

# Vitamin D to Improve Health Outcomes?

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## Overview (1):

- The major evidence for vitamin D activities concern two distinct bone diseases, osteomalacia and osteoporosis.
- To prevent osteomalacia vitamin D exerts **endocrine** activities to maintain plasma calcium and phosphate homeostasis, regulating intestinal calcium absorption, kidney reabsorption of calcium and, most importantly, resorb bone.

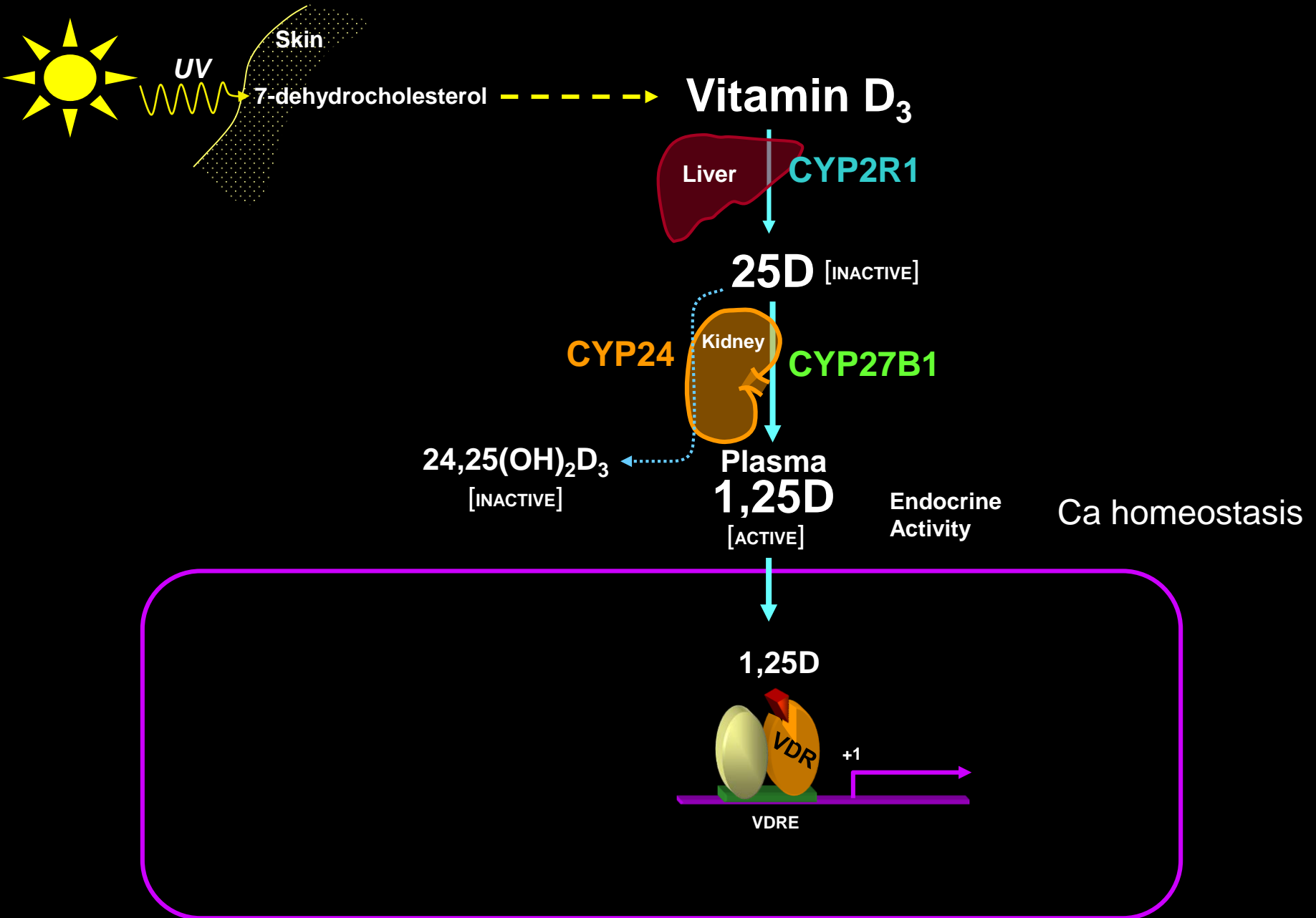
## Overview (2):

- To prevent osteoporosis, Vitamin D exerts **autocrine** activities in bone, in conjunction with adequate dietary calcium, to reduce bone resorption and stimulate bone formation
- These vitamin D activities for bone health provide information of the potential activities of vitamin D for broader health outcomes.

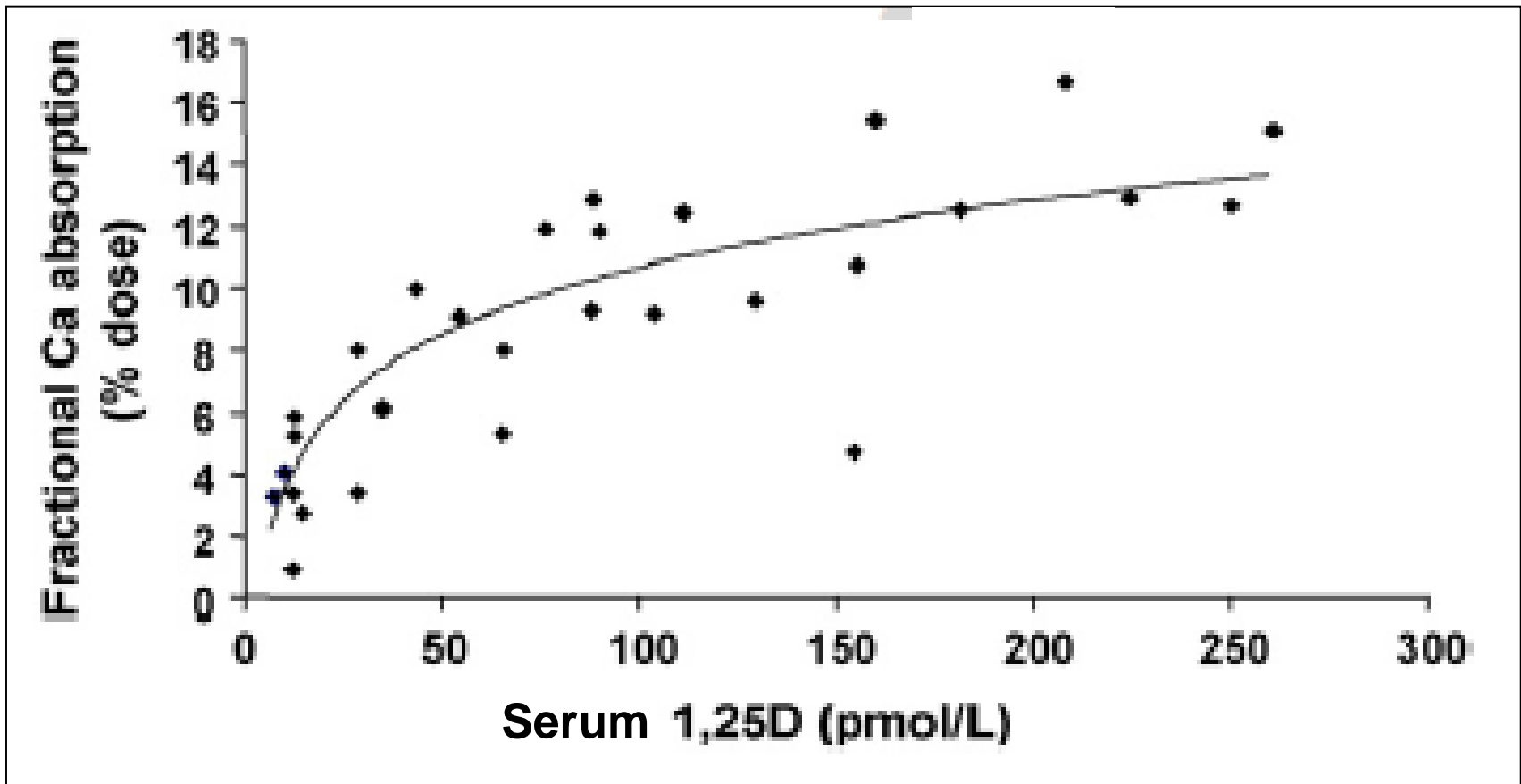
## Overview (3):

- Vitamin D exerts activities across a wide range of tissues modulating expression of least 900 genes.
- Many of these activities involve autocrine activities highlighting the importance for maintaining adequate levels of 25-hydroxyvitamin D, the prohormone.

# Vitamin D Synthesis and Activity



# The Endocrine Action of Vitamin D Regulates Intestinal Calcium Absorption



# Critical serum 25D Level for Osteomalacia amongst Indian Females New Delhi (Lat. 29°N)

	<u>Female patients</u> (90)	<u>Siblings</u> Sister (51) Brother (74)		<u>Parents</u> Mother (49) Father (47)	
Age (years)	24 (9.5)	18 (7)	21(10)	43 (9)	50 (9)
<b>Serum 25D</b> <b>(nmol/L)</b>	<b>14.4 (5.7)</b>	<b>18.3 (9.9)</b>	<b>30.4 (14.3)</b>	<b>24.5 (17.6)</b>	<b>49.8 (9.2)</b>
<b>(ng/mL)</b>	<b>5.8 (2.3)</b>	<b>7.3 (4.0)</b>	<b>12.2 (5.7)</b>	<b>9.8 (7.0)</b>	<b>19.9 (3.7)</b>
Serum PTH (pmol/L)	26.1(16)	8.7 (8.6)	3.8 (3.4)	5.5 (3.8)	4.9 (3.7)
<b>Biochemical Osteomalacia</b>	<b>90/90</b>	<b>11/45</b>	<b>3/61</b>	<b>5/42</b>	<b>5/40</b>

Critical level for plasma 25D  $\geq$  8 ng/mL (20 nmol/L )

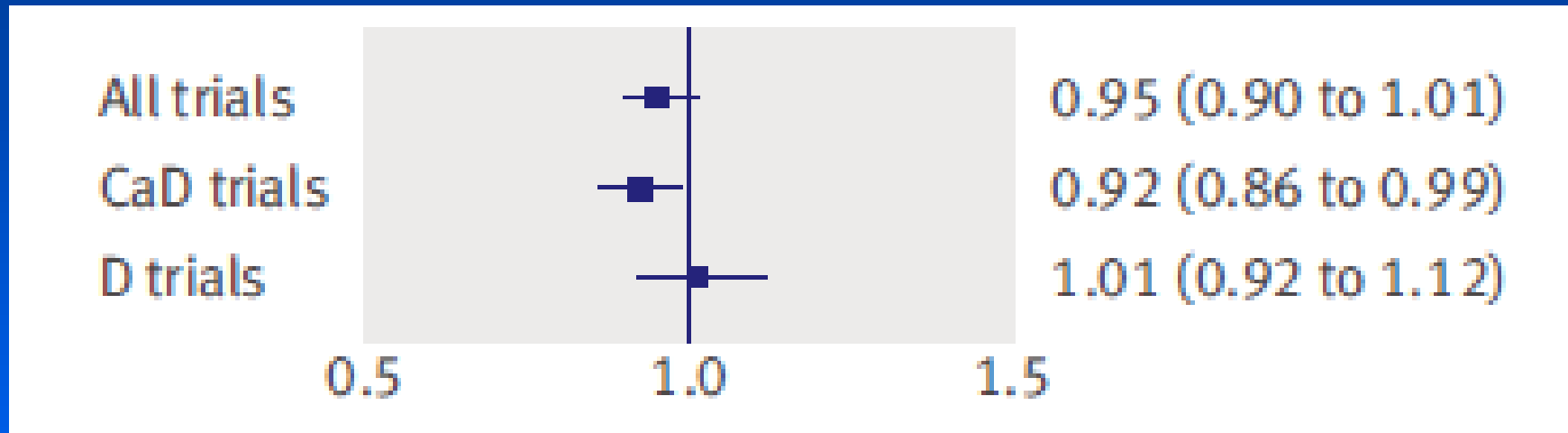
**Hip fracture patients arising from osteoporosis  
have provided new insights into requirements for  
vitamin D**





# Vitamin D plus Dietary Calcium but Not Vitamin D alone Protects against Fracture

Data from 68,500 patients



DIPART Group Brit Med J 2010; 340: b5463

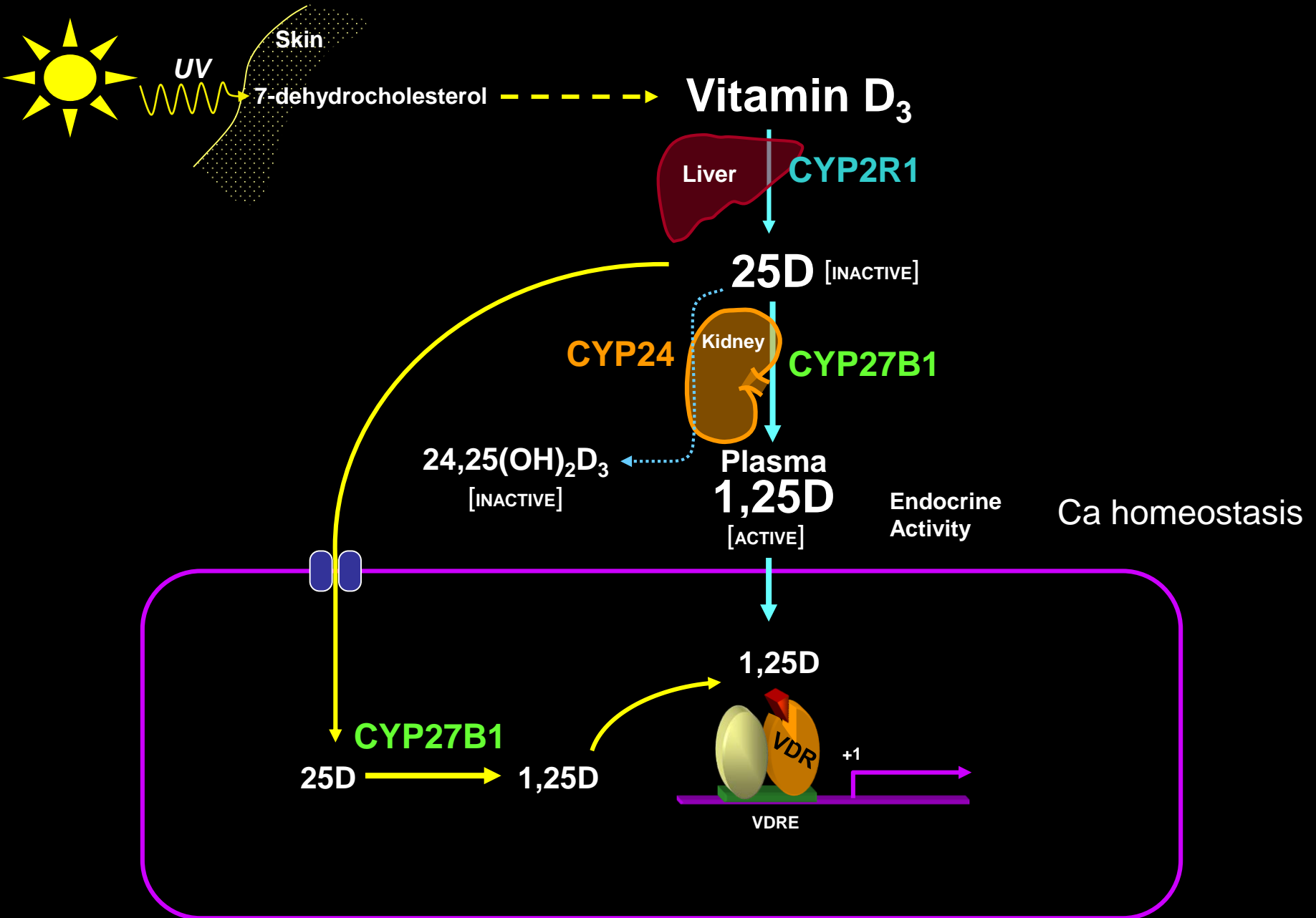
## Serum 25D less than 20 ng/mL (50 nmol/L) stimulates bone loss and increases risk of fracture

- The rate of bone loss in older, community dwelling men was significantly less (-0.35%/yr) when serum 25D levels were between 20 to 30 ng/mL (51 to 75 nmol/L) compared to -0.54%/yr when levels were 15 to 20 ng/mL (37.5 to 50 nmol/L) (Ensrud et al JCEM 2009;94:2773-2780)
- Postmenopausal women with serum 25D levels < 19 ng/mL (47.5 nmol/L) increased their risk of hip fracture by 71% compared with women with serum 25D levels  $\geq$  28 ng/mL (70 nmol/L) (Cauley et al Ann Intern Med 2008;149:242-250)

Clinical and pre-clinical studies indicate different activities for the serum 25D and 1,25D metabolites on bone mineral status.

**All evidence suggests that the effect of serum 25D arises from within-tissue synthesis of 1,25D**

# Vitamin D Synthesis and Activity



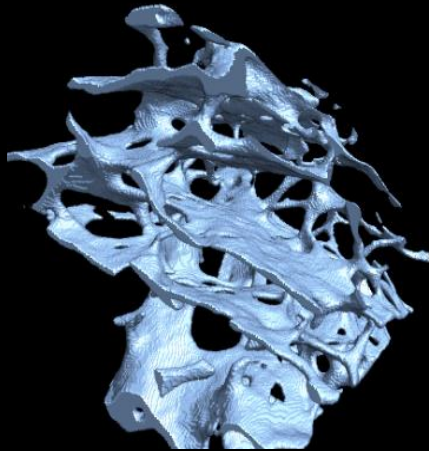
# What is the evidence in humans for bone autocrine activities of vitamin D?



Ms Deepti Sharma,  
PhD student

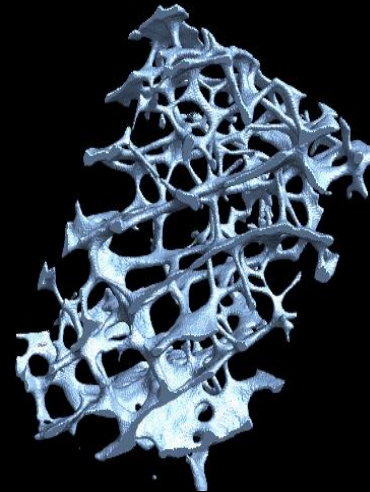
# Structural characteristics of Fracture Patients and Non-fracture controls

MicroCT Images



Non-fracture Control 86 year old female

BV/TV= 9.96  
BS/BV= 22.8mm<sup>-1</sup>  
Tb.Th = 0.16mm  
Tb.Pf = 5.2 mm<sup>-1</sup>

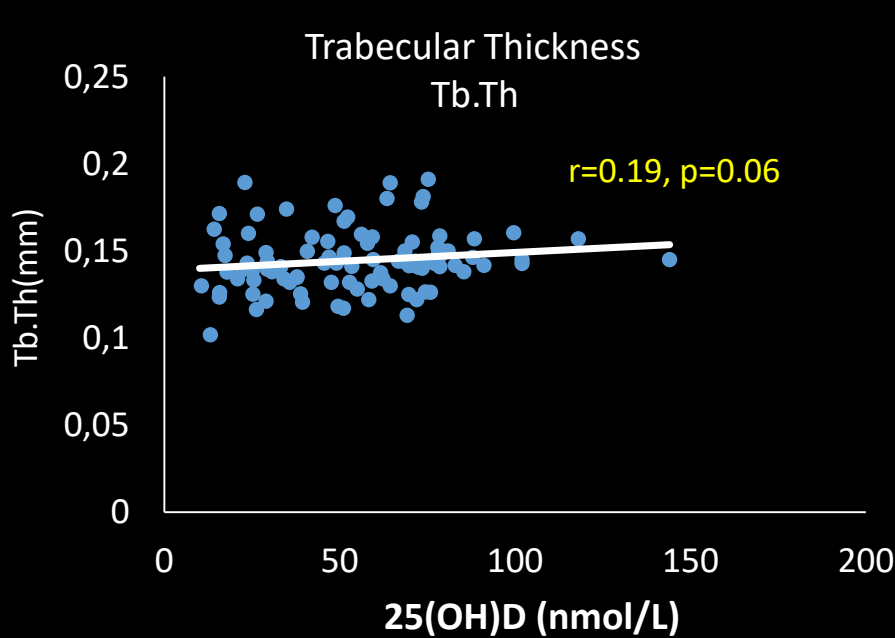


Hip fracture 87 year old female

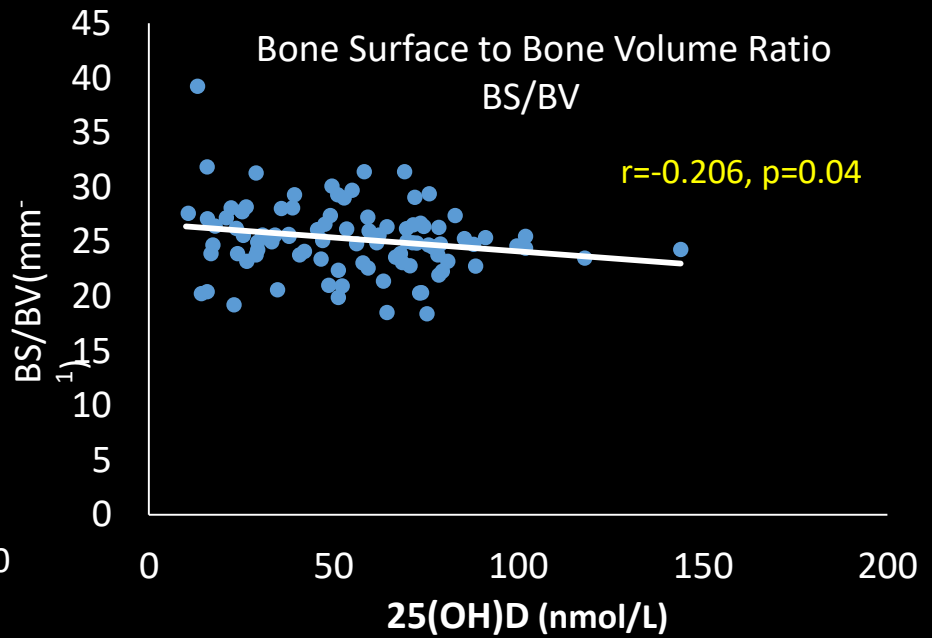
BV/TV = 10.5  
BS/BV=27.1mm<sup>-1</sup>  
Tb.Th= 0.12mm  
Tb.Pf= 6.4 mm<sup>-1</sup>

**Age is not associated with any of the bone mass or quality variables**

# Serum 25(OH)D and its impact on Bone Quality parameters



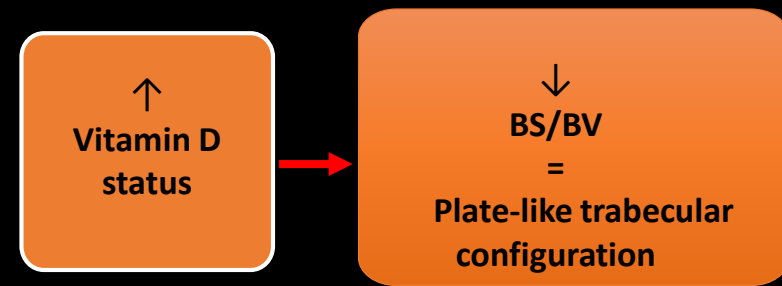
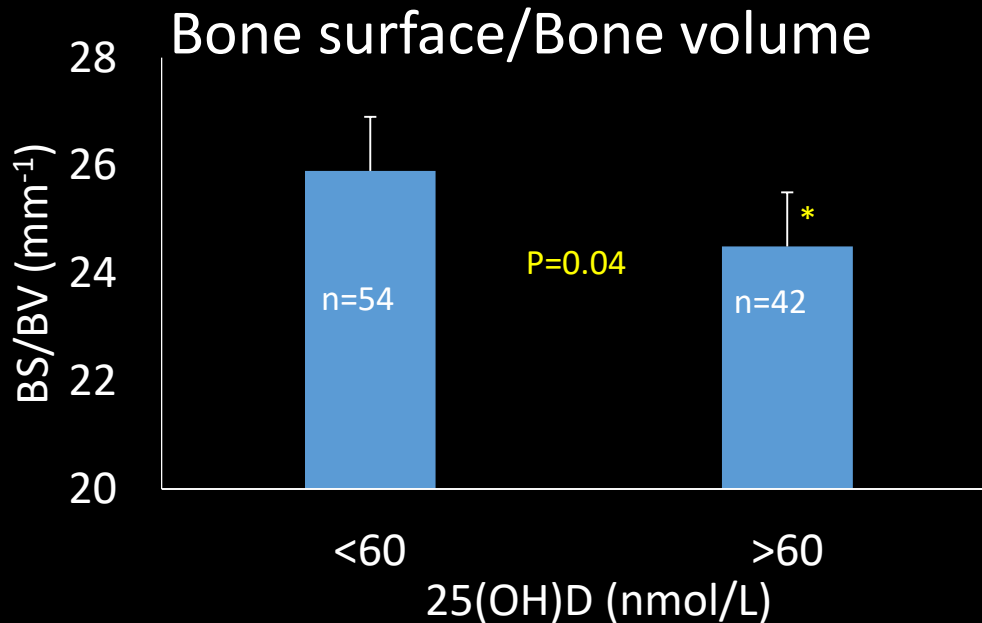
Serum 25(OH)D is positively associated with Trabecular Thickness (Tb.Th)



Serum 25(OH)D is negatively associated with Bone surface to bone volume ratio (BS/BV)

No association was observed between circulating 1,25(OH)<sub>2</sub> D, the biological active form of Vitamin D

# Patients with 25(OH)D > 60 nmol/L have lower BS/BV as compared to patients with 25(OH)D < 60 nmol/L



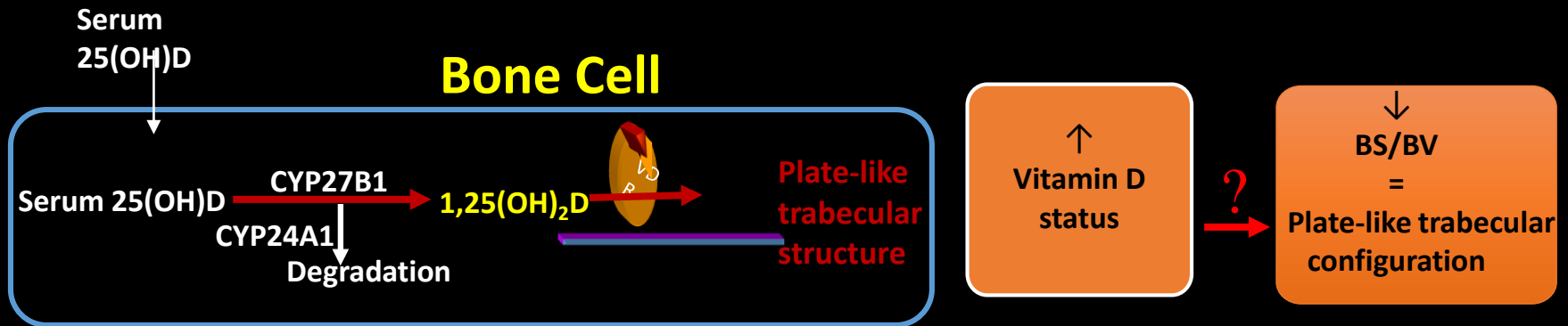
BS/BV (mm<sup>-1</sup>) was significantly lower in patients with s25OHD > 60 nmol/L, indicating higher bone strength



# Determinants of bone-derived $1,25(\text{OH})_2\text{D}$ : Serum $25(\text{OH})\text{D}$ , Bone CYP27B1 and Bone CYP24A1 are independent predictors of BS/BV

- ❖ Serum  $25(\text{OH})\text{D}$ , Bone CYP27B1, Bone CYP24A1 - 19% variance in BS/BV along with gender.
- ❖ Effect on BS/BV is independent of age, s $1,25(\text{OH})_2\text{D}$  and PTH

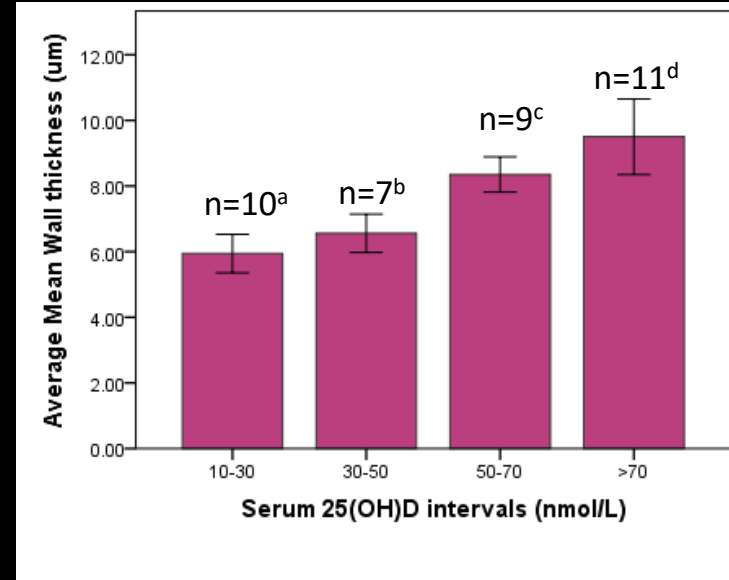
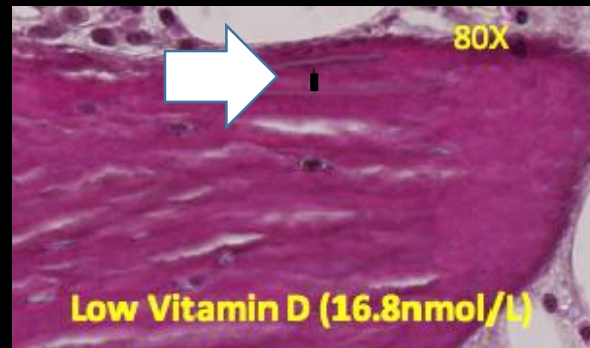
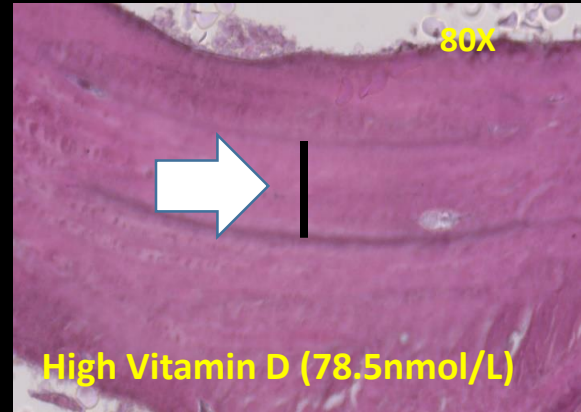
	Independent variables	Adj. R <sup>2</sup>	P-value
BS/BV =	-0.04 x $25(\text{OH})\text{D}$ -8.3 x Bone CYP27B1 +19.6 x Bone CYP24A1 +2.3 x Gender	0.19	0.001



# Is there a cellular mechanism for the plate-like structure?

## Mean Wall Thickness (MWT) – A measure of bone formation period

- ❖ Indicator of how long osteoblast work during each remodelling cycle
- ❖ Measured as the distance between the cement line and last completed bone packet
- ❖ Preliminary data suggest that serum 25(OH)D levels are strongly related to MWT



a vs b,  $p=0.8$ , NS

a vs c,  $p=0.001$

a vs d,  $p<0.0001$

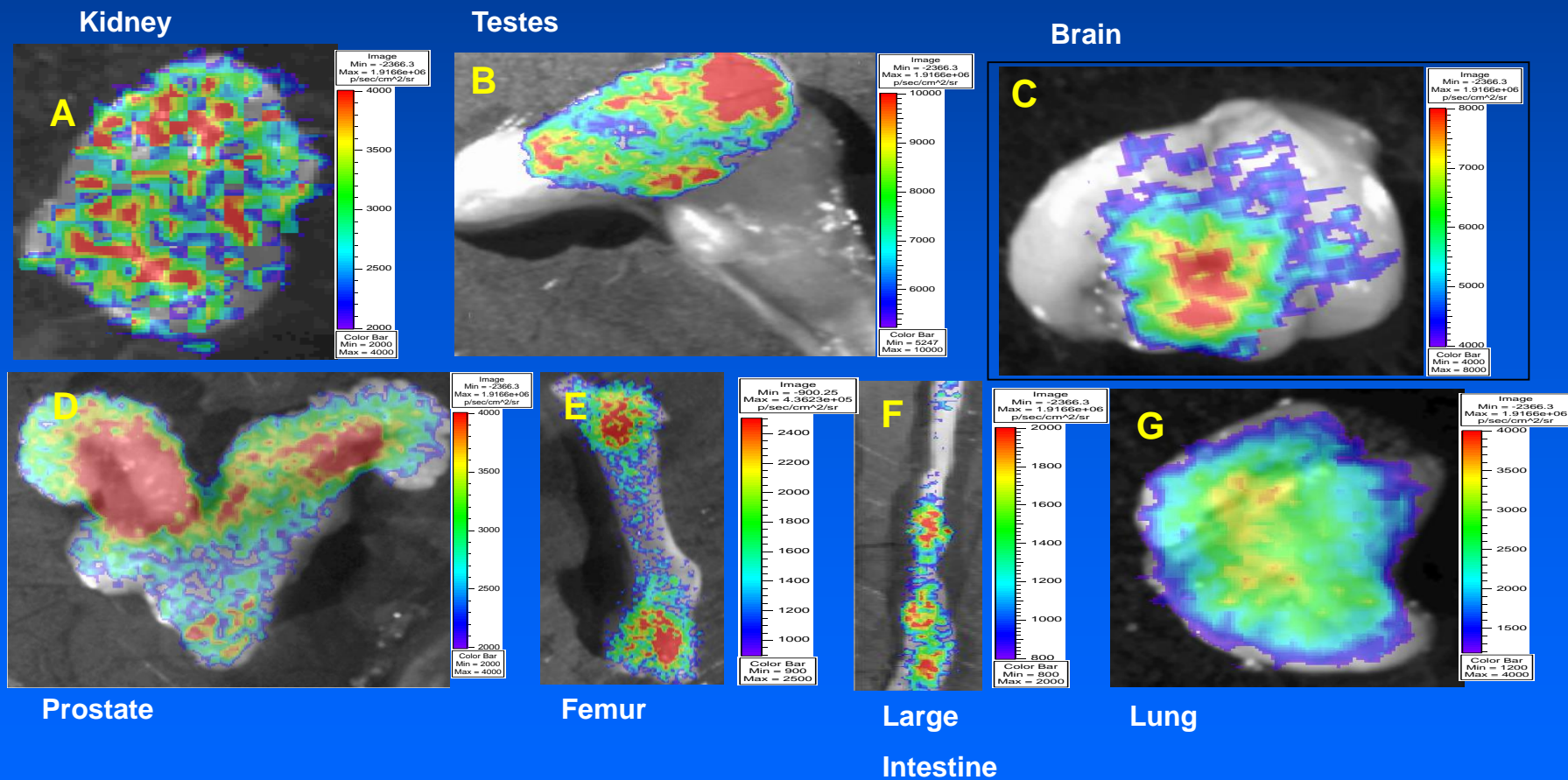
b vs c,  $p=0.04$

b vs d,  $p=0.00018$

c vs d,  $p=0.20$

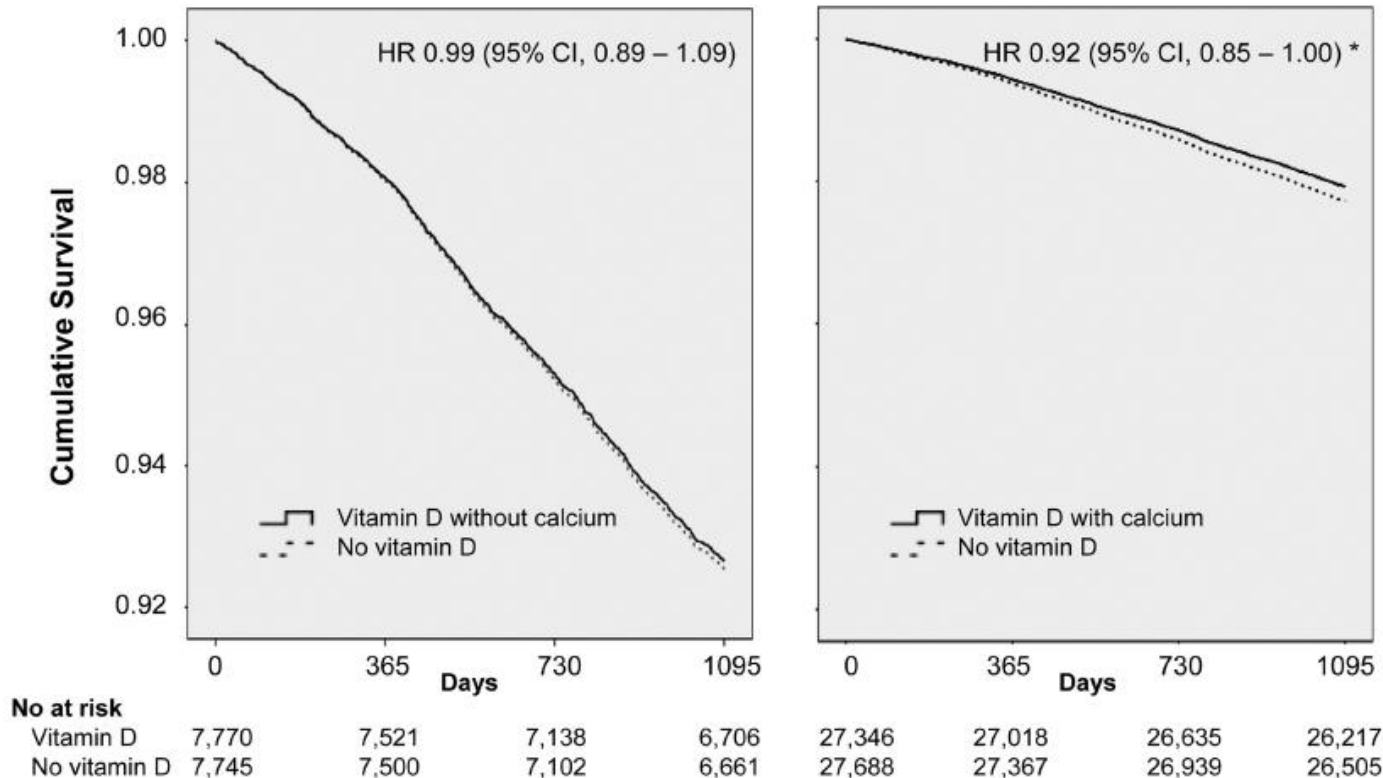
- These data provide evidence for assessing serum 25-hydroxyvitamin D as a biomarker for bone quality
- The critical level for serum 25-hydroxyvitamin D is 20 to 24 ng/mL (50 – 60 nmol/L)

# In vivo bioluminescence pCYP27B1-luciferase in the transgenic mouse tissues



# Are strong data available to support vitamin D status exerting non-skeletal health benefits?

All Cause Mortality – Vitamin D plus calcium but not Vitamin D alone



RCT's involving 70,528 patients;

151 patients needed to be treated to prevent one death within 3 years

Rejnmark L et al., J Clin Endocrinol Metab 2012; 97: 2670-2681



# Adequate Vitamin D Status Associates with Premature Mortality

Keith AK et al "25-Hydroxyvitamin D concentration and all-cause mortality: the Melbourne Collaborative Cohort Study" Public Health Nutrition 2016  
doi:10.1017/S1368980016000501

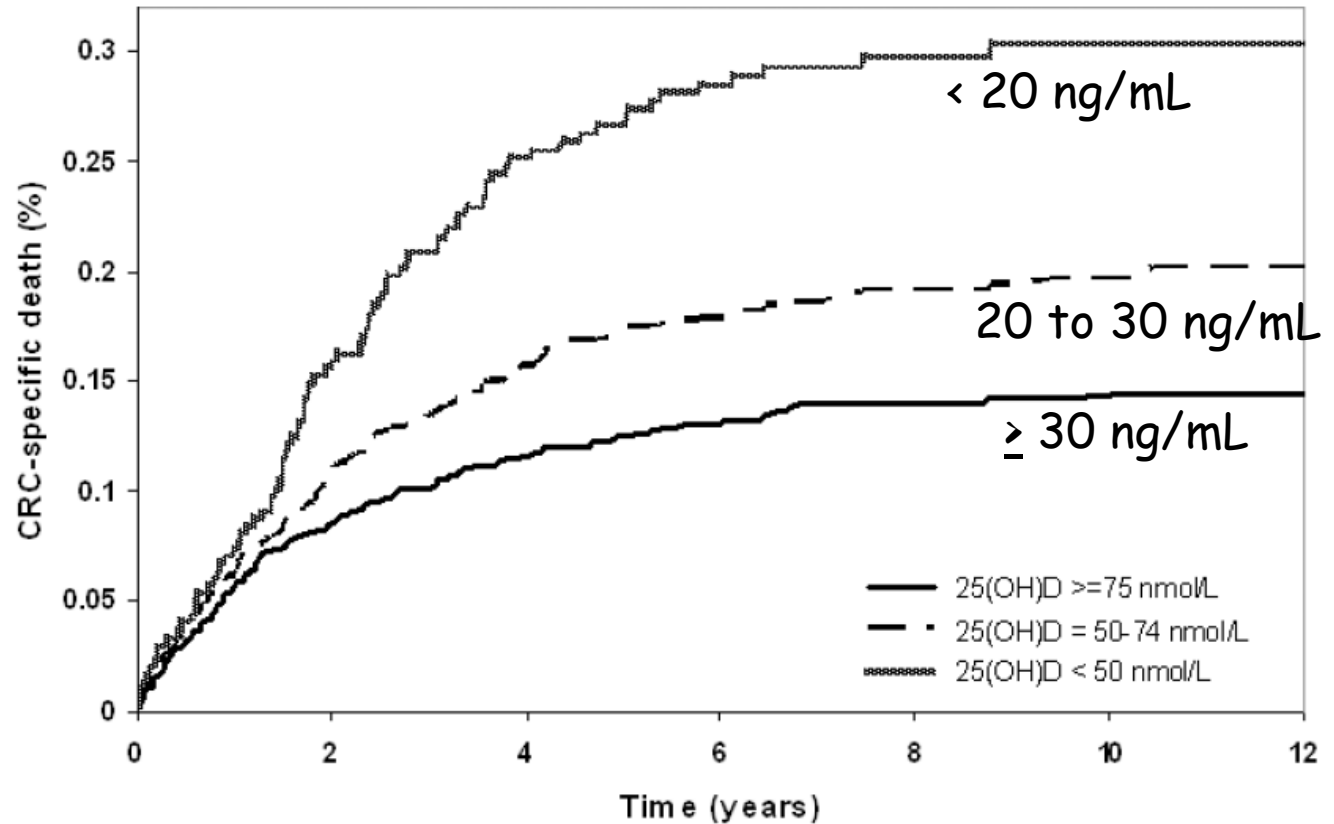
Total plasma 25(OH)D§ Quintile	Mean nmol/L	IQR ng/mL	n	Deaths	HR	95% CI
Q1	30.3	12 7.6	1067	545	7885	1.00 ref. 0.001
Q2	41.3	16.5 8.9	1008	485	7977	0.85 0.68, 1.06
Q3	51.6	21 11.8	992	458	8020	0.90 0.72, 1.11
→ Q4	61.0	24.4 14.9	958	417	8056	0.80 0.64, 1.00
→ Q5	77.0	31 21.1	939	402	8150	0.67 0.54, 0.84
Per 25 nmol/l increase			4964	2307	40 088	0.86 0.78, 0.96 0.007

‡Adjusted for age, socio-economic disadvantage, education, total energy intake, Mediterranean diet pattern, alcohol intake, smoking status, physical activity, waist measurement, diabetes mellitus at baseline, history of hypertension, history of angina, history of myocardial infarction, history of stroke, and stratified by sex and Southern European migrant status.

# Pre-diagnosis Vitamin D status Associates with Improved Survival in Cancer Patients

Cancer mortality and pre-diagnostic vitamin D status

Risk of death from colorectal cancer is reduced by 50% if serum 25D is  $\geq 30$  ng/mL compared with  $< 20$  ng/mL at diagnosis



1,202 Colorectal Cancer patients with 444 CRC-specific deaths and overall mortality 541

## Does vitamin D supplementation improve treatment of TB patients? Meta-analysis data

- 8 studies with 898 patients receiving vitamin D and 889 receiving placebo as adjunctive therapy
- Wide range of dosages and length of studies
- Vitamin D increased the proportion of sputum smear conversions (OR 1.21, (95%CI 1.05-1.39),  $P = 0.007$ ) and sputum culture conversions (OR 1.22, (95%CI 1.04-1.43),  $P = 0.02$ )
- Vitamin D decreased the mean no. of zones involved observed on chest radiograph (MD -0.33, - 0.57 - 0.08,  $P = 0.01$ )



# Vitamin D deficiency in Iran

- Prevalence of vitamin D deficiency (<20 ng/mL)  
(<50 nmol/L)
- Male 46% (95% CI: 29.63 to 61.65)
- Female 62% (95% CI: 48.85 to 74.96)
- Pregnant women 61% (95% CI: 23.73 to 97.16)

Meta-analysis of 48 studies (2000-2016) identified 18,531 individuals with vitamin D deficiency (<20 ng/mL)

Tabrizi R, Moosazadeh M, Akbari M, Dabbaghmanesh MH, Mohamadkhani M, Asemi Z, Heydari ST, Akbari M, Lankarani KB.

High Prevalence of Vitamin D Deficiency among Iranian Population: A Systematic Review and Meta-Analysis. *Iran J Med Sci.* 2018 Mar;43(2):125-13

# Iranian Maternal Outcomes according to Vitamin D Supplementation and Baseline Vitamin D Status

Rostami M, Tehrani FR, Simbar M, Bidhendi Yarandi R, Minooe S, Hollis BW, Hosseinpanah F.  
 J Clin Endocrinol Metab. 2018 Aug 1;103(8):2936-2948.

	Baseline Vit D Status	Suppl. N (%)	Non-suppl. N (%)	OR (95% CI) (p-value)	Number Needed to Screen
Composite adverse pregnancy outcomes <sup>#</sup>	Moderate deficiency	62 (16)	94 (23)	0.6 (0.4-0.9) (0.01)*	20 (13-55)
	Severe deficiency	71 (18)	129 (39)	0.3 (0.2-0.5) (<0.001)*	8 (5-13)

# Includes pre-eclampsia, gestational diabetes and pre-term delivery

Moderate deficiency – 25-hydroxyvitamin D 10-20 ng/mL  
 25-50 nmol/L  
 Severe deficiency – 25-hydroxyvitamin D < 10 ng/mL  
 <25 nmol/L

# Conclusions:

Vitamin D and dietary calcium are essential nutrients

Adequate dietary calcium is 1300 mg/day for postmenopausal women and men >70 yrs; 1000 mg/d for adults

Current clinical trial data indicate that serum 25D levels above 20 ng/mL (50 nmol/L) reduce the risk of fractures, falls, premature mortality, TB, adverse maternal outcomes, ...

There is no evidence of benefit for serum 25D levels >40 ng/mL (>100 nmol/L)





Thankyou