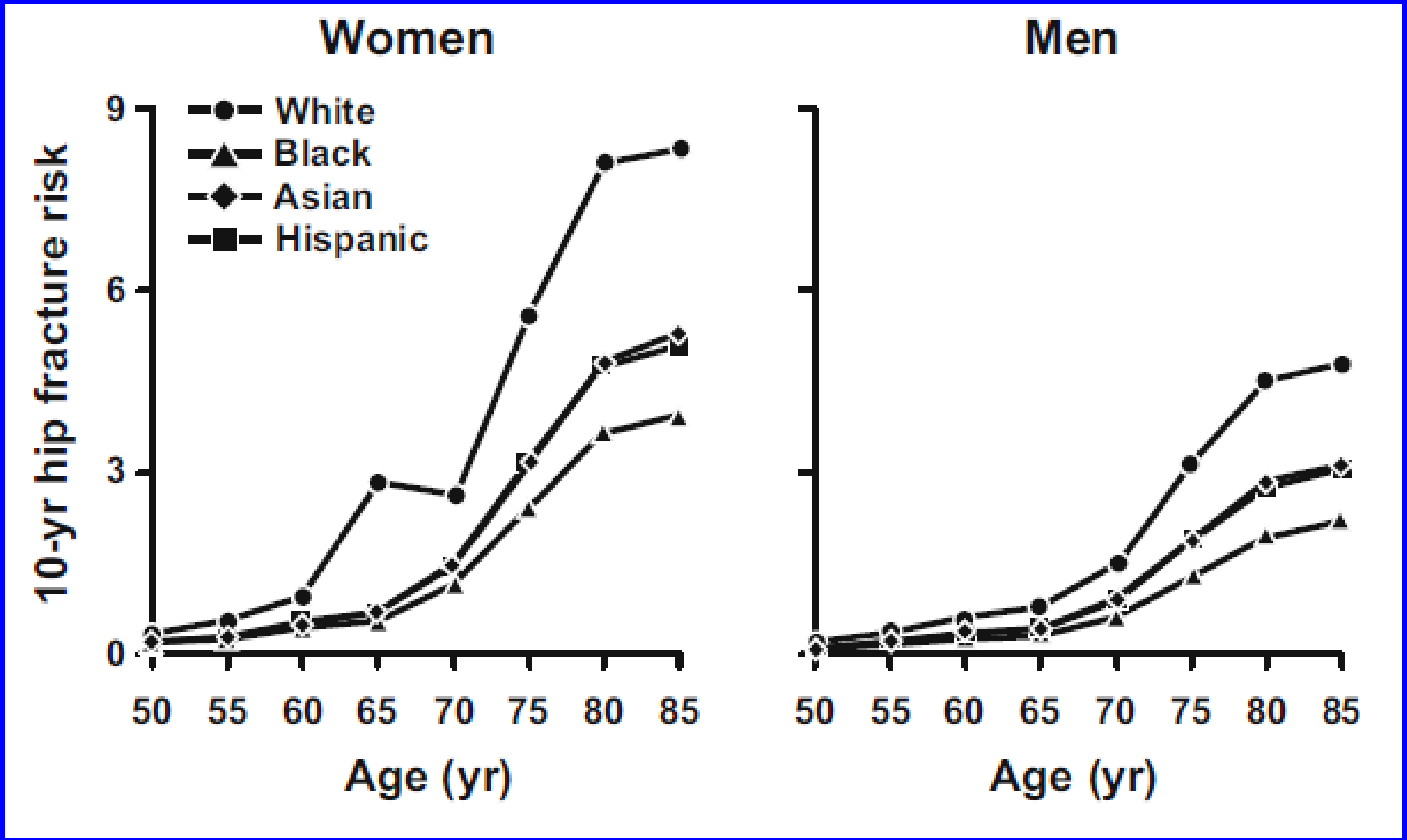
Osteoporosis, sarcopenia, and fall risk in women

Bess Dawson-Hughes, MD

Objectives

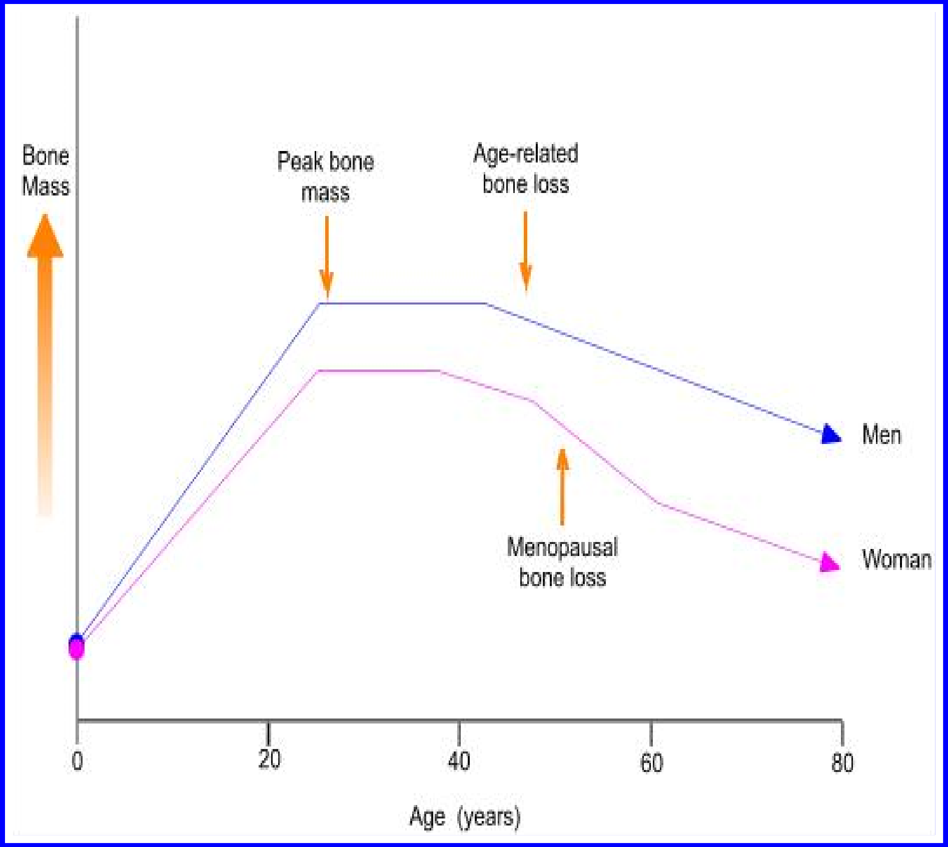
- Prevalence, prevention, treatment, and risk factors for osteoporosis, sarcopenia and frailty in women
- Age-related skeletal muscle dysfunction and link to falls and fractures
- Research accomplishments in treating musculoskeletal disorders
- Research gaps and opportunities to advance the treatment of musculoskeletal disorders

FRAX based 10-year probability of a hip fracture in US women and men by race/ethnicity



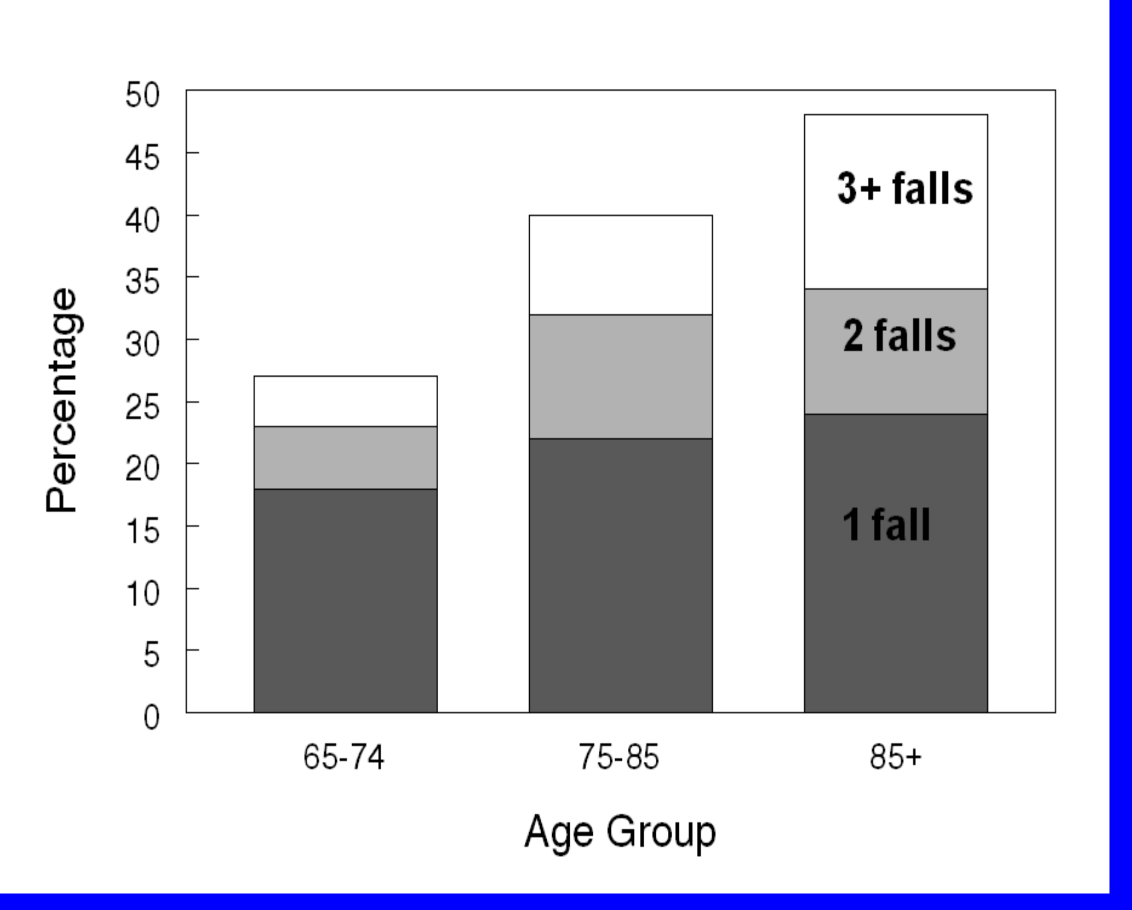
Dawson-Hughes B. Osteoporosis Int 2008; 19:449-58.

Why are women at higher risk of fracture than men?



Aging and compounding falls

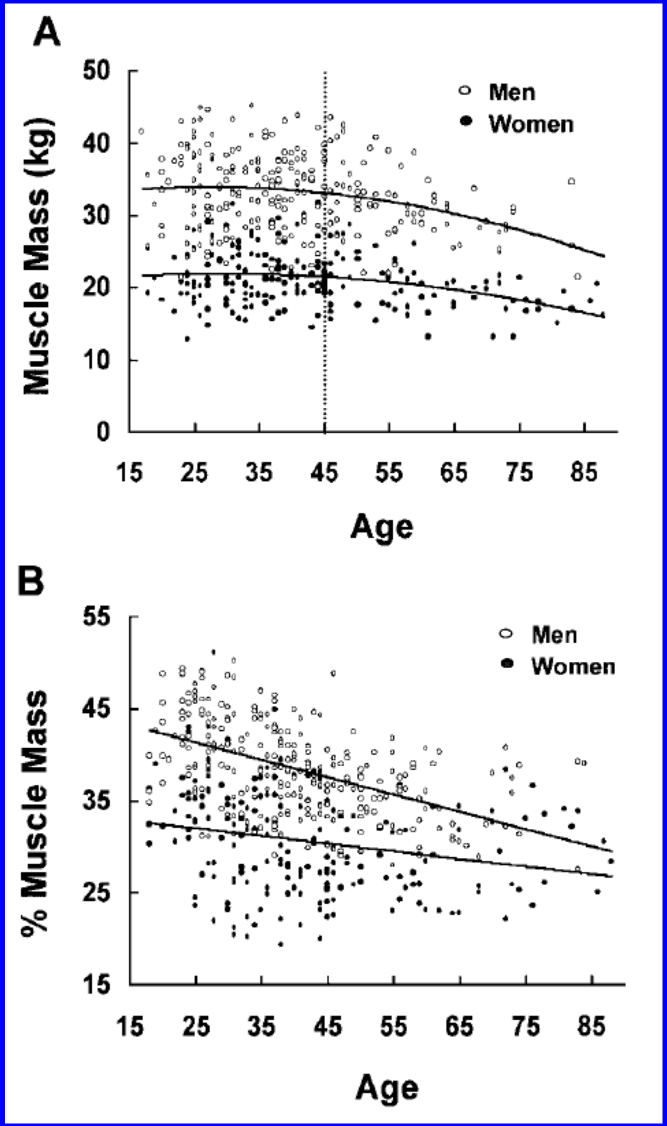
Proportions of older community-dwelling women who reported falling in a 12-month period (The Randwick Study)



Lord SR. Australian J Pub Health 1993;17:240-5

Muscle mass by whole body MRI in 468 men and women

(67% Caucasian, 17% African-American, 8% Asian, 7% Hispanic)



Men 33 kg
Women 21 kg

Men 38.4%
Women 30.6%

Janssen I. J Appl Physiol 2000;89:81-88.

Sarcopenia contributes to frailty

Components of Frailty

- Unintentional wt loss (>10 lb in last yr)
- Exhaustion
- Weakness (grip strength in lowest 20%ile)
- Slow gait (slowest 20%ile by gender and height)
- Low physical activity (<383 kcal/wk males, <270 females)

Fried LP. J Gerontol 2001;56:M146-156.

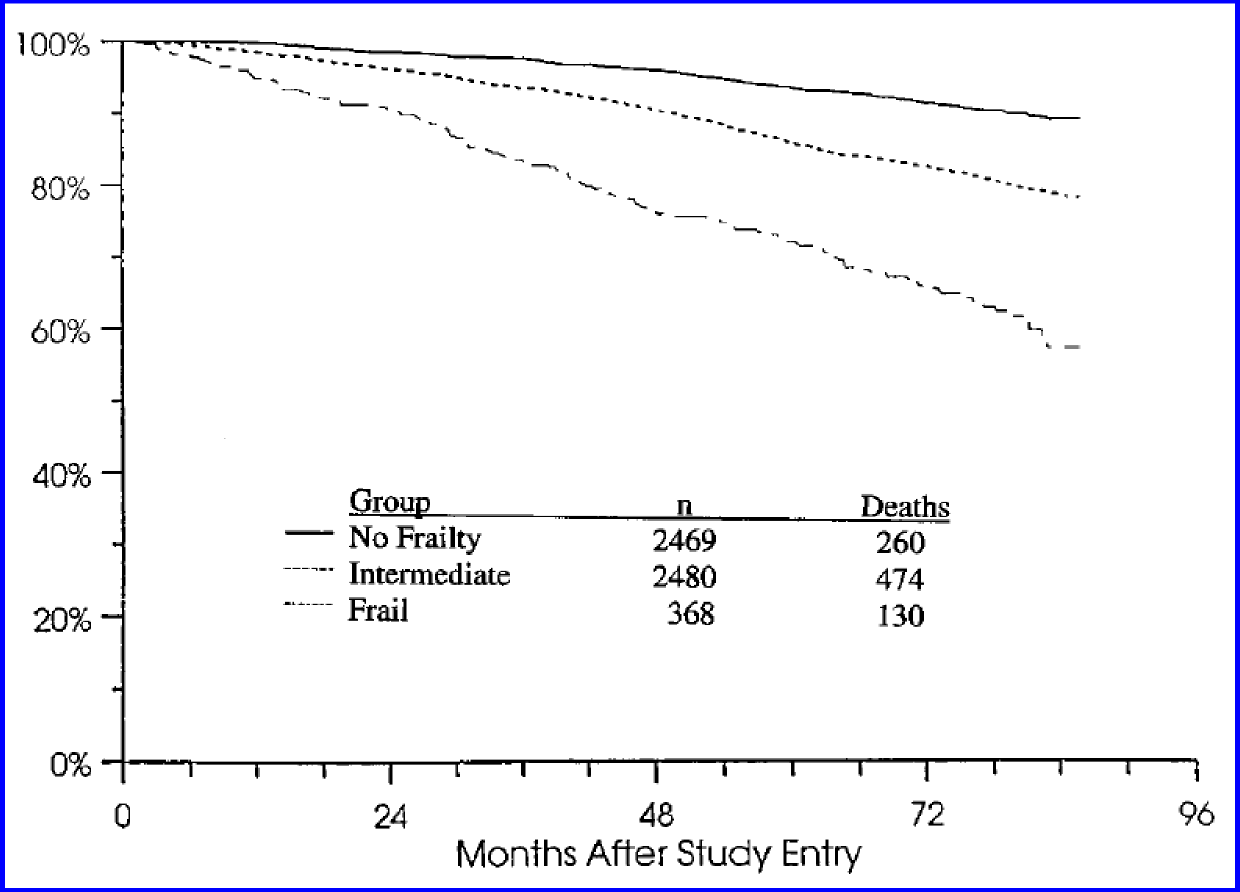
Prevalence of pre-frailty and frailty
(in 5317 adults age 65+ in Cardiovascular Health Study)

# of components	Men %	**Women %**	Total %
0	45	48	46
1	32	33	32
2 (**pre-frail**)	**15**	**14**	**15**
3 (**frail**)	**6**	**6**	**6**
4	2	1	1
5	0.2	0.1	0.2

Fried LP. J Gerontol 2001;56:M146-156.

Survival curves by frailty status

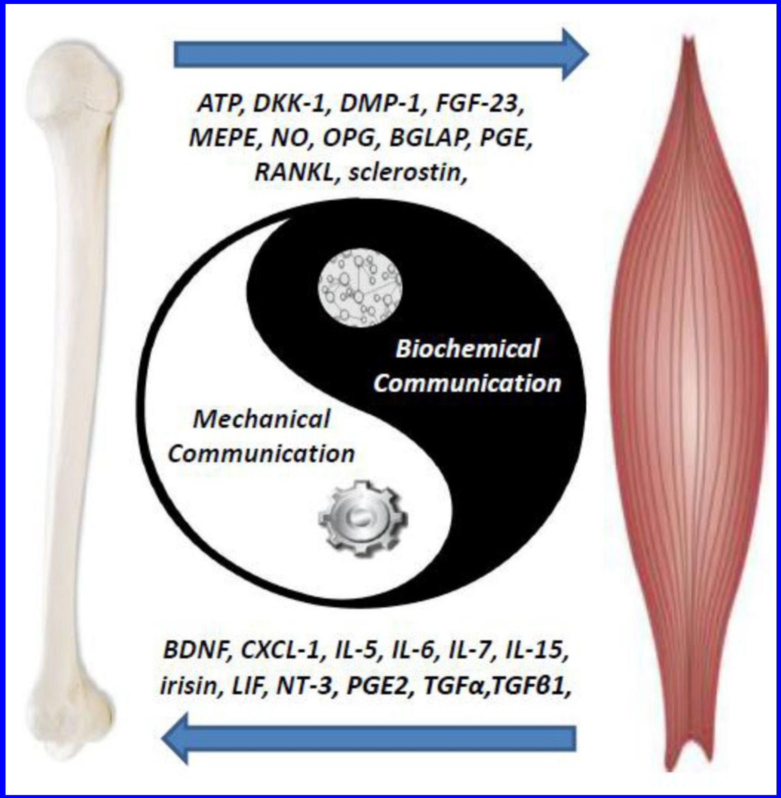
(in 5317 adults age 65+ in Cardiovascular Health Study)



Fried LP. J Gerontol 2001;56:M146-156.

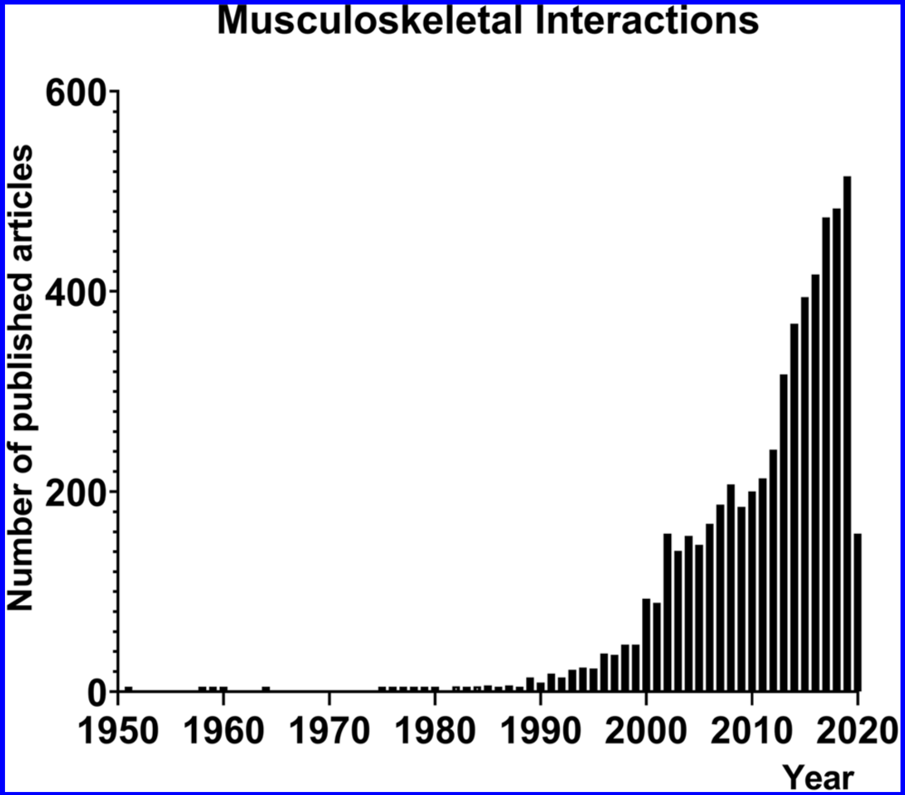
Bone-muscle cross-talk

Mechanisms



Brotto M, Bonewald L. Bone 2015;80:109-114.

Number of published articles



Lara-Castillo N and Johnson ML. Current osteoporosis reports 2020;18:408-421.

“Osteosarcopenia”

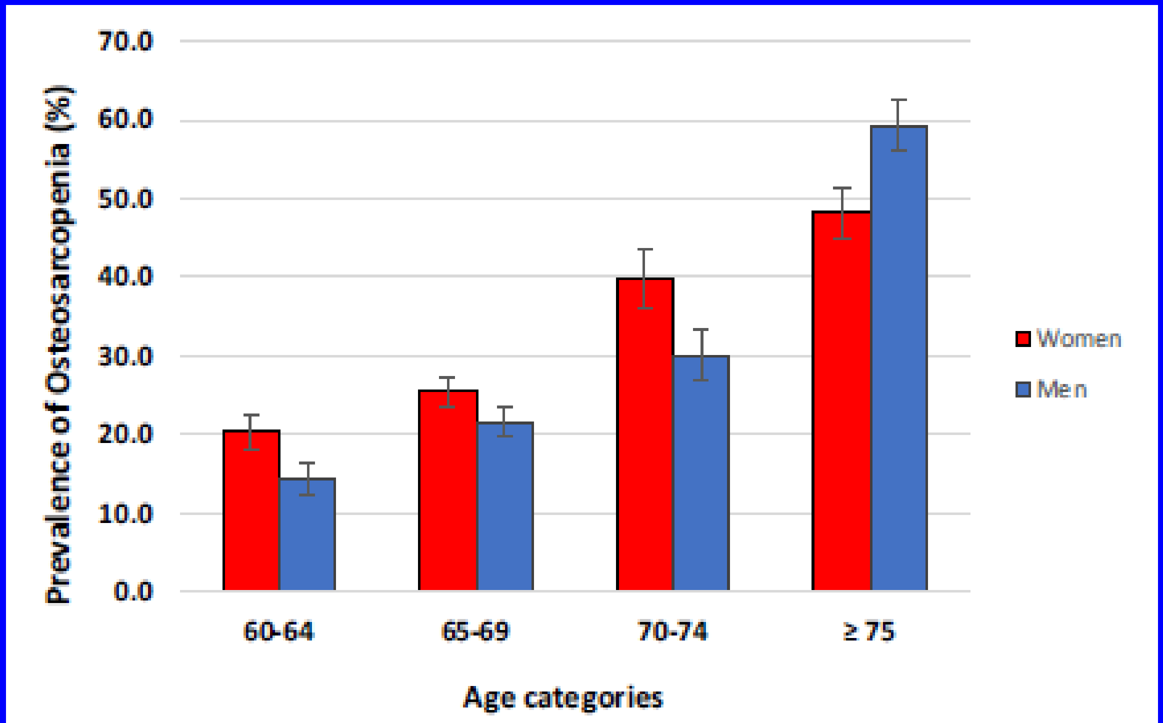
- Osteosarcopenia is characterized by loss of appetite, weight loss, and loss of bone and muscle mass

- The definition of osteopenia/osteoporosis is standardized (WHO T-score < -1)

- The definition of sarcopenia is *not standardized*; common definitions include:
  - low lean mass by DXA
  - low lean mass by DXA + low grip strength
  - low lean mass by DXA + slow gait speed
  - low lean mass by DXA + low grip and low gait speed

Prevalence of osteosarcopenia by age category in men and women

(population based study in 2353 adults age 60+ in Iran; sarcopenia defined as DXA lean mass/ht^2 <7.0 kg/m^2 for men and <5.4 for women)

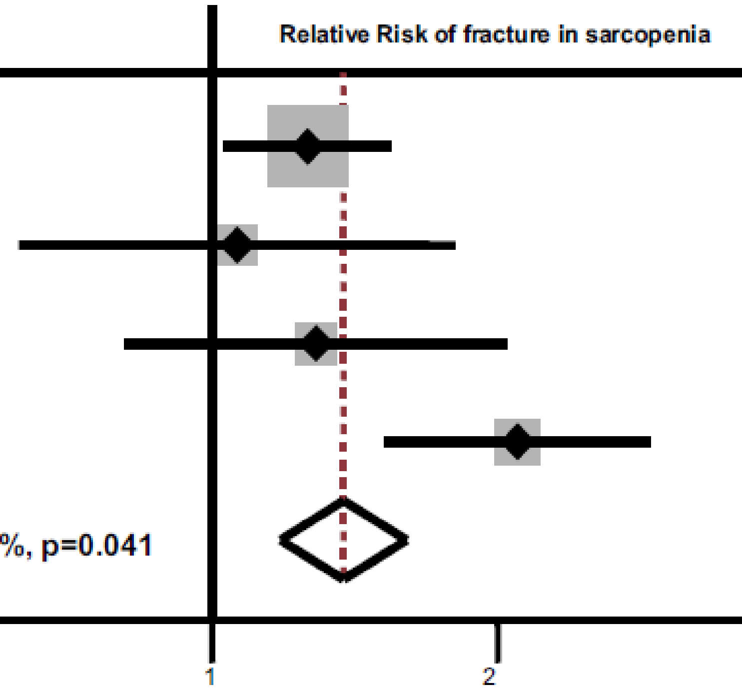


	N	Crude rate	Age-standardized rate (95% CI)
Women	1205	30.6	33.9 (30.9, 36.8)
Men	1148	29.5	33.8 (31.0, 36.5)

Fahimfar N. Calcif Tissue Int 2020;106:364-370.

Meta-analysis: Relative risk of fracture in adults with sarcopenia

Study	Sarcopenia N: + F	Sarcopenia N: Total	No Sarcopenia N: + F	No Sarcopenia N: Total	RR (95% CI)	Weight%
Cawthon	79	257	1305	5677	1.26 (1.03, 1.53)	59.71
Hars	14	102	104	811	1.06 (0.63, 1.79)	11.66
Huo	26	87	33	151	1.28 (0.81, 2.03)	12.51
Locquet	48	64	54	208	2.08 (1.51, 2.86)	16.12
Overall p<0.001, Heterogeneity: I^2= 63.6%, p=0.041					1.37 (1.18, 1.59)	100.00

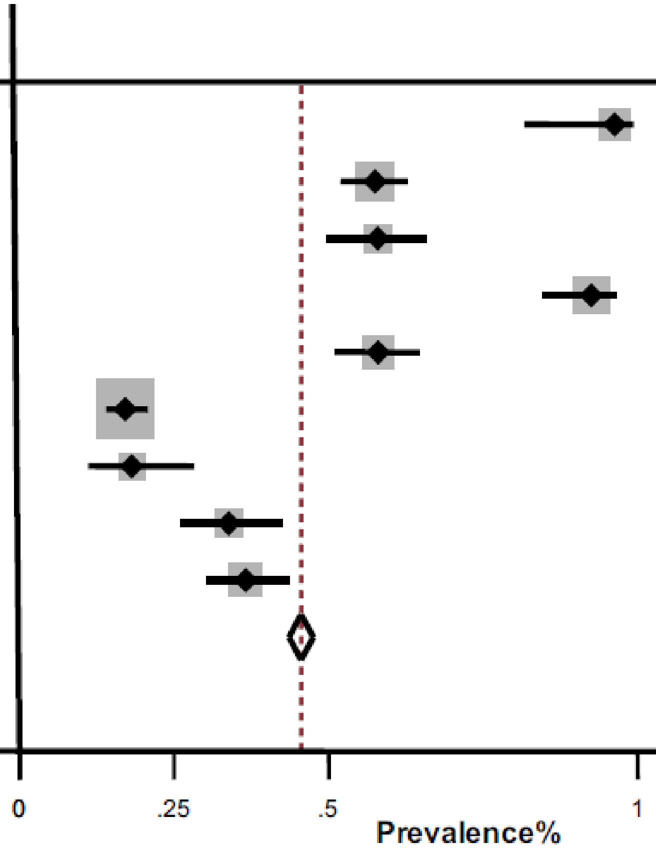


Nielsen BR. Eur Geriatr Med 2018; 9:419-434.

Meta-analysis: Prevalence of sarcopenia in adults with a fracture

Study	Sarcopenia (n)	Total (n)	ES (95% CI)	Weight%
Di Monaco 2007	26	27	0.96 (0.82, 0.99)	7.66
Di Monaco 2011	180	313	0.58 (0.52, 0.63)	12.96
Di Monaco 2015	80	138	0.58 (0.50, 0.66)	5.73
Di Monaco 2017	74	80	0.93 (0.85, 0.97)	11.67
Fiatarone	112	193	0.58 (0.51, 0.65)	8.02
Gonzales-M.	82	479	0.17 (0.14, 0.21)	34.17
Iolascon	14	77	0.18 (0.11, 0.28)	5.24
Landi	43	127	0.34 (0.26, 0.42)	5.74
Steihaug	74	202	0.37 (0.30, 0.43)	8.81
Overall p<0.001			**0.46 (0.44, 0.48)**	**100.00**

Heterogeneity: I^2=99.0%, p<0.001

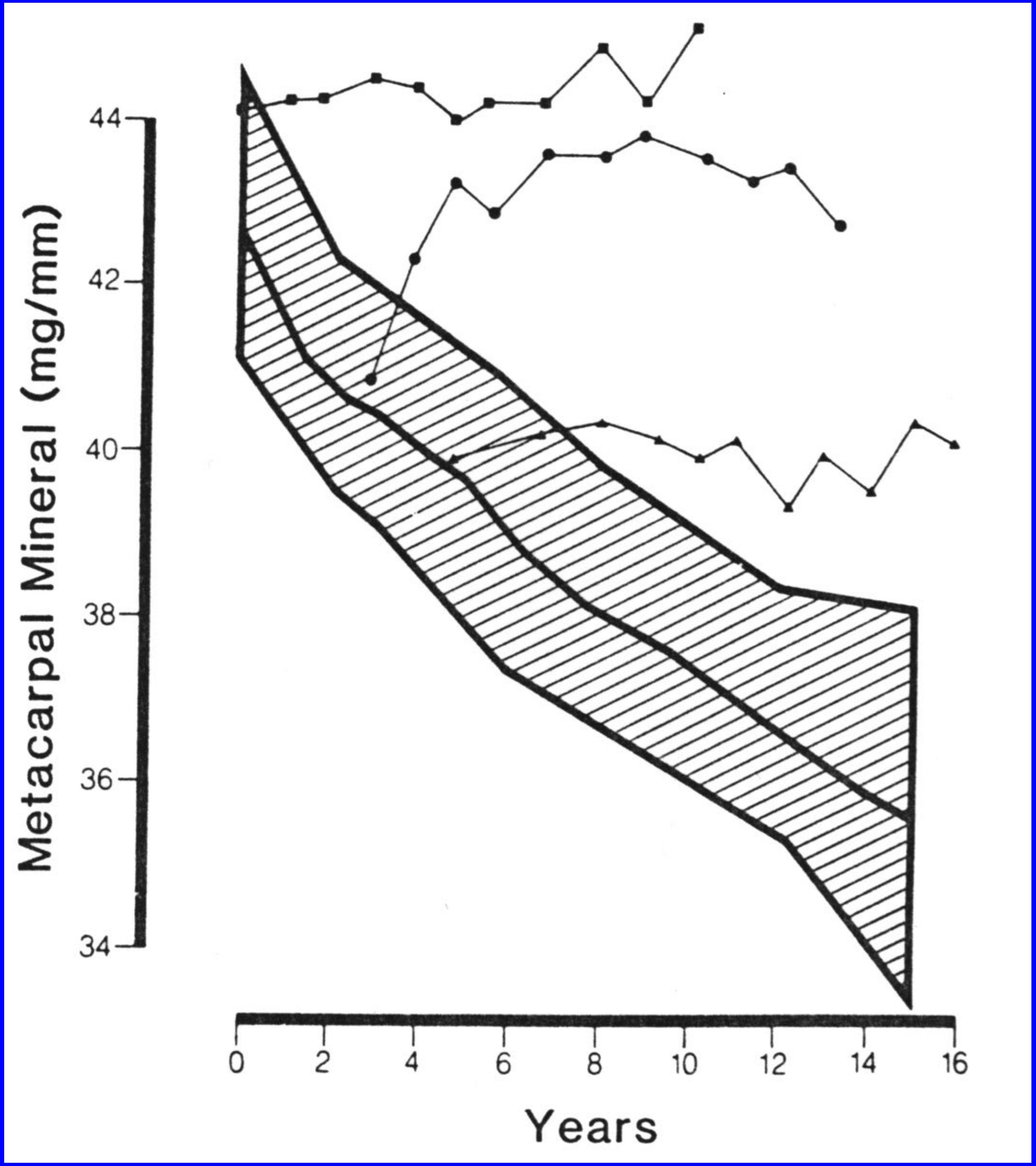


Nielsen BR. Eur Geriatr Med 2018; 9:419-434.

Common causes of bone and muscle loss in women

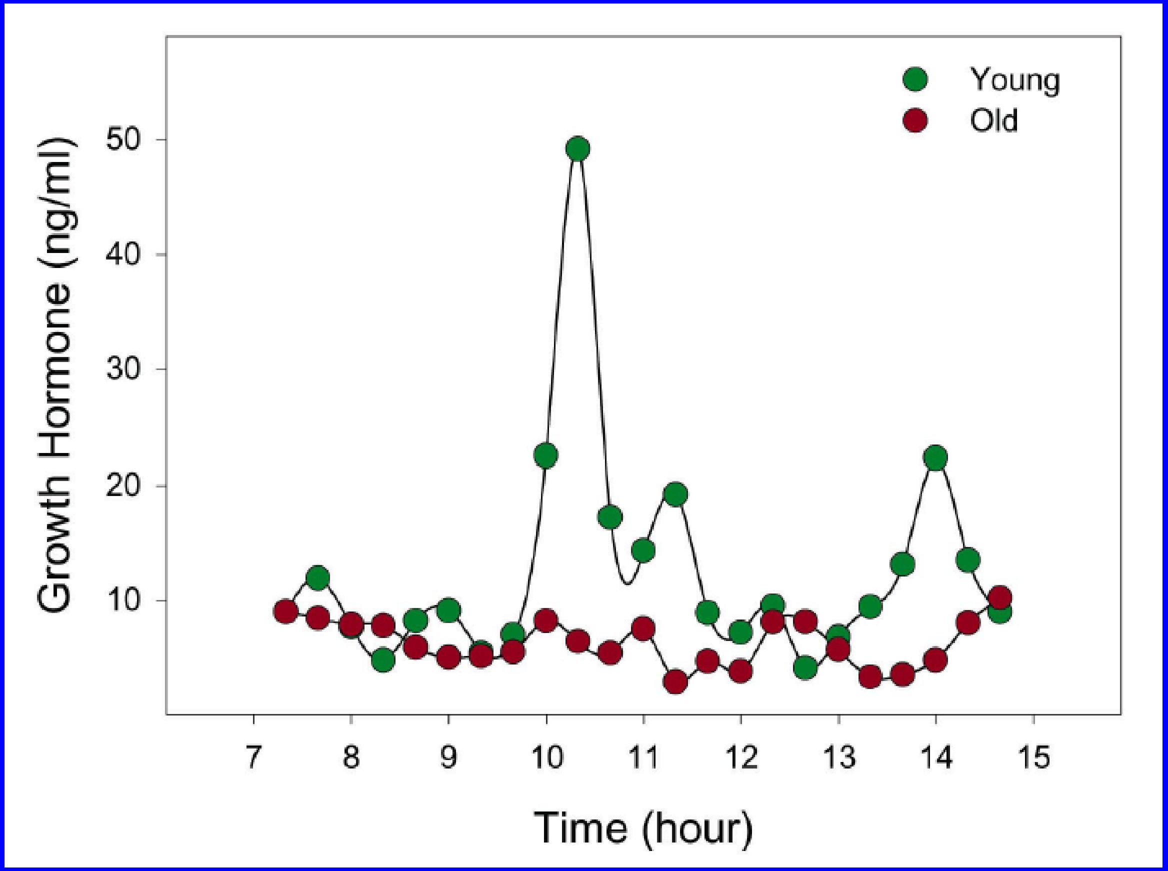
- Abrupt loss of estrogen at menopause causes rapid loss of *bone* mass.
- The amplitude of normal pulsatile pituitary growth hormone secretion declines with aging $\longrightarrow \downarrow$ hepatic production of IGF-1, the hormone that is anabolic to bone and muscle.
- 'Anorexia of aging' results in reduced intake of protein, calcium, vitamin D and other nutrients essential for bone and muscle formation and in *weight loss*.
- An age-related, generalized decline in physical activity contributes to losses of bone and muscle. The adherence rate to exercise recommendations in older adults is <50% at 6 mo.

Effect of HRT on Bone Loss after Menopause (shaded area = untreated normal range)



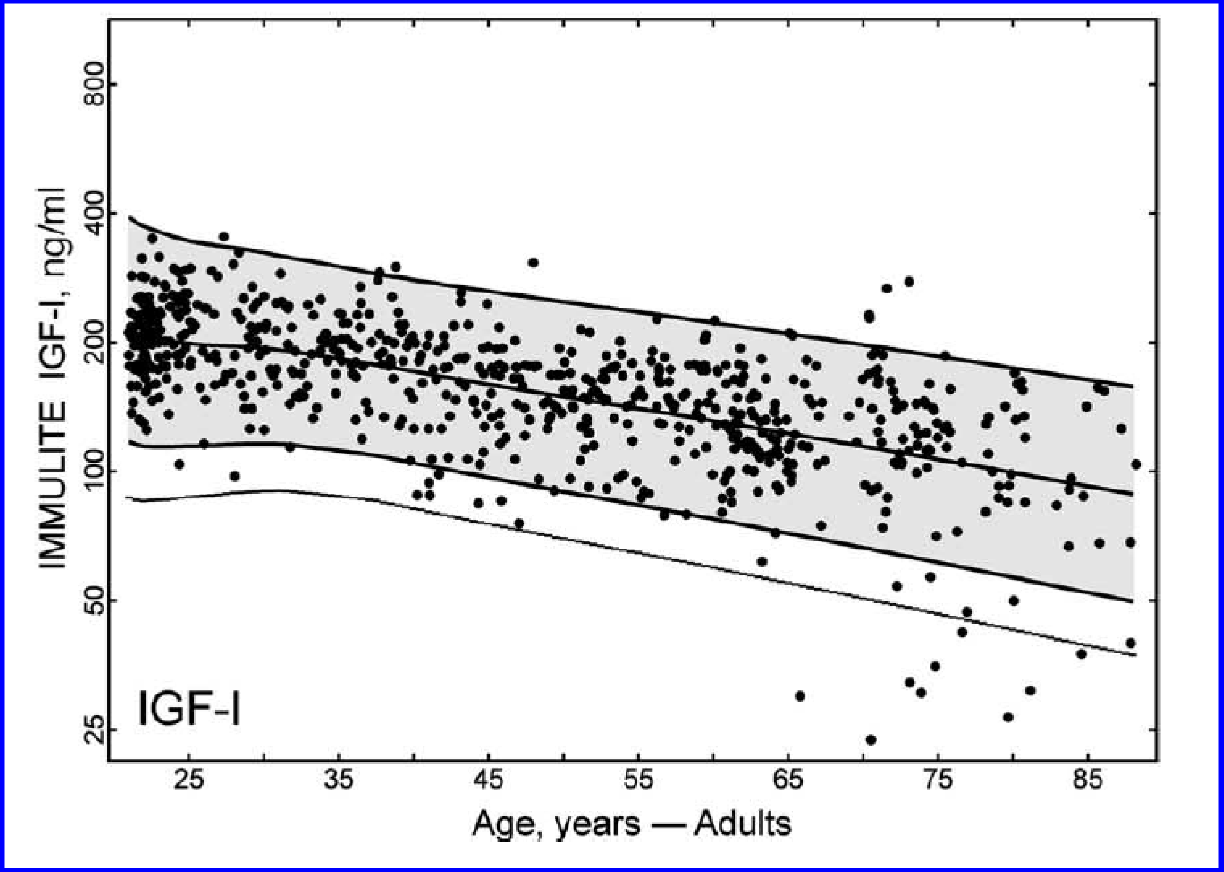
Lindsay R. JBMR 1992; 7: 55-63.

Growth hormone release from the pituitary declines with aging



Sonntag WE. Endocrinol 1980;107:1875-9.

IGF-1 levels decline with age



Elmlinger MW. Clin Chem Lab Med 2004;42:654-64.

FDA approved pharmacologic Interventions

To reduce fracture risk – multiple anti-resorptive and anabolic interventions are approved.

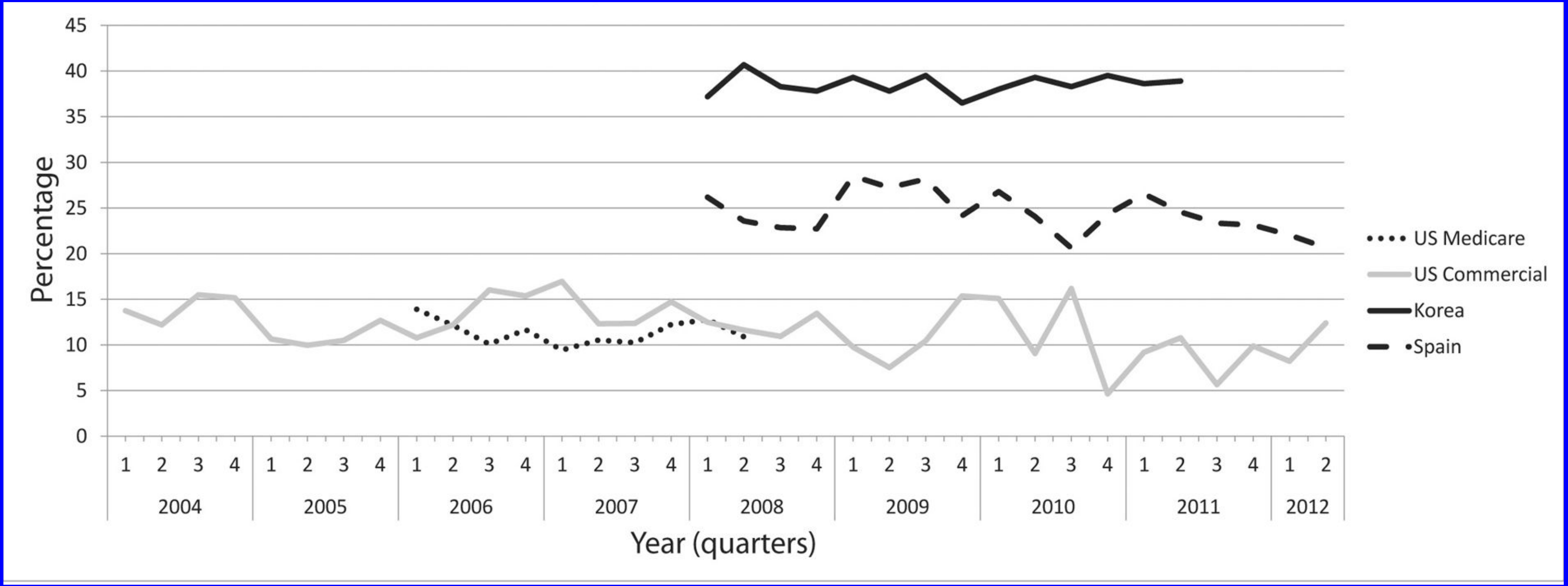
To improve muscle performance and reduce risk of falling – ***no*** pharmacologic interventions are approved.

Pivotal (registration) **fracture prevention trials** in older women

Drug/Study	Calcium, mg/d	Vitamin D, IU/d	Vert fx risk reduction, %	Hip fx risk reduction, %
1. Alendronate	500	250	47%	51%
2. Risedronate	1000	500	41%	30%
3. Ibandronate	500	400	62%	na
4. Zoledronate	1000-1500	800-1200	70%	41%
5. Raloxifene	500	400-600	30%	na
6. Teriparatide	1000	400-1200	65%	na
7. Abaloparatide	yes	yes	86%	43% (non-vert)
8. Denosumab	≥1000	≥400	68%	40%
9. Romoszumab	500-1000	600-800	73%	36% (non-vert)

1.Black DM. Lancet 1996;348:1535-1541; 2. Reginster J. Osteoporor Int 2000;11:83-91; McClung MR. N Engl J Med 2001;344:333-340; 3. Chesnut CH. J Bone Miner Res 2004;19:1241-1249; 4. Lyles K. N Engl J Med 2007;357:1799-1809.; 5. Ettinger B. JAMA 1999;282:637-645; 6. Neer RM. N Engl J Med 2001;344:1434-1441; 7. Miller P. JAMA 2016;316:722-733; 8. Cummimgs SR. N Engl J Med 2009;361:756-765; 9. Cosman F. N Engl J Med 2016;375:1532-1543.

Osteoporosis treatment after acute hip fracture is lagging in the US



Compliance in first year

US: 67-70%
Spain: 66%
Korea: 43%

Kim SC. AM J Med 2015;128:519-526.

New Frontier: Senolytics as potential treatment to increase bone mass

(and other chronic diseases)

- Preclinical studies in mice indicate that removal of senescent cells from the bone microenvironment improves bone mass.
- A phase 2 trial is underway now in 120 women age 60+ to test the effect of intermittent Dasatinib treatment for 20 weeks on markers of bone turnover, CTX and P1NP. (NCT04313634)
- Dasatinib (in a higher dose) is used to treat chronic myeloid leukemia.

Vitamin D Insufficiency

↓ Ca absorption

↑ PTH

↑ Bone TO and loss

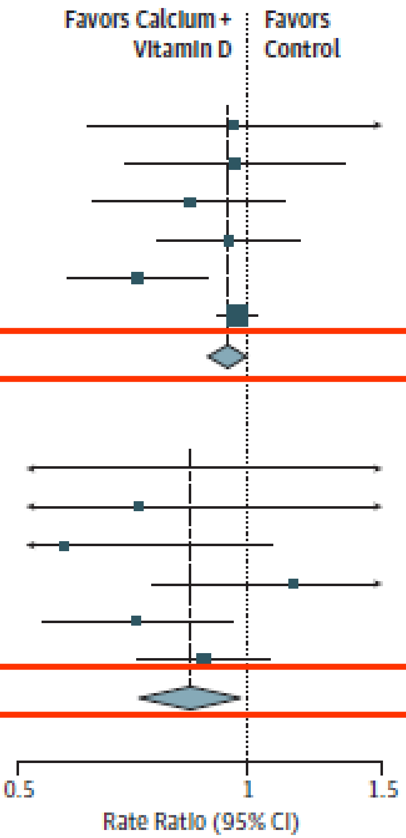
↓ Muscle mass (?) or balance

↑ Falls

↑ Fractures

Meta-analysis of RCTs: vitamin D + calcium – effect on any fracture and hip fracture

Source	Calcium + Vitamin D: Calcium, mg/d	Calcium + Vitamin D: Vitamin D, IU/d	Calcium + Vitamin D: Events, No./Total Participants, No.	Control: Events, No./Total Participants, No.	Risk of Bias	Rate Ratio (95% CI)	Weight, %
Any fracture							
Chapuy et al,[50] 2002	1200	800	70/393	35/190	High	0.96 (0.61-1.51)	1.6
Porthouse et al,[51] 2005	1000	800	58/1321	91/1993	High	0.96 (0.69-1.34)	2.8
Salovaara et al,[52] 2010	1000	800	86/1586	103/1609	High	0.84 (0.63-1.13)	3.7
Grant et al,[47] 2005	1000	800	179/1306	192/1332	High	0.94 (0.76-1.17)	6.6
Chapuy et al,[53] 1992	1200	800	160/1634	215/1636	High	0.72 (0.58-0.89)	7.0
Jackson et al,[54] 2006	1000	400	2102/18176	2158/18106	Low	0.97 (0.91-1.03)	78.3
All			2655/24416	2794/24866		0.94 (0.89-0.99)	100.0
Subtotal (Q = 7.3, *df* = 5, *P* = .20; I^2 = 31.4%)							
Hip fracture							
Salovaara et al,[52] 2010	1000	800	4/1586	2/1609	High	1.98 (0.40-9.81)	0.9
Porthouse et al,[51] 2005	1000	800	8/1321	17/1993	High	0.72 (0.32-1.61)	3.4
Chapuy et al,[50] 2002	1200	800	27/393	21/190	High	0.58 (0.31-1.08)	5.5
Grant et al,[47] 2005	1000	800	46/1306	41/1332	High	1.15 (0.75-1.76)	12.0
Chapuy et al,[53] 1992	1200	800	80/1634	110/1636	High	0.72 (0.53-0.96)	25.5
Jackson et al,[54] 2006	1000	400	175/18176	199/18106	Low	0.87 (0.71-1.07)	52.7
All			340/24416	390/24866		0.84 (0.72-0.97)	100.0
Subtotal (Q = 6.0, *df* = 5, *P* = .31; I^2 = 16.5%)							



Yao P. JAMA Open 2019;2(12)e1917789.

How much vitamin D to reduce fracture risk?

The evidence supports 800 IU/d (in combination with calcium)

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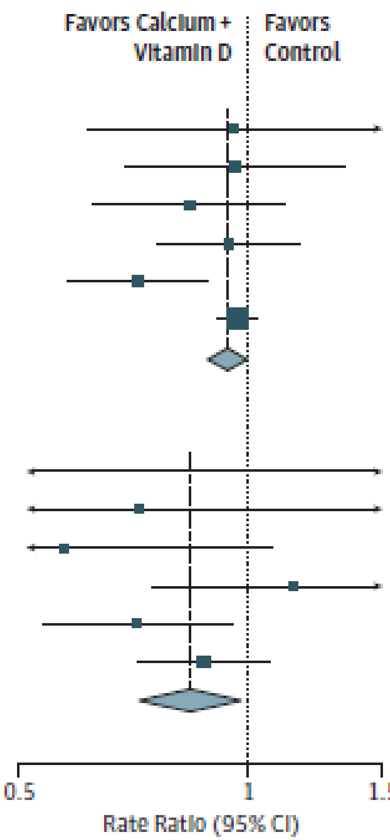

Yao P. JAMA Open 2019;2(12)e1917789.

Meta-analysis of RCTs: vitamin D alone – effect on any fracture and hip fracture

Source	Vitamin D: Treatment	Vitamin D: Events, No./Total Participants, No.	Control: Events, No./Total Participants, No.	Risk of Bias	Rate Ratio (95% CI)	Weight, %
Any fracture						
Glendenning et al,[39] 2012	150000 IU/3 mo	10/353	10/333	High	0.94 (0.39-2.29)	0.8
Larsen et al,[40] 2018	20000 IU/wk	15/256	13/255	Unclear	1.16 (0.54-2.48)	1.0
Law et al,[41] 2006	100000 IU/3 mo	66/1762	53/1955	High	1.39 (0.97-2.01)	4.5
Meyer et al,[42] 2002	400 IU/d	69/569	76/575	High	0.90 (0.64-1.28)	4.9
Lips et al,[43] 1996	400 IU/d	135/1291	122/1287	High	1.12 (0.86-1.45)	8.9
Trivedi et al,[44] 2003	100000 IU/4 mo	119/1345	149/1341	High	0.78 (0.61-1.00)	9.6
Sanders et al,[45] 2010	500000 IU/y	171/1131	135/1127	High	1.31 (1.03-1.67)	10.4
Khaw et al,[46] 2017	100000 IU/mo	156/2558	136/2550	Low	1.15 (0.91-1.46)	10.8
Grant et al,[47] 2005	800 IU/d	208/1343	192/1332	High	1.08 (0.88-1.35)	13.0
Lyons et al,[48] 2007	100000 IU/4 mo	205/1725	218/1715	High	0.92 (0.76-1.14)	14.2
Smith et al,[49] 2007	300000 IU/y	306/4727	279/4713	High	1.11 (0.93-1.30)	21.9
All		1460/17060	1383/17183		1.06 (0.98-1.14)	100.0
Subtotal ($Q = 14.5$, $df = 10$, $P = .15$; $I^2 = 31.1\%$)						
Hip fracture						
Sanders et al,[45] 2010	500000 IU/y	19/1131	15/1127	High	1.22 (0.64-2.48)	4.7
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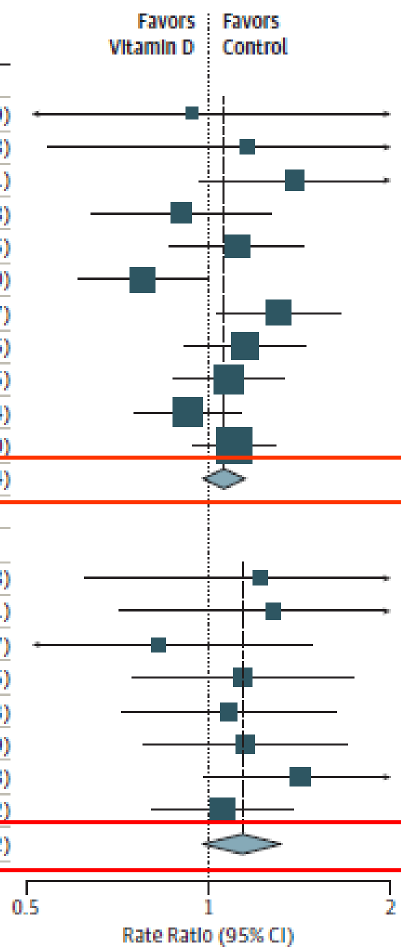
Smith et al,[49] 2007	300000 IU/y	66/4727	44/4713	High	1.42 (1.03-2.18)	15.4
Lyons et al,[48] 2007	100000 IU/4 mo	112/1725	104/1715	High	1.06 (0.82-1.42)	28.6
All		397/13893	343/14045		1.14 (0.98-1.32)	100.0
Subtotal ($Q = 3.0$, $df = 7$, $P = .89$; $I^2 = 0.0\%$)						



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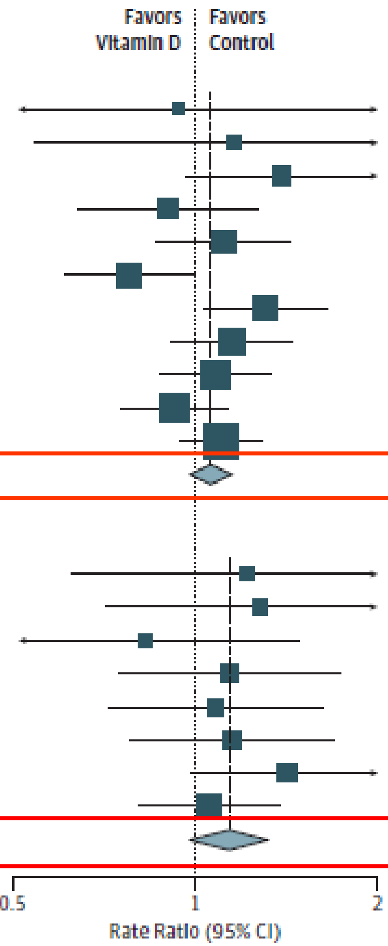
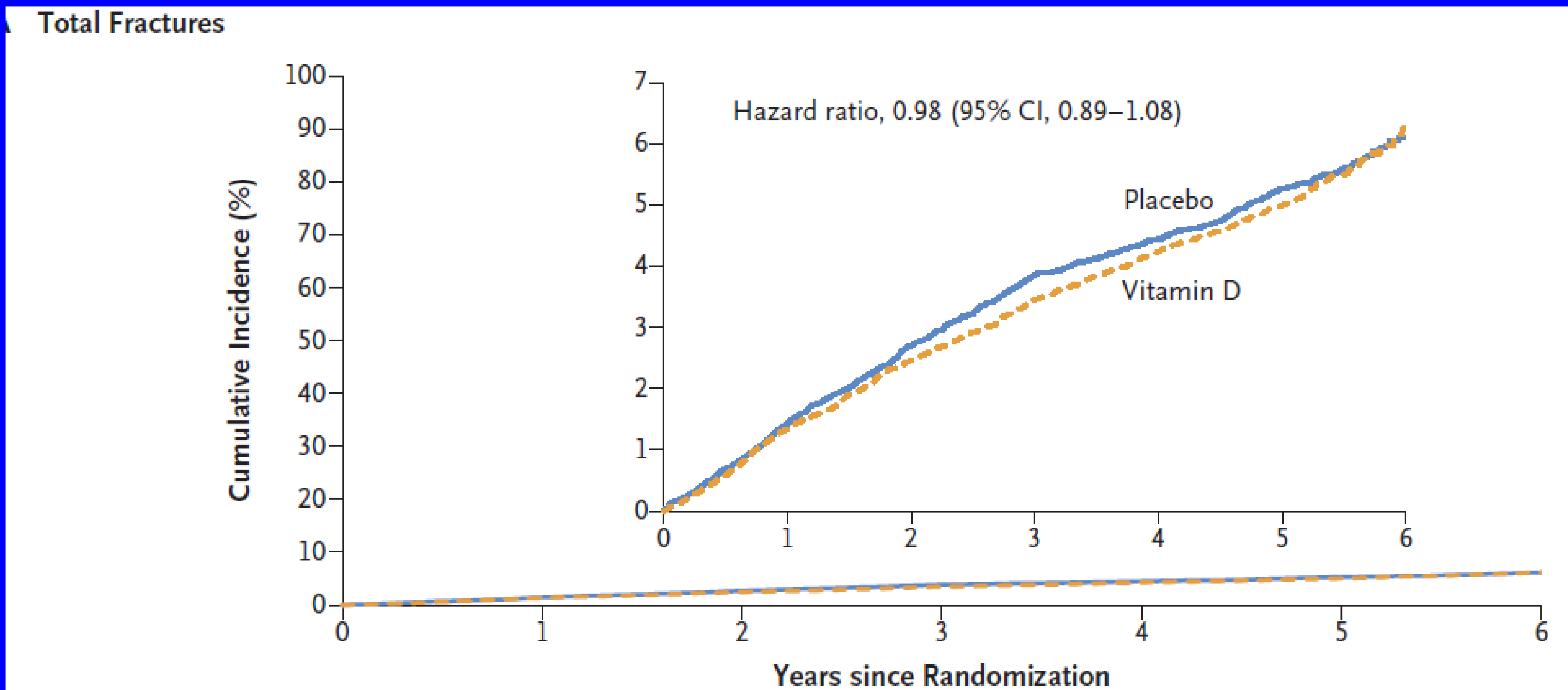


Yao P. JAMA Open 2019;2(12)e1917789.

VITAL: No effect of vitamin D, 2000 IU/d, on fracture risk

(N = 25,871 older adults; baseline 25(OH)D level = 30.8 ng/ml)



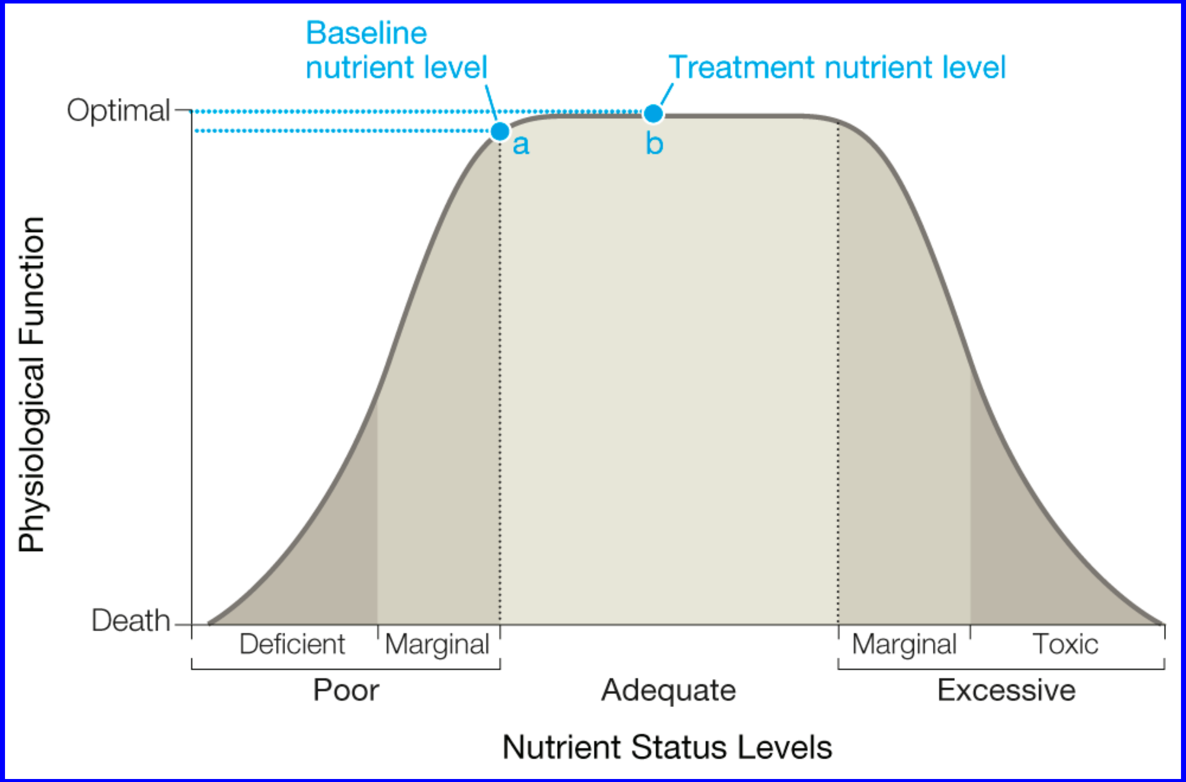
No. at Risk

	0	1	2	3	4	5	6
Placebo	12,927	12,737	12,578	12,438	12,218	9830	793
Vitamin D	12,944	12,742	12,561	12,399	12,188	9785	782

LeBoff MS. NEJM 2022;387:299-309.

What could explain the mix of findings that vitamin D *does* and *does not reduce* fall risk and may actually *increase* fall risk?

Nutrient intake and physiologic function



Morris MC. JAMA 2011;305, no.13.

Role of vitamin D in fall risk

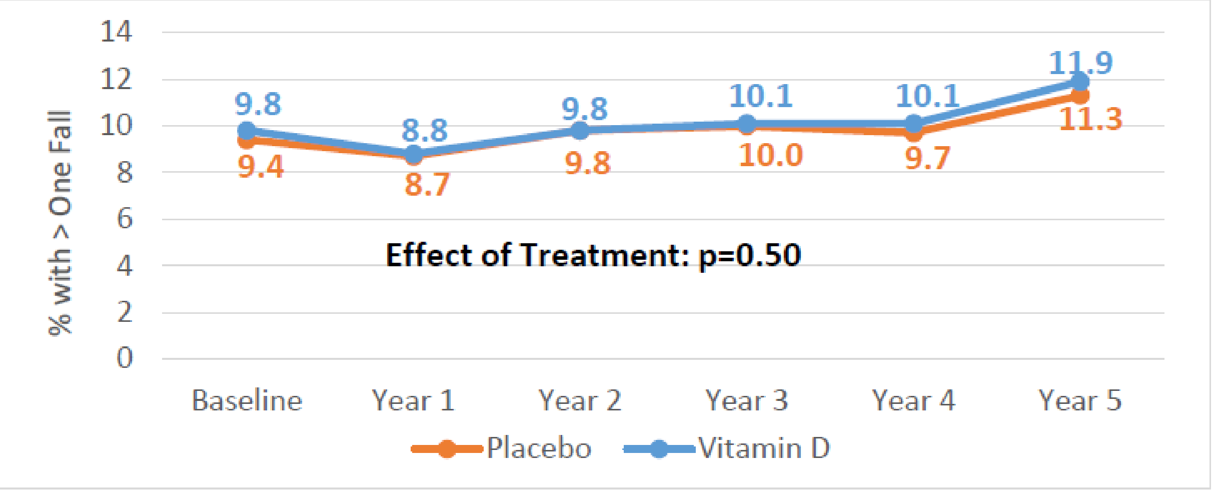
- Controversial
  - Meta-analysis found no effect of D on muscle strength
    (Bislev LS. JBMR 2021; 36:1651-1660).
  - Recent mega-trials have been null.

- Was it because they tested replete populations?
- Did bolus dosing in some trials contribute to the null?
- Or does vitamin D have no effect on fall risk?

VITAL: Impact of 2,000 IU/d of vitamin D_3 vs P on risk of falling
N=25,871; mean age 67.1 yr; 5 year intervention
25(OH)D = 30.8→41.6 ng/ml

2a. Percent with Two or More Falls

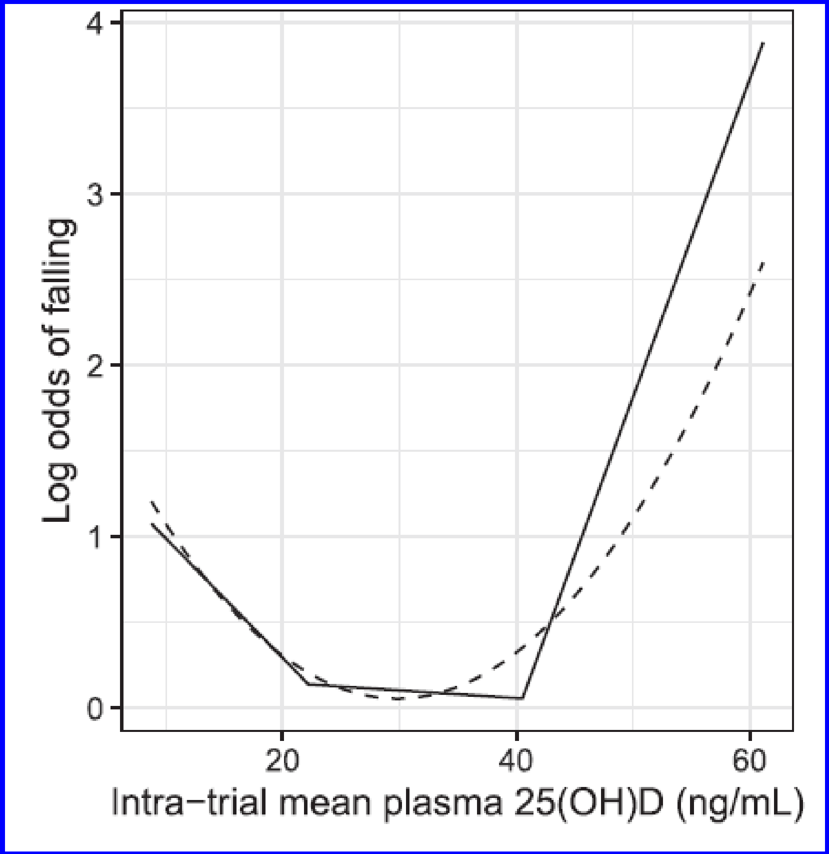
Group	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Placebo	1207/12867	1059/12119	1158/11861	1130/11334	1048/10764	1127/9960
Vitamin D	1260/12848	1075/12168	1167/11879	1155/11410	1102/10914	1202/10099



Leboff MS. J Clin Endo Metab 2020;105:2929-2938.

STOP IT: Intra-trial mean 25(OH)D and risk of falling

(in 410 men and women mean age 71 yrs and mean 25(OH)D = 22.5 ng/ml (56 nmol/L); using quadratic and piecewise logistic regression)



P < 0.05

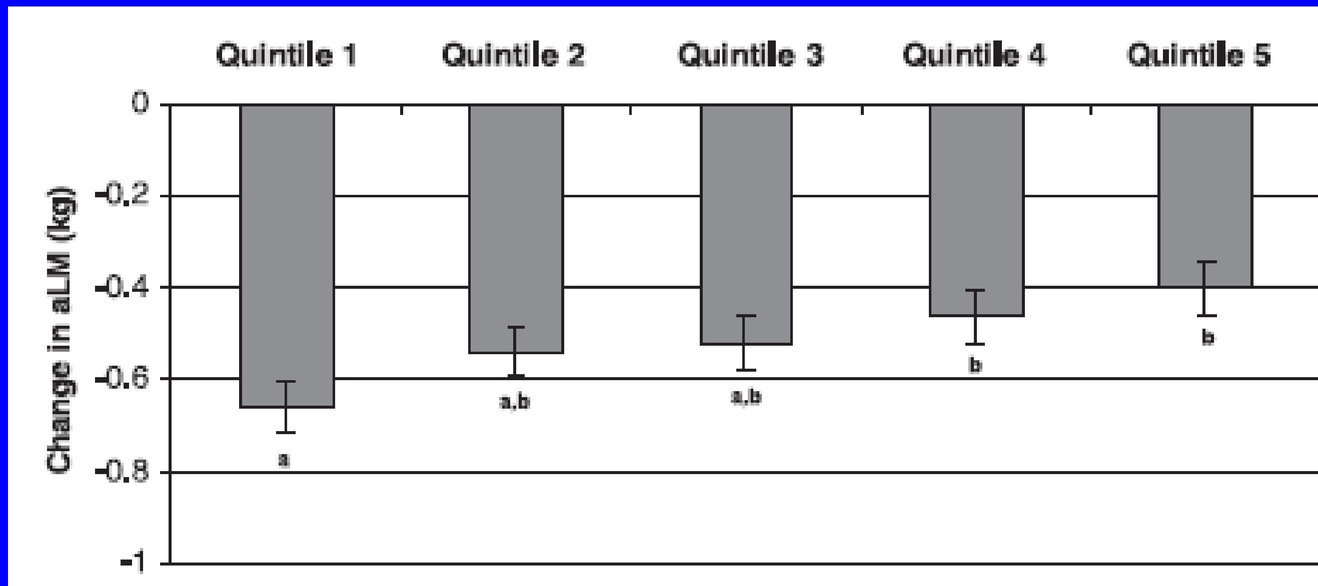
Proportion of fallers: 57% 50% 67%

Dawson-Hughes B. J Clin Endocrinol Metab 2022; 107, e1932–37.

Dietary protein intake

Association with lean mass by DXA

(2066 men and women age 70-79; 3-yr follow-up; Health ABC)



Protein intake, g/kg/d	0.8	0.7	0.8	0.9	1.2

Houston DK. Am J Clin Nutrit 2008;87:150-5.

Cochrane review of exercise and falls
(81 RCTs in 19,684 participants)

Exercise (all types)

↓ risk of falls (all falls) by 23%	(strong evidence)
↓ risk of falling (≥1 falls) by 15%	(strong evidence)
↓ risk of injurious falls by 39%	(low certainty)

Balance and functional exercise

↓ risk of falls (all falls) by 24%	(strong evidence)
↓ risk of falling (≥1 falls) by 13%	(strong evidence)

Tai Chi

↓ risk of falls (all falls) by 19%	(low-certainty evidence)
↓ risk of falling (≥1 falls) by 20%	(high-certainty evidence)

Sherrington C. Cochrane Database Syst Rev 2019;21.

Research gaps and opportunities

Bone

- Identify women at fracture and increase use of effective interventions
- Adequate nutrition (Ca + vitamin D, protein) and exercise
- Develop and validate effect of senolytic agents

Muscle loss/fall prevention

- Standardize the definition of sarcopenia
- Develop FDA-approved pharmacotherapies, senolytics
- Assess GH agonists to reverse loss in *pulsatile* GH + IGF-1
- Determine mechanism by which vitamin D affects fall risk and identify optimal vitamin D levels to prevent falls
- Optimize protein nutrition and safe and effective exercises