Supplementary Online Content

Zhao J-G, Zeng X-T, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2017.19344

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2017 American Medical Association. All rights reserved.

eTable 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "calcium"[MeSH Terms] OR "calcium"[All Fields] #2 "vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields] #3 "fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields] #4 systematic[sb] OR Meta-Analysis[ptyp] #5 #1 or #2 #6 #3 and #5 #7 #4 and #6
embase	#1 'calcium'/exp OR calcium #2 'vitamin d'/exp OR 'vitamin d' #3 'fracture'/exp OR fracture #4 [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim #5 #1 or #2 #6 #3 and 5 #7 #4 and #6
Cochrane library	#1 vitamin d:ti,ab,kw (Word variations have been searched) #2 calcium:ti,ab,kw (Word variations have been searched) #3 fracture:ti,ab,kw (Word variations have been searched) #4 #1 or #2 #5 #3 and #4 (restricted as Cochrane Reviews or other reviews)

© 2017 American Medical Association. All rights reserved.

eTable 2. Randomized Trials Included in Systematic Reviews or Meta-Analyses Evaluating Calcium Supplements With or Without Vitamin D for Fracture Incidence

Trials	Systematic reviews or meta-analyses			
	Bischoff-Ferrari 2007[1]	Tang 2007[2]	Rabenda 2011[3]	Bolland 2015[4]
Inkovaara 1983[5]				Y
Hansson 1987[6]				Y
Chapuy 1992[7]		Y	Y	Y
Reid 1995[8]	Y	Y	Y	Y
Chevalley 1994[9]	Y	Y	Y	Y
Recker 1996[10]		Y		Y
Dawson-Hughes 1997[11]		Y	Y	Y
Riggs 1998[12]	Y	Y	Y	Y
Baron 1999[13, 14]	Y			Y
Ruml 1999[15]				Y
Peacock 2000[16]		Y	Y	Y
Chapuy 2002[17]		Y	Y	Y
Fujita 2004[18]		Y	Y	Y
Avenell 2004[19]				Y
NoNOF 2004[20]		Y	Y	Y
Larsen 2004[21]		Y		Y

© 2017 American Medical Association. All rights reserved.

eTable 2. Randomized Trials Included in Systematic Reviews or Meta-Analyses Evaluating Calcium Supplements With or Without Vitamin D for Fracture Incidence (continued)

Trials	Systematic reviews or meta-analyses			
	Bischoff-Ferrari 2007[1]	Tang 2007[2]	Rabenda 2011[3]	Bolland 2015[4]
Porthouse 2005[22]		Y		Y
RECORD 2005[23]	Y	Y		Y
Prince 2006[24]	Y	Y	Y	Y
Reid 2006[25]	Y	Y	Y	Y
WHI 2006[26]		Y	Y	Y
Bolton-Smith 2007[27]			Y	Y
Bonnick 2007[28]				Y
Reid 2008[29]			Y	Y
OSTPRE-FPS 2010[30]			Y	Y
Sambrook 2012[31]				Y

Abbreviation: Y, yes (Each "Y" indicates that this trial was included in the systematic reviews or meta-analyses of corresponding column).

Bischoff-Ferrari 2007[1] only included double-blind randomized controlled trials with a minimum follow-up of 1 year and a minimum 100 participants.

Rabenda 2011[3] only included randomized controlled trials reporting bone mineral density changes during the follow-up.

References

1. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *The American journal of clinical nutrition.* 2007; 86(6): 1780-90.
2. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet.* 2007; 370(9588): 657-66.
3. Rabenda V, Bruyere O, Reginster JY. Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. *Osteoporosis international.* 2011; 22(3): 893-901.
4. Bolland MJ, Leung W, Tai V, et al. Calcium intake and risk of fracture: systematic review. *Bmj.* 2015; 351: h4580.
5. Inkovaara J GG, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroids in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. *Age and Ageing.* 1983; 12: 124-30.
6. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int.* 1987; 40(6): 315-7.
7. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *The New England journal of medicine.* 1992; 327(23): 1637-42.

© 2017 American Medical Association. All rights reserved.

8. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *The American journal of medicine.* 1995; 98(4): 331-5.
9. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporosis international.* 1994; 4(5): 245-52.
10. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *Journal of bone and mineral research.* 1996; 11(12): 1961-6.
11. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *The New England journal of medicine.* 1997; 337(10): 670-6.
12. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ, 3rd. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *Journal of bone and mineral research.* 1998; 13(2): 168-74.
13. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *The New England journal of medicine.* 1999; 340(2): 101-7.
14. Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA. Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. *The American journal of clinical nutrition.* 2008; 87(6): 1945-51.
15. Ruml LA, Sakhaee K, Peterson R, Adams-Huet B, Pak CY. The effect of calcium citrate on bone density in the early and mid-postmenopausal period: a randomized placebo-controlled study. *Am J Ther.* 1999; 6(6): 303-11.
16. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab.* 2000; 85(9): 3011-9.
17. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporosis international.* 2002; 13(3): 257-64.
18. Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y. Reappraisal of Katsuragi calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture. *J Bone Miner Metab.* 2004; 22(1): 32-8.
19. Avenell A, Grant AM, McGee M, et al. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clinical trials.* 2004; 1(6): 490-8.
20. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ, Nottingham Neck of Femur S. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. *Age Ageing.* 2004; 33(1): 45-51.
21. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *Journal of bone and mineral research.* 2004; 19(3): 370-8.
22. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ.* 2005; 330(7498): 1003.
23. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* 2005; 365(9471): 1621-8.
24. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med.* 2006; 166(8): 869-75.

© 2017 American Medical Association. All rights reserved.

25. Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med.* 2006; 119(9): 777-85.
26. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *The New England journal of medicine.* 2006; 354(7): 669-83.
27. Bolton-Smith C, McMurdo ME, Paterson CR, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *Journal of bone and mineral research.* 2007; 22(4): 509-19.
28. Bonnick S, Broy S, Kaiser F, et al. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. *Curr Med Res Opin.* 2007; 23(6): 1341-9.
29. Reid IR, Ames R, Mason B, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med.* 2008; 168(20): 2276-82.
30. Salovaara K, Tuppurainen M, Karkkainen M, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. *Journal of bone and mineral research.* 2010; 25(7): 1487-95.
31. Sambrook PN, Cameron ID, Chen JS, et al. Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: a cluster randomised controlled trial. *Osteoporosis international.* 2012; 23(2): 615-24.

© 2017 American Medical Association. All rights reserved.

eTable 3. Randomized Trials Included In Systematic Reviews or Meta-Analyses Evaluating Vitamin D Supplements With or Without Calcium for Fracture Incidence

Trials	Systematic reviews or meta-analyses																
	Boonen 2007[1]	Cranney 2007[2,3]	Izaks 2007[4]	Jackson 2007[5]	Avenell 2009[6]	Bischoff-Ferrari 2009[7]	Bergman 2010[8]	DIPART 2010[9]	Lai 2010[10]	Chung 2011[11]	Bischoff-Ferrari 2012[12]	Geddes 2013[13]	Avenell 2014[14]	Bolland 2014[15]	LeBlanc 2014[16,17]	Zheng 2015[18]	Weaver 2016[19]
Inkovaara 1983[20]					Y								Y				
Chapuy 1992[21]	Y	Y	Y		Y	Y	Y			Y	Y	Y	Y	Y			Y
Heikinheimo 1992[22]												Y					
Lips 1996[23]	Y	Y	Y	Y	Y	Y			Y	Y	Y	Y	Y	Y	Y		
Dawson-Hughes 1997[24]	Y	Y	Y		Y	Y	Y			Y	Y		Y	Y			Y
Komulainen 1998[25]		Y		Y						Y				Y			
Peacock 2000[26]				Y	Y								Y				
Pfeifer 2000[27]		Y	Y	Y		Y	Y			Y	Y			Y	Y		
Chapuy 2002[28]	Y	Y	Y		Y	Y	Y			Y		Y	Y	Y	Y		Y
Meyer 2002[29]	Y		Y		Y	Y		Y	Y		Y	Y	Y	Y			
Bischoff-Ferrari 2003[30]														Y			
Trivedi 2003[31]	Y	Y	Y	Y	Y	Y	Y		Y	Y			Y	Y		Y	
Avenell 2004[32]					Y								Y	Y			
NoNOF 2004[33]		Y			Y					Y			Y	Y			Y

© 2017 American Medical Association. All rights reserved.

eTable 3. Randomized Trials Included In Systematic Reviews or Meta-Analyses Evaluating Vitamin D Supplements With or Without Calcium for Fracture Incidence (continued)

Trials	Systematic reviews or meta-analyses																
	Boonen 2007[1]	Cranney 2007[2,3]	Izaks 2007[4]	Jackson 2007[5]	Avenell 2009[6]	Bischoff-Ferrari 2009[7]	Bergman 2010[8]	DIPART 2010[9]	Lai 2010[10]	Chung 2011[11]	Bischoff-Ferrari 2012[12]	Geddes 2013[13]	Avenell 2014[14]	Bolland 2014[15]	LeBlanc 2014[16,17]	Zheng 2015[18]	Weaver 2016[19]
Larsen 2004[34]		Y						Y									
Flicker 2005[35]		Y	Y			Y				Y	Y	Y		Y			
Porthouse 2005[36]	Y	Y	Y		Y		Y	Y		Y		Y	Y	Y			Y
RECORD 2005[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y			Y
Law 2006[38]		Y			Y				Y	Y			Y			Y	
WHI 2006[39]	Y	Y	Y		Y	Y		Y		Y	Y	Y	Y	Y	Y		Y
Bolton-Smith 2007[40]					Y								Y	Y			
Burleigh 2007[41]														Y			
Lyons 2007[42]					Y	Y		Y	Y	Y	Y	Y	Y	Y		Y	
Smith 2007[43]		Y			Y			Y	Y			Y	Y	Y		Y	
Prince 2008[44]														Y			
Pfeifer 2009[45]						Y					Y			Y	Y		
Bischoff-Ferrari 2010[46]											Y						
OSTPRE-FPS 2010[47]										Y			Y	Y			Y
Vital D 2010[48]										Y	Y		Y	Y		Y	

© 2017 American Medical Association. All rights reserved.

eTable 3. Randomized Trials Included In Systematic Reviews or Meta-Analyses Evaluating Vitamin D Supplements With or Without Calcium for Fracture Incidence (continued)

Trials	Systematic reviews or meta-analyses																
	Boonen 2007[1]	Crannney 2007[2, 3]	Izaks 2007[4]	Jackson 2007[5]	Avenell 2009[6]	Bischoff-Ferrari 2009[7]	Bergman 2010[8]	DIPART 2010[9]	Lai 2010[10]	Chung 2011[11]	Bischoff-Ferrari 2012[12]	Geddes 2013[13]	Avenell 2014[14]	Bolland 2014[15]	LeBlanc 2014[16, 17]	Zheng 2015[18]	Weaver 2016[19]
Witham 2010[49]													Y				
Mitri 2011[50]													Y				
Glendenning 2012[51]													Y	Y			
VitDISH 2013[52]													Y				

Abbreviation: Y, yes (Each "Y" indicates that this trial was included in the systematic reviews or meta-analyses of corresponding column)

Boonen 2007[1] only included randomized controlled trials reporting hip fracture.Jackson 2007[5] only evaluated vitamin D3 on the incidence of fracture.

Bischoff-Ferrari 2009[7] only included double-blind randomized controlled trials with a minimum follow-up of 1 year.

Bergman 2010[8] only evaluated vitamin D3 for women over 50 years of age.

DIPART 2010[9] only included randomized controlled trials with at least one intervention arm in which vitamin D was given and at least 1000 participants.

Lai 2010[10] only included randomized controlled trials reporting hip fracture.

Bischoff-Ferrari 2012[12] only included double-blind randomized controlled trials involving participants aged ≥65 years.

Geddes 2013[13] only included randomized controlled trials enrolling participants living in residential care or participants aged ≥70 years living in community.

Avenell 2014[14] updated the meta-analysis by Avenell 2009[6].

LeBlanc 2014[16, 17] only included randomized controlled trials recruiting participants with vitamin D deficiency.

Zheng 2015[18] only included randomized controlled trials involving high dose intermittent vitamin D supplementation.

Weaver 2016[19] updated the meta-analysis by Chung 2011[11].

© 2017 American Medical Association. All rights reserved.

References

1. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab.* 2007; 92(4): 1415-23.
2. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evidence report/technology assessment.* 2007; (158): 1-235.
3. Cranney A, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *The American journal of clinical nutrition.* 2008; 88(2): 513s-9s.
4. Izaks GJ. Fracture prevention with vitamin D supplementation: considering the inconsistent results. *BMC Musculoskelet Disord.* 2007; 8: 26.
5. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *Qjm.* 2007; 100(4): 185-92.
6. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev.* 2009; (2): Cd000227.
7. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2009; 169(6): 551-61.
8. Bergman GJ, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. *Curr Med Res Opin.* 2010; 26(5): 1193-201.
9. DIPART. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *Bmj*. 2010; 340: b5463.
10. Lai JK, Lucas RM, Clements MS, Roddam AW, Banks E. Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies. *BMC Public Health.* 2010; 10: 331.
11. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011; 155(12): 827-38.
12. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *The New England journal of medicine.* 2012; 367(1): 40-9.
13. Geddes JA, Inderjeeth CA. Evidence for the treatment of osteoporosis with vitamin D in residential care and in the community dwelling elderly. *Biomed Res Int.* 2013; 2013: 463589.
14. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev.* 2014; (4): Cd000227.
15. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *The lancet Diabetes & endocrinology.* 2014; 2(4): 307-20.
16. LeBlanc E, Chou R, Zakher B, Daeges M, Pappas M. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.

© 2017 American Medical Association. All rights reserved.

Screening for Vitamin D Deficiency: Systematic Review for the US Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
17. LeBlanc ES, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2015; 162(2): 109-22.
18. Zheng YT, Cui QQ, Hong YM, Yao WG. A meta-analysis of high dose, intermittent vitamin D supplementation among older adults. *PLoS One.* 2015; 10(1): e0115850.
19. Weaver CM, Alexander DD, Boushey CJ, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporosis international.* 2016; 27(1): 367-76.
20. Inkovaara J GG, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroids in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. *Age and Ageing.* 1983; 12: 124-30.
21. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *The New England journal of medicine.* 1992; 327(23): 1637-42.
22. Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int.* 1992; 51(2): 105-10.
23. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Ann Intern Med.* 1996; 124(4): 400-6.
24. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *The New England journal of medicine.* 1997; 337(10): 670-6.
25. Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas.* 1998; 31(1): 45-54.
26. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab.* 2000; 85(9): 3011-9.
27. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *Journal of bone and mineral research.* 2000; 15(6): 1113-8.
28. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporosis international.* 2002; 13(3): 257-64.
29. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *Journal of bone and mineral research.* 2002; 17(4): 709-15.
30. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *Journal of bone and mineral research.* 2003; 18(2): 343-51.
31. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in

© 2017 American Medical Association. All rights reserved.

the community: randomised double blind controlled trial. *BMJ.* 2003; 326(7387): 469.
32. Avenell A, Grant AM, McGee M, et al. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clinical trials.* 2004; 1(6): 490-8.
33. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ, Nottingham Neck of Femur S. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. *Age Ageing.* 2004; 33(1): 45-51.
34. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *Journal of bone and mineral research.* 2004; 19(3): 370-8.
35. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc.* 2005; 53(11): 1881-8.
36. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ.* 2005; 330(7498): 1003.
37. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* 2005; 365(9471): 1621-8.
38. Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing.* 2006; 35(5): 482-6.
39. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *The New England journal of medicine.* 2006; 354(7): 669-83.
40. Bolton-Smith C, McMurdo ME, Paterson CR, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *Journal of bone and mineral research.* 2007; 22(4): 509-19.
41. Burleigh E, McColl J, Potter J. Does vitamin D stop inpatients falling? A randomised controlled trial. *Age Ageing.* 2007; 36(5): 507-13.
42. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporosis international.* 2007; 18(6): 811-8.
43. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology.* 2007; 46(12): 1852-7.
44. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med.* 2008; 168(1): 103-8.
45. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporosis international.* 2009; 20(2): 315-22.
46. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Arch Intern Med.* 2010; 170(9): 813-20.

© 2017 American Medical Association. All rights reserved.

47. Salovaara K, Tuppurainen M, Karkkainen M, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. *Journal of bone and mineral research.* 2010; 25(7): 1487-95.
48. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *Jama.* 2010; 303(18): 1815-22.
49. Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circulation Heart failure.* 2010; 3(2): 195-201.
50. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *The American journal of clinical nutrition.* 2011; 94(2): 486-94.
51. Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *Journal of bone and mineral research.* 2012; 27(1): 170-6.
52. Witham MD, Price RJ, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA internal medicine.* 2013; 173(18): 1672-9.

© 2017 American Medical Association. All rights reserved.

eTable 4. Excluded Trials and Reasons for Exclusion

Excluded trials	Reason for exclusion
Chapuy 1992[1]	This randomised trial exclusively enrolled participants living in institution
Heikinheimo 1992[2]	Although it is an open quasi-randomised trial. But the design and management of this trial were obviously unreasonable. Participants in vitamin D injection group who rejected injection were added to the control group. Like previous meta-analyses, we also excluded this trial.
Chevalley 1994[3]	In this trial, although subjects were randomly allocated to three groups receiving 800 mg elemental calcium in two different forms or a placebo, authors also described “All the participants received a single oral dose of 300 000 IU vitamin D3 (cholecalciferol) at the beginning of the study”. In other word, there was no real placebo group in this trial.
Komulainen 1998[4]	This randomized trial did not designed placebo or no treatment group
Pfeifer 2000[5]	This randomized trial did not include placebo or no treatment group
Chapuy 2002[6]	This randomized trial exclusively enrolled participants living in institution
Meyer 2002[7]	This randomized trial exclusively enrolled participants living in institution
Bischoff 2003[8]	This randomized trial did not include placebo or no treatment group
Fujita 2004[9]	This randomized trial exclusively enrolled participants living in institution
Larsen 2004[10]	In this cluster trial, no treatment group received vitamin D and calcium alone. In addition, the reports of the design do not appear to fit that description.
Flicker 2005[11]	This randomized trial did not include placebo or no treatment group
Law 2006[12]	This randomized trial exclusively enrolled participants living in institution
Bonnick 2007[13]	This randomized trial did not include placebo or no treatment group
Burleigh 2007[14]	This randomized trial did not include placebo or no treatment group
Lyons 2007[15]	This randomized trial exclusively enrolled participants living in institution
Prince 2008[16]	This randomized trial did not include placebo or no treatment group
Reid 2008[17]	In this trial, almost all fracture caused by substantial trauma, not fragility fractures

© 2017 American Medical Association. All rights reserved.

eTable 4. Excluded Trials and Reasons for Exclusion (continued)

Excluded trials	Reason for exclusion
Pfeifer 2009[18]	This randomized trial did not include placebo or no treatment group
Bischoff-Ferrari 2010[19]	This randomized trial did not include placebo or no treatment group
Witham 2010[20]	This randomized trial exclusively enrolled participants living in institution
Sambrook 2012[21]	In the calcium group of this cluster trial, sunlight exposure also was specifically imposed
Schaller 2012[22]	This randomized trial did not include placebo or no treatment group
Sakalli 2012[23]	This study did not reported fracture data
Rossini 2012[24]	This is a non- randomized trial
Bang 2013[25]	This trial only enrolled HIV-1-infected patients, with mean age < 50, and did not reported fracture data
Tella 2014[26]	This is a conference abstract. This randomized trial did not include real placebo group because calcium supplements were given to maintain total calcium intake of 1200-1400 mg/day for all participants
Takano 2014[27]	This randomized trial did not include placebo or no treatment group
REVITAHIP trial 2014 2016[28,29]	This randomized trial did not include placebo or no treatment group
Wang 2015[30]	Intervention group included multivitamin and mineral supplementation
Rolighed 2015[31]	This study did not reported fracture data
Martineau 2013[32]2015[33]	This is a cluster randomised trial, without placebo or no treatment group
Schwetz 2017[34]	This study did not reported fracture data
Laiz 2017[35]	In the vitamin D group, exercise also was specifically combined
Holmoy 2017[36]	Participants were not older people. This randomized trial did not include placebo or no treatment group
Hejazi 2017[37]	This study did not reported fracture data
Ginde 2017[38]	This study only enrolled long-term care residents, and did not include placebo or no treatment group
Pop 2017[39]	This randomized trial did not include placebo or no treatment group
VITAL trial[40,41]	This is an ongoing study, and no fracture data is available now

© 2017 American Medical Association. All rights reserved.

References

1. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *The New England journal of medicine.* Dec 03 1992;327(23):1637-1642.
2. Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int.* Aug 1992;51(2):105-110.
3. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporosis international.* Sep 1994;4(5):245-252.
4. Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas.* Nov 30 1998;31(1):45-54.
5. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *Journal of bone and mineral research.* Jun 2000;15(6):1113-1118.
6. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporosis international.* Mar 2002;13(3):257-264.
7. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *Journal of bone and mineral research.* Apr 2002;17(4):709-715.
8. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *Journal of bone and mineral research.* Feb 2003;18(2):343-351.
9. Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y. Reappraisal of Katsuragi calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture. *J Bone Miner Metab.* 2004;22(1):32-38.
10. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *Journal of bone and mineral research.* Mar 2004;19(3):370-378.
11. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc.* Nov 2005;53(11):1881-1888.
12. Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing.* Sep 2006;35(5):482-486.
13. Bonnick S, Broy S, Kaiser F, et al. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. *Curr Med Res Opin.* Jun 2007;23(6):1341-1349.
14. Burleigh E, McColl J, Potter J. Does vitamin D stop inpatients falling? A randomised controlled trial. *Age Ageing.* Sep 2007;36(5):507-513.
15. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporosis international.* Jun 2007;18(6):811-818.
16. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch*

© 2017 American Medical Association. All rights reserved.

Intern Med. Jan 14 2008;168(1):103-108.

17. Reid IR, Ames R, Mason B, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med.* Nov 10 2008;168(20):2276-2282.

18. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporosis international.* Feb 2009;20(2):315-322.

19. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Arch Intern Med.* May 10 2010;170(9):813-820.

20. Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circulation. Heart failure.* Mar 2010;3(2):195-201.

21. Sambrook PN, Cameron ID, Chen JS, et al. Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: a cluster randomised controlled trial. *Osteoporosis international.* Feb 2012;23(2):615-624.

22. Schaller F, Sidelnikov E, Theiler R, et al. Mild to moderate cognitive impairment is a major risk factor for mortality and nursing home admission in the first year after hip fracture. *Bone.* Sep 2012;51(3):347-352.

23. Sakalli H, Arslan D, Yucel AE. The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. *Rheumatology international.* 2012;32(8):2279-2283.

24. Rossini M, Gatti D, Viapiana O, et al. Short-term effects on bone turnover markers of a single high dose of oral vitamin D? *The Journal of clinical endocrinology and metabolism.* 2012;97(4):E622-626.

25. Bang UC, Kolte L, Hitz M, et al. The effect of cholecalciferol and calcitriol on biochemical bone markers in HIV type 1-infected males: results of a clinical trial. *AIDS research and human retroviruses.* Apr 2013;29(4):658-664.

26. Tella H, Gallagher JC, Smith L. Effect of vitamin D supplementation on BMD in young and elderly caucasian and African American women: two randomized, placebo controlled trials. *Endocrine reviews. Conference: 96th annual meeting and expo of the endocrine society, ENDO 2014. Chicago, IL united states.* 2014;35(no pagination).

27. Takano T, Kondo S, Saito H, Matsumoto T. Relationship between the effect of eldecalcitol and serum 25(OH)D level. *The Journal of steroid biochemistry and molecular biology.* Oct 2014;144 Pt A:124-127.

28. Mak JC, Mason RS, Klein L, Cameron ID. An initial loading-dose vitamin D versus placebo after hip fracture surgery: randomized trial. *BMC Musculoskeletal Disorders.* 2016;17(1):1-11.

29. Mak JC, Klein LA, Finnegan T, Mason RS, Cameron ID. An initial loading-dose vitamin D versus placebo after hip fracture surgery: baseline characteristics of a randomized controlled trial (REVITAHIP). *BMC geriatrics.* 2014;14:101.

30. Wang SM, Yin LY, Zhang Y, et al. Multivitamin and mineral supplementation is associated with the reduction of fracture risk and hospitalization rate in Chinese adult males: a randomized controlled study. *Journal of Bone and Mineral Metabolism.* 2015;33(3):294-302.

© 2017 American Medical Association. All rights reserved.

31. Rolighed L, Rejnmark L, Sikjaer T, et al. No beneficial effects of vitamin D supplementation on muscle function or quality of life in primary hyperparathyroidism: Results from a randomized controlled trial. *European journal of endocrinology.* 2015;172(5):609-617.

32. Martineau AR, Hanifa Y, Hooper RL, Witt KD, Patel M, Syed A. Increased risk of upper respiratory infection with addition of intermittent bolus-dose vitamin D supplementation to a daily low-dose regimen [Abstract]. *Thorax.* 2013;68(Suppl 3):A64 [s123]

33. Martineau AR, Hanifa Y, Witt KD, et al. Double-blind randomised controlled trial of vitamin D supplementation for the prevention of acute respiratory infection in older adults. *Thorax.* 2015.

34. Schwetz V, Trummer C, Pandis M, et al. Effects of vitamin D supplementation on bone turnover markers: A randomized controlled trial. *Nutrients.* 2017;9(5).

35. Laiz A, Malouf J, Marin A, et al. Impact of 3-monthly vitamin D supplementation plus exercise on survival after surgery for osteoporotic hip fracture in adult patients over 50 years: A pragmatic randomized, partially blinded, controlled trial. *Journal of Nutrition, Health and Aging.* 2017;21(4):413-420.

36. Holmoy T, Lindstrom JC, Eriksen EF, Steffensen LH, Kampman MT. High dose vitamin D supplementation does not affect biochemical bone markers in multiple sclerosis - a randomized controlled trial. *BMC neurology.* Apr 04 2017;17(1):67.

37. Hejazi ME, Modarresi-Ghazani F, Hamishehkar H, Mesgari-Abbasi M, Dousti S, Entezari-Maleki T. The Effect of Treatment of Vitamin D Deficiency on the Level of P-Selectin and hs-CRP in Patients With Thromboembolism: A Pilot Randomized Clinical Trial. *Journal of Clinical Pharmacology.* 2017;57(1):40-47.

38. Ginde AA, Blatchford P, Breese K, et al. High-Dose Monthly Vitamin D for Prevention of Acute Respiratory Infection in Older Long-Term Care Residents: A Randomized Clinical Trial. *Journal of the American Geriatrics Society.* 2017;65(3):496-503.

39. Pop LC SD, Schneider SH, Schlussel Y, Stahl T, Gordon C, Wang X, Papathomas TV, Shapses SA. Three doses of vitamin D, bone mineral density, and geometry in older women during modest weight control in a 1-year randomized controlled trial. *Osteoporosis International. (pp 1-12), 2016. Date of Publication: 17 Aug 2016.* 2016.

40. Manson JE, Bassuk SS, Lee IM, et al. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemporary clinical trials.* 2012;33(1):159-171.

41. LeBoff MS, Yue AY, Copeland T, Cook NR, Buring JE, Manson JE. VITAL-Bone Health: Rationale and design of two ancillary studies evaluating the effects of vitamin D and/or omega-3 fatty acid supplements on incident fractures and bone health outcomes in the VITamin D and OmegA-3 TriaL (VITAL). *Contemporary Clinical Trials.* 2015;41:259-268.

© 2017 American Medical Association. All rights reserved.

eTable 5. Results of Sensitivity Analyses With Exclusion of the Listed Trials[a]

Removed trials	Fracture site	No of studies	No of participants	Relative risk (95% CI)
Calcium versus placebo or no treatment				
Inkovaara 1983[1]				
Before sensitivity analysis	Total fracture	7	6787	0.88 [0.75, 1.03]
After sensitivity analysis	Total fracture	6	6703	0.88 [0.75, 1.04]
Hansson 1987[2]				
Before sensitivity analysis	Vertebral fracture	9	6517	0.83 [0.66, 1.05]
After sensitivity analysis	Vertebral fracture	8	6467	0.83 [0.66, 1.05]
Baron 1999[3,4]				
Before sensitivity analysis	Hip fracture	6	6703	1.53 [0.97, 2.42]
After sensitivity analysis	Hip fracture	5	5773	1.56 [0.91, 2.69]
Before sensitivity analysis	Total fracture	7	6787	0.88 [0.75, 1.03]
After sensitivity analysis	Total fracture	6	5857	0.91 [0.80, 1.03]
Vitamin D versus placebo or no treatment				
Inkovaara 1983[1]				
Before sensitivity analysis	Total fracture	14	13106	1.01 [0.87, 1.17]
After sensitivity analysis	Total fracture	13	13019	1.02 [0.88, 1.18]
Mitri 2011[5]				
Before sensitivity analysis	Non-vertebral fracture	8	20443	1.10 [1.00, 1.21]
After sensitivity analysis	Non-vertebral fracture	7	20396	1.10 [1.00, 1.21]
Before sensitivity analysis	Total fracture	14	13106	1.01 [0.87, 1.17]
After sensitivity analysis	Total fracture	13	13059	1.01 [0.87, 1.17]
TIDE 2012[6]				
Before sensitivity analysis	Total fracture	14	13106	1.01 [0.87, 1.17]
After sensitivity analysis	Total fracture	13	11885	1.01 [0.86, 1.18]

© 2017 American Medical Association. All rights reserved.

eTable 5. Results of Sensitivity Analyses by Excluding of the Listed Trials[a] (continued)				
Removed trials	**Fracture site**	**No of studies**	**No of participants**	**Relative risk (95% CI)**
Vitamin D versus placebo or no treatment				
VitDISH 2013[7]				
Before sensitivity analysis	Non-vertebral fracture	8	20443	1.10 [1.00, 1.21]
After sensitivity analysis	Non-vertebral fracture	7	20284	1.10 [1.00, 1.21]
Before sensitivity analysis	Total fracture	14	13106	1.01 [0.87, 1.17]
After sensitivity analysis	Total fracture	13	12947	1.01 [0.87, 1.18]
VitaDial 2014[8]				
Before sensitivity analysis	Total fracture	14	13106	1.01 [0.87, 1.17]
After sensitivity analysis	Total fracture	13	13051	1.02 [0.90, 1.16]
Calcium plus vitamin D versus placebo or no treatment				
Inkovaara 1983[1]				
Before sensitivity analysis	Total fracture	8	10064	0.90 [0.78, 1.04]
After sensitivity analysis	Total fracture	7	9976	0.91 [0.79, 1.05]

[a] Sensitivity analysis was performed by excluding each listed trial.

References

1. Inkovaara J GG, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroids in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. *Age and Ageing.* 1983;12:124-130.
2. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int.* Jun 1987;40(6):315-317.
3. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *The New England journal of medicine.* Jan 14 1999;340(2):101-107.
4. Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA. Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. *The American journal of clinical nutrition.* Jun 2008;87(6):1945-1951.
5. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *The American journal of clinical nutrition.* Aug 2011;94(2):486-494.

© 2017 American Medical Association. All rights reserved.

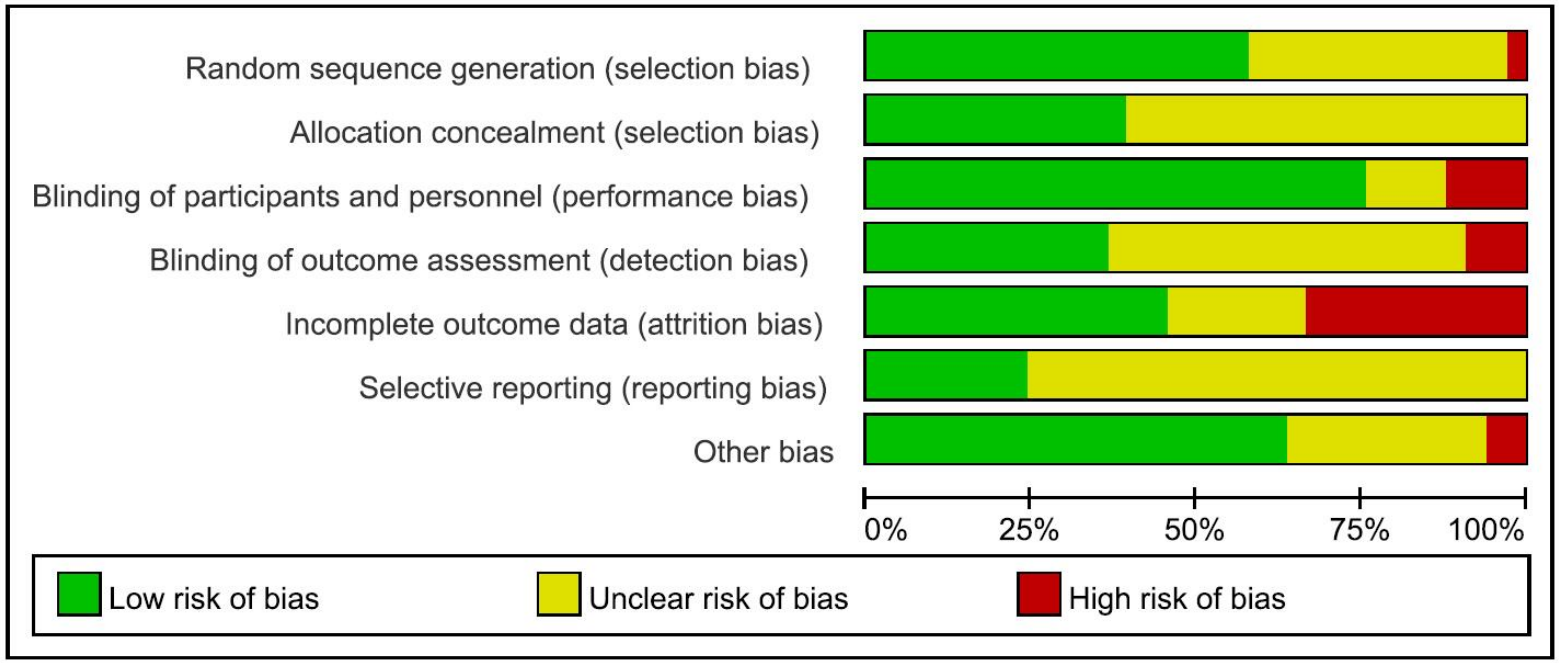
6. Punthakee Z, Bosch J, Dagenais G, et al. Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. *Diabetologia.* 2012;55(1):36-45.

7. Witham MD, Price RJ, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA internal medicine.* Oct 14 2013;173(18):1672-1679.

8. Massart A, Debelle FD, Racapé J, et al. Biochemical parameters after Cholecalciferol repletion in hemodialysis: Results from the vitadial randomized trial. *American Journal of Kidney Diseases.* 2014;64(5):696-705.

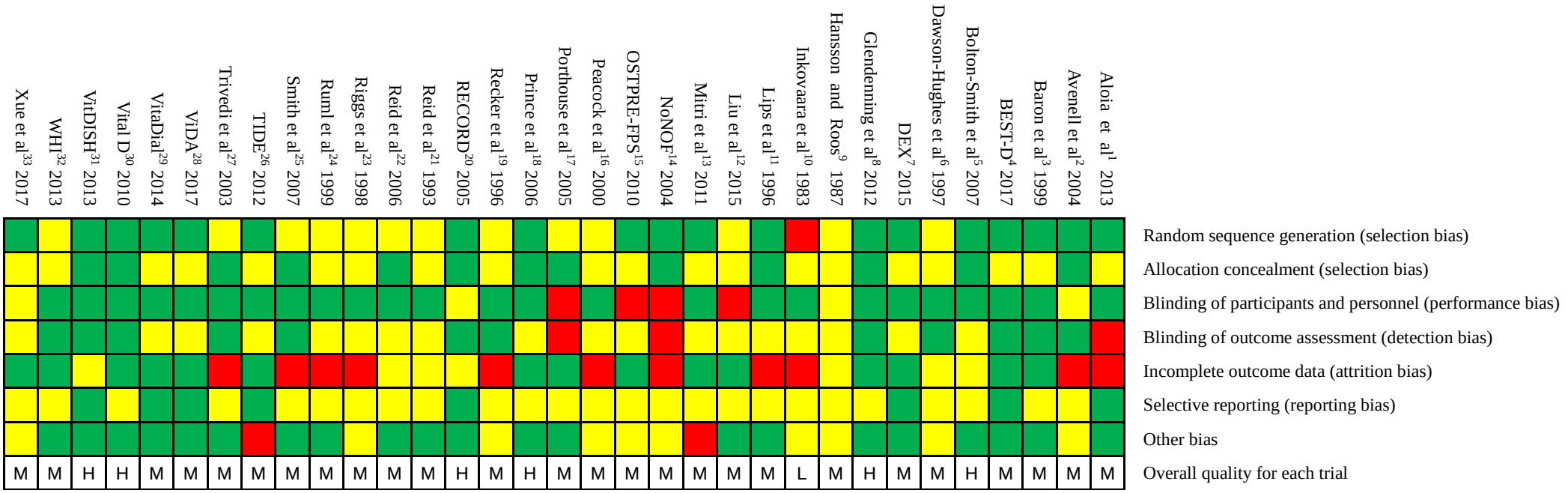
© 2017 American Medical Association. All rights reserved.

eFigure 1. Number/Proportions of Trials That Met Each Criterion for Risk of Bias Across the 33 Included Trials



© 2017 American Medical Association. All rights reserved.

eFigure 2. Results of the Risk of Bias for 33 Included Trials



Abbreviations: H, high quality; L, low quality; M, moderate quality. Green means low risk; yellow means unclear risk; red means high risk

References

1. Aloia JF, Dhaliwal R, Shieh A, Mikhail M, Islam S, Yeh JK. Calcium and vitamin d supplementation in postmenopausal women. *J Clin Endocrinol Metab.* Nov 2013;98(11):E1702-1709.
2. Avenell A, Grant AM, McGee M, et al. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clinical trials.* 2004;1(6):490-498.
3. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *The New England journal of medicine.* Jan 14 1999;340(2):101-107.

© 2017 American Medical Association. All rights reserved.

4. Hin H, Tomson J, Newman C, et al. Optimum dose of vitamin D for disease prevention in older people: BEST-D trial of vitamin D in primary care. *Osteoporosis International.* 2017;28(3):841-851.

5. Bolton-Smith C, McMurdo ME, Paterson CR, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *Journal of bone and mineral research.* Apr 2007;22(4):509-519.

6. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *The New England journal of medicine.* Sep 04 1997;337(10):670-676.

7. Uusi-Rasi K, Patil R, Karinkanta S, et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA internal medicine.* May 2015;175(5):703-711.

8. Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *Journal of bone and mineral research.* Jan 2012;27(1):170-176.

9. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int.* Jun 1987;40(6):315-317.

10. Inkovaara J GG, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroids in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. *Age and Ageing.* 1983;12:124-130.

11. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Ann Intern Med.* Feb 15 1996;124(4):400-406.

12. Liu BX, Chen SP, Li YD, et al. The Effect of the Modified Eighth Section of Eight-Section Brocade on Osteoporosis in Postmenopausal Women: A Prospective Randomized Trial. *Medicine.* Jun 2015;94(25):e991.

13. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *The American journal of clinical nutrition.* Aug 2011;94(2):486-494.

14. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ, Nottingham Neck of Femur S. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. *Age Ageing.* Jan 2004;33(1):45-51.

15. Salovaara K, Tuppurainen M, Karkkainen M, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. *Journal of bone and mineral research.* Jul 2010;25(7):1487-1495.

16. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab.* Sep 2000;85(9):3011-3019.

17. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of

© 2017 American Medical Association. All rights reserved.

fractures in primary care. *BMJ.* Apr 30 2005;330(7498):1003.

18. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med.* Apr 24 2006;166(8):869-875.

19. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *Journal of bone and mineral research.* Dec 1996;11(12):1961-1966.

20. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* May 7-13 2005;365(9471):1621-1628.

21. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Effect of calcium supplementation on bone loss in postmenopausal women. *The New England journal of medicine.* Feb 18 1993;328(7):460-464.

22. Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. *The American journal of medicine.* Sep 2006;119(9):777-785.

23. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ, 3rd. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *Journal of bone and mineral research.* Feb 1998;13(2):168-174.

24. Ruml LA, Sakhaee K, Peterson R, Adams-Huet B, Pak CY. The effect of calcium citrate on bone density in the early and mid-postmenopausal period: a randomized placebo-controlled study. *Am J Ther.* Nov 1999;6(6):303-311.

25. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology.* Dec 2007;46(12):1852-1857.

26. Punthakee Z, Bosch J, Dagenais G, et al. Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. *Diabetologia.* 2012;55(1):36-45.

27. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ.* Mar 01 2003;326(7387):469.

28. Khaw KT, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. *The Lancet Diabetes and Endocrinology.* 2017;5(6):438-447.

29. Massart A, Debelle FD, Racapé J, et al. Biochemical parameters after Cholecalciferol repletion in hemodialysis: Results from the vitadial randomized trial. *American Journal of Kidney Diseases.* 2014;64(5):696-705.

30. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *Jama.* May 12 2010;303(18):1815-1822.

31. Witham MD, Price RJ, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA internal medicine.* Oct 14 2013;173(18):1672-1679.

32. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *The New England journal of medicine.* Feb

© 2017 American Medical Association. All rights reserved.

16 2006;354(7):669-683.

33. Xue Y, Hu Y, Wang O, et al. Effects of Enhanced Exercise and Combined Vitamin D and Calcium Supplementation on Muscle Strength and Fracture Risk in Postmenopausal Chinese Women. *Chinese medical sciences journal.* Jun 20 2017;39(3):345-351.

© 2017 American Medical Association. All rights reserved.