Gruppo di ricerca geriatrica

Journal Club

17 Luglio 2009

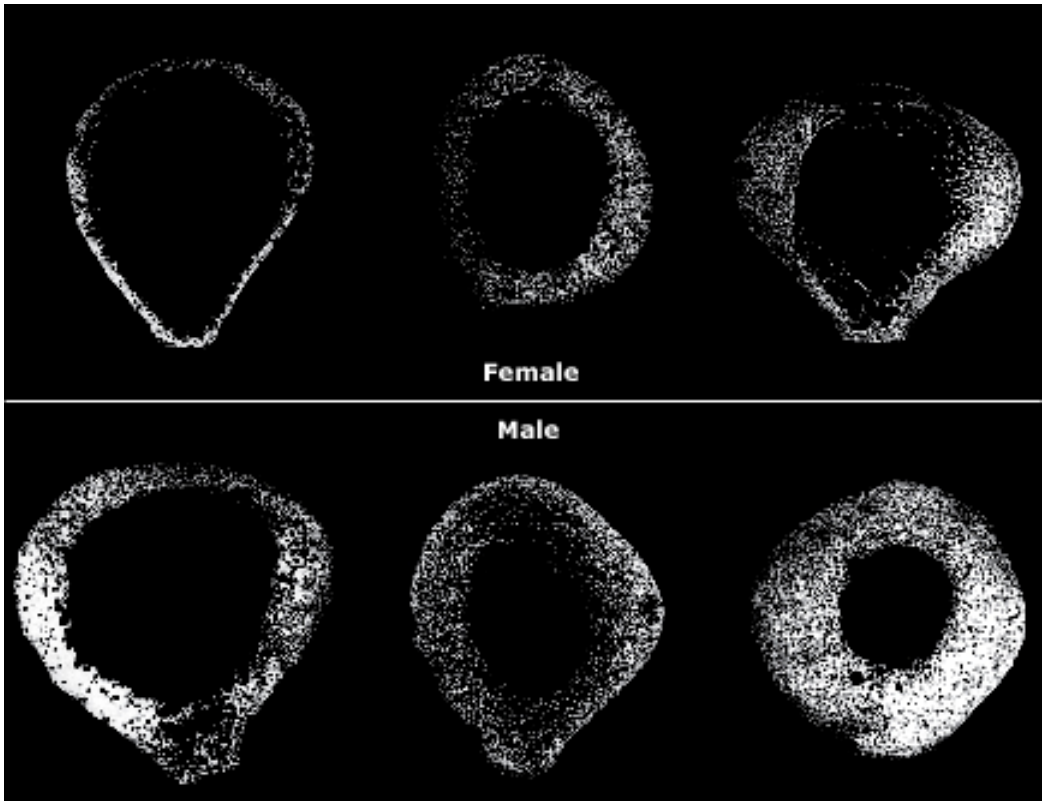
La terapia dell'osteoporosi

Intissar Sleiman

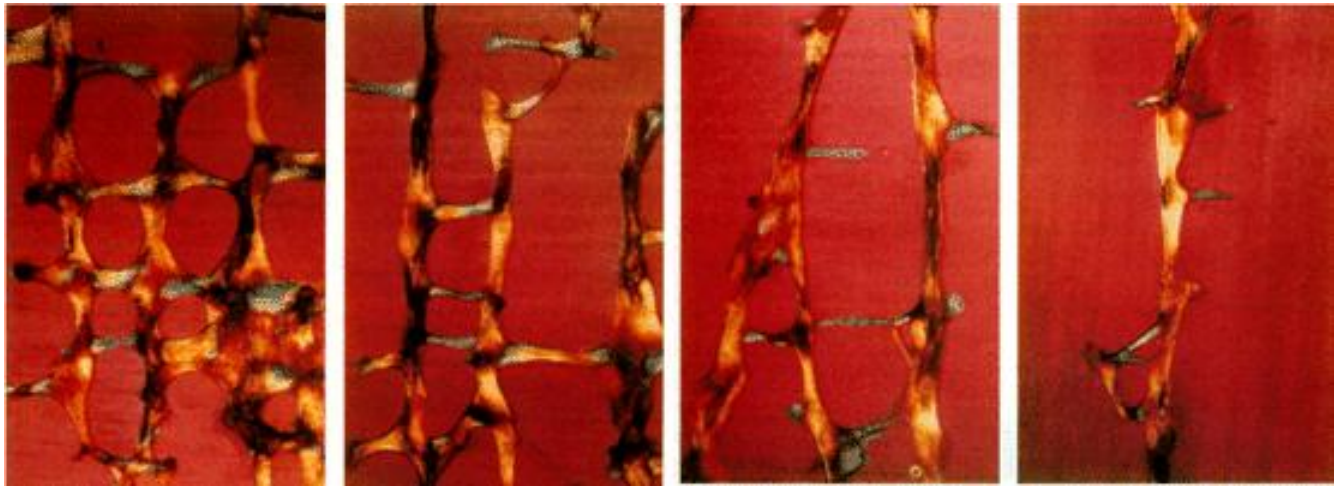
Definition

Osteoporosis is a skeletal disorder characterized by low bone mass with micro architectural disruption and fragility, resulting in an increased risk of fracture.

Variations in bone mass in the femur

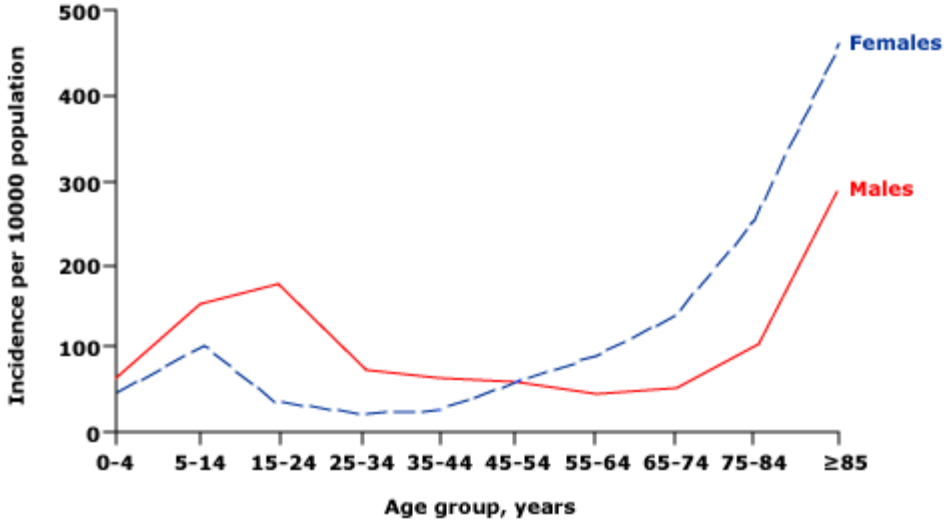


Age-related loss of trabecular bone



Normal 50-year-old man | 58-year-old man | 76-year-old man | 87-year-old woman

Average Annual Fracture Incidence Rate per 10,000 Men and Women in Leicester, United Kingdom.



Donaldson et al, J Epidemiol Commun Health 1990; 44:241.

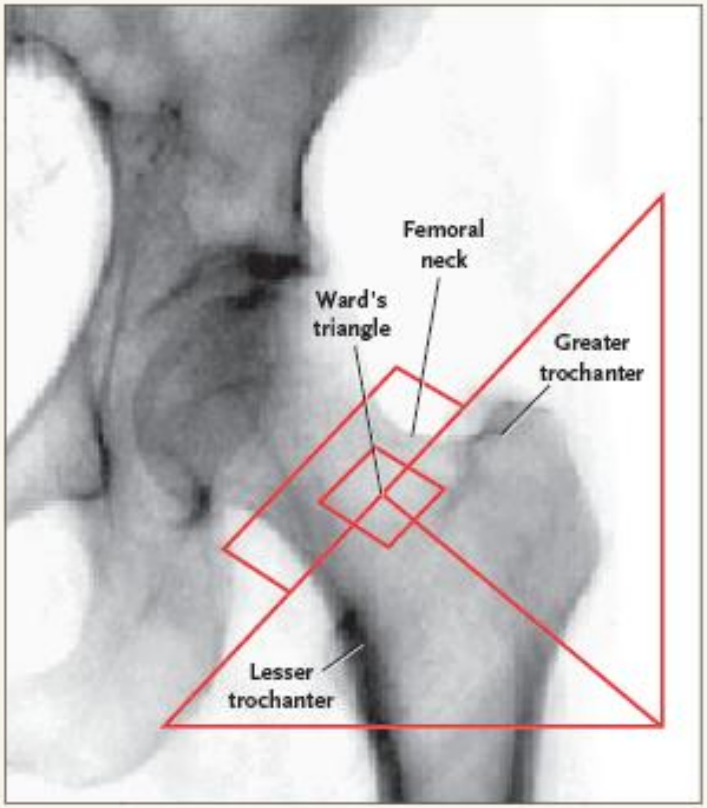
Markers of Bone Turnover

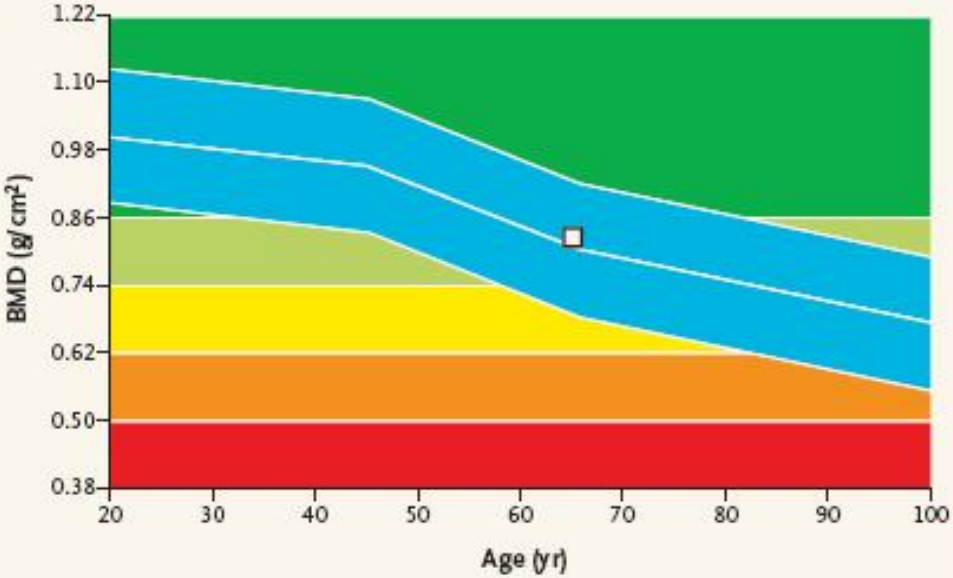
- **Urinary or serum C-terminal and N-terminal telopeptide of type I collagen**
- **Bone specific alkaline phosphatase**
- **Osteocalcin**
- **N-terminal propeptide of type I collagen**

Other laboratory testing

- Complete blood count
- Serum calcium and phosforus
- Tests of renal and hepatic function
- TSH
- Vitamin D
- Testosterone (man only)

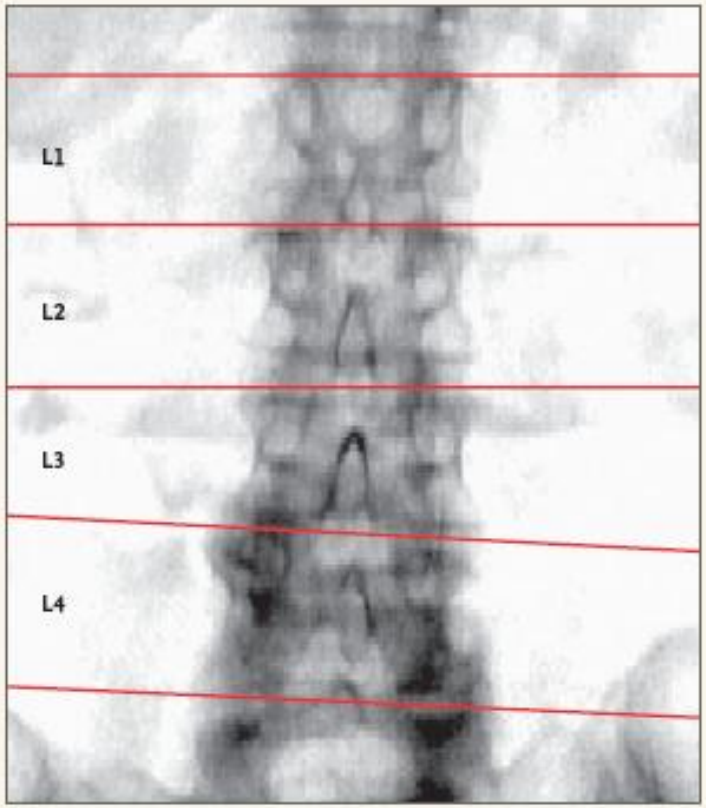
A

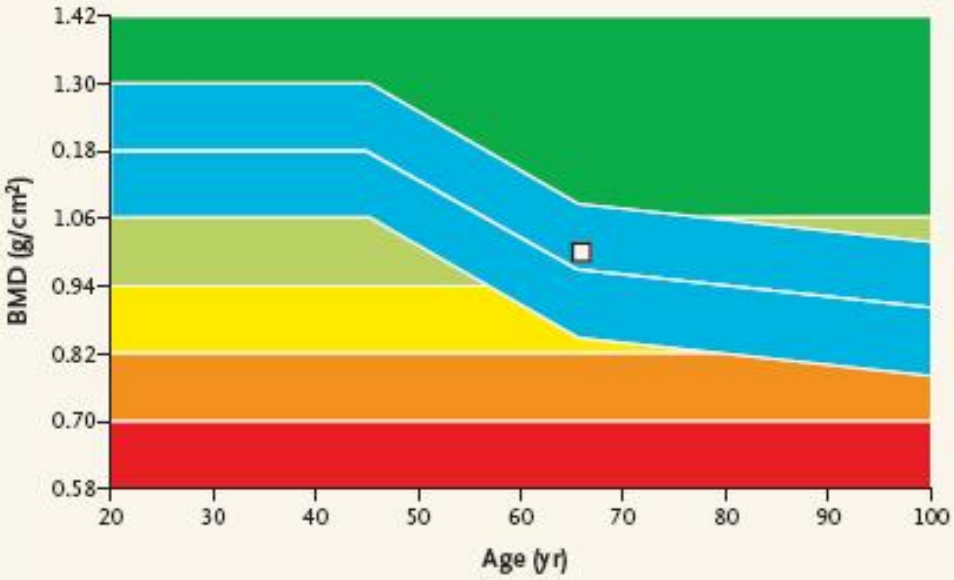




Region	BMD (g/cm2)	Young adult (%)	Young adult (T)	Age-matched (%)	Age-matched (Z)
Neck	0.829	85	−1.3	101	+0.1
Ward's triangle	0.670	74	−1.8	101	+0.1
Trochanter	0.769	97	−0.2	107	+0.5
Total	0.941	94	−0.5	106	+0.4

B





Region	BMD (g/cm2)	Young adult (%)	Young adult (T)	Age-matched (%)	Age-matched (Z)
L1	0.772	68	−3.0	84	−1.3
L2	0.975	81	−1.9	98	−0.2
L3	1.039	87	−1.3	104	+0.4
L4	1.203	100	0.0	121	+1.7
L2–L4	1.086	91	−0.9	109	+0.8

WHO Diagnostic Categories of Bone Mineral Density

Diagnostic Category	Criterion
Normal	A value for BMD or BMC that is within 1.0 SD of the reference mean for young adults
Low bone mass (osteopenia)	A value for BMD or BMC that is more than 1.0 but less than 2.5 SD below the mean for young adults
Osteoporosis	A value for BMD or BMC that is 2.5 SD or more below the mean for young adults
Severe osteoporosis (established osteoporosis)	A value for BMD or BMC that is 2.5 SD or more below the mean for young adults in combination with one or more fragility (low-trauma) fractures.

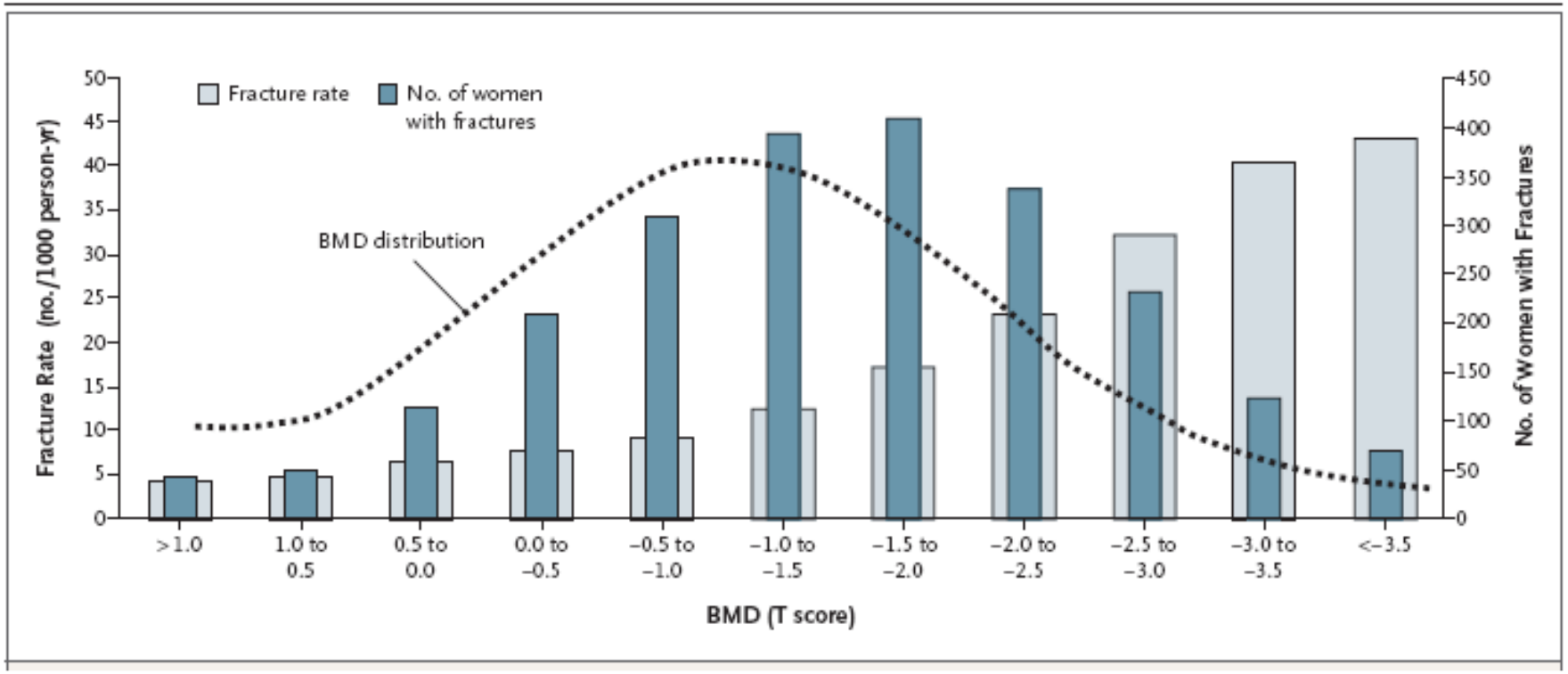
* The information is from the WHO.[4] BMD denotes bone mineral density, and BMC bone mineral content.

- **Bone mineral density is a better predictor of fractures than blood pressure is of stroke.**

- **Relative risk of hip fracture of 2.6 for each 1 SD decrease in bone mineral density at the hip.**

- **The relation between bone mineral density and the risk of fracture is continuous, with non absolute cutoff value to define a pathologic state.**

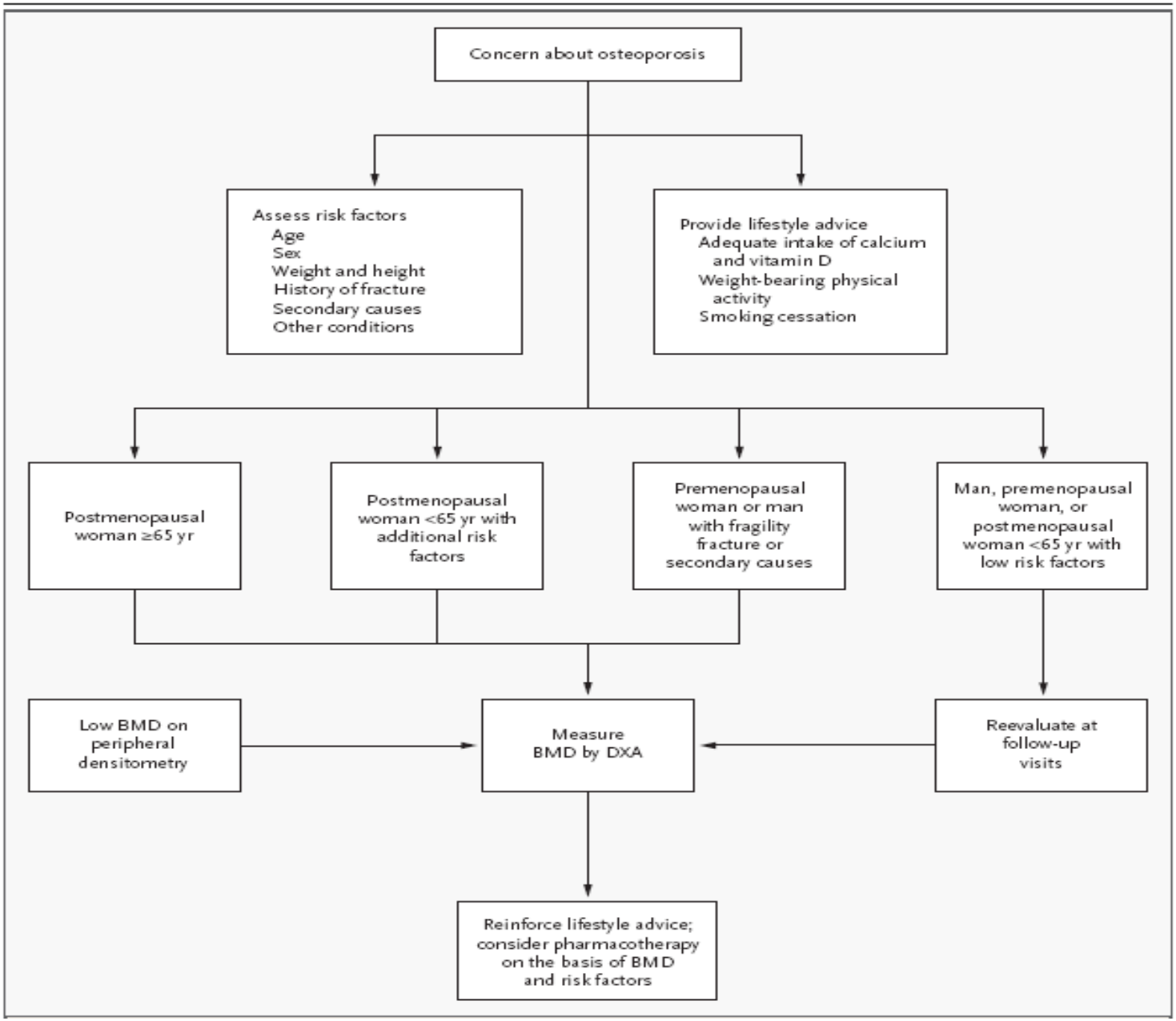
Fracture Rate and the Number of women with Fractures According to Peripheral Bone Mineral Density (BMD)



Siris et al. Arch. Intern. Med; 2004.

The National Osteoporosis Foundation Indications for Bone Density Testing

- Women aged 65 years and older and men age 70 and older, regardless of clinical risk factors.
- Younger postmenopausal women and men age 50 to 70 about whom you have concern based on their clinical risk factor profile.
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk, such as low body weight, prior low-trauma fracture, or high risk medication.
- Adults who have a fracture after age 50.
- Adults with a disease or condition (e.g., rheumatoid arthritis) associated with low bone mass or bone loss.
- Adults taking medication (e.g., glucocorticoids, 5 mg or more daily for 3 or more months) associated with low bone mass or bone loss.
- Anyone being considered for pharmacologic osteoporosis therapy.
- Anyone being treated for osteoporosis, to monitor treatment effect.
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.
- Postmenopausal women discontinuing estrogen should be considered for bone density testing according to the indications listed above.


Concern about osteoporosis
Assess risk factors
Age
Sex
Weight and height
History of fracture
Secondary causes
Other conditions
Provide lifestyle advice
Adequate intake of calcium and vitamin D
Weight-bearing physical activity
Smoking cessation
Postmenopausal woman ≥65 yr
Postmenopausal woman <65 yr with additional risk factors
Premenopausal woman or man with fragility fracture or secondary causes
Man, premenopausal woman, or postmenopausal woman <65 yr with low risk factors
Low BMD on peripheral densitometry
Measure BMD by DXA
Reevaluate at follow-up visits
Reinforce lifestyle advice; consider pharmacotherapy on the basis of BMD and risk factors

Risk Factors for Osteoporosis and Fracture in Women and Men

Major risk factors
Personal history of fracture as an adult
History of fragility fracture in a first-degree relative
Low body weight†
Current smoking
Use of oral corticosteroid therapy (daily dose equivalent, ≥5 mg of prednisone) for more than 3 months
Additional risk factors
Impaired vision
Estrogen deficiency at an early age (before 45 years)
Dementia
Poor health or frailty
Recent falls
Low calcium intake (lifelong)
Low physical activity
Alcohol in amounts greater than two drinks per day

† Low body weight is defined as a weight below 127 lb (58 kg), which is based on the lowest quartile for weight of the cohort in the Study of Osteoporotic Fractures, but the definition varies among populations.

National osteoporosis Foundation, 2004

Risk Ratio for Hip Fracture According to Risk Factors Adjusted for Age and for Bone Mineral Density in Men and Women

Risk Factor	Adjusted Risk Ratio with Adjustment for Bone Mineral Density (95% CI)
Low or high BMI	
20 vs. 25	1.42 (1.23–1.65)
30 vs. 25	1.00 (0.82–1.21)
Prior fracture at >50 years of age	1.62 (1.30–2.01)
Parental history of hip fracture	2.28 (1.48–3.51)
Current smoking	1.60 (1.27–2.02)
Use of systemic corticosteroids for >3 months	2.25 (1.60–3.15)
Excessive alcohol use†	1.70 (1.20–2.42)
Rheumatoid arthritis	1.73 (0.94–3.20)
Low testosterone‡	
Hip fracture	1.88 (1.24–2.82)
Other nonvertebral fracture	1.32 (1.03–1.68)

* Adapted from Kanis et al.[22] BMI denotes body-mass index, and CI confidence interval.

† Excessive use is defined as more than 2 units, or 18 g per day, equivalent to 18 oz (533 ml) or more of full-strength beer, 7 oz (207 ml) or more of wine, or 2 oz (59 ml) or more of spirits per day.

‡ Data on low testosterone are from Meier et al.[23]

NEJM, 2007

Lifestyle Measures Recommended for Patients with Ospteopenia

Adequate weight-bearing exercise (e.g., walking, moderate resistance training)
Smoking cessation
Avoidance of excessive alcohol intake (no more than two drinks/day)
Calcium supplementation to a total intake of 1200–1500 mg/day for all postmenopausal women and for men over the age of 65 years
Vitamin D supplementation (400 to 800 IU/day) to achieve a serum 25-hydroxyvitamin D concentration >25–30 ng/ml*

* Although some experts have advocated higher doses of vitamin D for possible nonskeletal benefits (e.g., cancer prevention), the efficacy and long-term safety of higher doses remain to be established. Depending on the serum 25-hydroxyvitamin D concentration, higher doses of vitamin D may be necessary to replete vitamin D stores.

NEJM, 2008

National Osteoporosis Foundation Guidelines (2008) for Pharmacologic Intervention in Postmenopausal Women and Men 50 Years of Age

History of hip or vertebral fracture.

Other prior fractures and T-score between -1.0 and -2.5 at the femoral neck, total hip, or spine, as measured by dual-energy X-ray absorptiometry (DXA).

T-score -2.5 (DXA) at the femoral neck, total hip, or spine, after appropriate evaluation to exclude secondary causes.

T-score between -1.0 and -2.5 at the femoral neck, total hip, or spine and secondary causes associated with high risk of fracture, such as Glucocorticoid use or total immobilization.

T-score between -1 and -2.5 at the femoral neck, total hip, or spine, and a 10-year probability of hip fracture 3 percent or a 10-year probability of any major osteoporosis-related fracture 20 percent based upon the US-adapted WHO algorithm.

Table 5. Medications Approved by the Food and Drug Administration for the Prevention of Osteoporosis.*

Drug	Dose	Side Effects
Bisphosphonates		Esophagitis, rare occurrence of osteonecrosis of the jaw
Alendronate (Fosamax, Merck)	35 or 70 mg weekly or 5 or 10 mg daily, taken orally†	
Risedronate (Actonel, Procter & Gamble)	35 mg weekly or 5 mg daily, taken orally	
Ibandronate (Boniva, Roche)	150 mg monthly or 2.5 mg daily, taken orally	
Selective estrogen-receptor modulators		
Raloxifene (Evista, Eli Lilly)	60 mg daily, taken orally	Hot flashes, nausea, deep venous thrombosis, stroke, leg cramps
Estrogens‡		Deep venous thrombosis, myocardial infarction, stroke, breast cancer; endometrial hyperplasia and cancer if used without concomitant progestin therapy
Conjugated equine estrogens	0.30–1.25 mg daily, taken orally	
17β-estradiol	0.014–0.1 mg daily, administered either orally or transdermally	

* Specific data on the reduction of fracture risk among patients with osteopenia are available only for alendronate and raloxifene and are limited to reduction of vertebral fractures. These medications are appropriate for only a carefully selected subgroup of women with osteopenia. Data are from Rosen.[32]

† A dose of 35 mg weekly (or 5 mg daily) is the dose approved for prevention of osteoporosis; however, many clinicians use the higher dose approved for treatment, 70 mg weekly (or 10 mg daily), in patients with osteopenia.

‡ On the basis of the risks associated with its use, postmenopausal estrogen therapy is not currently recommended as a first-line option for reducing the risk of osteoporosis. Estrogens are given with concomitant progestin therapy in women with an intact uterus.

NEJM, 2008

Anabolic Agent

- **Teriparatide**
- **Strontium ranelate**
- **Growth Hormone and IGF-I**
- **Sclerotin antagonism**

Causes of osteoporosis in men and women

Endocrine diseases
- Hypogonadism
  - Primary
  - Secondary
- Delayed puberty
- Estrogen deficiency
- Hypercortisolism
- Hyperthyroidism
- Hyperparathyroidism
- Vitamin D deficiency
- Growth hormone deficiency
- Diabetes mellitus

Gastrointestinal diseases
- Subtotal or total gastrectomy
- Malabsorption syndromes
- Inflammatory bowel disease
- Chronic biliary tract obstruction
- Alactasia
- Cirrhosis

Hematologic disorders
- Multiple myeloma
- Lymphoma
- Leukemia
- Chronic hemolytic anemia
- Systemic mastocylosis
- Disseminated carcinoma

Connective tissue diseases
- Osteogenesis imperfecta
- Ehlers-Danlos syndrome
- Marfan's syndrome
- Homocystinuria

Drugs
- Alcohol
- Heparin
- Glucocorticoids
- Thyroxine suppressive therapy
- Anticonvulsant drugs
- Gonadotropin-releasing hormone analogs
- Cyclosporine
- Chemotherapy

Miscellaneous causes
- Anorexia nervosa
- Hypercalciuria
- Immobilization
- Rheumatoid arthritis

Excess Mortality from all causes after diagnosis of Subclinical Hyperthyroidism

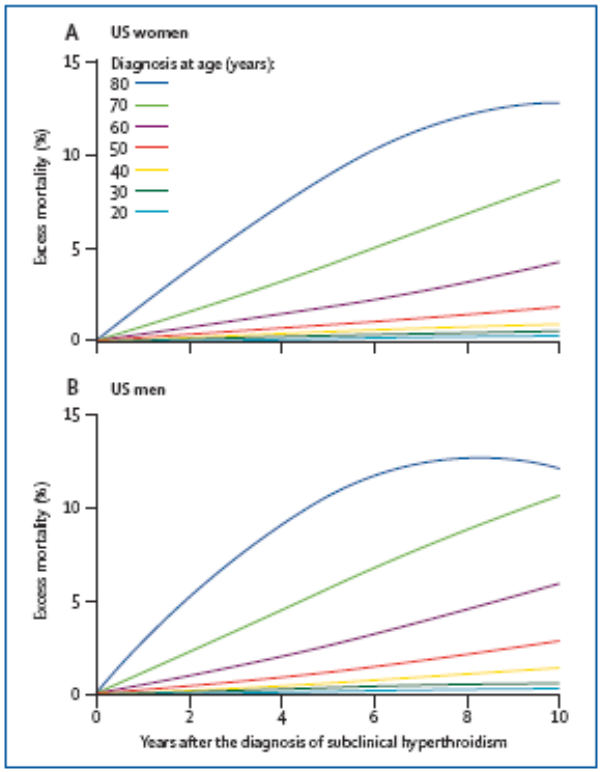


Figure: Excess mortality from all causes after diagnosis of subclinical hyperthyroidism
Data are from mathematical modelling not from individual patients' data and show (A) US women and (B) US men.

Lancet, 2009

Vitamin D Deficiency

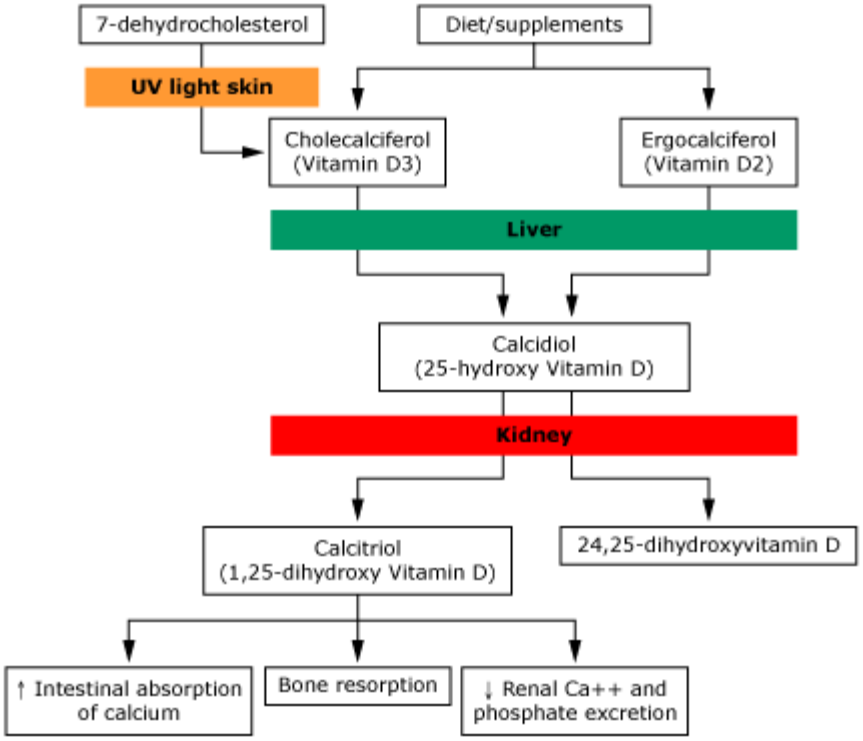
Insufficiency is defined as a 25OHD concentration of 20 to 30 ng/ml (50 to 75 nmol/L)

Deficiency is defined as a 25OHD level less than 20 ng/ml (50 nmol/L).

With these definitions, 40 to 100 percent of community dwelling elderly men and women are deficient in vitamin D.

NEJM, 2007

Vitamin D Metabolism



Cutaneous vitamin D production and vitamin D stores decline with age.

This change is most prominent in the winter. In temperate areas, cutaneous production of vitamin D virtually ceases in winter, in the elderly.

Vitamin D intake is often low in older subjects.

One-half of elderly women consume less than 137 IU/day of vitamin D, and nearly one-quarter consume less than 65 IU/day (recommended intake 400 IU/day for people 51 to 70 years old and 600 IU/day for people 71 years old and older).

Moreover, even in those with adequate vitamin D intake, achlorhydria, which is common in the elderly, limits calcium absorption. The net effect is that many elderly people have relative hypocalcemia and high serum (PTH) concentrations; this secondary hyperparathyroidism can be attenuated by the administration of physiological doses of vitamin D.

However, older persons confined indoors may have low serum calcidiol (25OHD) concentrations even with the current recommendations for vitamin D intake.

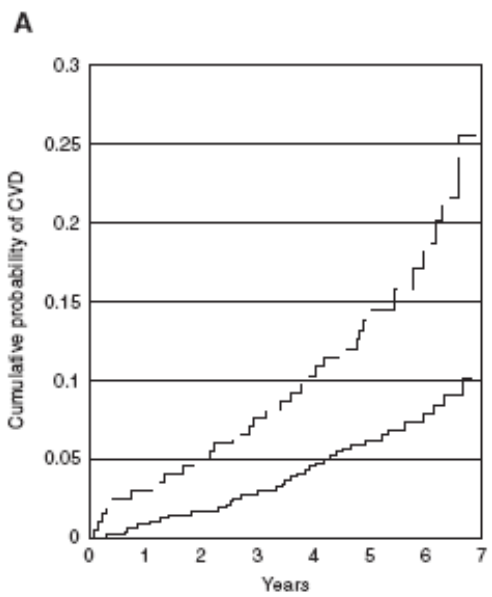
Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D_3
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D_3
Fortified orange juice	About 100 IU/8 oz vitamin D_3
Infant formulas	About 100 IU/8 oz vitamin D_3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D_3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3
Supplements	
Prescription	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D_2, or D_3‡
Vitamin D_3	400, 800, 1000, and 2000 IU

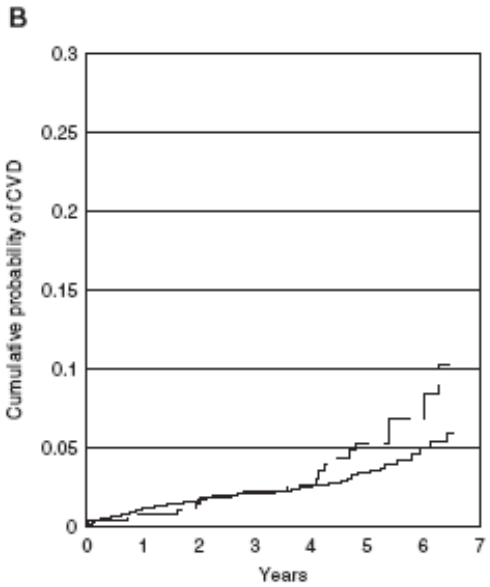
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Vitamin D Deficiency and Risk of Cardiovascular Disease

Thomas J. Wang, Michael J. Pencina, Sarah L. Booth, Paul F. Jacques, Erik Ingelsson, Katherine Lanier, Emelia J. Benjamin, Ralph B. D'Agostino, Myles Wolf and Ramachandran S. Vasan

Circulation 2008;117;503-511; originally published online Jan 7, 2008;





Prospective Study of Serum 25-Hydroxyvitamin D Level, Cardiovascular Disease Mortality, and All-Cause Mortality in Older U.S. Adults

Adit A. Ginde, MD, MPH, Robert Scragg, MBBS, PhD,† Robert S. Schwartz, MD,‡ and Carlos A. Camargo, Jr., MD, DrPH§*

Table 3. Risk of All-Cause and Cause-Specific Mortality According to Serum 25-Hydroxyvitamin D Level in 3,408 Older Adult Participants of the Third National Health and Nutrition Examination Survey

	Hazard Ratio (95% Confidence Interval)		
Cause of Mortality	**Model 1 (n = 3,408)**	**Model 2 (n = 3,303)**	**Model 3 (n = 3,265)**
All cause (n = 1,493)			
<25.0 nmol/L	**2.28** (1.44–3.59)	**2.19** (1.34–3.55)	**1.83** (1.14–2.94)
25.0–49.9 nmol/L	**1.63** (1.24–2.15)	**1.61** (1.21–2.16)	**1.47** (1.09–1.97)
50.0–74.9 nmol/L	1.23 (0.95–1.60)	1.26 (0.96–1.66)	1.21 (0.92–1.59)
75.0–99.9 nmol/L	1.19 (0.91–1.57)	1.24 (0.93–1.64)	1.15 (0.86–1.53)
≥100.0nmol/L	1.00 (ref)	1.00 (ref)	1.00 (ref)
Cardiovascular related (n = 767)			
<25.0 nmol/L	**2.81** (1.48–5.32)	**2.97** (1.53–5.78)	**2.36** (1.17–4.75)
25.0–49.9 nmol/L	**1.74** (1.16–2.63)	**1.76** (1.16–2.68)	**1.54** (1.01–2.34)
50.0–74.9 nmol/L	1.34 (0.91–1.99)	1.37 (0.92–2.04)	1.26 (0.85–1.88)
75.0–99.9 nmol/L	1.30 (0.86–1.96)	1.34 (0.88–2.02)	1.20 (0.79–1.81)
100.0 nmol/L	1.00 (ref)	1.00 (ref)	1.00 (ref)
Noncardiovascular (n = 726)			
<25.0 nmol/L	1.83 (0.97–3.45)	1.62 (0.82–3.18)	1.42 (0.73–2.79)
25.0–49.9 nmol/L	**1.53** (1.04–2.24)	1.49 (0.99–2.24)	1.42 (0.94–2.13)
50.0–74.9 nmol/L	1.13 (0.80–1.60)	1.17 (0.81–1.71)	1.16 (0.79–1.68)
75.0–99.9 nmol/L	1.10 (0.76–1.59)	1.17 (0.79–1.72)	1.11 (0.75–1.63)
100.0 nmol/L	1.00 (ref)	1.00 (ref)	1.00 (ref)

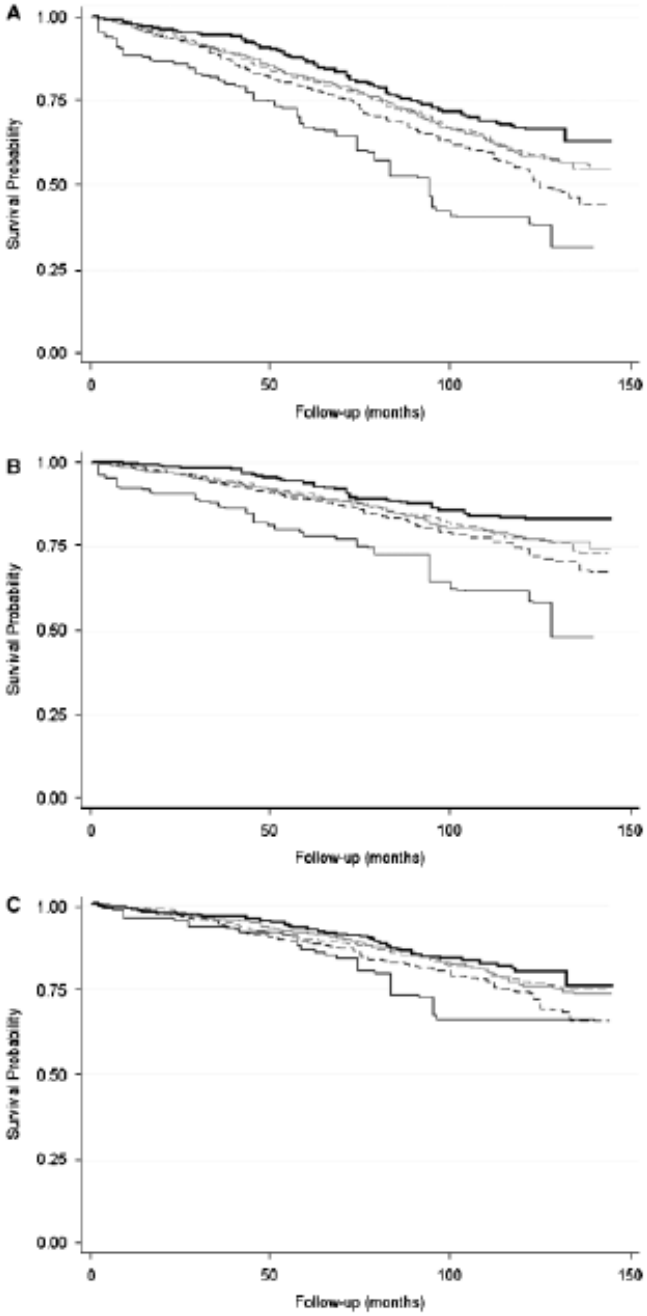
Model 1: age, sex, race/ethnicity, and season.

Model 2 (+confounders): Model 1 plus poverty:income ratio, region, body mass index, physical activity, smoking status, cigarette pack years, asthma, chronic obstructive pulmonary disease, and renal function.

Model 3 (+intermediates): Model 2 plus hypertension, diabetes mellitus, hyperlipidemia, history of myocardial infarction, history of stroke, and history of cancer (nonskin).

Bold values denote $P < .05$.

JAGS; 2009



Survival (Kaplan-Meier) curves for mortality according to serum 25-hydroxyvitamin D levels.

(A) All-cause mortality.

(B) Cardiovascular disease mortality.

(C) Noncardiovascular disease mortality.

Serum 25- hydroxyvitamin D levels:

Dark solid: 100.0 nmol/L

Gray dashed: 75.0–99.9 nmol/L

Gray solid: 50.0–74.9 nmol/L;

Black dashed: 25.0–49.9 nmol/L;

Black solid: o25.0 nmol/L.

Falls

Between 30 and 40 percent of community-dwelling people over the age of 65 years fall each year, increasing to about fifty percent for those 80 years and older.

Almost 60 percent of those with a history of a fall in the previous year will have a subsequent fall.

Five to ten percent of falls among community-dwelling elderly result in major injuries: fracture, head trauma or major lacerations.

Rates of fall-related major injuries for nursing home residents are higher (10 to 30 percent).

Falls accounted for 62 percent of non-fatal injuries leading to US emergency department visits for people over 65 years. Approximately five percent of falls in older persons will lead to hospitalization.

Fall-related injuries are associated with significant subsequent morbidity: decline in functional status, increased likelihood of nursing home placement, and greater use of medical services.

Among community-living elders who sustain hip fractures, 25 to 75 percent do not recover pre-injury functional status.

Complications resulting from falls are the leading cause of death from injury in men and women older than age 65, and the fifth leading cause of death in older adults.

JAMA®

Online article and related content current as of July 13, 2009.

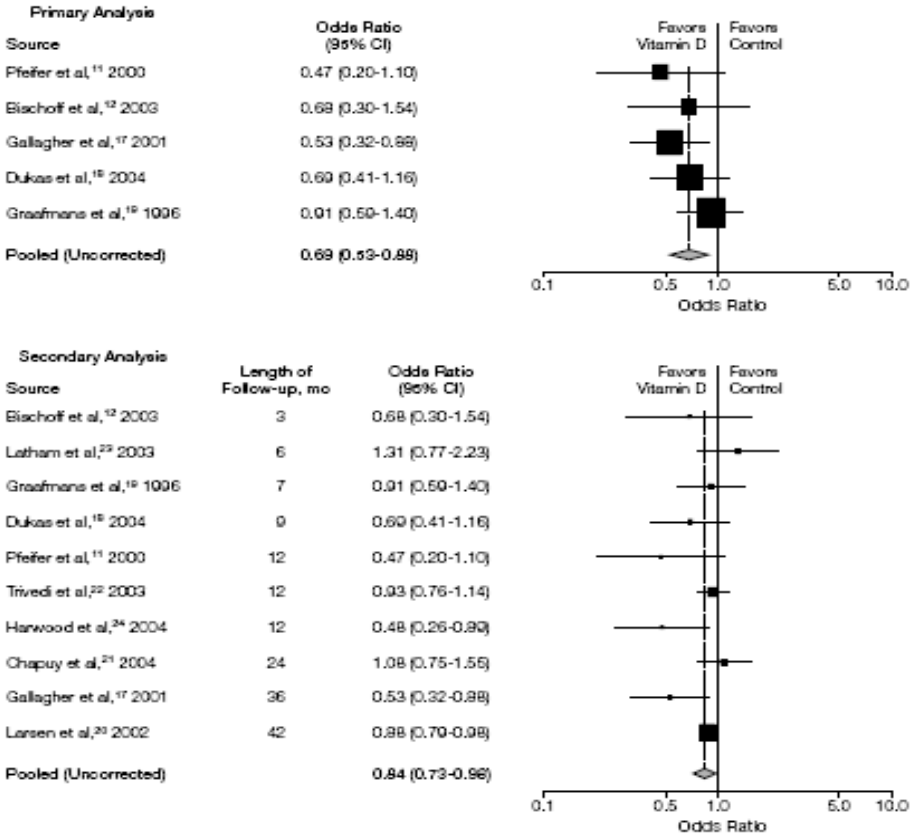
Effect of Vitamin D on Falls: A Meta-analysis

Heike A. Bischoff-Ferrari; Bess Dawson-Hughes; Walter C. Willett; et al.

JAMA. 2004;291(16):1999-2006 (doi:10.1001/jama.291.16.1999)

http://jama.ama-assn.org/cgi/content/full/291/16/1999

Figure 2. Forest Plots Comparing the Risk of Falling Between Vitamin D–Treated Groups and Control Groups for the Primary and Sensitivity Analyses



Squares represent the odds ratios for the risk of falling among those who took vitamin D treatment (or analog) vs those in the control group. Size of the squares is proportional to the size of the trials. Error bars represent 95% confidence interval (CIs). The diamond shape represents the pooled estimates within each analysis. The corrected pooled odds ratio for the primary analysis was 0.78 (95% CI, 0.64-0.92). The primary analysis excluded randomized controlled trials for which authors did not state how falls were ascertained or how they were defined. Also, preliminary studies and studies performed in populations with an unstable health state were excluded from the primary analysis. The corrected pooled odds ratio for the sensitivity analysis was 0.87 (95% CI, 0.80-0.96). Studies for the sensitivity analysis were sorted by trial duration in months.

Interventions for Preventing Falls in Older People Living in the Community

Summary

As people get older, they may fall more often for a variety of reasons including problems with balance, poor vision, and dementia. Up to 30 % may fall per year. Although one in five falls may require medical attention, less than one in 10 results in a fracture. Fear of falling can results in self-restricted activity levels. It may not be possible to prevent falls completely, but people who tend to fall frequently may be enabled to fall less often

This review looked at which methods are effective for older people living in the community, and includes 111 randomized controlled trials, with a total of 55,303 participants.

Exercise programmes may target strength, balance, flexibility, or endurance. Programmes that contain two or more of these components reduce rate of falls and number of people falling. Exercising in supervised groups, participating in Tai Chi, and carrying out individually prescribed exercise programmes at home are all effective.

Multifactorial interventions assess an individual person's risk of falling, and then carry out or arrange referral for treatment to reduce their risk. They have been shown in some studies to be effective, but have been ineffective in others. Overall current evidence shows that they do reduce rate of falls in older people living in the community. These are complex interventions, and their effectiveness may be dependent on factors yet to be determined.

Taking vitamin D supplements probably does not reduce falls, except in people who have a low level of vitamin D in the blood. These supplements may be associated with high levels of calcium in the blood, gastrointestinal discomfort, and kidney disorders.

Interventions to improve home safety do not seem to be effective, except in people at high risk, for example with severe visual impairment. An anti-slip shoe device worn in icy conditions can reduce falls.

Some medications increase the risk of falling. Ensuring that medications are reviewed and adjusted may be effective in reducing falls. Gradual withdrawal from some types of drugs for improving sleep, reducing anxiety and treating depression has been shown to reduce falls.

Cataract surgery reduces falls in s in people having the operation on the first affected eye. Insertion of a pacemaker can reduce falls in people with frequent falls associated with carotid sinus hypersensitivity, a condition which may result in changes in heart rate an blood pressure

Cochrane Database, CD007146; 2009

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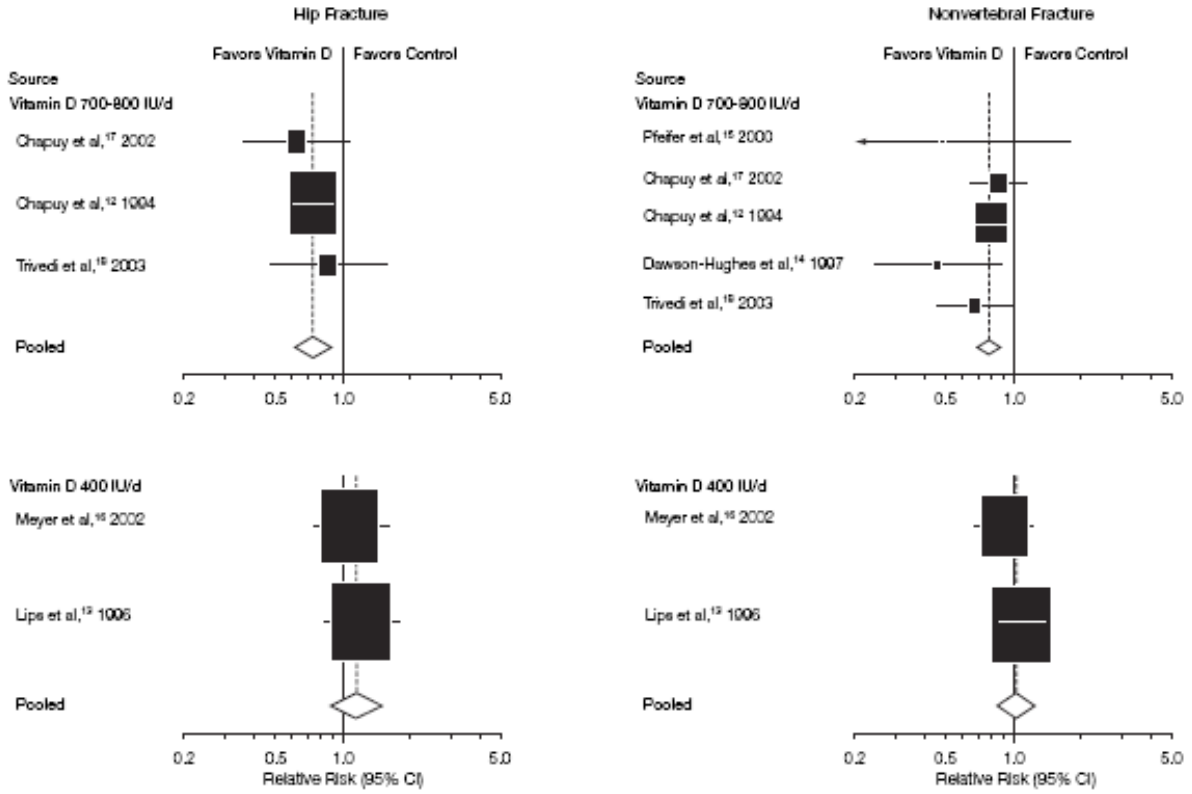
Fracture Prevention With Vitamin D Supplementation: A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari; Walter C. Willett; John B. Wong; et al.

JAMA. 2005;293(18):2257-2264 (doi:10.1001/jama.293.18.2257)

http://jama.ama-assn.org/cgi/content/full/293/18/2257



Squares represent relative risks (RRs) and size of squares is proportional to the size of the trials. Error bars represent 95% confidence intervals (CIs). Trials are sorted by trial duration ranging from 24 to 60 months for hip fracture and 12 to 60 months for nonvertebral fracture. For 3 trials with hip fractures,[12,17,18] which included 5572 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.74 (95% CI, 0.61-0.88; Q test $P=.74$). For 5 trials with nonvertebral fractures,[12,14,15,17,18] which included 6098 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.77 (95% CI, 0.68-0.87; Q test $P=.41$). For the 2 trials,[13,16] with a vitamin D dose of 400 IU/d, trial duration ranged from 24 months to 36 to 41 months.

We suggest not routinely screening elderly people for vitamin D deficiency.

Rather than screen, we suggest intake of at least 1200 mg of elemental calcium (total diet plus supplement) and 800 international units (UI) of vitamin D daily in all elderly people who do not have hypercalcemia

J. Morley, IAGS; 2009