Adjunctive vitamin D in tuberculosis treatment: meta-analysis of individual participant data. Online data supplement.

Search Strategies.

A. PubMed

Cochrane Highly Sensitive Search Strategy for identifying randomized controlled trials

#1. randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]

#2. animals [mh] NOT humans [mh]

#3. #1 NOT #2

Terms specific to vitamin D

#4. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Term specific to tuberculosis

#5. Tuberculosis

Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with tuberculosis

#3 AND #4 AND #5

B. EMBASE

Terms for identifying randomized controlled trials

#1 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEXT/1 blind*):ab,ti OR trial:ti
#3. #1 OR #2

Terms specific to vitamin D

#4. vitamin AND d OR vitamin AND d2 OR vitamin AND d3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Term specific to tuberculosis

#5. tuberculosis

Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with tuberculosis

#3 AND #4 AND #5

C. Cochrane Central

Terms specific to vitamin D

#1. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Term specific to tuberculosis

#2. Tuberculosis

Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with tuberculosis

#1 AND #2

D. Web of Science

TS =(Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol) AND TS =(Tuberculosis) AND TS =(placebo* or random* or clinical trial* or double blind* or single blind* or rct)

Results

Supplementary Table S1: Final treatment outcome by study and allocation[1]

	Ralph *et al*[1]		Wejse *et al*[2]	
	Placebo (n)	Vitamin D (n)	Placebo (n)	Vitamin D (n)
Cured	32	36	59	72
Completed	6	4	34	29
Failed	1	0	0	0
Defaulted	0	5	14	9
Died	0	2	9	12
Transferred	2	2	1	2
Total	**41**	**49**	**117**	**124**

1, data on final treatment outcome were available for 90 participants in the trial by Ralph et al and 241 participants in the trial by Wejse et al.

Supplementary Table S2: Baseline characteristics by allocation: all analyzed participants (n=1,850)

	Placebo group (n=923)	Vitamin D group (n=927)
Mean baseline 25(OH)D concentration, nmol/L (SD)[1]	41.0 (35.7)	41.3 (33.6)
Baseline 25(OH)D concentration (%)[1]		
<25 nmol/L	359 (38.9)	329 (35.4)
≥25 nmol/L	478 (51.8)	494 (53.3)
Mean age, years (SD)	34.0 (13.8)	33.0 (13.0)
Age (%)		
<30 years	450 (48.8)	467 (50.4)
≥30 years	473 (51.2)	460 (49.6)
Sex (%)		
Male	611 (66.2)	589 (63.5)
Female	312 (33.8)	338 (36.5)
Mean weight, kg (SD)[2]	51.2 (11.3)	51.0 (10.9)
Multidrug resistance (%)[3]		
No	619 (67.1)	600 (64.7)
Yes	25 (2.7)	30 (3.2)
HIV status[4]		
Seronegative	507 (54.9)	492 (53.1)
Seropositive	41 (4.4)	68 (7.3)
% zones involved, baseline CXR (%)[5]		
<50%	362 (39.2)	359 (38.7)
≥50%	146 (15.8)	137 (14.8)
Cavitation, baseline CXR (%)[6]		
No	330 (35.8)	341 (36.8)
Yes	334 (36.2)	324 (35.0)
Vitamin D Dosing Regimen (%)		
Daily/weekly	223 (24.2)	229 (24.7)
Bolus/2-weekly	700 (75.8)	698 (75.3)
***Fok*I *VDR* genotype (%)**[7]		
FF	183 (19.8)	194 (20.9)
Ff	150 (16.3)	149 (16.1)
ff	36 (3.9)	20 (2.2)
***Taq*I *VDR* genotype (%)**[8]		
TT	258 (28.0)	245 (26.4)
Tt	140 (15.2)	140 (15.1)
tt	29 (3.1)	32 (3.5)

25(OH)D, 25-hydroxyvitamin D; CXR, chest radiograph; SD, standard deviation; HIV, human immunodeficiency virus; VDR, vitamin D receptor.

1. Data available for n=837 in the placebo group and n=823 in the vitamin D group; 2. Data available for n=906 in the placebo group and n=914 in the vitamin D group; 3. Data available for n=644 in the placebo group and n=630 in the vitamin D group; multidrug resistance defined as being resistant to both isoniazid and rifampicin, at least; 4. Data available for n=548 in the placebo group and n=560 in the vitamin D group; 5. Data available for n=408 in the placebo group and n=496 in the vitamin D group; 6. Data available for n=664 in the placebo group and n=665 in the vitamin D group; 7. Data available for n=369 in the placebo group and n=363 in the vitamin D group; 8. Data available for n=427 in the placebo group and n=417 in the vitamin D group.

Supplementary Table S3: Baseline characteristics by allocation: participants with multidrug-resistant tuberculosis (n=55)[1]

		Placebo group (n=25)	Vitamin D group (n=30)
Mean age, years (SD)		30.7 (7.8)	31.8 (13.1)
Age (%)	<30 years	13 (52.0)	19 (63.3)
	≥30 years	12 (48.0)	11 (36.7)
Sex (%)	Male	15 (60.0)	16 (53.3)
Male	Female	10 (40.0)	14 (46.7)
Mean baseline 25(OH)D concentration, nmol/L (SD)[2]		21.6 (16.3)	26.7 (23.8)
Baseline 25(OH)D concentration (%)	<25 nmol/L	17 (68.0)	17 (56.7)
	≥25 nmol/L	7 (28.0)	12 (40.0)
	Not known	1 (4.0)	1 (3.3)
Mean weight, kg (SD)		54.1 (11.1)	55.5 (9.7)
HIV status (%)	Seronegative	11 (44.0)	13 (43.3)
	Seropositive	0 (0.0)	1 (3.3)
	Not known	14 (56.0)	16 (53.3)
Cavitation, baseline CXR (%)	No	13 (52.0)	21 (70.0)
	Yes	12 (48.0)	8 (26.7)
	Not known	0 (0.0)	1 (3.3)
Vitamin D dosing Regimen (%)	Daily/weekly	15 (60.0)	15 (50.0)
	Bolus/2-weekly	10 (40.0)	15 (50.0)
Other adjunctive therapy (%)	Phenylbutyrate	3 (12.0)	1 (3.3)
	L-arginine	1 (4.0)	0 (0.0)
	Nil	21 (84.0)	29 (96.7)
***FokI VDR* genotype (%)**[5]	FF	2 (8.0)	6 (20.0)
	Ff	5 (20.0)	6 (20.0)
	ff	2 (8.0)	1 (3.3)
	Not known	16 (64.0)	17 (56.7)
***TaqI VDR* genotype (%)**[6]	TT	9 (36.0)	13 (43.3)
	Tt	3 (12.0)	1 (3.3)
	tt	4 (16.0)	1 (3.3)
	Not known	9 (36.0)	15 (50.0)
Antimicrobial sensitivity	Resistant to isoniazid and rifampicin only	10 (40.0)	15 (50.0)
	Additionally resistant to at least one other anti-TB drug[3]	15 (60.0)	15 (50.0)

25(OH)D, 25-hydroxyvitamin D; CXR, chest radiograph; SD, standard deviation; HIV, human immunodeficiency virus; VDR, vitamin D receptor.

1. Multidrug-resistant tuberculosis defined as resistance of isolate to both isoniazid and rifampicin, at least.
2. Baseline 25(OH)D concentration missing for 1 participant in the placebo group and 1 participant in the vitamin D group
3. Isolates additionally resistant to ethambutol, streptomycin or both

Supplementary Table S4. Risk of Bias Assessment

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Wejse 2009 [2]	✓	✓	✓	✓	?[1]	✓	✓
Martineau 2011 [3]	✓	✓	✓	✓	✓	✓	✓
Salahuddin 2013 [4]	✓	✓	✓	✓	✓	✓	✓
Ralph 2013 [1]	✓	✓	✓	✓	?[1]	✓	✓
Mily 2015 [5]	✓	✓	✓	✓	?[1]	✓	✓
Daley 2015 [6]	✓	✓	✓	✓	?[1]	✓	✓
Tukvadze 2015 [7]	✓	✓	✓	✓	✓	✓	✓
Ganmaa 2017 [8]	✓	✓	✓	✓	✓	✓	✓

✓ = low risk of bias; ? = unclear risk of bias;
1, risk of bias due to incomplete outcome data assessed as 'unclear' due to relatively high rates of loss to follow-up (>20%)

Supplementary Table S5: One-step individual participant data meta-analysis, safety outcomes

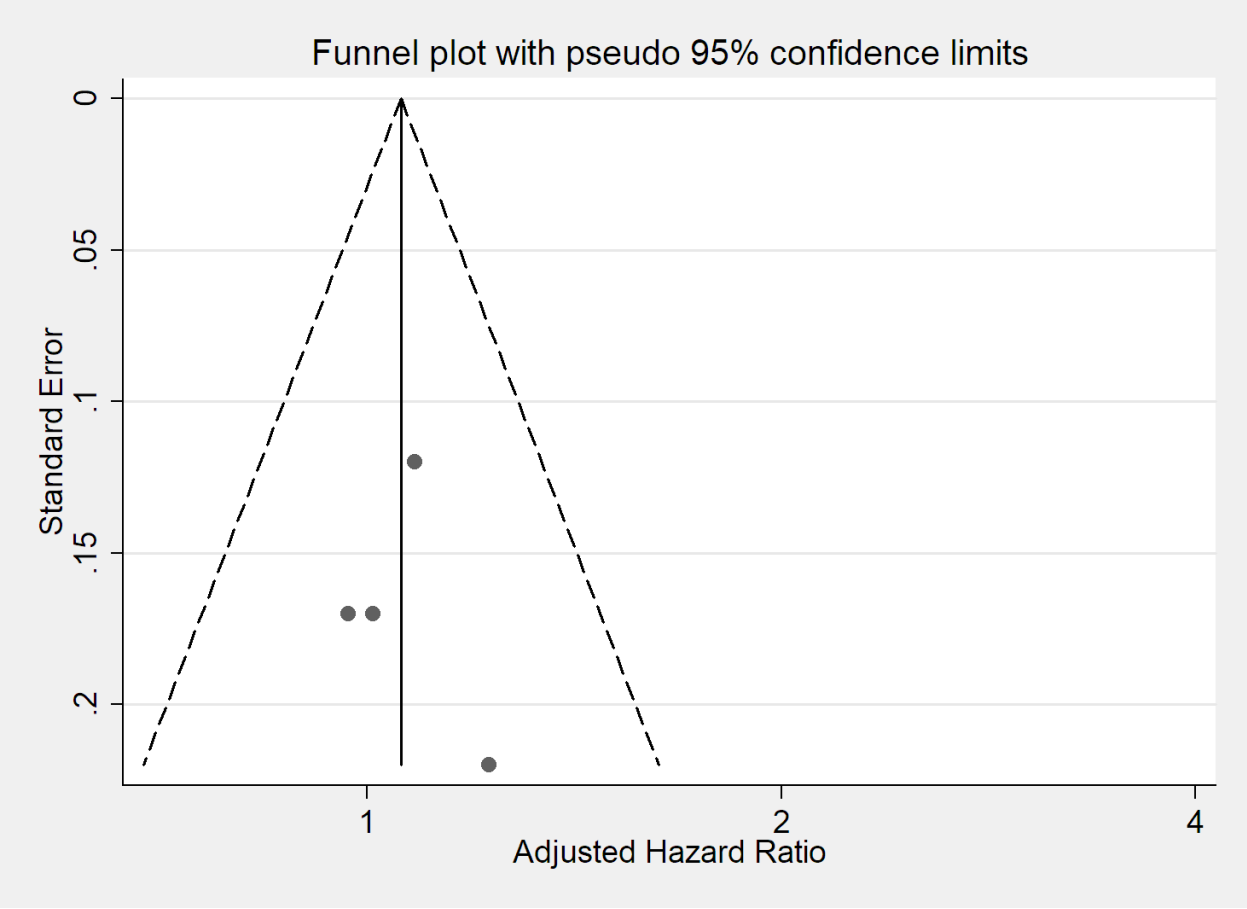
	N participants (trials)	Proportion with ≥1 event, placebo group (%)	Proportion with ≥1 event, vitamin D group (%)	Adjusted odds ratio (95% CI) [1]	P value
Hypercalcemia[2]	6	39/639 (6.1)	38/614 (6.2)	0.94 (0.55, 1.62)	0.83
Renal stones	8	0/923 (0.0)	0/927 (0.0)	--	--
Serious Adverse Events, any cause	8	32/923(3.5)	33/927 (3.6)	0.99 (0.59, 1.65)	0.96
Withdrawals/loss to follow-up	8	124/923 (13.4)	117/927 (12.6)	0.96 (0.73, 1.27)	0.79
Total Deaths	8	21/923 (2.3)	23/927 (2.5)	1.09 (0.59, 2.03)	0.79

1, adjusted for age, sex and clustering between trials
2, hypercalcemia defined as serum calcium concentration >2.65 mmol/L; serum calcium concentration was corrected for serum albumin concentration where this was also measured (4/6 studies). In all studies where serum calcium concentrations were measured, this was done routinely i.e. irrespective of symptoms

Supplementary Table S6: One-step individual participant data meta-analysis, responder analysis

	N participants (N trials)	Median time to sputum culture conversion, days (IQR)	Adjusted hazard ratio (95% CI)	P value
Intervention, end-study 25(OH)D < 75 nmol/L	34 (3)	28 (28, 56)	Referent	
Intervention, end-study 25(OH)D ≥ 75 nmol/L	232 (4)	28 (28, 53)	0.95 (0.63, 1.41)	0.78

Supplementary Figure S1: Funnel plot for individual patient data meta-analysis of time to sputum culture conversion.



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