



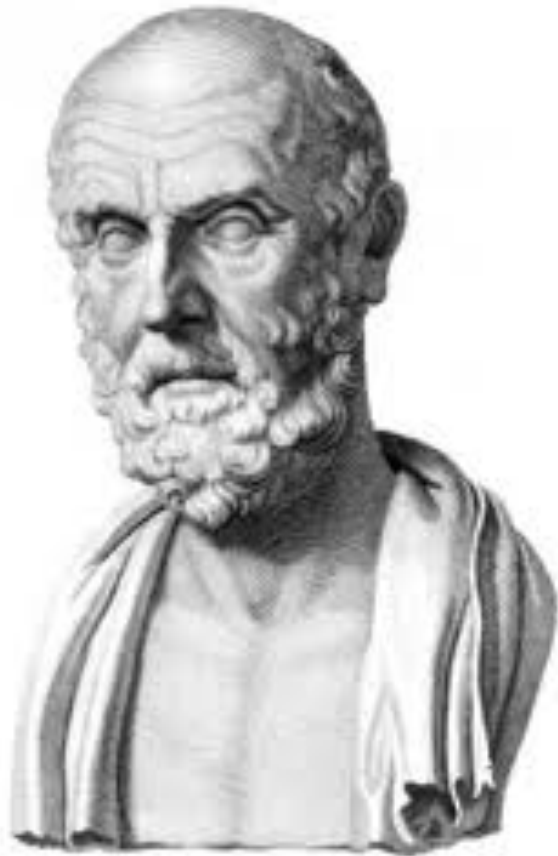
# VITAMIN D IN HEALTH AND DISEASE

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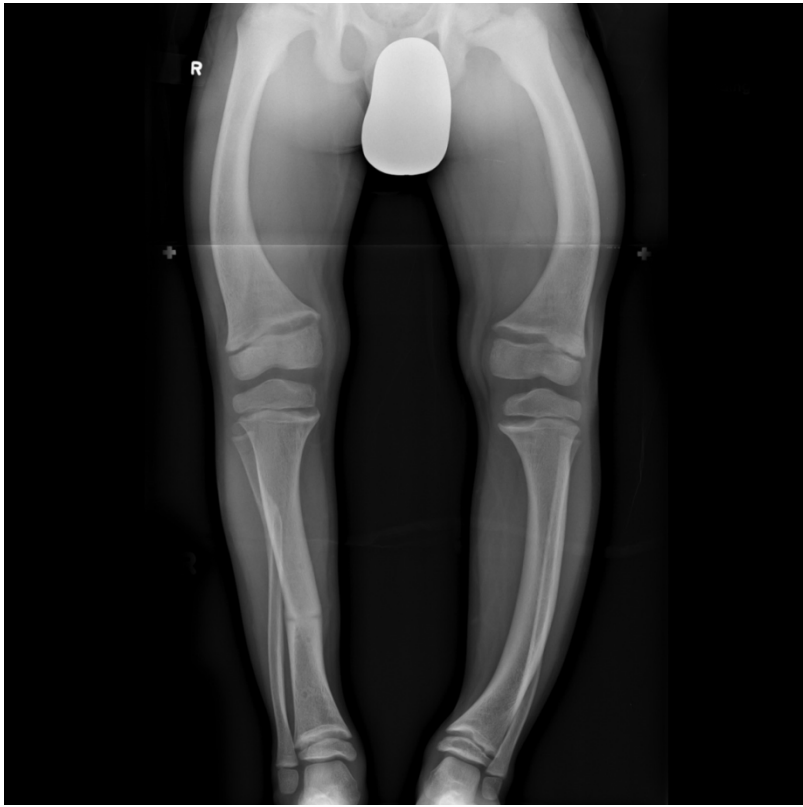
ESIM, Saas Fee, January 16, 2014





- It's most healthy to live on the southern side of a mountain
- Hippokrates of Kos 460-370 BC

# Rickets/Rachitis

- In mid 1600s most children in Northern Europe developed rickets (growth retardation, deformities, weak muscles)
- 1822- effect of Sun on rickets
- Connected to geographical location
- More in towns and cities
- Healing properties of the fish liver oil
- UV induces the synthesis of vitamin D



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- Vit D has been produced by phytoplankton for more than 500 million years
  - Protection of ultraviolet-sensitive macromolecules (incl proteins, DNA, RNA)
  - Maintenance of Ca homeostasis in vertebrates
  - Evolving into hormone having many extraskeletal effects
  - Ethnical and gender differences in skin pigmentation
  - Evolutionary selection pressure towards a lighter skin with higher ability to produce vit D

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- Vitamin D or D-hormone?
  - Organism synthesizes its own vit D (no other vitamins)
  - Organism turns vit D into hormone, metabolites are active, receptors needed VDR

## Colecalciferol-Vitamin D<sub>3</sub>

- biologically inert
- synthesized in the skin upon exposure to UVR
- also contained in certain nutrients
- activates in liver and kidneys

# Ergocalciferol- Vitamin D<sub>2</sub>

- another inactive type of vitamin D
- is formed by the irradiation of the plant sterol ergosterol
- weaker than D<sub>3</sub>
- activates in liver and kidneys



# Calcitriol (1,25[OH]<sub>2</sub>D)

- major biologically active metabolite of vitamin D (= active vitamin D)
- 1000 times more active than any of its precursors
- 1,25(OH)<sub>2</sub>D is formed by the metabolic conversion of the two inactive forms of vitamin D.


# Metabolism of vitamin D

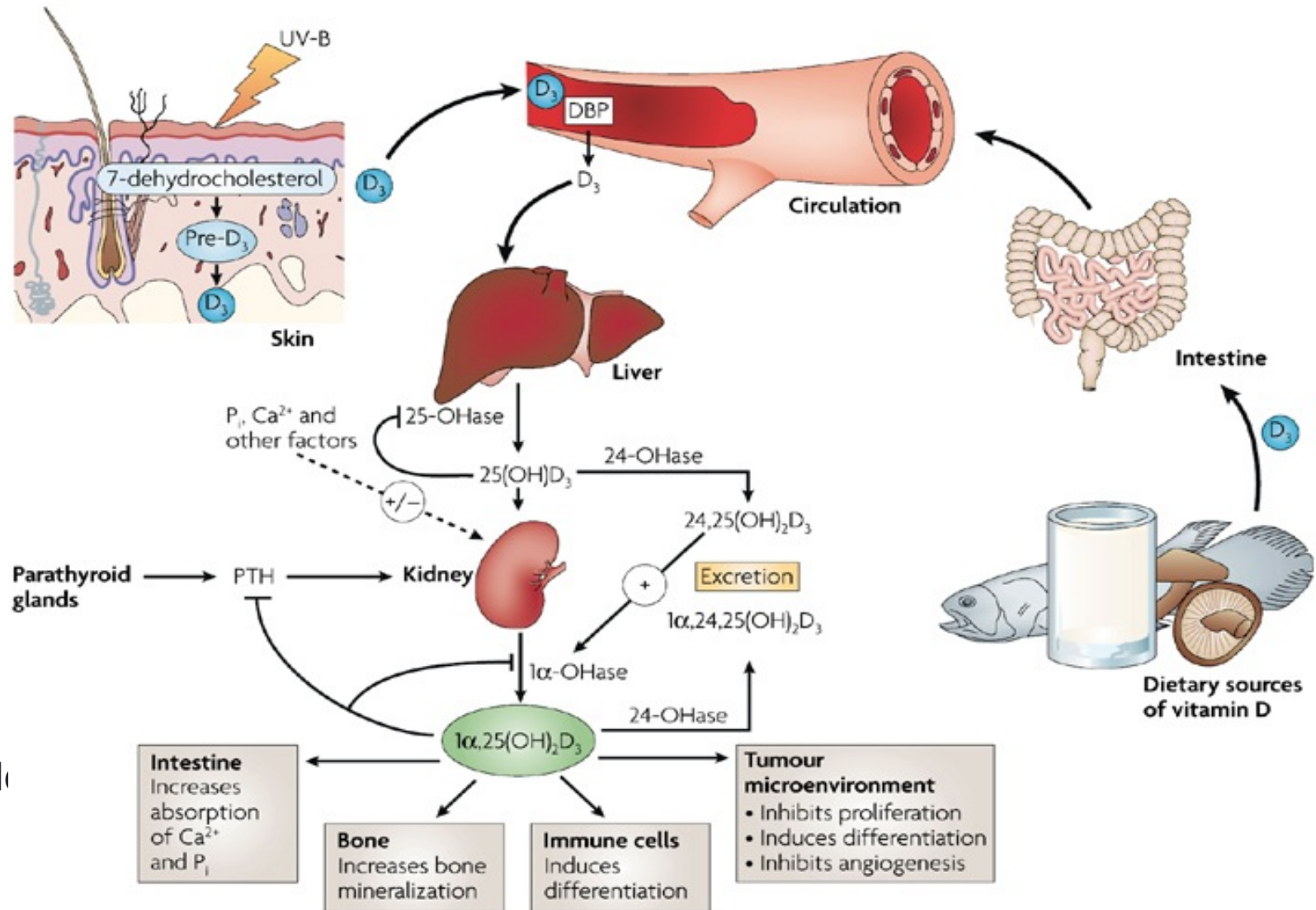
7-dehydrocholesterol (in cell membranes of keratinocytes) →  
pre vit D<sub>3</sub> on UVB

→ vit D<sub>3</sub> on heat

→ in liver pro-hormone 25(OH)D

- **25(OH)D is the main circulating metabolite**
- 25(OH)D → in kidneys etc 1,25(OH)<sub>2</sub> D<sub>3</sub>

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- Active vit D can penetrate to target cells and bind to specific VDR (VDR is expressed in several organs)
  - These complexes translocate to nucleus, where they activate or repress the expression of several genes.



• M H

# Where do we get vitamin D from? 1

- Exposure to sunlight, the cutaneous production of vit D
  - affected by season,
  - latitude (UVB exposure angle over 50 deg)
  - the duration of exposure, sunscreen use
  - skin pigmentation
  - and the ability of the skin to form and process vitamin D
- in southern areas 2 hr/week of sunshine on face and hands

## Where do we get vitamin D from? 2

- Rarely found in foods naturally, dietary intake is a minor source of vitamin D (no more than 100 IU/day)
- Fatty fish and eggs
- Vitamin D–fortified milk
- Multivitamins and supplements



**NUTRITION INFORMATION**

| PER 100g            | PER 50g        |
|---------------------|----------------|
| Energy              | 1700kJ/410kcal |
| Protein             | 12.0g          |
| Carbohydrate        | 0.5g           |
| Total fat           | 11.5g          |
| Saturated fat       | 6.5g           |
| Monounsaturated fat | 4.5g           |
| Trans fat           | 0.5g           |
| Salt                | 0.1g           |

These eggs have been laid by hens that are free to roam, forage, peck and scratch in a well-ventilated barn. All Green Eggs have been produced to high environmental and welfare standards.

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All UK Quality eggs are produced by hens that are laid in compliance with the UK Quality mark. Visit [www.ukquality.co.uk](http://www.ukquality.co.uk)

# Measurement of vit D status

- **Serum 25(OH)D** is the main circulating metabolite
- **Level of S- 25(OH)D is taken to assess vitamin D status**



# Vitamin D levels

|               | 25(OH)D <sub>3</sub><br>(nmol/L) |
|---------------|----------------------------------|
| Deficiency    | < 25                             |
| Insufficiency | < 50                             |
| Optimal       | > 75                             |
| Toxic         | > 370                            |

Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency  
Am J Clin Nutr. 2004 ;80:1706-9.

- Sometimes concentration of 25(OH) D<sub>3</sub> expressed in ng/mL:

$$C1 \times 2.5 \text{ ng/mL} = C2 \text{ nmol/L}$$

# Population study in Estonia

- N=357 (age 25-70), a random sample in GPs` list
- Average age  $48.9 \pm 12.2$  y
- 200 females, 167 males
- Measured in winter and summer

M.Kull, R.Kallikorm, A.Tamm, M.Lember BMC Public Health, 2009

# Seasonal variation



Hypovitaminosis  
1/3 in summer, 2/3 in  
winter

Avitaminosis in winter  
8%

M Kull, R Kallikorm, A Tamm, M Lember  
BMC Public Health, 2009

# Sunbathing and vitamin D

Summer:

- Avoids Sun: average 45 nmol/l
- Sunbathing face, arms: 55 nmol/l
- Sunbathing total body: 63nmol/l

Winter:

- Avoids Sun : 34 nmol/l
- Sunbathing face, arms : 41 nmol/l
- Sunbathing total body : 46 nmol/l

# D-vitamin in winter

|                     |           |
|---------------------|-----------|
| Estonia (59N)       | 44 nmol/l |
| Finland (60N)       | 46        |
| Belgium (50N)       | 48        |
| Germany             | 40-45     |
| Switzerland(46-47N) | 50        |
| USA (25-47N)        | 60-79     |

**Optimal is considered >75 nmol/l**

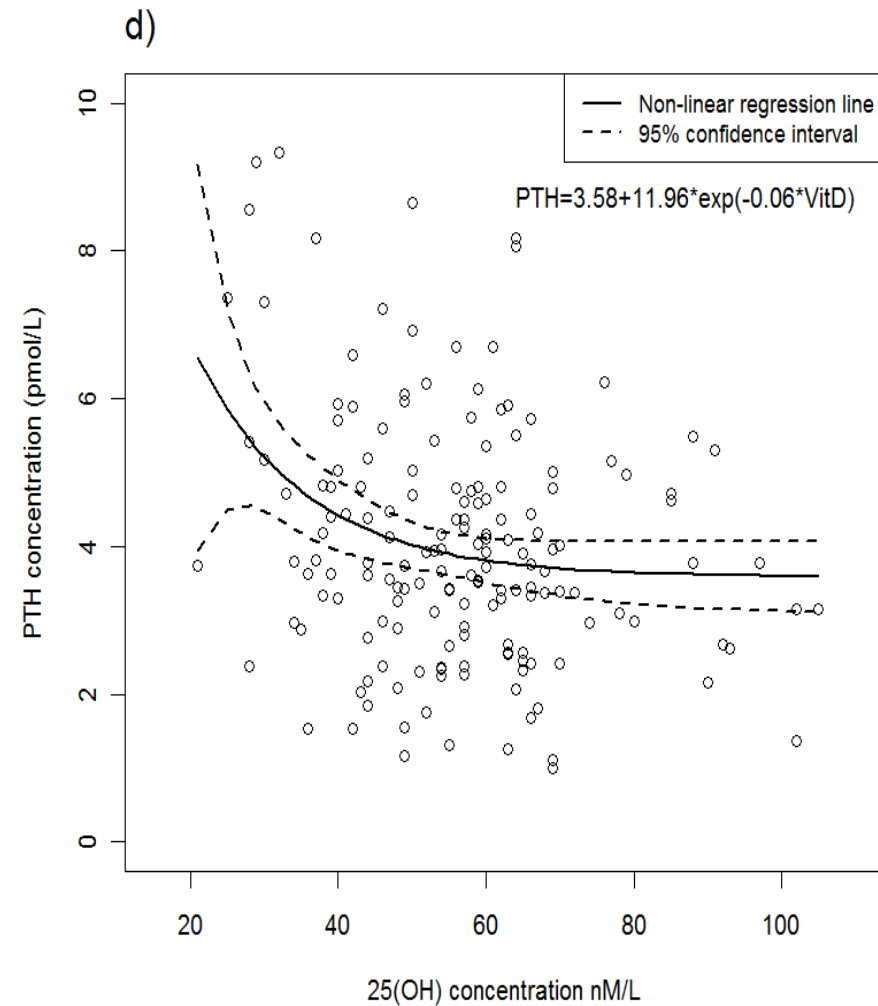
# Vit D in Ca metabolism

- helps to keep adequate levels of Ca and P
- enhances Ca absorption in intestine
- increases tubular Ca reabsorption
- helps to mobilize skeletal Ca
- Lower vit D → lower serum Ca → stimulates PTH↑
- PTH increases tubular Ca and decreases renal P reabsorption, stimulates osteoclasts to mobilize skeletal Ca stores

# Vitamin D vs PTH

- 367 Estonians
- (200 F, 167 M)
- Summer PTH and 25(OH) vit D
- PTH plateau ~80 nmol/L

Kull M, Kallikorm R, Lember M. BMC Public Health 2009





# Vitamin D and osteoporosis

- Impaired calcium absorption
- Increased PTH, increased bone resorption
- Decreased bone mineral density
- Decreased peak bone mass
- Decreased efficiency of osteoporosis medications
- Impaired muscle function, increased risk for falls

# Prevalence of osteoporosis in Estonia

Random sample of population, age 40-70, N= 271

Spinal 5.5-8.6%

Femoral neck 1.3-2.0%

Osteopenia in Estonia:

Spinal 30-34%

Femoral neck 15-39%

Kull M, Kallikorm R, Lember M. Int Med J 2012

# Vitamin D and bisphosphonates

Patients with nonsufficient response to treatment with bisphosphonates:

- 51% hypovitaminosis
- With correction of vit D -> in 85% cases positive dynamics of BMD

Ishijima et al. Calcif Tissue Int. 2009

Geller et al. Endocrine practice 2008

# Vitamin D and muscles

- VDR expressed on muscle cells
- Vit D level correlated with muscle contractility
- Vit D deficiency- impaired function of 1b type (fast-twitch) muscles
- In aging VDR number on muscle cells decreases

Bischoff-Ferrari H, Borchers M, Durmuller, JBMR 2004

M. Pfeifer, B. Begerow and H. W. Minne, Osteop. Int 2002

# Vit D and muscle

- Maintaining posture requires adequate sensory-motor signal processing and coordinated muscle contractions as a complex motor response.
- Link between vit D level and muscle power (first of all, contraction velocity, not so much on strength ). Intracellular Ca levels, actin and myosin fibres.

# Vitamin D and falls

- Metaanalysis: 5 RCTs
- Subjects: age 60+
- Follow-up: up to 3 years
- Conclusion: Vit D (compared to calcium only or calcium +placebo) decreases the risk for falls by **22%**
- NNT=15

Bischoff-Ferrari HA. *JAMA*. 2004;

Bischoff HA et al. *J Bone Miner Res*. 2003;

Gallagher JC et al. *J Clin Endocrinol Metab*. 2001;

Dukas L et al. *J Am Geriatr Soc*. 2004;

# Vit D and central nervous system

- Vit D has demonstrated neuroprotective effects (whatever the mechanism- oxidative stress, degeneration, inflammation, vascular disorders)
- Cognitive function in the elderly

# Impact of vitamin D

PubMed papers 57706 (14.01.14)


- Autoimmune diseases
- Cancer
- Cardiovascular diseases
- Diabetes and other metabolic
- Infections
- Falls, fractures, osteoporosis
- Depression
- Pregnancy

Grant WB, Cross HS, Garland CF et al. /Progress in Biophysics and Molecular Biology (2009)104-113



# Vitamin D and cancer

- Vit D affects cell proliferation, inhibits cancer cell division, decreases angiogenesis, diminishes risk of metastases
- Some tumors produce  $1,25(\text{OH})_2 \text{D}_3$  locally
- Protective effect of vit D from animal models. But in humans?


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- Observational studies: vit D over 82.5 vs vit D less than 30: 2-fold difference in risk of colorectal cancer and breast cancer, but not in prostate cancer.
  - Interventional studies have not proved so far usefulness of vit D in cancer prevention, methodological problems of the trials.


# Obesity


- An independent risk factor for vit D deficiency
- Low dietary intake
- Sedentary lifestyle, limited sun exposure
- Decreased bioavailability of vit D due to sequestration of vit D within adipocytes
- After bariatric surgery vit D deficiency
- Increased dosages for supplementation, guidance on actual vit D measurements in blood


# Vit D and immune system

- VDR is expressed by immune cells (lymphocytes, macrophages, neutrophils, dendritic cells)
- Local production of active vitamin D
- Vit D production locally in skin in case of skin barrier damage leads to increased antimicrobial defence

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- Clinical data: vit D lower in patients with active tuberculosis
  - Vit D deficiency may increase the risk of influenza, other viral and bacterial infections
  - DM 1: more spread in countries with less sunshine and more expressed vit D deficiency

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- Vit D deficiency and/or VDR absence predisposes to different immune-mediated disorders.
  - Baeke F et al Mol Aspects Med 2008

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- RA: Greater RA activity in patients with lower vit D levels
  - Associations with multiple sclerosis, Crohn`s disease, RA, DM1
  - Many confounding factors

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- Mixed results of vit D links with infections and sepsis: more studies needed (type of infection, dosage and time for supplementation, outcome measures etc)




# Vit D and cardiovascular risk

- Inverse association between vit D levels and cardiovascular risk
- Inverse association between vit D levels and hypertension
- Cerebrovascular events risk higher with low vit D
- Possible antidiabetic effects?


# Prevention and treatment

- Screening recommended only for individuals at risk
- Infants: immediate daily supplementation (first year of life)  
400 IU/daily
- Institute of Medicine (US):
  - Age 1-70 600 IU/daily
  - Age 70+ 800 IU/daily
- Endocrine society:
  - children 400-1000 IU
  - adults 1500-2000 IU

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- Obese individuals, patients with malabsorption syndromes, patients on glucocorticoids, anti-seizure and AIDS medications may require 2-3 times higher doses
  - Treatment of vit D deficiency: higher doses, 50000 IU/ once a week for 8 weeks or 6000 IU /daily for 8 weeks, thereafter maintenance 600-1000 IU /daily

# Conclusions

- Vit D level is a powerful biomarker for the overall health status in populations over the age of 50.
- Uncertainties: is it only a marker or contributes directly to induce health conditions (via genomic and cellular effects in immune cells or dysplastic precancerous cells)?
- Convincing evidence of vit D supplementation in preventing falls and fractures

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- Low serum vit D levels should lead to a lifestyle evaluation, advice about outdoor activities, a reasonable amount of sunshine, fish consumption, vit D supplementation in winter if needed.
  - High-dose vit D supplementation is useful in osteoporosis or severe vit D deficiency
  - Uncertain whether supplementation decreases the risk for cancer or cardiovascular disease
  - Bouvard B et al Joint Bone Spine 2011; 78: 10-16





