

Osteoporose Zentrum
Zimmerberg (OZZ)

NierensteinZentrum
Zürich

HIRSLANDEN 
KLINIK IM PARK

Warum verirrt sich Kalzium in die Gefässe und fehlt im Knochen ?

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Innere Medizin & Nephrologie

Kliniken Im Park & Hirslanden, Zürich & Paracelsus-Spital Richterswil

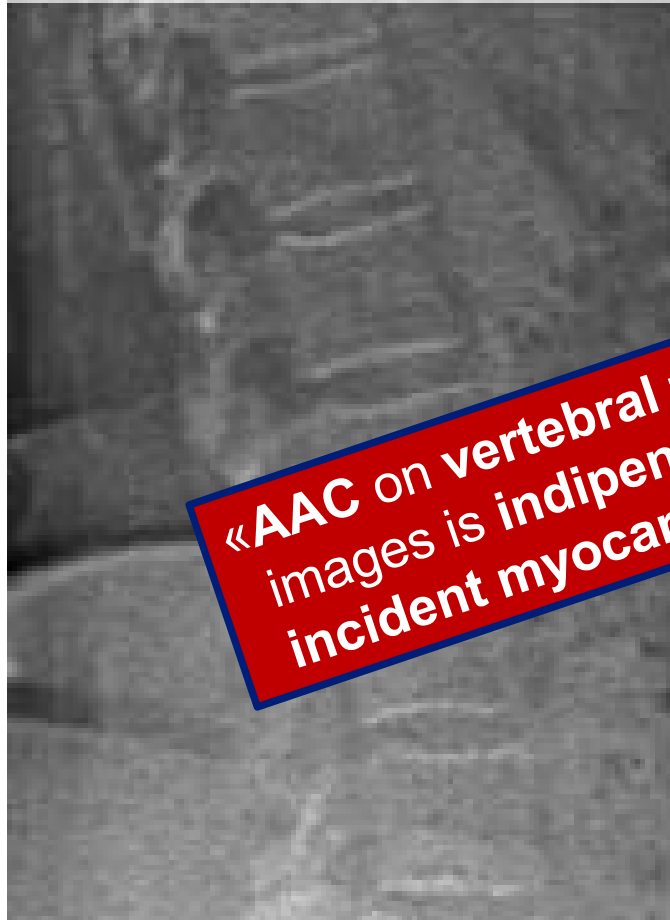
Konsiliararzt Nephrolithiasis, Nephrologie, Kantonsspital Baden

Leiter NierensteinZentrum Zürich & OsteoporoseZentrum Zimmerberg

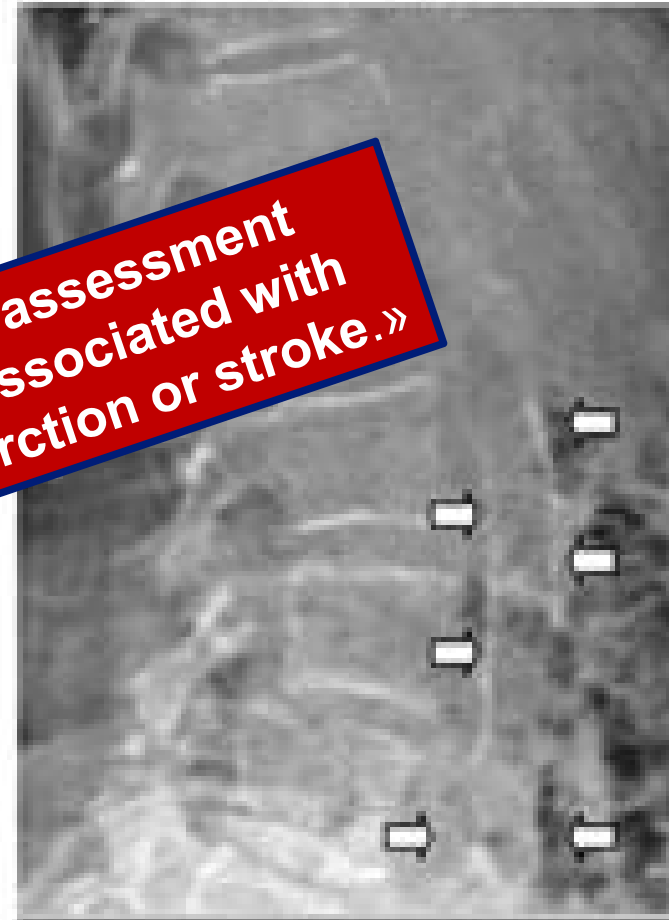
Aortic calcifications & osteoporosis

- why does calcium go astray ?

A No AAC



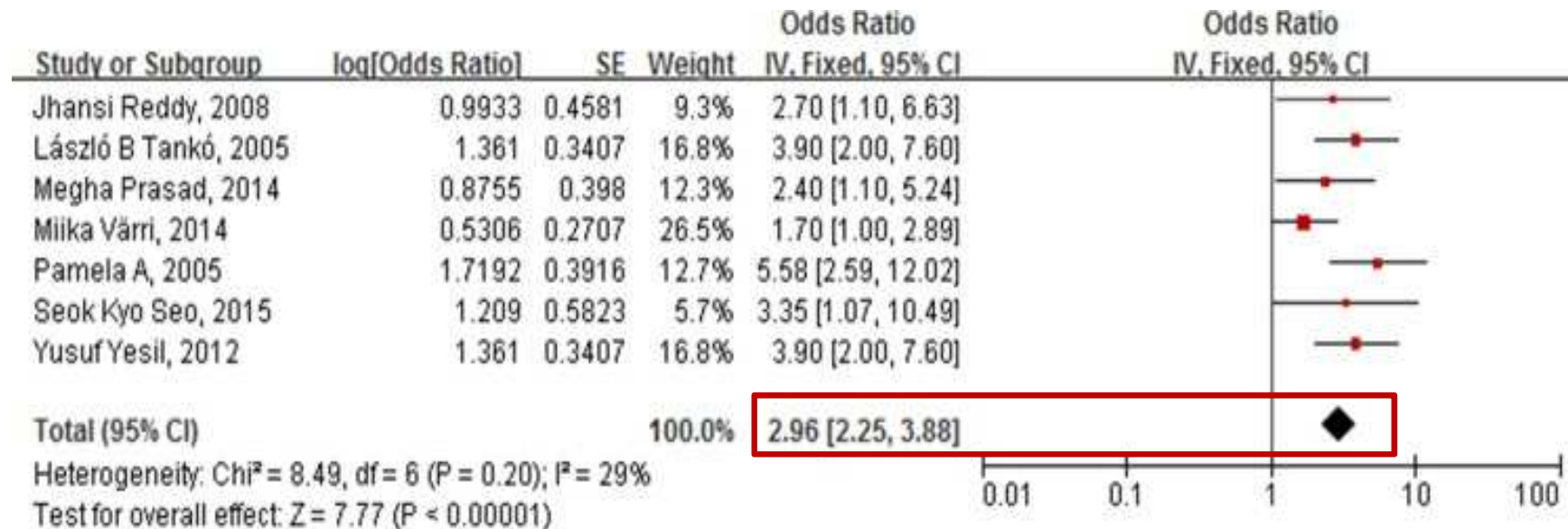
C AAC-24 =12, AAC-8 =4



«AAC on vertebral fracture assessment images is independently associated with incident myocardial infarction or stroke.»

Vascular calcifications & osteoporosis - Epidemiology

Meta-analysis, 7 case control or cohort studies, 5850 subjects



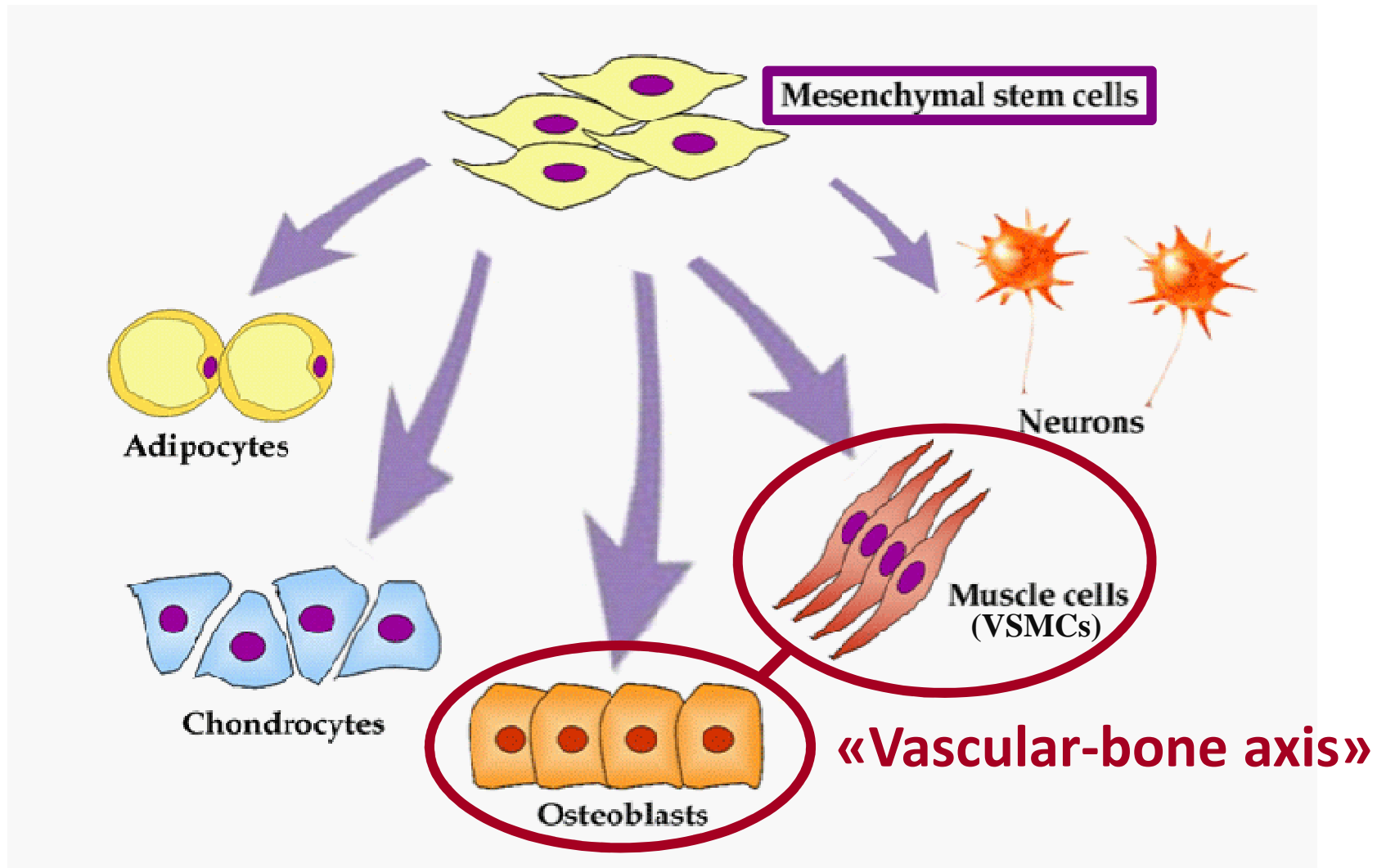
Odds ratio of atherosclerotic vascular abnormalities in individuals with low BMD vs. normal BMD, adjusted for age, gender, BMI, hypertension, and other vascular risk factors

Conclusions

- Risk for **atherosclerosis increases as BMD decreases**
- Patients with **decreased BMD** scores should be **screened for CV risks**

Vascular calcification & osteogenesis

- Pathogenetic pathways



Vascular calcifications & low bone mass

- clinically relevant pathways

Mechanisms involved in both loss of bone mass and cardiovascular disease

- Increase in inflammatory cytokines
- Lack of endogenous sex hormones
- Oxidized lipids
- Diabetes mellitus
- **Calcium intake**
- Effects of vitamins D and K
- Drug effects & Lifestyle

Welches Kalzium ist am gesündesten ?



Viva! Calcium-rich foods



**Knochen : Calciumzufuhr
1000-1200 mg/d**

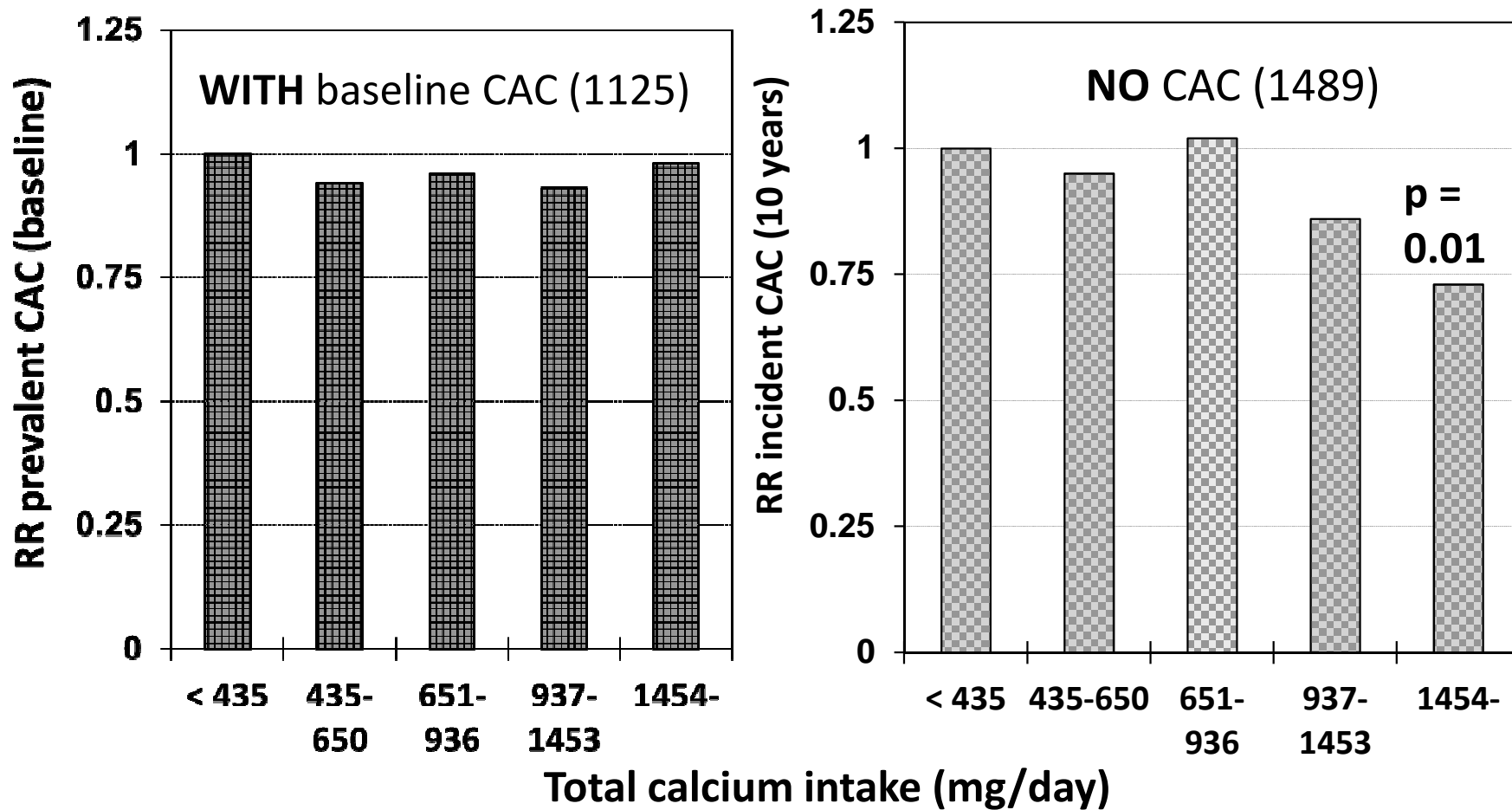


www.viva.org.uk

Vascular calcifications - relevant pathways:

Calcium intake from diet vs. supplements

2742 adults, no CVD, age 45-84 yrs., 52% women, excluded 128 (missing data), analysis based on CT scans: 1489 without CAC / 1125 with CAC score > 0



Vascular calcifications - relevant pathways : Calcium intake from diet vs. supplements (2)

BUT : subjects without CAC

**Multivariate model additionally
adjusted for total calcium intake :**

- Intake of calcium supplements ⇒
RR for incident CAC 1.22
(1.07-1.39)
- Calcium supplement users with
lowest total calcium intake
(average 306 mg/day) ⇒
RR for incident CAC 1.41
(1.02-1.97)

(from Anderson JJB et al. J Am Heart Assoc,
DOI: 10.1161/JAHA.116.003815, 2016)

EPIC-Heidelberg Study

23'980 participants, **35-64 years**,
free of CVD at baseline, average
follow-up **11 years**

- HR for MI with moderate intake
of dietary calcium (820 mg/d)
0.69 (95% CI 0.50-0.94)
- HR for MI in users of calcium
supplements 2.39 (95% CI
1.12-5.12) vs. non-users

(from Li K et al, Heart 98: 920-925, 2012)

Vascular calcifications & low bone mass

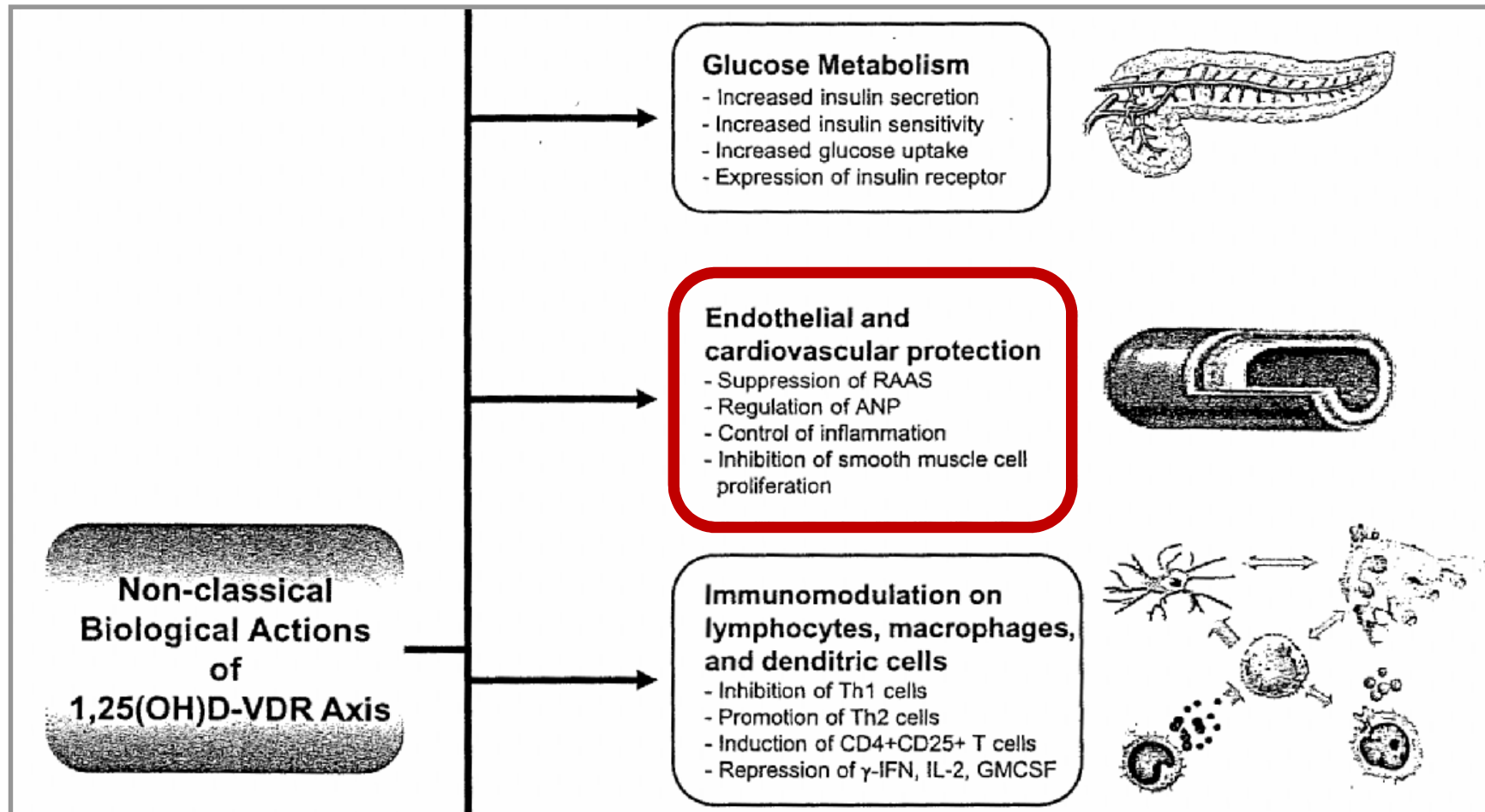
- clinically relevant pathways

Mechanisms involved in both bone and cardiovascular disease

- Increase in inflammatory cytokines
- Lack of endogenous sex hormones
- Oxidized lipids
- Diabetes mellitus
- Low calcium intake
- **Effects of Vitamin D**
- Drug effects & Lifestyle

Non-classical extrarenal biological functions of vitamin D

Vitamin D deficiency → ↓ local calcitriol → ↓ activation of non-renal VDR
→ ↓ non-classical, extrarenal biological functions of vitamin D



Vascular-bone axis - role of Vitamin D

Vitamin D deficiency (25-OH-D < 30 ng/ml or < 75 nmol/l)

- ↑ risk of **vascular** (incl. coronary arteries) **calcifications** and **cardiovascular diseases** (epidemiologic data)
- ↑ prevalence of **low bone mass and fractures**

Vitamin D receptors present in cardiovascular cells

- **Vascular smooth muscle cells** also express **1-hydroxylase** → ↑ **1,25 (OH)₂-D** → ↑ **production of MGP** (strong calcification inhibitor)
- **Low 1,25(OH)₂-D** → ↓ **MGP** → ↑ **vascular calcification**

Low vitamin D-diet (50 IU/kg/day) in mice

- more pronounced calcification of aortic valve / adjacent aorta
- **Phenotypic switch**: vascular cells → **osteoblast-like cells** → ↑ bone matrix protein production

Vascular calcifications & low bone mass

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Mechanisms involved in both bone and cardiovascular disease

- Increase in inflammatory cytokines
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- Low calcium intake
- **Effects of Vitamin K**
 - Phylloquinones (Vit. K1)
 - Menaquinones (Vit. K2)
- Drug effects & Lifestyle

Vitamin K2 = menaquinones

(in meat, cheese, curd)

Protein carboxylation

Matrix GLA Protein
ucMGP → cMGP

Coagulation
factors

Osteocalcin
ucOc → cOc

Calcium ↓

Calcium ↑

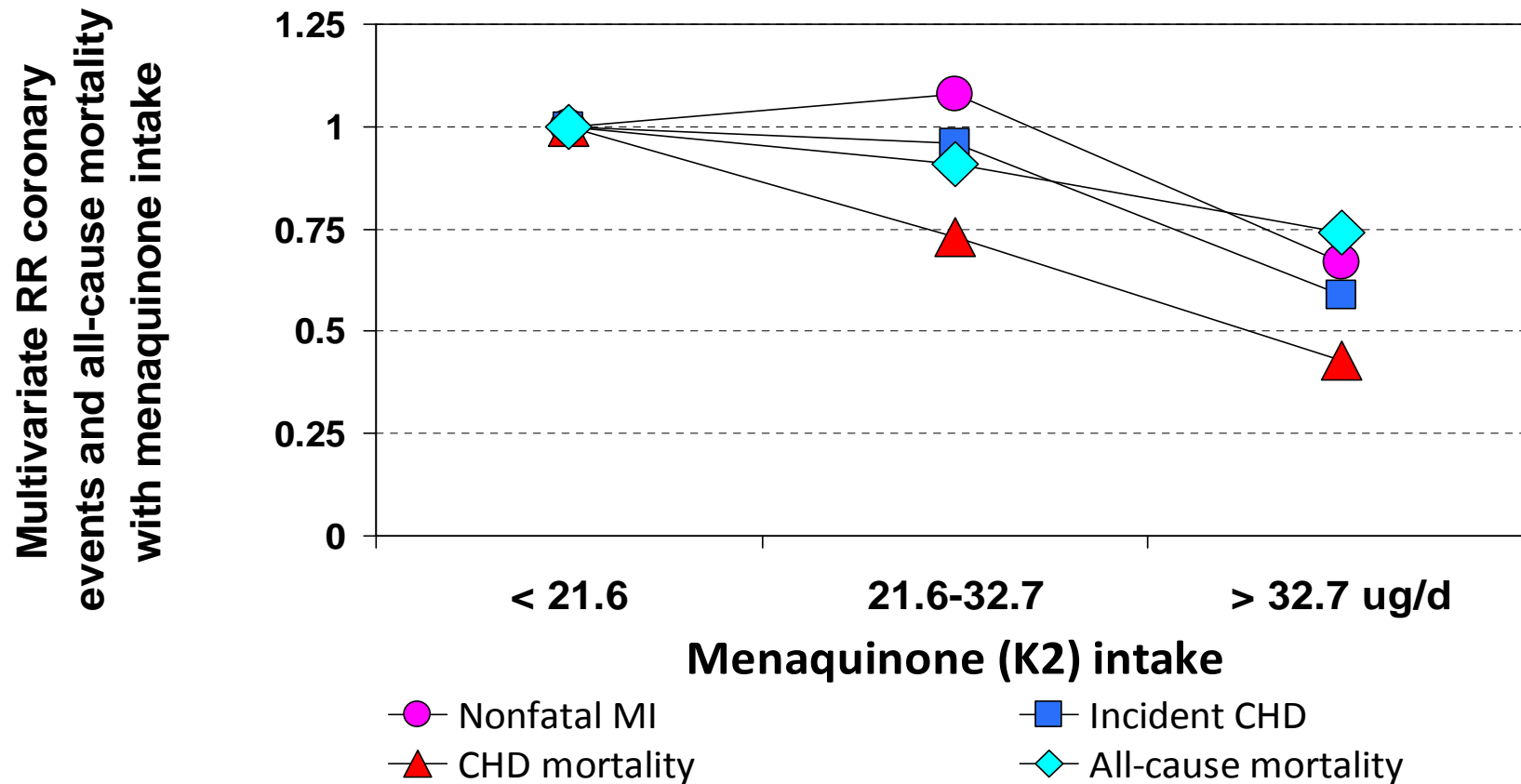
**Inhibition of vascular
calcification**

**Promotion of bone
mineralization**

Vitamin K and vascular calcification

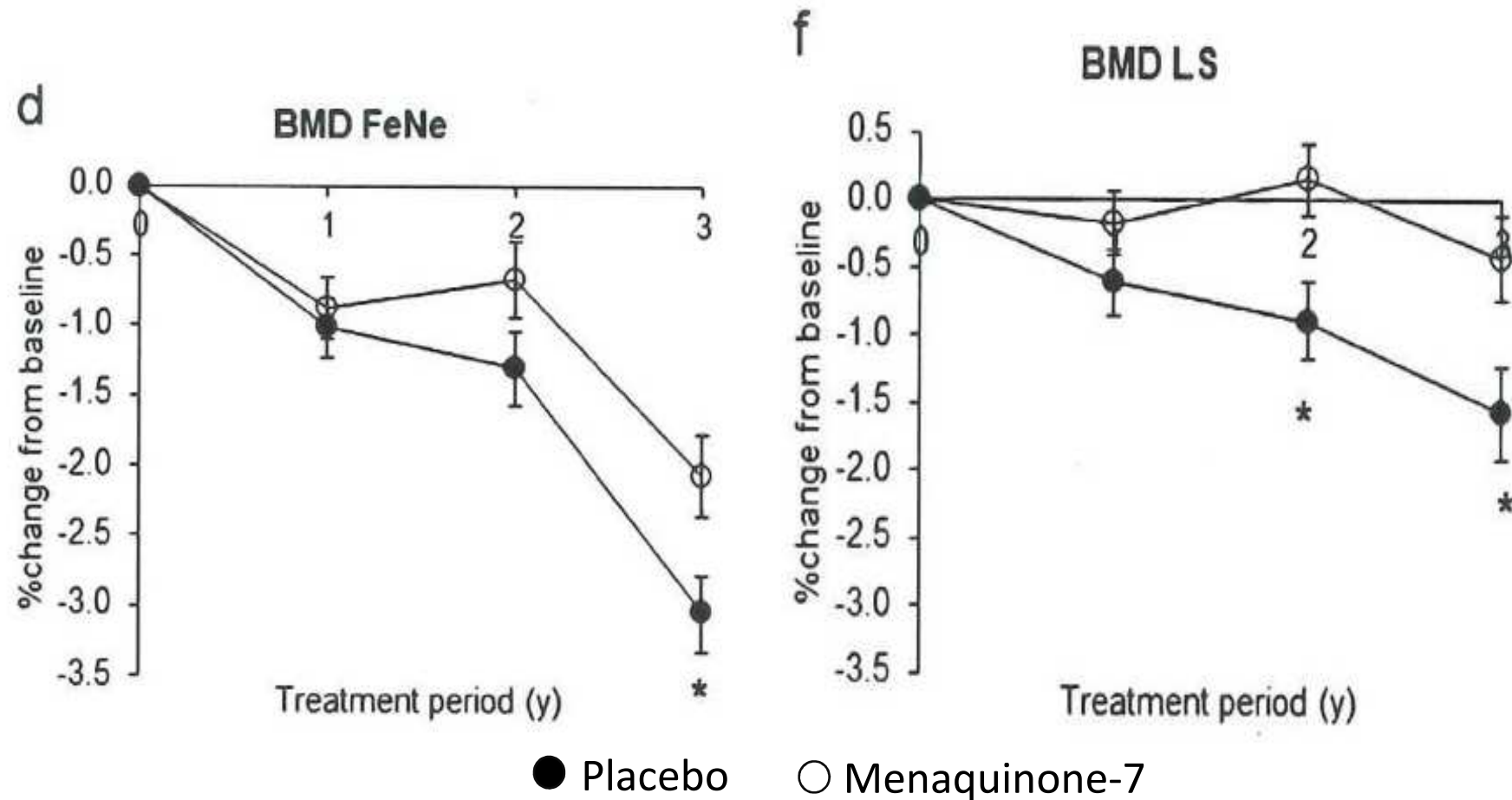
Rotterdam Study: population-based, assessment of disease occurrence, 7983 subjects ≥ 55 yrs., **4807 with dietary data & without MI, F/U 7-10 years**

- **Phylloquinone (K1) intake NOT associated** with CV endpoints/mortality



Vitamin K and decreased bone loss

244 healthy post-menopausal women, 3 years placebo vs. menaquinone-7 (capsules), DXA measurements



Vascular calcifications & low bone mass

- clinically relevant pathways

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- Low calcium intake
- Effects of vitamins D and K
- **Drug effects & Lifestyle**

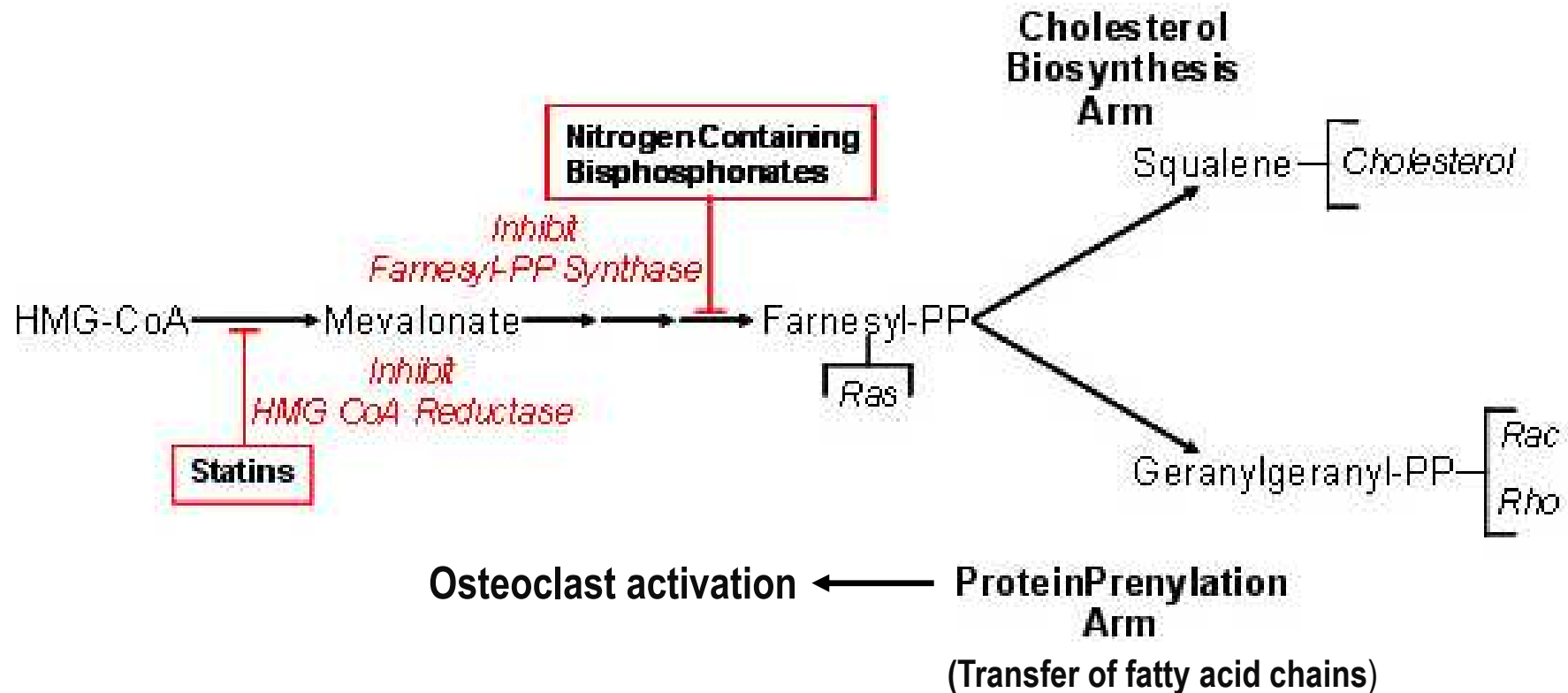
Vascular calcifications & osteoporosis

- Drug effects

Medications effective in osteoporosis *and* CV disease – animal studies

- Statins
- Bisphosphonates
- **Raloxifene** (selective modulator of estrogen receptors)
- **Insulin**

© B. Hess 11/2016 (adapted from Sprini D et al., Clin Cases Min Bone Metabol 11: 117-119, 2014)



Vascular calcifications & osteoporosis

- potential therapeutic approaches

- **Benefits of bisphosphonate use on vascular disease**

- Meta-analysis: ♦ HR for all-cause mortality (48 trials with 43'568 pts.)
0.90 (0.84-0.98, p = 0.01)
- ♦ HR for CV mortality (10 trials with 12'276 pts.)
0.81 (0.64-1.02, p = 0.07)

(Kranenburg G et al, Atherosclerosis 252: 106-115, 2016)

- **The other way round: benefits of statins on bone disease**

- Simvastatin : significant increases in BMD/bone formation markers and reductions in bone resorption markers (106 pts.) vs. no statin (106 pts.)

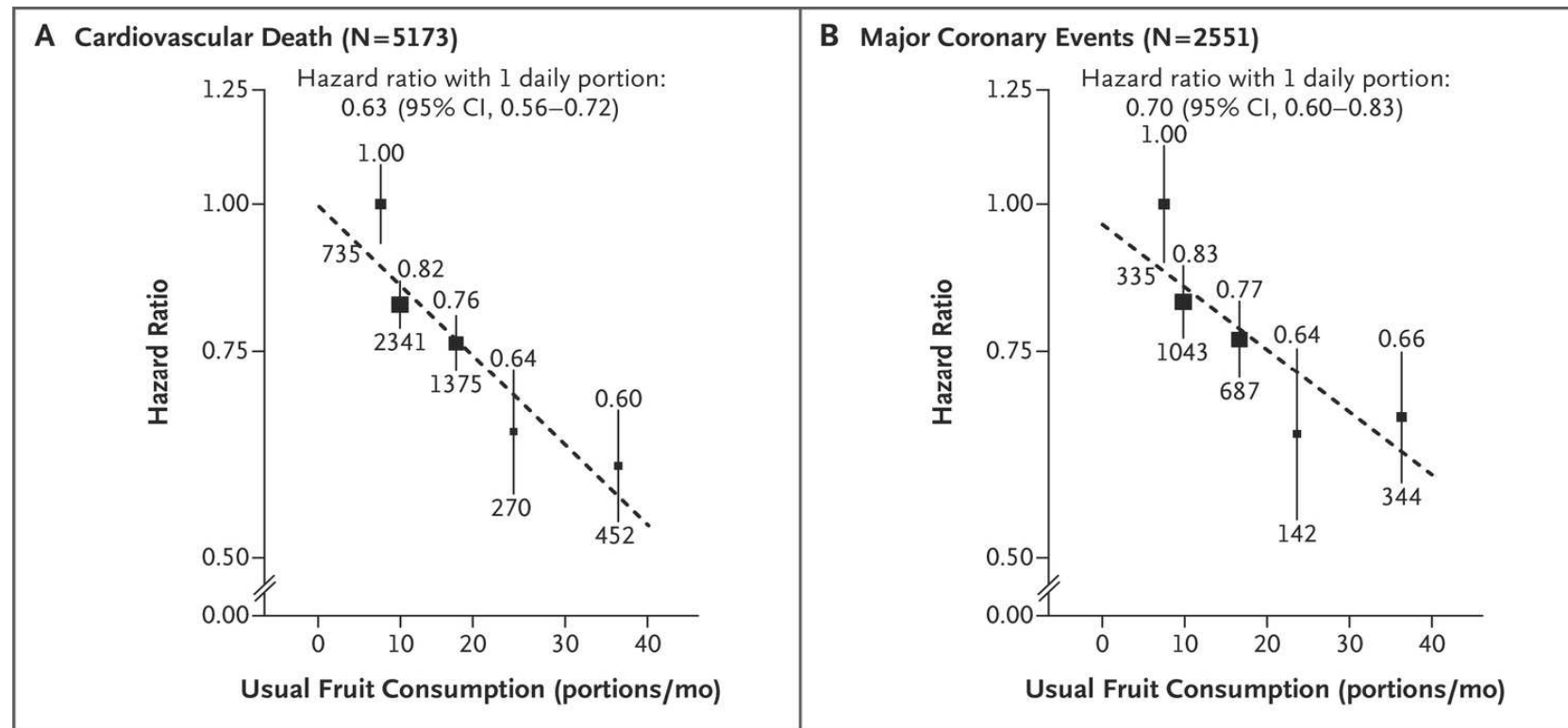
(Chuengsamarn S et al., Bone 46: 1011-1015, 2010)

«Lifestyle» & vascular-bone axis



Lifestyle – Fresh fruit consumption & cardiovascular disease

China Kadoorie Biobank Study: prospective cohort study in 10 regions, 512'891 participants without CV disease or antihypertensive treatment



«...the most commonly consumed fruits in China are **apples (flavonoids !)**, citrus fruit, and pears.»

Gefäss-Knochen-Achse – wie lenkt man Calcium ins «richtige» Organ ?

1. Genügend Calcium and Vitamin D

- ⇒ 1000-1200 mg Calcium/d (NATÜRLICHE Quellen !)
- ⇒ Serum 25-OH-Vitamin D > 75 nmol/l (> 30 ng/ml)



2. Genügend Vitamin K2 (Menaquinone)

- ⇒ Fleisch
- ⇒ Käse und Quark



3. Lifestyle: Früchte/Alkali: «An apple a day....»

4. Wenn medikamentöse Primärprävention : STATIN

- ↓↓ Risiko vs. Aspirin: CV 25% vs. 10%, Mortalität 14% vs. 6%
(Karmali KN et al. JAMA Cardiol 1: 341-349, 2016)
- potentiell positive Knocheneffekte