



# **VITAMIN D: ARE THE DATA FOR THE NON-SKELETAL EFFECTS ROBUST ENOUGH TO JUSTIFY HEALTH CLAIMS?**

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# New recommendations on Vitamin D



The IOM concluded in their 2010 assessment that data vitamin D is beneficial for bone health

– **target blood level 50 nmol/l for 25(OH)D**

- 600 IU per day in all < 70 years of age
- **800 IU per day in all age 70+ years of age**
- Safe upper intake in adults = 4000 IU per day
- **Skeletal plus non-skeletal endpoints:** „There is no evidence that a serum level greater than 50nmol/l is beneficial to health“



# New recommendations on Vitamin D



**IOF position statement on Vitamin D and US Endocrine Society Task Force on Vitamin D concluded that vitamin D reduces the risk of falls and fractures**

**– target blood level 75 nmol/l for 25(OH)D**

- **800 IU per day age 60+**
- **Non-skeletal endpoints:** the US Endocrine Society and the IOF recommend vitamin D for fall and fracture prevention.
- The Endocrine Society states that they do not recommend prescribing vitamin D supplementation beyond recommended daily needs for the purpose of prevention cardiovascular disease or death or improving quality of life.
- The Endocrine Society however states that for other endpoints than muscle health, evidence from randomized controlled trials is lacking. However, they also state that numerous epidemiological studies have suggested that 25(OH)D blood concentrations above 75 nmol/l have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease, and infectious diseases



# Vitamin D is a special case for health claims

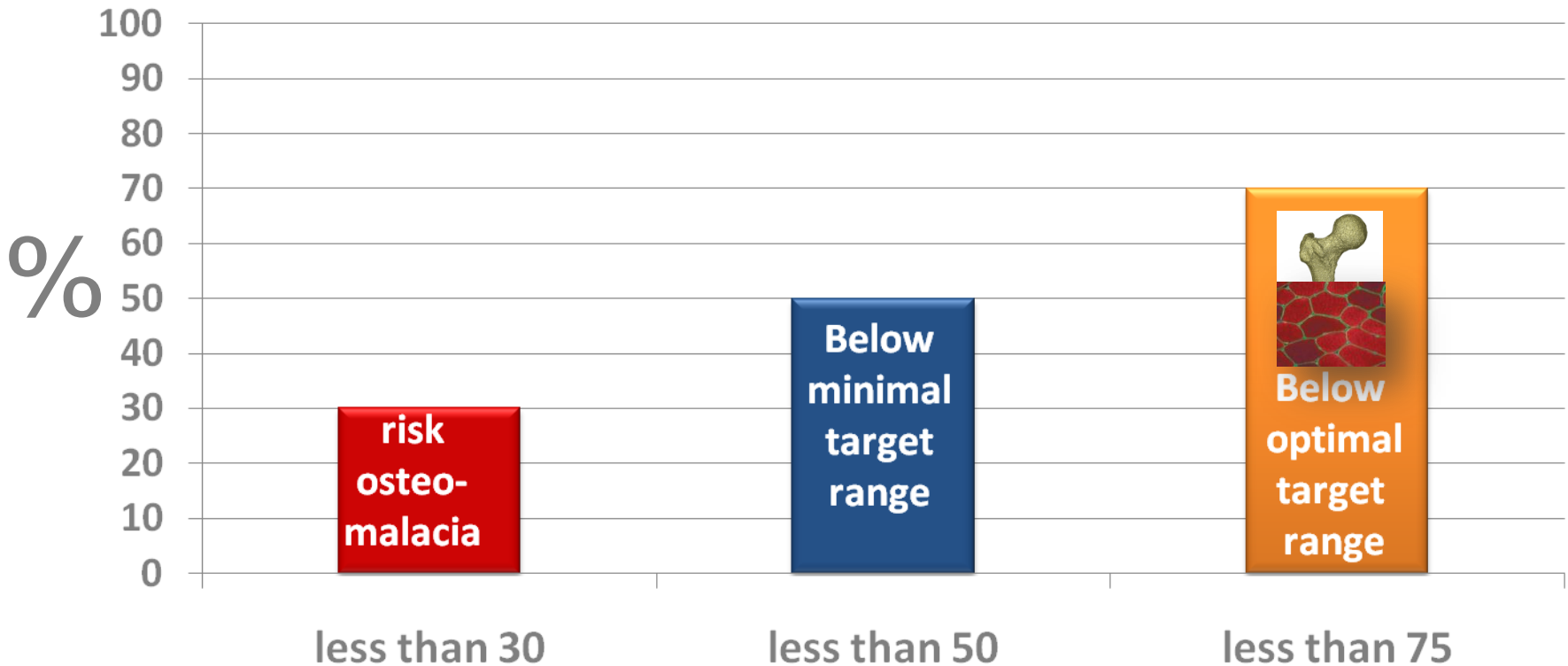
- A large part of the population is deficient by any definition
- To sustain health claims we need to build evidence that supplementation reduces risks (as available for fall and fracture prevention)
- Another claims basis may be that deficiency of vitamin D is a risk factor for non-skeletal endpoints
  - risk factor' for the development of disease
    - ❖ Has to be independent predictor of the disease
    - ❖ Has to be plausible (mechanistic data, validation)



# How many are deficient?

EU-Parliament Hearing 3-2010

## Adult European Population



Threshold for 25-hydroxyvitamin D serum concentration in nmol/l

*van der Wielen RP, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet 1995;346:207-10 (SENECA).*

*Burnand B, Burckhardt P et al. Serum 25-hydroxyvitamin D: Swiss population. Am J Clin Nutr 1992;56:537-42.*

# Children in Germany- KIGGS 2009

**Based on means about 50% are below 50 nmol/l**

(Institute of Medicine 2010 threshold for deficiency)

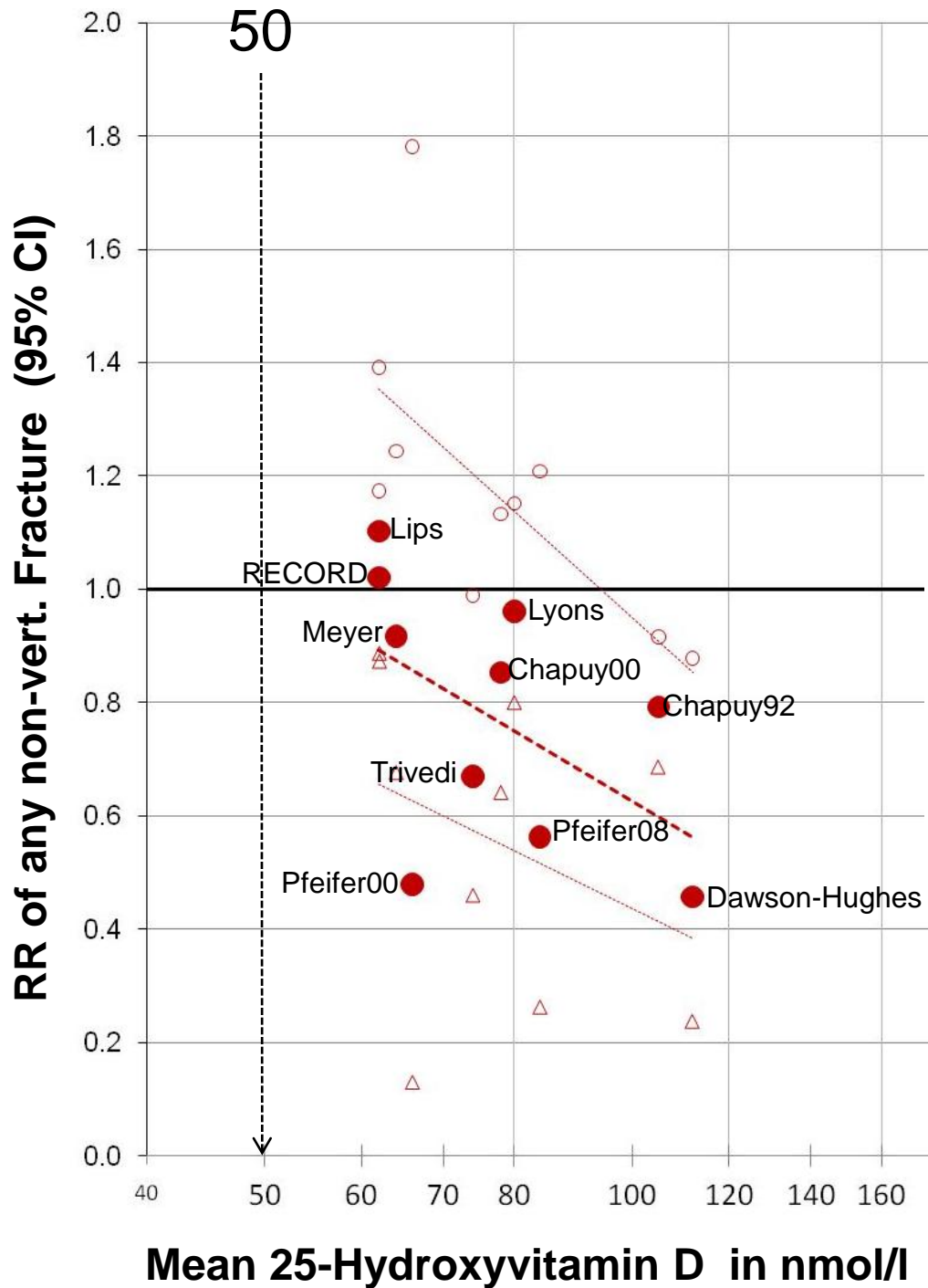
25-Hydroxyvitamin D Levels (median; 90 percentiles) by age group in German children with or without a migration background

Altersgruppe Jahre	Boys		Girls		Total	
	Med	p5-p95	Med	p5-p95	Med	p5-p95
1-2	63,6	20,5-119,0	59,8	19,4-114,0	61,9	19,4-115,0
3-6	44,0	13,9-97,4	44,1	16,1-93,6	44,1	15,0-95,8
7-10	42,9	15,2-90,8	40,3	14,1-86,9	41,7	14,8-89,1
11-13	39,6	14,9-87,9	35,7	9,0-74,5	38,0	12,7-80,9
14-17	36,8	11,9-88,8	41,1	13,5-104,0	39,3	12,3-96,3
Gesamt	42,4	14,1-96,2	41,4	13,8-96,4	41,9	13,9-96,3
Migrant	35,5	10,1-89,7	34,2	8,0-94,1	34,8	8,9-92,5
Nicht-Migrant	43,9	15,1-97,2	42,9	15,4-97,0	43,5	15,2-97,2

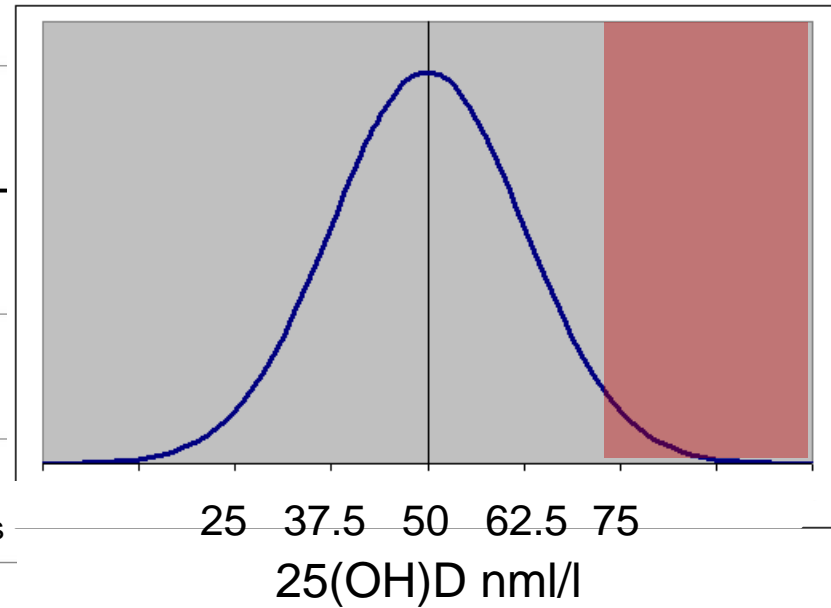
# Threshold of 50 nmol/l

**IOM:** „ Benefit for most in the population is associated with serum 25OHD levels of **approximately 50 nmol/L (20 ng/mL)**”

**Concern:** With this recommendation, in reality, we will end up with some people above 50 and some below, with perhaps an average of 50.



assume **normal distribution** with mean 50 nmol/l and SD of 26 nmol/l (as observed in fracture RCTs on the left), **the probability of having a value of 75+ nmol/l is 0.18**







„ There is inconsistent evidence that supplemental vitamin D reduces falls in postmenopausal women and older men”



Agency for Healthcare Research and  
Quality (AHRQ) for the U.S. Preventive  
Services Task Force

„ Vitamin D supplementation is an effective  
strategy in fall prevention”

Subgroup analysis	Subgroup fall meta-analyses IOM open design and blinded / any quality	N	Pooled OR
1	<b>12 RCTs of oral or injectable vitamin D with or without calcium</b> versus calcium or placebo A) Combining the data of 9 RCTs of oral or injectable vitamin D with or without calcium versus placebo B) Combining the data of 4 RCTs of oral or injectable vitamin D with or without calcium versus calcium	<b>14,101</b>  11,895  4,855	<b>OR = 0.89; 95% CI 0.80-0.99</b>  OR = 0.91; 95% CI 0.81-1.01  OR = 0.88; 95% CI 0.70-1.10
2	Combining the data of <b>11 RCTs of oral vitamin D</b> with or without calcium versus calcium or placebo	<b>13,888</b>	<b>OR = 0.92; 95% CI 0.85-1.00</b>
3	Combining the data of <b>8 RCTs of oral vitamin D with calcium</b> versus calcium or placebo A) Combining the data of 5 RCTs of oral vitamin D with calcium versus placebo B) Combining the data of 4 RCTs of oral vitamin D with calcium versus calcium	<b>9,262</b>  7,056  3,512	<b>OR = 0.84; 95% CI 0.76-0.93</b>  OR = 0.85; 95% CI 0.76-0.96  OR = 0.81; 95% CI 0.68-0.97
4	Combining the data of <b>4 RCTs of oral vitamin D without calcium versus calcium or placebo</b> A) Combining the data of 4 RCTs of oral vitamin D without calcium versus placebo B) Data of 1 RCTs of oral vitamin D without calcium versus calcium	<b>7,269</b>  5,958  2,654	<b>OR = 1.05; 95% CI 0.93-1.19</b>  OR = 1.03; 95% CI 0.91-1.17  OR = 1.19; 95% CI 0.96-1.47



# IOM - Falls

- The IOM *overall analysis of 12 RCTs (n = 14,101) showed a significant benefit of vitamin D on fall prevention (OR = 0.89; 95% CI 0.80-0.99), as did the majority of their subset analyses, clearly supporting the use of vitamin D in the prevention of falling.*
- **The set of analyses which showed no benefit on falls (4, 4A+B) were based on 4 studies, which either**
  - used low dose vitamin D (Graafmans 1996)
  - had less than 50% adherence (RECORD 2005)
  - had a low-quality fall assessment (Trivedi 2003)
  - used one large bolus dose of vitamin D among seniors in unstable health (Latham 2003)

Falls are a difficult endpoint to assess and seniors tend to forget falls\*.

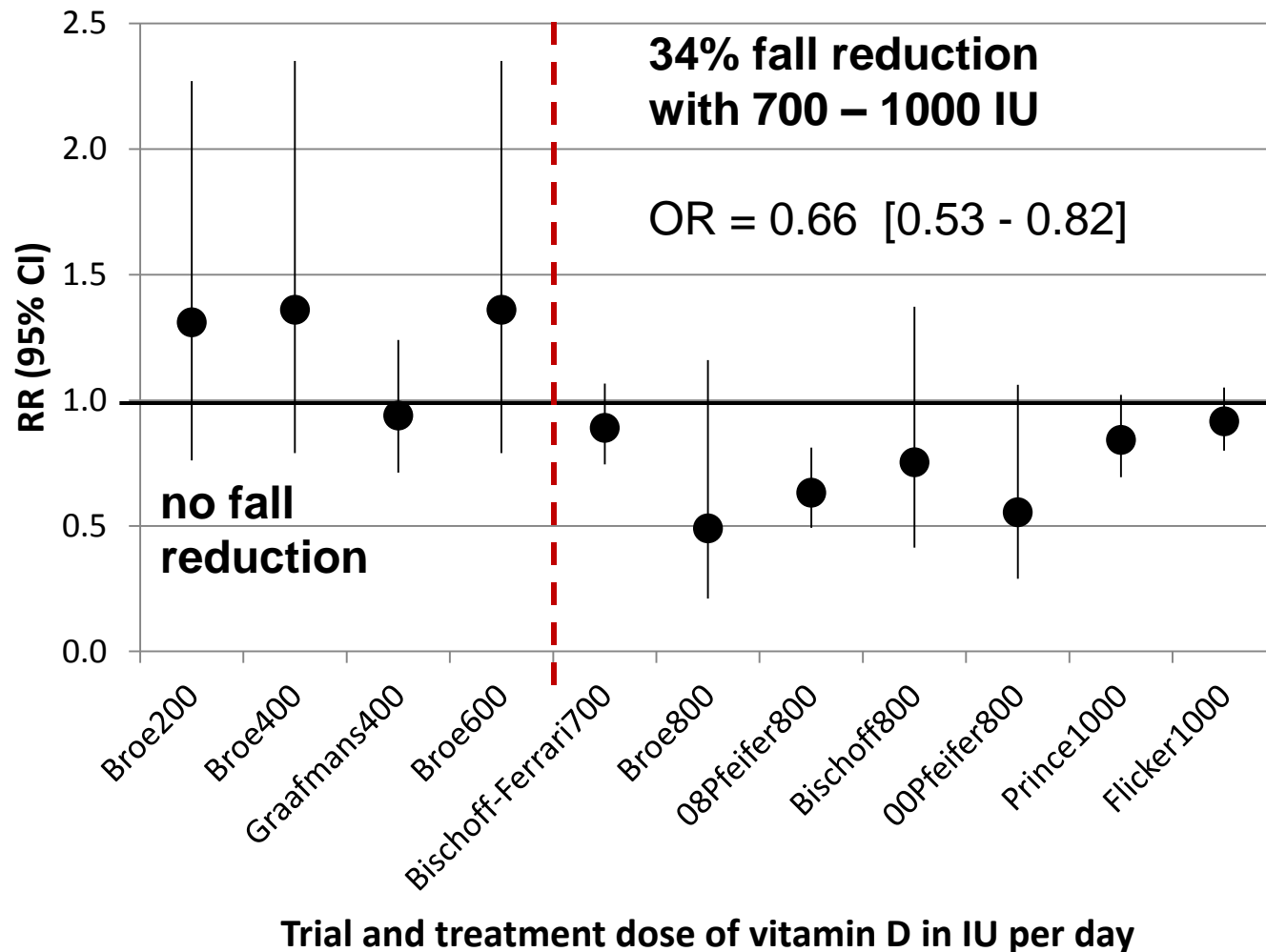
**IOM sensitivity analysis of 6 trials with high quality fall assessment showed a 21% reduction in the odds of falling (OR = 0.79; 0.65-0.96; heterogeneity  $I^2 = 0$  percent )**

**This analysis reflects true treatment efficacy indicating a consistent benefit with „zero“ heterogeneity**

\*Cumming SR et al. Forgetting falls. The limited accuracy of recall of falls in the elderly; JAGS 1998

# Dose-response confirmed for fall reduction in high quality trials

8 double-blind RCTs (n = 2426)





# Vitamin D – Muscle Link

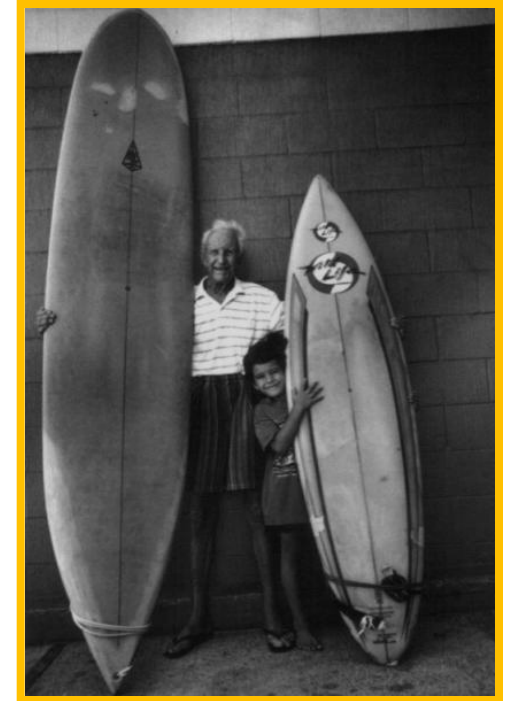
- (1) Severe deficiency -- Myopathy**
- (2) VDR present in muscle**
- (3) Type II muscle fibre atrophy in biopsies of patients with severe deficiency**
  - Fast twitch
  - First to recruit for fall prevention
- (4) Two small studies demonstrate increase in relative number and size of type II fibers**

after treatment with 1-alpha vitamin D (3 mo)

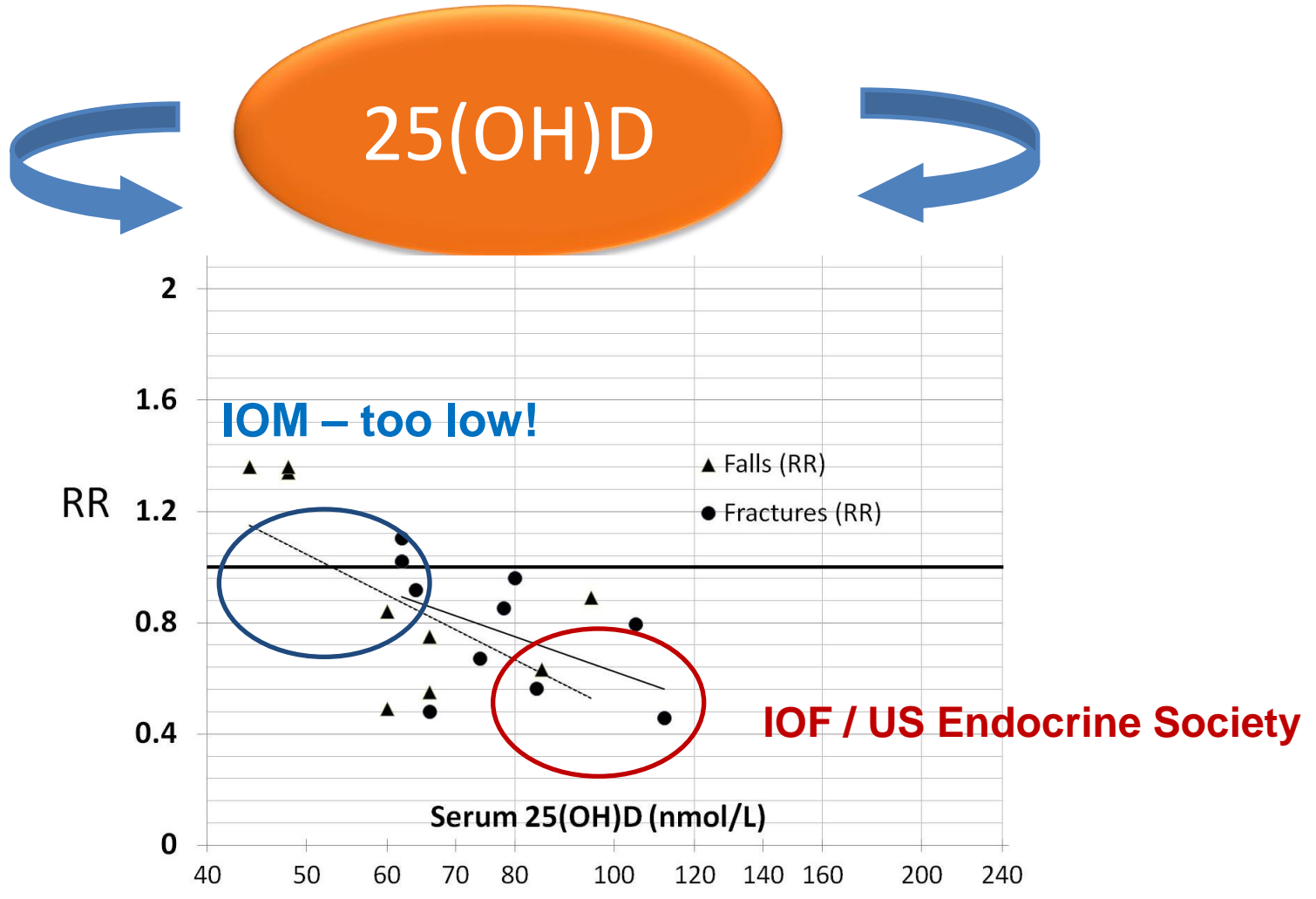
*(Soerensen OH et al. Clin Sci 1979)*

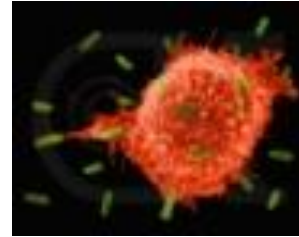
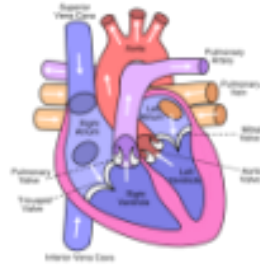
after treatment with 1000 IU D2 (2 yrs)

*(Sato et al. 2005; Cerebrovasc Dis)*



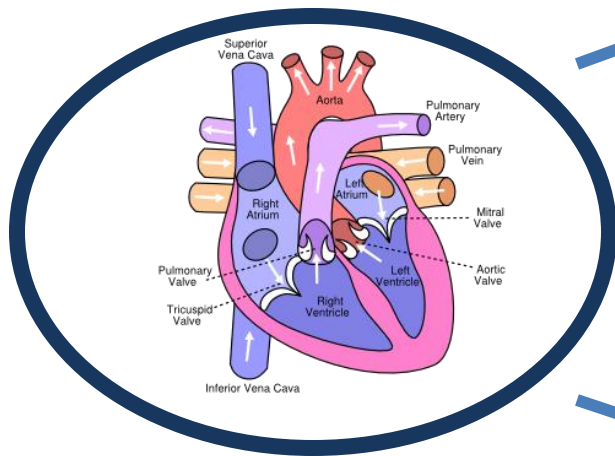
based on RCT data on fall and fracture prevention





# Small clinical trials, mechanistic and large cohort studies suggest **benefit of vitamin D on cardio-vascular health**

**Large clinical trials needed  
to confirm such benefits**



**Mouse without the VDR:**  
has hypertension  
and dies from heart failure

*Bouillon R, Bischoff-Ferrari H, Willett W. JBMR 2008;  
Endo I et al. Endocrinology 2003*

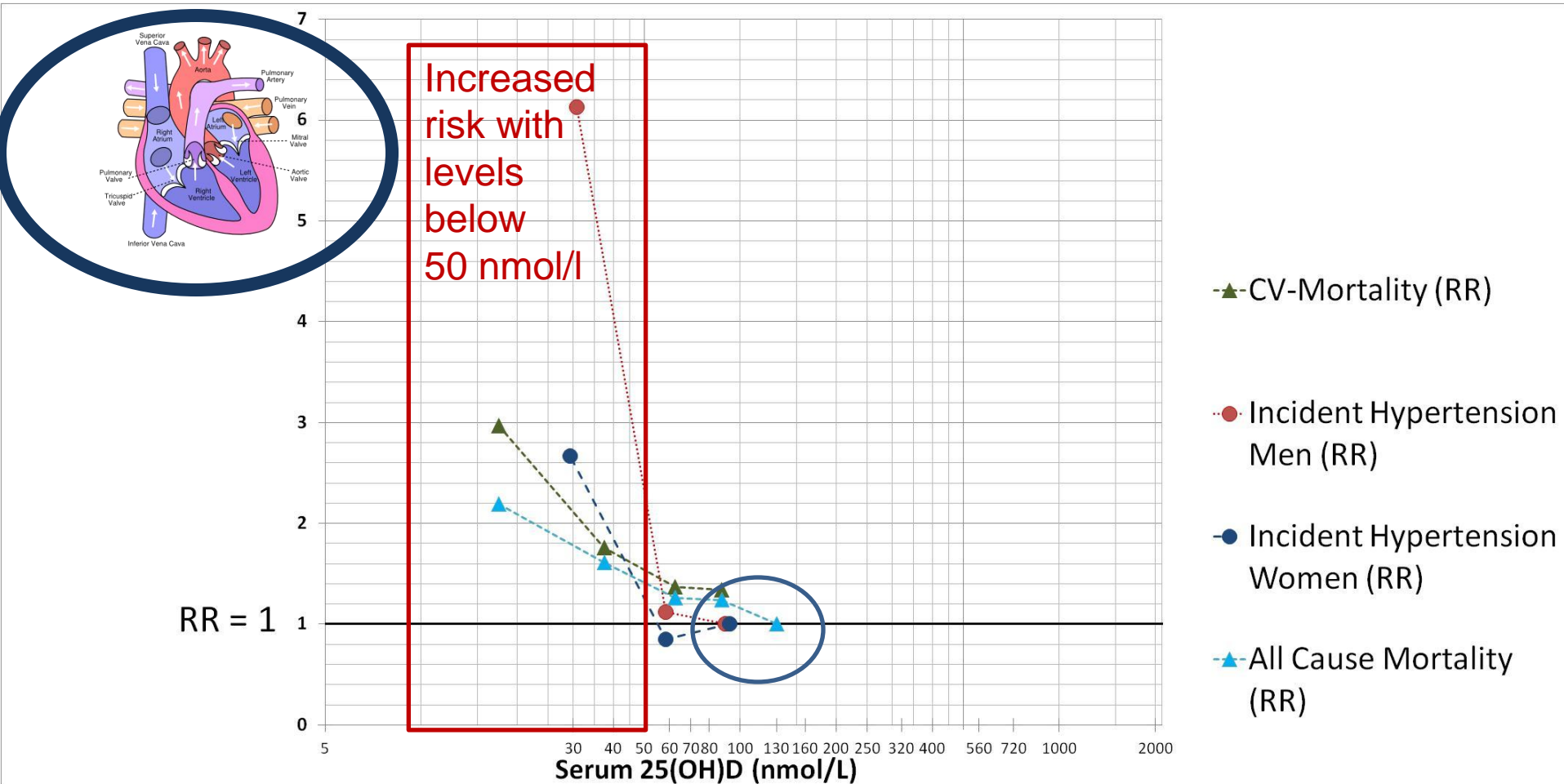
**2 Small clinical trials in humans:**  
UVB-irradiation or  
800 IU vitamin D reduces blood pressure  
by about 6 mmHG

*Pfeifer M et al. J Clin Endocrinol Metab. 2001 ;  
Krause et al. The Lancet 1998*

**Large cohort studies:**  
Benefit on CV health

*Giovannucci E et al. Archives of Int. Med. 2008;*

# Large Cohort Studies: Optimal 25(OH)D Levels for cardio-vascular health

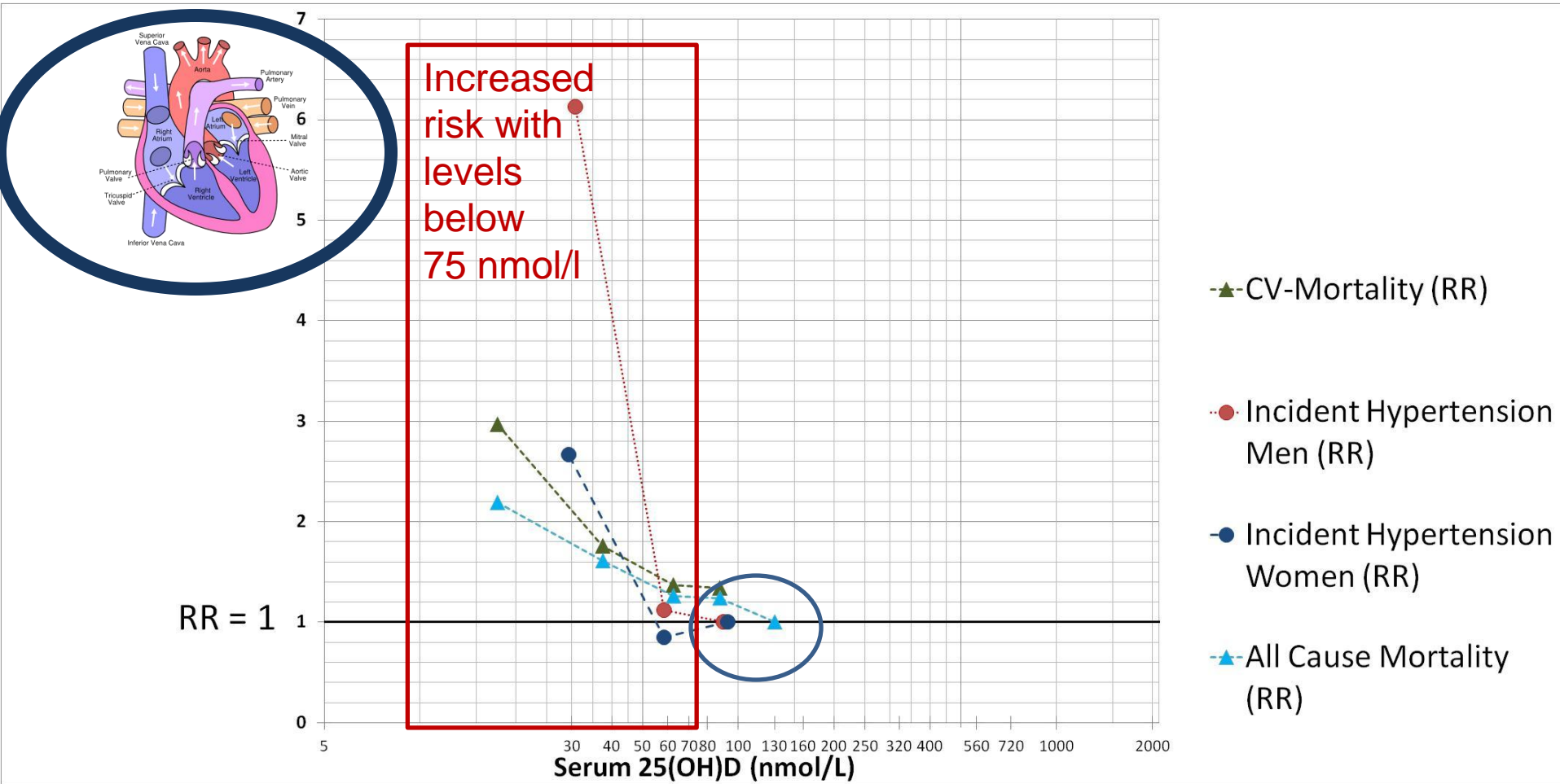


**Incident hypertension: Forman JP et al. (NHS + HP); Hypertension 2007.**

**All-cause and cardiovascular mortality: Ginde AA (NHANES III); Am J Prev. Med. 2007**

*Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Giovannucci E, Willett WC, Hathcock J; Benefit-Risk Assessment of Vitamin D; Osteoporosis International 2009*

# Large Cohort Studies: Optimal 25(OH)D Levels for cardio-vascular health

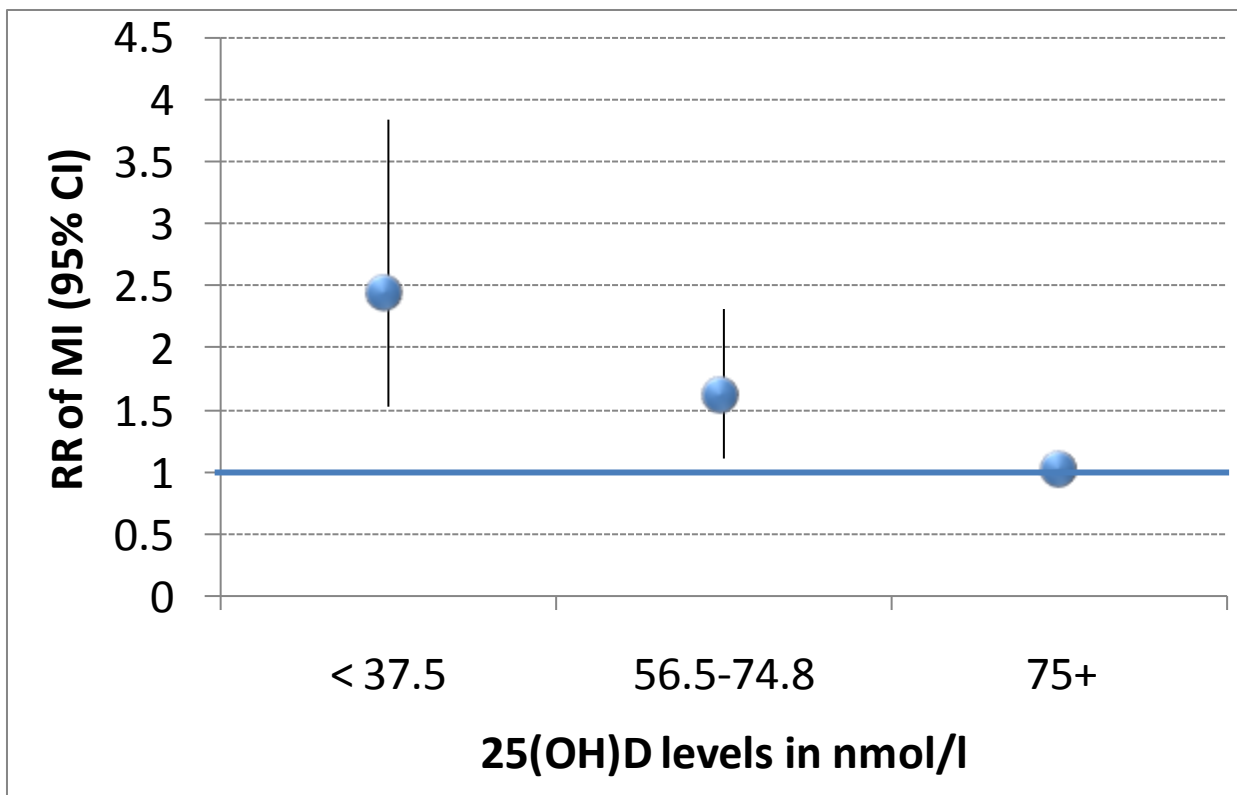
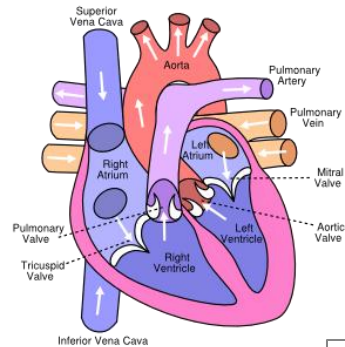


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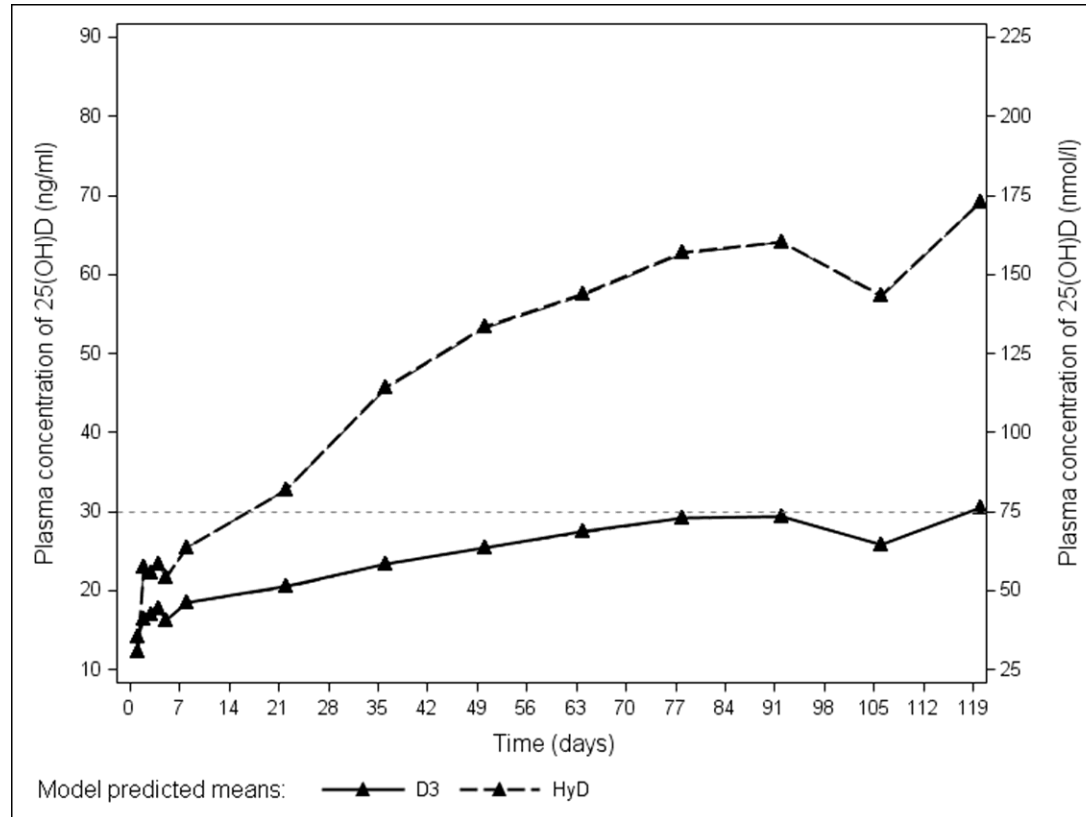
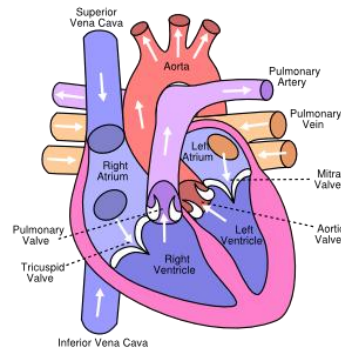
# 25(OH)D status and 10-yr risk of Myocardial Infarction



Nested case-control study, controlling for age, date of blood draw, smoking status. Similar with full adjustment. 454 cases, 900 controls.

# Oral supplementation with 25(OH)D<sub>3</sub> versus vitamin D<sub>3</sub>: effects on 25(OH)D levels, lower extremity function, blood pressure and markers of innate immunity

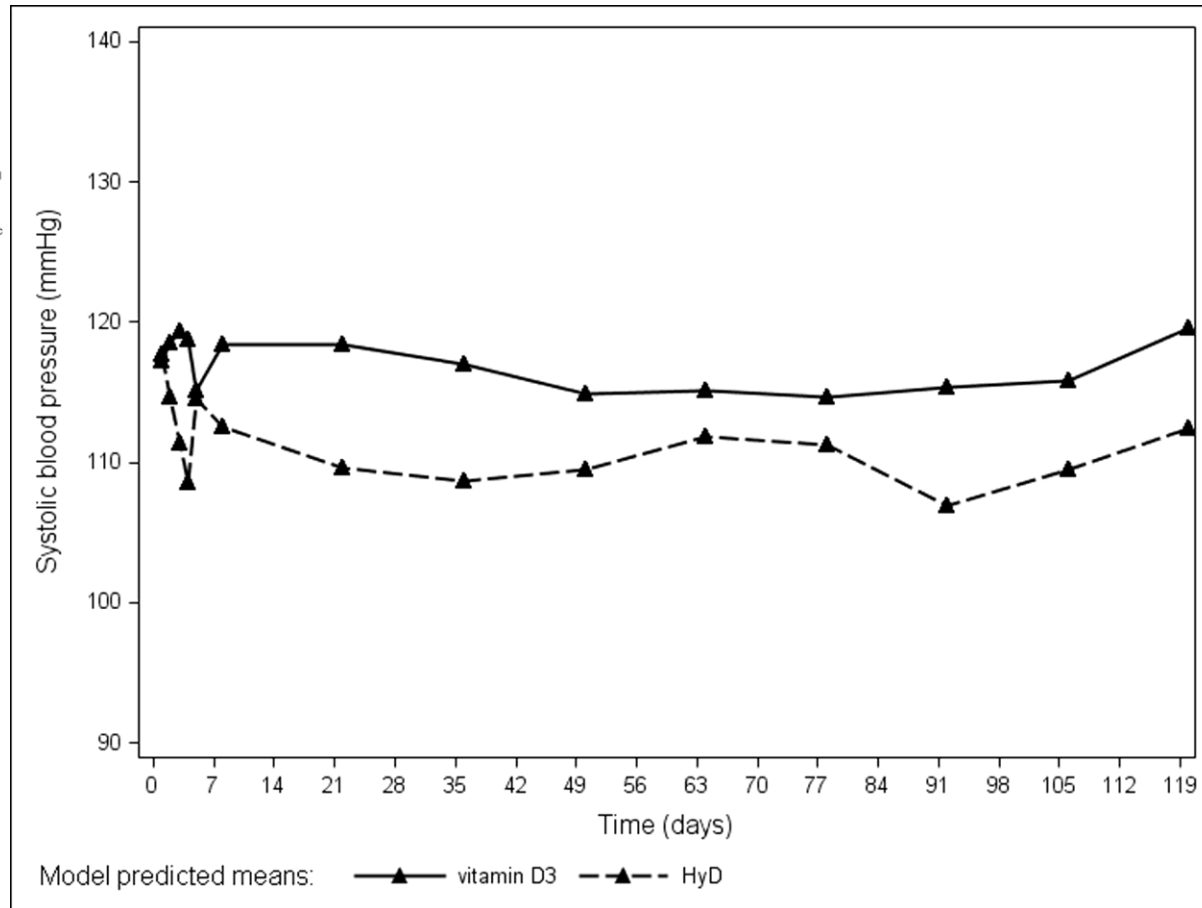
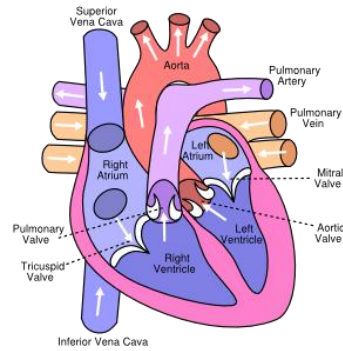
*Bischoff-Ferrari HA et al. JBMR 2011*



20 healthy postmenopausal women with an average 25(OH)D level of 32 nmol/l (SD = ±9.8) and a mean age of 61.5 years (SD = ±7.2) were randomized to either 20 µg of HyD or 20 µg (800 IU) of vitamin D<sub>3</sub> per day in a double-blind manner; followed in 14 clinical visits

# Effect on systolic blood pressure

*Bischoff-Ferrari HA et al. JBMR 2011*



Vitamin D3

25(OH)D

25(OH)D compared with vitamin D<sub>3</sub> lowered systolic blood pressure on average by 5.7 mmHg ( $p = 0.002$ ) over 4 months, independent of age, BMI, and baseline systolic blood pressure



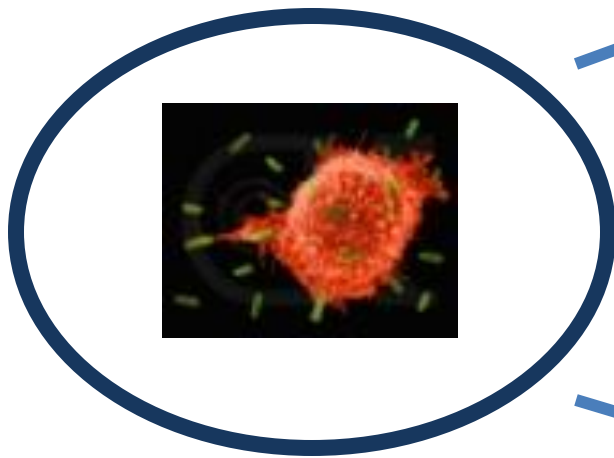
# Mortality

- 25(OH)D levels were inversely associated with mortality in 5 epidemiologic studies, most of which suggested a continuous inverse relationship between 25(OH)D concentrations and risk of mortality.
- The inverse association is supported by a meta-analysis of 9 randomized controlled trials documenting a 7% significant reduction of mortality with vitamin D supplementation compared to control (placebo or calcium)
- A similar trend for risk reduction was observed in the large Women's Health Initiative trial (hazard ratio for total mortality: 0.91; 95% confidence interval, 0.83-1.01).
- Notably, however, in two observational studies, a U-shaped relationship has been described with an increased risk of mortality both at low (< 50 nmol/l) and very high concentrations of 25(OH)D (> 220 nmol/l)
- **The threshold concentrations that confer the maximum risk reduction for mortality across all studies was 75 to 110 nmol/l**

One small clinical trial, mechanistic studies and large cohort studies suggest a benefit of vitamin D on

# cancer prevention

**Large clinical trials needed to confirm such benefits**



**Vitamin D inhibits cell proliferation:**

Shown for fibroblasts, colo-rectal, breast and prostate cancer cells

**Clinical trial in humans:**

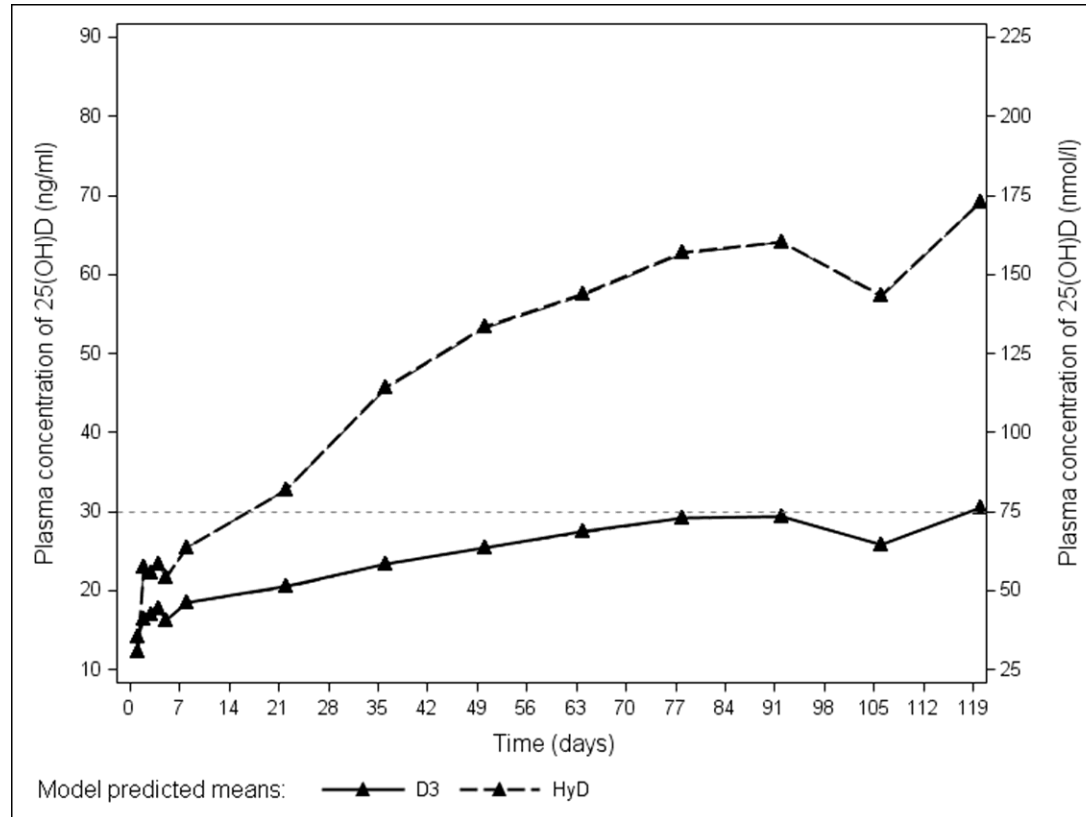
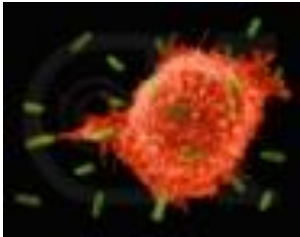
Among 1179 women age 55+  
1100 IU vitamin D + calcium compared to placebo reduced cancer risk by 60% in 4 yrs

**Large cohort studies:**

Higher vitamin D levels associated with lower cancer risk, and less mortality from cancer, strongest data for colo-rectal cancer

# Oral supplementation with 25(OH)D<sub>3</sub> versus vitamin D<sub>3</sub>: effects on 25(OH)D levels, lower extremity function, blood pressure and markers of innate immunity

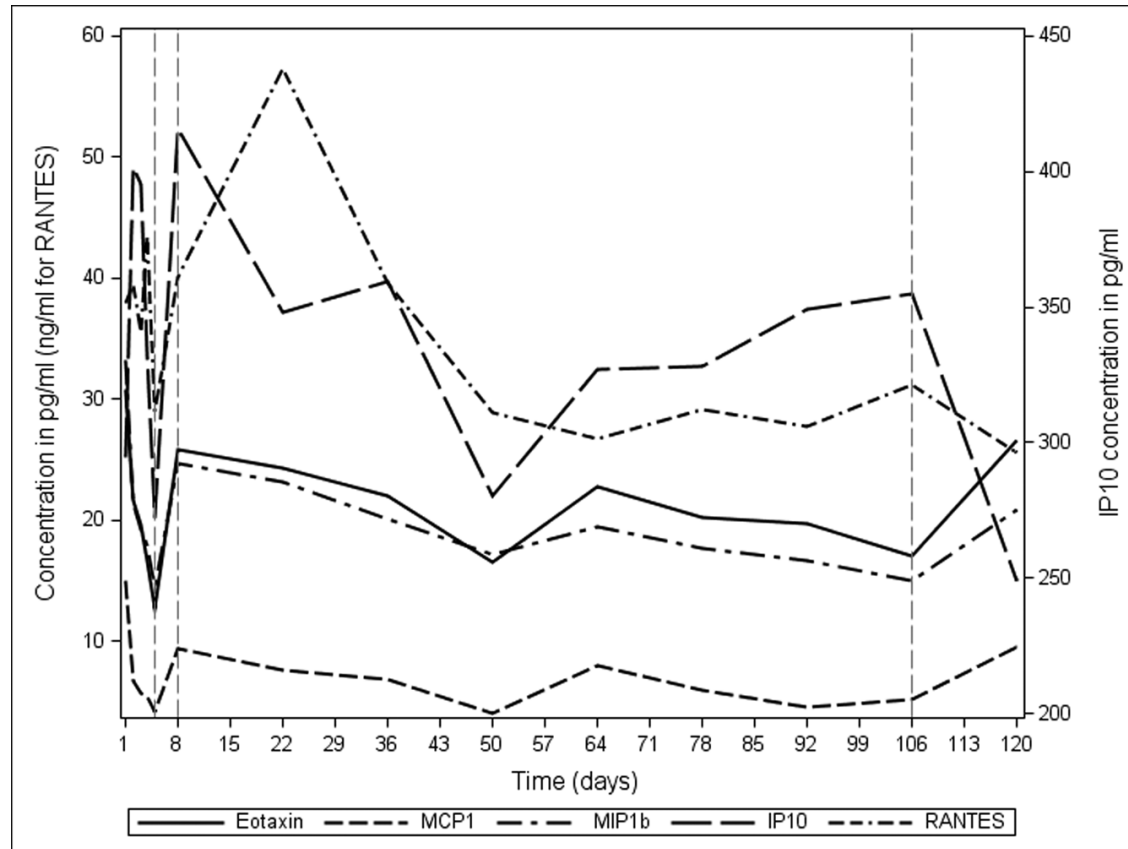
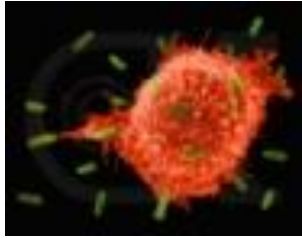
*Bischoff-Ferrari HA et al. JBMR 2011*



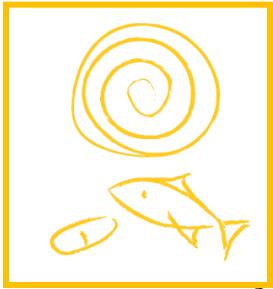
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# Effect on biomarkers of innate immunity

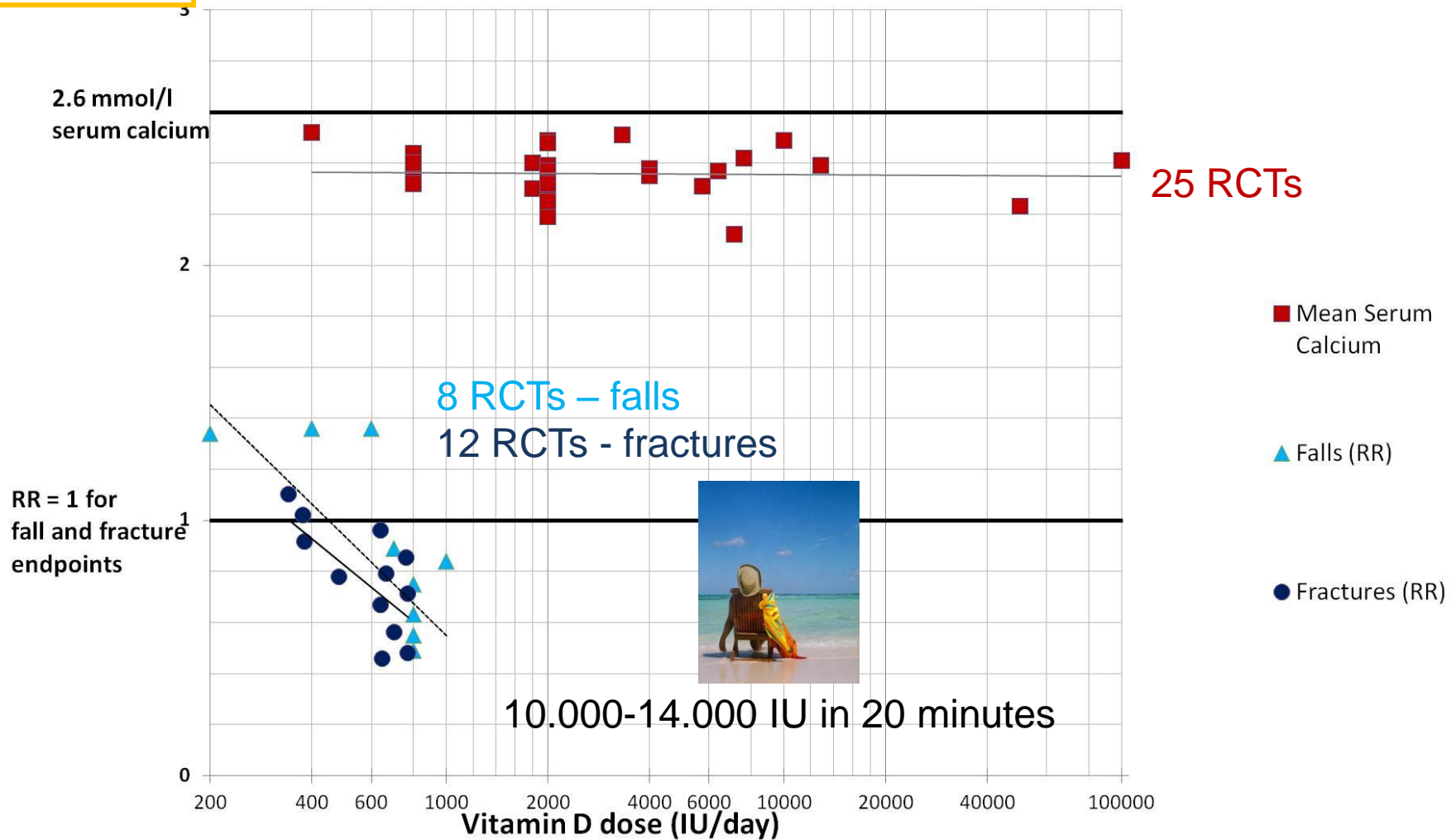
*Bischoff-Ferrari HA et al. JBMR 2011*

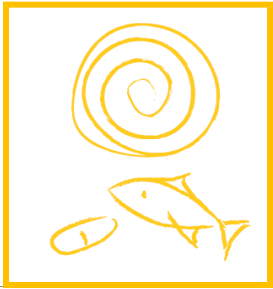


25(OH)D and vitamin D contributed to a decrease in 5 out of 7 markers of innate immunity, significantly more pronounced with HyD for eotaxin, IL-12, MCP-1 and MIP1 $\beta$ .

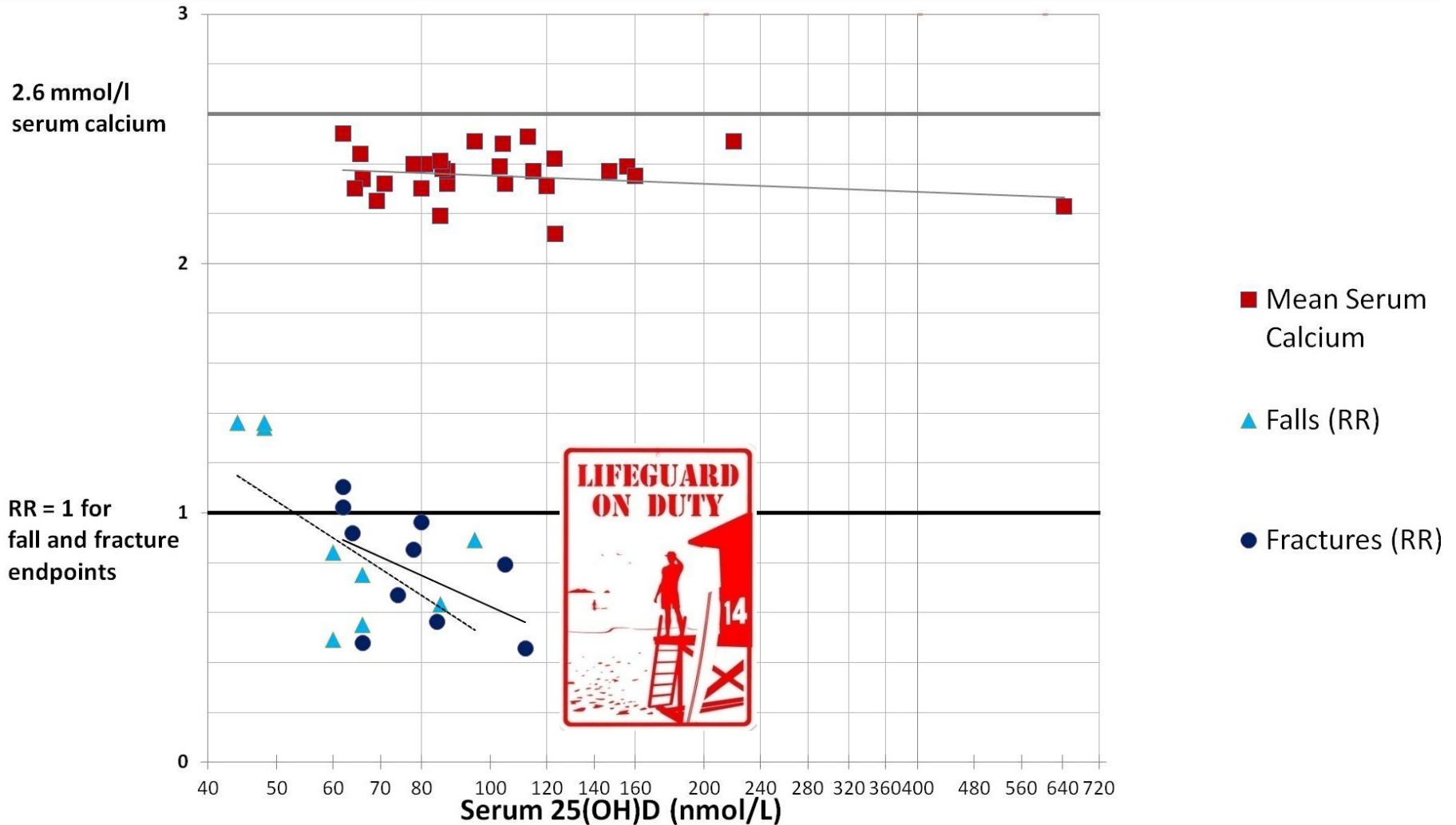


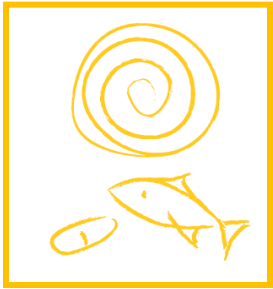
# Safety based on Trials with Vitamin D // dose





# Safety based on Trials with Vitamin D // levels





# Summary

- We have health claims for vitamin D for bone health and fall prevention (EFSA 2011) which are based on RCT data
- Further health claims on non-skeletal endpoints cannot be substantiated today based on the lack of evidence from larger RCTs
- Whether claims can be made based on the harm from deficiency is unclear
- Clearly, there is a great need for large clinical trials to define the role of vitamin D with respect to non-skeletal endpoints
  - VITAL (US)
  - DO-HEALTH (Europe – Framework 7 RCT currently under negotiation)