pregnancy, clinical signs of comorbidity (diabetes, malignancy, hepatic/renal failure, HIV-positive), L-arginine supplementation during the past month, and allergic reactions to L-arginine. Baseline characteristics • Nutritional status (BMI < 18.5 kg/m^2): arginine 46.9%; placebo 45.2%. • HIV status: all HIV-negative. • MDR/XDR-TB: not reported on.
Interventions	Both groups received anti-TB treatment. Arginine group: 1000 mg pure L-arginine hydrochloride; twice daily for 30 days. Placebo group: 1000 mg sugar (capsules identical to L-arginine capsule); twice daily for 30 days.
Outcomes	• Treatment success. • Sputum conversion. • Weight gain. • Clinical symptoms at 1 and 2 months. Not included in review: ESR, CRP.
Notes	Location: Markazi Province, Iran. Setting: clinics. Funding: Arak University of Medical Science.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number tables".
Allocation concealment (selection bias)	Low risk	"Preparation of the randomization envelopes was performed by a member of the staff who was not directly involved in the study and a sealed copy of the treatment code was kept by the project leader until all data had been collected and analyzed".
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical capsules of L-arginine...or placebo".
Incomplete outcome data (attrition bias)	Low risk	Supplement: 2/34 (6%). Placebo: 3/34 (9%).

Farazi 2015 IRN *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported in the publication match those set out in the protocol.
Other bias	Low risk	Baseline and demographic characteristics were similar between groups. Funding source: Arak University of Medical Sciences. Conflicts of interest: all trial authors declared no conflict of interest.

Ginawi 2013 IND

Methods	Study design: RCT. Study dates and duration: not stated. Standard care: not stated.
Participants	Number: 178 randomized, 127 analysed. Inclusion criteria: category 1 pulmonary tuberculosis patients attending the DOTS centre. Exclusion criteria: those who did not take medication regularly (missing even 1 dose in the first 2 months), had severe adverse reactions, or drug-resistant tuberculosis. Baseline characteristics • Nutritional status: not stated. • HIV status: not stated. • MDR/XDR-TB: excluded. • Vitamin A status µg/dL (SD): unclear if it is baseline data or % increase from baseline. • Zinc status µg/L (SD): unclear if it is baseline data or % increase from baseline.
Interventions	Placebo group: lactose only. Vitamin A group: 1500 retinol equivalents (5000 IU) vitamin A (as retinyl acetate). Zinc group: 15 mg zinc (as zinc sulfate). Vitamin A and zinc group: 1500 retinol equivalents (5000 IU) vitamin A (as retinyl acetate) and 15 mg zinc (as zinc sulfate). Supplement and placebo were given to the participants with the antituberculous drugs on DOTS day.
Outcomes	• Sputum positivity: sputum smear negative for tubercle bacilli at 2 months. • Blood chemistry: haemoglobin, white blood cell count, erythrocyte sedimentation rate (ESR), serum albumin, serum retinol, and serum zinc concentration at 2 and 6 months.
Notes	Location: Lucknow, North India. Setting: not stated. Funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement

Ginawi 2013 IND *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors described the trial as a double blind, placebo-controlled trial. Supplement and placebo capsules were indistinguishable in appearance both externally and internally.
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial authors stated that they excluded non-compliant participants, participants who experienced severe adverse reactions, and participants with drug-resistant tuberculosis from the analysis. The trial authors did not describe reasons for loss to follow-up of 51 participants. 178 participants randomized. 127 participants completed the trial. 28.6% loss to follow-up (> 10% therefore high risk of bias).
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain the trial protocol so it is unclear if there is selective outcome reporting in this instance.
Other bias	Unclear risk	Baseline comparability: no significant difference in biochemical status at baseline. No information on age, gender, or nutritional status at baseline. Conflicts of interest: not reported. Funding: no information provided on funding resources.

Hanekom 1997 ZAF

Methods	Study design: RCT. Study dates and duration: dates not stated, follow-up 3 months. Standard care: all participants received directly observed antituberculous therapy, without any routine multivitamin preparations.
Participants	Number: 110 enrolled; 85 analysed. Inclusion criteria: children aged under 15 years with pulmonary tuberculosis. Exclusion criteria: HIV-positive. Baseline characteristics • Nutritional status: mean weight z score (SD): −1.41 (1.41) treatment group versus −1.44 (1.34) control group. • HIV status: all negative. • MDR/XDR-TB: not described. • Vitamin A status µg/dL (SD): 17.6 (10.1) supplement group versus 18.6 (10.6) placebo group; normal range 20 to 80.
Interventions	Group 1: vitamin A 200,000 IU; 2 doses before beginning antituberculous therapy. Group 2: placebo with identical appearance.

Hanekom 1997 ZAF *(Continued)*

Outcomes	• Resolution of respiratory symptoms at 6 weeks and 3 months. • Change-in-weight z scores. • Vitamin A levels at baseline, 6 weeks, and 3 months. Not included in review: chest X-ray changes, retinol binding protein, and prealbumin levels: at baseline, 6 weeks, and 3 months.
Notes	Location: Cape Town, South Africa. Setting: children's hospital (outpatient or inpatient not stated in report). Funding: the Glaxo 'Action TB' International Research Initiative, Medical Research Council of South Africa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors described the trial as "randomised"; but did not provide any further details.
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors described the trial as "double blind", with an "identical appearing placebo". No comment on outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial enrolled 110 participants, of which 15 were later excluded for not attending the last follow-up appointment and 10 for not meeting the inclusion criteria. The trial authors presented data for 76 of the remaining 85 (85%) participants.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Jahnavi 2010 IND

Methods	Study design: RCT. Study dates and duration: August to December 2005, follow-up 1-year. Standard care: all participants received directly observed antituberculous therapy according to the Revised National Tuberculosis Control Programme, India, without any routine multivitamin preparations.
Participants	Number: 100 participants randomized. Inclusion criteria: adults aged 18 to 65 years; with active tuberculosis; pulmonary or extrapulmonary smear/culture positive, BMI < 20 kg/m^2. Exclusion criteria: HIV-positive, diabetes, other severe underlying disease. Baseline characteristics • Nutritional status: mean weight kg (SD):43.0 (8.2) treatment group versus 44.2 (8.2) control group; mean BMI (SD): 17.1 kg/m^2 (2.8) treatment group versus 17.9 kg/m^2 (2.1) control group.

Jahnavi 2010 IND *(Continued)*

	• HIV status: all negative. • MDR/XDR-TB: unknown. • Micronutrient status: not assessed at baseline.
Interventions	Group 1: Control group: standard tuberculosis treatment as per the Revised National Tuberculosis Control Programme. A general instruction to "increase food intake". Group 2: targeted dietary advice to reach 35 kcal/kg/day and food supplements that consisted of "sweet balls" made of wheat flour, caramel, groundnuts, vegetable ghee, sprouted gram, and nuts — each containing 6 g protein and 600 kcal — consumed daily under supervision for 3 months.
Outcomes	• Body weight at baseline and 3 months. • Maximum grip strength and timed stand test at baseline and 3 months. • Quality of life at baseline and 3 months. • Sputum conversion at 2, 4, and 6 months. • Completion of the entire course of treatment. • Deaths during study.
Notes	Location: Krishna district, Andhrapradesh, India. Setting: community-based catchment area of 1 medical college and 1 DOTS centre. Funding: University of Padova, Italy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"randomisation performed by randomly shuffling the envelopes that contained the study codes".
Allocation concealment (selection bias)	Unclear risk	The trial did not describe this, but given that the envelopes with codes were shuffled it would seem adequate.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial did not make any attempt to blind the participants; the trial report does not mention whether or not the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were no apparent losses to follow-up.
Selective reporting (reporting bias)	High risk	Despite 1 year of follow-up, the trial authors only reported outcomes at 3 months, and incompletely reported sputum conversion.
Other bias	Low risk	We did not identify any other sources of bias.

Jeremiah 2014 TZA

Methods	Study design: open label RCT. Study dates and duration: September 2010 to August 2011. Standard care: treatment was given as FDC tablets, each contained Isoniazid (75 mg), rifampin (150 mg), pyrazinamide (400 mg), and ethambutol (275 mg) during the intensive phase, and for continua-

Jeremiah 2014 TZA *(Continued)*

	tion phase the tablet contained isoniazid (75 mg) and rifampicin (150 mg) only. If body weight < 50 kg then 3 tablets, and > 50 kg 4 tablets.
Participants	Number: 469 screened, 100 randomized (by HIV status). Inclusion criteria: sputum smear positive pulmonary tuberculosis patients 15 years or older, regardless of HIV status, with written informed consent. Exclusion criteria: HIV-positive participants on ART, pregnant women, terminally sick patients unlikely to survive > 48 hrs, and non-residents of Mwanza City. Baseline characteristics • Nutritional status: median BMI (kg/m^2) pulmonary tuberculosis-positive/HIV-positive supplement group: 19.4; 18.3, 20.5 pulmonary tuberculosis positive/HIV-positive no supplement group: 18.8; 17.4, 20.1, pulmonary tuberculosis positive/HIV-negative supplement group: 18; 16.9, 19.7. Pulmonary tuberculosis positive/HIV-negative no supplement group: 18.6; 17.3,19.6. Median weight (kg): pulmonary tuberculosis positive/HIV-positive supplement group: 52.3; 49.9, 56.6. pulmonary tuberculosis positive/HIV-positive no supplement group: 51.9; 49.2, 56.1. Pulmonary tuberculosis positive/HIV-negative supplement group: 50.7; 48.2, 57.7. Pulmonary tuberculosis positive/HIV-negative no supplement group: 52; 44.6, 58.8. • HIV status: median CD4 cell count; IQR cells/µL pulmonary tuberculosis-positive/HIV-positive supplement: 243.5; 140.5, 337.5 pulmonary tuberculosis-positive/HIV-positive no supplement: 168; 64, 338 pulmonary tuberculosis positive/HIV-negative supplement: 611; 457; 726 pulmonary tuberculosis positive/HIV-negative no supplement: 637; 433, 812. • MDR/XDR-TB: not described.
Interventions	• Group 1: pulmonary tuberculosis-positive/HIV-positive and Group 2: pulmonary tuberculosis positive/HIV-negative: no supplement. • Group 3: pulmonary tuberculosis-positive/HIV-positive and Group 4: pulmonary tuberculosis positive/HIV-negative: daily 5 high energy and vitamin/mineral enriched biscuit bars containing about 1000 kcal and additional vitamins and minerals (including zinc and selenium). Produced by Compact A/S. Supplement provided during first 2 months of tuberculosis treatment. Intake monitored by patient treatment supporter. Basic biscuit (30 g): 4.5 g protein, 615 kJ energy, 120 mg phosphorous, 120 mg calcium, 36 mg magnesium, 70 mg sodium, 150 mg potassium, and traces < 1 mg of iron and zinc. Biscuit with additional micronutrients: as above plus 1.5 mg vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B6, 50 µg vitamin B12, 0.8 mg folic acid, 40 mg niacin, 200 mg vitamin C, 60 mg vitamin E, 5 µg vitamin D, 0.2 mg selenium, 5 mg copper, 30 mg zinc.
Outcomes	• Mortality at 2 months. • Median weight gain at 2 months. • Sputum culture at 2 months. Not included in review: pharmacokinetics of rifampin and genotype of organic anion-transporting polypeptide encoded by SLCO1B1 rs149032 responsible for hepatic drug disposition.
Notes	Location: Mwanza, Tanzania. Setting: urban and suburban clinics. Funding: Danish Ministry of Foreign Affairs (DANIDA, DFC file no. 09-026RH) through Denmark's International Development Cooperation.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jeremiah 2014 TZA *(Continued)*

Random sequence generation (selection bias)	Low risk	The trial authors stated that simple randomization, stratified by HIV status, was computed using the website www.randomization.com.
Allocation concealment (selection bias)	High risk	This was an open-label trial, therefore it is likely that the people allocating the treatment where aware of which treatment group they were allocating the participants to.
Blinding (performance bias and detection bias) All outcomes	High risk	This was an open-label trial, therefore the participants and personnel were not blinded to the treatment. It is unclear if the outcome assessors were blinded to the treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial authors stated that they analysed all available data. Intervention arm: 2/51 (4%) lost to follow-up (died or defaulted); no supplement arm: 6/49 (12%) lost to follow-up (died or defaulted).
Selective reporting (reporting bias)	Low risk	We obtained the protocol obtained. The primary and secondary outcomes reported in the publication are in line with those set out in the protocol.
Other bias	Low risk	We did not identify any other sources of bias.

Karyadi 2002 IDN

Methods	Study design: RCT. Study dates and duration: December 1997 to December 1998, follow-up 6 months. Standard care: all participants received directly observed antituberculous therapy in line with WHO recommendations: 2RHZE/4HR.
Participants	Number: 110 enrolled; 80 analysed. Inclusion criteria: adults aged 15 to 55 years, 3 positive sputum smears, clinical and radiological signs consistent with pulmonary tuberculosis. Exclusion criteria: previous antituberculous therapy, drug resistance, extra-pulmonary tuberculosis, pregnancy, lactation, use of corticosteroids, vitamin A, zinc, or iron in the previous month, moderate to severe injury or surgery in the previous month, diabetes, renal failure, liver disease, neoplasm, or congestive heart failure. Baseline characteristics • Nutritional status: BMI < 18.5 kg/m^2: 25/40 treatment group versus 26/40 placebo group. • HIV status: not mentioned. • MDR/XDR-TB: excluded. • Vitamin A status: mean plasma retinol µmol/L (SD): 0.82 (0.04) supplement group versus 0.90 (0.04) placebo group; normal range > 0.7. • Zinc status: mean plasma zinc µmol/L (SD): 11.52 (0.26) supplement group versus 11.15 (0.28) placebo group; normal range > 10.7.
Interventions	Group 1: daily capsules of vitamin A 5000 IU and zinc 15 mg (as zinc sulphate) for 6 months. Group 2: placebo (lactose).
Outcomes	• Sputum-culture positive at 0, 2, and 6 months. • Body weight at 0, 2, and 6 months. • BMI at 0, 2, and 6 months.

Karyadi 2002 IDN *(Continued)*

	• MUAC, body fat percentage. • Karnofsky score at 0, 2, and 6 months. • Blood retinol and zinc levels. Not included in the review: biceps, triceps, subscapular, and supra-iliac skinfold thickness; blood haemoglobin, zinc protoporphyrin, x-ray changes.
Notes	Location: Jakarta, Indonesia. Setting: pulmonary outpatient clinics of 1 public hospital and 3 health centres. Funding: Gesellschaft fur Technische Zusammenarbeit (GTZ) GmbH, Eschborn, Germany; the Neys-van Hoogstraten Foundation; the Directorate General of Communicable Disease Control and Environmental Health, Indonesia; the Integrated Excellent Research Project, Ministry of Research and Technology Indonesia; PT Kimia Farma, Indonesia provided the supplements and placebo; PT Indo Farma provided the tuberculosis drugs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We used a table with randomly assorted digits to allocate patients into 2 groups".
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment but seems likely given the description of blinding.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Supplements and placebo were indistinguishable". "The authors, health staff, and patients were unaware of the treatment code until the study was completed".
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial authors appear to have added 2 exclusion criteria post-hoc: participants who missed even 1 day of treatment during the first 2 months, and participants who had severe adverse drug effects. The trial authors analysed 80/110 (72%) participants.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. Although cure is a standard outcome for tuberculosis programmes, this was not reported.
Other bias	Low risk	We did not identify any other sources of bias.

Kota 2011 IND

Methods	Study design: RCT. Study dates and duration: not stated. Standard care: all participants received intensive phase antimicrobial treatment comprising of isoniazid, rifampicin, pyrazinamide, and ethambutol. All participants were adjusted for oral hypoglycaemic agents and insulin for glycaemic control.
Participants	Number: 45 enrolled, (15 excluded), 30 randomized and included in the final analysis. Inclusion criteria: older than 15 years, newly diagnosed pulmonary tuberculosis patients, poorly controlled Type 2 diabetes mellitus (HbA1C > 7%) and serum 25(OH) D < 20 ng/mL. Pulmonary tuberculosis diagnosis based on 1 of the following criteria: at least 2 positive sputum smears (from 3), 1 positive smear and typical picture of lung infiltration on chest X-ray.

Kota 2011 IND *(Continued)*

	Exclusion criteria: younger than 15 years, patients already on ATT, serum 25(OH) D > 20ng/mL, diseases affecting vitamin D metabolism such as malabsorption, renal failure, or with prolonged immobilization. Baseline characteristics • Nutritional status: mean weight (kg ± SD) supplement group: 49.1kg ± 4.5, control: 44.6 ± 5.6. • HIV status: not stated. • MDR/XDR-TB: not stated. • Vitamin D 25-(OH) D (ng/mL) status: supplement group 12.8 ± 4.5, control group: 11.1 ± 4.7. • Vitamin A and zinc status: not reported.
Interventions	Group 1: vitamin D supplement along with intensive phase ATT. Oral cholecalciferol sachets (60,000 IU/week) and calcium carbonate (1000 mg/day). Group 2: no vitamin D supplement just intensive phase ATT. The trial authors did not state the duration of the intervention.
Outcomes	• Vitamin D levels every 4 weeks for 12 weeks. • Sputum smear conversion every 4 weeks for 12 weeks. • Fasting blood sugar and post lunch blood sugar monthly. • HbA1C monthly. • ESR monthly.
Notes	Location: Medwin Hospital, Hyderabad, India. Setting: hospital setting (inpatient). Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the randomization process.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not mention whether treatment allocation was concealed or not.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors did not describe any aspect of blinding in the paper.
Incomplete outcome data (attrition bias) All outcomes	Low risk	According to data provided, the trial authors included all of the participants randomized at baseline in the final analysis at 12 weeks.
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain the study protocol so it is unclear if all of the proposed outcomes have been reported on.
Other bias	Low risk	We did not identify any other sources of bias.

Lawson 2010 NGA

Methods	Study design: RCT.

Lawson 2010 NGA *(Continued)*

	Study dates and duration: September 2003 to June 2005, follow-up 6 months. Standard care: all participants received standard National Tuberculosis Programme treatment for tuberculosis: 2RHZE/4HE.
Participants	Number: 350 enrolled. Inclusion criteria: adults aged > 15 years with sputum positive pulmonary tuberculosis. Exclusion criteria: previous antituberculous therapy, pregnancy, lactation, use of corticosteroids or zinc in the previous month, major surgery in the previous month, diabetes, severe cardiovascular/renal or hepatic disease, currently taking oral contraceptives, unable to return. Baseline characteristics • Nutritional status: mean BMI (SD):19.8 kg/m^2 (3.3) placebo group, 21.3 kg/m^2 (4.7) zinc plus placebo group, 19.6 (3.5) zinc plus vitamin A group. • HIV status: 45% HIV-positive placebo group, 49% zinc plus placebo group, 42% zinc plus vitamin A group. • MDR/XDR-TB: not mentioned. • Vitamin A status: not reported. • Zinc status: not reported.
Interventions	Group 1: placebos (similar in appearance to zinc and vitamin A tablets). Group 2: 90 mg of elemental zinc per week plus daily placebo. Group 3: 90 mg of elemental zinc per week plus 1500 mcg retinol equivalents (5000IU vitamin A) weekly. Supplements were observed for 2 months then given as monthly supplies for the next 4 months.
Outcomes	• Time to sputum smear conversion. • Chest X-ray scores at 2 and 6 months. • Clinical symptoms (cough, fever and night sweats) at 2 and 6 months. • BMI at 2 and 6 months. • Karnofsky score at 2 and 6 months. • Deaths during the trial. Not included in the review: ESR and haemoglobin values.
Notes	Location: Abuja, Nigeria. Setting: 8 district hospitals. Funding: no sources stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Prepared the allocation sequence using random numbers generated in Minitab...using permuted block randomisation with four different black sizes".
Allocation concealment (selection bias)	Low risk	"One of the investigators who was not on the site prepared the allocation sequence...and the randomisation sequence was kept at the Liverpool School of Tropical Medicine Treatment...allocation was designated by a lettered code and concealed from the investigators and subjects until data analysis was completed".

Lawson 2010 NGA *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo tablets resembled the supplement tablets".
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 14 of 116 in the placebo group, 15 of 117 in the zinc group, and 21 of 117 in the zinc and vitamin A group lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We were unable to identify any other sources of bias.

Lodha 2014 IND

Methods	Study design: RCT. Study dates and duration: January 2008 to June 2012. Standard care: all children had 2 months intensive phase that used 3 or 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) followed by 4 months of isoniazid and rifampicin. Category 3 treatment was isoniazid, rifampicin, and pyrazinamide for 2 months followed by 4 months of rifampicin and isoniazid. Daily doses were based on weight: 5 to 7 mg isoniazid/kg; 10 to 13 mg rifampicin/kg; 35 to 40 mg pyrazinamide/kg; 20 to 25 mg ethambutol/kg. In case of non-response (clinical or radiological) antituberculous therapy was changed to 2 months streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol; followed by 1 month of isoniazid, rifampicin, and ethambutol; and 5 months of isoniazid, rifampicin, and ethambutol. Any child who did not respond on this regimen and for whom an alternative diagnosis was ruled out was started on 2nd line antituberculous therapy, which included an injection of kanamycin, ofloxacin, and ethionamide and an additional drug (cycloserine or co-amoxiclav). Participants were followed up every 2 weeks in the first 2 months, and then every 4 weeks for the remaining 4 months of ATT treatment.
Participants	Number: 403 randomized. At 2 months: data on 393 children; at 6 months: data on 381 children. Inclusion criteria: children 6 months to 15 years who presented with any of the following symptoms were considered tuberculosis suspects and screened: cough > 2 weeks with no improvement after 7 to 10 days amoxicillin, fever > 2 weeks with no improvement during 7 to 10 days amoxicillin, recent unexplained weight loss or failure to thrive, unusual or unexplained fatigue or lethargy or subtle clinical symptoms and history of close contact with adult tuberculosis patient. All had chest X-ray and tuberculin skin test. If the chest X-ray was consistent with intrathoracic tuberculosis, the child was considered to have tuberculosis. The trial enrolled children with newly diagnosed probable intrathoracic tuberculosis with or without extrapulmonary lesions. Exclusion criteria: bilateral pedal oedema; known HIV infection; history of antituberculous therapy or isoniazid prophylaxis > 4 weeks; signs of upper airway obstruction; O_2 saturation < 92%; signs of renal, hepatic, or cardiovascular disease; inability to attend follow-up session for reading of the skin test; documented intake of zinc continuously > 2 weeks in the 4 weeks preceding enrolment; CNS, osteoarticular, pericardial or renal tuberculosis; history of contact with a documented case of drug-resistant tuberculosis; or were non-residents of Delhi. Baseline characteristics • Nutritional status (weight-for-age z score): MN+Z group −2.72 ± 1.85; MN group −2.8 ± 1.6; zinc group −2.5 ± 1.5; placebo −2.8 ± 1.6.

Lodha 2014 IND *(Continued)*

- HIV status: HIV-negative only.
- MDR/XDR-TB (n/N tested): MN+Z group 1/18 (5.6%); MN group 1/29 (3.4%); zinc group 1: 1/21 (4.8%), placebo group 2/26 (7.9%).
- Serum zinc concentration < 65 µg/dL (n/N): MN + Z 60/102; MN 51/100; zinc 53/101; placebo 55/100.

Interventions	All children received antituberculous therapy. Supplemented daily for 6 months. Zinc group: zinc (20 mg elemental zinc). Micronutrient group: micronutrients (vitamin A, thiamine, riboflavin, vitamins B6 and B12, folic acid, niacin, vitamin C, vitamin E, vitamin D, selenium, and copper) without zinc. Micronutrient + zinc group: micronutrients (as above) in combination with zinc (20 mg elemental zinc). Placebo group: placebo.
Outcomes	• Change in weight-for-age z score at 6 months and resolution of pulmonary lesions using chest X-ray at 6 months. • Height-for-age z score. • Mid upper arm circumference. • Triceps skin fold thickness. • BMI-for-age z score at 2 and 6 months. • Resolution of symptoms at 2 months (as reported by parents). • Proportion of children requiring extension of intensive phase of therapy at 2 months. • Improvement in chest X-ray at 2 months.
Notes	Location: Delhi, India. All India Institute of Medical Sciences & Kalawati Saran Children Hospital associated with Lady Hardinge Medical College. Setting: urban, hospital. Funding: Norwegian Programme for Development, Research and Education and Research council of Norway and Global Health and Vaccination Research GLOBVAC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization described: a scientist who was not involved in the data collection and analysis, generated random-allocation sequences in permuted blocks of variable sizes separately for the 2 sites. Separate sequences were generated for the age groups 6 months to 3 years, 4 to 6 years, 7 to 9 years, and 10 to 15 years.
Allocation concealment (selection bias)	Low risk	Bottles that contained the micronutrient supplements were serially numbered for each stratum for the 2 sites. The 4 study syrup preparations had a similar packaging, appearance, and smell. The participant, physician, and laboratory personnel were blinded to the intervention.
Blinding (performance bias and detection bias) All outcomes	Low risk	The 4 study syrup preparations had a similar packaging, appearance, and smell. The participant, physician, and laboratory personnel were blinded to the intervention. They maintained masking during the data analysis by coding treatment allocation with 4 letters.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up overall 2 months: 10/403 (2.5%); 6 months: 22/403 (5.5%)

Lodha 2014 IND *(Continued)*

		6 month loss to follow-up per group: Micronutrient + zinc group: 8/102 (8%) Micronutrient group: 4/100 (4%) Zinc group: 7/101 (7%) Placebo group: 3/100 (3%)
Selective reporting (reporting bias)	Low risk	We obtained the study protocol and the trial authors reported all outcomes in the paper that they listed in the protocol. Five additional outcomes were listed in the protocol and will likely be reported in future papers. • Interferon gamma responses to *M. tuberculosis* antigens ESAT6 and CF10 by quantiferon assay at baseline, 2 months, and 6 months of treatment. • To study effect of zinc supplementation on ocular toxicity in children receiving ethambutol by VER. • To document drug resistance (S, I, R, E) patterns among children with culture confirmed tuberculosis. • To document genotypic strain diversity among children with culture confirmed tuberculosis, also associations between strain type and disease severity and drug resistance. • To document the spectrum of mycobacterial species by culture in children clinically suspected of having pulmonary tuberculosis.
Other bias	Low risk	Baseline characteristics: most demographic and clinical profiles were comparable at baseline. However, there were some differences regarding sex distribution, parental educational level, diagnosis, and energy and zinc intakes before enrolment. Fundings: non-biased source of funding.

Martineau 2011 GBR

Methods	Study design: RCT. Study dates and duration: January 2007 to July 2009, follow-up 8 weeks. Standard care: All participants received directly observed antituberculous therapy: 2RHZE.
Participants	Number: 146 enrolled; 128 in primary analysis. Inclusion criteria: adults aged over 18 years, newly diagnosed sputum positive pulmonary tuberculosis. Exclusion criteria: known intolerance to vitamin D or antituberculous therapy, sarcoidosis, hyperparathyroidism, nephrolithiasis, HIV infection, pulmonary silicosis, malignancy, renal or hepatic failure, oral corticosteroids, cytotoxic drugs or other immunosuppressant therapy in the last month, antituberculous therapy for > 7 days in the preceding 6 months, currently taking antituberculous therapy other than RHZE, known rifampicin resistance, serum corrected calcium > 2.65 mmol/L, aspartate transaminase or alanine transaminase > 120 IU/L, total serum bilirubin > 40 µmol/L, serum creatinine > 250 µmol/L, pregnant or breastfeeding. Baseline characteristics • Nutritional status: mean BMI (SD): 20.1 kg/m^2 (3.1) supplement group versus 20.2 kg/m^2 (2.7) placebo group. • HIV status: 5% positive supplement group versus 3% positive placebo group. • MDR/XDR-TB: rifampicin resistant isolate: 0% supplement group versus 4% placebo group.

Martineau 2011 GBR *(Continued)*

- Vitamin D status: mean serum 25-hydroxyvitamin D nmol/L (SD): 21.1 (20.0) supplement group versus 21.3 (19.0) placebo group; normal range > 75 nmol/L.

Interventions	Group 1: 4 oral doses of 2.5 mg vitamin D_3 (Viganol oil, Merck Serono) on or before day 7 after the start of tuberculosis treatment, day 14, day 28, and day 42. Group 2: an organoleptically identical placebo (Miglyol Oil, Caesar and Loretz) given as above.
Outcomes	• Median time to sputum conversion. • Serious adverse events. • Other adverse events. • Death. • Mean serum 25-hydroxyvitamin D at baseline and day 56. Not included in the review: haemoglobin level, mean corpuscular volume, total white blood cell count, lymphocyte count, monocyte count, neutrophil count, platelet count, erythrocyte sedimentation rate, C-reactive protein levels, chest radiography zones affected.
Notes	Location: London, UK. Setting: 10 National Health Service Trusts. Funding: British Lung Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"generated a random sequence using a computer program that assigned the term active or placebo to the numbers 1 to 200 by permuted block randomisation with blocks of 10".
Allocation concealment (selection bias)	Low risk	"The packs were then assigned a randomisation number according to this computer generated randomisation sequence", "Study staff who assigned patients to the active drug or placebo had no knowledge of the next assignment in the sequence, because they did not have access to the study code", "Treatment allocation was concealed from patients and study staff".
Blinding (performance bias and detection bias) All outcomes	Low risk	"organoleptically identical placebo". "adverse events judged to be potentially related to vitamin D by physicians unaware of allocation". "Those analysing the data were not masked to group assignment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors reported outcomes on an intention-to-treat basis. The number of participants lost to follow-up (3 in the placebo group and 6 in the placebo group) and the reasons were clearly reported for each group.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective outcome reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Martins 2009 TLS

Methods	Study design: RCT.

Martins 2009 TLS *(Continued)*

	Study dates and duration: March 2005 to November 2005, follow-up 8 months. Standard care: all participants received routine care including drugs (DOTS), default tracing, and clinical monitoring according to National TB Control Program guidelines: 2RHZE/6HE.
Participants	Number: 270 enrolled; numbers presented varies for each outcome. Inclusion criteria: adults aged > 18 years, pulmonary tuberculosis diagnosed by positive sputum criteria or NTP guidelines, willingness to receive treatment from the clinic for 8 months. Exclusion criteria: pregnancy, previous treatment for tuberculosis for > 1 month, unable to agree to complete treatment, unwilling to attend for a daily meal, chose community DOT. Description: adults aged > 18 years. Baseline characteristics • Nutritional status: BMI < 18.5 kg/m^2: 108/137 treatment group versus 105/133 control group. • HIV status: not mentioned. • MDR/XDR-TB: not mentioned. • Described as poor; 80% had no formal income, food was readily available but expensive.
Interventions	Group 1: a daily meal (intensive phase; week 1 to 8) followed by a food parcel (continuation phase; week 9 to 32). The meal consisted of a bowl of meat, kidney beans, and vegetable stew with rice. The food parcel contained unprepared red kidney beans, rice, and oil adequate for 1 meal per day. Group 2: verbal and written nutritional advice concerning locally available food that would constitute a balanced diet.
Outcomes	• Treatment completion at 8 months. • Mean weight gain (%) at 8 weeks and 32 weeks. • Cough clearance at 4, 8, and 32 weeks. • Sputum clearance. • Adverse events. • Deaths during study. Not included in review: mean compliance, default rate.
Notes	Location: Dili, Timor-Leste. Setting: 3 primary care clinics. Funding: the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, Australian National Health and Research Council.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An independent statistician computer generated a random allocation sequence with randomly varying block sizes in Stata (version 8)".
Allocation concealment (selection bias)	Low risk	"The sequence was concealed from all investigators with sequentially numbered opaque sealed envelopes prepared distant from the study site".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both participants and treatment providers were aware of an individual's allocation status after randomisation. An independent observer, who was blinded to the intervention received by the patients, however, determined the primary outcome".

Martins 2009 TLS *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	High levels of missing data for the outcomes of cough clearance (28% intervention versus 27% control at 8 weeks) and weight gain (12% intervention versus 9% control at 8 weeks, 29% intervention versus 33% control at 32 weeks). These could significantly affect the result.
Selective reporting (reporting bias)	Low risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Mehta 2011 TZA

Methods	Study design: RCT. Standard care: all participants received antituberculous therapy (6 months DOT: isoniazid 50 mg, rifampicin 200 mg, ethambutol 10 to 15 mg/kg, and pyrazinamide 20 to 30 mg/kg daily for 2 months; isoniazid 50 mg and rifampicin 200 mg daily for 4 months) and were visited at home by the study nurse every 2 weeks. Study dates and duration: May 2005 to September 2007. Follow-up 8 weeks.
Participants	Number: 255 enrolled and randomized; outcomes presented for 237. Inclusion criteria: aged 6 weeks to 5 years; loss of > 10% maximum weight or failure to gain weight for 2 months; cough with wheeze for ≥ 4 weeks; history of household contact with a probable or confirmed tuberculosis case in the past 6 months; pyrexia of unknown origin; painless swelling in a group of cervical lymph nodes; children who were diagnosed with tuberculosis in the past 5 years and have received antituberculous therapy for a period < 4 weeks. Positive TST (≥ 10 mm induration in HIV-negative and ≥ 5 mm in HIV-positive; after 48 to 72 hours) or with chest X-ray indicative of tuberculosis (based on unequivocal lymphadenopathy or military tuberculosis) eligible for enrolment. Exclusion criteria: children who had been treated with antituberculous therapy exceeding 4 weeks in the past 1 year. Baseline characteristics • Nutritional status: median (IQR) MUAC cm: 13.0 (11.9 to 14.25) multivitamin group versus 13.0 (11.2 to 14.0) placebo group; weight (kg): 8.48 multivitamin group versus 7.95 placebo group. • HIV status: 39.1% HIV-positive in the multivitamin group, 29.1% HIV-positive in the placebo group. • MDR/XDR-TB: not mentioned. • Micronutrient status: not documented.
Interventions	Group 1: multivitamin supplements daily for the first 2 months. Composition: vitamin B1 0.5 mg, vitamin B2 0.6 mg, niacin 4 mg, vitamin B6 0.6 mg, folate 130 µg, vitamin B12 1 µg, vitamin C 60 mg, and vitamin E 8 mg. • Age < 6 months: 1 capsule daily. • Age 7 to 36 months: 2 capsules daily. • Age > 36 months: 3 capsules daily. Group 2: placebo daily for the first 2 months.
Outcomes	• Weight gain at 2 months. • Deaths during treatment. Not included in this review: height, MUAC, and triceps skin-fold thickness changes at 2 months, clearance on chest x-ray at 2 months, immunological outcomes.

Mehta 2011 TZA *(Continued)*

Notes	Location: Dar Es Salaam, Tanzania. Setting: hospital paediatric clinic. Registration number: NCT00145184. Source of funding: National Institutes of Health Grant, the Harvard School of Public Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An off-site statistician generated the randomization sequence; a list from 1 to 400 was prepared according to this randomization sequence in blocks of 20.
Allocation concealment (selection bias)	Low risk	At enrolment, the trial staff assigned each eligible child to the next numbered bottle of regimen at the site. The statistician kept the randomization list confidential, with the exception of the pharmaceutical company that prepared the blinded treatment.
Blinding (performance bias and detection bias) All outcomes	Low risk	To minimize the risk of loss of blinding, the regimen bottles, with no visual difference between active regimen and placebo, were received from the manufacturer without any identification; the study staff then labelled the bottles with the participant's initials and identification number. Both the clinicians and the participants were blinded to the study regimen.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were low: 2.3% supplement group versus 1.6% placebo group.
Selective reporting (reporting bias)	Low risk	Although we were unable to retrieve the trial protocol, there was no evidence of selective reporting.
Other bias	High risk	There was a large difference in HIV status between the intervention and control groups at baseline.

Mily 2015 BGD

Methods	Study design: RCT. Standard care: all participants received antituberculous therapy (isonizaid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg for 2 months, followed by rifampicin 150 mg plus isonizaid 75 mg for 4 months), given under direct observation. Study dates and duration: December 2010 to December 2013. Follow-up 24 weeks.
Participants	Number: 288 enrolled and randomized. Inclusion criteria: age > 18 years, newly diagnosed sputum smear-positive tuberculosis, consent. Exclusion criteria: pregnancy and lactation, relapse tuberculosis, HIV infection, hypercalcaemia, regular intake of vitamin D, diabetes, cardiovascular, hepatic and renal diseases and malignancy, suspicion of prolonged drug abuse. Baseline characteristics • Nutritional status: mean weight (kg): males: 47.9 vitamin D group versus 46.3 placebo group; females: 38.4 vitamin D group versus 39.8 placebo group.

Mily 2015 BGD *(Continued)*

- HIV status: excluded.
- MDR/XDR-TB: not mentioned.
- Micronutrient status: mean plasma 25(OH)D_3 level: 28.0 vitamin D group versus 28.1 placebo group.

Interventions	Group 1: vitamin D 5000 IU daily for 8 weeks. Group 2: placebo. Not included in the review: Group 3: 4-phenylbutyrate 500 mg twice daily. Group 4: vitamin D plus 4-phenylbutyrate.
Outcomes	• Culture conversion at 4 weeks. • Time to sputum conversion. • Vitamin D levels. • Weight gain. • Adverse events. Not included in this review: Cough remission, CXR changes, normalization of fever, immunological measures.
Notes	Location: Dhaka, Bangladesh. Setting: National Institute of the Diseases of the Chest Hospital (NIDCH). Registration number: NCT01580007. Source of funding: International Centre for Diarrheal Disease Research, Bangladesh, Sida Agreement support Grant 384, and Swedish Strategic Foundation, and the Swedish Heart-Lung Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization sequence".
Allocation concealment (selection bias)	Low risk	"Independent assistants from the Hospital pharmacy prepared the study medication packs (PBA and placebo tablets; with identical appearance, colour and taste), and labelled these tablets with a randomization number".
Blinding (performance bias and detection bias) All outcomes	Low risk	"placebo with identical appearance, colour and taste".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up in the first 8 weeks were low.
Selective reporting (reporting bias)	Low risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Morcos 1998 EGY

Methods	Study design: RCT. Study dates and duration: not stated. Standard care: all participants received standard anti-tuberculous therapy: HRS for 2 months (beyond 2 months therapy is not described).
Participants	Number: 24 enrolled; outcomes presented for 24. Inclusion criteria: children with active tuberculosis; pulmonary or extrapulmonary. Exclusion criteria: none stated. Baseline characteristics • Nutritional status: not stated. • HIV status: not mentioned. • MDR/XDR-TB: not mentioned. • Vitamin D1: the mean vitamin D level at baseline is not given for the separate groups.
Interventions	Group 1: usual treatment plus vitamin D (1000 IU/day) for 8 weeks. Group 2: usual treatment.
Outcomes	• Body weight before and after treatment. • Vitamin D levels.
Notes	Location: Cairo, Egypt. Setting: inpatients and outpatients at a children's hospital. Funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly divided into 2 groups". The trial authors did not provide any further details.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe any allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial authors did not describe any blinding and did not use a placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up: 24/24 (100%) analysed.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol.
Other bias	High risk	The trial authors did not state important baseline characteristics.

Nursyam 2006 IDN

Methods	Study design: RCT. Study dates and duration: January 2001 to August 2001, follow-up 8 weeks. Standard care: all participants received antituberculous therapy in accordance with DOTS program, first category: 2RHZE/4RH.
Participants	Number: 67 enrolled; outcomes presented for 67. Inclusion criteria: adults aged 15 to 59 with sputum-culture positive pulmonary tuberculosis and moderately advanced lesion. Exclusion criteria: corticosteroids or immunosuppressive treatment, AIDS, renal failure, diabetes mellitus, liver cirrhosis, measles, malignancies, leprosy, or severe nutritional deficiency. Baseline characteristics • Nutritional status: mean BMI (SD): 16.87 kg/m^2 (2.06) treatment group versus 17.68 kg/m^2 (2.54) placebo group. • HIV status: negative. • MDR/XDR-TB: not described. • Described as: 67.2% had low income, 71.6% were low in nutritional status. • Vitamin D status at baseline not described.
Interventions	Group 1: vitamin D (0.25 mg/day for the first 6 weeks). Group 2: placebo.
Outcomes	• Sputum-culture positive at 6 weeks. • BMI at 0 and 6 weeks. Outcomes not included in this review: x-ray improvement at 6 weeks, default rate.
Notes	Location: Jakarta, Indonesia. Setting: outpatients at a pulmonary clinic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors described it as "randomised"; but gave no further details.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors described the trial as "double blind" and stated "the placebo were manufactured in the same shape and size". They did no provide any further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up. The trial authors analysed 67/67 (100%) for sputum conversion at 6 weeks.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Pakasi 2010 IDN

Methods	Study design: RCT. Study dates and duration: January 2004 to December 2005, follow-up 6 months. Standard care: all participants received antituberculous therapy in accordance with DOTS program; 2RHZE (daily)/4HR (thrice weekly), given by a treatment partner who was paid if the participant successfully completed treatment.
Participants	Number: 300 enrolled; 76 zinc; 72 vitamin A; 66 vitamin A + zinc; 86 placebo - 255 completed 6 months and were analysed. Inclusion criteria: adults aged 15 to 55, newly diagnosed sputum AFB positive pulmonary tuberculosis. Exclusion criteria: pregnancy, lactation, underlying chronic, or degenerative diseases. Baseline characteristics • Nutritional status: mean BMI (SD): 16.5 kg/m^2 (2.2) Zinc; 16.5 kg/m^2 (2.2) Vit A; 16.6 kg/m^2 (2.1) zinc + vitamin A, and 16.4 kg/m^2 (2.5) in the placebo group. • HIV status: not mentioned. • MDR/XDR-TB: not mentioned. • Vitamin A status: median plasma retinol µmol/L (IQR): 0.75 (0.5 to 1.0) zinc; 0.7(0.5 to 1.5) vitamin A; 0.7(0.4 to 1.1) zinc + vitamin A and 0.7(0.5 to 1.0) placebo group. • Zinc status: mean plasma zinc µmol/L (SD): 11.6(2.2) zinc; 11.9(3.0) vitamin A; 12.1(3.0), zinc + vitamin A and 11.8(2.4) placebo group.
Interventions	Zinc group: 15 mg zinc sulphate daily for 6 months as a capsule. Vitamin A group: 5000 IU (1500 retinol equivalents) daily as a capsule. Zinc + vitamin A group: both the above capsules for 6 months. Placebo group: lactose capsule daily for 6 months.
Outcomes	• Sputum smear conversion weekly for 8 weeks. • Anthropometry: weight, BMI, skin folds, percentage body fat. • Blood tests: plasma zinc, vItamin A. • Deaths during study. Not included in this review: chest X-ray cavity size, C-reactive protein, ESR, Hemoglobin, leukocyte count, and serum albumin.
Notes	Location: Nusa Tenggara Timur Province, Indonesia. Setting: community-based trial. Funding: Canadian International Development Agency through World Vision International Indonesia:Food integrated to Hinder TB Project (WVI-FIGHT Project).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation was done using a computer program".
Allocation concealment (selection bias)	Unclear risk	"a treatment code was given to each subject". The trial authors did not provide any further details.

Pakasi 2010 IDN *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"All capsules were identical in shape ,colour and size".
Incomplete outcome data (attrition bias) All outcomes	High risk	There was greater than 10% loss to follow-up in each group.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Paliliewu 2013 IDN

Methods	Study design: RCT. Study dates and duration: not described. Standard care: short course directly observed antibiotic therapy. Intensive 60-day treatment with isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1600 mg/day), and ethambutol (1200 mg/day) followed by a sustained 45-dose therapeutic phase with isoniazid (800 mg/dose) and rifampicin (600 mg/dose).
Participants	Number: 36 enrolled. Inclusion criteria: 14 to 50 years, ≥ 2 sputum smear positive, minimal-medium radiological lesion, 16 to 23 mg/kg^2 (BMI), ≥ 2.5 to 4.5 g/dL albumin levels and no prior history of tuberculosis or tuberculosis treatment. Exclusion criteria: pregnant, breast feeding, used corticosteroids, had HIV, diabetes or another serious co morbidity. Baseline characteristics • Nutritional status: not stated. • HIV status: not stated. • MDR/XDR-TB: not stated. • Micronutrient levels not stated. • Sputum positivity: 18 (100%) in intervention group, 18 (100%) in placebo group.
Interventions	*Channa striata* group: *C. striata* capsules, 4 months supplementation with 2 g/day, 3 times/day of *C. striata* for 12 weeks. Placebo group: organoleptically matched placebo with identical dosage regime.
Outcomes	• Percentage sputum conversion. • Disease signs & symptoms – cough, haemoptysis, dyspnoea, fever, night sweats, fatigue. • Laboratory indicators- AST, ALT, creatinine, uric acid, albumin. • TNF-α, IFN-γ, and IL-10 levels.
Notes	Location: Indonesia. Setting: clinic, patients attending Department of Internal Medicine, University of Sam Ratulangi, Manado, North Sulawesi, Indonesia. Funding: research grant from PT. Royal Medicalink Pharmalab, Makassar South Sulawessi, Indonesia.

Paliliewu 2013 IDN *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not explicitly describe this process.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants were blinded to the treatment allocation as organoleptically identical capsules were provided to both groups at similar times. Blinding of study personnel and outcome assessors was not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors did not provide any information on the number of participants lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain a copy of the trial protocol so it is unclear if the authors presented data on all of the stipulated outcomes.
Other bias	Low risk	Baseline comparability: figure in paper provides information on the sex, clinical signs, and symptoms and lab indicators at baseline. There was no difference in any of these variables at baseline. Funding source: research grant from PT. Royal Medicalink Pharmalab. Conflict of interest: not stated.

Paton 2004 SGP

Methods	Study design: RCT. Study dates and duration: November 2000 to July 2002. Follow-up 24 weeks. Standard care: all participants received combination antituberculous drug treatment, ancillary care, and follow-up according to standard protocols of the Tuberculosis Control Unit.
Participants	Number: 36 enrolled; outcomes presented for 34. Inclusion criteria: adults aged 18 to 69 years, with pulmonary tuberculosis and a body mass index < 20 kg/m^2. Exclusion criteria: diabetes or other severe underlying disease, concomitant corticosteroid or immunosuppressive therapy, HIV-positive or considered to be at risk of HIV and refused testing, history of noncompliance to tuberculosis therapy, unable to tolerate conventional regimen, required inpatient care. Baseline characteristics • Nutritional status: mean BMI (SD): 16.7 kg/m^2 (1.5) supplement group versus 17.9 kg/m^2 (1.9) control group. • HIV status: all negative. • MDR/XDR-TB: not mentioned. • Description: no comment on the social economic status of participants.
Interventions	Group 1: a target energy intake was calculated for each participant and advice given to them on how to reach this target based on a 24-hour food diary; participants were also supplied with high-energy oral nutritional supplements (6.25 g protein, 20.2 g carbohydrate, 4.29 g fat, 150 kcal/100 mL) and advised

Paton 2004 SGP *(Continued)*

	to consume 2 packets/day between meals (600 kcal total), which increased to 3 packets/day if tolerated, until they reached a body mass index of 20 or usual body weight. Group 2: participants were advised to increase their food intake and given advice to address any imbalances in their diet based on a 24-hour food diary.
Outcomes	• Body weight, total lean mass, and total fat mass. • Change in maximum grips strength and time stands test. • Change in quality of life score. Not included in the review: total energy intake; total energy intake from normal diet. Outcomes measured at 6, 12, and 24 weeks.
Notes	Location: Singapore. Setting: outpatients attending a tuberculosis control unit. Funding: National Medical Research Council of Singapore, Ensure donated by Abbott Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was 1:1 for the 2 groups and was performed by randomly shuffling opaque envelopes containing study codes. Preparation of the randomisation envelopes was performed by a member of the staff who was not directly involved in the study".
Allocation concealment (selection bias)	Unclear risk	See above. The trial authors did not report any further details.
Blinding (performance bias and detection bias) All outcomes	High risk	None described. Given the nature of the intervention, only outcome assessors could reasonably have been blinded but the trial authors did not describe this.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up were low at 6 weeks (3%), but high at 24 weeks: 21% in the supplement group versus 35% in the advice only group.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Praygod 2011a TZA

Methods	Study design: RCT. Study dates and duration: April 2006 to March 2009, follow-up 5 months. Standard care: all participants received standardized antituberculous drug treatment for 6 to 8 months according to national guidelines: 2RHZE/6HE.
Participants	Number: 865 enrolled. Inclusion criteria: adults aged > 15 years, with new or relapse pulmonary tuberculosis.

Praygod 2011a TZA *(Continued)*

	Exclusion criteria: extra-pulmonary tuberculosis, terminal illness, pregnancy, sputum-positive patients with HIV co-infection. Note: the trial included patients with sputum-negative pulmonary tuberculosis and HIV co-infection. Baseline characteristics • Nutritional status: mean BMI (SD): 18.9 kg/m^2 (2.8) intervention group versus 18.9 kg/m^2 (3.1) control group. • HIV status: 27% HIV-positive intervention group versus 29% control group. • MDR/XDR-TB: not mentioned. • Description: no comment on the social economic status of participants. • Micronutrient status: at baseline not reported.
Interventions	Group 1: the intervention group received a daily energy-protein similar to the control biscuit but with additional: 1.5 mg vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B6, 50 µg vitamin B12, 0.8 mg folic acid, 40 mg niacin, 200 mg vitamin C, 60 mg vitamin E, 5 µg vitamin D, 0.2 mg selenium, 5 mg copper, 30 mg zinc. Group 2: the control group received a daily energy-protein biscuit for the first 60 days of treatment. Composition: 4.5 g protein, 615 kJ energy, 120 mg phosphorous, 120 mg calcium, 36 mg magnesium, 70 mg sodium, 150 mg potassium, and traces < 1 mg of iron and zinc
Outcomes	• Body weight, arm fat area, arm muscle area at 0, 2, and 5 months. • Maximum hand grips strength at 0, 2, and 5 months.
Notes	Location: Mwanza, Tanzania. Setting: 4 tuberculosis clinics serving urban and suburban patients. Funding: the Danish Council for Independant Research, Danida and the University of Copenhagen. Clinical trial registry number: NCT00311298.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation to treatment arms followed a computer-generated randomisation sequence using permuted blocks of ten".
Allocation concealment (selection bias)	Low risk	"The random sequence was used by a designated research staff member who was not involved in any clinical work in TB clinics to arrange and label the supplement packs with identity numbers ranging from 1 to 1500. During the study, the randomisation sequence and code were kept in a safe cabinet and were accessible only to the research staff. Recruitment of study participants was done by clinic staff. Then the same designated research staff assigned the recruited patient an identity number and sent the corresponding nutritional supplement pack to the respective clinic".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both control and experimental supplements were of the same size and colour but had slightly different tastes and were wrapped in grey-coloured paper box with 6 bars each".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up at 2 months and 5 months were 10.2% and 18.0% respectively. However, the proportion lost to follow-up did not differ significantly between the groups.

Praygod 2011a TZA *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Outcomes reported in the publication match those set out in the protocol. However, mortality, a secondary outcome was not reported on.
Other bias	Low risk	The baseline characteristics of the 2 arms were comparable. Funding: Danish council for independent research - Medical sciences; Danida through Consultative Research Committee for Development Research; University of Copenhagen. Conflict of interest: all trial authors reported no conflicts of interest.

Praygod 2011b TZA

Methods	Study design: RCT. Study dates and duration: April 2006 to March 2009, follow-up 5 months. Standard care: all participants received standardized antituberculous drug treatment for 6 to 8 months according to national guidelines: 2RHZE/6HE.
Participants	Number: 377 randomized. Inclusion criteria: adults aged > 15 years, with new or relapse sputum-positive pulmonary tuberculosis with HIV co-infection. Exclusion criteria: extra-pulmonary tuberculosis, terminal illness, pregnancy. Baseline characteristics • Nutritional status: mean BMI (SD): 18.7 kg/m^2 (2.9) intervention group versus 18.5 kg/m^2 (2.8) control group. • HIV status: all HIV positive. • MDR/XDR-TB: not mentioned. • Description: no comment on the social economic status of participants.
Interventions	Group 1: the intervention group received 6 daily energy-protein biscuits for the first 60 days of treatment, of which 1 contained the additional micronutrients. Group 2: the control group received 1 daily energy-protein biscuit with additional micronutrients. Basic biscuit: composition: 4.5 g protein, 615 kJ energy, 120 mg phosphorous, 120 mg calcium, 36 mg magnesium, 70 mg sodium, 150 mg potassium, and traces < 1 mg of iron and zinc. Biscuit with additional micronutrients: as above plus 1.5 mg vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B6, 50 µg vitamin B12, 0.8 mg folic acid, 40 mg niacin, 200 mg vitamin C, 60 mg vitamin E, 5 µg vitamin D, 0.2 mg selenium, 5 mg copper, 30 mg zinc.
Outcomes	• Body weight, arm fat area, arm muscle area at 0, 2, and 5 months. • Maximum hand grips strength at 0, 2, and 5 months.
Notes	Location: Mwanza, Tanzania. Setting: 4 tuberculosis clinics serving urban and suburban patients. Funding: The Danish Council for Independant Research, Danida and the University of Copenhagen. Clinical trial registry number: NCT00311298.

Risk of bias

Praygod 2011b TZA *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation sequence, using permuted blocks of ten".
Allocation concealment (selection bias)	Low risk	"The allocation sequence was used by designated research staff to sequentially arrange and label supplement packs with identity numbers ranging from 1 to 500. During the study the randomisation sequence and code were kept in a safe cabinet only accessible by designated research staff. Recruitment was done by clinic staff. The same designated research staff not employed at the study clinics assigned an identity number to the recruited patient and sent the corresponding nutritional pack to the respective clinic".
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible due to the nature of the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 2 and 5 months, 12.2% and 19.1% of participants were lost to follow-up. However, the proportions lost to follow-up were similar across the intervention and control arms of the study.
Selective reporting (reporting bias)	Low risk	Outcomes reported in the publication match those set out in the protocol. However, mortality, a secondary outcome was not reported on.
Other bias	Low risk	The baseline characteristics of the 2 arms were comparable. Funding: Danish council for Independent Research - Medical sciences; Danida through Consultative Research Committee for Development Research; University of Copenhagen. Conflict of interest: all trial authors reported no conflicts of interest.

Pérez-Guzmán 2005 MEX

Methods	Study design: RCT. Study dates and duration: March 2001 to January 2002, follow-up 8 weeks. Standard care: all participants received a short-course regimen with 4 antituberculous drugs under the DOTS strategy according to WHO guidelines.
Participants	Number: 21 enrolled; outcomes presented for 21. Inclusion criteria: adults aged 17 to 60 years with sputum-culture positive pulmonary tuberculosis. Exclusion criteria: diabetes mellitus; HIV-positive; signs of coronary heart disease. Baseline characteristics • Nutritional status: mean BMI (SEM): 19.9 kg/m^2 (1.2) intervention group versus 19.2 kg/m^2 (0.8) normal diet group. • HIV status: excluded. • MDR/XDR-TB: not reported
Interventions	Group 1: normal diet containing 2500 calories a day, 16% protein, 54% carbohydrate, and 30% lipids for 8 weeks; included 250 mg cholesterol/day.

Pérez-Guzmán 2005 MEX *(Continued)*

	Group 2: high cholesterol diet containing 2500 kcal per day, 16% protein, 54% carbohydrate, and 30% lipids for 8 weeks; included 850 mg cholesterol/day.
Outcomes	• Sputum-culture positive at end of weeks 2, 4, and 8. Not included in the review: mean number of colony-forming units and acid-fast bacilli in sputum smear; self reported severity of cough, sputum production, and dyspnoea. Outcomes measured at weeks 1, 2, 3, 4, 5, 6, 7, and 8.
Notes	Location: Mexico City, Mexico. Setting: hospital inpatients. Funding: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors described the trial as "randomised"; but did not provide any further details.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Patients were unaware of the group to which they had been assigned".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. 21/21 (100%).
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Ralph 2013 IDN

Methods	Study design: RCT. Study dates and duration: June 2008 to February 2010. Standard care: participants received directly observed antituberculous therapy: weight-dosed rifampicin, isoniazid, pyrazinamide, ethambutol daily for 2 months; then rifampicin, isoniazid 3 times a week for 4 months.
Participants	Number: 548 assessed for eligibility; 200 randomized (45% of planned sample size); 155 analysed. Inclusion criteria: consecutive patients referred to Timika tuberculosis clinic with newly diagnosed with pulmonary tuberculosis (≥ 2 direct sputum specimens positive for acid fast bacilli (AFB)) were assessed for eligibility: sputum smear positive, > 15 years, not pregnant, without hypercalcaemia (ionized calcium ≤ 1.32 mmol/L), not previously treated for tuberculosis, agreeing to stay in Timika for 6 months and providing written informed consent. Exclusion criteria: not specified.

Ralph 2013 IDN *(Continued)*

	Baseline characteristics • Nutritional status: arginine + vitamin D group 49 ± 8.9 kg; arginine group 47.9 ± 9 kg; vitamin D group 48.1 ± 6.6 kg; placebo group 48.7 ± 5.5 kg. • HIV status: arginine + vitamin D group 28% HIV-positive; arginine group 6% HIV-positive; vitamin D group 15% HIV-positive; placebo group 5% HIV-positive. • MDR/XDR-TB: not reported. • Vitamin D levels: not reported. • Arginine levels: not reported. Difference in sex, HIV status, and X-ray severity at baseline.
Interventions	L-Arginine + vitamin D group: active L-arginine (L-arginine hydrochloride, Argimax®) 6 g (6 tablets) daily for 8 weeks and active cholecalciferol (vitamin D3, Calciferol Strong®) 50,000 IU (1250 mcg, 1 tablet) at baseline and on day 28. L-Arginine + placebo vitamin D group: active L-arginine (L-arginine hydrochloride, Argimax®) 6 g (6 tablets) daily for 8 weeks and placebo cholecalciferol: 1 tablet at baseline, 1 tablet at 28 days. Placebo L-arginine + vitamin D group: placebo L-arginine: 6 tablets daily for 8 weeks and active cholecalciferol (vitamin D3, Calciferol Strong®) 50,000 IU (1250 mcg, 1 tablet) at baseline and on day 28. Placebo group: placebo L-arginine: 6 tablets daily for 8 weeks and placebo cholecalciferol: 1 tablet at baseline, 1 tablet at 28 days.
Outcomes	• Proportion of participants with negative sputum culture on liquid medium at 4 weeks. • Composite clinical severity score at week 8 (points allocated on weight change, forced expiratory value (FEV_1), cough and presence/absence of sputum and haemoptysis. • Safety (death, hospitalization, hypercalcaemia). • Sputum smear conversion time (≥ 2 consecutive negative smears without a subsequent positive). • Change in 6 minute walk test. • Modified St George's respiratory questionnaire. • Chest X-ray severity score (0, 8, and 24 weeks). • FEV1. • Primary endpoint stratified by HIV and ethnicity. • Serious adverse events: death, hospitalization, and life-threatening conditions. • Adverse events: new symptoms or hypercalcaemia.
Notes	Location: Timika, Indonesia. Setting: Timika tuberculosis clinic and community hospital. Funding: Australian Respiratory Council, Royal Australasian College of Physicians Covance Award (APR), National Health and Medical Research Council of Australia. Trial registration: NCT00677339.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block random allocation sequence stratified by ethnicity (Papuan/non-Papuan) was generated and remained concealed from all investigators throughout study. Independent assistants prepared packs labelling them with a code corresponding to the randomization sequence.

Ralph 2013 IDN *(Continued)*

Allocation concealment (selection bias)	Low risk	Participants were assigned the next sequential code and dispensed an opaque envelope containing study medication. Active and placebo medications appeared identical.
Blinding (performance bias and detection bias) All outcomes	Low risk	Randomization sequence was unknown to all investigators. Independent assistants labelled medication packs with codes corresponding to random sequence. Active and placebo medications appeared identical.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial authors stated that they conducted a modified intention-to-treat analysis. They kept participants in the arm to which they were randomized, but excluded protocol violators and participants lost to follow-up from the final analysis. Loss to follow-up per arm at end of 4 weeks (primary outcomes time point) • L-arginine + vitamin D: 4/50 (8%). • L-arginine: 3/50 (6%). • Vitamin D: 3/50 (6%). • Placebo: 2/50 (4%). (Loss to follow-up < 10%).
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	High risk	Baseline comparability: there were differences in sex, HIV status, and X-ray severity between groups at baseline. Funding sources: non-commercial funding sources. Conflict of interest: the trial authors stated there were no competing interests. Other: grouping the data could lead to confounders.

Range 2005 TZA

Methods	Study design: RCT with 2 x 2 factorial design. Study dates and duration: August 2001 to July 2002, follow-up 7 months. Standard care: all participants received antituberculous therapy according to WHO guidelines.
Participants	Number: 530 enrolled; 31 later found ineligible and excluded; number with available outcomes data varied by outcome. Inclusion criteria: adults aged > 15 years, sputum-culture or sputum-smear positive pulmonary tuberculosis. Exclusion criteria: returning to treatment after default or previous treatment failure; thought unlikely to survive; pregnant or lactating. Baseline characteristics • Nutritional status: mean BMI (SD): 18.3 kg/m^2 (2.5) zinc + multivitamins group versus 18.0 kg/m^2 (2.5) multivitamin + placebo group versus 17.8 kg/m^2 (2.5) zinc+placebo group versus 18.7 kg/m^2 (2.7) placebo group. • HIV status: 39% zinc + multivitamins group versus 46% multivitamin + placebo group versus 47% zinc + placebo group versus 38% placebo group. • MDR/XDR-TB: not mentioned.

Range 2005 TZA *(Continued)*

	• Zinc or micronutrient status at baseline not given.
Interventions	Factorial design, giving daily supplements or placebo for 8 months. Group 1: zinc 45 mg plus placebo. Group 2: multivitamin and mineral tablet (vitamin A 1.5 mg, vitamin B1 20 mg, vitamin B2 20 mg, vitamin B6 25 mg, vitamin B12 50 µg, folic acid 0.8 mg, niacin 40 mg, vitamin C 200 mg, vitamin D3 5 µg, vitamin E 60 mg, selenium 0.2 mg, and copper 5 mg) plus placebo. Group 3: zinc 4 mg plus multivitamin and mineral tablet (as above). Group 4: placebo plus placebo.
Outcomes	• Death before 8 months. • Sputum positive at weeks 2, 4, and 8. • Weight gain at 8 weeks and 7 months. Not included in the review: HIV viral load and CD4 count at baseline and 8 weeks.
Notes	Location: Mwanza region, Tanzania. Setting: outpatients at 5 health facilities.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Before recruitment of patients, all the letters on the containers were replaced with study serial numbers from 1 to 550 based on the computer-generated random sequences, using permuted blocks of four".
Allocation concealment (selection bias)	Unclear risk	"The codes for the MVM and Zn tablets remained in a sealed envelope, and were only broken after completion of the initial data analysis".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo tablets were identical in colour, shape and size to the corresponding white Zn and green MVM tablets".
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: mortality: 9% zinc group versus 14% placebo group, weight gain: 22% zinc group versus 22% placebo group. These could significantly alter the result.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Schön 2003 ETH

Methods	Study design: RCT. Study dates and duration: recruited December 2000 to December 2001. Follow-up 8 weeks. Standard care: all participants received DOTS in line with Ethopian National Guidelines.
Participants	Number: 120 enrolled, outcomes presented for 115.

Schön 2003 ETH *(Continued)*

	Inclusion criteria: adults aged 15 to 60 years, smear positive pulmonary tuberculosis. Exclusion criteria: admitted to hospital; pregnant; signs of any concomitant disease other than HIV; or lived too far away to take part in the directly observed therapy short Direct Observed Treatment Short-Course (DOTS) programme. Baseline characteristics • Nutritional status: Mean weight in HIV-negative group: 47.8 kg intervention group versus 45.3 kg control group, mean weight in HIV-positive group: 45.0 kg intervention group versus 45.3 kg control group. • HIV status: 52% HIV-positive. • MDR/XDR-TB: not mentioned.
Interventions	Group 1: arginine capsules (1 g arginine) daily for 4 weeks. Group 2: placebo.
Outcomes	• Death during 8 weeks follow-up. • Sputum positive at week 8. • Cough at weeks 2 and 8. • Weight gain at 1, 2, 4, and 8 weeks. Not included in the review: serum arginine, citrulline, and nitric oxide metabolite levels at weeks 0, 2, and 8.
Notes	Location: Ethiopia. Setting: Outpatient DOTS programme.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized in blocks of six (performed by the state pharmacy of Sweden)".
Allocation concealment (selection bias)	Low risk	"The study was double blinded and a sealed copy of the treatment code was kept by the project leader until all data had been collected and analysed".
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as "double blind" and placebos were used: the trial authors did not give any further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 115/120 included in the final analysis(96%). Three of these died, 2 moved out of the study area.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any sources of bias.

Schön 2011 ETH

Methods	Study design: RCT. Study dates and duration: recruited February 2004 to December 2006. Follow-up until August 2007.

Schön 2011 ETH *(Continued)*

	Standard care: all participants received DOTS in line with Ethopian National Guidelines.
Participants	Number randomized: 80. Inclusion criteria: newly diagnosed sputum smear positive older than 15 years. Exclusion criteria: admitted to hospital; peanut allergy, pregnant; signs of any concomitant disease other than HIV; previous treatment for tuberculosis. Baseline characteristics • Nutritional status: high arginine group - mean BMI: 16.9 95% CI 16.4 to 17.4; low arginine group - mean BMI 16.4 95%CI 16 to 16.8. • HIV status: high arginine group - 37% HIV-positive; low arginine group - 32% HIV-positive. • MDR/XDR-TB: not mentioned.
Interventions	All participants received antituberculous therapy. High arginine group: 30 g peanuts (1 g arginine, 750 kJ) daily for 4 weeks. Low arginine group: 30 g wheat cracker (0.1 g arginine, 623 kJ) daily for 4 weeks.
Outcomes	Primary outcome: cure rate (smear positive at start of Rx, completed Rx, and smear negative at end of Rx and 1 previous occasion). Secondary outcomes: sputum smear conversion, weight gain, sedimentation rate, reduction of cough, and chest X-ray improvement at 2 months. Not eligible for review: levels of nitric oxide (NO) metabolites in urine and NO in exhaled air at 2 weeks and 2 months.
Notes	Location: Gondar, Ethiopia. Setting: DOTS clinic at Gondar University Hospital. Funding: Swedish Heart and Lung Foundation. Trial number: NCT00857402.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The Department of Epidemiology at the Karolinska Institute, Sweden performed randomization in blocks of 6.
Allocation concealment (selection bias)	Low risk	The randomization code was concealed in 180 sealed individual envelopes. The envelopes were only opened when the person was enrolled in the study.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not possible due to the nature of the intervention (wheat cracker versus peanuts).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Regarding loss to follow-up, 7/180 (4%) did not complete the supplement.
Selective reporting (reporting bias)	Low risk	Outcomes reported on in the published study match those set out in the study protocol.
Other bias	Low risk	There were no differences in baseline characteristics between the 2 groups.

Schön 2011 ETH *(Continued)*

	Funding: Swedish Heart and Lung Foundation, The Swedish SAREC/SIDA Foundation and the Swedish Research Council. Conflict of interest: the trial authors had no conflicts of interest.

Semba 2007 MWI

Methods	Study design: RCT. Study dates and duration: July 1999 to February 2005, follow-up 24 months. Standard care: all participants received standard antituberculous therapy as recommended by the Malawi NTP: 2RHZE/6HE.
Participants	Number: 1148 enrolled; number with available outcomes data varied by outcome. Inclusion criteria: adults aged 18 to 60 years, sputum positive pulmonary tuberculosis. Exclusion criteria: planning to move away from the study area within the next 2 years; already taking vitamin supplements; already being treated for tuberculosis; previously treated for tuberculosis. Baseline characteristics • Nutritional status: geometric mean BMI (SD): HIV-positive participants 18.3 kg/m^2 (2.5) supplement group versus 18.1 kg/m^2 (2.5) placebo group; HIV-negative participants 18.5 kg/m^2 (2.6) supplement group versus 18.8 kg/m^2 (2.9) placebo group. • HIV status: 71% HIV-positive supplement group versus 74% placebo group. • MDR/XDR-TB: not mentioned.
Interventions	Group 1: daily micronutrient supplementation for 24 months; supplement consisted of vitamins A (8000 IU), C (500 mg), D (400 IU), E (200 IU), B6 (2 mg), B12 (6 µg), riboflavin (1.7 mg), thiamin (1.5 mg), niacin (20 mg), folate (0.4 mg), zinc (10 mg), iodine (175 µg), and selenium (65 µg). Group 2: daily placebo.
Outcomes	• Death after 8 months follow-up. • Vitamin A, vitamin E, and selenium levels at 8 months.
Notes	Location: Zomba and Blantyre, Malawi. Setting: participants diagnosed at a hospital clinic and treated at a community clinic near where they lived. Funding: the National Institutes of Health; the Fogarty International Centre.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer random number generator was used to generate a random allocation schedule in permuted blocks of 10".
Allocation concealment (selection bias)	Low risk	"Treatment assignment was concealed by pre-packing study supplements in sequentially numbered series according to the allocation schedule".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both the study staff and the participants were blinded to the treatment assignment".

Semba 2007 MWI *(Continued)*

		"The placebo and active supplements were of identical appearance in size, shape and colour. The placebo and active supplements were packed in identical opaque, white plastic bottles with sealed caps".
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up were high: 13.2% in the supplement group and 12.9% in the placebo group.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other potential sources of bias identified.

Seyedrezazadeh 2006 IRN

Methods	Study design: RCT. Study dates and duration: recruited April 2003 to May 2004. Follow-up 60 days. Standard care: all participants received the same antituberculous standard therapy in accordance with the DOTS strategy.
Participants	Number: 42 enrolled; outcomes data available for 37. Inclusion criteria: adults (age range not stated), with sputum positive tuberculosis. Exclusion criteria: previous antituberculous treatment; concurrent use of supplements containing selenium and vitamin E; illicit drug addiction; signs of severe effects of antituberculous drug treatment during treatment. Baseline characteristics • Nutritional status: median BMI (IQR): men 19.6 kg/m^2 (16.0 to 27.1) supplements group versus 21.0 kg/m^2 (16.8 to 23.1) placebo group; women 19.5 kg/m^2 (16.6 to 25.8) supplements group versus 22.0 kg/m^2 (17.0 to 26.7) in placebo group. • HIV status: not mentioned. • MDR/XDR-TB: not mentioned.
Interventions	Group 1: daily supplements containing vitamin E (140 mg) and selenium (200 µg) for 4 months. Group 2: placebo.
Outcomes	• Sputum positive at days 15, 30, 45, and 60. • Change in body mass index at 2 months. Not included in the review: number of lung cavities; cavity surface area; and mean lesion area at 0, 2, and 6 months.
Notes	Location: Tabriz, Iran. Setting: outpatient clinic at research centre. Funding: the Tuberculosis and Lung Disease Research Centre.

Risk of bias

Bias	Authors' judgement	Support for judgement

Seyedrezazadeh 2006 IRN *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The trial authors described the sequence generation as "randomised", but did not provide any further details.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe any allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial authors described the trial as double blind, and capsules as being "similar in size and red in colour", which makes true blinding unlikely.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Regarding losses to follow-up, 37/37 (100%) participants were eligible.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Singh 2013 IND

Methods	Study design: RCT. Study dates and duration: September to October 2010 (enrolment), 6 months study period (Oct 2010 to March 2011). Standard care: initial 2-month phase of antituberculous therapy. The trial authors did not describe the precise content of the tuberculosis treatment.
Participants	Number: 40 enrolled and randomized. 37 included in the final analysis (3 excluded because of poor compliance). Inclusion criteria: newly diagnosed sputum smear positive pulmonary tuberculosis patients taking not more than 7 days of antituberculous therapy aged 18 to 60 years. Exclusion criteria: known history of drug resistant tuberculosis and renal disease. Baseline characteristics • Nutritional status: mean BMI kg/m^2 placebo group: 17.7; vitamin D and calcium group: 16.37, vitamin A and zinc group: 17.52 (no SDs provided). • HIV status: not reported. • MDR/XDR-TB: not mentioned. • Micronutrient status at baseline not described.
Interventions	All groups received antituberculous therapy. Control group: antituberculous therapy only. Vitamin D and calcium group: tablet containing vitamin D and calcium (250 IU of vitamin D3, and 500 mg as calcium carbonate). One tablet per day for first 10 days, then 3 tablets per week for the remainder of the 2 months. Vitaimn A and zinc group: zinc tablet (50 mg elemental zinc as zinc sulphate) and vitamin A tablet (25,000 IU vitamin A as vitamin A palmitate). One vitamin A tablet and 1 zinc tablet per day for first 10 days, then 3 tablets of each per week for the remainder of the 2 months.
Outcomes	Sputum smear conversion rates every 20 days from enrolment.

Singh 2013 IND *(Continued)*

	Time to sputum smear conversion. Weight gain at enrolment and 60 days (no SDs provided). BMI at enrolment and 60 days (no SDs provided). Not relevant to review: neutrophil count at enrolment and 60 days; lymphocyte count at enrolment and 60 days; serum alanine transaminase and aspartate transaminase at enrolment and 60 days; serum haemoglobin at enrolment and end of 2 months (60 days).
Notes	Location: India, HNB hospital attached to the Veer Chandra Singh Garhwali Govt. Medical Science and Research Institute, Srinagar – Pauri Garhwal (Uttarakhand). Setting: hospital. Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe this and simply stated randomly assigned.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe this.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors did not describe blinding of participants, personnel, and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 40 patients randomized to the 3 groups. The trial excluded 3 patients due to non-compliance and excluded them from the analysis (8% loss to follow-up).
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain the study protocol, and therefore there is unclear risk of selective outcome reporting. In the abstract the trial authors stated that the aim of the study was to assess sputum conversion and blood profiles during the initial phase of tuberculosis treatment. They reported on these outcomes.
Other bias	Unclear risk	The trial authors did not report baseline characteristics. There was no description of funding sources or conflict of interest statement.

Sudarsanam 2010 IND

Methods	Study design: RCT. Study dates and duration: recruitment January to Nov 2005, follow-up 1 year. Standard care: All participants received the same antituberculous standard therapy in accordance with the DOTS strategy.
Participants	Number: 103 enrolled, 99 analysed at 6 months, 91 at 1 year. Inclusion criteria: age > 12 years, either sputum positive tuberculosis or clinical and radiological evidence of pulmonary tuberculosis or biopsy proven extra pulmonary tuberculosis, informed consent

Sudarsanam 2010 IND *(Continued)*

	Exclusion criteria: relapse of previous antituberculous treatment, end stage renal or liver disease, CD4 count > 200 (if HIV-positive), BMI < 19 kg/m^2, patients not from Vellore. Baseline characteristics • Nutritional status: mean BMI supplement: 17.2 kg/m^2; mean BMI no supplement: 18.2 kg/m^2. • HIV status: 20 out of 103 were HIV co-infected. • MDR/XDR-TB: not mentioned. • All participants belonged to lower socioeconomic strata. • Micronutrient status at baseline not described.
Interventions	Group 1: macronutrient and micronutrient supplementation for 6 months. The macronutrient was a ready-to-serve powder, given as monthly rations to supply 930 kcal and 31.5 g protein per day 3 divided servings. The micronutrient as a once-a-day multivitamin tablet containing: copper sulphate 0.1 mg, D-pantheol 1 mg, dibasic calcium phosphate 35 mg, folic acid 500 µg, magnesium oxide 0.15 mg, manganese sulphate 0.01 mg, nicotinamide 25 mg, potassium iodide 0.025 mg, vitamin A 5000 IU, vitamin B1 2.5 mg, vitamin B12 2.5 µg, vitamin B2 2.5 mg, vitamin B6 2.5 mg, vitamin C 40 mg, vitamin D3 200 IU, vitamin E 7.5 mg, zinc sulphate 50 mg. Group 2: dietary advice alone.
Outcomes	• Death. • Cure. • Treatment completion. • Weight gain. Not included in the review: adherence.
Notes	Location: Vellore, India. Setting: tuberculosis clinics. Funding: The Fogarty AIDS International Research and Training Program.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer generated randomisation code".
Allocation concealment (selection bias)	Low risk	"Allocation was concealed, the randomisation codes were in opaque envelopes opened by the dietician after dietary counselling".
Blinding (performance bias and detection bias) All outcomes	High risk	"There were no attempts made to blind any of the study team or participants".
Incomplete outcome data (attrition bias) All outcomes	High risk	3.9% were lost to follow-up at 6 months and 11.7% at 1 year.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Tukvadze 2015 GEO

Methods	Study design: RCT. Standard care: all participants received antituberculous therapy (isonizaid, rifampicin, pyrazinamide, and ethambutol - no further details given), given under direct observation. Study dates and duration: July 2009 to April 2012. Follow-up 16 weeks.
Participants	Number: 199 enrolled and randomized. Inclusion criteria: age > 18 years, newly diagnosed pulmonary tuberculosis disease with a positive AFB sputum smear, < 7 days of antituberculous drug therapy before entry, informed consent. Exclusion criteria: previous tuberculosis, extrapulmonary tuberculosis, pregnancy or lactation, a history of hypercalcaemia, nephrolithiasis, hyperparathyroidism, sarcoidosis, organ transplant, hepatic cirrhosis, seizures, or cancer in the past 5 years, baseline plasma calcium concentration > 2.6 mmol/L, creatinine concentration > 250 mmol/L, or aspartate aminotransferase concentrations > 3 times the upper limit of normal, renal replacement therapy, corticosteroid use in the past 30 days, current use of cytotoxic or immunosuppressive drugs, known MDR-TB before study enrolment, current imprisonment. Baseline characteristics • Nutritional status: BMI < 18.5 kg/m^2: 18% vitamin D group versus 28 % placebo group. • HIV status: 191/199 were tested. 1% HIV positive in the vitamin D group versus 3% HIV positive in the placebo group. • MDR/XDR-TB: isoniazid and rifampicin resistance: 12% vitamin D group versus 11% placebo group. • Micronutrient status: plasma 25(OH)D_3 below 30 nmol/L: 92% vitamin D group versus 92% placebo group.
Interventions	Vitamin D group: 50,000 IU vitamin D_3 3 times a week for 8 consecutive weeks followed by 50,000 IU every 2 weeks for a further 8 weeks. Placebo group: placebo tablet for similar dosing regime.
Outcomes	• Time to sputum culture conversion. • Culture conversion at 8 weeks. • Vitamin D levels at baseline and every 2 weeks of follow-up. • Adverse effects. Not included in this review: calcium level every 4 weeks, multiple subgroup analyses looking at predictors of culture conversion.
Notes	Location: Tbilisi, Georgia. Setting: National Centre for TB and Lung Disease and affiliated clinics. Registration number: NCT00918086. Source of funding: National Institutes of Health Grant, the Emory University Global Health Institute. Additional publications: Frediani JK, et al (2015) Macronutrient intake and body composition changes during antituberculous therapy in adults, Clinical Nutrition, http://dx.doi.org/10.1016/j.clnu.2015.02.007

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment assignments were generated by the Emory University–based study biostatistician and implemented locally through a distributed study database with

Tukvadze 2015 GEO *(Continued)*

		the use of a randomized permuted block algorithm stratified by clinical center site".
Allocation concealment (selection bias)	Low risk	"All study medication bottles had a unique bottle number to allow for blinded dispensing".
Blinding (performance bias and detection bias) All outcomes	Low risk	"The study drugs vitamin D3 and the placebo were identical in shape and colour". The trial authors did not report blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	20/100 (20%) were lost to follow-up or discontinued intervention in the vitamin D group versus 30/99 (30%) in the placebo group.
Selective reporting (reporting bias)	Low risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Villamor 2008 TZA

Methods	Study design: RCT. Study dates and duration: April 2000 to April 2005, follow-up 24 months. Standard care: all participants received standard antituberculous treatment following the DOTS scheme: 2RHZE/6HE.
Participants	Number: 887 enrolled, number with available outcomes data varied by outcome. Inclusion criteria: adults aged 18 to 65 years, sputum positive pulmonary tuberculosis. Exclusion criteria: Karnofsky score < 40%; pregnant; received more than 4 weeks of antituberculous therapy in the past year; plans to move away from the study area within the next 2 years Baseline characteristics. • Nutritional status: mean BMI (SD): 18.9 kg/m^2 (2.5) in HIV-negative placebo group versus 18.9 kg/m^2 (2.5) in HIV-negative supplement group, 19.6 kg/m^2 (2.9) in HIV-positive placebo group versus 19.3 kg/m^2 (2.8) in HIV-positive supplement group. • HIV status: 53% HIV-positive in supplement group versus 53% in placebo group. • MDR/XDR-TB: not mentioned. • Description: > 85% had primary school education. • Micronutrient status at baseline not described.
Interventions	For 24 months Group 1: daily oral dose in tablet form of mixed micronutrients containing retinol (5000 IU), vitamin B1 (20 mg), vitamin B2 (20 mg), vitamin B6 (25 mg), niacin (100 mg), vitamin B12 (50 µg), vitamin C (500 mg), vitamin E (200 mg), folic acid (0.8 mg), and selenium (100 µg). Group 2: placebo.
Outcomes	• Sputum-culture positive at 1 month. • Recurrence of positive culture between 1 and 8 months. • Mortality within 2 years. • Nutritional parameters: body weight, mid-upper arm circumference, fat-mass, fat-free mass.

Villamor 2008 TZA *(Continued)*

	Not included in the review: CD4, CD8, CD3 count and HIV viral load, haemoglobin, albumin levels, peripheral neuropathy, and genital ulcers.
Notes	Location: Dar es Salaam, Tanzania. Setting: 5 outpatient clinics. Funding: The National Institute of Allergy and Infectious Diseases, US Department of Agriculture.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Consenting subjects were randomly assigned in computer-generated permuted blocks of 20".
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe any allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Active tablets and placebo were indistinguishable in size, taste, and colour. All clinical and research staff were unaware of the subjects' treatment assignment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 628/725 (85%) for sputum-culture positive at 1 month; for mortality the trial authors included all participants in the analysis up to the point of loss to follow-up if before end of trial, and presented hazard ratios.
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Visser 2011 ZAF

Methods	Study design: RCT. Study dates and duration: May 2005 to August 2008, follow-up 8 weeks. Standard care: all participants received antituberculous therapy: 2RHZE plus pyridoxine 25 mg/day.
Participants	Number: 154 enrolled; 124 completed study. Inclusion criteria: 18 to 60 years old, 2 positive sputum smears for acid-fast bacilli or 1 positive plus suggestive chest X-ray findings, written informed consent to a HIV test. Exclusion criteria: previous treatment of tuberculosis, known or suspected multidrug resistant tuberculosis, clinical evidence of extrapulmonary tuberculosis or liver disease, renal failure, congestive heart failure or neoplasm, pregnancy. Baseline characteristics • Nutritional status: mean BMI (SD): males; supplement group 18.9 kg/m^2 (2.7) versus 19.0 kg/m^2 (2) placebo group, females; supplement group 23.0 kg/m^2 (4.3) versus 21.6 kg/m^2 (4.8) placebo group. • HIV status: 9% HIV positive supplement group versus 11% HIV-positive placebo group. • MDR/XDR-TB: excluded. • Median retinol (range): 21.1 µg/dL (15.1 to 27.8) supplement group versus 21.2 (15.7 to 28.9) placebo group (normal range: > 20 µg/dL).

Visser 2011 ZAF *(Continued)*

	• Median Zinc (range): 62 µg/dL (53 to 71.8) supplement group versus 59 (51.8 to 65.3) placebo group (normal range: > 70 µg/dL).
Interventions	Group 1: a single capsule that contained 200,000 IU vit A (retinyl palmitate) within 24 hours of starting tuberculosis treatment plus 15 mg zinc (zinc gluconate) daily for 5 days per week for 8 weeks. Group 2: placebo capsule (sunflower oil) within 24 hours of starting tuberculosis treatment plus placebo tablet (starch/gelatin base) daily for 5 days per week for 8 weeks.
Outcomes	• Death. • Sputum-smear positive at baseline and 8 weeks. • Adverse events. • Weight gain at 2 months. • Arm muscle circumference at 2 months. • Vitamin A and zinc status at 2 and 8 weeks. Outcomes not included in review: adherence, lung cavities at 2 months, copper, CRP, albumin, haemoglobin, WBC, and neutrophil levels at 2 and 8 weeks.
Notes	Location: Cape Town, South Africa. Setting: primary care tuberculosis clinics. Funding: research grants from the National Research Foundation South Africa, the Norwegian Programme for Development, Research and Higher Education, the Research Council of Norway, the National Research Foundation, the South African Sugar Association, and the Fogarty International Centre. The South African Department of Health and Pharma Natura Pty donated the vitamin A and placebo capsules respectively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated permuted blocks of 8, generated by an independent epidemiologist".
Allocation concealment (selection bias)	Low risk	"Treatment allocations was concealed by prepackaging supplements in sequentially numbered packets according to the allocation schedule".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Active and placebo capsules and tablets for both groups were identical in size, shape and colour. All research team members as well as laboratory staff involved in the trial were blinded".
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up was high in both groups: 12/77 (16%) supplement group versus 19/77 placebo group (25%).
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	"Because of a change in national policy in April 2008 15 participants received TB treatment 7 days per week with unsupervised weekend doses". Comment: this was unlikely to introduce significant bias.

Wejse 2008 GNB

Methods	Study design: RCT. Study dates and duration: November 2003 to December 2005, follow-up 12 months. Standard care: all participants received antituberculous therapy: 2RHZE/6HE.
Participants	Number: 367 enrolled; number with available outcomes data varied by outcome. Inclusion criteria: adults aged > 15 years, diagnosis of tuberculosis by smear positive (pulmonary tuberculosis) or WHO clinical criteria (extrapulmonary tuberculosis). Exclusion criteria: none stated. Baseline characteristics • Nutritional status: mean BMI (range): 18.8 kg/m^2 (12 to 33) treatment group versus 18.5 kg/m^2 (12 to 27) placebo group. • HIV status: 39% HIV-positive supplement group versus 33% HIV-positive placebo group. • MDR/XDR-TB: not mentioned. • Mean serum 25-hydroxyvitamin D_3 nmol/L (SD): 77.5 (23.8) supplement group versus 79.1 (21.8) placebo group (normal range: > 75 nmol/L). • Described as a poor urban population.
Interventions	Vitamin D group: 3 doses cholecalciferol (100,000 IU) in drinkable ampoules; given at start of treatment, 5 months, and 8 months. Placebo group: vegetable oil without cholecalciferol.
Outcomes	• Death at 12 months in HIV-positive and HIV-negative participants. • Sputum-smear positive at baseline, 2 weeks, 4 weeks, 6 weeks, 2 months, 5 months, and 8 months. • Adverse events. • Weight gain at 8 months. • Changes in tuberculosis score at 2, 5, and 8 months. • Vitamin D status at 2 and 8 months. Outcomes not included in review: change in CD4 count at 8 months.
Notes	Location: Guinnea-Bassau. Setting: 3 health centres and a tuberculosis hospital in a demographic surveillance area.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random allocation sequence was computer generated; a list of continuous study numbers was generated with a random allocation to treatment 1 or 2".
Allocation concealment (selection bias)	Low risk	"Study numbers were consecutive and given to patients by the field assistant at inclusion, and patients were recorded in a book with pre-written study numbers and allocation sequence number 1 or 2", "A physician gave the trial information and obtained consent...a trial nurse administered study medicine according to sequence number".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Study medicine was provided in identical containers labelled lot 204 (allocation sequence number 1) or lot 205 (allocation sequence number 2)". "Patients, staff, and researchers assessing outcome were blinded".

Wejse 2008 GNB *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imbalanced attrition: 20/187 (11%) supplement group versus 10/180 placebo group (6%).
Selective reporting (reporting bias)	Unclear risk	We were unable to retrieve the trial protocol. There was no evidence of selective reporting.
Other bias	Low risk	We did not identify any other sources of bias.

Abbreviations: RCT = randomised controlled trial; AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; E = ethambutol; H = isoniazid; R = rifampicin; S = streptomycin; Z = pyrazinamide; CRP = C-reactive protein; CD4/CD8/CD3 = a measure of immunological function in HIV-positive people; MDR = multidrug-resistant TB; XDR = extensively drug-resistant TB; DOTS = directly observed therapy short course; TST = tuberculin skin testing; BMI = body mass index; CXR = chest X-ray; ESR = erythrocyte sedimentation rate; WBC = white blood cell count; 2RHZE/4HE = 2 months of isoniazid, rifampin, prazinamide, and ethambutol followed by 4 months of ethambutol and isoniazid; 2RHZE/4HR = 2 months of isoniazid, rifampin, prazinamide, and ethambutol followed by 4 months of rifampin and isoniazid; INH = isoniazid; 2RHZE/6HE = 2 months of isoniazid, rifampin, prazinamide, and ethambutol followed by 6 months of ethambutol and isoniazid.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Denti 2015	Ineligible outcomes: pharmacokinetics.
Dibari 2013	Ineligible intervention. Looks at acceptability of ready to eat foods.
Gwinup 1981	Outcomes were irrelevant to this Cochrane review's objectives (assessed effect of vitamin supplementation on serum calcium levels in people with tuberculosis).
Hasan 2015	Ineligible intervention: propolis.
Kawai 2014	Ineligible outcomes: linked to Villamor 2008 TZA.
Khandelwal 2014	Ineligible study design: cohort study.
Lin 2014	Ineligible intervention; no relevant outcomes.
Lutge 2013	Ineligible intervention; food vouchers.
Martineau 2009	Excluded as evaluates a single dose of vitamin D.
Mbala 1998	Outcomes were not relevant to review's objectives (assessed neurological and neuropsychiatric symptoms in children being treated for tuberculosis using isoniazid with or without vitamin B6 supplementation).
Narang 1984	Groups were not randomly allocated, participants not being treated for active tuberculosis, and outcomes were not relevant to review's objectives.
Oluboyede 1978	It was unclear whether the groups were randomized; we were unable to contact the trial authors.
Permatasari 2014	Ineligible intervention: propolis.
Ramakrishnan 1961	Groups were not randomized to different dietary interventions.
Samsidi 2013	Ineligible control/comparison; the control group received milk-based protein supplement.

Study	Reason for exclusion
Shi 2001	The study authors assessed only partial parenteral nutrition, which we excluded from this Cochrane review.
Srivastava 2011	The study only provided vitamin D for 5 days.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Al Mamun 2014

Methods	RCT
Participants	Smear-positive tuberculosis participants (N = 111)
Interventions	Vitamin A (5000 IU daily) + zinc (15 mg daily) Placebo
Outcomes	Smear conversion, radiology, haemoglobin, erythrocyte sedimentation rate, C-reactive protein
Notes	The abstract does not provide any data for any of the measured outcomes. We contacted the study authors but did not receive a response

Chandra 2004

Methods	RCT Duration: not described
Participants	Number: 44 enrolled (28 men and 16 women)
Interventions	Group 1: 3 tablets 3 times weekly of multiple micronutrients Group 2: placebo
Outcomes	Sputum-smear test positive at 2, 3, 5, and 6 months Chest x-ray findings positive at 3 and 6 months
Notes	Location: India Setting: unclear Information still pending: Ranjit Kumar Chandra is a researcher in the field of nutrition and immunology who has been accused of committing scientific fraud by the British Medical Journal. A jury trial in July 2015 concluded that the allegations of fraud were truthful. Due to these allegations, a number of his scientific articles have been subject to retraction (see https://en.wikipedia.org/wiki/Ranjit_Chandra).

Guzman-Rivero 2013

Methods	RCT (pilot study)

Guzman-Rivero 2013 *(Continued)*

Participants	Pulmonary tuberculosis patients
Interventions	Antituberculous treatment combined with zinc (45 mg/day) or placebo for 3 months
Outcomes	Clinical outcomes, sputum clearance, radiological improvement and nutritional status
Notes	Conference abstracts (2) Information still pending: Neither of the abstracts provides data for any of the measured outcomes. We contacted the authors for information but have not received a response.

Nagrale 2013

Methods	RCT
Participants	Newly diagnosed sputum positive pulmonary tuberculosis
Interventions	Antituberculous treatment with N-acetylcysteine (600 mg, 2 tablets daily) or placebo for 2 months
Outcomes	Sputum conversion, radiological improvement, DTH response, glutathione peroxidase levels
Notes	Conference abstract Information still pending: The abstract does not provide any data for any of the measured outcomes. We contacted the study authors in May 2015 for full text but did not receive a response

Nawas 2013

Methods	RCT; November 2010 to October 2011
Participants	100 newly diagnosed sputum positive pulmonary tuberculosis
Interventions	Antituberculous treatment (fixed-dose combination) with *Morinda citrifolia* (125 mg) and *Zinger officinale* (125 mg) extract or placebo
Outcomes	Sputum conversion at 6 months
Notes	Conference abstract Information still pending: the abstract does not provide any data for any of the measured outcomes. We contacted the study authors in May 2015 for the full-text article but did not receive a response

Abbreviations: RCT = randomised controlled trial; N = number of participants.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IPR-15006395

Trial name or title	The influence and mechanism of vitamin D3 supplementation on the treatment outcomes of tuberculosis patients of different glucose tolerance.
Methods	RCT.
Participants	Inclusion criteria: new diagnosed tuberculosis, sputum smear positive, aged ≥ 18, stable address. Exclusion criteria: HIV-positive, tumour, pregnant or lactating women, injured lately, adjusted calcium concentration > 2.65 mmol/L. Gender: both.
Interventions	NTB: vitamin D3; HTB: vitamin D3; NTB: control; HTB: control.
Outcomes	Primary: treatment outcomes; CD4+/CD8+; quantity of life (SF-36v2). Secondary: oxidative stress; serum 25(OH)D.
Starting date	25 May 2015.
Contact information	kevin_1971@126.com
Notes	China.

ChiCTR-TRC-12002546

Trial name or title	The effect and mechanism of retinol and vitamin A supplementation in patients with diabetes and pulmonary TB.
Methods	RCT.
Participants	Inclusion criteria: participants with pulmonary tuberculosis and diabetes, aged 18 to 75 years, diagnosed by the golden criteria of pulmonary tuberculosis and diabetes; no vitamin or mineral supplement 1 month before the screening. Exclusion criteria: no severe complications of diabetes including diabetic eye diseases, renal disease and foot disease, etc; pregnancy or lactation women; cancer; coronary heart disease; recent suffered trauma or recent surgery.
Interventions	Vitamin D (400 IU/d). Vitamin A (2000 IU/d). Vitamin D (400 IU/d) + vitamin A (2000 IU/d). Placebo control.
Outcomes	Retinol; vitamin D; fasting glucose; fasting insulin; CD4+/D8+; protein kinase C (PKC); blood lymphocyte proliferation.
Starting date	20 October 2012.
Contact information	kevin_1971@126.com; maiguo@public.qd.sd.cn
Notes	China.

ChiCTR-TRC-14005241

Trial name or title	A prospective study of oral nutritional supplement in perioperative application with pulmonary TB patients.
Methods	RCT.
Participants	Inclusion criteria: diseases mainly included tuberculosis cavity, tuberculous bronchiectasis disease, pulmonary tuberculosis and pneumothorax, tuberculosis and pulmonary bulla, tuberculous pyothorax, who were all the hospitalized patients with video assisted thoracoscopic surgery; by NRS2002 screening score greater than or equal to 3 points to consider the risk of malnutrition in this study; ranging in age from 18 to 80. Exclusion criteria: pregnancy and lactation women; having the injection contraindication; having nutrition agent or medication allergy or a history of asthma; diabetes medication; fat metabolism, liver and kidney dysfunction; on the day of surgery transfusion volume above 800 mL; unstable endocrine disease; unstable vital signs.
Interventions	Nutrison Fibre + normal diet or normal diet.
Outcomes	Serum albumin and pre-albumin, weight, T cell subset.
Starting date	From 01 October 2014 to 01 October 2016.
Contact information	daoren_000113@126.com
Notes	Shenzhen, China. Hospital setting.

IRCT201112178429N1

Trial name or title	Effect of zinc supplementation in improving pulmonary TB patients in Qom.
Methods	RCT.
Participants	Inclusion criteria: active tuberculosis and filling the informed consent. Exclusion criteria: diseases such as cancer, stroke, immunosuppressive diseases, and not agreeing to take mineral supplement or placebo.
Interventions	Intervention 1: zinc supplement (30 mg zinc) every second day for 6 months. Intervention 2: placebo every second day for 6 months.
Outcomes	Radiological signs: timepoint: at baseline, 2 months, and 6 months later. Method of measurement: chest radiology. Smear negative: timepoint: at baseline, 2 months, and 6 months later. Method of measurement: smear. Stop coughing: timepoint: at baseline, 2 months and 6 months later. Method of measurement: physical exam. Stop fever: timepoint: at baseline, 2 months and 6 months later. Method of measurement: physical exam.
Starting date	21 January 2012.
Contact information	fpourfallah@pasteur.ac.ir

IRCT201112178429N1 *(Continued)*

Notes	Recruitment complete. Iran.

IRCT201211179855N2

Trial name or title	Randomized, double-blind, placebo-controlled trial of L-arginine supplementation for the treatment of pulmonary TB.
Methods	RCT.
Participants	Inclusion criteria: adults over 15 years; new cases of positive sputum smear. Exclusion criteria: pregnant women; aged under 15 years; patients who during the past month received L-arginine; sensitivity to L-arginine.
Interventions	Intervention 1: standard antituberculous treatment for 6 months plus L-arginine, 2 g daily in first month. Intervention 2: standard 6-month antituberculous treatment plus placebo 2 g daily in first month.
Outcomes	Improved para-clinical tests. Timepoint: day 14, 28, 42, and 56. Measurement method: check of CRP. Improved para-clinical tests. Timepoint: day 14, 28, 42, and 56. Measurement method: check of ESR. Improved para-clinical tests. Timepoint: day 14, 28, 42, and 56. Measurement method: check of CBC. Weight gain: timepoint: 0 and 56. Measurement method: weight measurement. Improve of life quality: timepoint: 0 and 56. Measurement method: standard questionnaire of GHQ-28.
Starting date	21 December 2012.
Contact information	farazialiasghar@yahoo.com gakbarifard@yahoo.com
Notes	Recruitment complete. Iran.

ISRCTN16469166

Trial name or title	Nutrition and wasting in TB: Can nutritional supplementation in TB patients improve body weight gain, body composition and treatment outcome?
Methods	RCT.
Participants	Expected enrolment: adults > 18 years with sputum positive pulmonary tuberculosis.
Interventions	• Standard treatment plus nutritional supplementation (supplements containing 450 kcal energy plus a wide range of vitamins and minerals in doses of approximately half the required daily intakes (but no iron)).

ISRCTN16469166 *(Continued)*

	• Standard treatment only.
Outcomes	Primary: body weight gain and body composition. Secondary: micronutrient status and production of inflammatory cytokines.
Starting date	15 May 2007. Anticipated end date: 1 January 2008.
Contact information	Dr Frank Wieringa (wieringa@tiscali.nl), Dept. of Internal Medicine, Hasan Sadikin Hospital, Bandung, Indonesia.
Notes	We attempted to contact the author for results on 25 January 2010 and 05 May 2010 with no reply. Location: Indonesia. Registration number: ISRCTN16469166. Source of funding: Netherlands Organisation for Scientific Research (The Netherlands). We contacted the trial authors for information on 20 July 2015. There was no sign of publication of the data (PubMed search).

NCT00507000

Trial name or title	Role of oral vitamin D as an adjunct therapy in Category I pulmonary TB along with assessment of immunological parameters.
Methods	RCT.
Participants	Adults aged 18 to 60 years with newly diagnosed sputum-smear positive pulmonary tuberculosis.
Interventions	• Cholecalciferol (vitamin D) and calcium carbonate. • Placebo (lactose granules).
Outcomes	Primary: time to becoming sputum-smear negative. Secondary: relapse rate; safety assessment; immune function.
Starting date	May 2008. Anticipated end date: September 2010.
Contact information	Dr Ravinder Goswami (gosravinder@hotmail.com), Department of Endocrinology and Metabolism, All India Institue of Medical Sciences, New Delhi, India.
Notes	Location: India. Registration number: NCT00507000. Source of funding: Indian Council of Medical Research; Ministry of Science and Technology, India. We contacted the trial authors for information. There was no sign of publication of the data (PubMed search).

NCT00698386

Trial name or title	Efficacy of oral zinc administration as an adjunct therapy in new pulmonary TB (Category I) patients.
Methods	RCT.
Participants	Adults with newly diagnosed smear positive pulmonary tuberculosis.
Interventions	50 mg zinc as zinc sulphate daily for 6 months during DOTS versus placebo.
Outcomes	Time to sputum conversion, cure rate, relapse, adverse events, patient and physician global assessment of cure.
Starting date	February 2008.
Contact information	Surendra K Sharma, MD, PhD, All India Institute of Medical Sciences, New Delhi. surensk@gmail.com, sksharma@aiims.ac.in
Notes	Location: India. Registration number: NCT0069386. Source of funding: Ministry of Science and Technology, India. We contacted the trial authors for information. No sign of publication of the data (PubMed search).

NCT00788320

Trial name or title	Antimicrobial peptide LL-37 (cathelicidin) production in active TB disease: role of vitamin D supplementation.
Methods	RCT.
Participants	Adults aged > 18 years with newly diagnosed pulmonary tuberculosis.
Interventions	Drug: vitamin D3. Drug: placebo.
Outcomes	LL-37 level, time to sputum conversion, vitamin D and calcium levels.
Starting date	October 2008.
Contact information	Not stated.
Notes	Location: USA. Registration number: NCT00788320. Source of funding: Emory University. This study has been withdrawn prior to enrolment (inadequate enrolment). See https://clinicaltrials.gov/ct2/show/NCT00788320 for details.

NCT01635153

Trial name or title	Effects of a protein calorie supplement in HIV-infected women with TB DarDar.
Methods	RCT.
Participants	Inclusion criteria: female, HIV, age > 18, CD4 > 50, BMI > 16 new tuberculosis diagnosis, not on anti-retroviral therapy, residence in Dar es Salaam. Exclusion Criteria: current anti-retroviral therapy, serious co-morbidities.
Interventions	Group 1: micronutrient supplement. Group 2: protein calorie supplement.
Outcomes	Primary outcomes: change in CD4 count (time frame: baseline to 8 months). Secondary outcomes: body mass index at 6 months (time frame: baseline to 6 months); proportion of subjects who achieve 100 cell count increase in CD4 cell count (Time frame: baseline to 8 months).
Starting date	May 2012.
Contact information	Charles F von Reyn, MD, Geisel School of Medicine at Dartmouth.
Notes	Active, not recruiting.

NCT01657656

Trial name or title	Vitamin D supplementations as adjunct to anti-TB drugs in Mongolia.
Methods	RCT.
Participants	Inclusion criteria: sputum positive tuberculosis patients. Exclusion criteria: abnormal LFTs at baseline (2.5 times upper limit of normal), as they will be at higher risk of developing drug-induced hepatitis.
Interventions	Vitamin D (does not state what comparator group receiving).
Outcomes	The primary endpoint will be time to sputum culture conversion from positive to negative (time frame: 8 weeks).
Starting date	October 2012.
Contact information	gdavaasa@hsph.harvard.edu (Ganmaa Davaasambuu).
Notes	Study status: completed. Mongolia.

NCT01722396

Trial name or title	Pharmacogenetics of Vitamin D Supplementation in TB.

NCT01722396 *(Continued)*

Methods	Open label study of vitamin D supplementation.
Participants	Patients with active or latent tuberculosis.
Interventions	Active tuberculosis patients take 100,000 units of vitamin D every 8 weeks during their tuberculosis treatment.
Outcomes	• Ex vivo responses of monocytes to vitamin D (time frame: 0 and 8 weeks). • Ex vivo responses of T cells to vitamin D (time frame: 0 and 8 weeks).
Starting date	March 2011.
Contact information	Alice Turner, University of Birmingham.
Notes	Status: completed.

NCT01992263

Trial name or title	A trial of vitamin D supplementation among TB patients in South India.
Methods	RCT.
Participants	Inclusion criteria: 18 to 60 years old, active tuberculosis diagnosis by GeneXpert®; HIV infection status (according to AMC HIV clinic medical records of enzyme-linked immunosorbent assay (ELISA) results). Exclusion criteria: children (< 18 years of age) and older than 60 years, pregnant at baseline, other severe complications or illnesses requiring hospitalisation, received tuberculosis treatment for greater than 4 weeks in the past 5 years, refused to participate, residing in a geographic location > 1 hour from AMC (by public transit).
Interventions	Vitamin D (2000 IU/4000 IU/600 IU) or placebo.
Outcomes	Primary outcomes • Cell-mediated immunological markers (T cells) (time frame: 1 year). • Immune function (time frame: 1 year). • Serum 25(OH)D concentrations (time frame: 1 year). Secondary outcomes • HIV disease progression (time frame: 1 year). • tuberculosis treatment outcomes (time frame: 1 year).
Starting date	January 2015.
Contact information	smehta@cornell.edu
Notes	Not yet recruiting.

NCT02169570

Trial name or title	Effect of supplementary vitamin D in patients with diabetes mellitus and pulmonary TB (EVIDENT).

NCT02169570 *(Continued)*

Methods	RCT.
Participants	Inclusion criteria: 30 to 60 years; patients having both tuberculosis and type 2 DM; consenting to participate; no history of previous ATT; plan to have ATT and DM treatment. Exclusion criteria: pregnant women; patients with extra-pulmonary tuberculosis or multi-drug resistant (MDR)-tuberculosis or relapse cases, hepatic or renal diseases or HIV infection, hypo- or hyper-parathyroidism; patients on corticosteroids, or immunosuppressive, or thiazides diuretics, or any other drugs known to interfere with vitamin D levels.
Interventions	Calcium; placebo calcium; placebo vitamin D; vitamin D.
Outcomes	Primary outcomes • Change acid fast bacilli (AFB) smear (sputum) (time frame: 0, 4, 8, 12, 16, and 24 weeks, and 6 months). • Change in chest X-ray (time frame: 0, 8, 16, and 24 weeks, and 6 months). • Change in tuberculosis score (time frame: 0, 4, 8, 12, 16, 20, and 24 weeks, and 6 months). • Change in weight (time frame: 0, 4, 8, 12, 16, 20, and 24 weeks, and 6 months). Secondary outcomes • Change haemoglobin A1c (HbA1c) (time frame: 0, 8, 16, and 24 weeks, and 6 months). • Change in fasting blood test (FBS) (time frame: 0, 8, 16, and 24 weeks, and 6 months). • Change in random blood sugar (RBS) (time frame: 0, 8, 16, and 24 weeks, and 6 months).
Starting date	December 2014.
Contact information	nadia.shah@live.com
Notes	Pakistan. Status: not yet recruiting.

NCT02464683

Trial name or title	Effect of vitamin D as adjunctive therapy in patients with pulmonary evolution TB (Vitamin D).
Methods	RCT.
Participants	Inclusion criteria: men and women over 18 and under 65 years old, with tuberculosis confirmed by positive smear and positive culture, without documented evidence of previous treatment for tuberculosis, with haemoglobin values greater than 10 g/dL, and written consent. Exclusion criteria: HIV-positive, no written consent, chronic lung disease, clinical evidence of infectious or chronic inflammatory disease processes such as: rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren Sx, dermatomyositis, scleroderma, seronegative arthritis, gout, inflammatory bowel disease, chronic active hepatitis, glomerulonephritis, rheumatic fever and cardiac disease, cancer, and history of alcohol or drug abuse.
Interventions	Vitamin D (200 IU) or placebo daily for 60 days.
Outcomes	Determination of cytokines.
Starting date	April 2014.
Contact information	Martha Torres Rojas, PhD marthatorres98@yahoo.com

NCT02464683 *(Continued)*

Notes	Mexico.

NCT02554318

Trial name or title	The effect of fermented soybean supplementation on the body weight and physical function of TB patients with standard therapy in Indonesia.
Methods	RCT.
Participants	Inclusion criteria: newly diagnosed adult male and female tuberculosis active patients with clinical evidences of active tuberculosis symptoms (positive or negative sputum smears, positive chest X-ray that compatible with a diagnosis of tuberculosis); no history of previous antituberculous treatment. Exclusion criteria: heavy smoker (> 20 cigarettes per day); pregnancy and lactation; extrapulmonary tuberculosis; known allergy to soybean; clinical evidences of any underlying disease.
Interventions	Fermented soybean.
Outcomes	Body weight, body mass index, handgrip strength, 6-minute walk test.
Starting date	October 2013.
Contact information	Michael B Krawinkel, Prof Dr University of Gleesen.
Notes	Uncertain what the comparison group received.

DATA AND ANALYSES

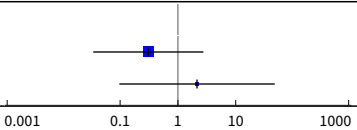
Comparison 1. Macronutrient supplementation

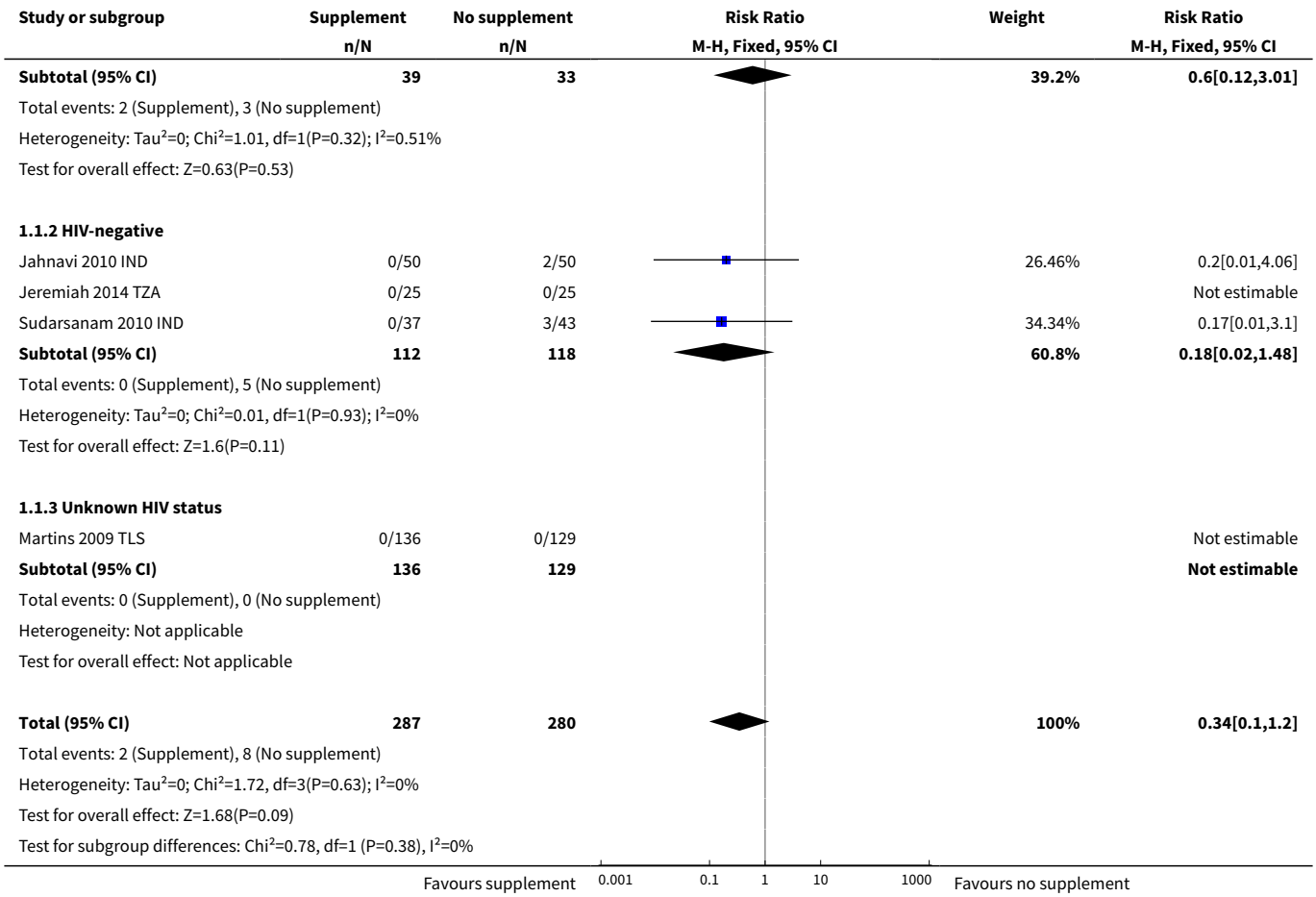
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (1 year of follow-up)	4	567	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.20]
1.1 HIV-positive	2	72	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.12, 3.01]
1.2 HIV-negative	3	230	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.48]
1.3 Unknown HIV status	1	265	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Cured (at 6 months)	1	102	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.59, 1.41]
2.1 HIV-positive	1	22	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.46, 4.14]
2.2 HIV-negative	1	80	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.35]
3 Treatment completion	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 HIV-negative	1	100	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.04, 1.37]
3.2 Unknown HIV status	1	265	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
4 Sputum negative at 8 weeks	3	222	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.37]
5 Mean weight gain	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 After 6 weeks	1	34	Mean Difference (IV, Random, 95% CI)	1.73 [0.81, 2.65]
5.2 After 8 weeks	3	689	Mean Difference (IV, Random, 95% CI)	0.78 [-0.05, 1.60]
5.3 After 12 weeks	1	100	Mean Difference (IV, Random, 95% CI)	2.6 [1.74, 3.46]
5.4 After 20 weeks (12 weeks post supplementation)	1	306	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.34, 0.94]
5.5 After 24 weeks	1	26	Mean Difference (IV, Random, 95% CI)	1.78 [-0.25, 3.81]
5.6 After 32 weeks	1	265	Mean Difference (IV, Random, 95% CI)	2.60 [0.52, 4.68]
6 Change in maximum grip strength (kg)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 At 6 weeks	1	34	Mean Difference (IV, Random, 95% CI)	3.44 [0.78, 6.10]
6.2 At 8 weeks	1	332	Mean Difference (IV, Random, 95% CI)	0.50 [-0.63, 1.63]
6.3 At 12 weeks	1	100	Mean Difference (IV, Random, 95% CI)	1.50 [1.08, 1.92]
6.4 At 20 weeks	1	303	Mean Difference (IV, Random, 95% CI)	1.30 [-0.11, 2.71]
6.5 At 24 weeks	1	26	Mean Difference (IV, Random, 95% CI)	0.39 [-3.05, 3.83]
7 Change in quality of life score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 At 6 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 At 24 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

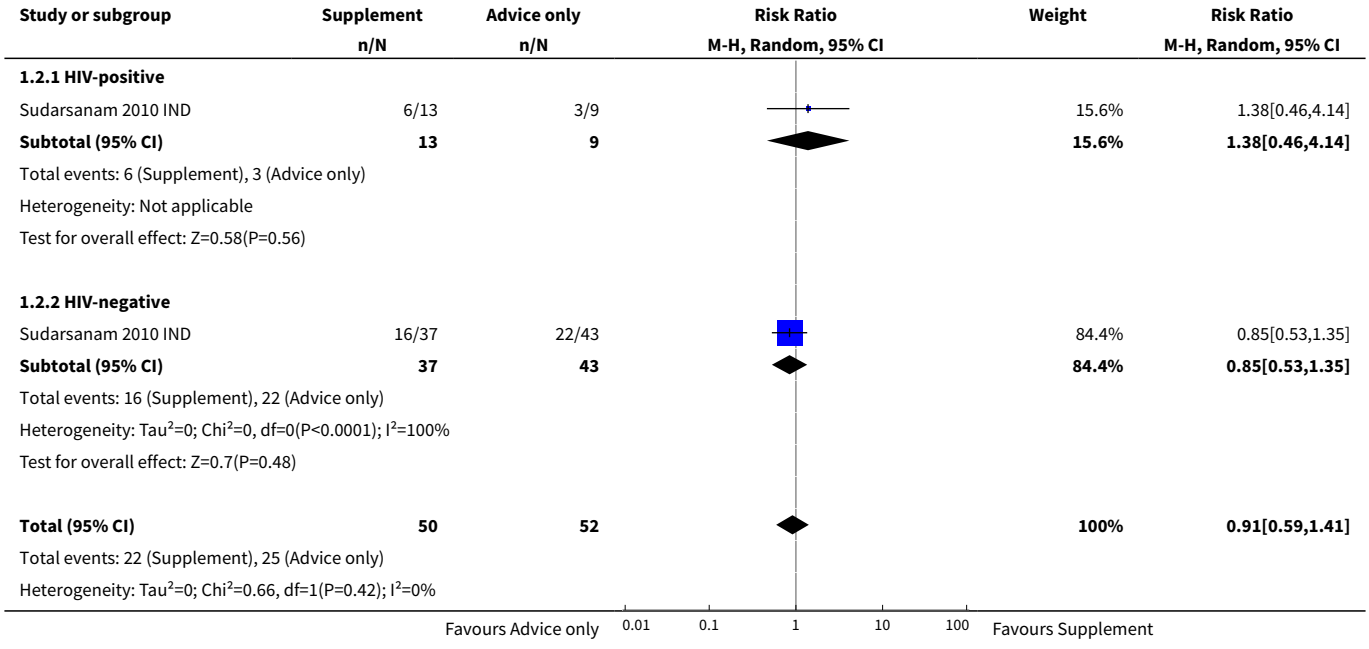
Analysis 1.1. Comparison 1 Macronutrient supplementation, Outcome 1 Death (1 year of follow-up).

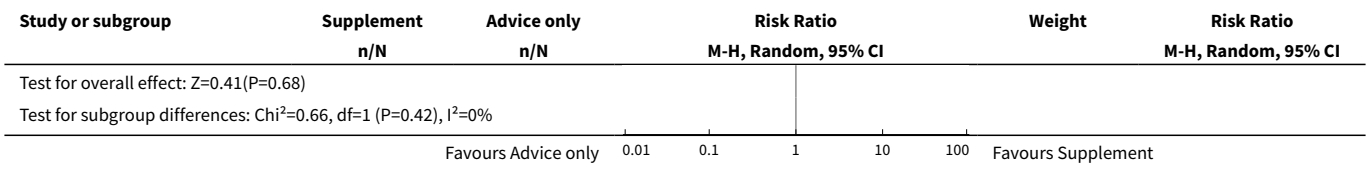
Study or subgroup	Supplement n/N	No supplement n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 HIV-positive					
Jeremiah 2014 TZA	1/26	3/24		33.03%	0.31[0.03,2.76]
Sudarsanam 2010 IND	1/13	0/9		6.17%	2.14[0.1,47.38]



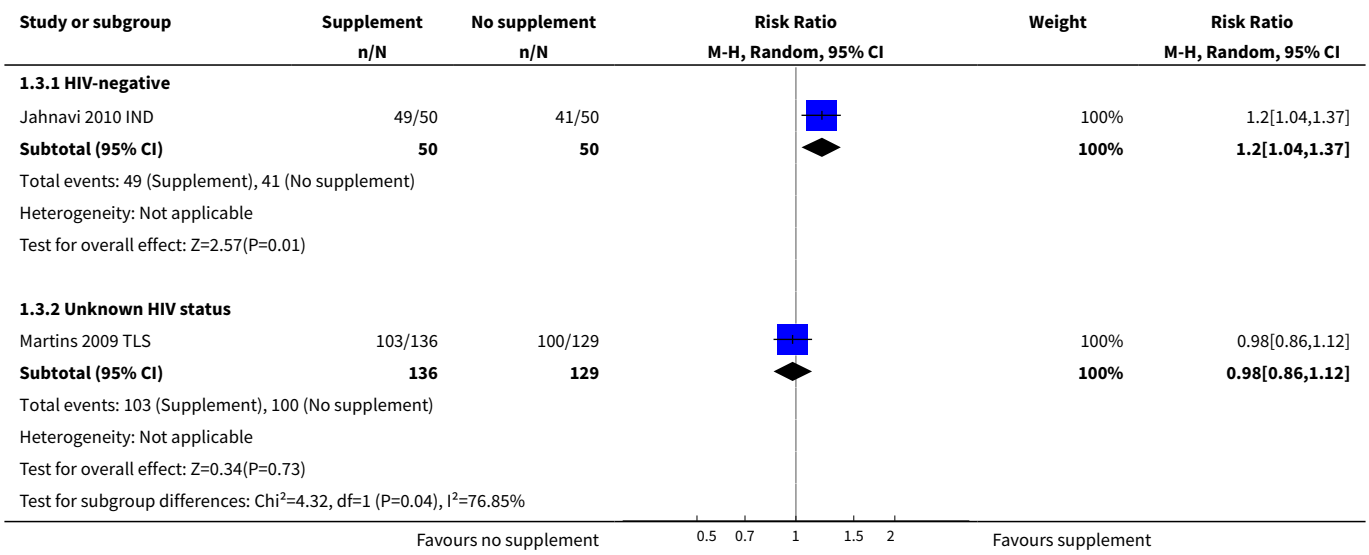


Analysis 1.2. Comparison 1 Macronutrient supplementation, Outcome 2 Cured (at 6 months).

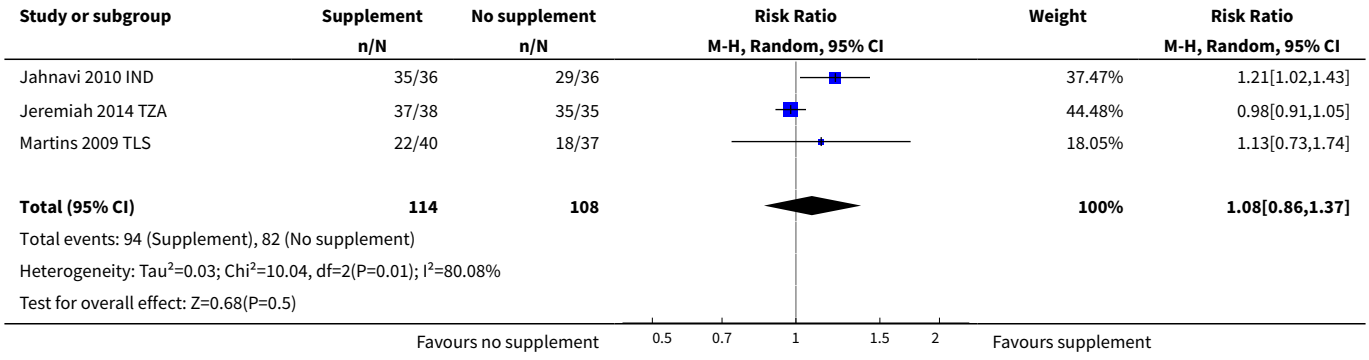




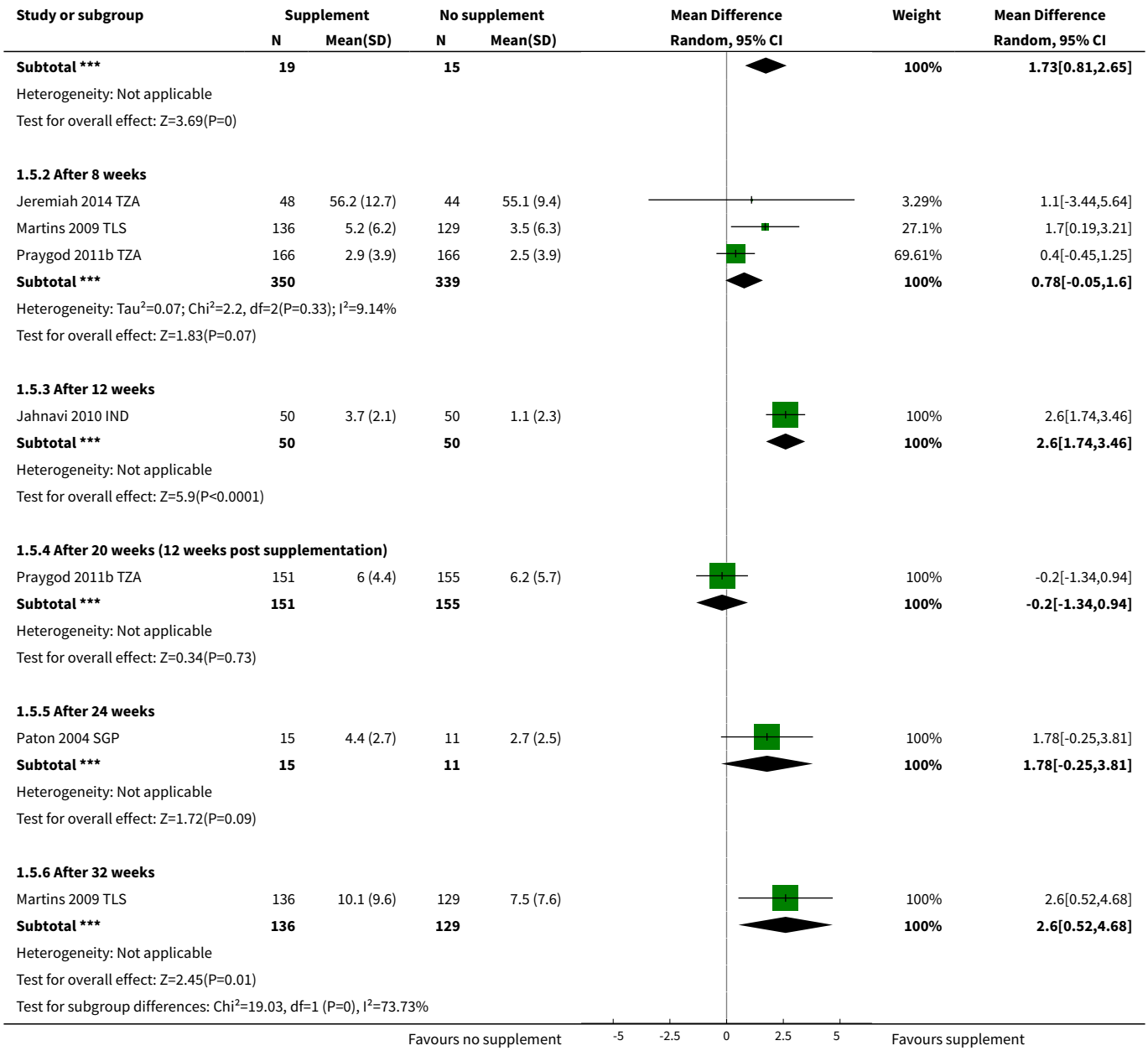
Analysis 1.3. Comparison 1 Macronutrient supplementation, Outcome 3 Treatment completion.



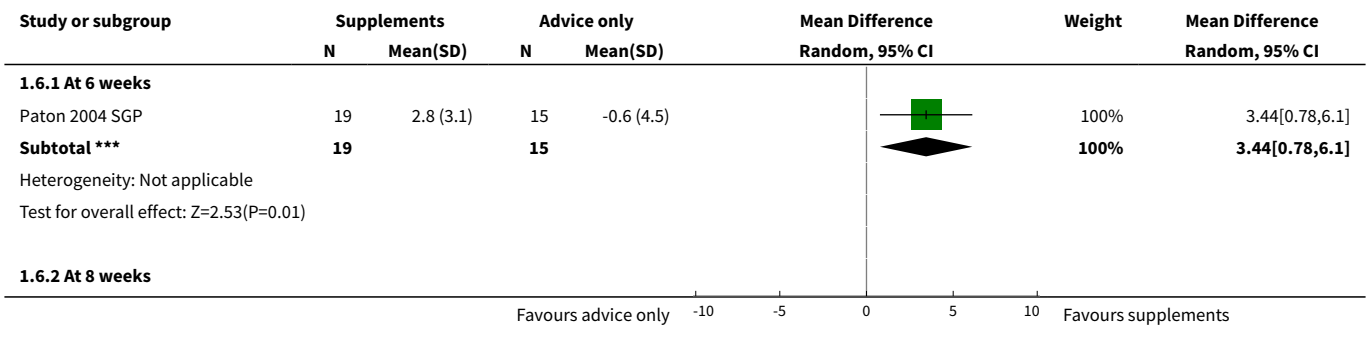
Analysis 1.4. Comparison 1 Macronutrient supplementation, Outcome 4 Sputum negative at 8 weeks.

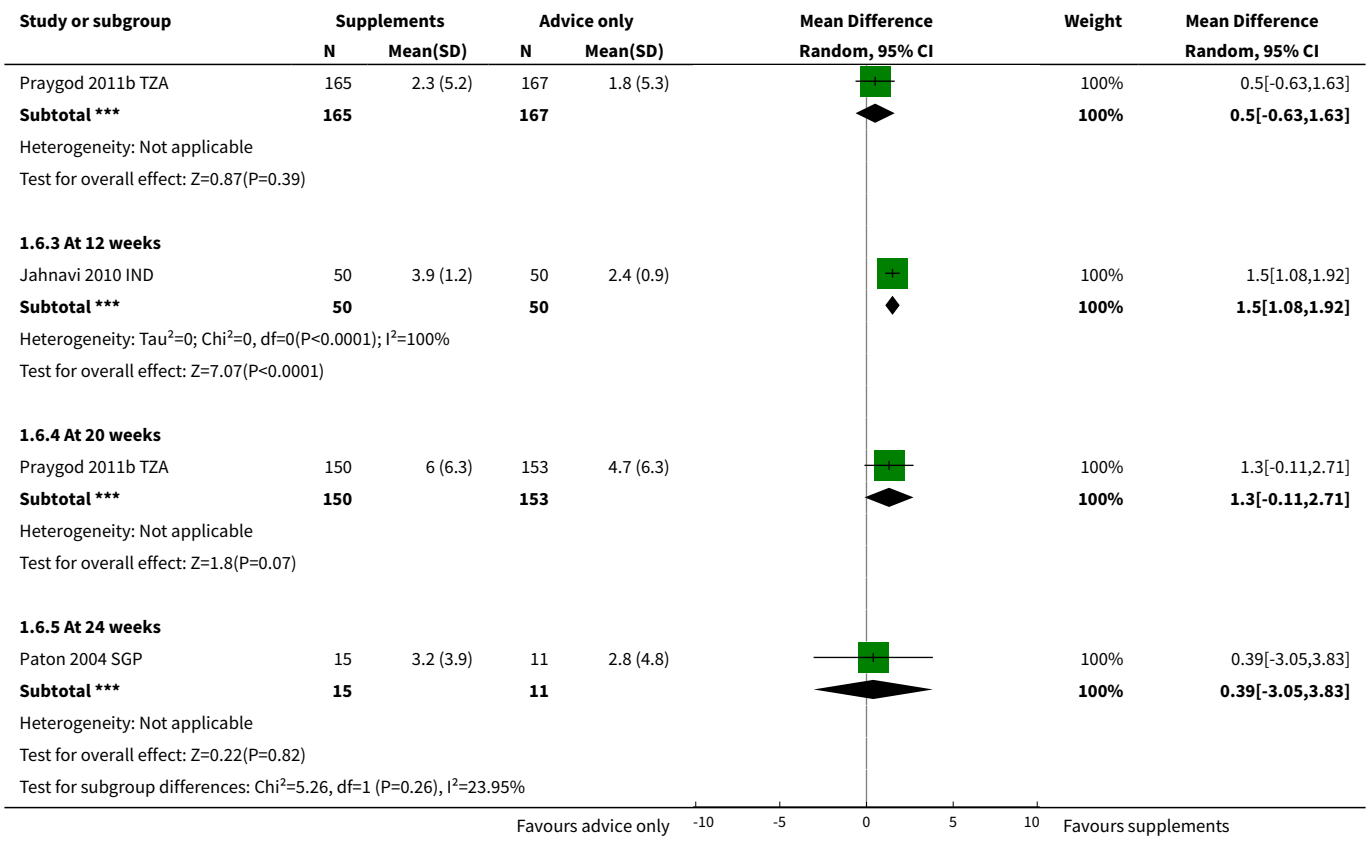


Analysis 1.5. Comparison 1 Macronutrient supplementation, Outcome 5 Mean weight gain.

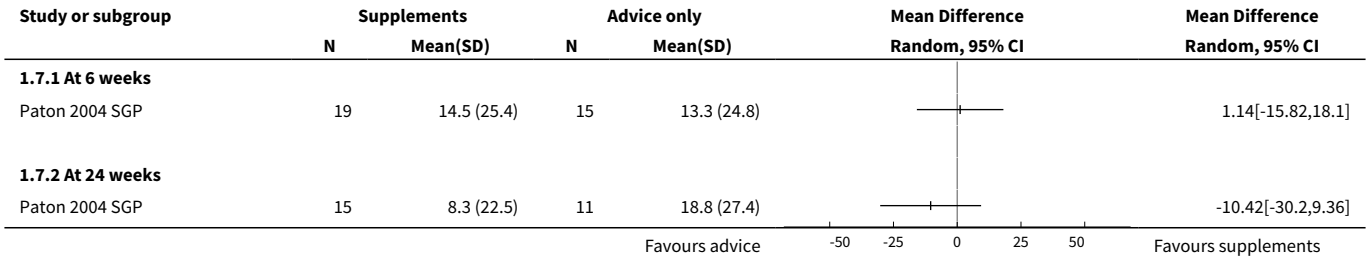


Analysis 1.6. Comparison 1 Macronutrient supplementation, Outcome 6 Change in maximum grip strength (kg).





Analysis 1.7. Comparison 1 Macronutrient supplementation, Outcome 7 Change in quality of life score.

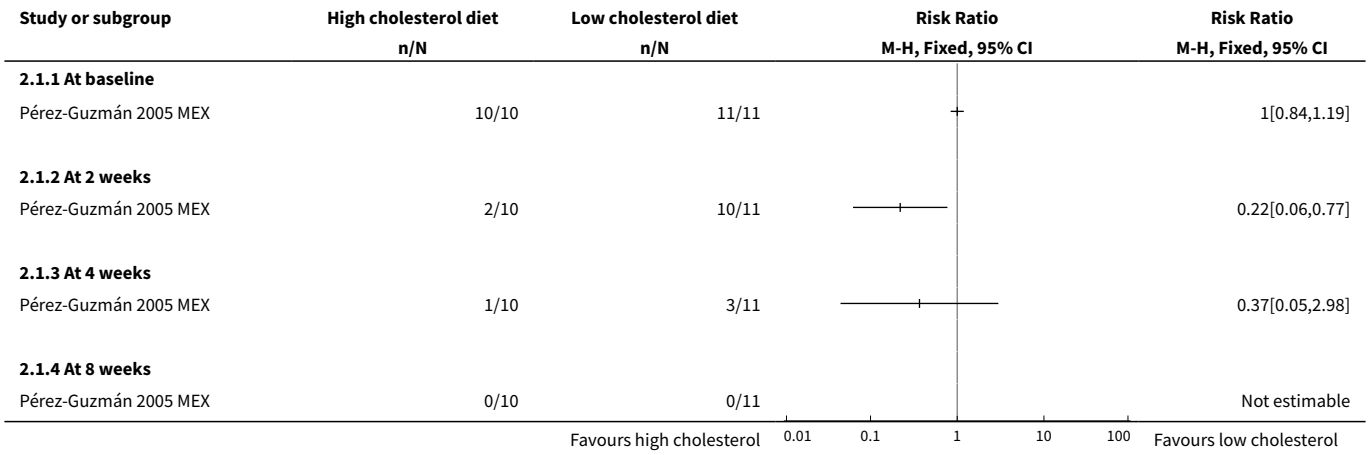


Comparison 2. High cholesterol (850 mg/day) versus low cholesterol (250 mg/day) diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sputum-culture positive	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 2 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 At 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 At 8 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 High cholesterol (850 mg/day) versus low cholesterol (250 mg/day) diet, Outcome 1 Sputum-culture positive.



Comparison 3. Multivitamin and trace element tablets versus placebo

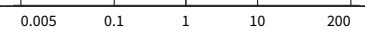
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death during follow-up in adults and children	5	2902	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.18]
1.1 HIV-negative individuals	4	1218	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.46, 1.60]
1.2 HIV-positive individuals	3	1429	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.23]
1.3 HIV-positive and HIV-negative individuals	1	255	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.53, 4.72]
2 Tuberculosis treatment completion	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.04]
3 Sputum-smear or sputum-culture positive at 1 month	2	1020	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.63, 1.35]
3.1 Mixed HIV-positive and HIV-negative	1	392	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.99, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 HIV-negative individuals only	1	306	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.47, 1.13]
3.3 HIV-positive individuals only	1	322	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.31]
4 Sputum-smear or sputum-culture positive at 2 months	2	731	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.35]
5 Clearance of chest X-ray at 6 months	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.18]
6 Weight	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 After 2 months of supplementation	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 After 5 months follow-up (3 months post supplementation)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 After 6 months supplementation (children)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 After 7 months of supplementation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Anthropometrical changes at follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Weight-for-age z score at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Weight-for-age z score at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Weight (kg) at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Weight (kg) at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Height-for-age z score at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.6 Height-for-age z score at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.7 BMI z score at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.8 BMI z score at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Mean change in handgrip strength (kg)	1	1480	Mean Difference (IV, Fixed, 95% CI)	1.16 [0.50, 1.81]
8.1 At 2 months	1	771	Mean Difference (IV, Fixed, 95% CI)	1.22 [0.49, 1.95]
8.2 At 5 months	1	709	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.56, 2.36]

Analysis 3.1. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 1 Death during follow-up in adults and children.

Study or subgroup	Multimicronutrient n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 HIV-negative individuals					
Range 2005 TZA	2/55	1/32		0.71%	1.16[0.11,12.33]
Range 2005 TZA	4/61	1/33		0.85%	2.16[0.25,18.58]
Semba 2007 MWI	9/169	8/150		4.37%	1[0.4,2.52]
Villamor 2008 TZA	4/208	11/208		3.01%	0.36[0.12,1.12]
Lodha 2014 IND	2/102	0/50		0.44%	2.48[0.12,50.62]
Lodha 2014 IND	2/100	0/50		0.44%	2.52[0.12,51.61]
Subtotal (95% CI)	**695**	**523**		**9.81%**	**0.86[0.46,1.6]**
Total events: 23 (Multimicronutrient), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.07, df=5(P=0.54); I^2=0%					
Test for overall effect: Z=0.49(P=0.62)					
3.1.2 HIV-positive individuals					
Range 2005 TZA	11/45	7/21		5.83%	0.73[0.33,1.62]
Range 2005 TZA	4/42	7/21		3.09%	0.29[0.09,0.87]
Semba 2007 MWI	157/406	171/423		47.92%	0.96[0.81,1.13]
Villamor 2008 TZA	74/233	66/238		30.14%	1.15[0.87,1.51]
Subtotal (95% CI)	**726**	**703**		**86.99%**	**0.92[0.69,1.23]**
Total events: 246 (Multimicronutrient), 251 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=6.52, df=3(P=0.09); I^2=53.96%					
Test for overall effect: Z=0.55(P=0.58)					
3.1.3 HIV-positive and HIV-negative individuals					
Mehta 2011 TZA	8/128	5/127		3.21%	1.59[0.53,4.72]
Subtotal (95% CI)	**128**	**127**		**3.21%**	**1.59[0.53,4.72]**
Total events: 8 (Multimicronutrient), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.41)					
Total (95% CI)	**1549**	**1353**		**100%**	**0.96[0.79,1.18]**
Total events: 277 (Multimicronutrient), 277 (Placebo)					
Heterogeneity: Tau^2=0.01; Chi^2=11.52, df=10(P=0.32); I^2=13.21%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi^2=0.99, df=1 (P=0.61), I^2=0%					



Analysis 3.2. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 2 Tuberculosis treatment completion.

Study or subgroup	Multimi-cronutrient n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Lodha 2014 IND	97/102	48/50		49.65%	0.99[0.92,1.06]
Lodha 2014 IND	97/100	49/50		50.35%	0.99[0.94,1.04]
Total (95% CI)	**202**	**100**		**100%**	**0.99[0.95,1.04]**
Total events: 194 (Multimicronutrient), 97 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					

Analysis 3.3. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 3 Sputum-smear or sputum-culture positive at 1 month.

Study or subgroup	Multimi-cronutrient n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Mixed HIV-positive and HIV-negative					
Range 2005 TZA	115/201	91/191		44.3%	1.2[0.99,1.45]
Subtotal (95% CI)	**201**	**191**		**44.3%**	**1.2[0.99,1.45]**
Total events: 115 (Multimicronutrient), 91 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
3.3.2 HIV-negative individuals only					
Villamor 2008 TZA	27/149	39/157		30.26%	0.73[0.47,1.13]
Subtotal (95% CI)	**149**	**157**		**30.26%**	**0.73[0.47,1.13]**
Total events: 27 (Multimicronutrient), 39 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.42(P=0.16)					
3.3.3 HIV-positive individuals only					
Villamor 2008 TZA	21/165	26/157		25.43%	0.77[0.45,1.31]
Subtotal (95% CI)	**165**	**157**		**25.43%**	**0.77[0.45,1.31]**
Total events: 21 (Multimicronutrient), 26 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					
Total (95% CI)	**515**	**505**		**100%**	**0.92[0.63,1.35]**
Total events: 163 (Multimicronutrient), 156 (Placebo)					
Heterogeneity: Tau^2=0.08; Chi^2=6.24, df=2(P=0.04); I^2=67.95%					
Test for overall effect: Z=0.42(P=0.68)					
Test for subgroup differences: Chi^2=5.85, df=1 (P=0.05), I^2=65.82%					

Analysis 3.4. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 4 Sputum-smear or sputum-culture positive at 2 months.

Study or subgroup	Multimi-cronutrient n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Lodha 2014 IND	12/102	5/50		16.11%	1.18[0.44,3.16]
Lodha 2014 IND	10/100	4/50		12.8%	1.25[0.41,3.79]
Range 2005 TZA	23/219	29/210		71.08%	0.76[0.46,1.27]
Total (95% CI)	**421**	**310**		**100%**	**0.89[0.59,1.35]**
Total events: 45 (Multimicronutrient), 38 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.03, df=2(P=0.6); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					

Favours MMN — Favours placebo

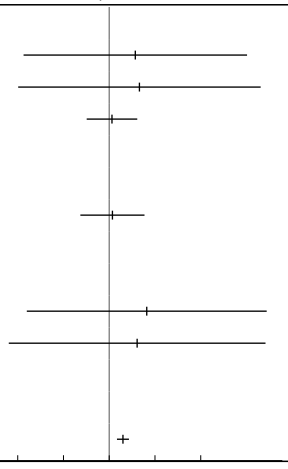
Analysis 3.5. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 5 Clearance of chest X-ray at 6 months.

Study or subgroup	Multimi-cronutrient n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Lodha 2014 IND	75/99	36/50		33.35%	1.05[0.86,1.29]
Lodha 2014 IND	67/99	36/50		33.35%	0.94[0.75,1.17]
Mehta 2011 TZA	51/97	49/102		33.3%	1.09[0.83,1.44]
Total (95% CI)	**295**	**202**		**100%**	**1.03[0.9,1.18]**
Total events: 193 (Multimicronutrient), 121 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					

Favours placebo — Favours MMN

Analysis 3.6. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 6 Weight.

Study or subgroup	Multimicronutrient N	Multimicronutrient Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.6.1 After 2 months of supplementation						
Lodha 2014 IND	102	22.9 (8.9)	100	22.3 (8.8)		0.57[-1.87,3.01]
Lodha 2014 IND	100	23 (10.2)	100	22.3 (8.8)		0.66[-1.99,3.31]
Praygod 2011a TZA	383	2.9 (3.6)	392	2.9 (4.2)		0.06[-0.49,0.61]
3.6.2 After 5 months follow-up (3 months post supplementation)						
Praygod 2011a TZA	349	4.9 (4.6)	360	4.8 (4.9)		0.07[-0.63,0.77]
3.6.3 After 6 months supplementation (children)						
Lodha 2014 IND	102	24.8 (9.7)	100	24 (9.4)		0.82[-1.8,3.44]
Lodha 2014 IND	100	24.6 (10.8)	100	24 (9.4)		0.61[-2.2,3.42]
3.6.4 After 7 months of supplementation						
Range 2005 TZA	101	6.6 (0.4)	97	6.3 (0.5)		0.3[0.17,0.43]



Favours placebo — Favours MMN

Study or subgroup	Multimicronutrient N	Multimicronutrient Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Range 2005 TZA	95	8.7 (0.6)	97	6.3 (0.5)		2.37[2.21,2.53]

Favours placebo -2 -1 0 1 2 Favours MMN

Analysis 3.7. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 7 Anthropometrical changes at follow-up.

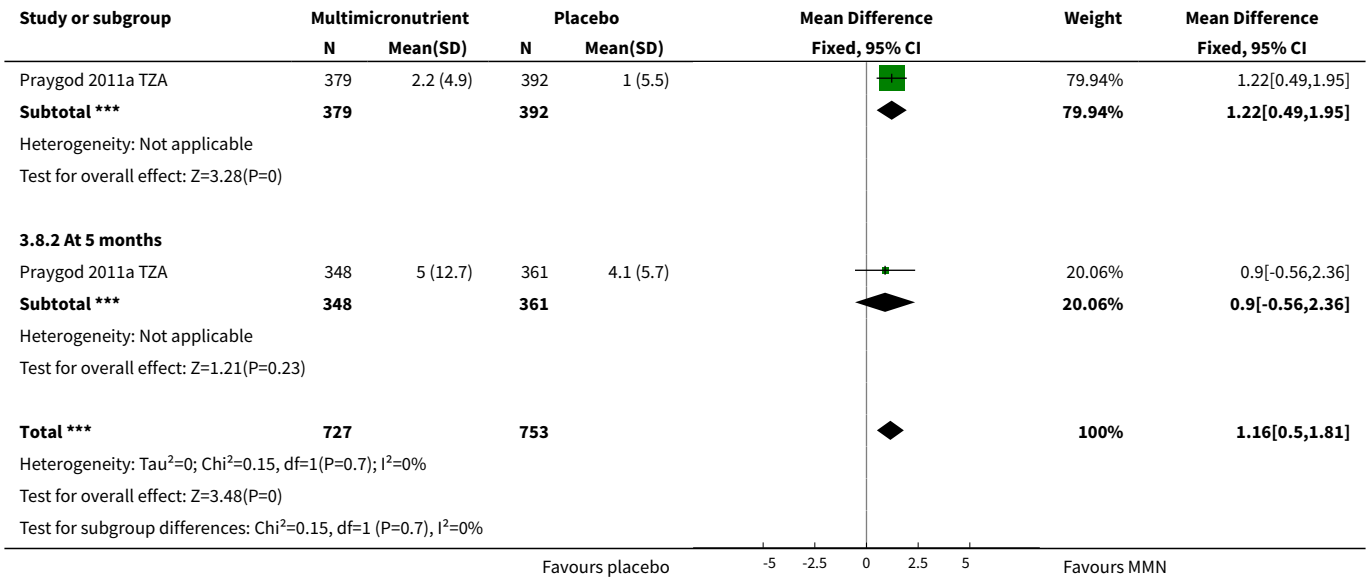
Study or subgroup	Multimicronutrient N	Multimicronutrient Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.7.1 Weight-for-age z score at 2 months						
Lodha 2014 IND	99	-2.2 (1.7)	99	-2.4 (1.6)		0.21[-0.24,0.66]
Lodha 2014 IND	99	-2.4 (1.4)	99	-2.4 (1.6)		0.01[-0.4,0.42]
3.7.2 Weight-for-age z score at 6 months						
Lodha 2014 IND	99	-2.1 (1.3)	99	-2.4 (1.6)		0.32[-0.08,0.72]
Lodha 2014 IND	99	-1.9 (1.5)	99	-2.4 (1.6)		0.52[0.09,0.95]
3.7.3 Weight (kg) at 2 months						
Lodha 2014 IND	99	23 (10.2)	99	22.3 (8.8)		0.66[-2,3.32]
Lodha 2014 IND	99	22.9 (8.9)	99	22.3 (8.8)		0.57[-1.9,3.04]
3.7.4 Weight (kg) at 6 months						
Lodha 2014 IND	99	24.6 (10.8)	99	24 (9.4)		0.61[-2.21,3.43]
Lodha 2014 IND	99	24.8 (9.7)	99	24 (9.4)		0.82[-1.83,3.47]
3.7.5 Height-for-age z score at 2 months						
Lodha 2014 IND	99	-1.7 (1.2)	99	-1.6 (1.4)		-0.02[-0.38,0.34]
Lodha 2014 IND	99	-1.5 (1.5)	99	-1.6 (1.4)		0.1[-0.3,0.5]
3.7.6 Height-for-age z score at 6 months						
Lodha 2014 IND	99	-1.5 (1.5)	99	-1.6 (1.4)		0.18[-0.21,0.57]
Lodha 2014 IND	99	-1.5 (1.2)	99	-1.6 (1.4)		0.1[-0.26,0.46]
3.7.7 BMI z score at 2 months						
Lodha 2014 IND	100	-1.7 (1.2)	100	-1.7 (1.3)		0.02[-0.33,0.37]
Lodha 2014 IND	102	-1.6 (1.2)	100	-1.7 (1.3)		0.16[-0.18,0.5]
3.7.8 BMI z score at 6 months						
Lodha 2014 IND	102	-1.2 (1.2)	100	-1.3 (1.2)		0.09[-0.24,0.42]
Lodha 2014 IND	100	-1.4 (1.1)	100	-1.3 (1.2)		-0.16[-0.48,0.16]

Favours placebo -10 -5 0 5 10 Favours MMN

Analysis 3.8. Comparison 3 Multivitamin and trace element tablets versus placebo, Outcome 8 Mean change in handgrip strength (kg).

Study or subgroup	Multimicronutrient N	Multimicronutrient Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.8.1 At 2 months							

Favours placebo -5 -2.5 0 2.5 5 Favours MMN



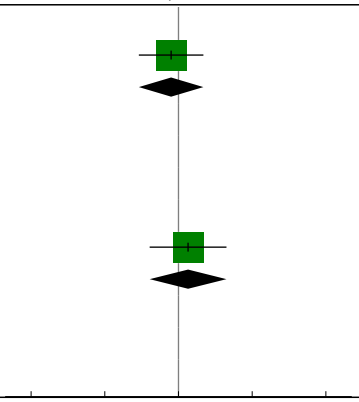
Comparison 4. Vitamin A versus placebo

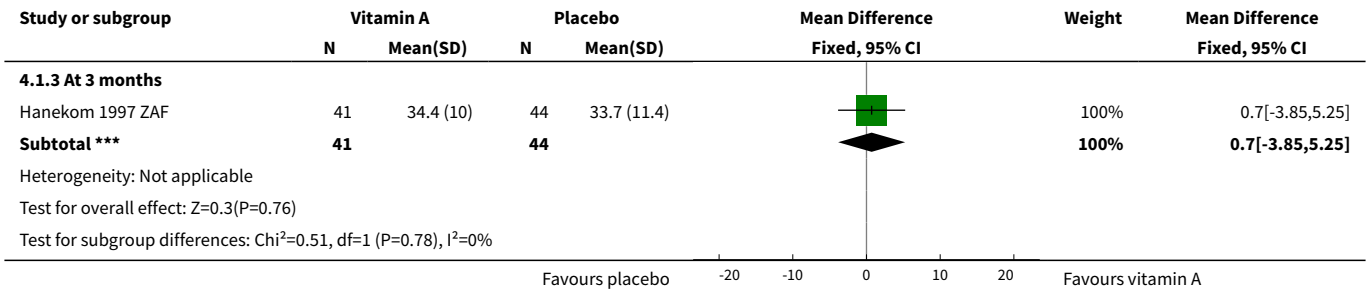
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Children: mean serum retinol (normal range > 20 µg/L)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At baseline	1	85	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-5.38, 3.38]
1.2 At 6 weeks	1	85	Mean Difference (IV, Fixed, 95% CI)	1.30 [-3.91, 6.51]
1.3 At 3 months	1	85	Mean Difference (IV, Fixed, 95% CI)	0.70 [-3.85, 5.25]
2 Adults: mean serum retinol (normal range > 70 µmol/L)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At baseline	3	242	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.13, 0.01]
2.2 At 2 months	3	242	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.03, 0.14]
2.3 At 6 months	3	242	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.02, 0.16]
3 Death	8	3308	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.12]
3.1 Vitamin A alone	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.19, 16.69]
3.2 Vitamin A plus zinc	4	535	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.87, 6.53]
3.3 Vitamin A as part of a multi-micronutrient supplement	4	2658	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Treatment completion	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.80, 1.04]
5 Symptomatic at 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Sputum-smear and sputum-culture positive during follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Baseline	1	158	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.98, 1.03]
6.2 2 weeks	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.50, 1.28]
6.3 1 month	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.33, 1.48]
6.4 2 months	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.23, 4.73]
7 BMI (kg/m^2)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Baseline	1	158	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.63, 0.83]
7.2 2 months	1	148	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.44, 1.04]
7.3 6 months	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.15, 0.55]
8 Body fat (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Baseline	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.80, 1.00]
8.2 2 months	1	148	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.84, 1.04]
8.3 6 months	1	136	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.96, 0.36]

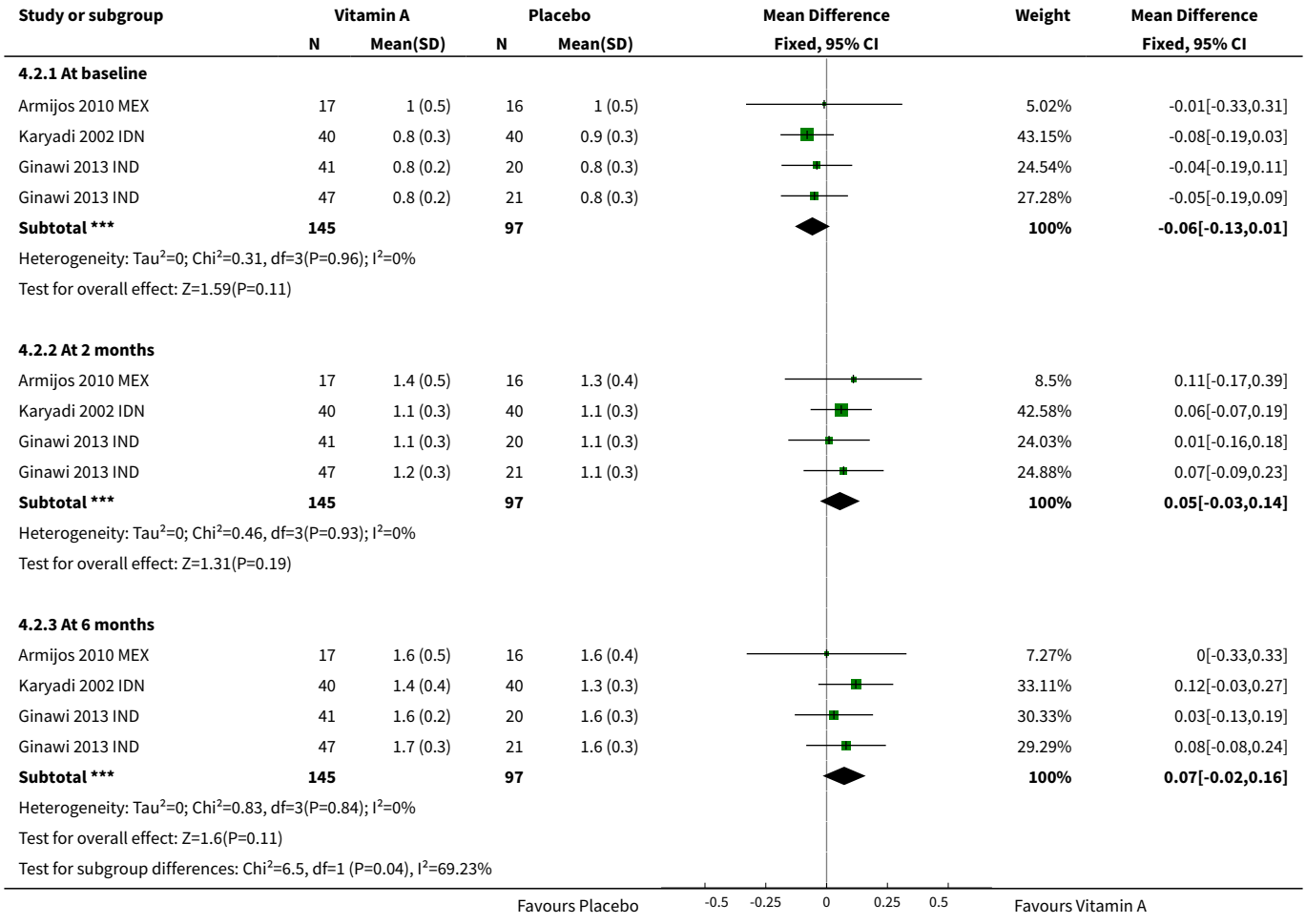
Analysis 4.1. Comparison 4 Vitamin A versus placebo, Outcome 1 Children: mean serum retinol (normal range > 20 µg/L).

Study or subgroup	Vitamin A N	Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.1.1 At baseline							
Hanekom 1997 ZAF	41	17.6 (10.1)	44	18.6 (10.5)		100%	-1[-5.38,3.38]
Subtotal ***	**41**		**44**			**100%**	**-1[-5.38,3.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.45(P=0.65)							
4.1.2 At 6 weeks							
Hanekom 1997 ZAF	41	34.8 (10.1)	44	33.5 (14.2)		100%	1.3[-3.91,6.51]
Subtotal ***	**41**		**44**			**100%**	**1.3[-3.91,6.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.49(P=0.62)							

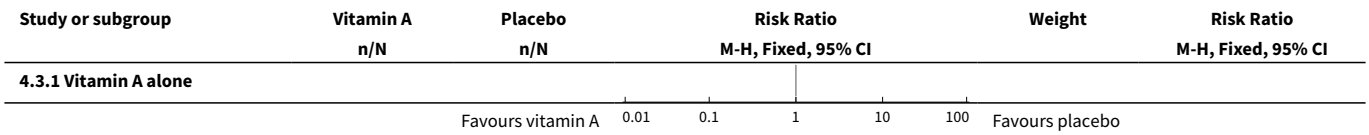


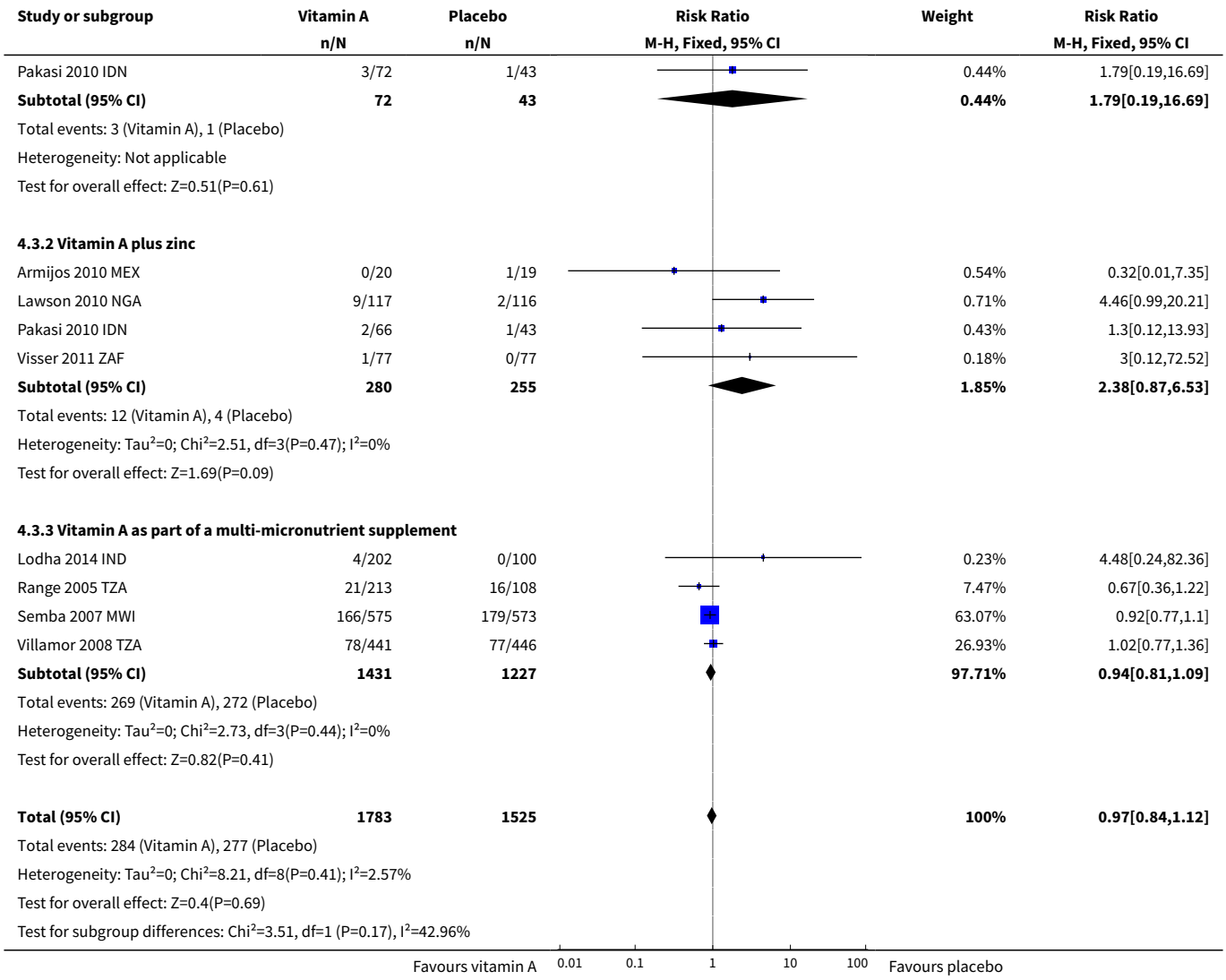


Analysis 4.2. Comparison 4 Vitamin A versus placebo, Outcome 2 Adults: mean serum retinol (normal range > 70 µmol/L).

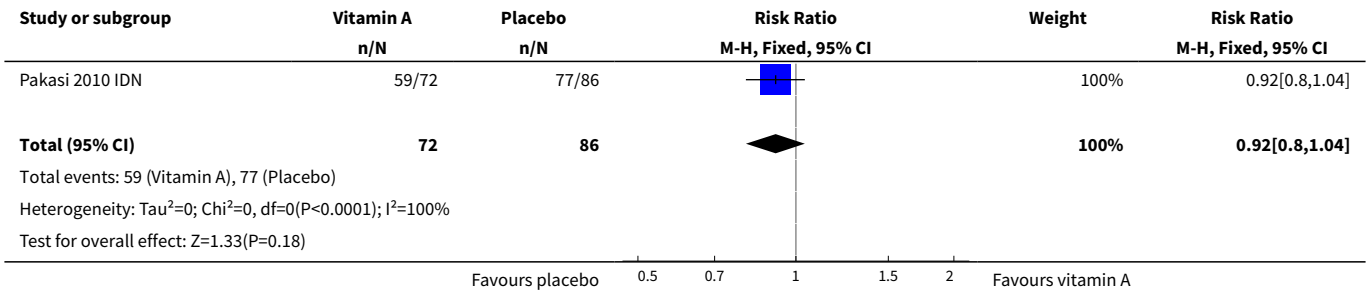


Analysis 4.3. Comparison 4 Vitamin A versus placebo, Outcome 3 Death.



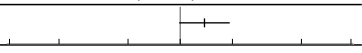


Analysis 4.4. Comparison 4 Vitamin A versus placebo, Outcome 4 Treatment completion.



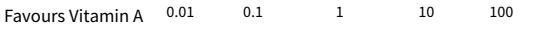
Analysis 4.5. Comparison 4 Vitamin A versus placebo, Outcome 5 Symptomatic at 6 weeks.

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Hanekom 1997 ZAF	29/38	21/38		1.38[0.99,1.93]



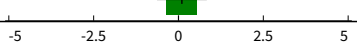
Analysis 4.6. Comparison 4 Vitamin A versus placebo, Outcome 6 Sputum-smear and sputum-culture positive during follow-up.

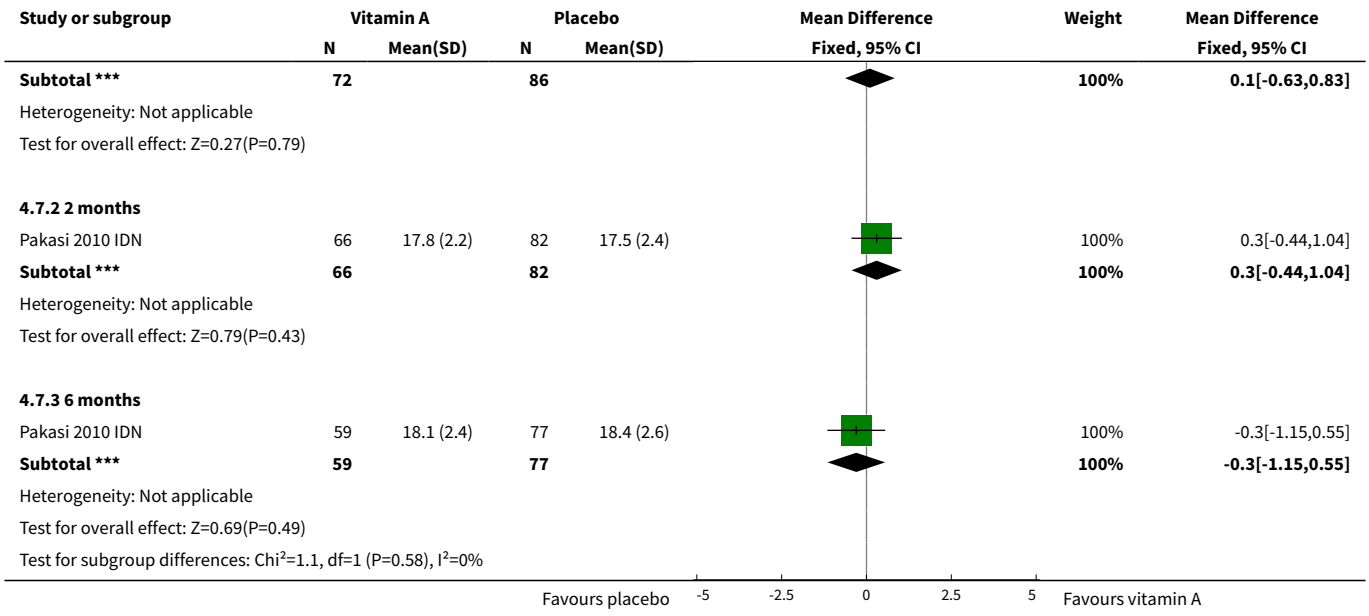
Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 Baseline					
Pakasi 2010 IDN	72/72	86/86		100%	1[0.98,1.03]
Subtotal (95% CI)	**72**	**86**		**100%**	**1[0.98,1.03]**
Total events: 72 (Vitamin A), 86 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.6.2 2 weeks					
Pakasi 2010 IDN	20/72	30/86		100%	0.8[0.5,1.28]
Subtotal (95% CI)	**72**	**86**		**100%**	**0.8[0.5,1.28]**
Total events: 20 (Vitamin A), 30 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
4.6.3 1 month					
Pakasi 2010 IDN	9/66	16/82		100%	0.7[0.33,1.48]
Subtotal (95% CI)	**66**	**82**		**100%**	**0.7[0.33,1.48]**
Total events: 9 (Vitamin A), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.94(P=0.35)					
4.6.4 2 months					
Ginawi 2013 IND	3/31	3/32		100%	1.03[0.23,4.73]
Pakasi 2010 IDN	0/59	0/77			Not estimable
Subtotal (95% CI)	**90**	**109**		**100%**	**1.03[0.23,4.73]**
Total events: 3 (Vitamin A), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
Test for subgroup differences: Chi^2=1.77, df=1 (P=0.62), I^2=0%					



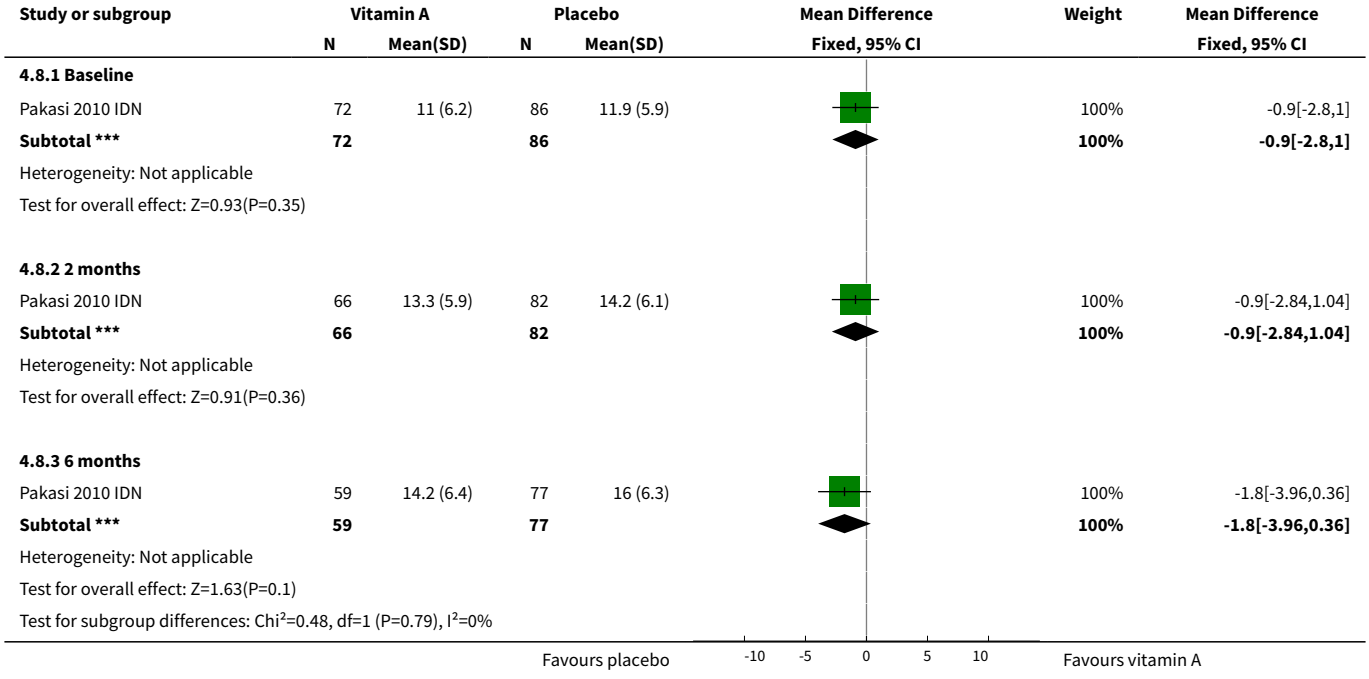
Analysis 4.7. Comparison 4 Vitamin A versus placebo, Outcome 7 BMI (kg/m^2).

Study or subgroup	Vitamin A N	Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.7.1 Baseline							
Pakasi 2010 IDN	72	16.5 (2.2)	86	16.4 (2.5)		100%	0.1[-0.63,0.83]





Analysis 4.8. Comparison 4 Vitamin A versus placebo, Outcome 8 Body fat (%).



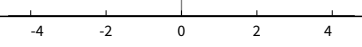
Comparison 5. Zinc versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum zinc level (normal range > 10.7 µmol/L)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At baseline	4	472	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.36, 0.30]
1.2 At 2 months	4	452	Mean Difference (IV, Fixed, 95% CI)	0.59 [0.24, 0.93]
1.3 At 6 months	4	440	Mean Difference (IV, Fixed, 95% CI)	0.60 [0.31, 0.88]
2 Death by 6 to 8 months	7	2862	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
2.1 Zinc alone	4	714	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.70, 2.22]
2.2 Zinc plus vitamin A	4	477	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [0.65, 6.64]
2.3 Zinc as part of a multi-micronutrient supplement	3	1671	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.07]
3 Death by 6 to 8 months (subgrouped by HIV status)	4	815	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.75, 2.09]
3.1 HIV-negative individuals	3	442	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.53, 6.98]
3.2 HIV-positive individuals	2	211	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.59, 1.91]
3.3 HIV status unknown	1	162	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.29, 9.89]
4 Treatment completion at 6 months	2	353	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.04]
5 Sputum-smear or sputum-culture positive during follow-up	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At baseline	3	596	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.92, 1.03]
5.2 At 2 weeks	3	806	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.02, 1.17]
5.3 At 4 weeks	3	783	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.20]
5.4 At 8 weeks	5	1076	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.28]
6 Clearance of chest X-ray at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7 Weight at follow-up	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Baseline: weight (kg)	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 2 months: weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 6 months: weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4 7 months: weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 BMI (kg/m^2)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Baseline	1	162	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.62, 0.82]
8.2 2 months	1	151	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.55, 0.95]
8.3 6 months	1	140	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.70, 0.90]
9 Body fat (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Baseline	1	162	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.51, 0.71]
9.2 2 months	1	151	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.07, 0.47]
9.3 6 months	1	140	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-3.51, 0.51]
10 Weight-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Baseline: weight-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 2 months: weight-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 6 months: weight-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 BMI-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Baseline: BMI-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 2 months: BMI-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 6 months: BMI-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Height-for-age z score at follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Baseline: height-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 2 months: height-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 6 months: height-for-age z score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

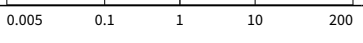
Analysis 5.1. Comparison 5 Zinc versus placebo, Outcome 1 Serum zinc level (normal range > 10.7 µmol/L).

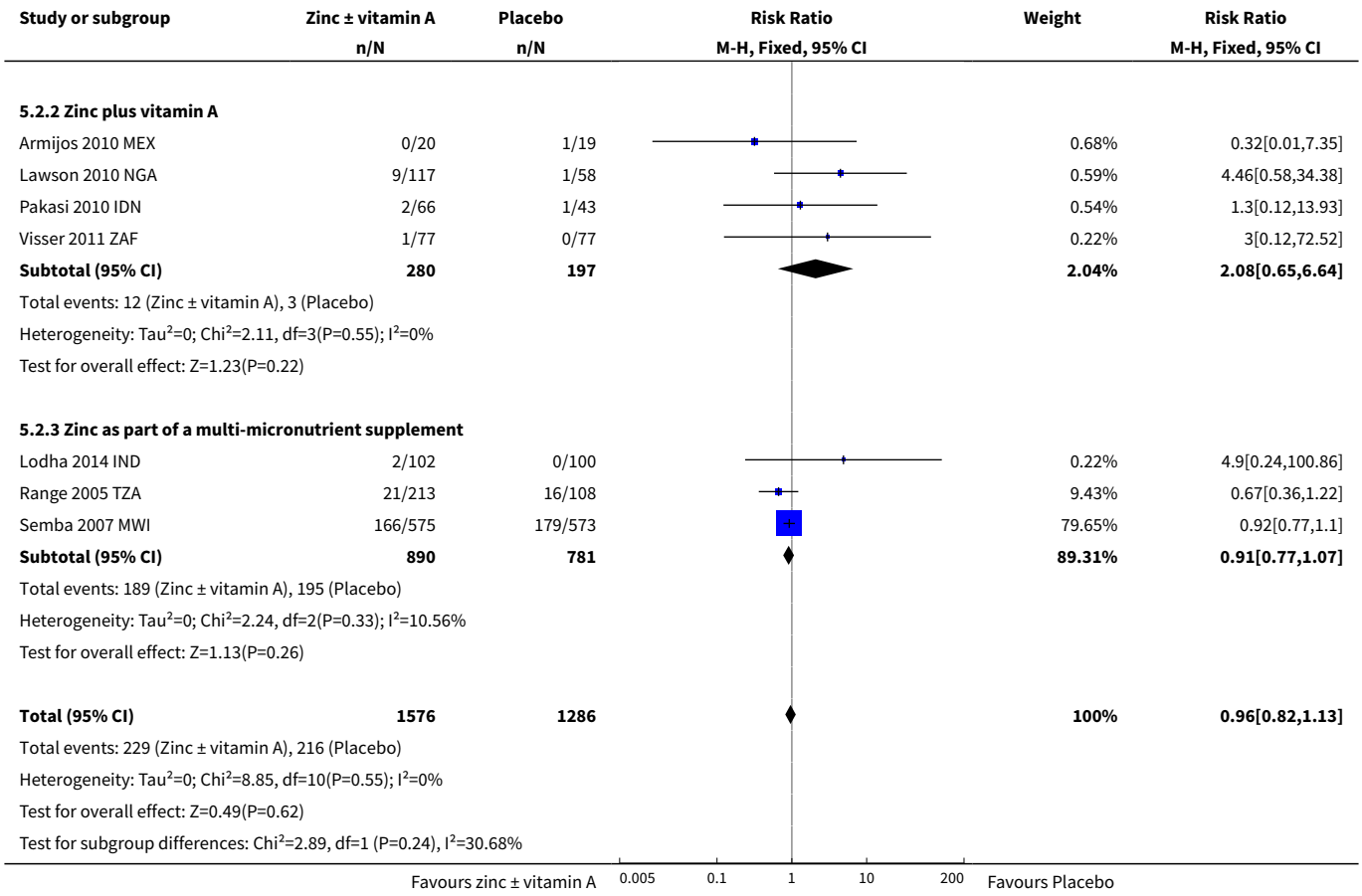
Study or subgroup	Zinc ± Vitamin A N	Zinc ± Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.1.1 At baseline							
Ginawi 2013 IND	49	9.9 (0.9)	21	9.9 (1.4)		26.1%	-0.02[-0.67,0.63]
Pakasi 2010 IDN	76	11.6 (2.2)	43	11.8 (2.4)		14.37%	-0.2[-1.07,0.67]
Armijos 2010 MEX	17	11.3 (2.6)	16	11.7 (2.1)		4.28%	-0.4[-2,1.2]
Karyadi 2002 IDN	40	11.5 (1.6)	40	11.2 (1.8)		19.51%	0.37[-0.38,1.12]
Ginawi 2013 IND	41	9.6 (0.8)	20	9.9 (1.4)		25.25%	-0.32[-0.98,0.34]
Pakasi 2010 IDN	66	12.1 (3)	43	11.8 (2.4)		10.5%	0.3[-0.72,1.32]
Subtotal ***	**289**		**183**			**100%**	**-0.03[-0.36,0.3]**
Heterogeneity: Tau²=0; Chi²=2.6, df=5(P=0.76); I²=0%							
Test for overall effect: Z=0.17(P=0.87)							
5.1.2 At 2 months							
Ginawi 2013 IND	49	12.2 (1.1)	21	11.2 (1.3)		28.05%	1[0.35,1.65]
Pakasi 2010 IDN	69	11.7 (2.4)	41	11.7 (2.3)		14.29%	0[-0.92,0.92]
Armijos 2010 MEX	17	12.9 (3.4)	16	10.1 (1.6)		3.7%	2.72[0.92,4.52]
Karyadi 2002 IDN	40	11.2 (2.4)	40	10.2 (2.3)		11.37%	1[-0.03,2.03]
Ginawi 2013 IND	41	11.2 (0.9)	20	11.2 (1.3)		28.9%	-0.06[-0.7,0.58]
Pakasi 2010 IDN	57	12.5 (2.3)	41	11.7 (2.3)		13.69%	0.8[-0.14,1.74]
Subtotal ***	**273**		**179**			**100%**	**0.59[0.24,0.93]**
Heterogeneity: Tau²=0; Chi²=13.22, df=5(P=0.02); I²=62.19%							
Test for overall effect: Z=3.33(P=0)							
5.1.3 At 6 months							
Ginawi 2013 IND	49	14 (0.8)	21	12.9 (1)		34.33%	1.12[0.63,1.61]
Pakasi 2010 IDN	63	13.1 (1.9)	39	12.6 (1.7)		16.14%	0.5[-0.22,1.22]
Armijos 2010 MEX	17	10.4 (1.5)	16	11.3 (2.1)		5.25%	-0.9[-2.16,0.36]
Karyadi 2002 IDN	40	12.5 (2.2)	40	12.1 (2)		10%	0.37[-0.55,1.29]
Ginawi 2013 IND	41	13.3 (1.2)	20	12.9 (1)		24.75%	0.49[-0.09,1.07]
Pakasi 2010 IDN	56	12.8 (2.9)	38	12.6 (1.7)		9.53%	0.2[-0.74,1.14]
Subtotal ***	**266**		**174**			**100%**	**0.6[0.31,0.88]**
Heterogeneity: Tau²=0; Chi²=10.81, df=5(P=0.06); I²=53.76%							
Test for overall effect: Z=4.03(P<0.0001)							
Test for subgroup differences: Chi²=9.33, df=1 (P=0.01), I²=78.55%							



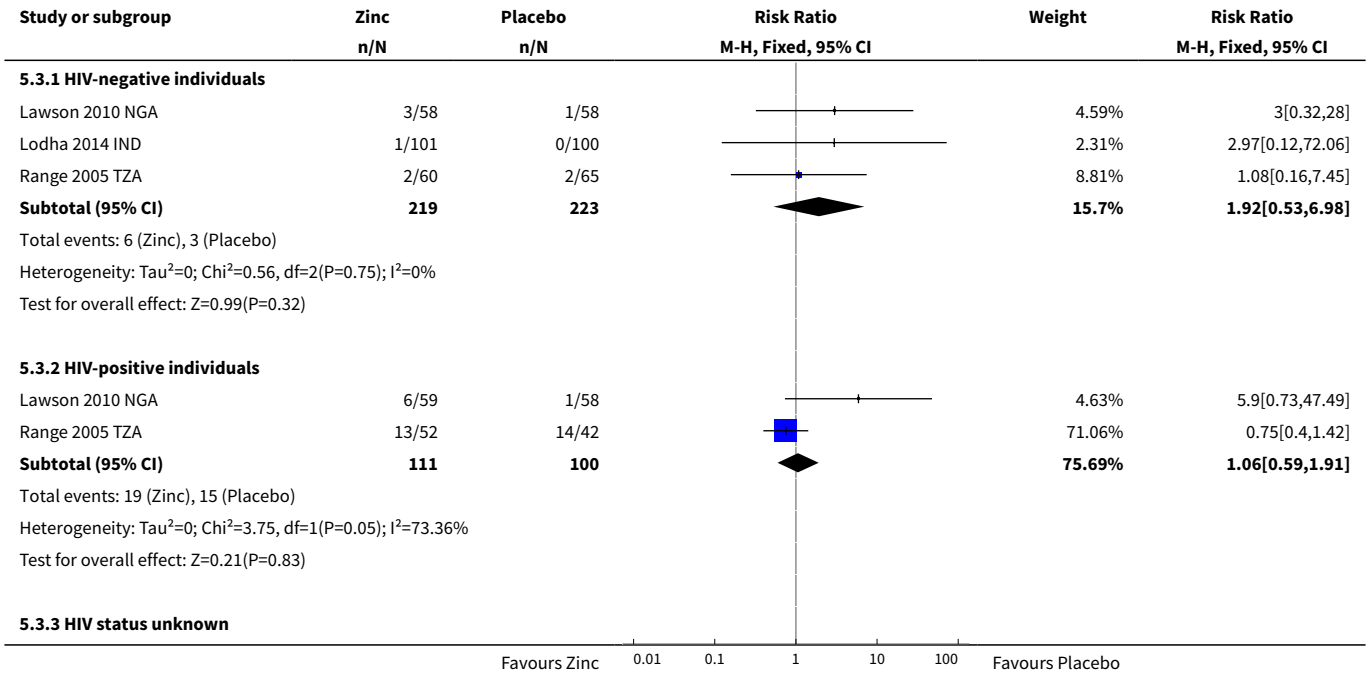
Analysis 5.2. Comparison 5 Zinc versus placebo, Outcome 2 Death by 6 to 8 months.

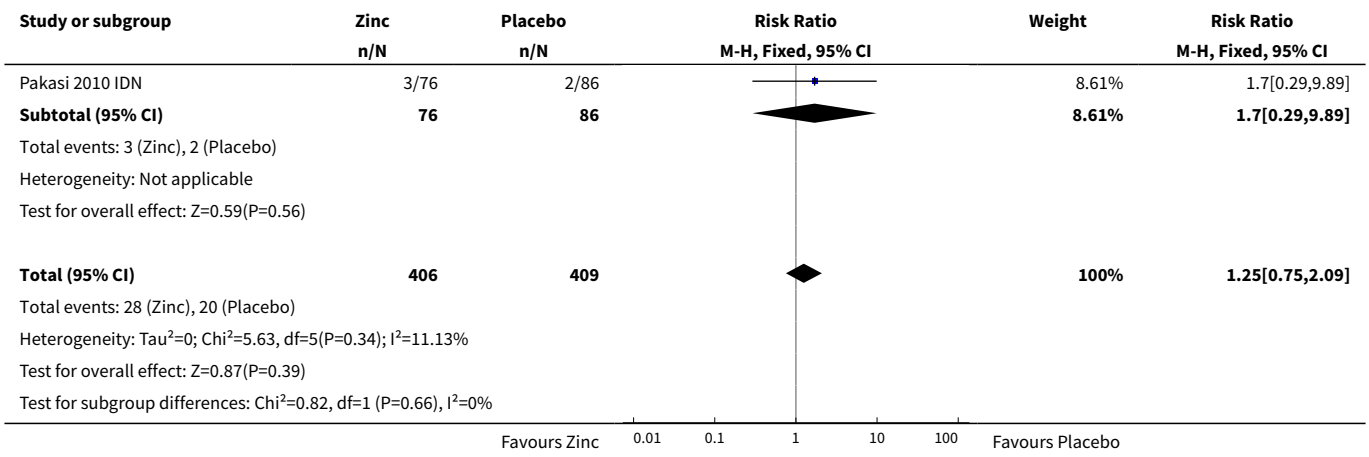
Study or subgroup	Zinc ± vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Zinc alone					
Lawson 2010 NGA	9/117	1/58		0.59%	4.46[0.58,34.38]
Lodha 2014 IND	1/101	0/100		0.22%	2.97[0.12,72.06]
Pakasi 2010 IDN	3/76	1/43		0.57%	1.7[0.18,15.82]
Range 2005 TZA	15/112	16/107		7.27%	0.9[0.47,1.72]
Subtotal (95% CI)	**406**	**308**		**8.65%**	**1.25[0.7,2.22]**
Total events: 28 (Zinc ± vitamin A), 18 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.84, df=3(P=0.42); I²=0%					
Test for overall effect: Z=0.75(P=0.45)					



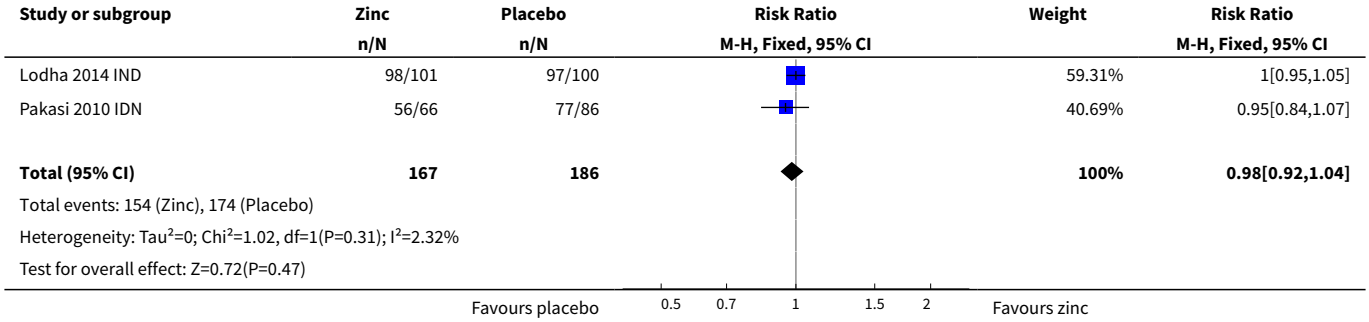


Analysis 5.3. Comparison 5 Zinc versus placebo, Outcome 3 Death by 6 to 8 months (subgrouped by HIV status).

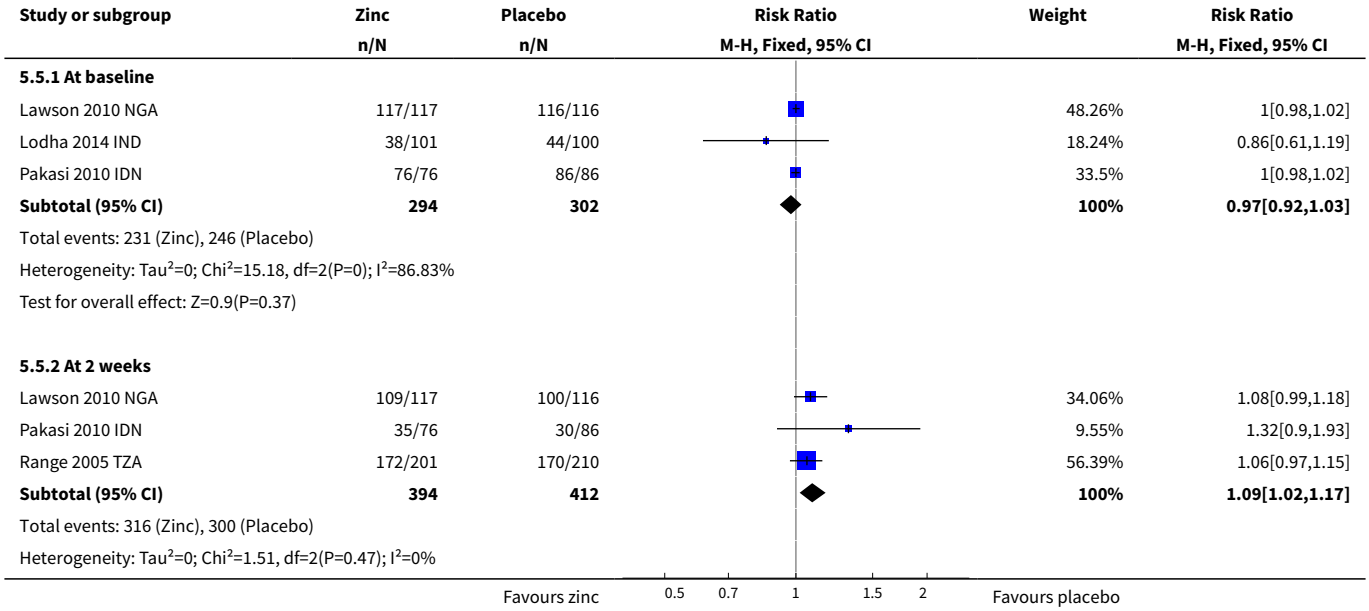


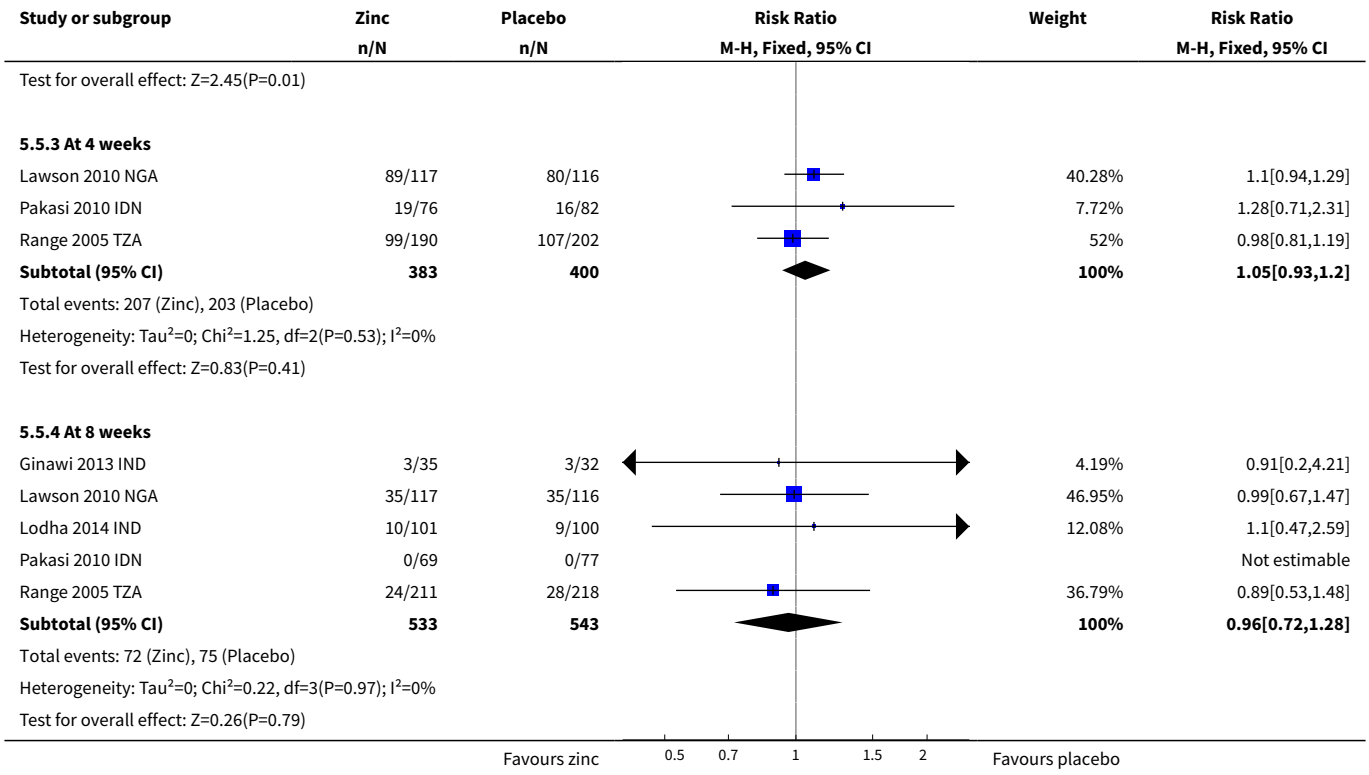


Analysis 5.4. Comparison 5 Zinc versus placebo, Outcome 4 Treatment completion at 6 months.

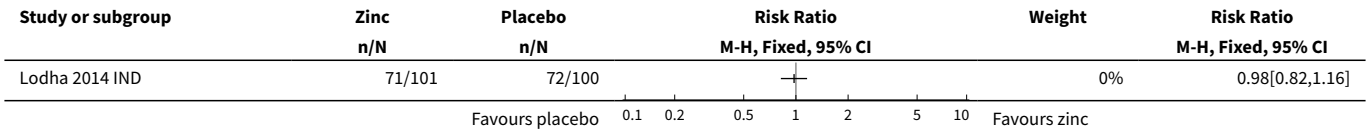


Analysis 5.5. Comparison 5 Zinc versus placebo, Outcome 5 Sputum-smear or sputum-culture positive during follow-up.

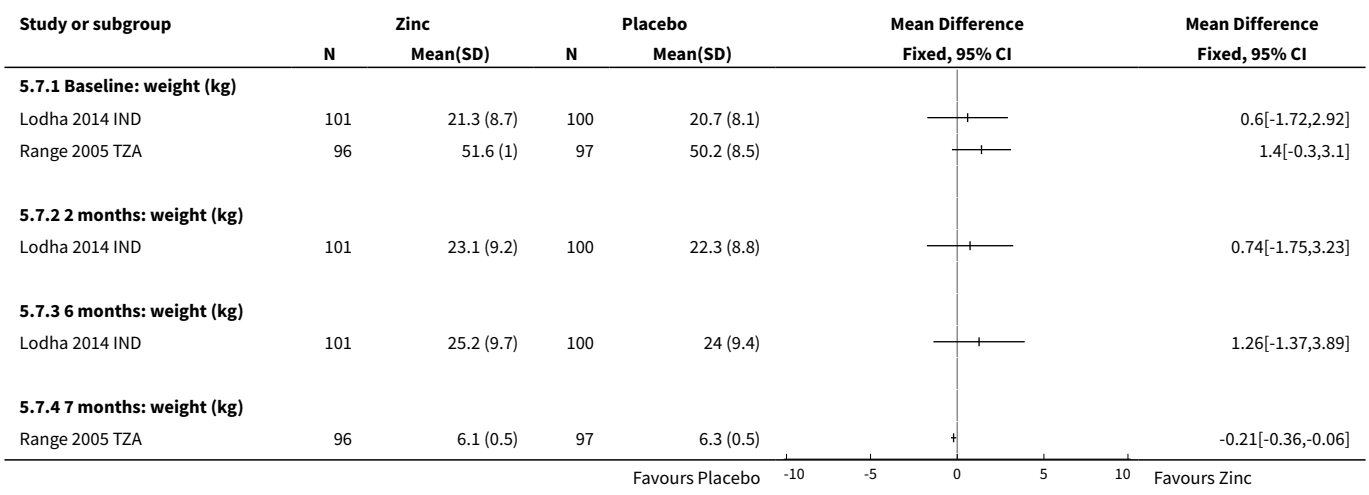




Analysis 5.6. Comparison 5 Zinc versus placebo, Outcome 6 Clearance of chest X-ray at 6 months.



Analysis 5.7. Comparison 5 Zinc versus placebo, Outcome 7 Weight at follow-up.



Analysis 5.8. Comparison 5 Zinc versus placebo, Outcome 8 BMI (kg/m²).

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.8.1 Baseline							
Pakasi 2010 IDN	76	16.5 (2.2)	86	16.4 (2.5)		100%	0.1[-0.62,0.82]
Subtotal ***	**76**		**86**			**100%**	**0.1[-0.62,0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.27(P=0.79)							
5.8.2 2 months							
Pakasi 2010 IDN	69	17.7 (2.3)	82	17.5 (2.4)		100%	0.2[-0.55,0.95]
Subtotal ***	**69**		**82**			**100%**	**0.2[-0.55,0.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.52(P=0.6)							
5.8.3 6 months							
Pakasi 2010 IDN	63	18.5 (2.2)	77	18.4 (2.6)		100%	0.1[-0.7,0.9]
Subtotal ***	**63**		**77**			**100%**	**0.1[-0.7,0.9]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.24(P=0.81)							
Test for subgroup differences: Chi²=0.05, df=1 (P=0.98), I²=0%							

Favours placebo — Favours zinc

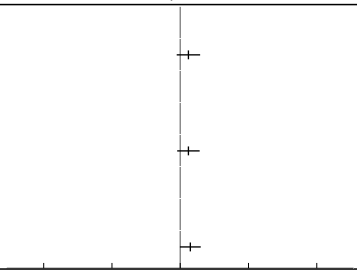
Analysis 5.9. Comparison 5 Zinc versus placebo, Outcome 9 Body fat (%).

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.9.1 Baseline							
Pakasi 2010 IDN	76	11 (4.5)	86	11.9 (5.9)		100%	-0.9[-2.51,0.71]
Subtotal ***	**76**		**86**			**100%**	**-0.9[-2.51,0.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							
5.9.2 2 months							
Pakasi 2010 IDN	69	12.9 (5)	82	14.2 (6.1)		100%	-1.3[-3.07,0.47]
Subtotal ***	**69**		**82**			**100%**	**-1.3[-3.07,0.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.44(P=0.15)							
5.9.3 6 months							
Pakasi 2010 IDN	63	14.5 (5.8)	77	16 (6.3)		100%	-1.5[-3.51,0.51]
Subtotal ***	**63**		**77**			**100%**	**-1.5[-3.51,0.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.46(P=0.14)							
Test for subgroup differences: Chi²=0.23, df=1 (P=0.89), I²=0%							

Favours placebo — Favours zinc

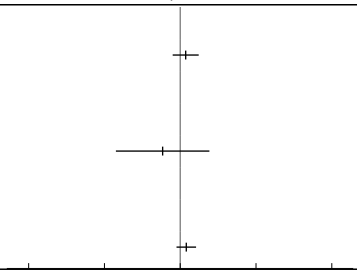
Analysis 5.10. Comparison 5 Zinc versus placebo, Outcome 10 Weight-for-age z score.

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.10.1 Baseline: weight-for-age z score						
Lodha 2014 IND	101	-2.5 (1.5)	100	-2.8 (1.6)		0.3[-0.13,0.73]
5.10.2 2 months: weight-for-age z score						
Lodha 2014 IND	101	-2.1 (1.4)	100	-2.4 (1.6)		0.3[-0.11,0.71]
5.10.3 6 months: weight-for-age z score						
Lodha 2014 IND	101	-1.7 (1.2)	100	-2.1 (1.5)		0.37[-0.01,0.75]



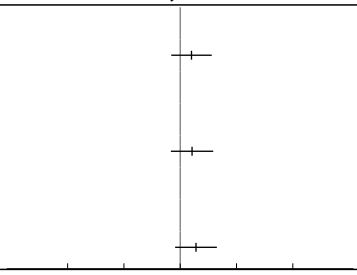
Analysis 5.11. Comparison 5 Zinc versus placebo, Outcome 11 BMI-for-age z score.

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.11.1 Baseline: BMI-for-age z score						
Lodha 2014 IND	101	-2.3 (1.6)	100	-2.5 (1.5)		0.18[-0.25,0.61]
5.11.2 2 months: BMI-for-age z score						
Lodha 2014 IND	101	-2.3 (7.8)	100	-1.7 (1.3)		-0.58[-2.12,0.96]
5.11.3 6 months: BMI-for-age z score						
Lodha 2014 IND	101	-1.1 (1.1)	100	-1.3 (1.2)		0.2[-0.12,0.52]



Analysis 5.12. Comparison 5 Zinc versus placebo, Outcome 12 Height-for-age z score at follow-up.

Study or subgroup	Zinc N	Zinc Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.12.1 Baseline: height-for-age z score						
Lodha 2014 IND	101	-1.4 (1.3)	100	-1.6 (1.3)		0.2[-0.16,0.56]
5.12.2 2 months: height-for-age z score						
Lodha 2014 IND	101	-1.4 (1.4)	100	-1.6 (1.4)		0.21[-0.17,0.59]
5.12.3 6 months: height-for-age z score						
Lodha 2014 IND	101	-1.4 (1.3)	100	-1.6 (1.4)		0.28[-0.09,0.65]



Comparison 6. Zinc plus vitamin A versus placebo

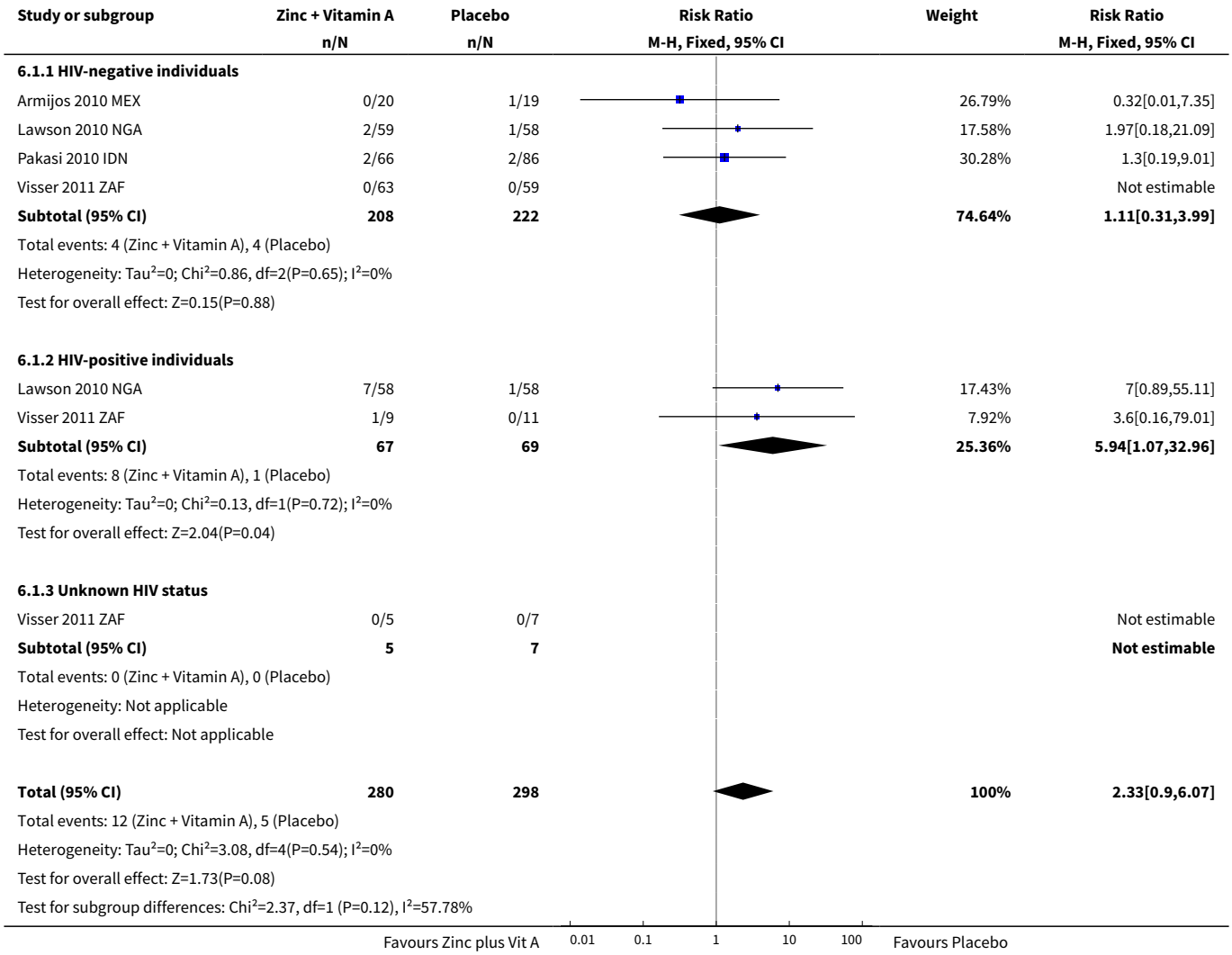
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death by 6 months	4	578	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.90, 6.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 HIV-negative individuals	4	430	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.31, 3.99]
1.2 HIV-positive individuals	2	136	Risk Ratio (M-H, Fixed, 95% CI)	5.94 [1.07, 32.96]
1.3 Unknown HIV status	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Treatment completion at 6 months	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
3 Sputum-smear and sputum-culture positive during follow-up	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 At baseline	5	652	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.99, 1.01]
3.2 1 month	4	485	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.17]
3.3 2 months	7	726	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.71, 1.15]
3.4 3 months	2	266	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.49]
3.5 4 months	2	266	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.86, 2.65]
3.6 5 months	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 6 months	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.04]
4 Body weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 BMI (kg/m^2)	2	664	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.45, 0.28]
5.1 Baseline	2	232	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.62, 0.61]
5.2 2 months	2	219	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.65, 0.58]
5.3 6 months	2	213	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.91, 0.43]
6 Mid upper arm circumference (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Biceps skinfold thickness (mm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Triceps skinfold thickness (mm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Subscapular skinfold thickness (mm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Suprailiac skinfold thickness (mm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Body fat (%)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Baseline	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 2 months	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 6 months	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Fat mass (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Karnofsky score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

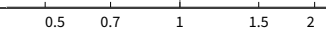
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 1 Death by 6 months.



Analysis 6.2. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 2 Treatment completion at 6 months.

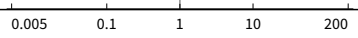
Study or subgroup	Zinc + Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pakasi 2010 IDN	56/66	77/86		100%	0.95[0.84,1.07]
Total (95% CI)	**66**	**86**		**100%**	**0.95[0.84,1.07]**
Total events: 56 (Zinc + Vitamin A), 77 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					



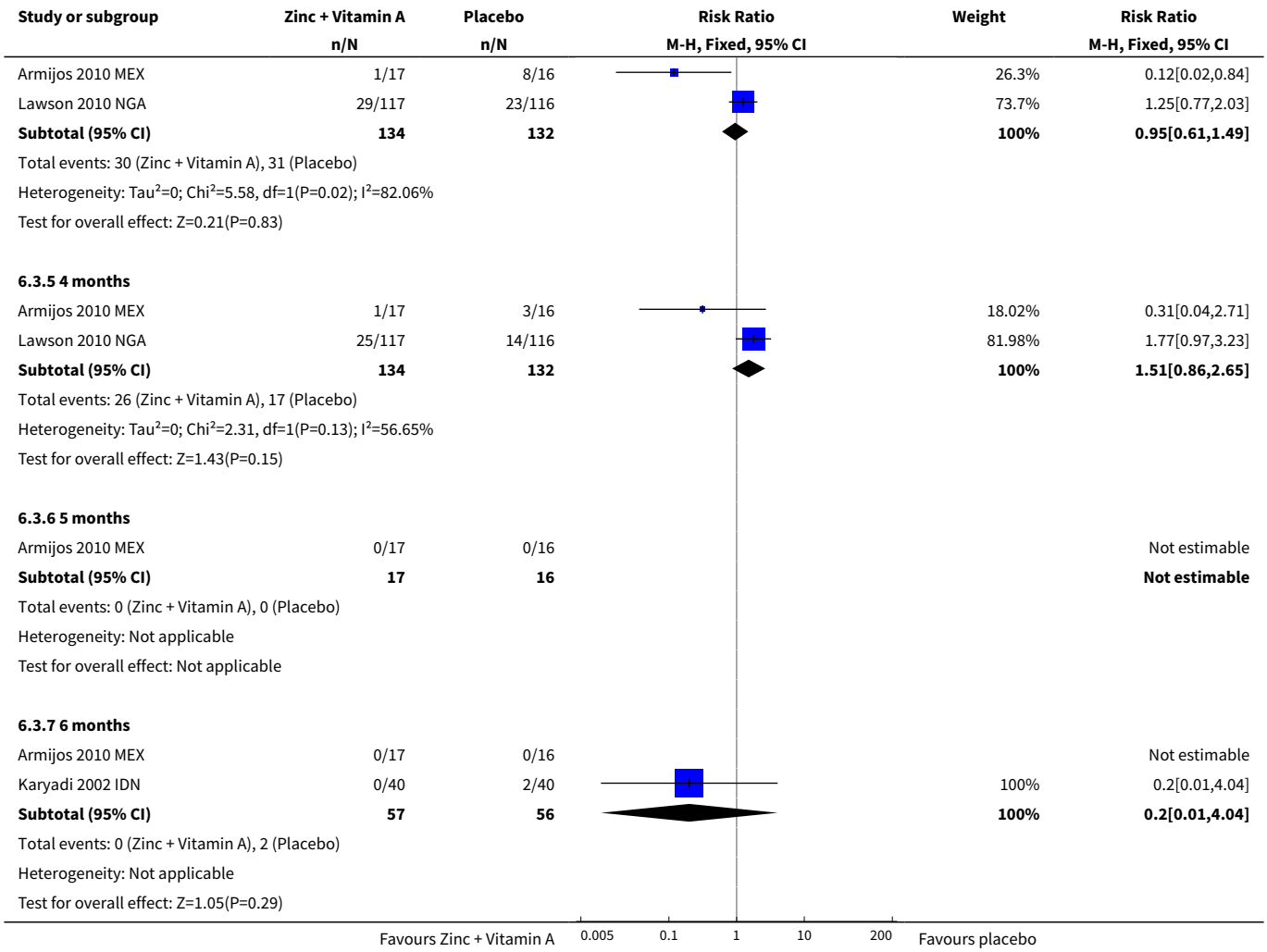
Favours placebo — Favours Zinc + Vitamin A

Analysis 6.3. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 3 Sputum-smear and sputum-culture positive during follow-up.

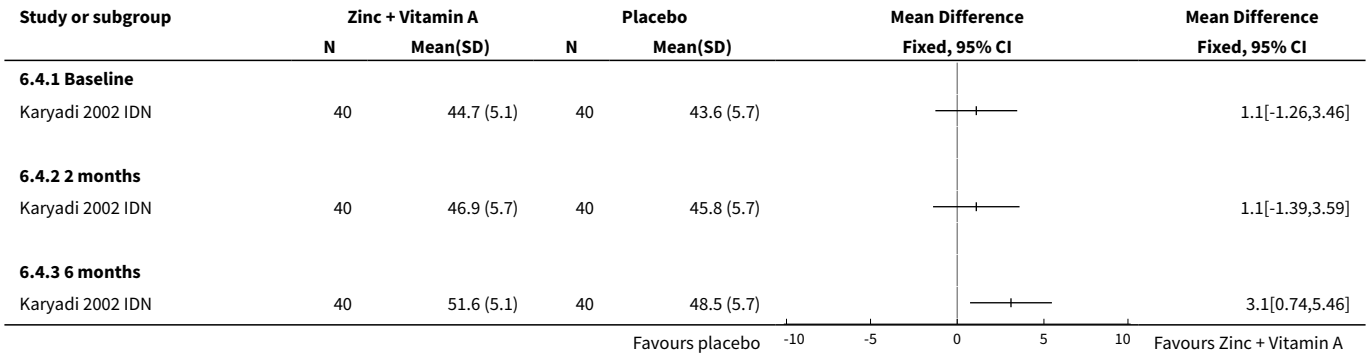
Study or subgroup	Zinc + Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 At baseline					
Armijos 2010 MEX	17/17	16/16		5.19%	1[0.89,1.12]
Karyadi 2002 IDN	40/40	40/40		12.38%	1[0.95,1.05]
Lawson 2010 NGA	117/117	116/116		35.75%	1[0.98,1.02]
Pakasi 2010 IDN	66/66	86/86		23%	1[0.97,1.03]
Visser 2011 ZAF	77/77	77/77		23.68%	1[0.98,1.03]
Subtotal (95% CI)	**317**	**335**		**100%**	**1[0.99,1.01]**
Total events: 317 (Zinc + Vitamin A), 335 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=4(P=1); I^2=0%					
Test for overall effect: Not applicable					
6.3.2 1 month					
Armijos 2010 MEX	10/17	10/16		8.46%	0.94[0.54,1.63]
Karyadi 2002 IDN	14/40	18/40		14.78%	0.78[0.45,1.34]
Lawson 2010 NGA	91/117	80/116		65.98%	1.13[0.97,1.32]
Pakasi 2010 IDN	7/57	16/82		10.78%	0.63[0.28,1.43]
Subtotal (95% CI)	**231**	**254**		**100%**	**1.01[0.86,1.17]**
Total events: 122 (Zinc + Vitamin A), 124 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.22, df=3(P=0.24); I^2=28.95%					
Test for overall effect: Z=0.08(P=0.93)					
6.3.3 2 months					
Armijos 2010 MEX	4/17	8/16		9.5%	0.47[0.18,1.26]
Ginawi 2013 IND	2/29	3/32		3.29%	0.74[0.13,4.1]
Karyadi 2002 IDN	0/40	0/40			Not estimable
Lawson 2010 NGA	41/117	35/116		40.52%	1.16[0.8,1.68]
Pakasi 2010 IDN	0/57	0/82			Not estimable
Singh 2013 IND	0/13	2/13		2.88%	0.2[0.01,3.8]
Visser 2011 ZAF	31/77	38/77		43.81%	0.82[0.57,1.16]
Subtotal (95% CI)	**350**	**376**		**100%**	**0.9[0.71,1.15]**
Total events: 78 (Zinc + Vitamin A), 86 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.82, df=4(P=0.31); I^2=17.05%					
Test for overall effect: Z=0.82(P=0.41)					
6.3.4 3 months					



Favours Zinc + Vitamin A — Favours placebo

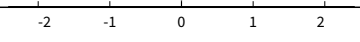


Analysis 6.4. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 4 Body weight (kg).



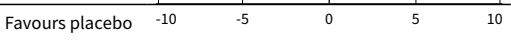
Analysis 6.5. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 5 BMI (kg/m²).

Study or subgroup	Zinc + Vitamin A N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.5.1 Baseline							
Karyadi 2002 IDN	40	17.6 (1.9)	40	18.1 (3.2)		10.22%	-0.5[-1.64,0.64]
Pakasi 2010 IDN	66	16.6 (2.1)	86	16.4 (2.5)		24.9%	0.2[-0.53,0.93]
Subtotal ***	**106**		**126**			**35.12%**	**-0[-0.62,0.61]**
Heterogeneity: Tau^2=0; Chi^2=1.02, df=1(P=0.31); I^2=2.17%							
Test for overall effect: Z=0.01(P=0.99)							
6.5.2 2 months							
Karyadi 2002 IDN	40	18.4 (1.9)	40	19 (3.2)		10.22%	-0.6[-1.74,0.54]
Pakasi 2010 IDN	57	17.7 (2)	82	17.5 (2.4)		24.74%	0.2[-0.53,0.93]
Subtotal ***	**97**		**122**			**34.96%**	**-0.03[-0.65,0.58]**
Heterogeneity: Tau^2=0; Chi^2=1.33, df=1(P=0.25); I^2=24.95%							
Test for overall effect: Z=0.11(P=0.91)							
6.5.3 6 months							
Karyadi 2002 IDN	40	19.4 (2.5)	40	20 (3.2)		8.48%	-0.6[-1.85,0.65]
Pakasi 2010 IDN	56	18.3 (2)	77	18.4 (2.6)		21.44%	-0.1[-0.89,0.69]
Subtotal ***	**96**		**117**			**29.92%**	**-0.24[-0.91,0.43]**
Heterogeneity: Tau^2=0; Chi^2=0.44, df=1(P=0.51); I^2=0%							
Test for overall effect: Z=0.71(P=0.48)							
Total ***	**299**		**365**			**100%**	**-0.09[-0.45,0.28]**
Heterogeneity: Tau^2=0; Chi^2=3.1, df=5(P=0.69); I^2=0%							
Test for overall effect: Z=0.46(P=0.65)							
Test for subgroup differences: Chi^2=0.3, df=1 (P=0.86), I^2=0%							



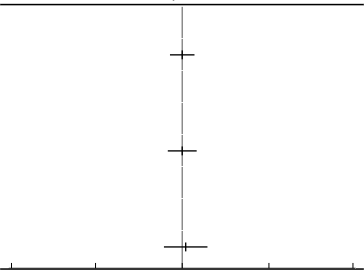
Analysis 6.6. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 6 Mid upper arm circumference (cm).

Study or subgroup	Zinc + Vitamin A N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.6.1 Baseline						
Karyadi 2002 IDN	40	22.8 (1.9)	40	21.8 (3.8)		1[-0.31,2.31]
6.6.2 2 months						
Karyadi 2002 IDN	40	23.4 (2.6)	40	22.8 (3.8)		0.6[-0.82,2.02]
6.6.3 6 months						
Karyadi 2002 IDN	40	25.2 (1.9)	40	24 (3.8)		1.2[-0.11,2.51]



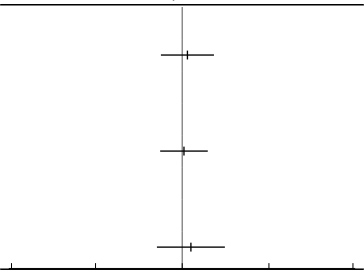
Analysis 6.7. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 7 Biceps skinfold thickness (mm).

Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.7.1 Baseline						
Karyadi 2002 IDN	40	4.2 (1.3)	40	4.2 (1.9)		0[-0.71,0.71]
6.7.2 2 months						
Karyadi 2002 IDN	40	4.9 (1.9)	40	4.9 (1.9)		0[-0.83,0.83]
6.7.3 6 months						
Karyadi 2002 IDN	40	5.7 (3.2)	40	5.5 (2.5)		0.2[-1.05,1.45]



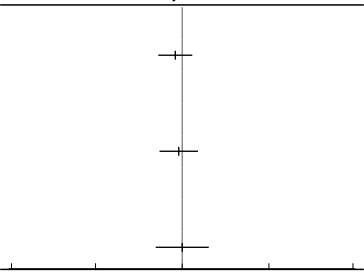
Analysis 6.8. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 8 Triceps skinfold thickness (mm).

Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.8.1 Baseline						
Karyadi 2002 IDN	40	5.8 (3.8)	40	5.5 (3.2)		0.3[-1.23,1.83]
6.8.2 2 months						
Karyadi 2002 IDN	40	6.7 (4.4)	40	6.6 (0.1)		0.1[-1.27,1.47]
6.8.3 6 months						
Karyadi 2002 IDN	40	8 (5.1)	40	7.5 (3.8)		0.5[-1.46,2.46]



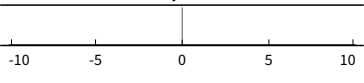
Analysis 6.9. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 9 Subscapular skinfold thickness (mm).

Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.9.1 Baseline						
Karyadi 2002 IDN	40	6.6 (1.9)	40	7 (2.5)		-0.4[-1.38,0.58]
6.9.2 2 months						
Karyadi 2002 IDN	40	7.5 (2.5)	40	7.7 (2.5)		-0.2[-1.31,0.91]
6.9.3 6 months						
Karyadi 2002 IDN	40	8.6 (3.8)	40	8.6 (3.2)		0[-1.53,1.53]



Analysis 6.10. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 10 Suprailiac skinfold thickness (mm).

Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.10.1 Baseline						



Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Karyadi 2002 IDN	40	5.2 (2.5)	40	5.7 (3.2)		-0.5[-1.75,0.75]
6.10.2 2 months						
Karyadi 2002 IDN	40	6.2 (3.2)	40	6.7 (3.2)		-0.5[-1.88,0.88]
6.10.3 6 months						
Karyadi 2002 IDN	40	7.2 (3.8)	40	7.8 (4.4)		-0.6[-2.41,1.21]

Favours placebo -10 -5 0 5 10 Favours Zinc + Vitamin A

Analysis 6.11. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 11 Body fat (%).

Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.11.1 Baseline						
Karyadi 2002 IDN	40	11.5 (6.3)	40	13 (6.3)		-1.5[-4.27,1.27]
Pakasi 2010 IDN	66	10.8 (4.7)	86	11.9 (5.9)		-1.1[-2.79,0.59]
6.11.2 2 months						
Karyadi 2002 IDN	40	13.1 (7)	40	14.6 (6.3)		-1.5[-4.41,1.41]
Pakasi 2010 IDN	57	12.9 (5.1)	82	14.2 (6.1)		-1.3[-3.17,0.57]
6.11.3 6 months						
Karyadi 2002 IDN	40	14.2 (7.5)	40	16 (6.3)		-1.8[-4.84,1.24]
Pakasi 2010 IDN	56	14.2 (6.4)	77	16 (6.3)		-1.8[-4,0.4]

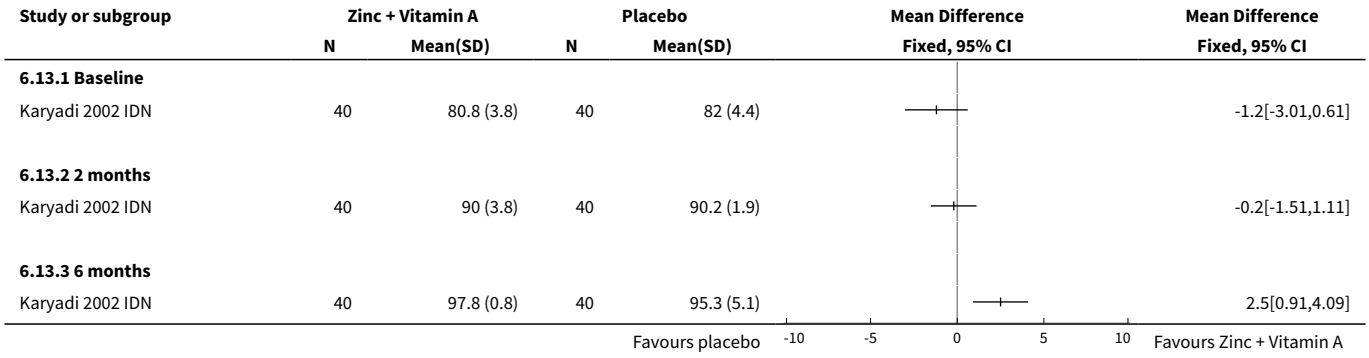
Favours placebo -10 -5 0 5 10 Favours Zinc + Vitamin A

Analysis 6.12. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 12 Fat mass (kg).

Study or subgroup	Zinc + Vitamin A N	Zinc + Vitamin A Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.12.1 Baseline						
Karyadi 2002 IDN	40	5.1 (3.2)	40	5.7 (3.2)		-0.6[-1.98,0.78]
6.12.2 2 months						
Karyadi 2002 IDN	40	6.1 (3.2)	40	6.7 (3.2)		-0.6[-1.98,0.78]
6.12.3 6 months						
Karyadi 2002 IDN	40	6.9 (3.2)	40	7.7 (3.2)		-0.8[-2.18,0.58]

Favours placebo -10 -5 0 5 10 Favours Zinc + Vitamin A

Analysis 6.13. Comparison 6 Zinc plus vitamin A versus placebo, Outcome 13 Karnofsky score.



Comparison 7. Vitamin D versus placebo or no supplement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum vitamin D levels (nmol/L)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 At baseline	5	894	Mean Difference (IV, Random, 95% CI)	-0.10 [-3.01, 2.82]
1.2 At 8 weeks	3	460	Mean Difference (IV, Random, 95% CI)	33.68 [3.99, 63.37]
1.3 At 6 to 8 months	2	376	Mean Difference (IV, Random, 95% CI)	7.90 [0.52, 15.28]
2 Death during follow-up (2 to 12 months)	7	2649	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.12]
2.1 Vitamin D alone	4	814	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.79, 2.02]
2.2 Vitamin D plus arginine	1	75	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.06, 36.25]
2.3 Vitamin D as part of a multi-micronutrient supplement	3	1760	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
3 Death during follow-up (2 to 12 months)	7	2649	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.13]
3.1 HIV-positive individuals	3	1089	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.09]
3.2 HIV-negative individuals	6	1403	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.72, 2.21]
3.3 HIV status mixed or unknown	2	157	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.30, 7.38]
4 Cure at 6 months	1	151	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.31]
5 Tuberculosis score	1	1142	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.32, 0.06]

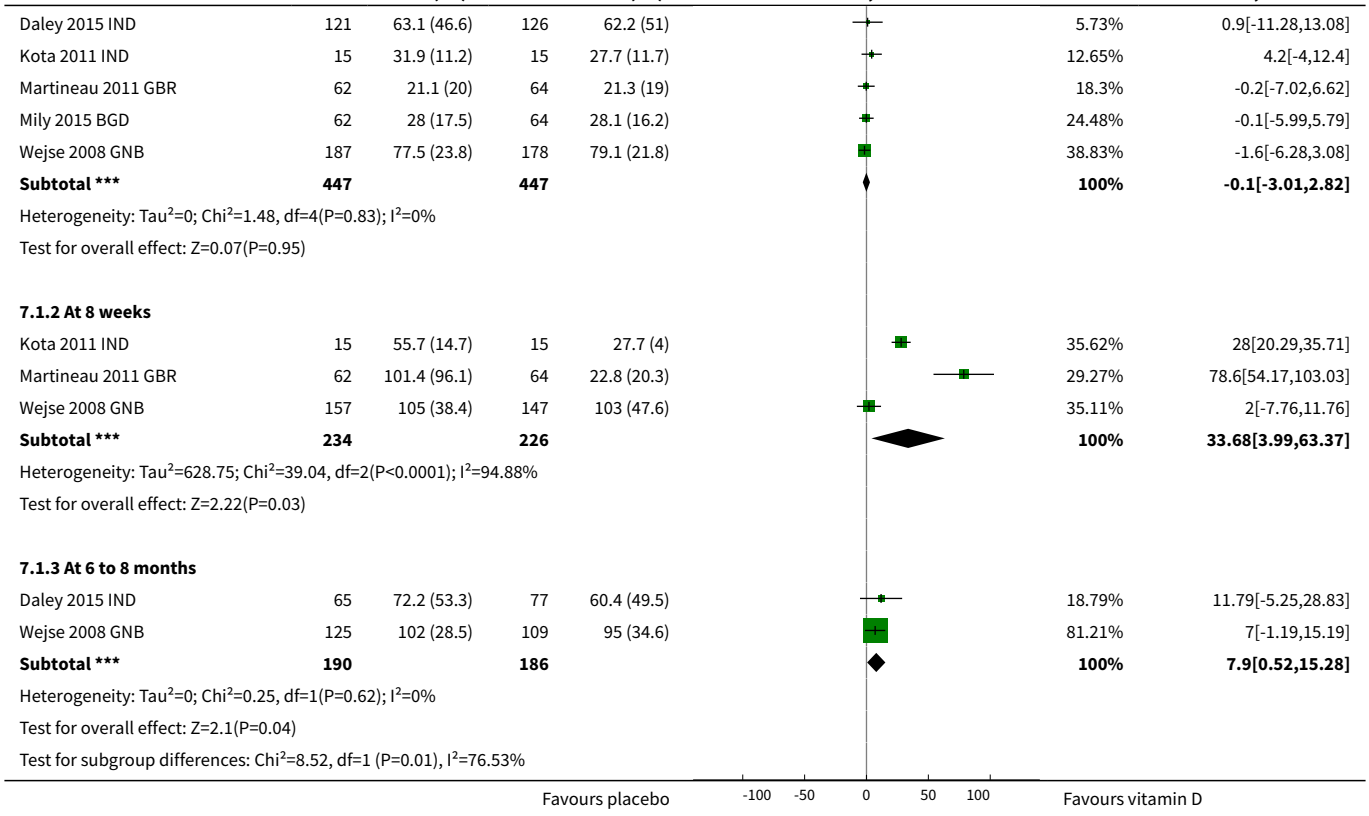
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 At baseline	1	348	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.52, 0.31]
5.2 2 months	1	297	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.47, 0.42]
5.3 5 months	1	271	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.51, 0.19]
5.4 8 months	1	226	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.52, 0.14]
6 Sputum-smear or sputum-culture positive	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 At baseline	5	1022	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.92, 1.03]
6.2 4 weeks	5	929	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.74, 1.03]
6.3 6 weeks	4	656	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.03]
6.4 8 weeks	6	856	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.20]
6.5 5 months	1	148	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 28.18]
6.6 6 months	1	247	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.37, 1.47]
6.7 8 months	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Body mass index	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 At baseline	4	464	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.71, 0.30]
7.2 At 6 to 8 weeks	4	430	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.70, 0.32]
8 Body weight (kg)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Before treatment	2	150	Mean Difference (IV, Fixed, 95% CI)	0.20 [-2.43, 2.83]
8.2 At 8 weeks	2	150	Mean Difference (IV, Fixed, 95% CI)	1.08 [-1.61, 3.77]
9 Karnofsky score at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 At baseline	1	247	Mean Difference (IV, Fixed, 95% CI)	-1.47 [-3.42, 0.48]
9.2 At 8 weeks	1	212	Mean Difference (IV, Fixed, 95% CI)	0.85 [-1.33, 3.03]

Analysis 7.1. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 1 Serum vitamin D levels (nmol/L).

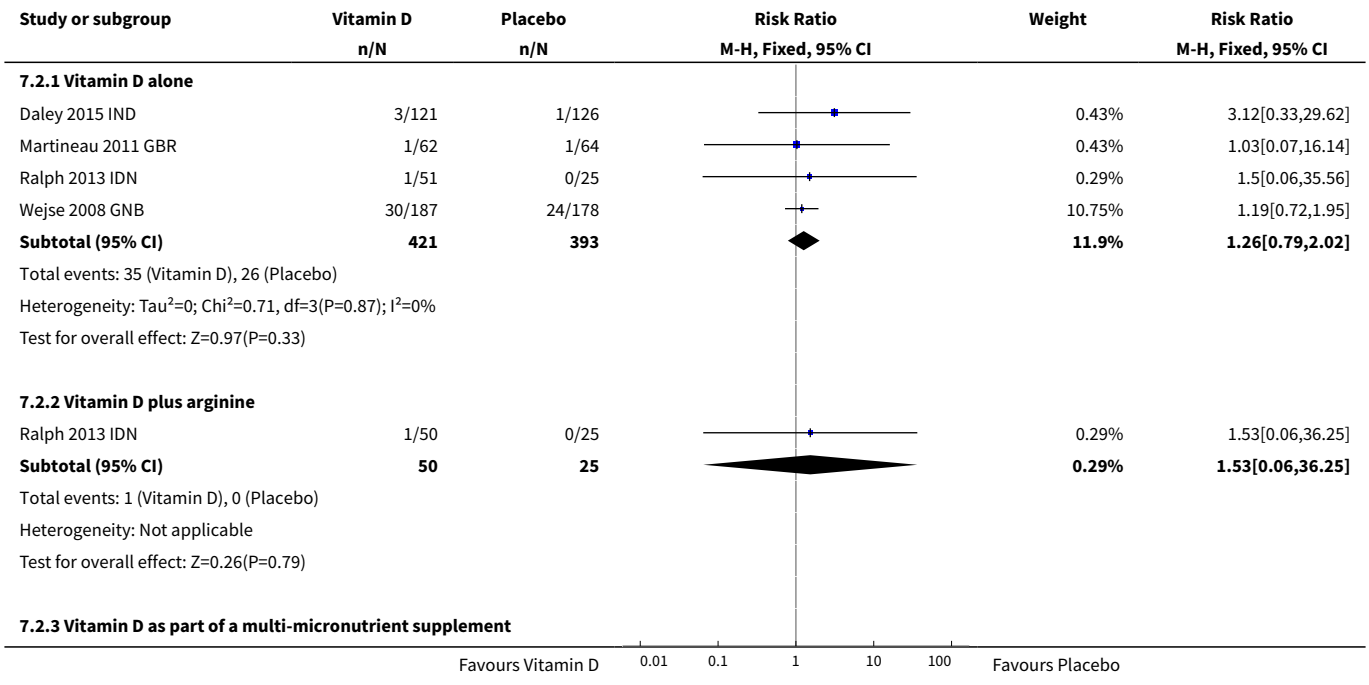
Study or subgroup	Vitamin D N	Vitamin D Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
7.1.1 At baseline							

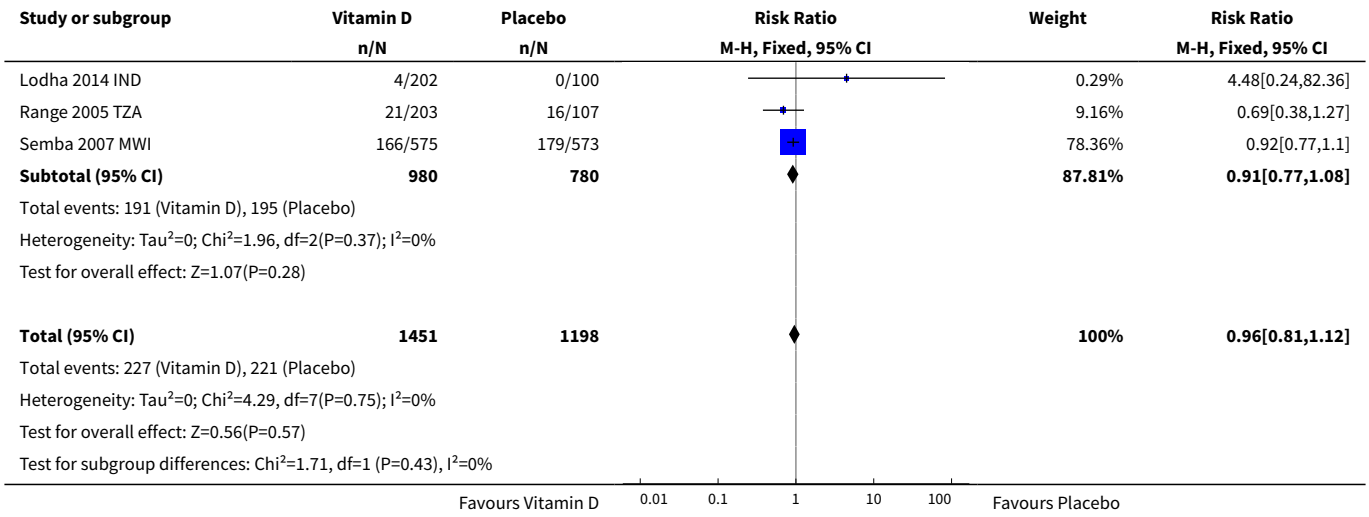
Favours placebo

Favours vitamin D

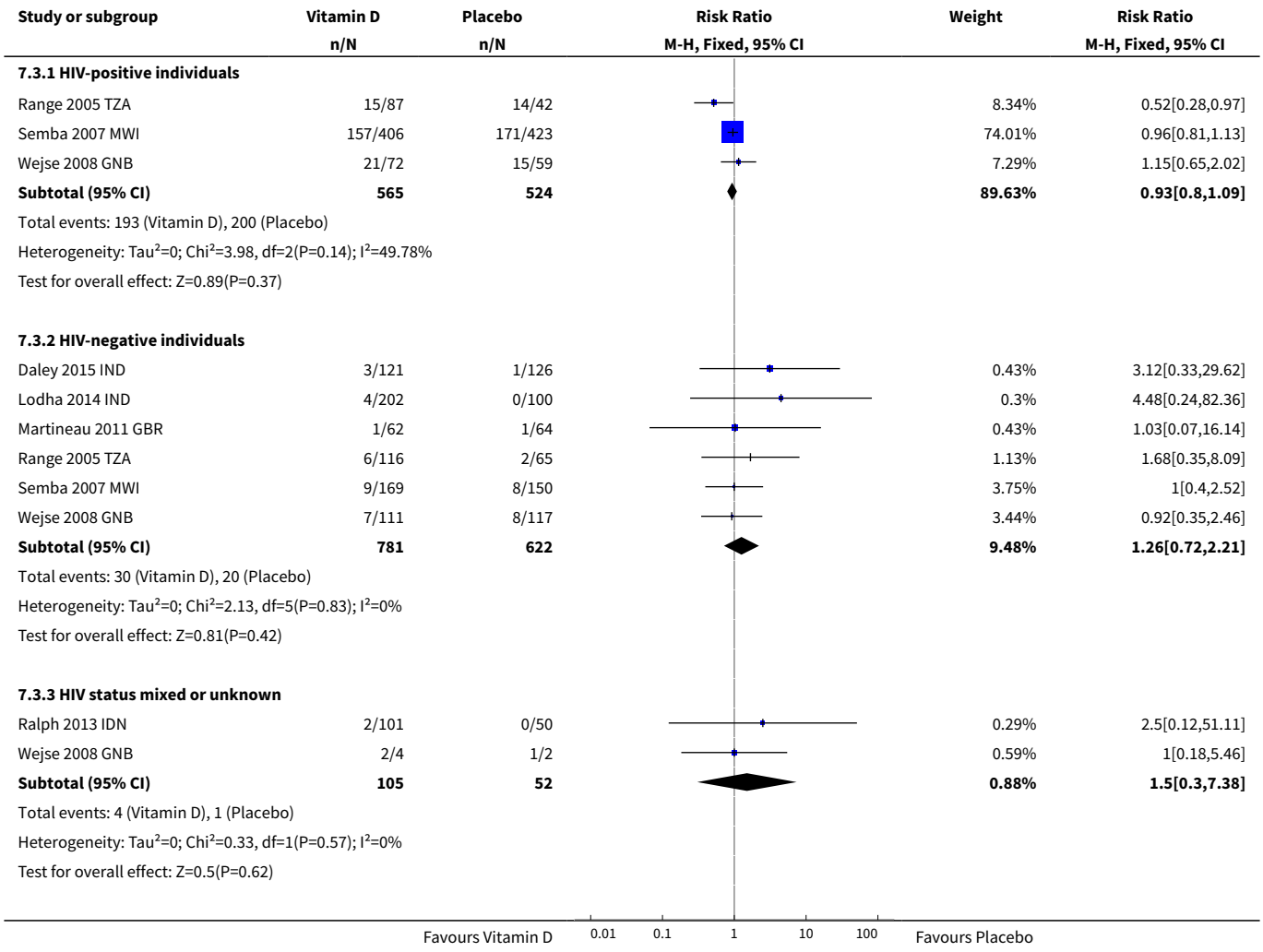


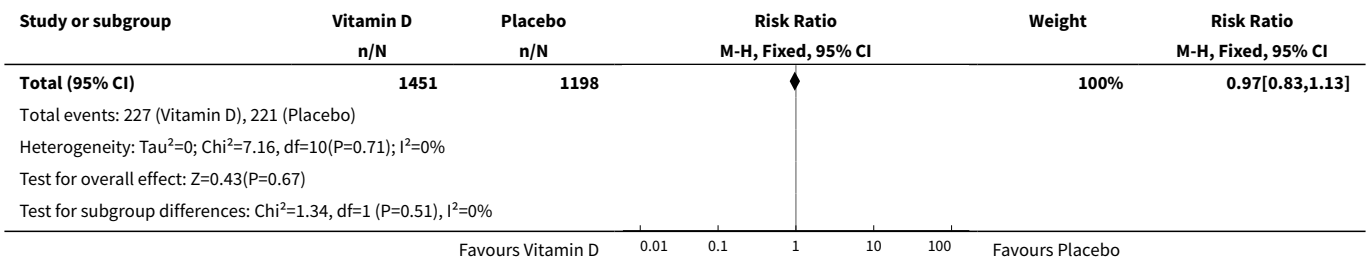
Analysis 7.2. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 2 Death during follow-up (2 to 12 months).



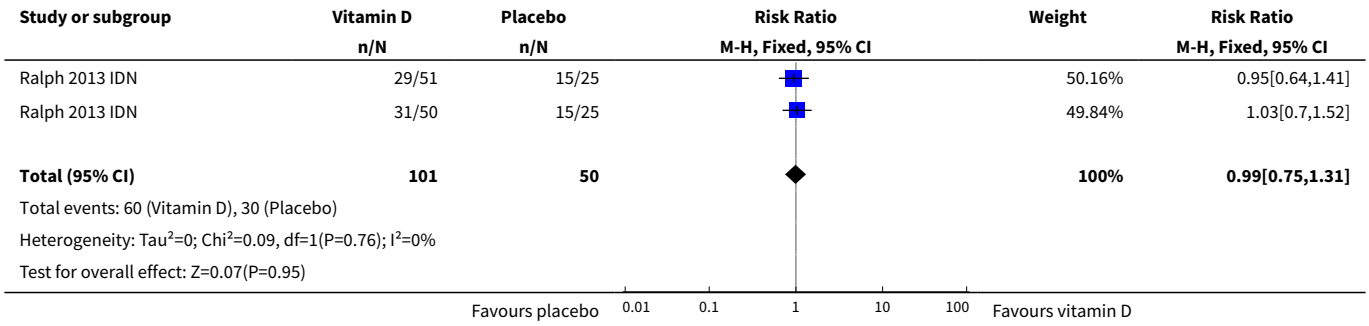


Analysis 7.3. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 3 Death during follow-up (2 to 12 months).

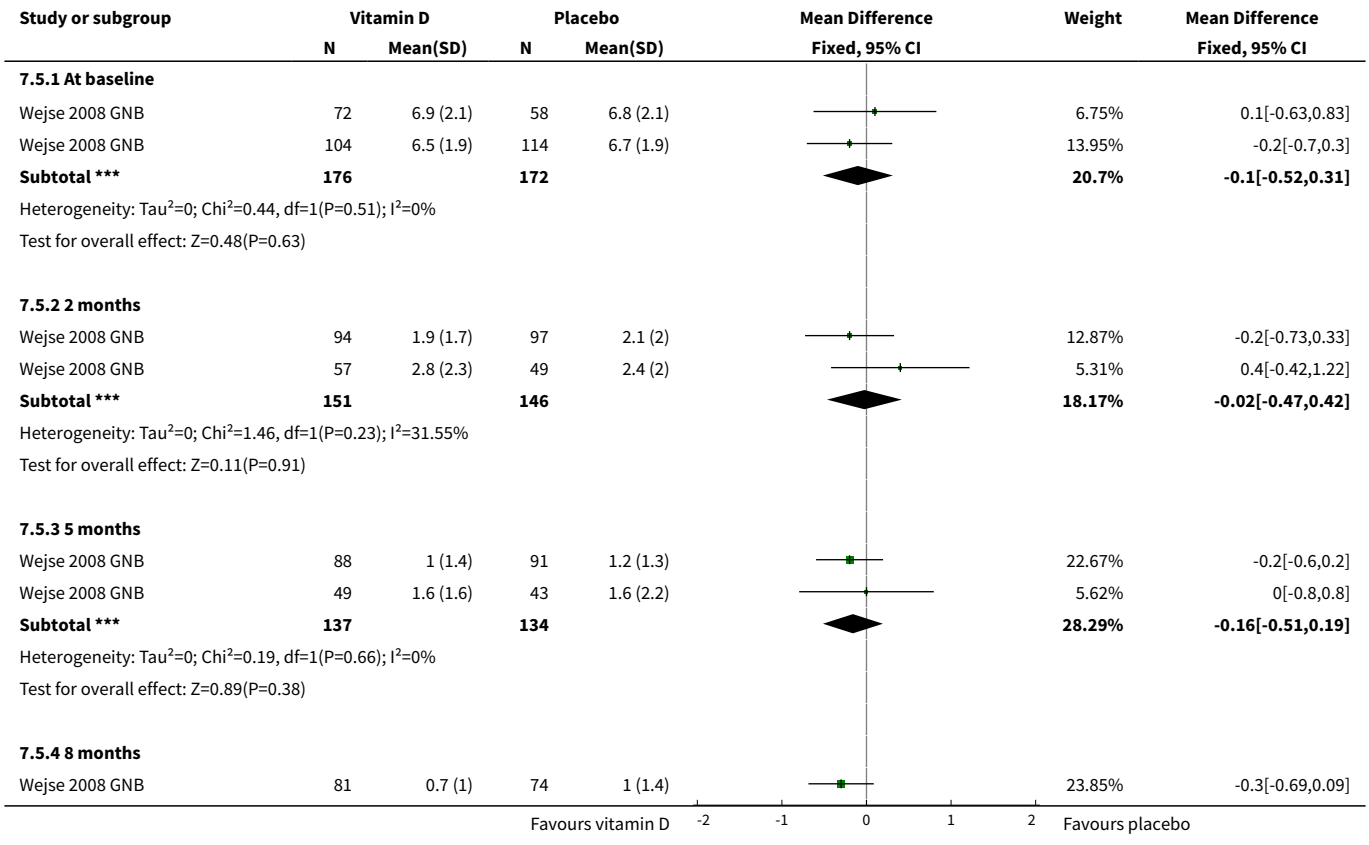


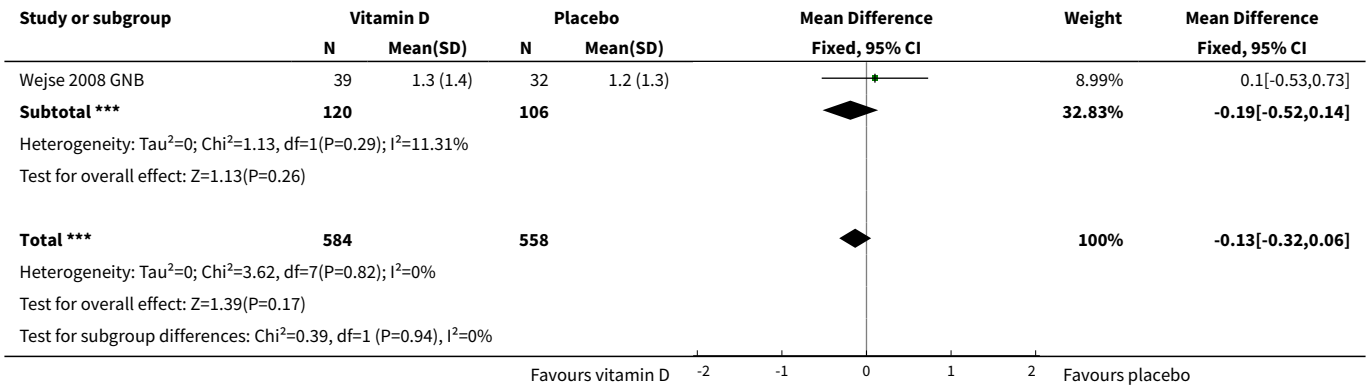


Analysis 7.4. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 4 Cure at 6 months.

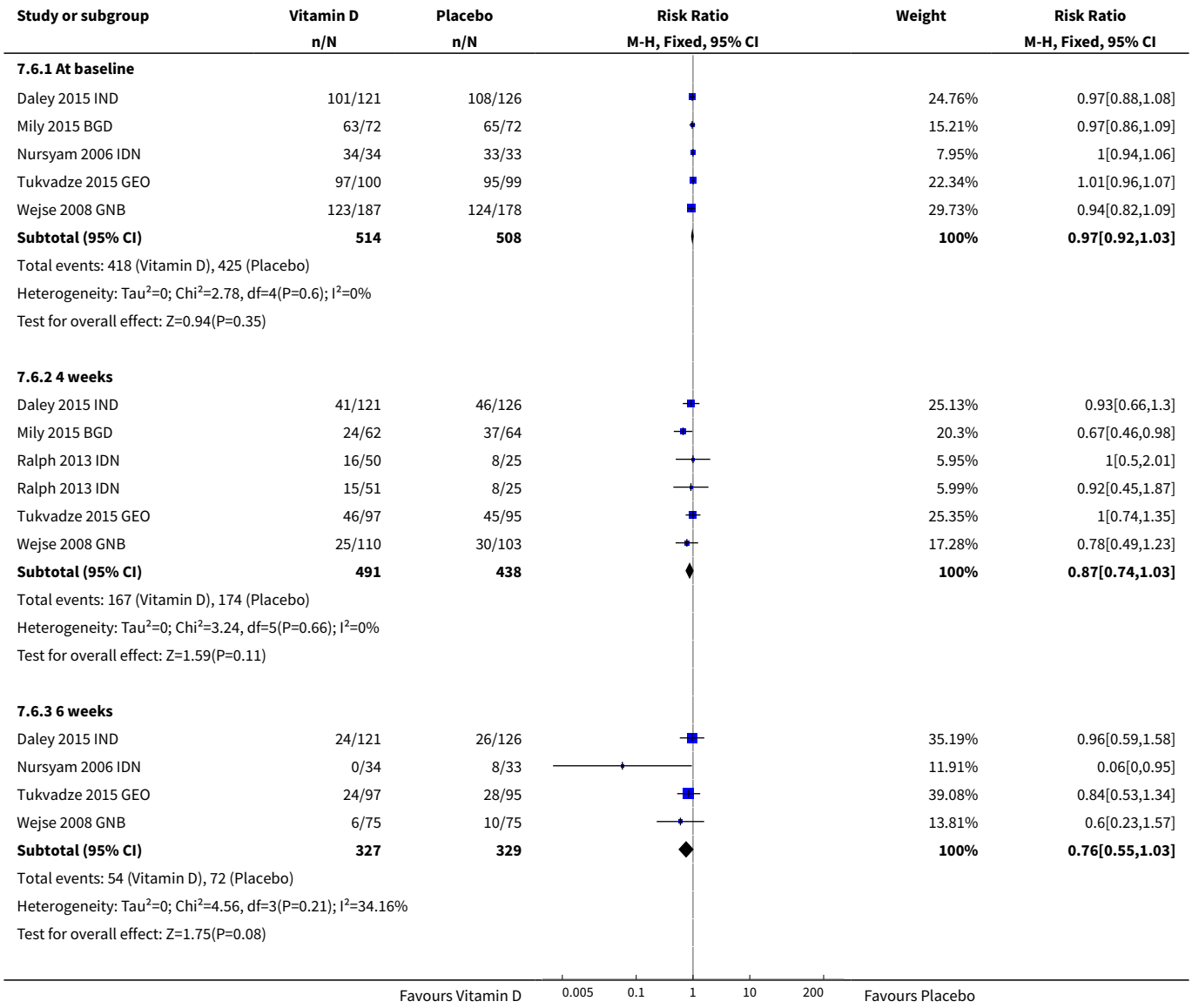


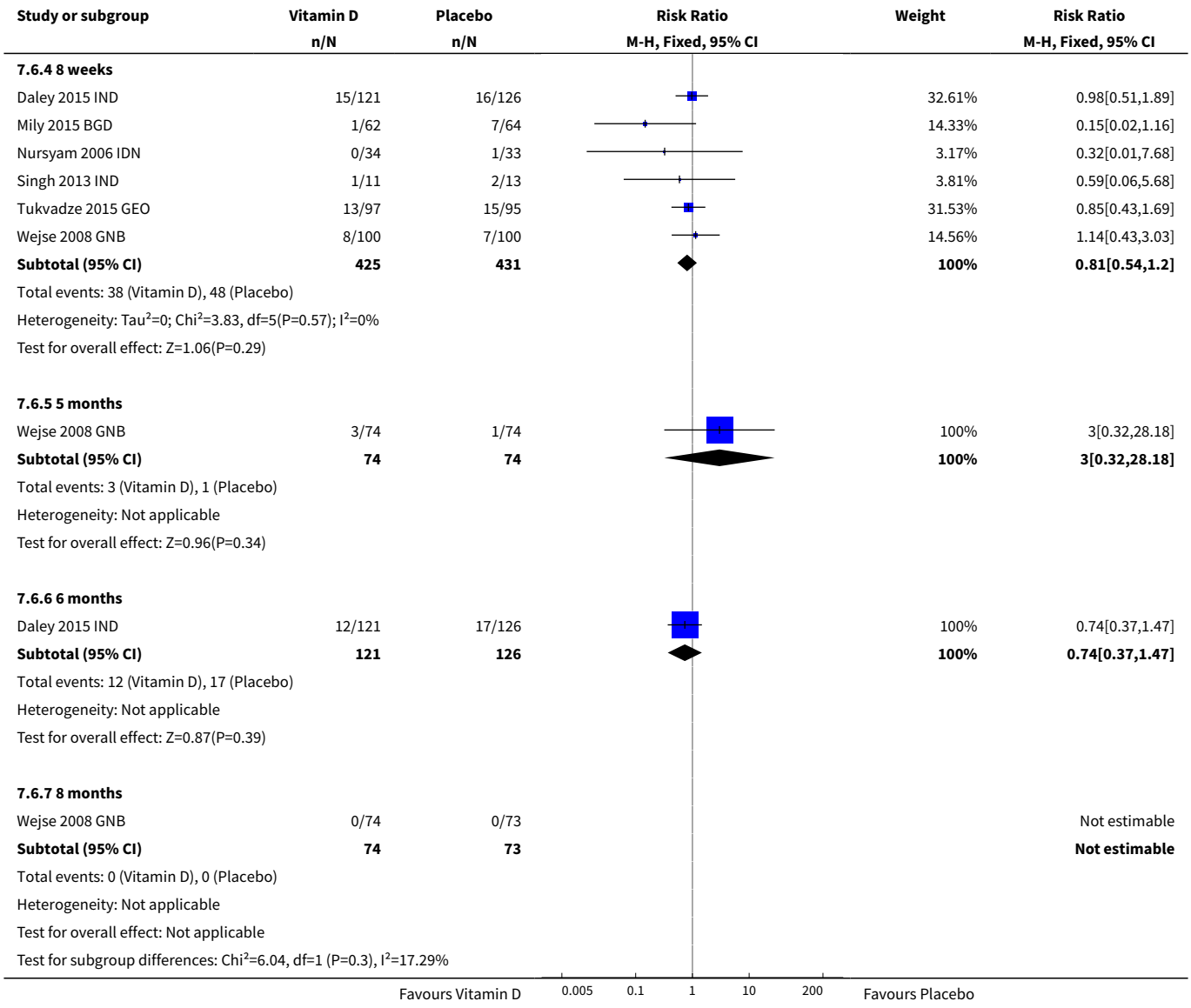
Analysis 7.5. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 5 Tuberculosis score.



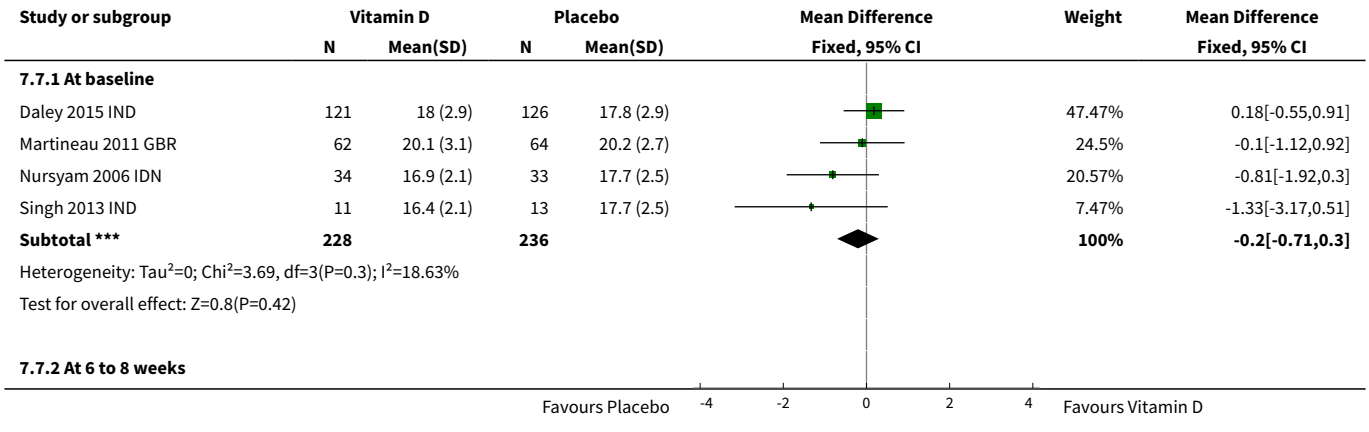


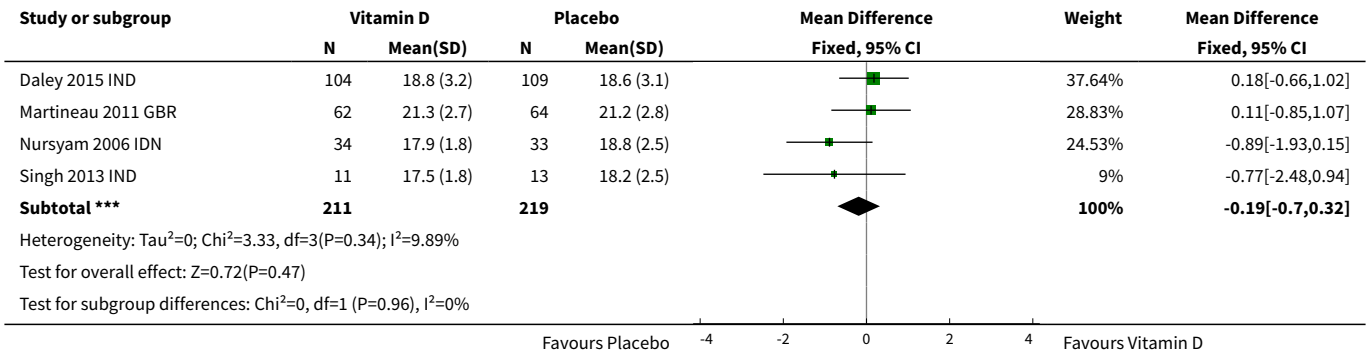
Analysis 7.6. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 6 Sputum-smear or sputum-culture positive.



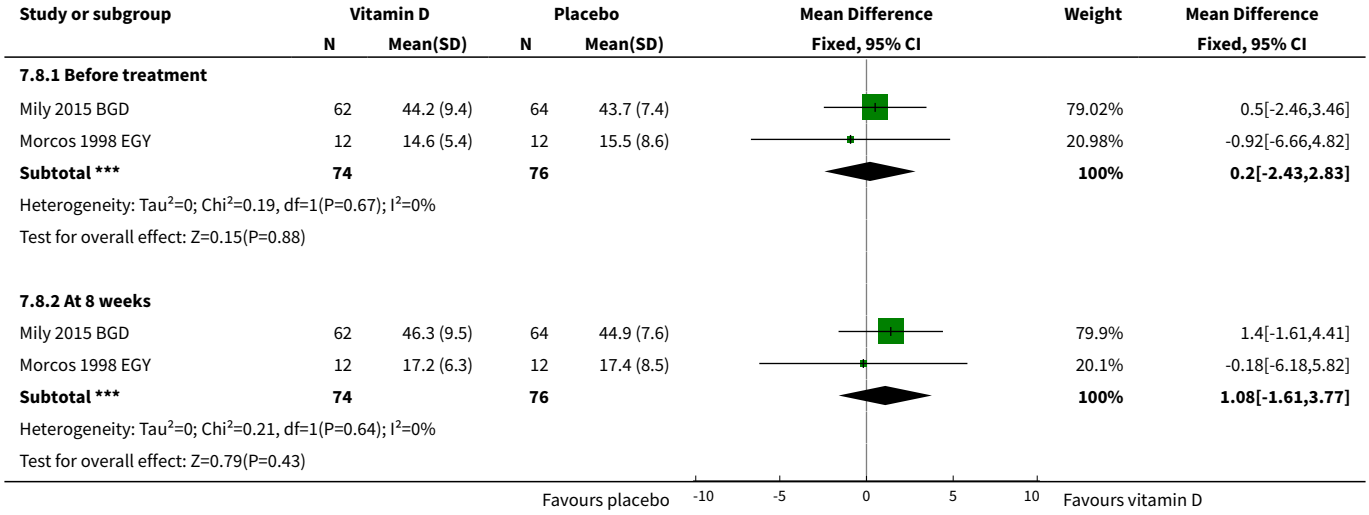


Analysis 7.7. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 7 Body mass index.

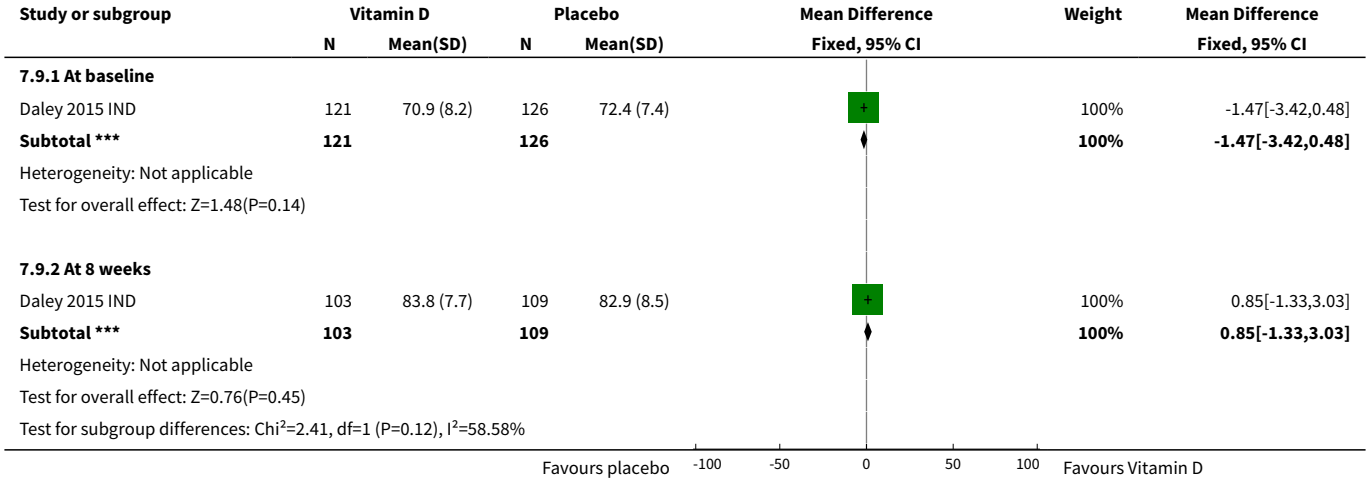




Analysis 7.8. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 8 Body weight (kg).



Analysis 7.9. Comparison 7 Vitamin D versus placebo or no supplement, Outcome 9 Karnofsky score at 8 weeks.

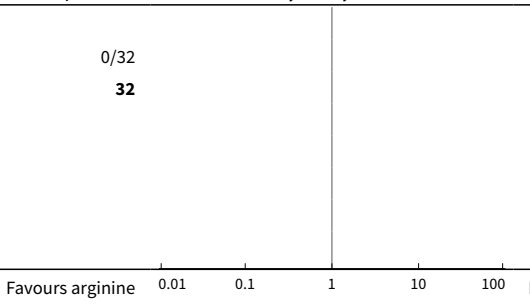


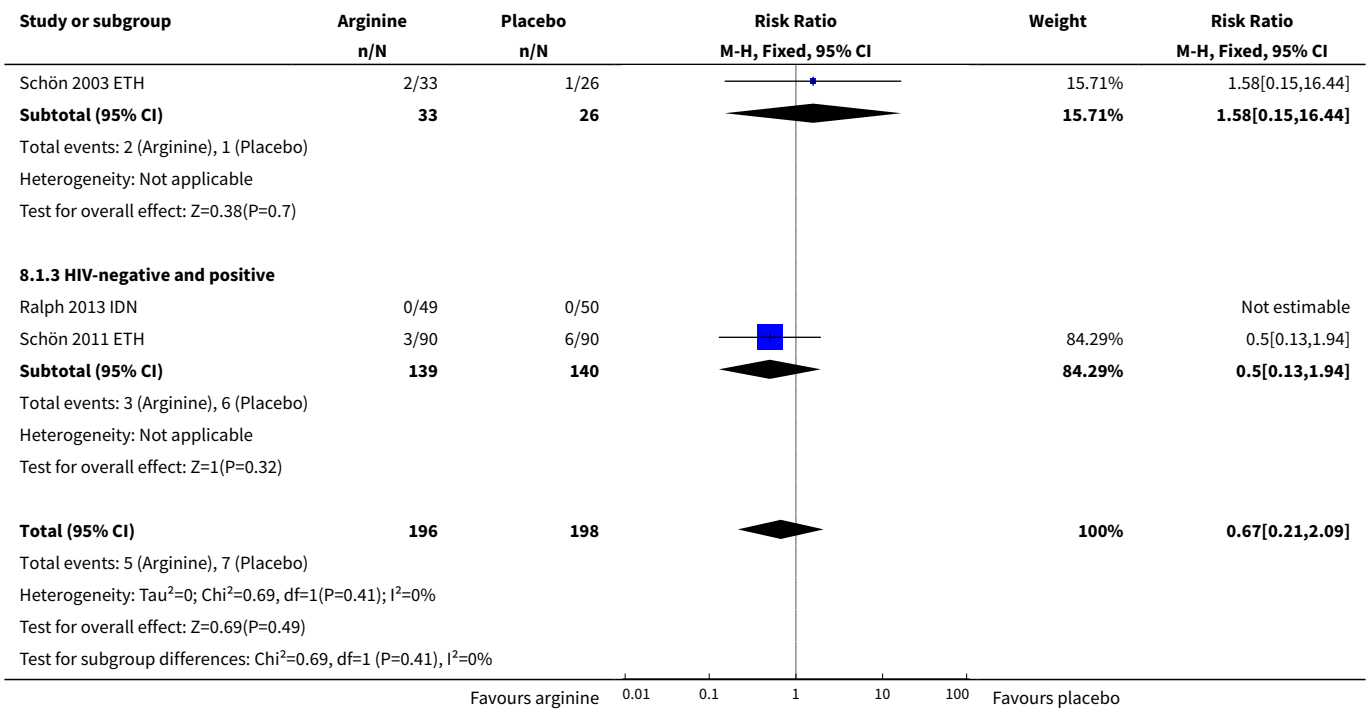
Comparison 8. Arginine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death during treatment	3	394	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.21, 2.09]
1.1 HIV-negative	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 HIV-positive	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.15, 16.44]
1.3 HIV-negative and positive	2	279	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.13, 1.94]
2 Cured at 6/8 months	2	279	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.90, 1.22]
3 Sputum-smear or sputum-culture positive	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 At baseline	4	464	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.98, 1.02]
3.2 At 4 weeks	2	162	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.12]
3.3 At 8 weeks	3	351	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.41, 1.42]
3.4 At 8 weeks (HIV-negative only)	1	56	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.07]
4 Cough	3	404	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.93]
4.1 At 2 weeks	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.53, 0.96]
4.2 At 8 weeks	3	348	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 0.99]
5 Weight gain > 10%	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 HIV-positive and HIV-negative	1	170	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.74, 1.84]
5.2 HIV-positive	1	65	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.96, 4.78]

Analysis 8.1. Comparison 8 Arginine versus placebo, Outcome 1 Death during treatment.

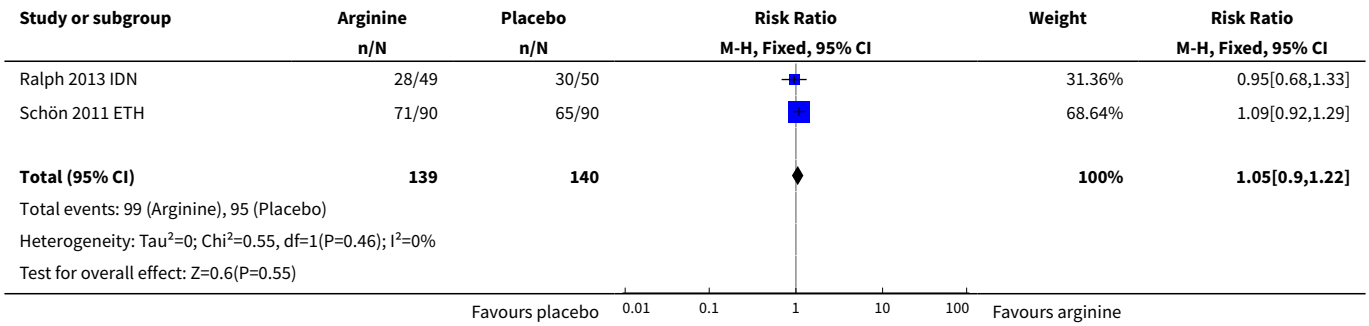
Study or subgroup	Arginine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 HIV-negative					
Schön 2003 ETH	0/24	0/32			Not estimable
Subtotal (95% CI)	**24**	**32**			**Not estimable**
Total events: 0 (Arginine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
8.1.2 HIV-positive					





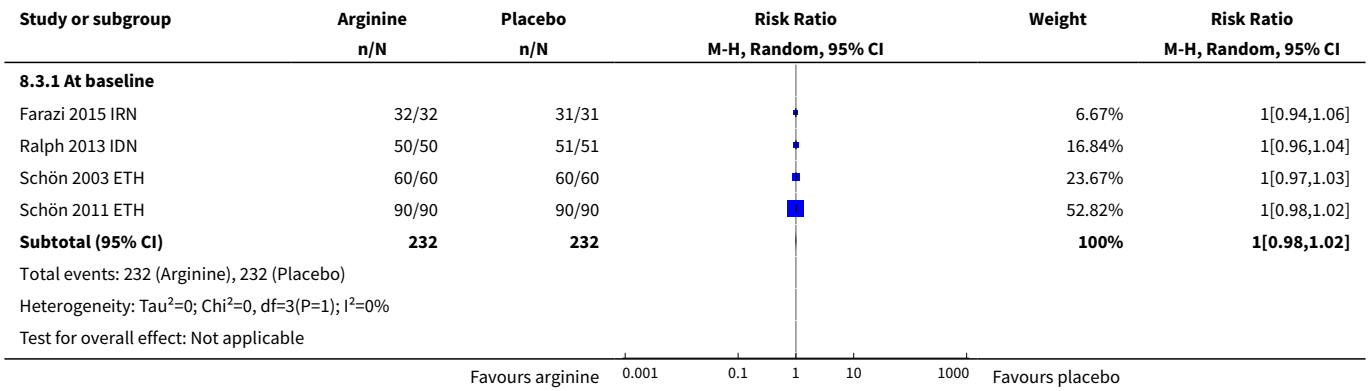
Study or subgroup	Arginine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schön 2003 ETH	2/33	1/26		15.71%	1.58[0.15,16.44]
Subtotal (95% CI)	**33**	**26**		**15.71%**	**1.58[0.15,16.44]**
Total events: 2 (Arginine), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.7)					
8.1.3 HIV-negative and positive					
Ralph 2013 IDN	0/49	0/50			Not estimable
Schön 2011 ETH	3/90	6/90		84.29%	0.5[0.13,1.94]
Subtotal (95% CI)	**139**	**140**		**84.29%**	**0.5[0.13,1.94]**
Total events: 3 (Arginine), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**196**	**198**		**100%**	**0.67[0.21,2.09]**
Total events: 5 (Arginine), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					
Test for subgroup differences: Chi^2=0.69, df=1 (P=0.41), I^2=0%					

Analysis 8.2. Comparison 8 Arginine versus placebo, Outcome 2 Cured at 6/8 months.

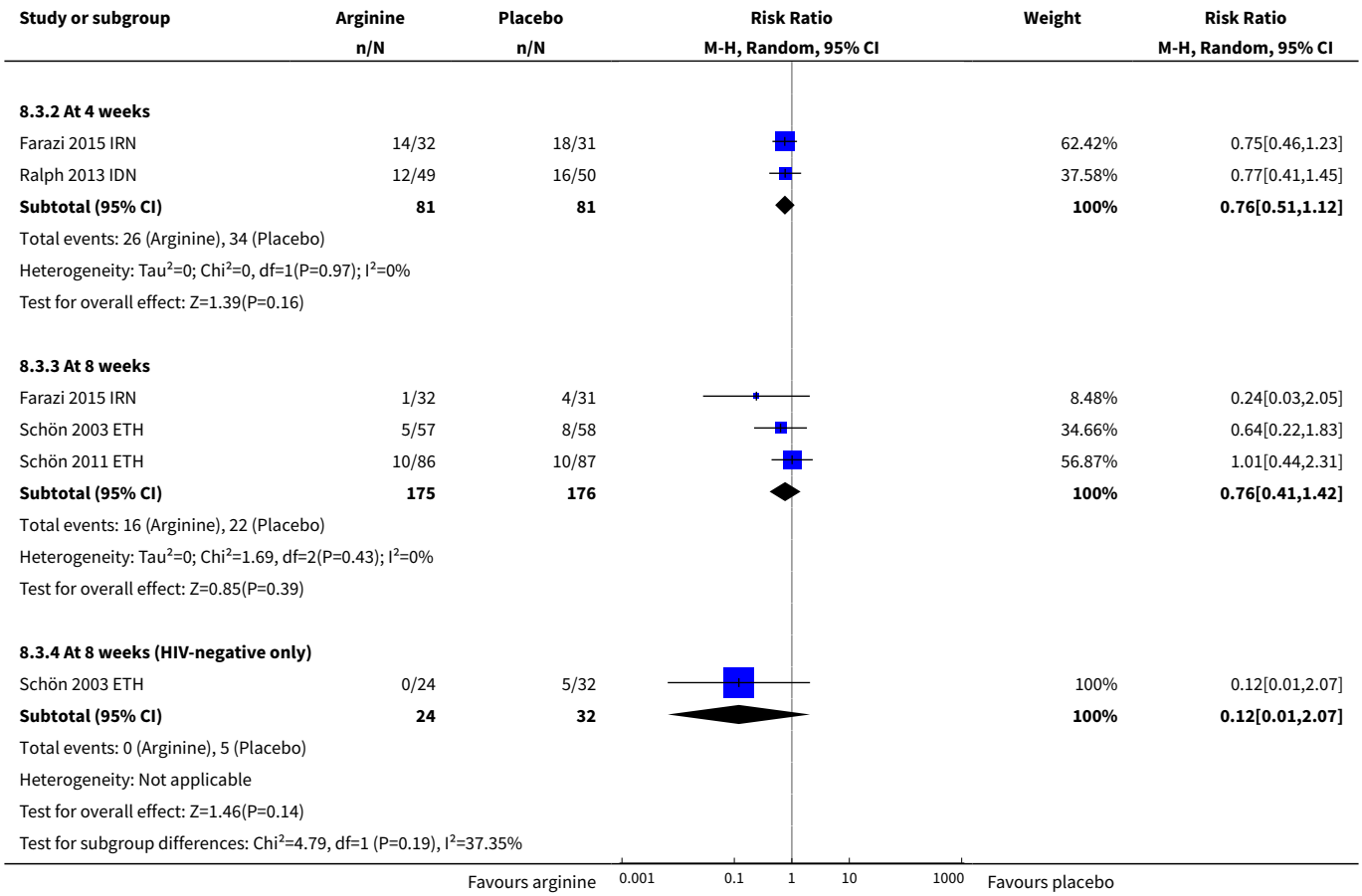


Study or subgroup	Arginine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ralph 2013 IDN	28/49	30/50		31.36%	0.95[0.68,1.33]
Schön 2011 ETH	71/90	65/90		68.64%	1.09[0.92,1.29]
Total (95% CI)	**139**	**140**		**100%**	**1.05[0.9,1.22]**
Total events: 99 (Arginine), 95 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					

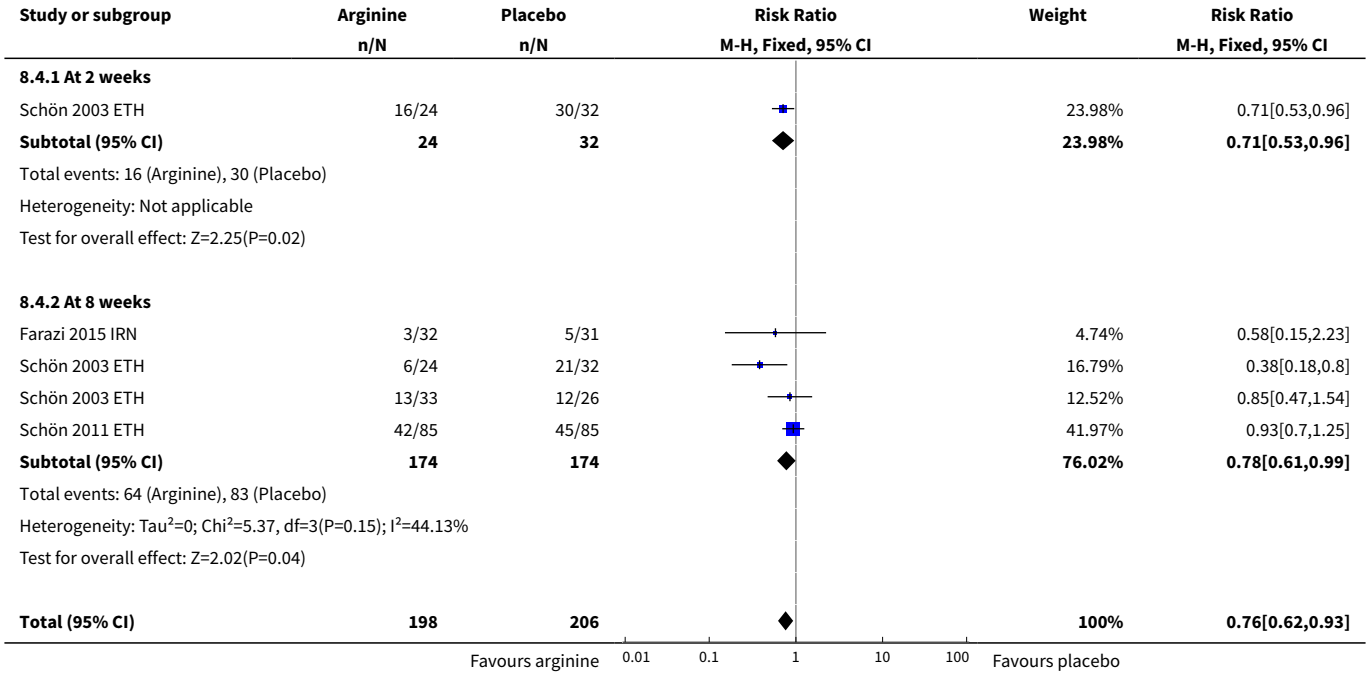
Analysis 8.3. Comparison 8 Arginine versus placebo, Outcome 3 Sputum-smear or sputum-culture positive.

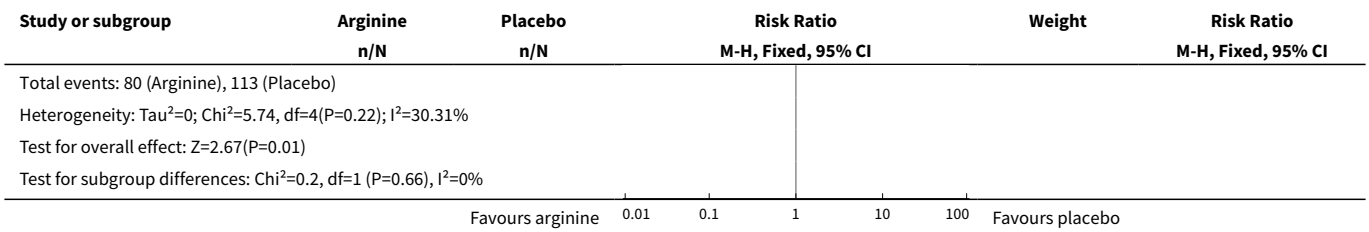


Study or subgroup	Arginine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 At baseline					
Farazi 2015 IRN	32/32	31/31		6.67%	1[0.94,1.06]
Ralph 2013 IDN	50/50	51/51		16.84%	1[0.96,1.04]
Schön 2003 ETH	60/60	60/60		23.67%	1[0.97,1.03]
Schön 2011 ETH	90/90	90/90		52.82%	1[0.98,1.02]
Subtotal (95% CI)	**232**	**232**		**100%**	**1[0.98,1.02]**
Total events: 232 (Arginine), 232 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=3(P=1); I^2=0%					
Test for overall effect: Not applicable					

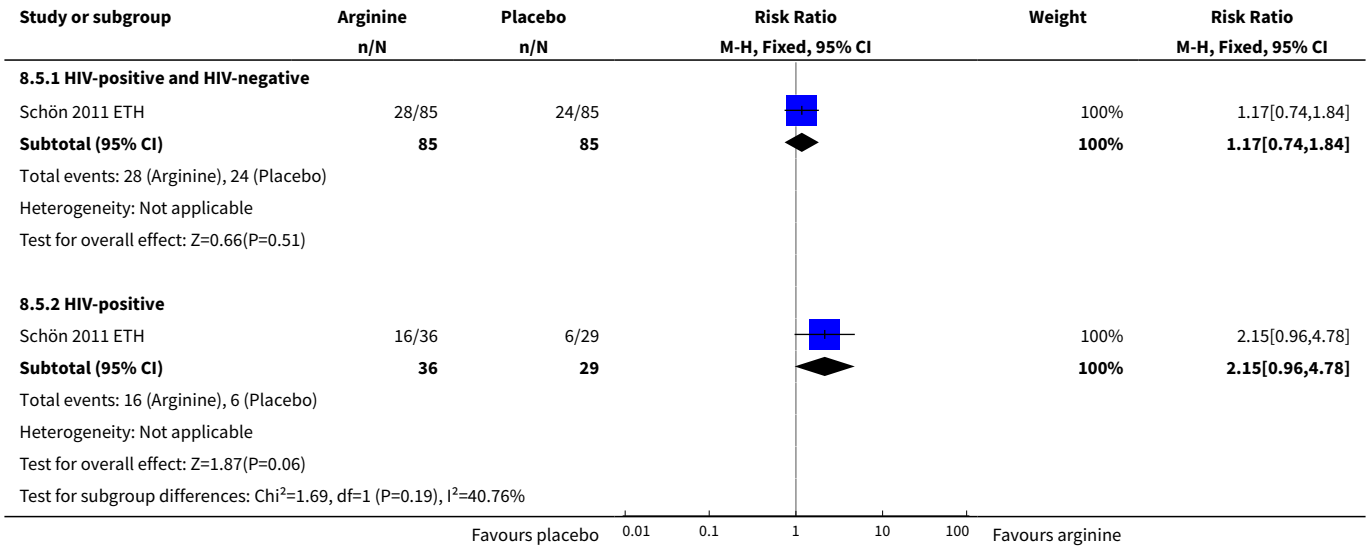


Analysis 8.4. Comparison 8 Arginine versus placebo, Outcome 4 Cough.





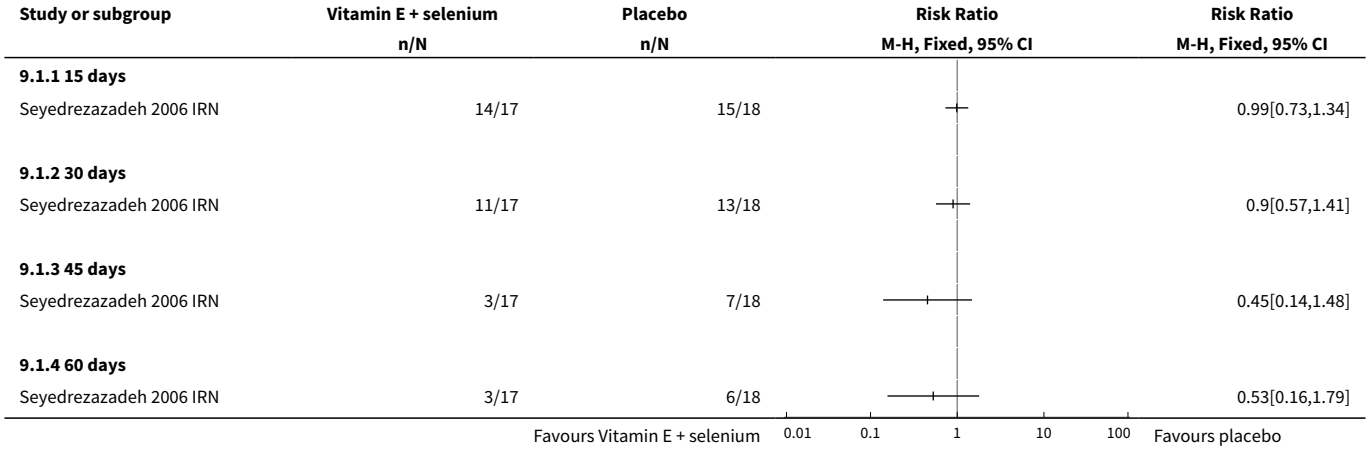
Analysis 8.5. Comparison 8 Arginine versus placebo, Outcome 5 Weight gain > 10%.



Comparison 9. Vitamin E plus selenium versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sputum-smear positive at follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 15 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 30 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 45 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 60 days	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Vitamin E plus selenium versus placebo, Outcome 1 Sputum-smear positive at follow-up.



ADDITIONAL TABLES

Table 1. Effect of multi-micronutrient supplementation on nutritional recovery

Trial ID	Population	Weight measurement	Baseline nutritional status		Duration of supplement and follow-up	Comment
			Supplement	Placebo		
Mehta 2011 TZA	HIV-positive and HIV-negative children	Weight gain median (IQR)	MUAC (cm) 13.0 (11.9 to 14.25) Weight: 8.48kg (NR)	MUAC (cm) 13.0 (11.2 to 14.0) Weight kg: 7.95 kg (NR)	Supplement and follow-up 2 months	The trial authors reported no effect of supplement on median weight, height, or mid-upper arm circumference at 2 months
Lodha 2014 IND	HIV-negative children	Change in weight-for-age z score	Weight-for-age z score (SD): −2.72 (1.85, MN+Z group); −2.8 (1.6, MN group)	Weight-for-age z score (SD): −2.8 (1.6)	Supplement and follow-up 6 months	The trial authors reported no difference in weight (kg), weight-for-age z score, height-for-age z score, or BMI z score after 2 or 6 months supplementation with micronutrients with or without zinc (1 trial, 302 participants, Analysis 3.7)
Praygod 2011a TZA [1]	HIV-positive and negative adults	Mean weight gain (SD)	Mean BMI (SD): 18.9 kg/m^2 (2.8)	mean BMI (SD): 18.9 kg/m^2 (3.1)	Supplement for 2 months Follow-up at 2 and 5 months	There was no statistically significant difference in weight gain at 2 or 5 months. Subgroup analysis by HIV status found a statistically significant difference in weight gain in favour of supplements in HIV-negative participants, and in favour of placebo in HIV-positive participants (trial authors' own figures)
Villamor 2008 TZA	HIV-positive and	Mean BMI (SD)	HIV-negative mean BMI	HIV-negative mean	Supplement for	The trial authors reported no statistically significant effect of supplement on BMI,

Table 1. Effect of multi-micronutrient supplementation on nutritional recovery *(Continued)*

	negative adults		(SD): 18.9 kg/m^2 (2.5) HIV-positive mean BMI (SD): 19.3 kg/m^2 (2.8)	BMI (SD): 18.9 kg/m^2 (2.5) HIV-positive mean BMI (SD): 19.6 kg/m^2 (2.9)	24 months and follow-up at 8 and 24 months	mid-upper arm circumference, fat mass, or fat free mass at 8 or 24 months, regardless of HIV status (no figures reported)
Range 2005 TZA [2]	HIV-positive and negative adults	Mean weight gain (SD)	Mean BMI (SD): 18.3 kg/m^2 (2.5) zinc + MMN group	Mean BMI (SD): 18.7 kg/m^2 (2.7)	Supplement for 8 months and follow-up 8 weeks and 7 months	There was a statistically significantly greater weight gain in supplemented group at 7 months. While the difference in weight was appreciable in both treatment (zinc + MMN and MMN groups) arms compared to placebo, the weight gain in the zinc + MMN arm appeared to be clinically important

Abbreviations: SD = standard deviation; BMI = body mass index; MMN = multi-micronutrient; HIV = human immunodeficiency virus; IQR = interquartile range; MUAC = mid-upper arm circumference; NR = not reported;

[1]The supplement administered by Praygod 2011a TZA included a similar dose of zinc to that used by Range 2005 TZA.

[2]2 X 2 factorial design; Group 1: zinc plus placebo; Group 2: multivitamin and mineral tablet plus placebo; Group 3: zinc plus multivitamin and mineral tablet; Group 4: placebo plus placebo.

Table 2. Effects of vitamin A supplementation on serum vitamin A levels

Trial ID	Supplement dose	Measure	Baseline		Follow-up		Follow-up	Comment
			Supplement	Control	Supplement	Control		
Hanekom 1997 ZAF	200 000 IU vitamin A 2 doses at baseline	Mean µg/L (SD)	17.6 (10.1)	18.6 (10.5)	34.8 (10.1)	33.5 (14.2)	6 weeks	No statistically significant difference in serum vitamin A levels at 6 weeks or 2 months
Ginawi 2013 IND	5000 IU vitamin A daily	Mean µmol/L (SD)	0.77 (0.21)	0.82 (0.29)	1.2 (0.27)	1.13 (0.34)	2 months	No statistically significant difference in serum vitamin A levels at 2 or 6 months
Pakasi 2010 IDN	5000 IU vitamin A daily for 6 months	Median µmol/L (IQR)	0.7 (0.5 to 1.5)	0.7 (0.5 to 1.0)	1.5 (1.0 to 2.0)	1.2 (0.9 to 1.6)	2 months	No statistically significant difference at 2 or 6 months
Armijos 2010 MEX	5000 IU vitamin A plus 50 mg zinc daily for 4 months	Mean µmol/L (SD)	1.03 (0.46)	1.04 (0.48)	1.4 (0.47)	1.29 (0.35)	2 months	No statistically significant difference in serum vitamin A levels at 2 or 6 months
Karyadi 2002 IDN	5000 IU vitamin A plus 15 mg zinc daily for 6 months	Mean µmol/L (SD)	0.82 (0.25)	0.9 (0.25)	1.14 (0.32)	1.08 (0.25)	2 months	No statistically significant difference in serum vitamin A levels at 2 or 6 months
Ginawi 2013 IND	5000 IU vitamin A plus 15 mg zinc sulphate daily	Mean µmol/L (SD)	0.78 (0.23)	0.82 (0.29)	1.14 (0.25)	1.13 (0.34)	2 months	No statistically significant difference in serum vitamin A levels at 2 or 6 months
Pakasi 2010 IDN	5000 IU vitamin A plus 15 mg zinc sulphate daily for 6 months	Median µmol/L (IQR)	0.7 (0.4 to 1.1)	0.7 (0.5 to 1.0)	1.3 (1.0 to 1.9)	1.2 (0.9 to 1.6)	2 months	No statistically significant difference in serum vitamin A levels at 2 or 6 months
Visser 2011 ZAF	200,000 IU vitamin A once plus 15 mg zinc sulphate 5 days per week for 8 weeks	Median µd/dL (IQR)	21.1 (15.1 to 27.8)	21.2 (15.7 to 28.9)	40.3 (28.7 to 48.5)	35.8 (27.7 to 43.2)	2 months	No statistically significant difference in serum vitamin A levels at 2 or 8 weeks

Table 2. Effects of vitamin A supplementation on serum vitamin A levels *(Continued)*

Semba 2007 MWI	8000 IU vitamin A daily as part of a multi-micronutrient supplement	Geometric mean µmol/L (95% CI)	0.60 (0.54 to 0.66)[1]	0.69 (0.63 to 0.75)[1]	NR	NR	8 months	Presented graphically with an increase in serum vitamin A levels in both groups

Abbreviations: IU = international units; IQR = interquartile range; CI = confidence interval; SD = standard deviation.
[1]Serum vitamin A levels for HIV-negative participants.

Table 3. Effects of zinc supplementation on serum zinc levels

Trial ID	Supplement dose	Measure	Baseline		Follow-up		Follow-up	Comment
			Supplement	Control	Supplement	Control		
Ginawi 2013 IND	15 mg zinc sulphate daily	Mean µmol/L (SD)	9.86 (0.87)	9.88 (1.44)	12.23 (1.12)	11.23 (1.34)	2 months	Statistically significant increase in serum zinc levels in the zinc group at 2 and 6 months
Pakasi 2010 IDN	15 mg zinc sulphate daily for 6 months	Mean µmol/L (SD)	11.6 (2.2)	11.8 (2.4)	11.7 (2.43)	11.7 (2.33)	2 months	No statistically significant difference in serum zinc levels at 2 months
Armijos 2010 MEX	50 mg zinc plus 5000 IU vitamin A daily for 4 months	Mean µmol/L (SD)	11.29 (2.57)	11.69 (2.1)	12.85 (3.4)	10.13 (1.61)	2 months	Statistically significant increase in serum zinc levels in zinc plus vitamin A group at 2 months. Increase not sustained post supplementation.
Karyadi 2002 IDN	15 mg zinc plus 5000 IU vitamin A daily for 6 months	Mean µmol/L (SD)	11.52 (1.64)	11.15 (1.77)	11.22 (2.4)	10.22 (2.28)	2 months	No statistically significant difference in serum zinc levels at 2 months
Ginawi 2013 IND	15 mg zinc sulphate plus 5000 IU vitamin A daily	Mean µmol/L (SD)	9.56 (0.77)	9.88 (1.4)	11.17 (0.86)	11.23 (1.34)	2 months	No statistically significant difference in serum zinc levels at 2 months
Pakasi 2010 IDN	15 mg zinc sulphate plus 5000 IU vitamin A daily for 6 months	Mean µmol/L	12.1 (3.0)	11.8 (2.4)	12.5 (2.33)	11.7 (2.33)	2 months	No statistically significant difference in serum zinc levels at 2 months

Table 3. Effects of zinc supplementation on serum zinc levels *(Continued)*

(SD)		

Abbreviations: IU = international unit; SD = standard deviation.

Table 4. Effect of vitamin A plus zinc supplementation on nutritional recovery

Trial ID	Population	Baseline nutritional status		Endpoint nutritional status		Comments
		Mean BMI (SD) kg/m²				
		Vitamin A plus zinc	Placebo	Vitamin A plus zinc	Placebo	
Karyadi 2002 IDN	Adults HIV status unknown	17.6 (1.9)	18.1 (3.2)	Mean BMI (SD) 6 months: 19.4 (2.5)	Mean BMI (SD) 6 months: 20.0 (3.2)	Statistically significantly greater body weight (kg) in supplemented group at 6 months (3.10 kg, 95% CI 0.74 to 5.46). No statistically significant differences in BMI, mid-upper arm circumference, biceps skinfold thickness, triceps skinfold thickness, subscapular skinfold thickness, supra-iliac skinfold thickness, body fat (%), or fat mass (kg) between groups at 2 or 6 months
Lawson 2010 NGA	Adults HIV-positive and HIV-negative	19.6 (3.5)	19.8 (3.3)	BMI data reported graphically		BMI appears to increase along a similar trajectory for both supplemented and placebo groups at 2 and 6 months
Pakasi 2010 IDN	Adults HIV status unknown	16.6 (2.1)	16.4 (2.5)	Mean BMI (SD) 6 months: 18.3 (2.0)	Mean BMI (SD) 6 months: 18.4 (2.6)	No statistically significant differences in BMI between the supplement and placebo group at 2 or 6 months
Visser 2011 ZAF	Adults HIV-positive and HIV-negative	Male: 18.9 (2.7) Female: 23.0 (4.3)	Male: 19.0 (2) Female: 21.6 (4.8)	Mean weight gain 2.3 kg	Mean weight gain 2.2 kg	No statistically significant difference in weight gain during the first 2 months of treatment (P = 0.68, trial authors' own figures)

Abbreviations: HIV = human immunodeficiency virus; BMI = body mass index; SD = standard deviation.

Table 5. Effects of vitamin D supplementation on serum vitamin D levels

Trial ID	Supplement dose	Measure	Baseline		Follow-up		Follow-up	Comment
			Supplement	Control	Supplement	Control		
Mily 2015 BGD	5000 IU daily for 8 weeks	Mean nmol/L (SD)	28.0 (17.5)	28.1 (16.2)	102 (NR)	30 (NR)	8 weeks	The follow-up mean values inserted here have been approximated from a graph in the published paper. The trial authors reported that the group receiving vitamin D_3 supplementation exhibited significantly higher concentration of plasma 25-hydroxyvitamin D[25(OH) D_3] at week 8 compared to placebo after initiation of therapy (P < 0.000)
Tukvadze 2015 GEO	50000 IU 3 times a week for 8 weeks, then every 2 weeks for 8 weeks	Mean nmol/L (SD)	30 (NR)	30 (NR)	250 (NR)	40 (NR)	8 weeks	The mean values inserted here have been approximated from a graph in the published paper. The trial authors reported that high-dose vitamin D_3 resulted in a significant increase in plasma 25(OH)D concentrations to 250 nmol/L at study week 8
Daley 2015 IND [1]	2.5 mg vitamin D_3 on days 0, 14, 28, and 42	Mean nmol/L (SD)	63.1 (46.6)	62.2 (51.0)	72.2 (NR)	60.4 (NR)	26 weeks	Authors reported significant increase serum vitamin D levels in supplement group (P = 0.001) but not in the placebo group (P = 0.15). No difference in serum vitamin D levels between groups at week 26 (P = 0.24)
Kota 2011 IND [2]	60,000 IU vitamin D_3 per week plus 1000 mg calcium carbonate per day	Mean ng/ml (SD)	12.8 (4.5)	11.1 (4.7)	22.3 (5.9)	11.1 (1.6)	8 weeks	Statistically significant increase in serum vitamin D level in the supplement group (P = 0.0001) at 4, 8, and 12 weeks
Martineau 2011 GBR [3]	2.5 mg on days 0, 14, 28, and 42	Mean nmol/L (SD)	21.1 (20.0)	21.3 (19.0)	101.4 (NR)	22.8 (NR)	8 weeks	Statistically significant increase in serum vitamin D level in the supplement group (P < 0.001)
Wejse 2008 GNB [4]	100,000 IU vitamin D_3 at 0, 5, and 8 months	Mean nmol/L	77.5 (23.8)	79.1 (21.8)	105	103	8 weeks	There was no statistically significant difference in serum vitamin D levels at 8 weeks or 8 months between the groups

Table 5. Effects of vitamin D supplementation on serum vitamin D levels *(Continued)*

		(SD)			(95% CI 99 to 110)	(95% CI 96 to 110)		
Morcos 1998 EGY [5]	1000 IU daily for 8 weeks	NR	NR	NR	NR	NR	16 weeks	The trial authors reported that the serum vitamin D level rose in both groups and was not statistically different between groups (P > 0.05).

Abbreviations: NR = not reported; IU = international units; SD = standard deviation; 25(OH) D_3 = 25-hydroxyvitamin D.

[1] Daley 2015 IND only included HIV-negative participants.

[2] Kota 2011 IND only enrolled newly diagnosed tuberculosis cases with uncontrolled diabetes and serum vitamin D < 20 ng/mL.

[3] Martineau 2011 GBR reported that at baseline almost all participants had serum vitamin D levels below the definition of insufficiency used by Wejse 2008 GNB (95% supplement group versus 98% control group).

[4] Wejse 2008 GNB reports that at baseline approximately 10% of participants were defined as being vitamin D deficient (serum 25 (OH)D_3< 50 nmol/L), and 45% as vitamin D insufficient (serum 25(OH)D_3 < 75 nmol/L).

[5] Morcos 1998 EGY reported a mean vitamin D level of 17.91 pg/mL at baseline which is below the normal reference range (20 to 42 pg/mL).

Table 6. Adverse effects of vitamin D

Trial ID	Dose	Severe adverse events	Effects on calcium	Other
Mily 2015 BGD	5000 IU daily for 8 weeks	None in the vitamin D group	Hypercalcemia: none Hypocalcemia: common but no differences between groups	No differences between study arms
Tukvadze 2015 GEO	50,000 IU 3 times a week for 8 weeks, then every 2 weeks for 8 weeks	5/100 vitamin D versus 15/99 placebo	Hypercalcemia: 3/100 vitamin D versus 7/99 placebo	No differences between study arms
Daley 2015 IND	2.5 mg vitamin D_3 on days 0, 14, 28, and 42	None in the vitamin D group	Hypercalcaemia: none	4/121 vitamin D versus 3/126 placebo (none required a change in medical therapy)
Martineau 2011 GBR	2.5 mg on days 0, 14, 28, and 42	7/71 vitamin D versus 2/70 placebo	Hypercalcemia: 2/71 vitamin D versus 0/70 placebo Hypocalcaemia: 5/71 vitamin D versus 2/70 placebo	No differences between study arms
Wejse 2008 GNB	100,000 IU vitamin D_3 at 0, 5, and 8 months	No comment	Hypercalcemia: at 2 months: 1/157 vitamin D versus 2/147 placebo At 8 months: none	At 2 months: only 24 reported any symptom, most commonly excessive thirst: 10/157 vitamin D versus 14/147 placebo (P = 0.31)

Abbreviations: IU = international units.

APPENDICES

Appendix 1. Composition of multi-micronutrient supplements: adults

Nutrient	Adults				
	DRI for males aged 19 to 70 years	Semba 2007 MWI	Range 2005 TZA	Villamor 2008 TZA	Praygod 2011a TZA
Vitamin A	900 µg (3000 IU)	2400 µg (8000 IU)	1500 µg (5000 IU)	1500 µg (5000 IU)	1500 µg (5000 IU)
Vitamin B1 (thiamine)	1.2 mg	1.5 mg	20 mg	20 mg	20 mg
Vitamin B2 (riboflavin)	1.3 mg	1.7 mg	20 mg	20 mg	20 mg
Vitamin B3 (niacin)	16 mg	20 mg	40 mg	100 mg	40 mg
Vitamin B6 (pyridoxine)	1.3 to 1.7 mg	2 mg	25 mg	25 mg	25 mg

(Continued)

Vitamin B9 (folic acid)	400 µg	400 µg	800 µg	800 µg	800 µg
Vitamin B12	2.4 µg	6 µg	50 µg	50 µg	50 µg
Vitamin C	90 mg	500 mg	200 mg	500 mg	200 mg
Vitamin D	5 to 15 µg	10 µg (400 IU)	5 µg	—	5 µg
Vitamin E	15 mg	133 mg (200 IU)	60 mg	200 mg	60 mg
Selenium	55 µg	65 µg	200 µg	100 µg	200 µg
Copper	0.9 mg	—	5 mg	—	5 mg
Zinc	11 mg	10 mg	± 45 mg (elementary zinc)	—	30 mg (as acetate)
Iodine	150 µg	175 µg	—	—	—
Calcium	1000 mg	—	—	—	—
Manganese	2.3 mg	—	—	—	—
Magnesium	410 to 420 mg	—	—	—	—
D-panthenol	—	—	—	—	—

Abbreviations: DRI = Dietary Reference Intake; IU = international unit.
Standards taken from the US Department of Agriculture Dietary Guidance available at http://fnic.nal.usda.gov/nal_display/index

Appendix 2. Search strategies for databases

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis
2	dietary supplements	DIETARY SUPPLEMENTS	DIETARY SUPPLEMENTS	dietary supplement$	dietary supplements
3	macronutrients	food supplement*	food supplement*	DIET-SUPPLEMENTATION	macronutrients
4	micronutrients	FOOD, FORTIFIED	FOOD, FORTIFIED	MACRONUTRIENT	micronutrients
5	zinc	macronutrients	macronutrients	micronutrient$	zinc
6	2 or 3 or 4 or 5	MICRONUTRIENTS	MICRONUTRIENTS	VITAMIN-SUPPLEMENTATION	2 or 3 or 4 or 5

(Continued)

7	1 and 6	TRACE ELEMENTS	TRACE ELEMENTS	IRON	1 and 6
8	—	VITAMINS	VITAMINS	ZINC	—
9	—	vitamin*	vitamin*	TRACE-ELEMENT	—
10	—	zinc	zinc	2-9	—
11	—	iron	iron	1 and 10	—
12	—	2-11/OR	2-11/OR	Limit 11 to human	—
13	—	1 and 12	1 and 12	—	—
14	—	—	Limit 13 to human	—	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011); upper case: MeSH or EMTREE heading, lower case: free text term.

Appendix 3. Optimal information size calculations (tuberculosis treatment outcomes)

Outcome	Power	Two-sided significance level	Ratio of group 1: group 2	Risk in control group	RR deemed clinically significant (examples)	Risk in intervention group	Sample size (total)
Death	80%	95%	1	5%[1]	0.8	4%[2]	13,890
Death	80%	95%	1	5%[1]	0.5	2.5%[3]	1968
Death	80%	95%	1	40%[4]	0.8	32%	1028
Death	80%	95%	1	40%[4]	0.5	20%	162
Cure	80%	95%	1	80%[5]	1.1	88%[6]	658
Cure	80%	95%	1	80%[5]	1.05	84%[6]	2894
Sputum positive at 1 month	80%	95%	1	30%[7]	0.75	22.5%	1078
Sputum positive at 2 months	80%	95%	1	10%[7]	0.75	7.5%	4010

Abbreviations: RR = risk ratio.

[1]Globally the risk of death in tuberculosis patients receiving treatment for tuberculosis is around 5%.
[2]Vitamins are relatively cheap and safe interventions, therefore even very modest reductions in the risk of death might be considered important.
[3]A sample size of 2000 participants (higher than any of the included studies) would be necessary to reliably detect even a very large relative reduction in death (50%).
[4]A very high risk of death was seen in HIV-positive participants in some trials due to antiretrovirals being unavailable at the study site at the time. Death rates this high should not be seen in patients taking antiretrovirals.
[5]The target cure rate for directly observed treatment, short course (DOTs) programmes is 80%. The current global average is 86%.
[6]Vitamins are relatively cheap and safe interventions, therefore even very modest increases in successful cure might be considered important.
[7]Sputum positivity rates in these trials were very variable. These examples are for illustrative purposes only.

We performed the calculations using nMaster 1.0 (nMaster 1.0), a sample size software that incorporates sample size calculation(STATA, EpiInfo, nQuery, etc.), in terms of contents, each of use and the cost.

Appendix 4. Optimal information size calculations (nutritional and quality of life outcomes)

Outcome	Power	Two-sided significance level	Ratio of group 1: group 2	Mean in control group	SD	Mean in supplement group	SD	Mean difference	Sample size (total)
Mean vitamin level[1]	80%	95%	1	35 µg/L	10	40 µg/L	10	5 µg/L	126
Mean increase in weight at 8 weeks[2]	80%	95%	1	3.5 kg	6.3	5.5 kg	6.3	2 kg	312
Mean increase in weight at 8 weeks[2]	80%	95%	1	3.5 kg	6.3	8.5 kg	6.3	5 kg	50
Mean BMI at 8 weeks[3]	80%	95%	1	18.5 kg/m^2	2.6	19.5 kg/m^2	2.6	1 kg/m^2	214
Mean change in BMI at 8 weeks[3]	80%	95%	1	18.5 kg/m^2	2.6	20.5 kg/m^2	2.6	2 kg/m^2	54
Mean Karnofsky score[4]	80%	95%	1	80	4.0	85	4.0	5 points	20

Abbreviations: BMI = body mass index; SD = standard deviation.

[1]We have taken this example from Hanekom 1997 ZAF
[2]We have taken this example from Martins 2009 TLS. This trial showed a 1.7 kg mean difference.
[3]This example uses the SD from Martins 2009 TLS but uses a 5 kg mean difference. This is for illustrative purposes.
[4]This example uses the SD taken from Karyadi 2002 IDN.

Appendix 5. Macronutrient supplements

Study ID	Jahnavi 2010 IND	Paton 2004 SGP	Jeremiah 2014 TZA	Praygod 2011b TZA	Martins 2009 TLS	Sudarsanam 2010 IND
Description of intervention	Advice on target energy intake and on how to achieve this with normal diet plus food supplements (daily: sweet balls made from wheat flour, caramel, groundnuts, and vegetable ghee as well as 100 g of sprouted grams and nuts for vitamins and minerals)	Advice on target energy intake and on how to achieve this with normal diet plus 2 to 3 high-energy oral nutritional supplements	4 high energy-protein biscuits plus 1 vitamin/mineral fortified biscuit	5 high energy-protein biscuits plus 1 vitamin/mineral fortified biscuit	A daily meal (intensive phase; week 1 to 8) followed by a food parcel (continuation phase; week 9 to 32). The meal consisted of a bowl of meat, kidney beans, and vegetable stew with rice. The food parcel contained unprepared red kidney beans, rice, and oil adequate for 1 meal per day. Control: nutritional advice alone.	Macronutrient (ready-to-serve powder, given as monthly rations) and micronutrient (daily multivitamin tablet) supplementation Control: dietary advice alone
Duration of supplementation	3 months	Until they reached a body mass index of 20 or usual body weight	2 months	60 days	8 months	6 months
Average dietary energy intake per day	Not stated	1560 kcal/day 1502 kcal/day	Not stated	Not stated	Not stated	2129 kcal 2072 kcal
Total daily energy intake through supplementation	Not stated (600 kcal per sweetball)	600 to 900 kcal (300 kcal per packet)	3075 kcal (615 kcal per biscuit)	3690 kcal (615 kcal per biscuit)	1800 kJ per daily meal	930 kcal

(Continued)

Carbohydrate	Not stated	40.4 to 60.6 g (20.2 g per packet)	Not stated	Not stated	55.6 g per daily meal	Not stated
Fat	Not stated	8.58 to 12.87 g (4.29 g per packet)	Not stated	Not stated	Not stated	Not stated
Protein	Not stated (6 g per sweetball)	12.5 to 18.75 g (6.25 g per packet)	22.5 g (4.5 g per biscuit)	27g (4.5 g per biscuit)	18.4 g per daily meal	31.5 g protein
Micronutrient	Not stated	Not stated	600 mg phosphorous, 600 mg calcium, 180 mg magnesium, 350 mg sodium, 750 mg potassium, and traces (< 1 mg) of iron and zinc, 1.5 mg vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B6, 50 µg vitamin B12, 0.8 mg folic acid, 40 mg niacin, 200 mg vitamin C, 60 mg vitamin E, 5 µg vitamin D, 0.2 mg selenium, 5 mg copper, 30 mg zinc	720 mg phosphorous, 720 mg calcium, 216 mg magnesium, 420 mg sodium, 900 mg potassium, and traces (< 1 mg) of iron and zinc, 1.5 mg vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B6, 50 µg vitamin B12, 0.8 mg folic acid, 40 mg niacin, 200 mg vitamin C, 60 mg vitamin E, 5 µg vitamin D, 0.2 mg selenium, 5 mg copper, 30 mg zinc	24.2 mg vitamin C, 363 µg vitamin A, 3.1 mg iron, 3 g zinc, 60 µg folate	Copper sulphate 0.1 mg, D-pantheol 1 mg, dibasic calcium phosphate 35 mg, folic acid 500 µg, magnesium oxide 0.15 mg, manganese sulphate 0.01 mg, nicotinamide 25 mg, potassium iodide 0.025 mg, vitamin A 5000 IU, vitamin B1 2.5 mg, vitamin B12 2.5 µg, vitamin B2 2.5 mg, vitamin B6 2.5 mg, vitamin C 40 mg, vitamin D3 200 IU, vitamin E 7.5 mg, zinc sulphate 50 mg

Appendix 6. High energy oral supplements versus dietary advice (additional data from Jahnavi 2010 IND and Paton 2004 SGP)

Outcome	Timepoint	Supplements			Dietary advice			P value
		Mean	SD	n	Mean	SD	n	
Change in physical function score (Jahnavi 2010 IND)	At 3 months	23.34	33.87	50	6.70	31.27	50	> 0.05
Change in physical function score (Paton 2004 SGP)	At 6 weeks	11.84	30.21	19	1.67	17.59	15	0.48
	At 12 weeks	24.44	26.44	15	6.41	16.37	11	0.052
	At 24 weeks	22.78	32.80	15	12.00	23.66	11	0.500
Change in emotional well-being score (Jahnavi 2010 IND)	At 3 months	22.32	22.69	50	2.56	21.45	50	> 0.05
Change in mental health score (Paton 2004 SGP)	At 6 weeks	9.05	16.48	19	10.07	22.20	15	0.781
	At 12 weeks	10.13	26.74	15	8.92	20.08	11	0.581
	At 24 weeks	11.20	24.94	15	11.00	23.01	11	0.810
Change in general health score (Jahnavi 2010 IND)	At 3 months	32.5	22.17	50	6.50	19.42	50	> 0.05
Change in overall health score (Paton 2004 SGP)	At 6 weeks	27.63	21.88	19	6.67	24.02	15	0.053
	At 12 weeks	30.00	19.36	15	25.00	27.00	11	0.544
	At 24 weeks	36.67	18.58	15	29.17	33.43	11	0.465

Abbreviations: SD = standard deviation.

In total Jahnavi 2010 IND reported 8 and Paton 2004 SGP reported 12 quality of life/physical function scores. See the original papers for full results.

Appendix 7. Composition of multi-micronutrient supplements: children

Children								
Nutrient	**Daily DRI for children aged 1 to 3 years**	**Lodha 2014 IND**				**Mehta 2011 TZA**		
		6 to 36 months	**4 to 6 years**	**7 to 9 years**	**10 to 15 years**	**< 6 months**	**7 to 36 months**	**> 36 months**
Vitamin A	300 µg	0.8 mg[1]	0.9 mg[1]	1 mg[1]	1.2 mg[1]	—	—	—
Vitamin B1 (thiamine)	0.5 mg	1 mg	1.2 mg	1.8 mg	2.4 mg	0.5 mg	1 mg	1.5 mg
Vitamin B2 (riboflavin)	0.5 mg	1 mg	1.2 mg	1.8 mg	2.6 mg	0.6 mg	1.2 mg	1.8 mg
Vitamin B3 (niacin)	6 mg	12 mg[2]	16 mg[2]	24 mg[2]	32 mg[2]	4 mg	8 mg	12 mg
Vitamin B6 (pyridoxine)	0.5 mg	1 mg	1.2 mg	2 mg	2.6 mg	0.6 mg	1.2 mg	1.8 mg
Vitamin B9 (folic acid)	150 µg	300 µg[3]	400 µg[3]	600 µg[3]	800 µg[3]	130 µg	260 µg	390 µg
Vitamin B12	0.9 µg	3.8 µg	2.4 µg	3.6 µg	4.8 µg	1 µg	2 µg	3 µg
Vitamin C	15 mg	60 mg	60 mg	70 mg	80 mg	60 mg	120 mg	180 mg
Vitamin D	5 µg	10 µg	10 µg	10 µg	10 µg	—	—	—
Vitamin E	6 mg	10 mg	10 mg	14 mg	20 mg	8 mg	16 mg	24 mg
Selenium	17 µg	10 µg	10 µg	10 µg	10 µg	—	—	—
Copper	260 µg	2 mg	3 mg	4 mg	5 mg	—	—	—
Zinc	2.5 mg	20 mg[4]	20 mg[4]	20 mg[4]	20 mg[4]	—	—	—
Iodine	65 µg	—	—	—	—	—	—	—
Calcium	500 mg	—	—	—	—	—	—	—
Manganese	—	—	—	—	—	—	—	—
Magnesium	65 mg	—	—	—		—	—	—

(Continued)

D-panthenol	—	—	—	—	—	—	—	—

Abbreviations: DRI = Dietary Reference Intake. Standards taken from the US Department of Agriculture Dietary Guidance available at https://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes

[1]mg retinol equivalent.

[2]mg niacin equivalent.

[3]µg dietary folate equivalent.

[4]One trial arm received zinc only; 1 arm received micronutrients plus zinc and 1 arm received micronutrients without zinc.

Appendix 8. Vitamin E and selenium levels (Seyedrezazadeh 2006)

Time point	Plasma vitamin E levels (µmol/L) Median value (range)		Serum selenium levels (µmol/L) Median value (range)	
	Supplement group (N = 17)	Placebo group (N = 18)	Supplement group (N = 17)	Placebo group (N = 18)
At baseline	24.7 (0 to 87)	20.2 (5.1 to 49)	1.0 (0.34 to 2.5)	0.93 (0.1 to 1.9)
At 8 weeks	28.2 (10.5 to 86.5)	19.3 (5.1 to 48.6)	Not reported	Not reported

Abbreviations: N = number of participants.

WHAT'S NEW

Date	Event	Description
28 June 2016	New citation required but conclusions have not changed	We performed a new literature search and included 12 new trials (from 15 articles). The author team has been updated.
28 June 2016	New search has been performed	We amended the objective of this Cochrane Review to simplify the wording and to reflect the need to assess any differences in response depending on HIV status. We amended some of the outcomes. Also, we added total calorie intake and micronutrient levels before and after supplementation as outcomes in the review as there are important explanatory factors for any effects seen. Also, we adapted the methods to reflect changes in the methods of assessing and reporting risk of bias.

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 4, 2008

Date	Event	Description
30 September 2011	New citation required but conclusions have not changed	We added eight new trials and have considered more carefully the nutritional status at baseline (both weight and biochemical status of individual micronutrients). The author team has also been updated.
20 September 2011	New search has been performed	We performed a new search, and included eight new trials. We constructed 'Summary of findings' tables, which summarize the quality of the evidence. Also we performed a calculation of the optimal information size to reliably detect clinically important effects if they exist. We updated the 'Risk of bias' assessments to the new format.

Date	Event	Description
10 November 2009	Amended	An observant reader noted that there was an error in referencing in the 'Risk of bias' tables. This error has now been corrected.
10 November 2008	Amended	We corrected minor errors. There were no changes to the conclusions.

CONTRIBUTIONS OF AUTHORS

Thambu David Sudarsanam conceived this Cochrane protocol, and designed it in collaboration with all review authors (Abba 2006). We performed the selection of trials for inclusion, 'Risk of bias' assessments, and data extraction as indicated in the Methods. Katharine Abba and David Sinclair mainly undertook the analyses of previous versions of the review, in consultation with the other review authors. In the most recent update of this Cochrane review, Liesl Grobler, Sukrti Nagpal, and Thambu David Sudarsanam screened the search results and extracted the data from the eligible studies. Liesl Grobler and David Sinclair, in consultation with the other review authors, analysed the data and wrote the review.

DECLARATIONS OF INTEREST

Liesl Grobler has no known conflicts of interest.
David Sinclair was previously a member of the World Health Organization (WHO) Technical Advisory Group on Nutrition. This work may contribute to future recommendations on nutritional care in tuberculosis.
Sukrti Nagpal has no known conflicts of interest.
Thambu D Sudarsanam has no known conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the objective of this Cochrane Review from "To assess the provision of oral nutritional supplements to promote the recovery of people being treated with anti-TB drug therapy for active TB" to the current objective to simplify the wording and reflect the need to assess any differences in response depending on HIV status.

Also we changed some of the outcomes, as follows: we expanded "change in weight or skinfold thickness" to "change in weight, skinfold thickness, or other measure of lean or total mass" because we became aware that other measures, besides skinfold thickness, are equally valid indicators of overall nutritional status; we added "any measure of growth in children" because it is a useful indicator of health and nutritional status in children, which we had overlooked at the protocol stage; and included "sputum positive at follow-up" because it was a primary outcome of many included trials, and it became apparent that it is a meaningful outcome as, depending on the period of follow-up, it may be used as a proxy for cure or as an indicator of the time taken to become sputum-smear negative. Early sputum conversion is a desirable outcome because on becoming smear-negative, patients become less ill and less infectious to those around them.

Between the publication of the original review (Abba 2008; Sinclair 2011), and this review update, the method of assessing and reporting risk of bias has changed slightly. We have adapted the methods to reflect this.

For this review update, we included additional details on the nutritional and micronutrient status at baseline. Where reported, we have also included plasma micronutrient levels during follow-up as an outcome. This outcome is not a patient important outcome, and is of little interest on its own, but does contribute to the understanding of the results.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Antitubercular Agents [therapeutic use]; Energy Intake; HIV Infections [complications] [mortality]; Malnutrition [complications] [*diet therapy]; Micronutrients [administration & dosage]; Randomized Controlled Trials as Topic; Tuberculosis [complications] [*diet therapy] [drug therapy] [mortality]

MeSH check words

Adult; Child; Humans