Die Bedeutung von Vitamin D – ein Update

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Chapters

1. *What are "Normal Levels" of 25-(OH)-Vitamin D_3?*

2. *Serum Levels of 25-(OH)-Vitamin D for optimal Bone Health*

3. *Cardiorespiratory Fitness and 25-(OH)-Vitamin D Levels*

4. *Lung Function, Seasonal Infections and Serum 25-(OH)-Vitamin D*

5. *Staphylococcus aureus and Vitamin D*

6. *Achieving Optimal Vitamin D Status*

7. *Genetic Factors for Serum 25-(OH)-Vitamin D Levels*

8. *Apolipoprotein E, Vitamin D: Better Bones, earlier Death?*

1. What are "Normal Levels" of 25-(OH)-Vitamin D_3?

- Modern Humans left Africa 100.000 to 50.000 years ago … as "Hunters and Gatherers"

- **Current Human Genes** are virtually ide … hose of our ancestors 50.000 years ago . . .

- Genetic evolution continued slow … ation of hair, eyes, skin, lactase retention beyond infancy, … tive defenses against malaria . . .)

- The **Paleolithic Diet** contained very … cium, no milk beyond infancy, but high amounts of … om game

Nutr. Clin. Pract. **25**, 594-602 (2010); *J. Clin. Densitom.* **14**, 95-99 (2011)

1. What are "Normal Levels" of 25-(OH)-Vitamin D_3?

Franchthi Cave, Peloponnes, Greece

J. Hum. Evol. **60**, 618-636 (2011)

1. What are "Normal Levels" of 25-(OH)-Vitamin D_3?

Modern Humans left Africa 100.000 to 50.000 years ago … as "Hunters and Gatherers"

Current Human Genes are virtually identical to those of our ancestors 50.000 years ago . . .

Genetic evolution continued slowly (pigmentation of hair, eyes, skin, lactase retention beyond infancy, adaptive defenses against malaria . . .)

The **Paleolithic Diet** contained very little calcium, no milk beyond infancy, but high amounts of **Meat from Game**

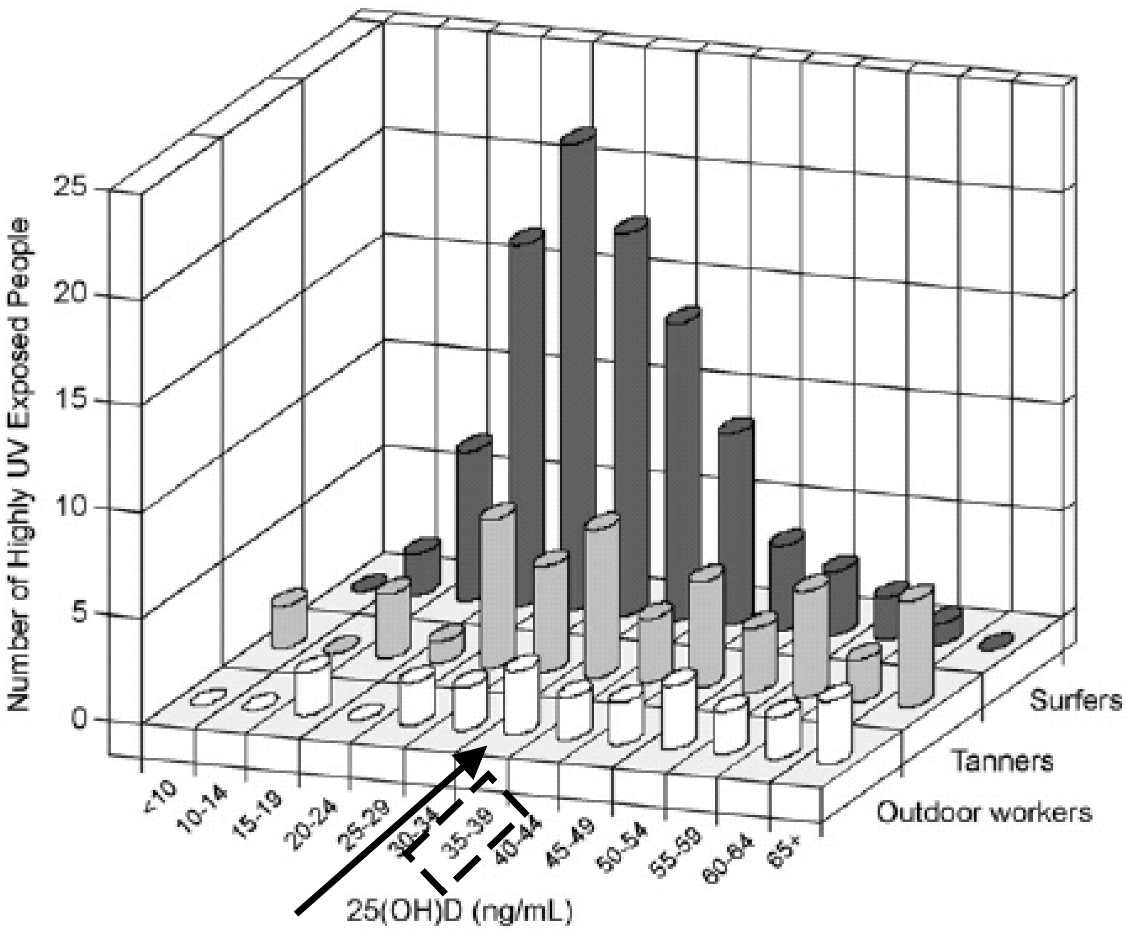
Our ancestors were highly exposed to the **Sun** . . .

Nutr. Clin. Pract. **25**, 594-602 (2010); *J. Clin. Densitom.* **14**, 95-99 (2011)

1. What are "Normal Levels" of 25-(OH)-Vitamin D?

1.1 Caucasians

Highly sun-exposed cohorts have
25-(OH)-Vitamin D_3 levels of 50 – 150 nmol/l

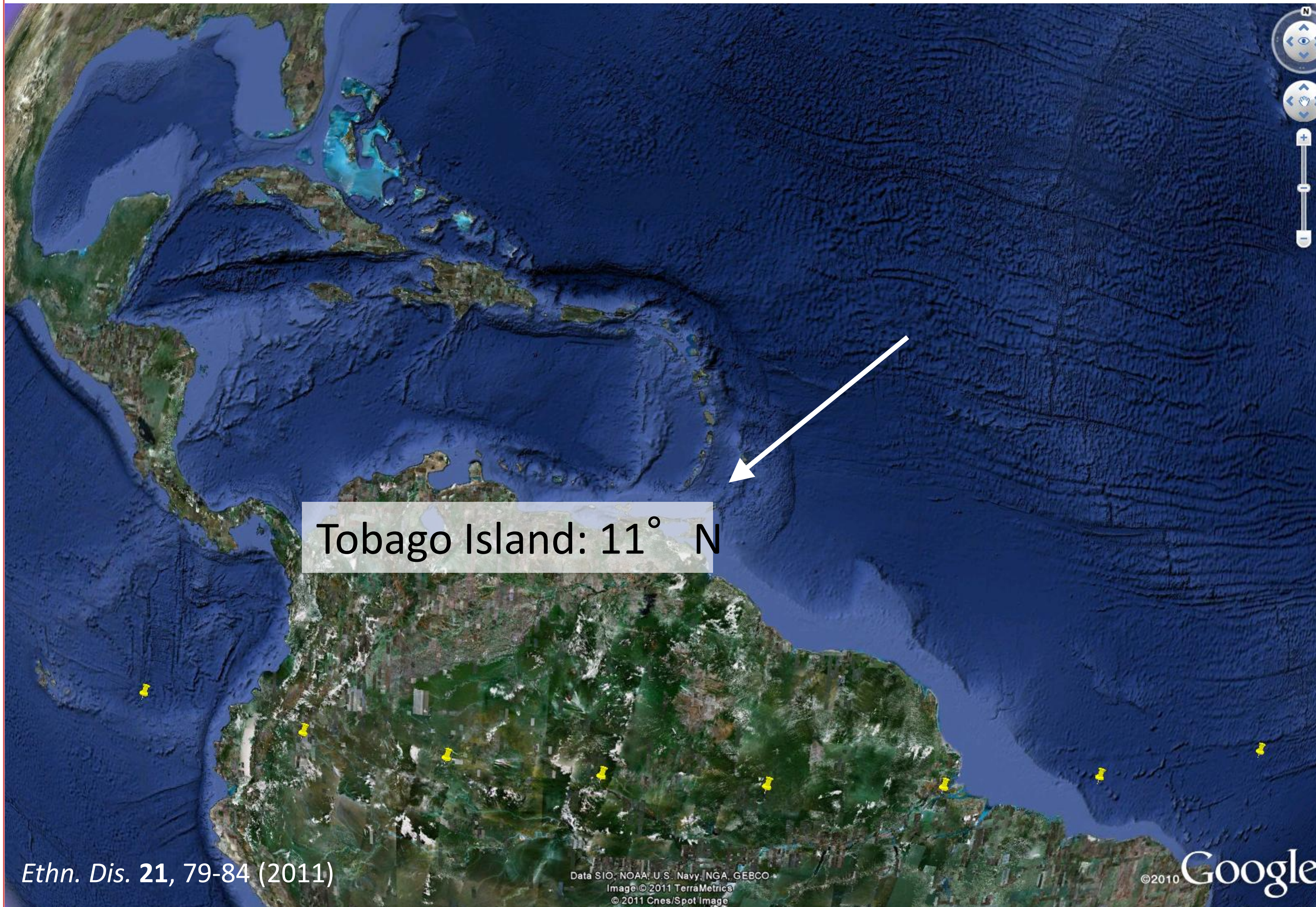


Mean Level ≈ 90 – 100 nmol/l

J. Clin. Densitom. **14**, 95-99 (2011)

1. What are "Normal Levels" of 25-(OH)-Vitamin D_3?

1.2 Afro-Caribbeans close to the Equator



Ethn. Dis. **21**, 79-84 (2011)

1. What are "Normal Levels" of 25-(OH)-Vitamin D_3?

1.2 Afro-Caribbeans close to the Equator

- 424 healthy Afro-Caribbean men (mean age 72.1 years) with all 4 Grandparents of African Ethnicity

- Mean **25-(OH) -Vitamin-D** Level: **90 nmol/l**

Despite of very high Melanin content in the Skin and old Age, the level is as high as 100.000 to 50.000 years ago

Ethn. Dis. **21**, 79-84 (2011)

1. What are "Normal Levels" of 25-(OH)-Vitamin D_3?

Mean Levels of 25-(OH)-D_3 of around 100 nmol/l – acquired by the Sun – are normal with respect to our Genetic Make-up – finished and optimized 50.000 years ago

Such Levels almost never exceeded 160 nmol/l and were never lower than 50 nmol/l

Distinction between deficiency and insufficiency in Vitamin D Status does not appear useful nor necessary!

Vitamin D deficiency is defined
by levels below 25 nmol/l!

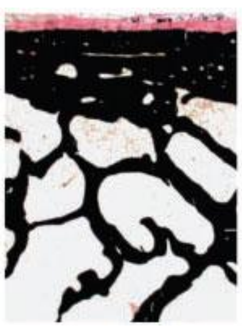
Curr Opin Clin Nutr Metab Care **14**, 440-444 (2011), Abstract: *Endocrine Rev* **32,** P2-130 (2011)

2. Serum levels of 25-(OH)-Vitamin D for optimal Bone Health

2.1. Histomorphometric Analysis

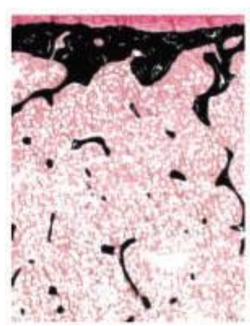
- Transiliac Bone Specimens from 675 Individuals
- Autopsies in the Department of Legal Medicine (Cancer, Renal Diseases, Hospitalization, Primary Hyperparathyreoidism excluded)
- Serum Test for **25-(OH)-Vitamin D**
- 2000 Sections stained for mineralized bone matrix and non-mineralized Osteoid
- Histomorphometric Analysis and Correlation with Serum **25-(OH)-Vitamin D**

High Bone Mass

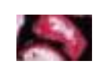


Bone

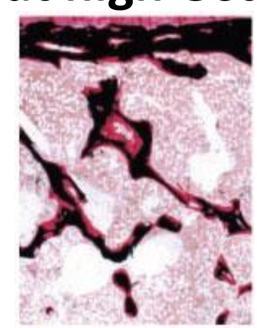
Low Bone Mass



Osteoid



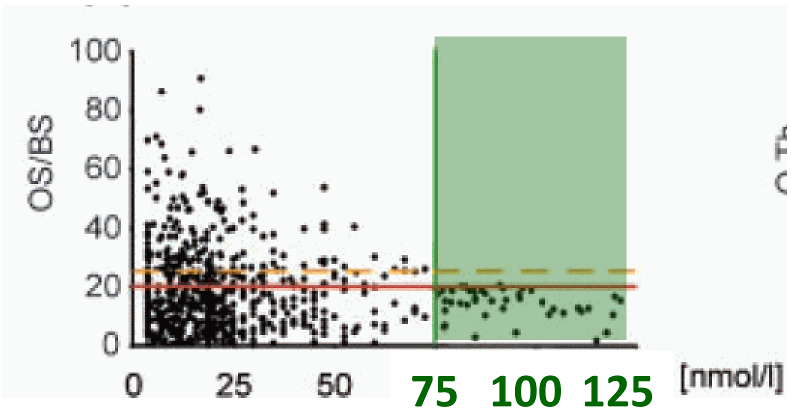
Normal Bone but high Osteoid



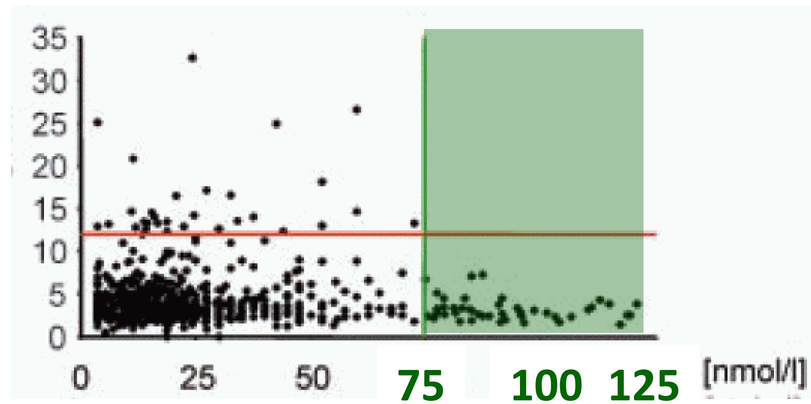
J. Bone Miner. Res. **25**, 305-312 (2010)

2.1. Histomorphometric Analysis

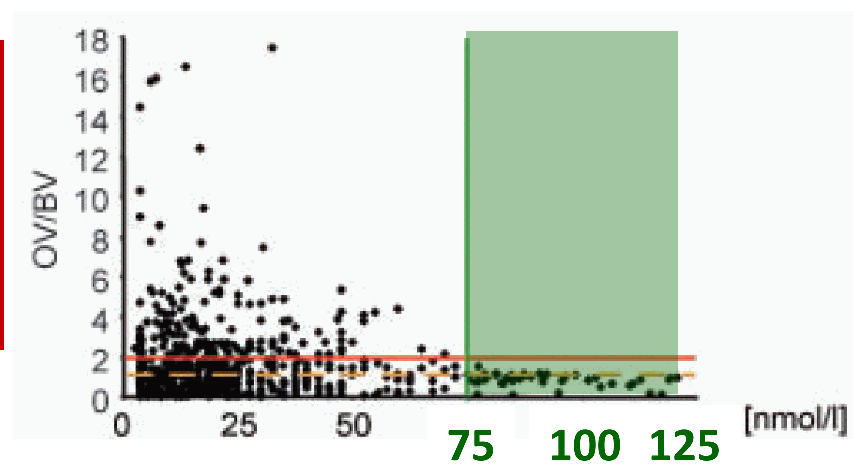
Osteoid Surface [%]



Osteoid Thickness [µm]



Osteoid Volume [%]



Levels above 75 nmol/l are optimal for Bone Health with any Age or Sex

J. Bone Miner. Res. **25**, 305-312 (2010)

2. Serum levels of 25-(OH)-Vitamin D for optimal Bone Health

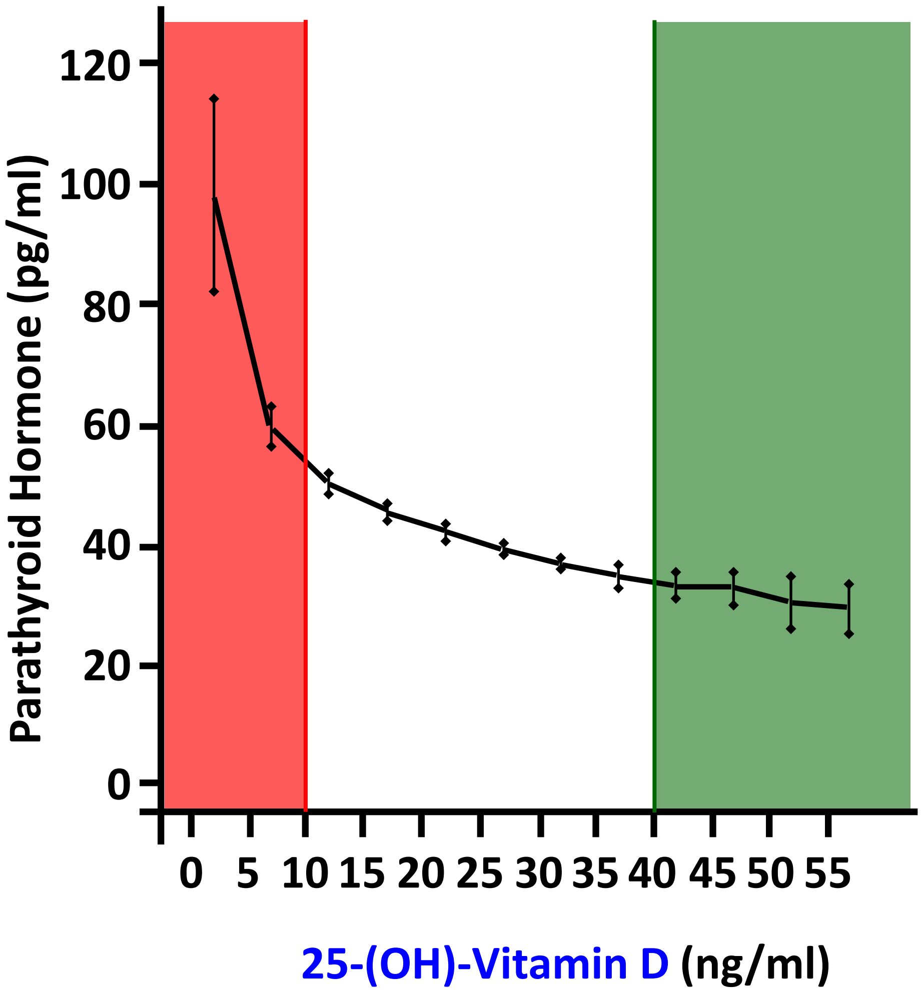
2.2. Correlation between PTH and Serum 25-(OH)-Vitamin D Levels

- Serum **25-(OH)-Vitamin D** and PTH levels were measured in 14.681 participants aged ≥6 years (NHANES 2003-2006)
- **25-(OH)-Vitamin D** thresholds are calculated for maximum PTH suppression
- Results were stratified by age, sex, race/ethnicity

J. Endocrinol. Invest. published ahead of print Doi: 10.3275/7742 (May 2011)

2. Serum levels of 25-(OH)-Vitamin D for optimal Bone Health

2.2. Correlation between PTH and Serum 25-(OH)-Vitamin D Levels



Optimal PTH Suppression is observed from 40 ng/ml (≈100 nmol/l) and higher

This is valid for all Ages, Males and Females and independent from Race/Ethnicity

J. Endocrinol. Invest. published ahead of print Doi: 10.3275/7742 (May 2011)

2.3. Risk of stress fractures

Stress fractures are frequently seen among military recruits

United States Marine Corps	1%
Finnish Army Units	64%
Israeli Defense Forces	12%

Observational Study

2591 Israeli Soldiers (2001)[1]

	Stress Fracture	Control
PTH [pg/ml]	28.7	25.7
25-(OH)-Vitamin D [nmol/l]	63.1	87

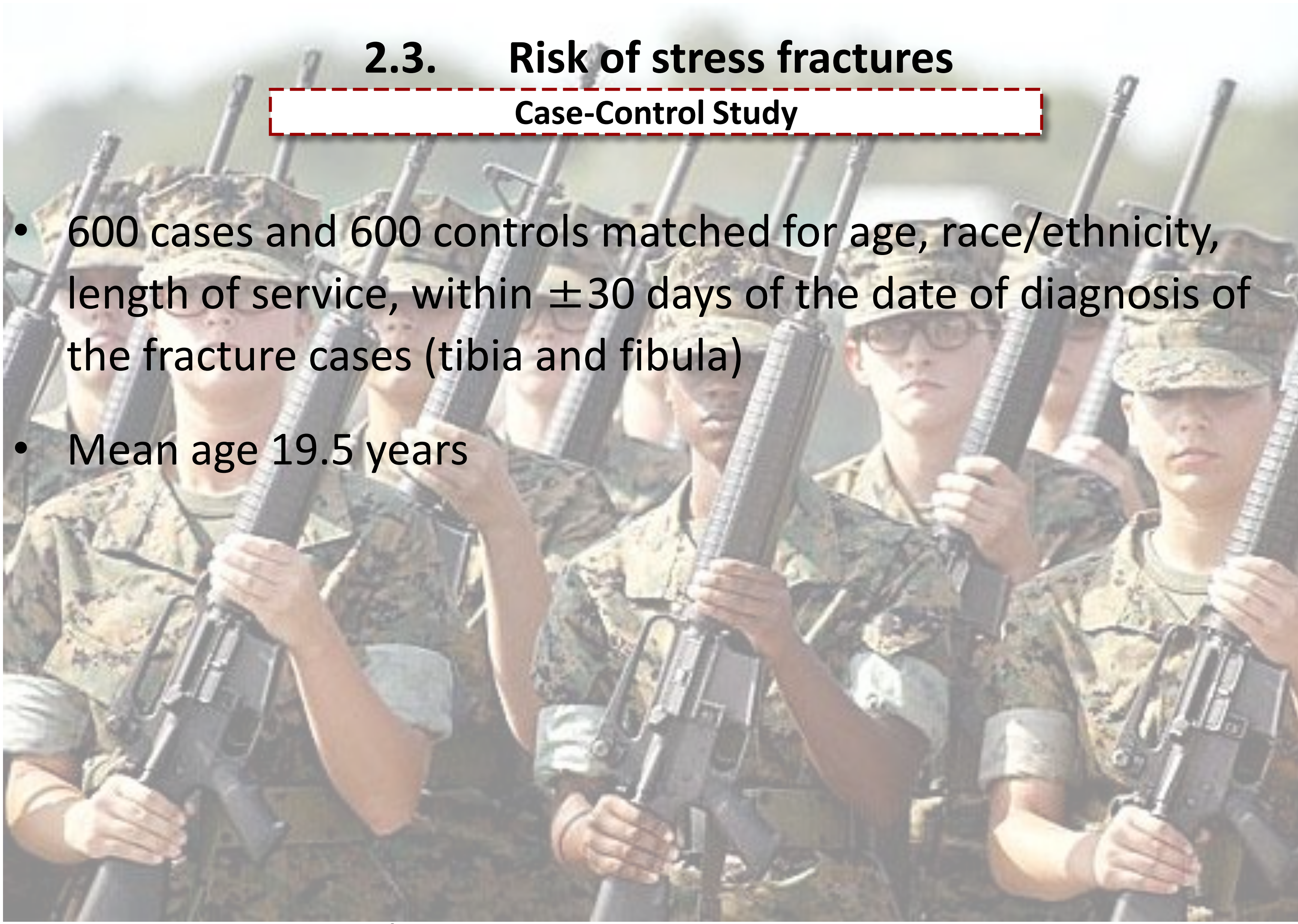
Prospective Observational Study

800 healthy Finnish Soldiers (2006)[2]

	Stress Fracture	Control
25-(OH)-Vitamin D [nmol/l]	64.3	76.2
Muscle Strength	7	9

[1]*Clin.Orthop.Relat.Res.* 373, 227-232 (1999); [2]*J. Bone Miner. Res.* 21, 1483-1489 (2006)

2. Serum levels of 25-(OH)-Vitamin D for optimal Bone Health



2.3. Risk of stress fractures

Case-Control Study

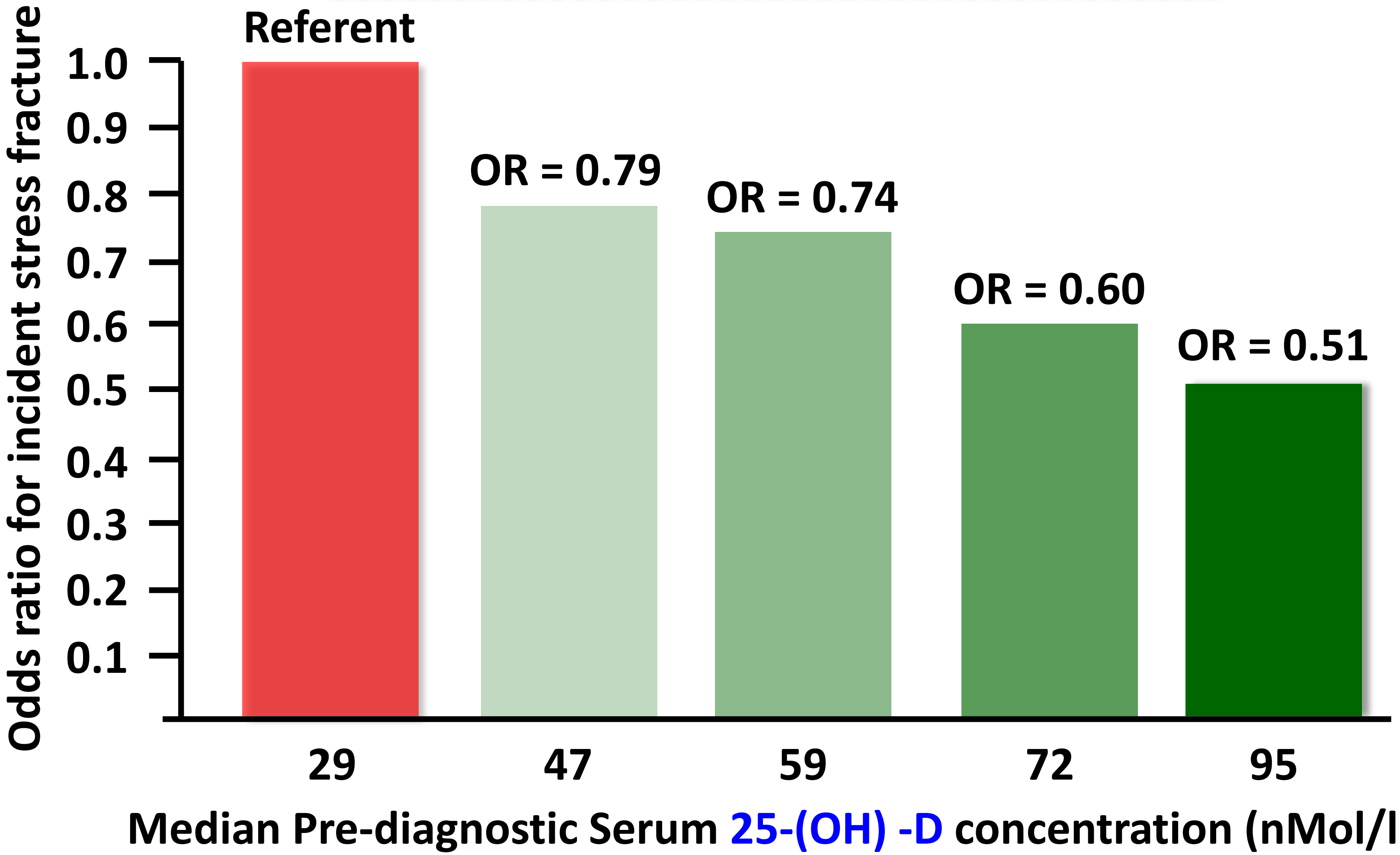
- 600 cases and 600 controls matched for age, race/ethnicity, length of service, within ±30 days of the date of diagnosis of the fracture cases (tibia and fibula)
- Mean age 19.5 years

J. Bone Miner. Res. **doi:10.1002/jbmr.451** (2011) PMID: 21698667

2. Serum levels of 25-(OH)-Vitamin D for optimal Bone Health

2.3. Risk of stress fractures

Case-Control Study



J. Bone Miner. Res. **doi:10.1002/jbmr.451** (2011) PMID: 21698667

Cum Gratia & Privilegio.

2.3. Risk of stress fractures

Randomized, double-blind, Placebo-controlled Trial

3700 female Navy Recruits (8 Weeks) (2008)[3] MARINES THE FEW. THE PROUD.

	Vitamin D + Calcium	Placebo	Decrease
Stress Fractures (total)	226	270	– 21%
Stress Fractures (severe)	11	27	– 50%

Important Finding: there was a highly significant correlation between physical fitness and risk of fracture in the Placebo group – but not in the supplemented Vitamin D group. Vitamin D benefits were the greater the lower the physical fitness was !

[3] *J. Bone Miner. Res.* 23, 741-749 (2008)

3. Cardiorespiratory Fitness and 25-(OH)-Vitamin D Levels

STOMP Study

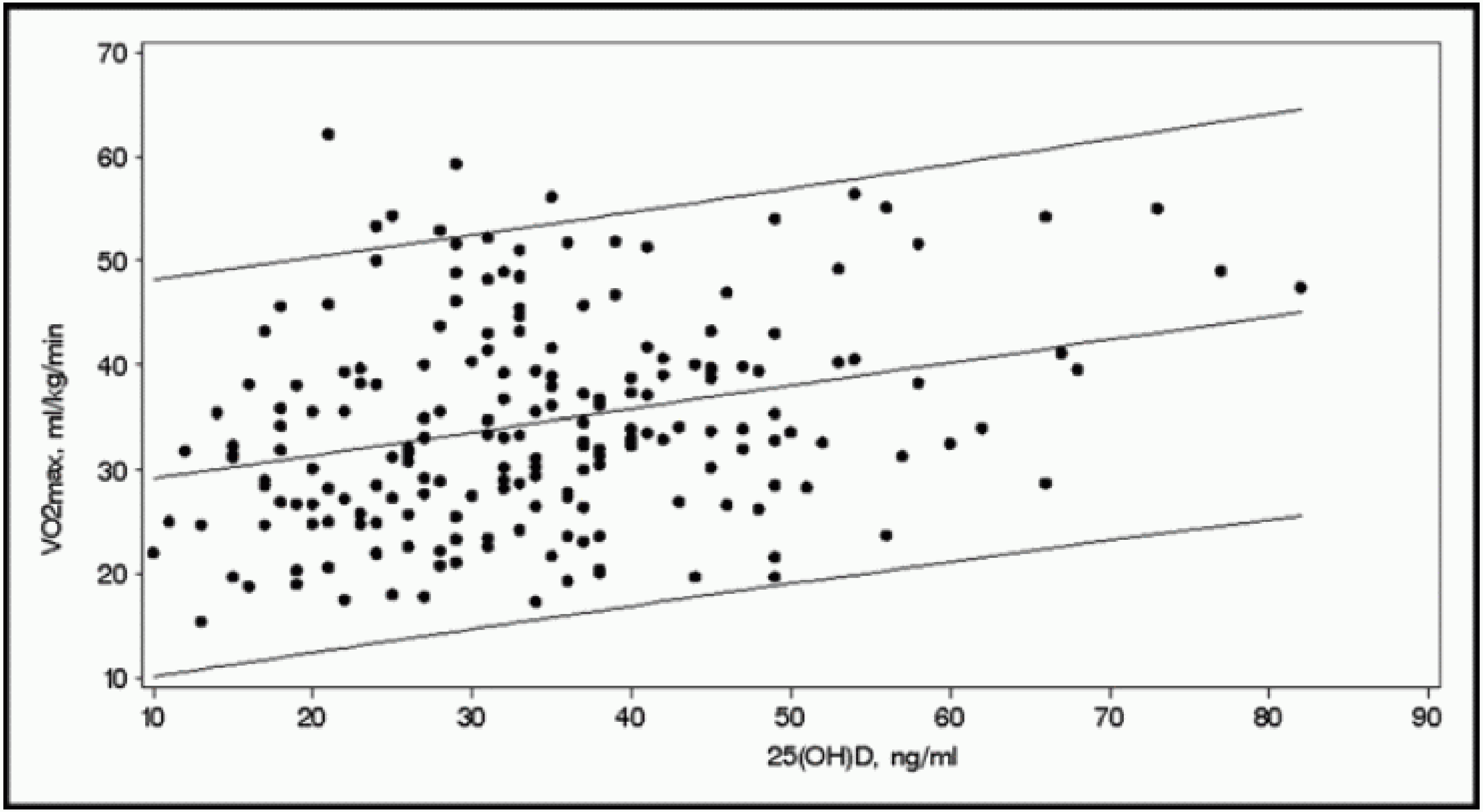
Cross-Sectional Study

- 200 healthy individuals (40 ±14 years), BMI = 25 ±5.1 (m/f ≈1:1)
- Aerobic Cardiorespiratory Fitness tested via Balke Treadmill Test to determine V_{O_2max} [ml*kg^{-1}*min^{-1}]
- Daily Physical Activity Levels at Baseline were recorded: **M**oderate to **V**igorous **P**hysical **A**ctivity, **MVPA**
- Mean Maximal Oxygen Uptake was 34 ±10.3 ml*kg-1*min-1
- Mean MVPA was 37 ±19 hours per week
- Mean Serum **25-(OH)-Vitamin D** was 34 ng/ml

Am. J. Cardiol. **107**, 1246-1249 (2011)

3. *Cardiorespiratory Fitness and 25-(OH)-Vitamin D Levels*

Cross-Sectional Study



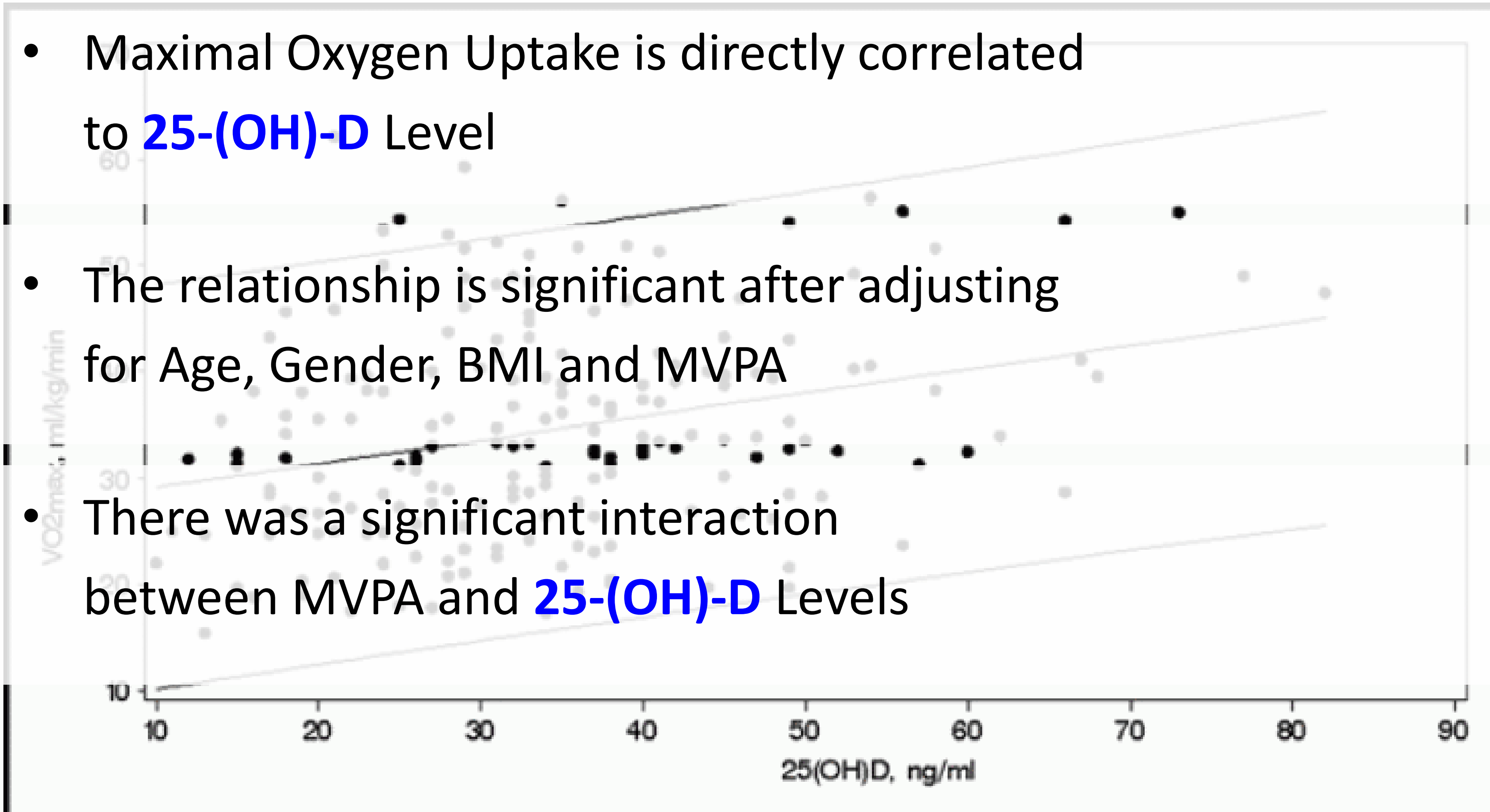
Am. J. Cardiol. **107**, 1246-1249 (2011)

3. *Cardiorespiratory Fitness and 25-(OH)-Vitamin D Levels*

Cross-Sectional Study

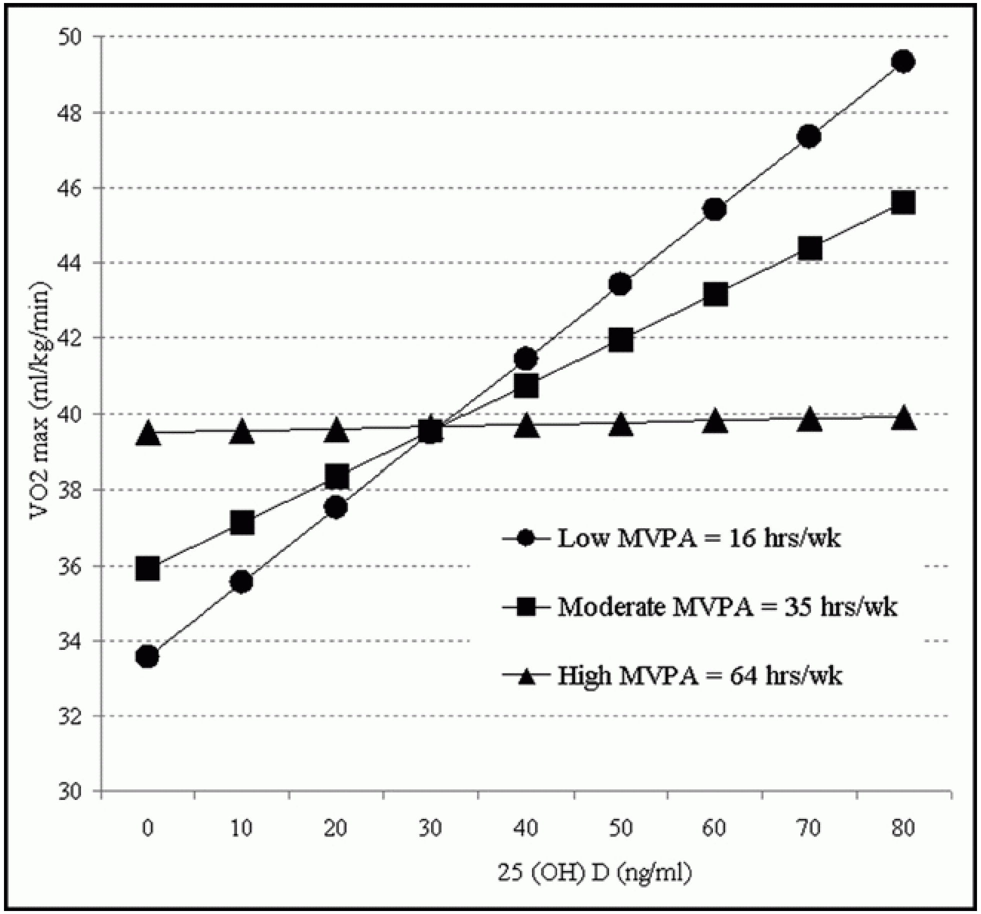
STOMP Study: *Results*

- Maximal Oxygen Uptake is directly correlated to **25-(OH)-D** Level
- The relationship is significant after adjusting for Age, Gender, BMI and MVPA
- There was a significant interaction between MVPA and **25-(OH)-D** Levels



Am. J. Cardiol. **107**, 1246-1249 (2011)

3. Cardiorespiratory Fitness and 25-(OH)-Vitamin D Levels



The effect of 25-(OH)-D Level on Cardiorespiratory Fitness depends on Training

The less "Training", the more pronounced is the Effect of higher Levels !

Am. J. Cardiol. **107**, 1246-1249 (2011)

4. Lung Function, Seasonal Infections and Serum 25-(OH)-Vitamin D

Cross-Sectional Study

- Nationwide 1958 British Cohort (n=6789)
- **F**orced **E**xpiratory **V**olume in 1 Second (**FEV$_1$**) and **F**orced **V**ital **C**apacity (**FVC**) were measured
- Respiratory Infections are self-reported

Results

Br. J. Nutr. **ePub**, doi:10.1017/S0007114511001991 (2011)

4. Lung Function, Seasonal Infections and Serum 25-(OH)-Vitamin D

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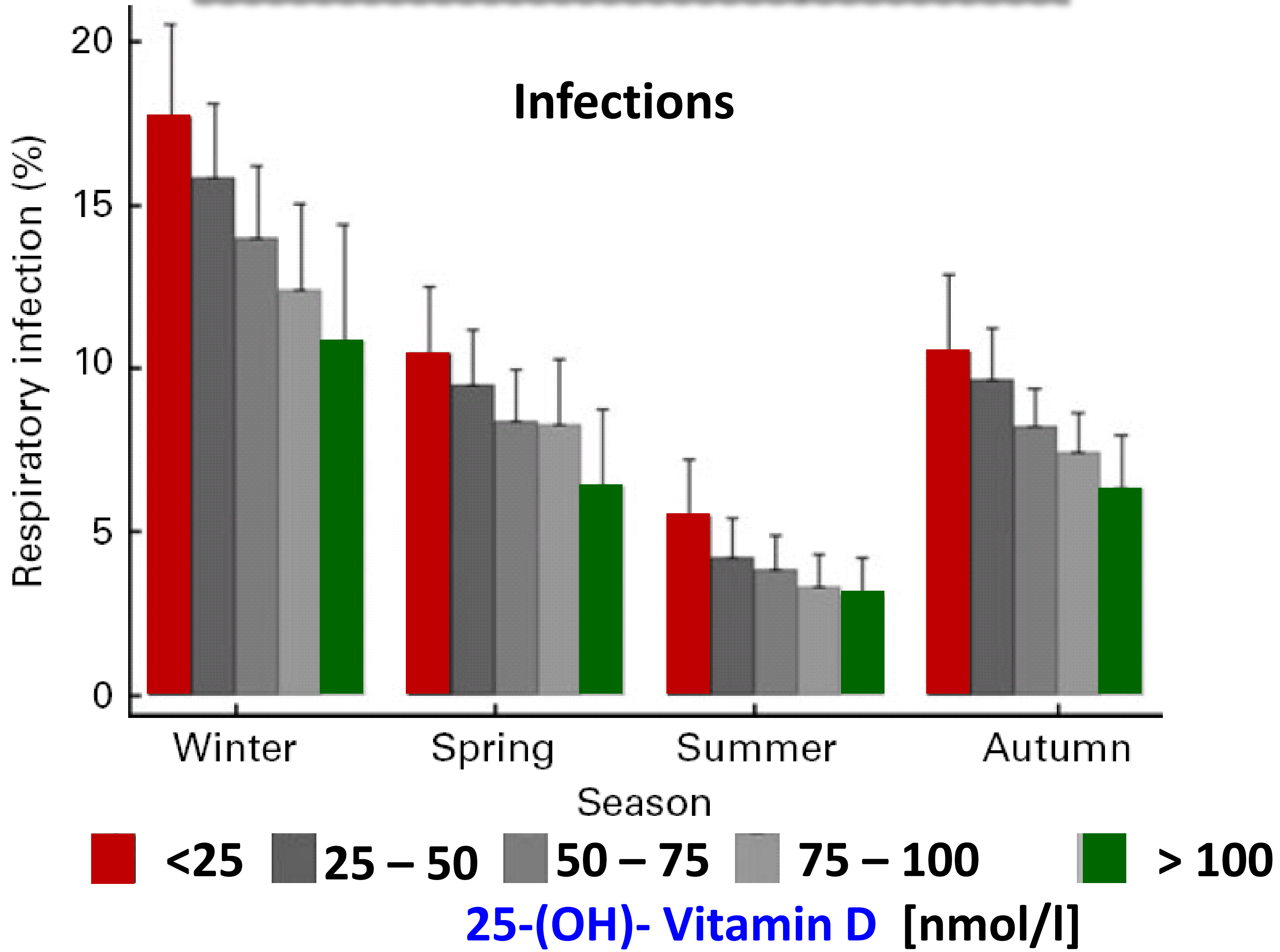
ÖQUASTA Annual Meeting Igls 2011

Cross-Sectional Study



Br. J. Nutr. **ePub**, doi:10.1017/S0007114511001991 (2011)

4. Lung Function, Seasonal Infections and Serum 25-(OH)-Vitamin D

Lung function depends on 25-(OH)-Vitamin D Level

FEV_1: Each 10 nmol/l increase of 25-(OH)- Vitamin D is associated with 8 ml increase

FVC: Each 10 nmol/l increase of 25-(OH)-Vitamin D is associated with 13 ml higher volume

Important Finding

- Individuals who **did not engage in** vigorous exercise had a much larger increase in **FEV_1**: 24 ml per 10 nmol/l 25-(OH)-Vitamin D increase than active participants (10 ml)
- Less active people benefit from higher levels!

Br. J. Nutr. **ePub**, doi:10.1017/S0007114511001991 (2011)

5. Staphylococcus aureus and Vitamin D

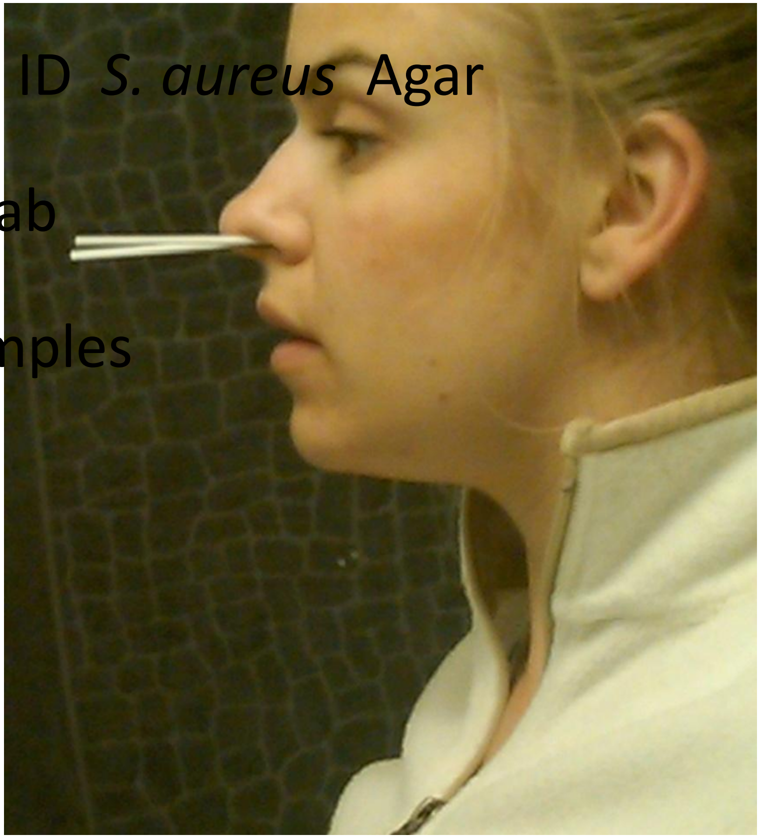
- About 20% of healthy adults are persistent nasal carriers of **Methicillin**-sensitive *S. aureus*
- About 1% of healthy adults are persistent nasal carriers of **Methicillin**-**resistant** *S. aureus*: ***MRSA***
- Smoking is the only identified protective Factor
- Nasal carriage is a major risk factor for infections with *S. aureus*
- Levels of Serum **25-(OH)- Vitamin D** < 20 ng/ml = 50 nM are associated with increased risk (OR = 2.04) of **Methicillin**-**resistant** *S. aureus* (NHANES)

5. Staphylococcus aureus and Vitamin D

The Tromsø Staph and Skin Study

Longitudinal, multi-purpose, population-based study

- Nasal Swabs (twice, interval: weeks)
- Incubation for 48 hours in Chrom ID *S. aureus* Agar
- Colonization = positive in first swab
- Carrier state = positive in two samples



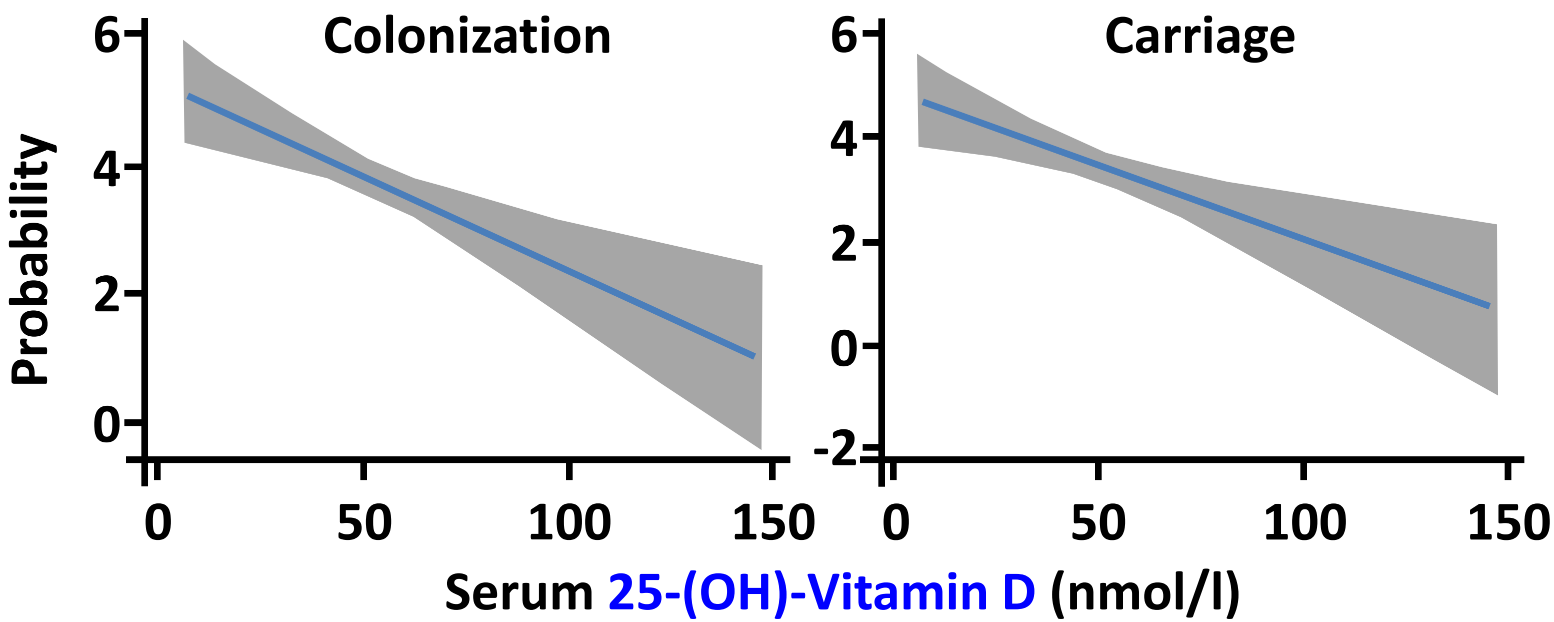
Eur. J. Clin. Microbiol. Infect. Dis. **doi:**10.1007/s10096-011-1331-x (2011)

5. *Staphylococcus aureus and Vitamin D*

The Tromsø Staph and Skin study

Longitudinal, multi-purpose, population-based study

In Non-Smokers and only in Males, Colonization and Carriage of *Staphylococcus aureus* are a function of 25-(OH)-Vitamin D



Serum Levels of 50-100 nmol/l or higher protect from *S. aureus* Colonization and Carriage

Eur. J. Clin. Microbiol. Infect. Dis. **doi:**10.1007/s10096-011-1331-x (2011)

6. Achieving optimal Vitamin D Status

6.1. UV-B from Sun or Sunbeds

- Skin-derived (UV-B) **Vitamin D_3** has a Bioavailability of 1.0
- Skin-derived (UV-B) **Vitamin D_3** is **always** converted into **25-(OH)-Vitamin D_3**

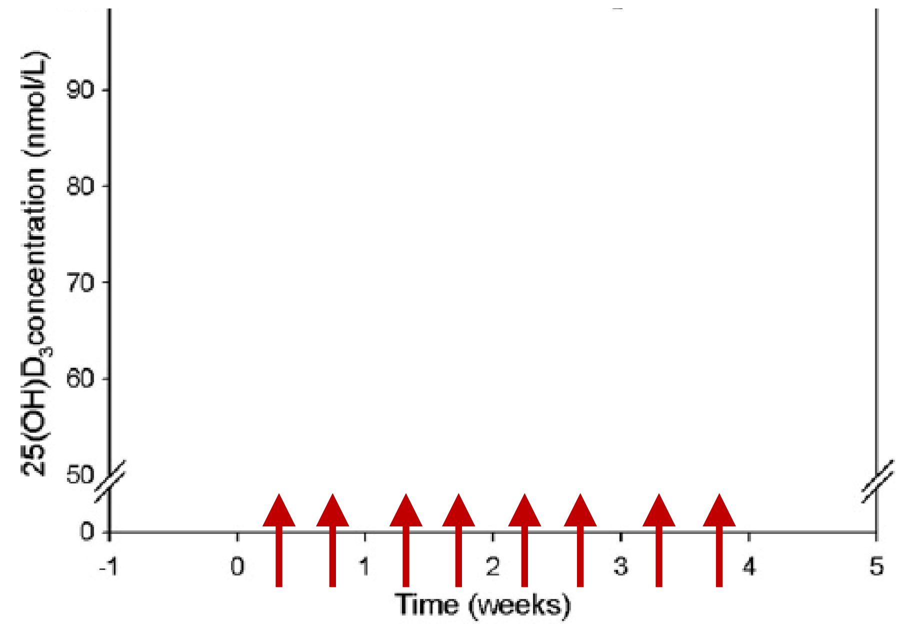
Gerontology **57**, 350-353 (2011); EAS Meeting 2011, Abstract 1479

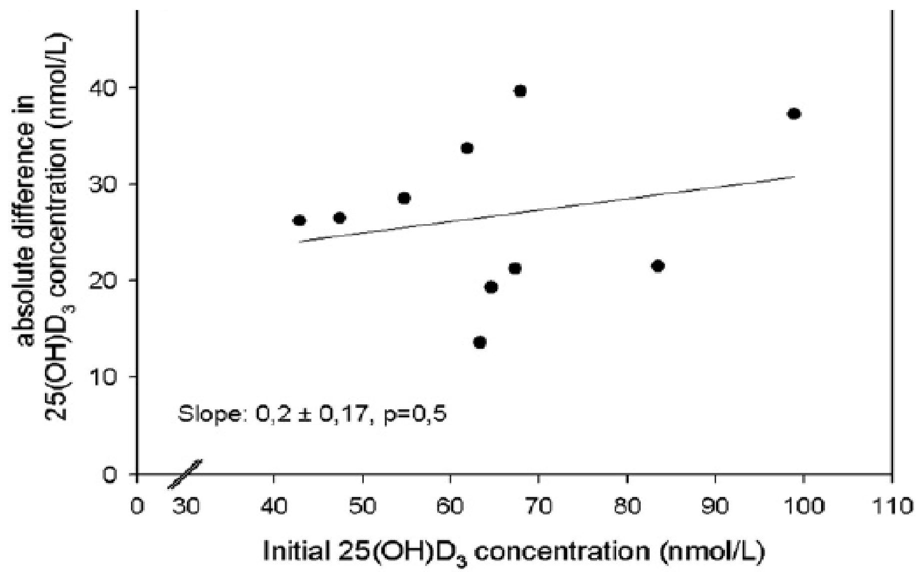
6. Achieving optimal Vitamin D Status

6.1. Sunbeds

Ten human volunteers treated with increasing exposure (1.0 MED) with a commercially available sunbed (UV-A 12 mW/cm², UV-B 0.48 mW/cm²) for a total of 4 weeks.

All of the participants (100%) increased their 25-(OH)-D_3 Levels from 12 to 40 nmol/l





J. Photochem. Photobiol. **91**, 125-131 (2008)

6. Achieving optimal Vitamin D Status

6.1. UV-B from Sun or Sunbeds

- Skin-derived (UV-B) **Vitamin D_3** has a Bioavailability of 1.0
- Skin-derived (UV-B) **Vitamin D_3** is **always** converted into **25-(OH)-Vitamin D_3**
- Increase in **25-(OH)-Vitamin D_3** is determined by starting level and/or ratio of:

24,25-Dihydroxyvitamin D_3 / 25-(OH)-Vitamin D_3

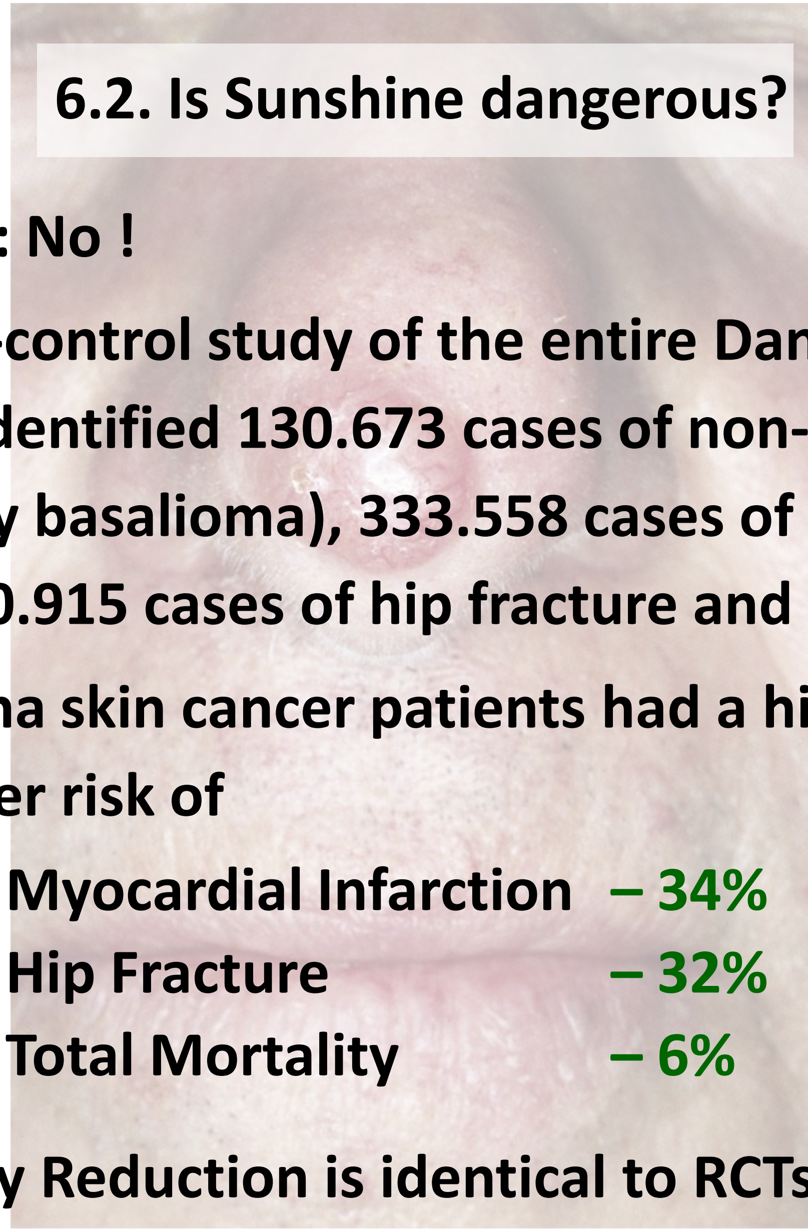
The most reliable source:

Sun (2 hours each day in

Bikini) or Sunbeds

Gerontology **57**, 350-353 (2011); EAS Meeting 2011, Abstract 1479

6. Achieving optimal Vitamin D Status



6.2. Is Sunshine dangerous?

- **The answer is: No !**
- **A recent case-control study of the entire Danish population (7.5 million) identified 130.673 cases of non-melanoma skin cancer (mainly basalioma), 333.558 cases of myocardial infarction, 130.915 cases of hip fracture and 1.688.830 deaths**
- **Non-melanoma skin cancer patients had a highly significant ($p<10^{-20}$!) lower risk of**
    - **Myocardial Infarction – 34%**
    - **Hip Fracture – 32%**
    - **Total Mortality – 6%**
- **Total Mortality Reduction is identical to RCTs with Vitamin D!**

Gerontology **57**, 350-353 (2011); EAS Meeting 2011, Abstract 1479

6. Achieving optimal Vitamin D Status

6.1. Oral Vitamin D_3 as a DRUG in Pharmacological Doses (>1.000 I.U. / day)

First Order Process

- **Systemic Bioavailability**: 0.6 to 1.0 if given with long-Chain Fatty Acids, Milk or a full Meal for healthy Persons
- **Vitamin D_3** travels as a „Blind Passenger“ in **Chylomicrons** in the **Lymph** with long-Chain Fatty Acids and Cholesterol bound to **Lipoproteins**
- „Half-time“ to Maximum of **25-(OH)-Vitamin D_3** at daily Doses: about 2 Months.
  It takes up to 8 Months until a Steady-State Level of **25-(OH)-Vitamin D_3** is achieved in a Population!

6. Achieving optimal Vitamin D Status

6.1. Oral Vitamin D_3 as a DRUG in Pharmacological Doses (>1.000 I.U. / day)

First Order Process

- The Fate of 70-90% of **Oral Vitamin D_3** is unknown!
- 70 to 90% are **never** converted into **25-(OH)-Vitamin-D_3**!
- There are many "**Non-Responders**" – despite complete "Systemic Absorption“

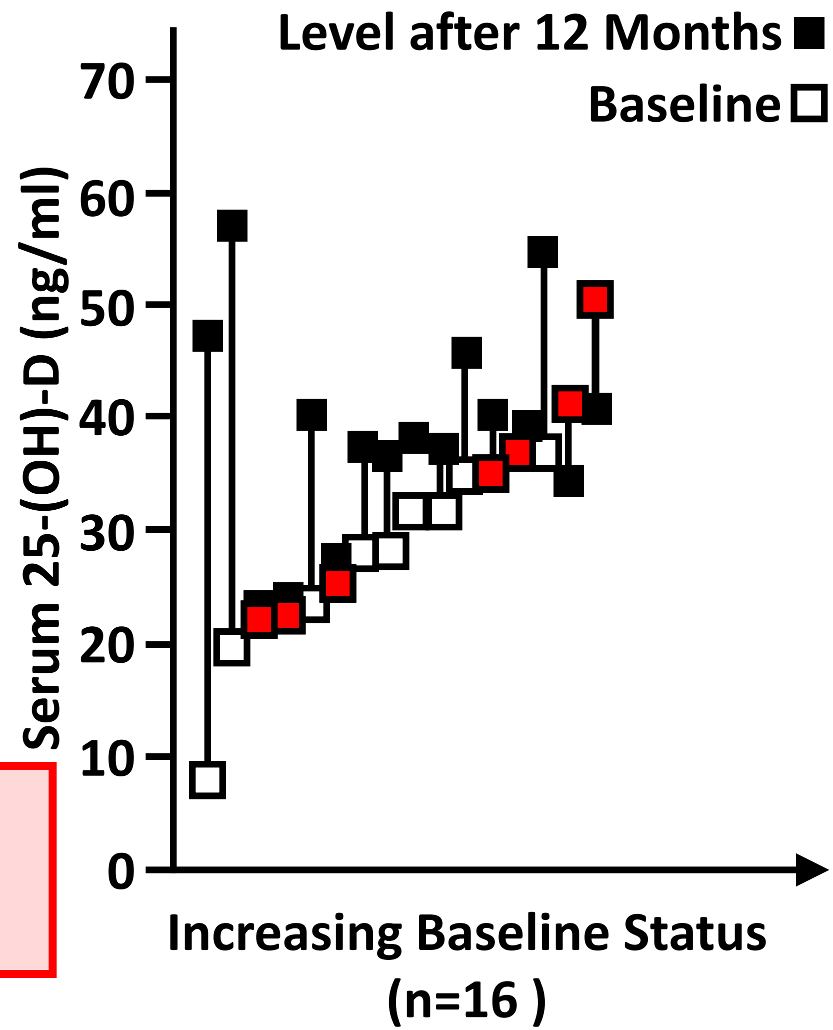
Pharmacokinetics of Oral Vitamin D_3

50% are Non-Responders

16 healthy participants

(74 years, mean level: 30 ng/ml **25-(OH)-Vitamin D**) received **1.600 I.U. Vitamin D_3** daily for 12 months.

Levels of **25-(OH)-Vitamin D_3** were measured monthly.



7 out of 16 did not increase or even decreased their Level!

J. Clin. Endocrinol. Metab. **96**, 981-988 (2011)

6. Achieving optimal Vitamin D Status

6.1. Oral Vitamin D_3 as a DRUG in Pharmacological Doses (>1.000 I.U. / day)

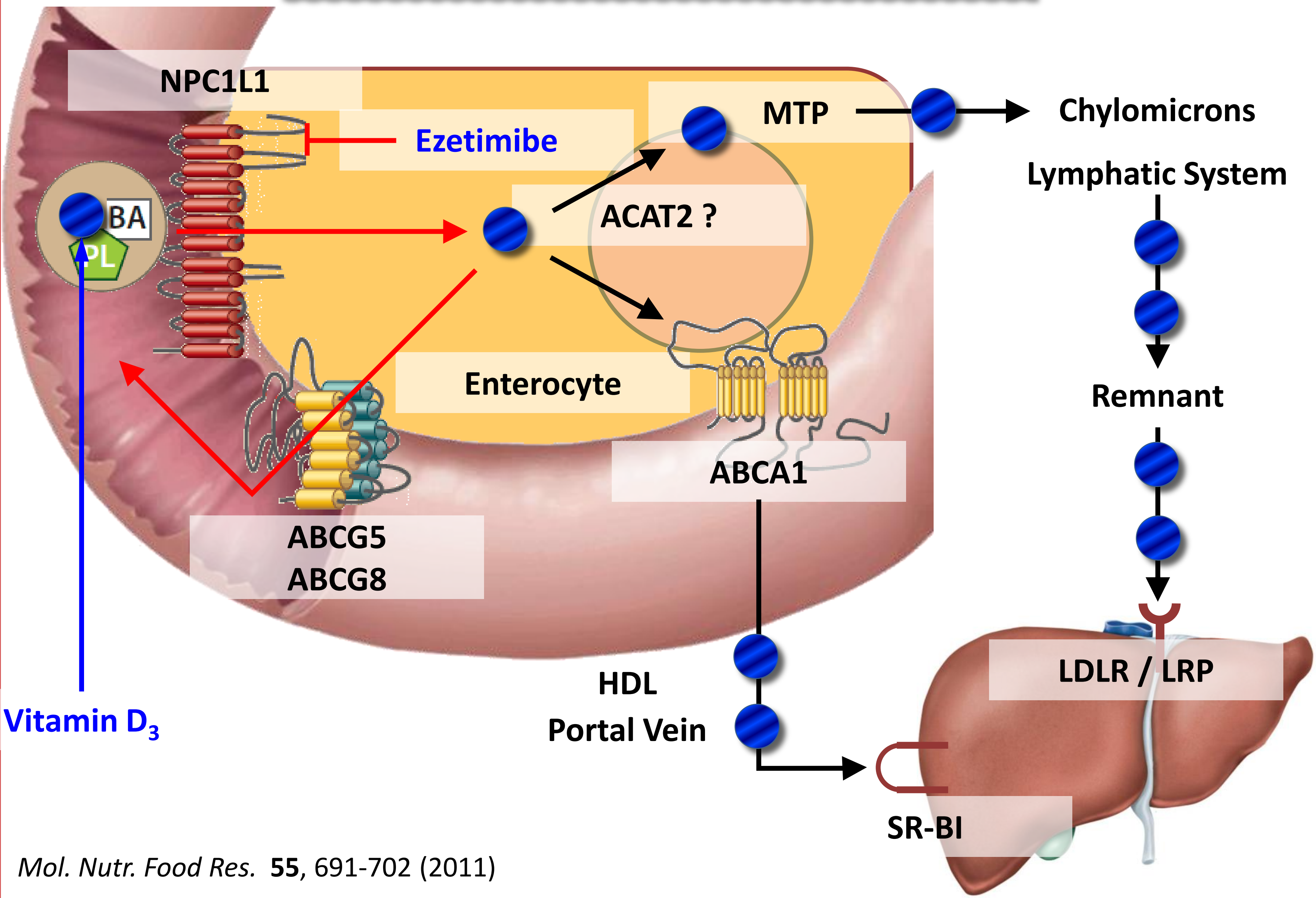
First Order Process

- The Fate of 70-90% of Oral **Vitamin D_3** is unknown!
- It is never converted into **25-(OH)-D_3**!
- There are many "**Non-Responders**" – despite complete "Systemic Absorption"
- Increase (if any) is determined by previous level and/or 24,25 dihydroxyvitamin D_3 to 25-(OH)-Vitamin D ratio: the lower the ratio, the higher the response

Oral Vitamin D_3 in pharmacological Doses is an unreliable Source for increasing Vitamin D_3 Status

6.2 Oral Vitamin D_3 in Food (<200 I.U. / day)

Second Order (Saturable) Process



Mol. Nutr. Food Res. **55**, 691-702 (2011)

Paleolithic Diet supplied 25-(OH)-D_3 and Vitamin D_3 in Meat

6. Achieving Optimal Vitamin D Status

6.3. 25-(OH)-Vitamin D_3

The most efficient and reliable Vitamin D Source

- Bioavailability: 0.6 to 1.0
- Transport in the **Portal Vein** bound to **V**itamin **D** **B**inding **P**rotein (**VDBP**)
- Half-life in Serum/Plasma: 10–12 days
- Distribution Volume (Vd, l/kg): 0.12–0.20
- Increase in **25-(OH)-Vitamin D_3** is immediate (2-3 days) and can be calculated for any Individual exactly by a formula:

$$327.5 * \text{ng/kg/day} = \text{Increase in nmol/l}$$

Public Health Nutr. **14**, 340-346 (2010); **14**, 1128-1129 (2011); Glossmann: *Osteologie* (in press,2011)

Changes of 25-(OH)-Vitamin D_3 Levels in Cows

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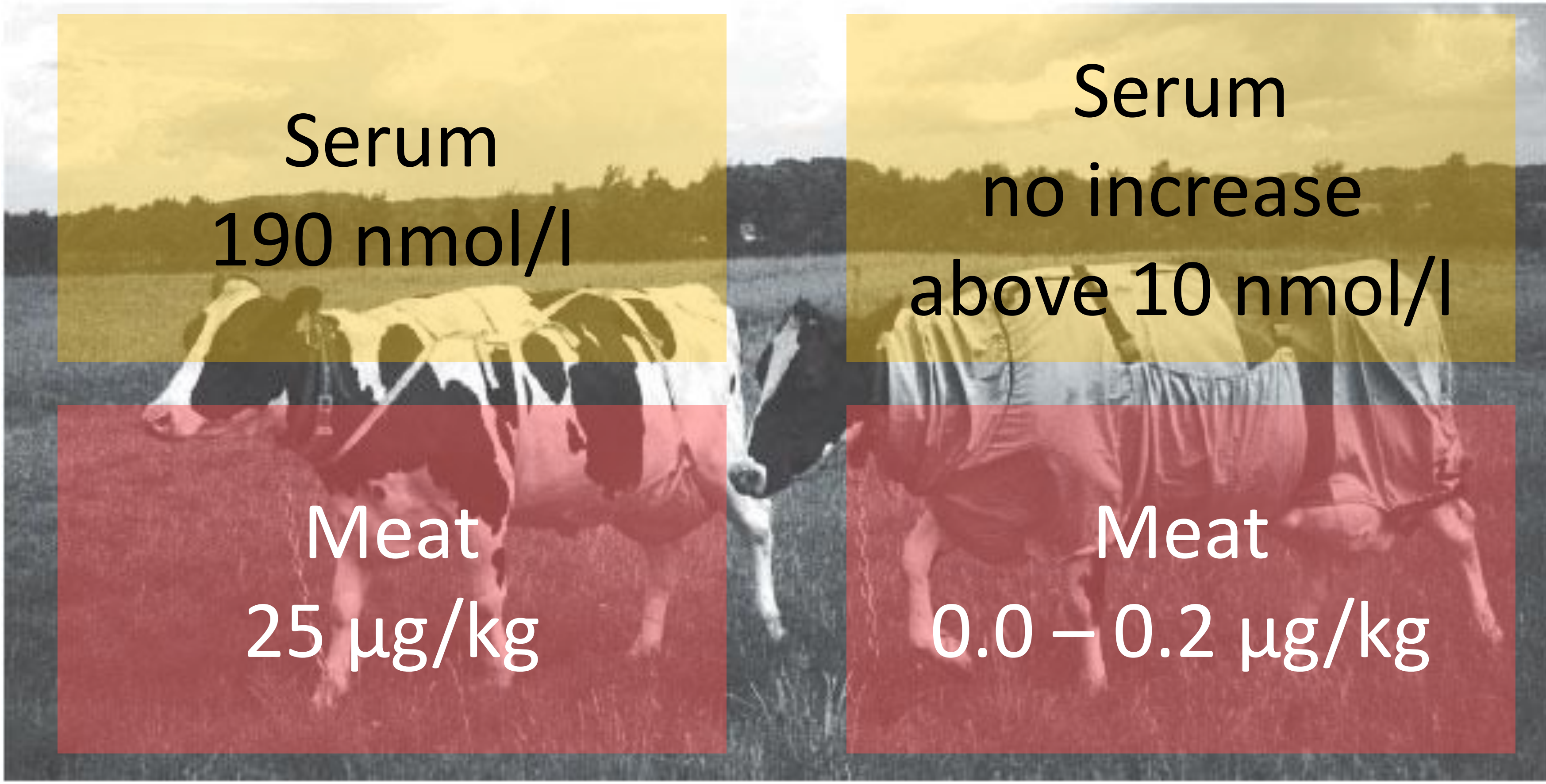


25 µg **25-(OH)-Vitamin D_3** equals 5.000 – 10.000 I.U. **Vitamin D_3**

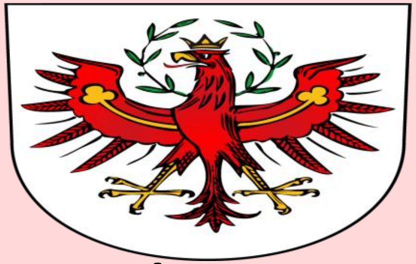
J. Dairy Sci. **93**, 2025-2029 (2010)

6. Achieving Optimal Vitamin D Status

6.3. 25-(OH)-Vitamin D_3

The best Source for 25-(OH)-Vitamin D_3 was (is) Beef

(e.g. Steaks from Cattle raised on Pasture – like in Tyrol)



Beef contains up to 25 ng/g or more of 25-(OH)-Vitamin D_3

3kg Steak per Month will increase

25-(OH)-Vitamin D_3 Levels by 12 nmol/l!

Meat Eaters have about 20 nmol/l higher 25-(OH)-Vitamin D

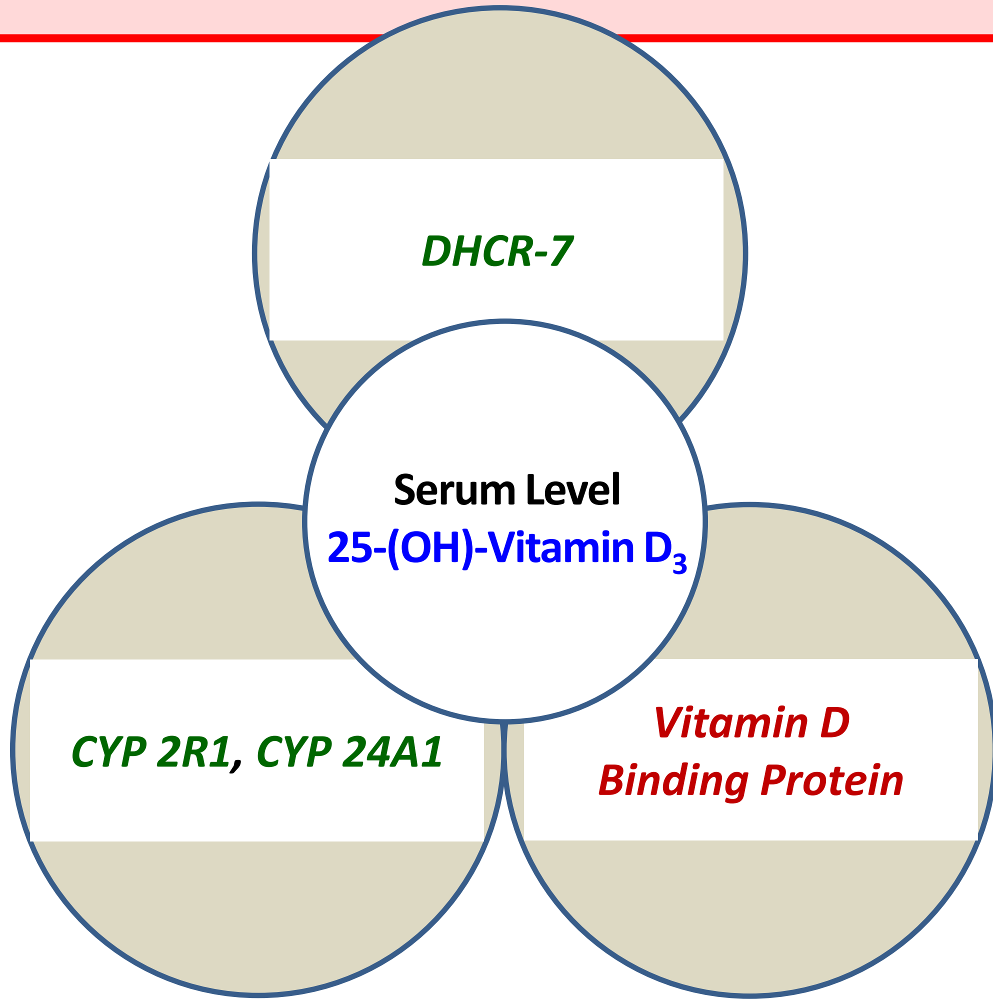
Levels than Vegans!

Public Health Nutr. **14**, 340-346 (2010); **14**, 1128-1129 (2011)

7. Genetic Factors for Serum 25-(OH)-Vitamin D Levels

7.1. Genome-wide Association Studies

Genome-wide Association Studies prove strong influence of Polymorphisms in **3 Enzymes** and in **VDBP** on the Serum Level



Lancet **376**, 180-188 (2010); *Diabetes* **60**, 1629-1631 (2011)

8. Apolipoprotein E, Vitamin D: Better Bones, earlier Death?

- Apolipoprotein E (a component of secreted VLDL) is important in transport and catabolism of cholesterol and triglycerides for chylomicrons and remnants

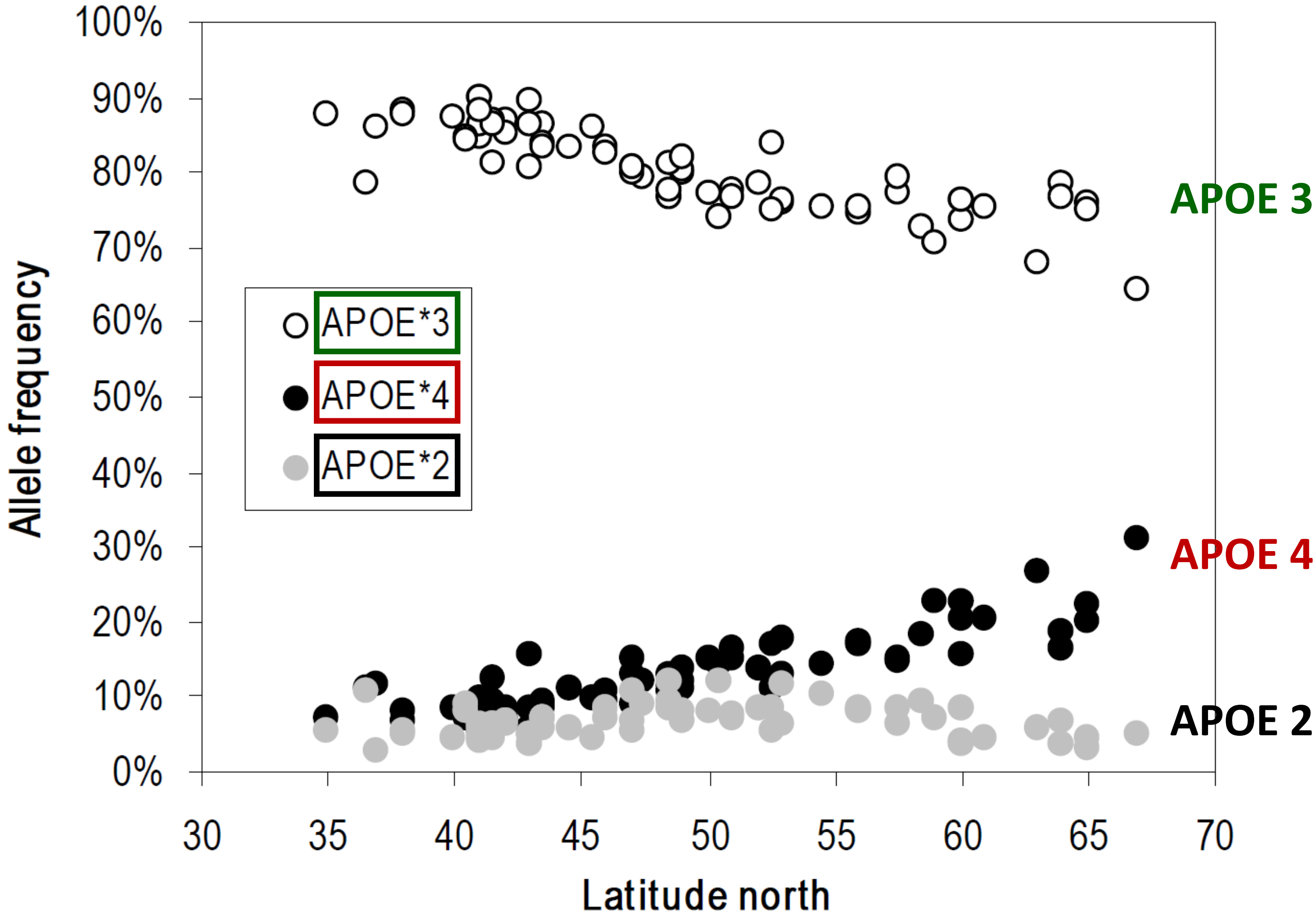
- There is a common polymorphism

Apo ε 3, **Apo ε 2**, **Apo ε 4**

- In Europe, the most ancient allele, **Apo ε 4**, shows a North–South gradient

Clin. Chem. Lab. Med. 41, 628-631 (2003); FASEB J. **doi:** 10.1096/fj.11-180935 (2011); Osteologie (in press)

8. Apolipoprotein E, Vitamin D: Better Bones, earlier Death?



Clin. Chem. Lab. Med. **41**, 628-631 (2003)

8. *Apolipoprotein E, Vitamin D: Better Bones, earlier Death?*

- Apolipoprotein E (a component of secreted VLDL) is important in transport and catabolism of cholesterol and triglycerides for chylomicrons and remnants

- There is a common polymorphism

Apo ε 3, **Apo ε 2**, **Apo ε 4**

- In Europe, the most ancient allele, **Apo ε 4**, shows a North–South gradient

- **Apo ε 4** carriers are higher absorbers of cholesterol and have higher serum cholesterol levels.

Clin. Chem. Lab. Med. 41, 628-631 (2003); FASEB J. **doi:** 10.1096/fj.11-180935 (2011); Osteologie (in press)

8. Apolipoprotein E, Vitamin D: Better Bones, earlier Death?

8.1. Population Studies

Serum Levels		APO ε 4	no APO ε 4
LDL Cholesterol	[mg/dl]	150	140
HDL Cholesterol	[mg/dl]	68	69
25-(OH)-Vitamin D_3	[nM]	49	42
PTH	[pg/ml]	60	72
Calcium	[mmol/l]	2.29	2.22

FASEB J. **doi:** 10.1096/fj.11-180935 (2011)

8. Apolipoprotein E, Vitamin D: Better Bones, earlier Death?

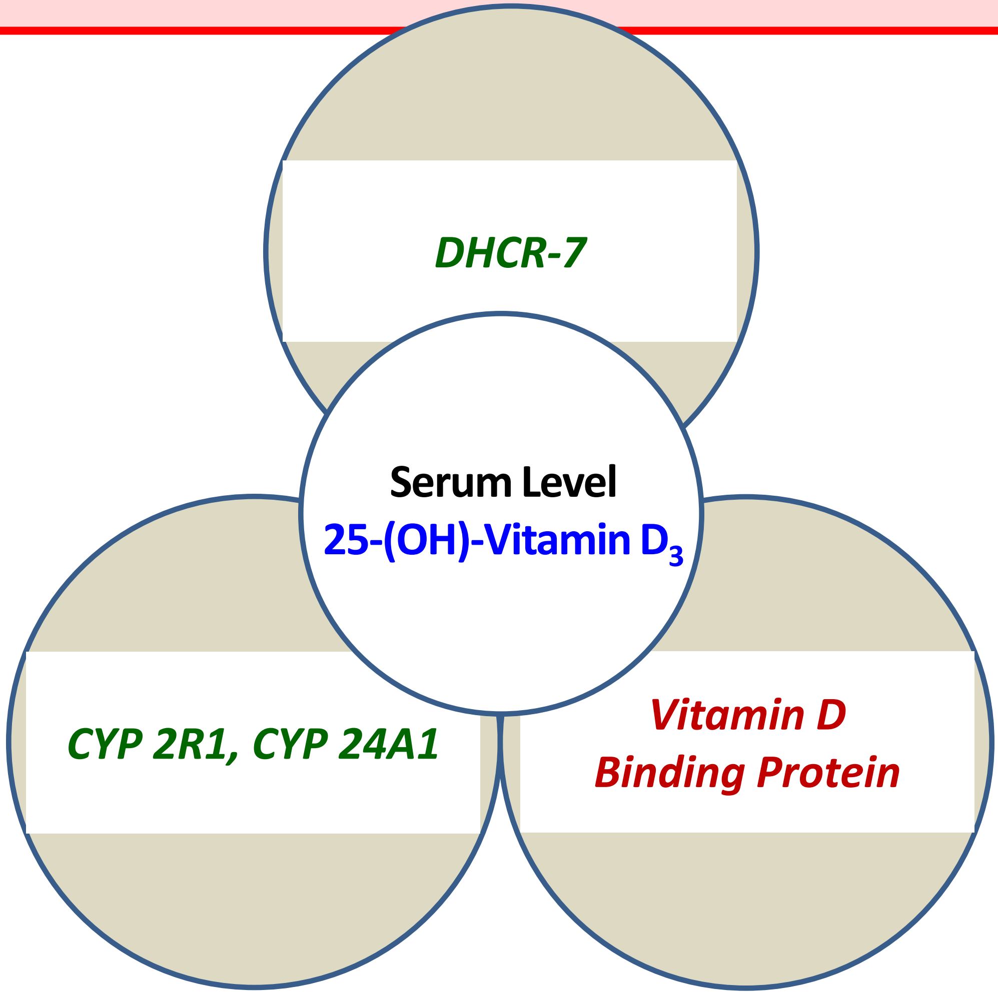
8.2. Knock-in Mouse Models

Serum Levels	APO ε 4	Wild-Type
25-(OH) Vitamin-D_3 [nM]	71	24
Hepatic Bile Acids [nmol/g]	140	98
Femoral Calcium [mg/g]	151	133
Urinary Calcium [mmol/l]	0.5	0.2
Calcium Resorption [%]	45	31

FASEB J. **doi:** 10.1096/fj.11-180935 (2011)

7. Genetic Factors for Serum 25-(OH)-Vitamin D Levels

Genome-wide Association Studies prove strong influence of Polymorphisms in **3 Enzymes** and in **VDBP** on the Serum Level



Lancet **376**, 180-188 (2010); *Diabetes* **60**, 1629-1631 (2011)

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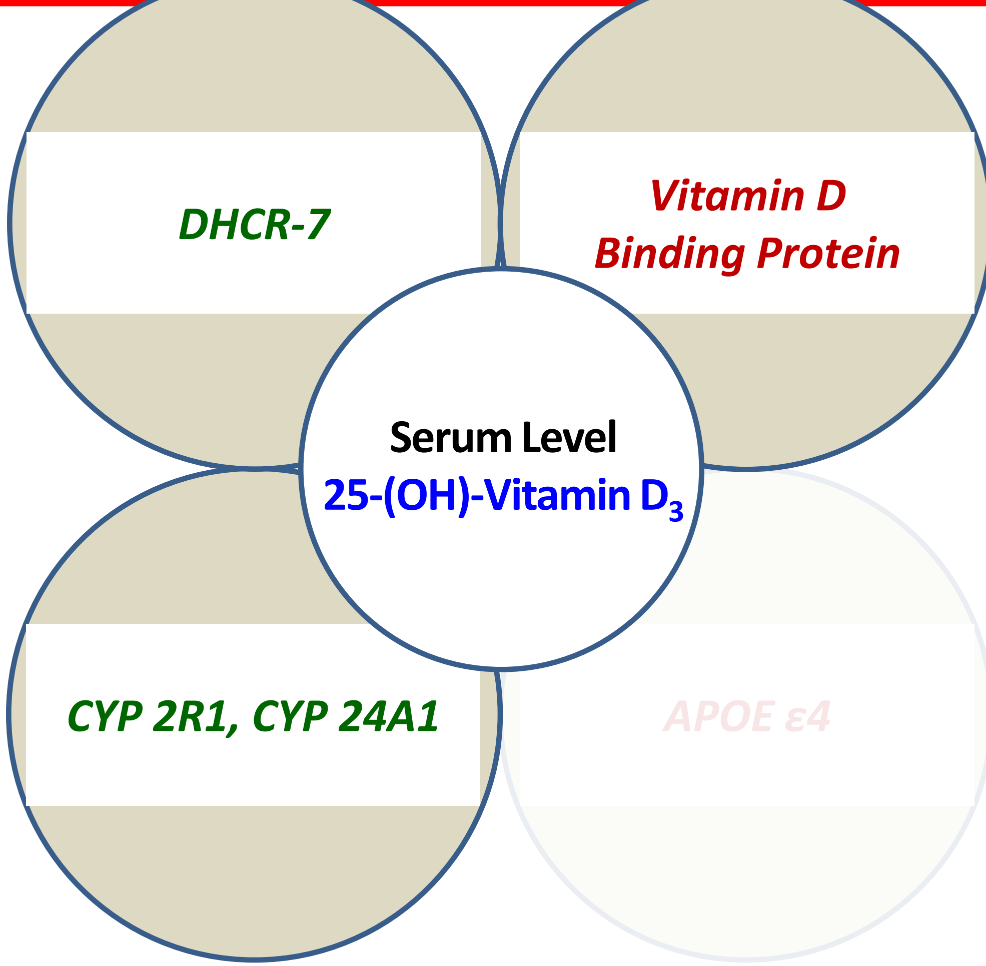

Lancet **376**, 180-188 (2010); *Diabetes* **60**, 1629-1631 (2011)


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