Appendix 1 (as submitted by author): Pertinent Systematic Reviews of Vitamin D Published since the 2002 Clinical Practice Guidelines, with AMSTAR Ratings of Quality [1]

Systematic Reviews of RCTs of Vitamin D on Fractures, Falls or Mortality			
Author, Yr AMSTAR Quality Score*	**Eligibility Criteria**	**Outcomes, Number of RCTs (n)**	**Summary Estimate (95%CI), Measure of Heterogeneity, Q test, and/or I^2**
FRACTURES			
Avenell [2], 2005 10/11	Postmenopausal women and men over 65 yrs, included trials of subjects with neurological diseases Vitamin D2 or D3 or 25-OH-D or Vitamin D analogues (+/-) Ca vs. Ca or placebo	Hip fractures Vitamin D alone vs. placebo 7 RCTs (n =18,688) Vitamin D + Ca vs placebo 7 RCTs, (n=10,376) Non-vertebral fractures 7 RCTs (Vit D3 + Ca) (n= 10,408) Vertebral fracture 4 RCTs (Vit D3 + Ca) (n= 5698)	RR, 95%CI, 1.17 (0.98-1.41), I^2 = 0% RR 95%CI, 0.81 (0.68-0.96), I^2 =0% RR 95%CI, 0.87 (0.78- 0.97), I^2 = 48 RR 95%CI, 1.13 (0.50-2.55) n =5698, I^2 =61%
Bischoff-Ferrari [3], 2005 11/11	Minimum follow-up of 1 yr and > 1 fracture/trial, mean age 60 years or older Trials of vitamin D2 or D3 (any dose) +/-Ca vs. placebo or Calcium	Hip Fractures 5 RCTs (n= 9294), all doses > 400 IU/d Vitamin D, 3 RCTs (n=5572) ≤ 400 IU/d Vitamin D, 3 RCTs (n=3722)	RR 95% CI, 0.88 (0.69-1.13) n=9294, (Q test P=0.09) RR 95%CI, 0.74 (0.61- 0.88) n=5572 (Q test p=0.74) RR 95% CI, 1.15 (0.88- 1.50) n=3722 (Q test p=0.68)
		Non-vertebral fractures All doses, 7 RCTs (n=9294) >400 IU/d Vitamin D +/-Ca 5 RCTs (n=6098) <400 IU/d Vitamin D +/-Ca, 2 RCTs (n=3722)	RR 95%CI, 0.83 (0.70-0.98) (Q test p=0.07) RR 95%CI, 0.77 (0.68- 0.87) (Q test p=0.41) RR 95%CI, 1.03 (0.86-1.24) Q test; p=0.36

Boonen [4], 2007 10/11	PM women and men ≥50 yrs update of 2005 Bischoff meta-analysis Vitamin D3 (+/- calcium) vs. placebo	<u>Hip Fractures</u> Vitamin D3 vs placebo, 4 RCTs (n=9083) Vitamin D3 + Ca vs. placebo, 6 RCTs (n= 45,509)	 RR 95%CI, 1.10 (0.89- 1.36), I^2=0% RR 95%CI, 0.82 (0.71-0.94), p<0.001, I^2=5% Adj indirect comparison of above results: RR 0.75 (0.58,0.96)
		<u>Non-vertebral fractures</u> Vitamin D vs placebo, 4 RCTs Vitamin D33 + Ca vs. placebo, 6 RCTs	 RR 95%CI, 0.98 (0.83-1.16), I^2=40% RR 95%CI, 0.88 (0.78- 0.99), I^2=50%, p=0.036,
Izaks [5], 2007 4/11	Postmenopausal women and men over 65 years Vitamin D2 or D3, follow-up of at least 1 year and >1 fracture/ trial	<u>Non-vertebral fractures</u> 11 RCTs (≥ 400 IU/day) Institutionalized, 3 RCTs (≥ 700 IU/day) General population, 5 RCTs (≥ 700 IU/day)	 RR 95%CI, 0.94 (0.89- 0.98), heterogeneity NR RR 95%CI, 0.80 (0.70-0.90) RR 95%CI, 0.88 (0.75-1.04)
		<u>Hip fractures</u> Institutionalized, 2 RCTs (≥ 700 IU/day) General population, 2 RCTs (≥ 700 IU/day)	 RR 95%CI, 0.72 (0.59-0.88) RR 95%CI 1.04 (0.72-1.50)
Jackson [6], 2007 4/11	PM women or men ≥ 65 yrs, 9 RCTs of D3 or 25-OH-D3 (300 -800 IU/day)	Non-vertebral fractures, 6 RCTs (n=8524) Vertebral fractures, 2 RCTs (n=902)	RR 95%CI, 0.96 (0.84-1.09) I^2=3.0% RR 95%CI, 1.22 (0.64-2.31) I^2=8.3%
		Falls, 5 RCTs (n=3776) Falls, 3 RCTs (n=784	RR 95%CI, 0.88 (0.78- 1.00) I^2=8.3% RR 95%CI, 0.92 (0.75-1.12) I^2=44.2%
Richy [7], 2005 7/11	RCTs comparing native Vit D and calcitriol or alphacalcidiol to placebo in primary osteoporosis	<u>Bone loss</u> Native Vitamin D Vitamin D analogues Analogues vs. Vitamin D	Effect Size = ES ES = 0.17, p<0.0001 ES = 0.36, p<0.0001 ES = 0.19, p<0.05
		<u>Vertebral Fractures</u> Native Vitamin D Vitamin D analogues Analogues vs. Vitamin D	Rate Difference = RD RD 95%CI = 1.6% (0.4- 2.6) RD 95%CI = 15% (10-20) Delta RD = 13.4% (7.7-19.8), p<0.001

Papadimitropoulos [8], 2002 9/11	Postmenopausal women and men RCTs of vit D2 or 3 or hydroxylated vit D (+/-) Ca vs. control or Ca	<u>Vertebral Fractures</u> All trials (analogues and D3), 8 RCTs (n=1130) Vitamin D3 alone1 RCT (n=160),	RR 95%CI, 0.63 (0.45-0.88), heterogeneity NR RR 95%CI, 0.33 (0.01-8.05)
		<u>Non-Vertebral Fractures</u> All trials, 6 RCTs (n=6187) Vitamin D3, 3 RCTs (n=5399)	RR 95%CI, 0.77 (CI 0.57-1.04), heterogeneity NR RR 95% CI, 0.78 (0.55-1.09)
Tang [9], 2007 11/11	Adults over age 50 years RCTs of calcium or calcium with vitamin D, outcomes of fracture and BMD	Fractures 8 trials vitamin D and calcium (N=46,108) 9 trials of calcium (N=6517)	Vitamin D and Ca: RR 95%CI, 0.87 (0.77-0.97), -greater risk reduction in those with serum 25 (OH)D < 25 nmol/L vs. normal 25-OH-D (0.86 vs. 0.94, p=0.06), and in those with lower dietary Ca intake -larger treatment effect in institutionalized vs. community dwelling (0.76 vs 0.94, p=0.003) and in trials with higher compliance (>80%: RR 0.76 , 0.67-0.86), and those over age 70 years -treatment effect similar across fracture sites and gender -history of prior fracture did not change treatment effect -positive effect in institutionalized subjects may be a combination of low vitamin D and increased compliance
FALLS			
Richy [10], 2008 5/11	Adults and falls in osteopenic or osteoporotic patients , trials of vitamin D, calcitriol or alfacalcidiol vs placebo,	Vitamin D or D –analogues, 14 trials, (n=21,268), Vitamin D analogues compared to native vitamin D	RR 95% CI, (0.94, 0.90-0.99) RR 95% CI, (0.79, 0.64-0.96) from 2 trials of D analogues vs. 12 trials of native D (0.95, 0.91-1.00), p=0.048 (21% vs. 5%), Heterogeneity not reported Participants receiving D-analogues had higher baseline levels of 25-OH-D, vs. those in native vitamin D trials.

Bischoff-Ferrari [11], 2004 11//11	Postmenopausal women or older men vitamin D2 or D3 or active preparations	Primary analysis: adequate definition and ascertainment of falls, 5 RCTs (n=1237) of vitamin D3 (400-800 IU), or D-analogues Vitamin D3 (400-800 IU/day), 3 trials (n=613) Vitamin D3, 800 IU/day, 2 trials (n=259) Active Vitamin D analogues, 2 trials (n=626)	Adjusted OR 95% CI ,0.78 (0.64, 0.92) Stated that heterogeneity not significant OR 95%CI, 0.83 (0.65-1.06) OR 95%CI, 0.65 (0.40-1.00) OR 95%CI, 0.71 (0.55-0.92)
Latham [12], 2003 7/11	Older adults, mean age = 60 years, vitamin D or calcitriol/alphacalcidiol, (+/- Ca), with placebo or standard care	Vitamin D (+/- Ca) vs. Ca or placebo, 4 RCTs, (n=1317)	RR 95% CI, 0.99 (0.89-1.11) Herterogeneity not reported
MORTALITY			
Autier [13], 2007 7/11	Adults, trials of vitamin D2 or D3	18 trials, n=57,331 Vitamin D 300-2000 IU/day (mean dose 528 IU/day) 1.4 -5.2 difference in serum 25-OH-D between intervention and controls	All Cause Mortality - Summary RR 95% CI, 0.93 (0.87-0.99), no evidence of heterogeneity, no appreciable change in RR according to trial duration or dose of vitamin D, Ca supplements did not seem to have an affect on RR

Systematic Reviews of Prevalence of Low Vitamin D Status in Adults with Osteoporosis and Fractures

Author, Yr Quality Score	**Included Studies**		**Results**
Gaugris [14], 2005 3/11	30 studies in postmenopausal women with and without musculoskeletal health issues	Osteoporotic population- prevalence of [25(OH) D] <12ng/ml (30 nmol/L) Population with fracture history - prevalence of [25-OH-D] <15 ng/ml (37.5 nmol/L) Post-menopausal population - prevalence of [25(OH) D] ≤20 ng/ml (50nmol/L)	Range 12.5% - 76% Range 50%-70% Range 1.6% - 86%

Systematic Reviews of Vitamin D Status and Association with Extra-skeletal Conditions			
Author, Yr Quality Score	**Outcome and Included Studies**		**Results**
Gorham [15], 2007 6/11	Association of 25-OH-D with risk of colorectal and colon cancer	5 observational studies, n=1448 Risk of colorectal cancer in the highest vs. lowest quintile, 2 studies adjusted for calcium intake	Pooled Peto OR 95%CI, 0.49 (0.35- 0.68), $p<0.0001$, no heterogeneity. Serum 25-OH-D of ≥ 83 nmol/L associated with 50% lower incidence of colorectal cancer versus < 30 nmol/L.
Pittas [16], 2007 5/11	Association between 25-OH-D, vitamin D intake and type 2 diabetes	4 observational studies, 25-OH-D & prevalent type 2 diabetes in highest (25-38 ng/ml, 62.5-95 nmol/L) vs. lowest 25-OH-D level (10-23 ng/ml, 25-57.5 nmol/L)	Overall OR 95%CI, 0.54 (0.23-1.27), significant heterogeneity, so when excluded data on non-Hispanic Blacks - OR 95%CI, 0.36 (0.16- 0.80) Nurses Health study found significant inverse association between total vitamin D intake and incident type 2 DM, which was attenuated after adjusting for dietary factors (e.g. Mg and Ca) Limitations include variability in cohorts, lack of adjustment for confounders, e.g. other risk factors for DM or calcium intake. Variable results from intervention studies with some suggesting that vitamin D + calcium may prevent development of type 2 DM in high risk populations.

Nnoaham, 2008 [17] 7/11	Association between 25-OH-D levels and development of Tb Studies of untreated tuberculosis patients community or hospital-based (culture positive) vs. healthy controls (healthy contacts of cases, or inpatients or outpatients from same hospital who did not have a condition that would affect vitamin D status) 1 study excluded Tb patients who had risk factors for vitamin D deficiency	7 studies (3 prospective and 4 case-controls) Newcastle-Ottawa Scale used to assess quality with scores ranging from 5-7 out of 9, Higher quality studies more rigorously controlled for confounders and performed better on selection of cases and controls.	5 of 7 studies found clear difference between serum 25-OH-D levels in Tb patients vs. controls, with effect sizes ranging from 0.18 to 1.04. In two studies, lower limit of 95% CI was negative. Summary effect size suggested 25-OH-D levels are 0.68 SD lower in Tb patients vs. controls - medium to large association of 25-OH-D deficiency with Tb risk. Between study heterogeneity was stated to be low.

Magnitude of heterogeneity, I^2 <25% low, moderate 25-50% and substantial > 50%, NR Not reported
* Assessment of Multiple Systematic Reviews (AMSTAR) [1], Maximum score= 11

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