

Calcium Supplementation: Good for the Bone, Bad for the Heart?



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Disclosures



Boards/Scientific Advisory Committees –

- National Osteoporosis Foundation Trustee and Clinical Director

I have no other disclosures related to this presentation

Objectives



At the conclusion of this presentation, participants should be able to:

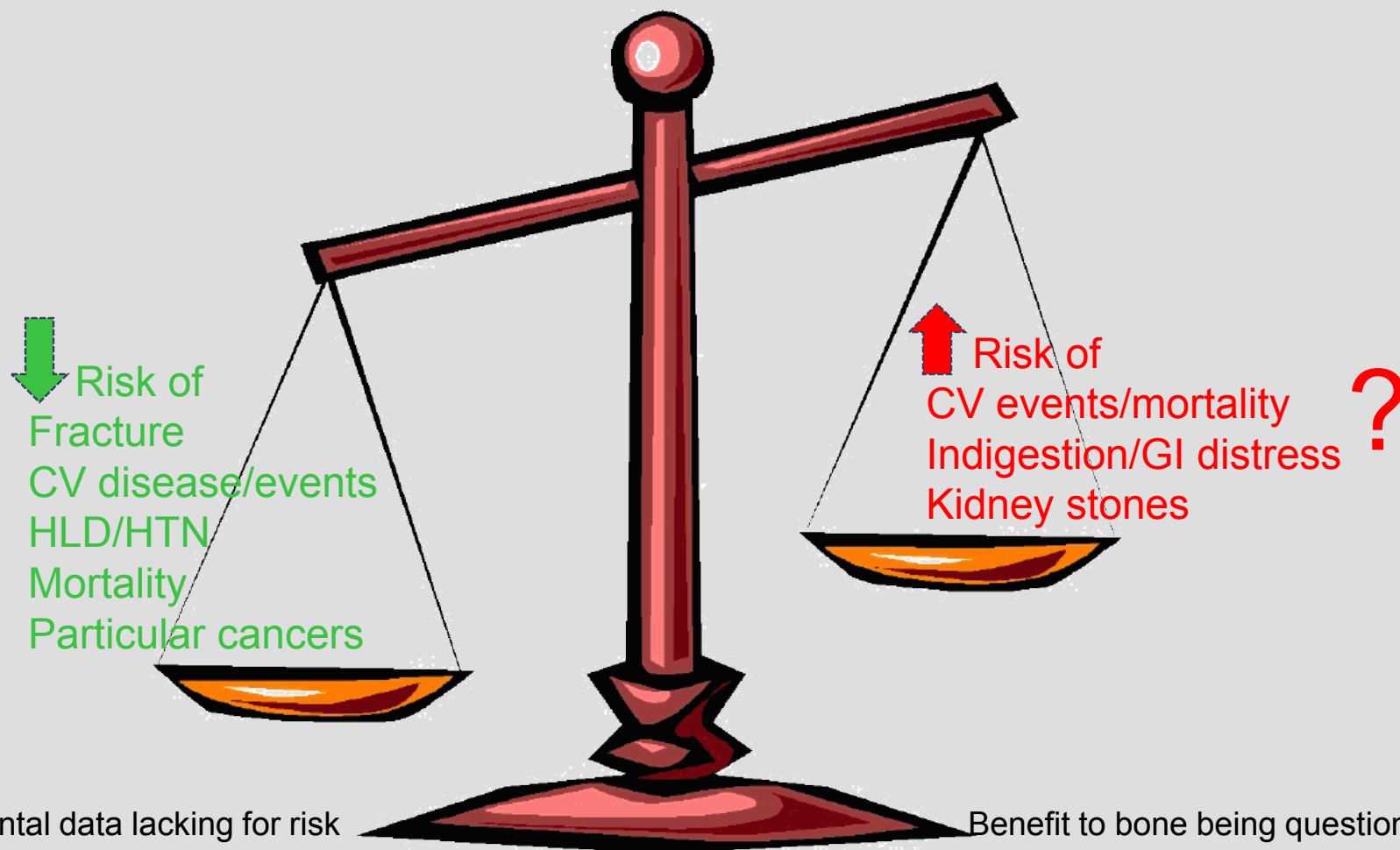
1. Discuss the daily requirements for calcium and vitamin D for bone health
2. Discuss recent controversies regarding calcium and vitamin D supplementation and cardiovascular events
3. Provide evidence-based patient counseling regarding the benefits and risks of calcium and vitamin D for bone health

Background



- Calcium and vitamin D supplementation has been an approved public health intervention to reduce fracture risk.
- Worldwide, many women and men fail to meet the recommended intake of calcium from food sources
 - Calcium is a shortfall nutrient in the diet
- A large number of adults, mostly older women, take calcium supplements to increase total calcium intake
- It is important to better understand the balance of risks and benefits related to calcium supplement use
 - Calcium has been linked to both increased and decreased cardiovascular disease, creating considerable uncertainty

The Controversy: Benefits vs Risks of Calcium Supplements



In The Beginning ...



2008 Studies Suggest Adverse Trend in CV Endpoints

- Vascular Events in Healthy Older Women Receiving Calcium Supplementation: RCT¹
 - MI was more commonly reported in the calcium group than in the placebo group (P=0.01) for self or family reported events.
 - When unreported events were added from the national database of hospital admissions, this was no longer statistically significant
- RCT of Calcium Supplementation in Healthy, Non-osteoporotic, Older Men²
 - “Non-significant, adverse trend” in CV endpoints reported

Effect of Calcium Supplements on Risk of MI and CV Events: Meta-Analysis, 2010³

- Design: Patient level and trial level meta-analyses
- Eligible studies were RCTs of calcium supplements (≥ 500 mg/day), with ≥ 100 subjects, mean age >40 , and study duration >1 year.
- 15 eligible trials included
- **In the 5 studies contributing patient level data, calcium supplementation was associated with 31% increase in MI**
- No significant increase in risk of stroke, death, or composite of MI, stroke, and sudden death
- The meta-analysis of trial level data showed similar results

Study Limitations/Criticisms



- None of the trials had CV outcomes as primary end-points
 - Primary endpoints were related to fracture, BMD, colorectal adenoma
- Inconsistent validation/potential bias in CV event ascertainment
 - >65% of the MIs in the meta-analysis were self-reported.
- Lack of information on and adjustment for known cardiovascular risk determinants
 - Excess of participants at higher risk for cardiac events (males, obese women, those taking oral thyroxine) in the calcium group in the meta-analysis.
- Trials in which no events occurred were not included
- Non-adherence to the analytical protocol, use of non-trial calcium supplements
- Exclusion of calcium plus vitamin D trials

Do self reported data introduce bias?

Adverse Events From Calcium Supplementation: Relationship to Errors in MI Self-Reporting in RCTs of Calcium Supplementation

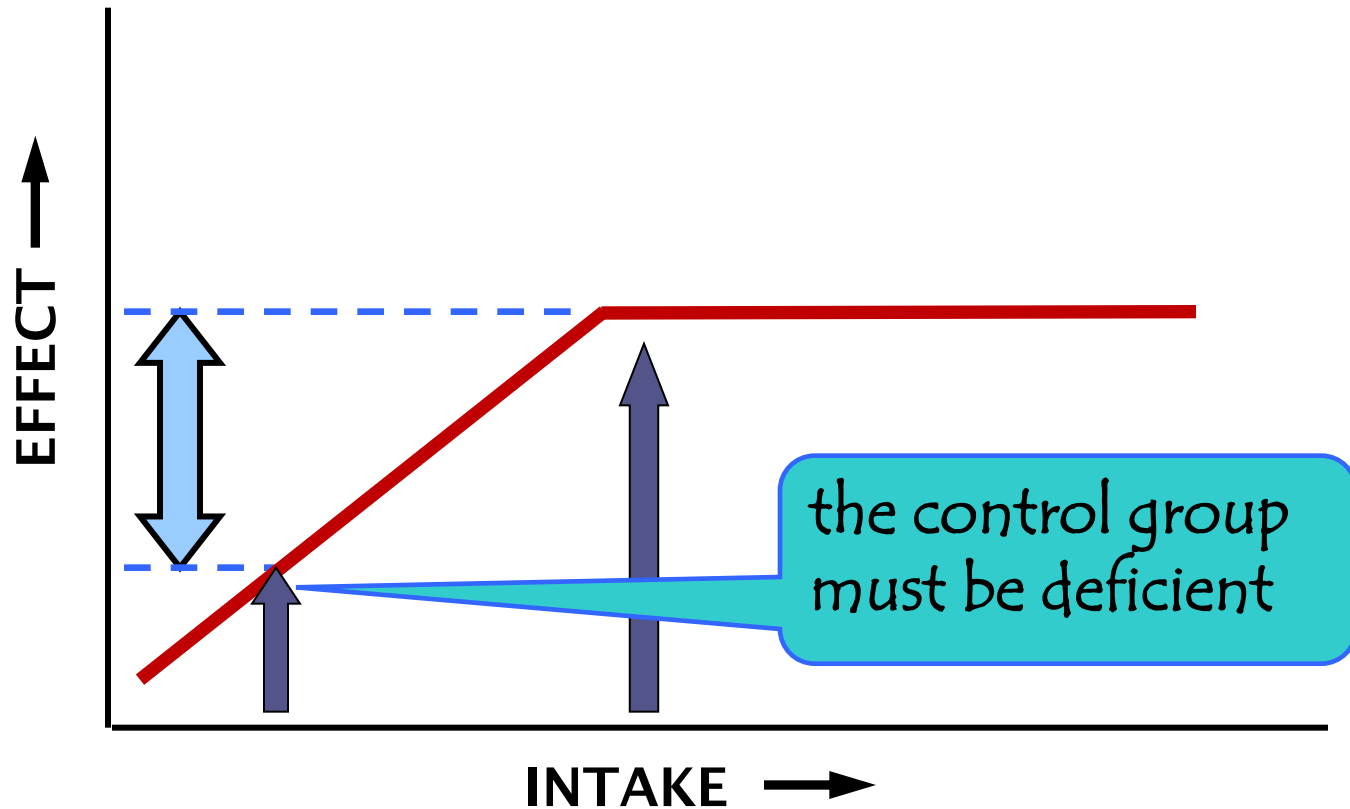
- In 7 RCTs, self-reported GI adverse event rates were more common in participants receiving calcium than placebo.
 - increased pooled RR for GI adverse events = 1.43 (1.28–1.59), $p < 0.001$.
- Patient self-reported and adjudicated MI were available for comparison from two similar RCTs of calcium supplementation
 - Data demonstrated an excess of self-reported MIs in the calcium treated patients RR 1.69 (1.09–2.61), $p = 0.020$.
 - However, after adjudication:
 - ✦ more events were found to be incorrectly classified in the calcium group than the placebo group resulting in a RR of misreported MI of 2.44 (1.02–5.87), $p = 0.046$
 - ✦ the rate of adjudicated MI was not increased in the calcium-treated patients compared with placebo RR 1.45 (0.88–2.45), $p = 0.145$.
- Combined data suggest that calcium supplements increase functional GI events, which may be mistaken by participants as MI leading to reporting bias

How do we evaluate the evidence?

Threshold Nutrients and Study Design



When baseline intakes are low, significant effects are more likely



Critical Evaluation: The Science and Strength of Evidence



- The effect of calcium (diet or supplement) on chronic disease risk is difficult to determine
 - Osteoporosis and CVD are long latency diseases
 - Single nutrient effects are small
 - Studies on the benefit or risk of supplements are relatively short compared to development of the disease
 - Studies are rarely designed as a dose response trial
 - Methods for assessing intake are weak
 - Studies rarely use background nutrient intake or status as an exclusion criteria
 - ✦ Many participants may be above the threshold for effect
 - Poor compliance in RCTs

Austin Bradford Hill Criteria to Validate the Cause of a Disease



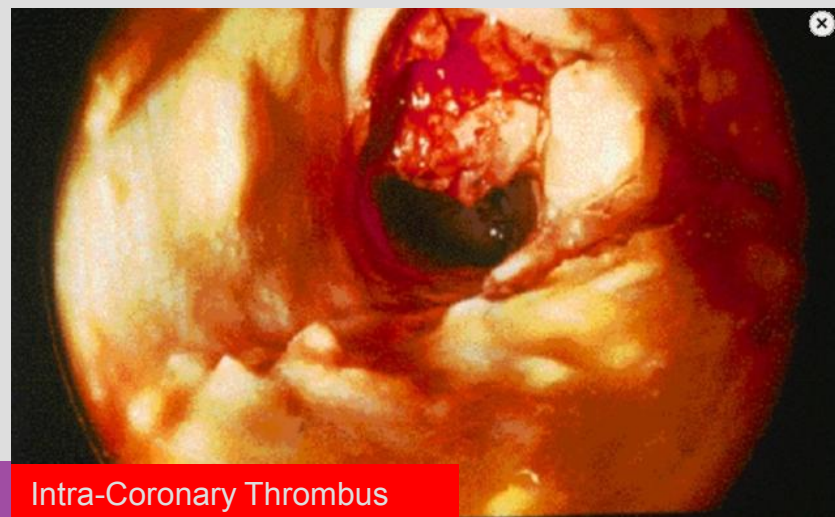
The evidence should:

- Be strong
- Reflect a biological gradient, i.e. a dose–response relationship
- Be found consistently
- Hold over time, i.e. the temporal incidence of the disease should reflect the prevalence of the offending agent in society.
- Be biologically plausible, i.e. demonstrate/support an underlying mechanism
- Preferably be confirmed by experiment

What is the Role of Calcium in Coronary Artery Disease (CAD) ?



- What causes coronary artery disease ?
- Why does calcium get deposited in coronary arteries ?
- What is the role of calcium in coronary artery plaque ?
- Does calcium cause CAD ?
- Does increased calcium intake lead to CAC ?
- Does increased calcium intake lead to CAD ?

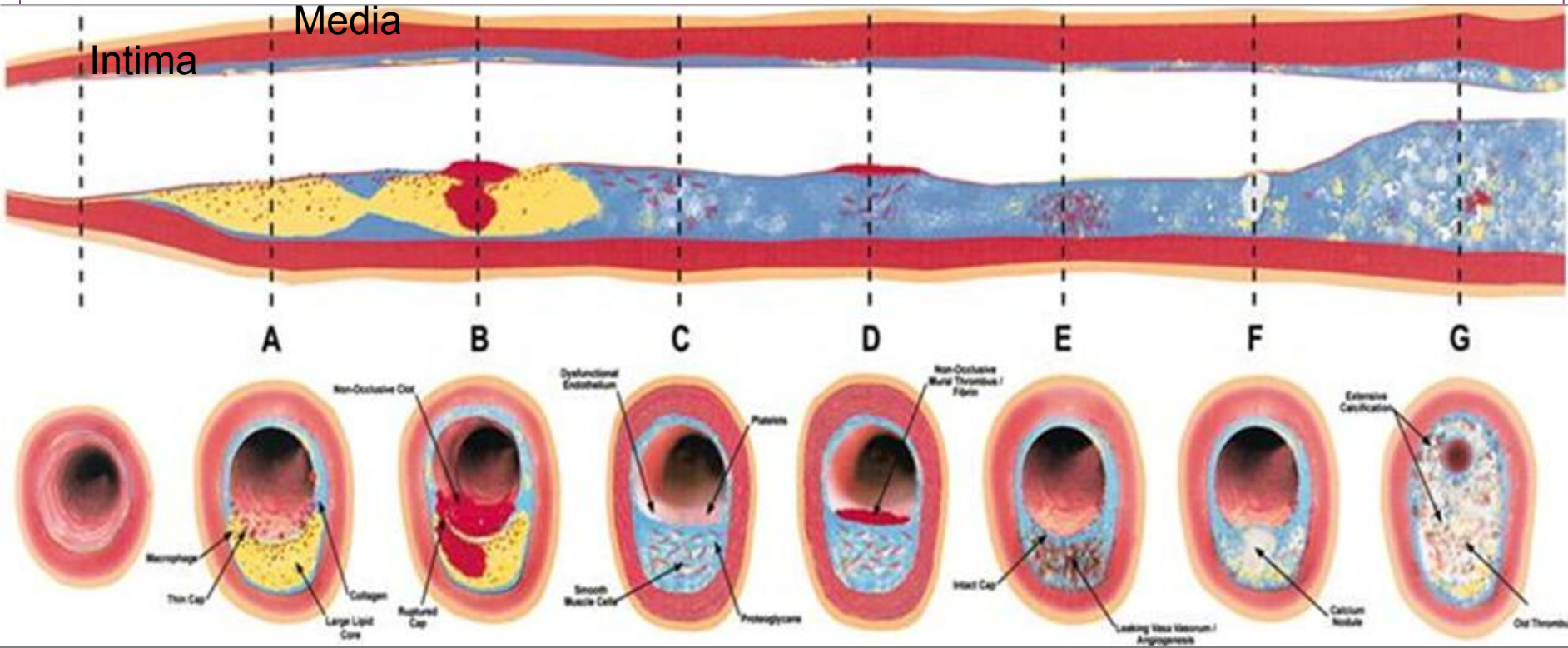


Intra-Coronary Thrombus

Normal

Plaque Rupture

Calcium Deposition



Intimal Injury-
Plaque
Formation

Intra-Plaque
Hemorrhage

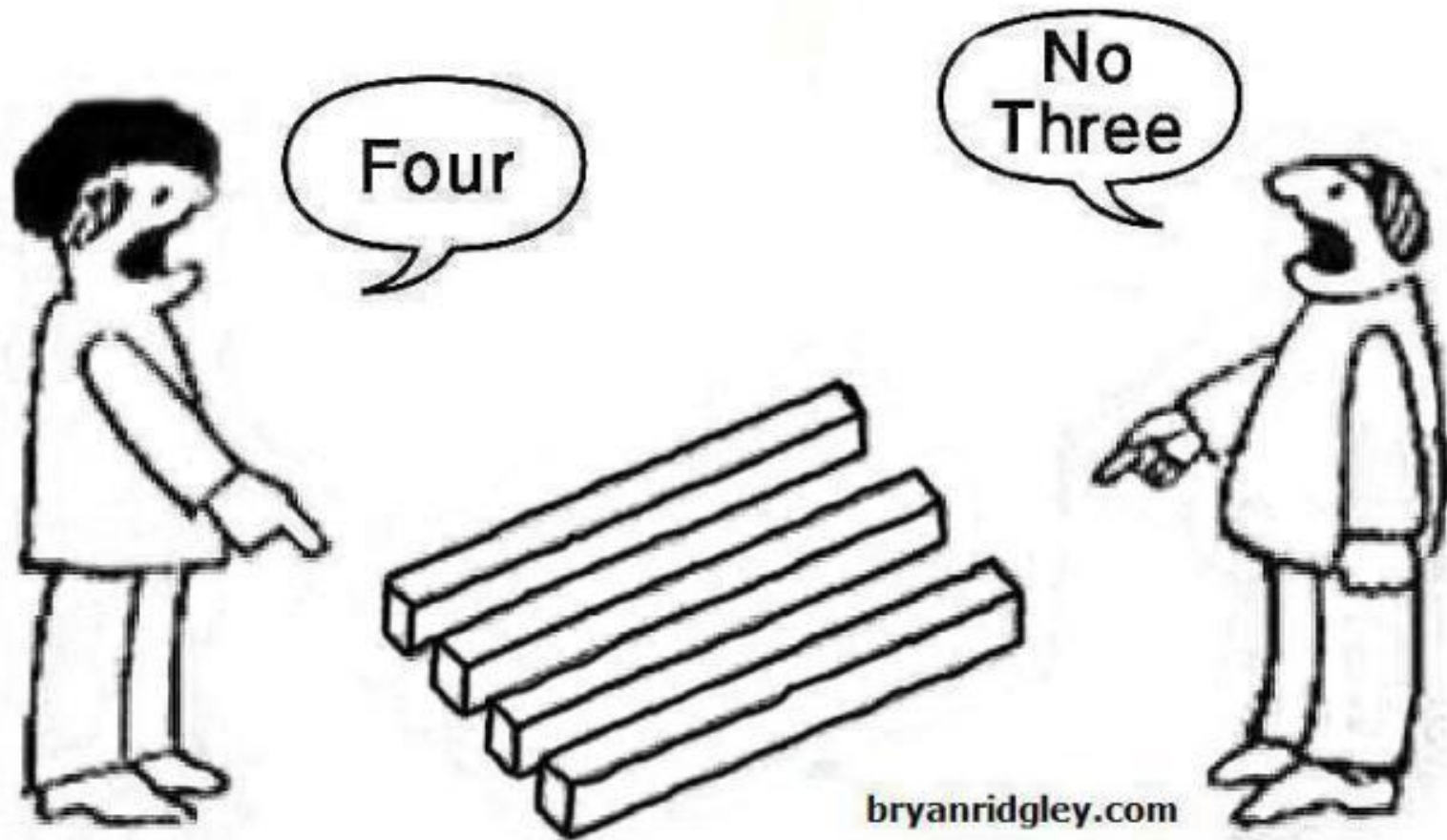
Calcification is
response, not cause

Recent Publications



CALCIUM SUPPLEMENTATION AND CARDIOVASCULAR RISK 2012-PRESENT

Reality can be so complex that equally valid observations from differing perspectives can appear to be contradictory.



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Heidelberg Cohort of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Heidelberg)



- Observational cohort study (N = 23,980)
- Aim: To prospectively evaluate the associations of dietary calcium intake and calcium supplementation with MI, stroke risk, and overall CVD mortality.
- Collection of extensive food intake data as well as calcium supplement use. Exact calcium supplement dosages, formulations, and salt forms were not reported for most patients.
- Data on 354 MI cases, 260 stroke cases, and 267 CVD deaths were documented over an 11-year period.
- CV events reported by participants or their next of kin in follow-up surveys.
- **Results: Calcium supplement users experienced a statistically significant increase in MI risk when compared with those who did not use any supplements.**
- Hazard ratio 1.86 with a 95% confidence interval of 1.17-2.96.
- No statistically significant association was found between calcium supplementation and either stroke risk or overall CVD mortality.

Long Term Calcium Intake and Rates of all Cause and Cardiovascular Mortality



- Prospective longitudinal cohort study (N = 61,433 women)
- Swedish mammography cohort, followed for median of 19 years
- Aim: To investigate the association between long term intake of dietary and supplemental calcium and death from all causes and CVD
- Diet was assessed by food frequency questionnaires. Total calcium intake was the sum of dietary and supplemental calcium.
- **The risk patterns with dietary calcium intake were non-linear, with higher rates concentrated around the highest intakes (≥ 1400 mg/day).**
- **Compared with intakes of 600-1000 mg/day, intakes > 1400 mg/day were associated with higher death rates from:**
 - all causes (hazard ratio 1.40, 95% confidence interval 1.17 - 1.67)
 - cardiovascular disease (1.49, 1.09 - 2.02)
 - ischemic heart disease (2.14, 1.48 - 3.09)
 - but not from stroke (0.73, 0.33 - 1.65).

National Institutes of Health-AARP Diet and Health Study



- Prospective trial, enrolled 388,229 men and women.
- Participants recorded their daily food composition and intake over 1 year, including use of multivitamins, calcium-containing antacids, and calcium supplements.
- Mean follow-up - 12 years
- 7904 CVD deaths reported in men and 3874 reported in women.
- After adjusting for CVD risk factors, supplemental calcium (1000 mg daily vs no calcium supplementation) was associated with a 19% increase in CVD death, including heart disease death, in men but not in women.
- Cerebrovascular mortality was not increased with calcium supplements in either men or woman.
- **High intake of supplemental calcium, *not* dietary calcium, was associated with the excess risk for CVD death in men.**

Health Risks and Benefits from Calcium and Vitamin D Supplementation: WHI Clinical Trial (CT) and Cohort Study



- Double-blind RCT (N=36,282 postmenopausal women)
- Aim: To test whether calcium plus vitamin D supplementation would reduce hip fracture, and secondarily, total fracture and colorectal cancer.
- 1000 mg elemental calcium carbonate plus 400 IU vitamin D₃ daily or placebo
- Average intervention period 7 years
- Among women not taking personal supplements at baseline, the hazard ratio [HR] for hip fracture occurrence in the CT following ≥ 5 years of supplementation versus placebo was 0.62 (95 % CI, 0.38–1.00).
- In combined analyses of CT and OS data, HR for hip fractures = 0.65 (95% CI 0.44-0.98)
- **No apparent risk of MI, CHD, CVA, overall cardiovascular disease, total mortality.**

Calcium plus Vitamin D Supplementation from the WHI CaD Trial and Observational Study: Cardiovascular Diseases



Years since CaD initiation	CaD trial				Observational study		Combined trial and OS			
	All participants		No personal supplements ^a		HR	95 % CI	All participants		No personal supplements ^a	
	HR	95 % CI	HR	95 % CI			HR	95 % CI	HR	95 % CI
Myocardial infarction										
<2	1.19	0.89,1.59	1.30	0.86,1.97	0.56	0.14,2.27	1.15	0.87,1.51	1.21	0.82,1.78
2-5	0.97	0.78,1.21	1.04	0.74,1.47	1.04	0.66,1.63	1.00	0.82,1.23	1.11	0.82,1.49
>5	1.01	0.80,1.29	1.06	0.74,1.50	0.89	0.73,1.08	1.00	0.80,1.24	1.05	0.78,1.41
Trend test ^b	0.46		0.49		0.94		0.49		0.54	
HR in OS/HR in trial ^c							0.90	0.69,1.18	0.85	0.61,1.18
Overall HR ^d	1.03	0.90, 1.19	1.11	0.90, 1.37	0.90	0.75, 1.09				
Total cardiovascular disease^b										
<2	0.97	0.85,1.11	1.02	0.84,1.23	0.87	0.55,1.35	0.97	0.86,1.10	1.02	0.85,1.21
2-5	0.99	0.89,1.10	1.03	0.89,1.21	0.91	0.74,1.11	1.01	0.92,1.10	1.04	0.91,1.19
>5	1.05	0.93,1.18	1.02	0.86,1.21	0.86	0.79,0.94	1.02	0.93,1.13	1.01	0.88,1.16
Trend test ^b	0.37		0.97		0.84		0.42		0.93	
HR in OS/HR in Trial ^c							0.85	0.75,0.96	0.85	0.73,0.99
Overall HR ^d	1.00	0.94, 1.07	1.03	0.93, 1.13	0.86	0.79, 0.94				

Dietary and Supplemental Calcium Intake and the Risk of Mortality in Older Men: the MrOS Study.



- Prospective cohort study (N=5967 men, age >65)
- Aim: to assess rates of dietary calcium intake, use of supplements, and mortality
- Extensive food surveys at baseline to assess dietary calcium. Supplementation assessed by pill count.
- Mean dietary calcium intake was 1142 ± 590 mg/day
- 65% of participants reported use of calcium supplements.
- Follow-up: 10 years

- **Total calcium intake, use of calcium supplements and the combination of high dietary calcium intake and supplement use were not associated with total or cardiovascular mortality.**

Dietary and Supplemental Calcium Intake and the Risk of Mortality in Older Men: the MrOS Study



ATTACHMENTS

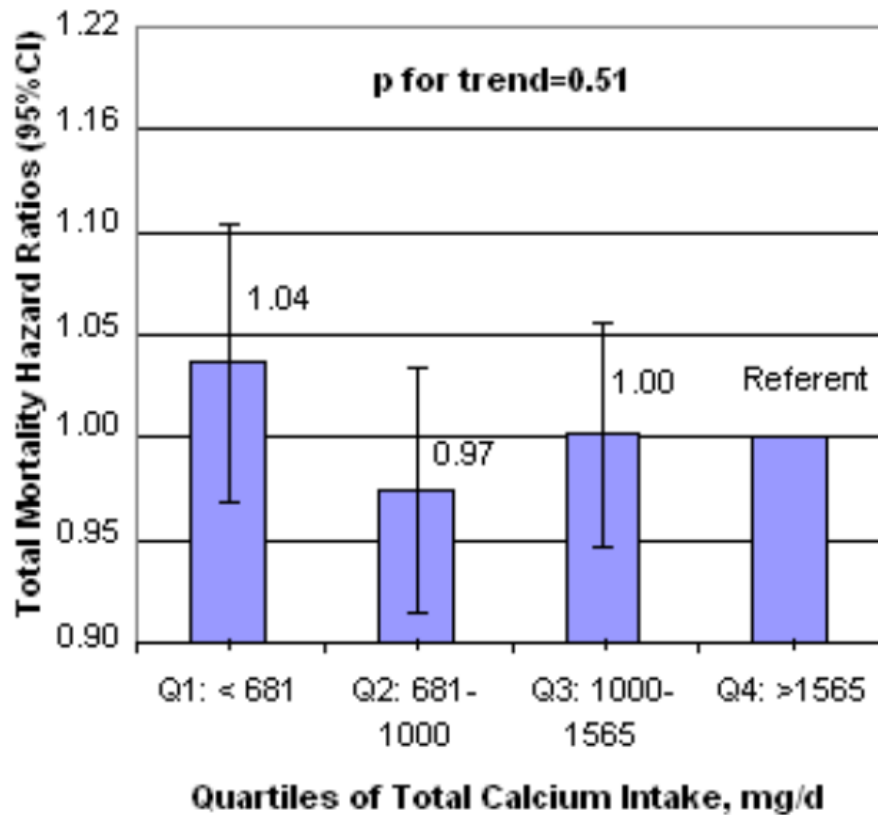


Figure. Adjusted total mortality by quartile of total calcium intake (dietary plus supplements).

- **The highest mortality for CVD was seen in the quartile with the lowest intake from calcium supplementation**
- Adjustment was made for age, energy intake, and calcium use as well as other confounding factors

Calcium Intake and Serum Concentration in Relation to Risk of Cardiovascular Death in NHANES III

- Nationally representative data for 20,024 men and women
- Dietary calcium intake and calcium supplement use were not associated with an increased risk of cardiovascular death**

	Hazard Ratios and 95% Confidence Intervals (CI) for Death due to:				P for interaction	
	MEN		WOMEN		Any CVD (ICD10: I00-I99)	IHD (ICD10: I20-I25)
	Any CVD (ICD10: I00-I99)	IHD (ICD10: I20-I25)	Any CVD (ICD10: I00-I99)	IHD (ICD10: I20-I25)		
Ionized serum calcium¹, mmol/L						
<1.16	1.85 (1.14–3.01)	2.32 (1.39–3.88)	1.23 (0.72–2.08)	1.53 (0.69–3.39)		
1.16–1.31	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	0.637	0.306
1.31+	0.93 (0.55–1.57)	0.87 (0.46–1.67)	1.33 (0.88–1.99)	1.72 (1.13–2.61)		
Dietary calcium intake² (SE), mg						
<500	1.23 (0.79–1.90)	1.13 (0.66–1.96)	0.86 (0.58–1.28)	1.13 (0.57–2.21)		
500–1000	1.06 (0.81–1.40)	0.99 (0.66–1.47)	0.86 (0.59–1.26)	1.03 (0.53–1.99)		
1000–1300	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	0.025	0.525
>1300	0.78 (0.50–1.22)	0.60 (0.28–1.31)	1.10 (0.61–1.97)	0.96 (0.43–2.15)		
Calcium supplement users² (versus no supplements)	0.81 (0.54–1.22)	0.78 (0.47–1.29)	0.85 (0.64–1.12)	0.98 (0.70–1.36)	0.580	0.403
Daily supplemental calcium intake², mg						
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	0.555	0.439
0–1000	0.78 (0.50–1.21)	0.75 (0.43–1.32)	0.90 (0.69–1.19)	1.07 (0.79–1.45)		
1000–2000	0.89 (0.32–2.45)	1.01 (0.32–3.22)	0.65 (0.33–1.30)	0.67 (0.29–1.53)		
≥2000	1.44 (0.37–5.66)	0.91 (0.13–6.67)	0.82 (0.54–1.25)	0.93 (0.38–2.28)		
Total daily calcium intake², mg						
<500	1.25 (0.79–1.97)	1.05 (0.61–1.82)	1.23 (0.86–1.74)	1.41 (0.83–2.39)	0.102	0.589
500–1000	1.14 (0.83–1.57)	1.03 (0.68–1.56)	1.01 (0.69–1.47)	1.20 (0.67–2.14)		
1000–1300	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)		
1300–2000	0.81 (0.52–1.26)	0.49 (0.25–0.98)	0.85 (0.49–1.47)	0.73 (0.35–1.52)		
>2000	1.01 (0.44–2.29)	0.98 (0.34–2.85)	0.84 (0.44–1.62)	0.92 (0.32–2.62)		

¹Adjusted for: age, race/ethnicity, poverty to income ratio, comorbidity index, serum vitamin D, alcohol consumption, smoking behaviour, vigorous physical activity, and BMI.

²Adjusted for: age, race/ethnicity, poverty to income ratio, comorbidity index, serum vitamin D, alcohol consumption, smoking behaviour, vigorous physical activity, total energy intake, and BMI.

doi:10.1371/journal.pone.0061037.t003

Calcium Supplement Intake and Risk of Cardiovascular Disease in Women



- Prospective cohort study of supplemental calcium use and incident CVD
- 74,245 women in the Nurses' Health Study (1984–2008) free of CVD and cancer at baseline.
- Calcium supplement intake assessed every 4 years.
- Outcomes: incident CHD and stroke, confirmed by medical record review.
- **After multivariable adjustment for age, BMI, dietary calcium, vitamin D intake, and other CVD risk factors, the RR for women taking >1000 mg/day calcium compared with none was:**
 - **0.82 (95 % CI 0.74 to 0.92; $p < 0.001$) for CVD**
 - **0.71 (0.61 to 0.83; $p < 0.001$) for CHD**
 - **1.03 (0.87 to 1.21; $p = 0.61$) for stroke.**
- The RR were similar in analyses limited to non-smokers, women without hypertension, and women who had regular physical exams.

2016 ASBMR Annual Meeting Abstracts



- All found no significant effect of calcium supplementation on risk of CVD
- **Calcium and/ or Vitamin D Supplementation are not Associated with Ischaemic Heart Disease: Findings from the UK Biobank Cohort** Harvey N, et al. JBMR 31(1), #1108
- **Calcium plus Vitamin D supplementation, fracture, and cardiovascular outcomes: A Bayesian meta-analysis** Frost S, et al. JBMR 31(1), #1008
- **Cardiovascular disease and calcium supplementation: a cross-sectional study of primary care in South Brazil** Godinho R, et al. JBMR 31(1), #SA0248
- **Dietary Calcium Intake and Cardiovascular Health: Is there any relationship?** Das S, et al. JBMR 31(1), #SA0373
- **Dietary Calcium Intake and Vascular Markers in Healthy Postmenopausal Women** Ong A, et al. JBMR 31(1), #SA0249

Experimental Models

Experimental Models



- **Animal Models and Methodology**
 - Advantage: Directly assess causal relationships by feeding protocols sufficiently long to develop disease
 - Disadvantages:
 - ✦ Different pathogenesis of coronary disease vs humans
 - ✦ Methodological barrier in that advanced calcification necessary in order to detect via usual imaging and histology
 - Recent study used both new approach for measuring early calcium accumulation & new model that better represents human pathogenesis

Impact of High Calcium Intake from Calcium Carbonate or Dairy on Cardiovascular Function and the Progression of CAD in Ossabaw Miniature Swine

- Ossabaw miniature swine mimic human metabolic syndrome and CAD on an atherogenic diet
- Aim: To examine the impact of high dietary calcium from supplement (calcium carbonate) or dairy (non-fat dry milk) on cardiovascular function, vascular calcification and the progression of CAD.
- Pigs (n=24) were fed an atherogenic diet and randomized to control calcium (0.5%Ca by weight), high calcium from calcium carbonate (2%Ca), or high calcium from dairy (2%Ca) diets.



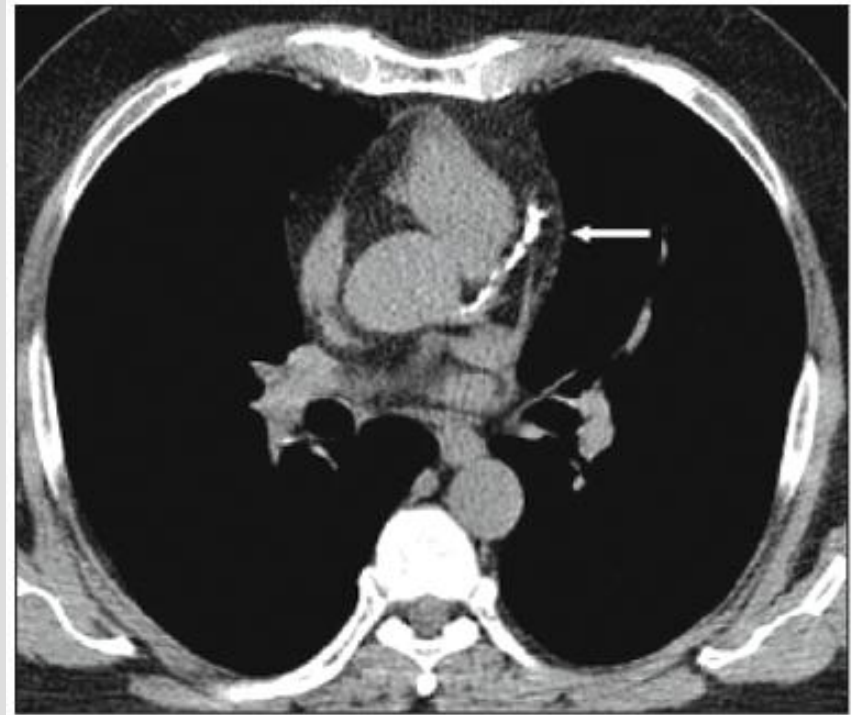
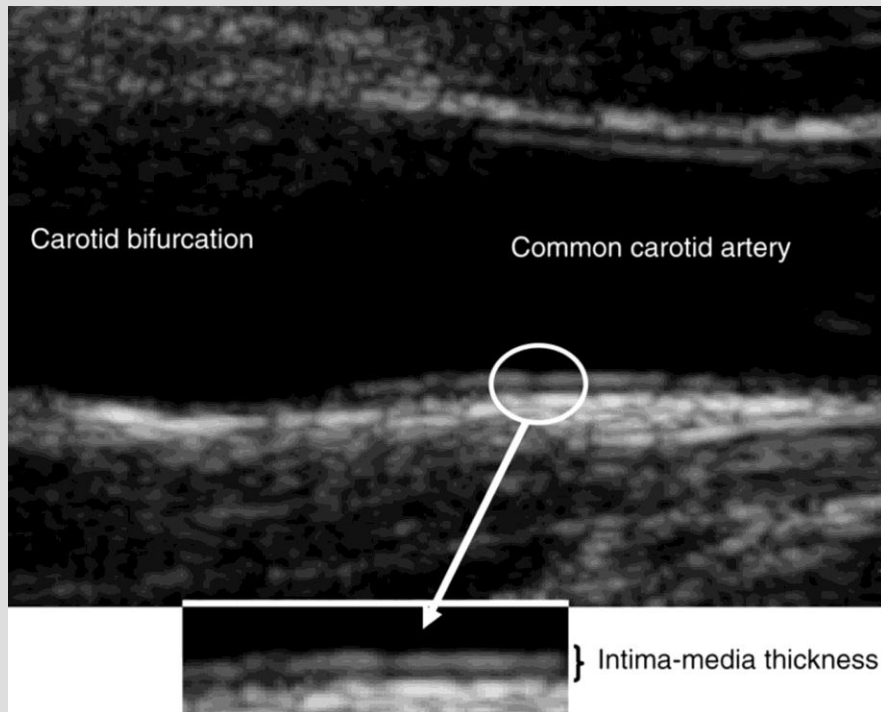
Impact of High Calcium Intake from Calcium Carbonate or Dairy on Cardiovascular Function and the Progression of CAD in Ossabaw Miniature Swine



High calcium feeding from either source had **no influence** on:

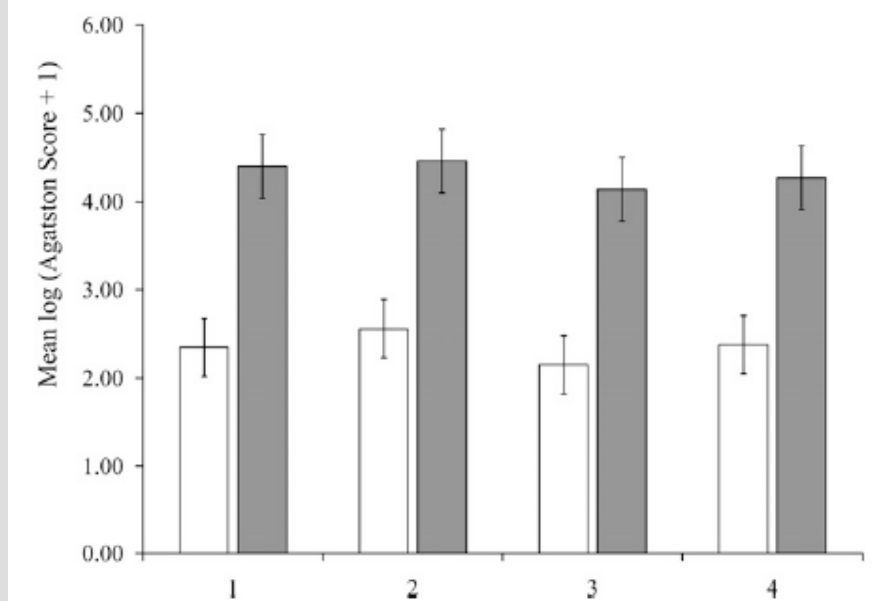
- Cardiovascular function
 - ✦ Stroke Volume or Ejection Fraction by CT
 - ✦ Endothelial and VSM cell function by *In Vitro* Wire Myography
- Coronary artery disease burden
 - ✦ Plaque wall coverage by Intravascular Ultrasound
 - ✦ Plaque coverage by Histopathology
- Coronary artery calcification
 - ✦ Calcified lesion presence by Histopathology
 - ✦ CAC scores by Computed Tomography
 - ✦ ^{41}Ca tracer accumulation and calcium movement from blood to coronary arteries

Calcium Supplementation and Surrogate Measurements of Cardiovascular Risk

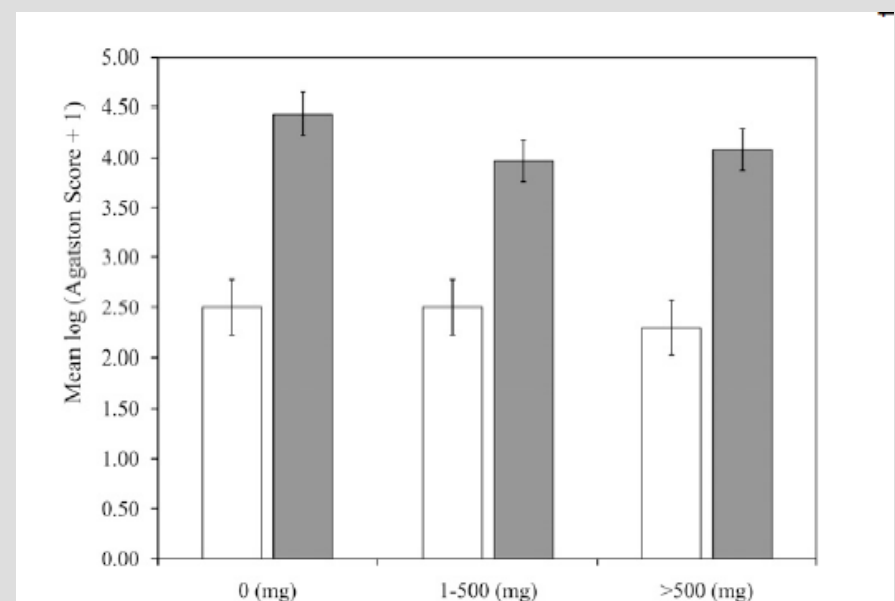


Measures of atherosclerosis that predicts risk of ischemic heart disease independent of other risk factors.

Calcium Intake is not Associated with Increased Coronary Artery Calcification: the Framingham Study



Total calcium intake quartile
690 Females
588 Males



Supplemental calcium intake

- **The mean age-adjusted coronary artery calcification (Agatston) score decreased with increasing total calcium intake**
- Trend was not significant after adjustment for age, BMI, smoking, alcohol intake, vitamin D supplement use, energy intake, and menopause status and estrogen use in women

Calcium Supplementation is not Associated with Increased Carotid Artery Intimal Medial Thickness or Atherosclerosis



- 5 year, randomized controlled trial (N = 1460 women) (mean age at baseline 75.2 ± 2.7 years)
- Preplanned ancillary study of 1103 women assessed common carotid artery intimal medial thickness (CCA-IMT) and carotid atherosclerosis at year 3
- 600 mg BID of elemental calcium (calcium carbonate) vs placebo
- Food frequency questionnaires to assess dietary calcium. Compliance assessed by pill count.
- Effects of supplementation were studied before and after adjustment for baseline cardiovascular risk factors
- **In the intention-to-treat analysis, there were no significant differences in either of the two measurements among calcium-treated or placebo-treated women. Results were similar in the per protocol analysis among women who were at least 80% compliant.**

Intention-To-Treat and Per Protocol ANCOVA for CCA-IMT and Atherosclerosis

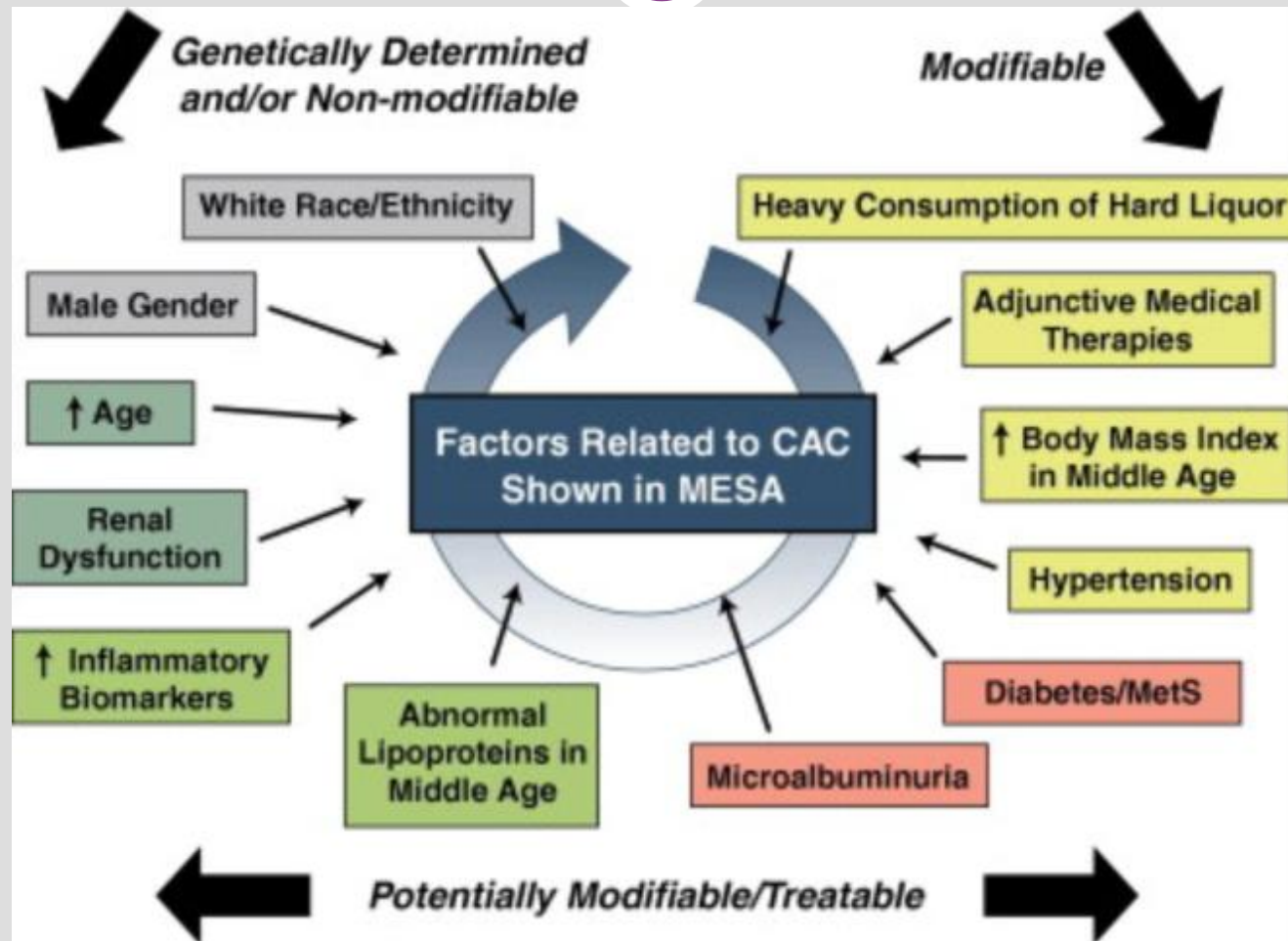


Intention-to-treat analysis	Placebo (n = 550)	Calcium (n = 553)	p Value
Mean CCA-IMT (mm)			
Unadjusted	0.780 (0.770–0.791)	0.779 (0.768–0.790)	0.869
Multivariable adjusted ^a	0.783 (0.772–0.794)	0.778 (0.766–0.789)	0.491
Maximum CCA-IMT (mm)			
Unadjusted	0.925 (0.913–0.938)	0.922 (0.910–0.935)	0.729
Multivariable adjusted ^a	0.929 (0.916–0.942)	0.921 (0.908–0.942)	0.404
Presence of carotid atherosclerosis (odds ratio)			
Unadjusted	1.00	0.80 (0.63–1.02)	0.066
Multivariable adjusted ^a	1.00	0.80 (0.62–1.04)	0.095
Per-protocol analysis	Placebo (n = 353)	Calcium (n = 362)	p Value
Mean CCA-IMT (mm)			
Unadjusted	0.785 (0.772–0.798)	0.778 (0.764–0.790)	0.386
Multivariable adjusted ^a	0.788 (0.774–0.801)	0.776 (0.762–0.789)	0.214
Maximum CCA-IMT (mm)			
Unadjusted	0.932 (0.917–0.948)	0.921 (0.905–0.936)	0.295
Multivariable adjusted ^a	0.935 (0.919–0.951)	0.919 (0.903–0.935)	0.172
Presence of carotid atherosclerosis (odds ratio)			
Unadjusted	1.00	0.73 (0.54–0.97)	0.033
Multivariable adjusted ^a	1.00	0.74 (0.54–1.02)	0.064

All values are mean or odds ratio and (95% CI).

^aMultivariable-adjusted model was adjusted for age, BMI, smoking history, history of atherosclerotic vascular disease, history of diabetes, cardiovascular medications, and estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology equation.

Multi-Ethnic Study of Atherosclerosis (MESA)



Calcium Intake from Diet and Supplements and the Risk of CAC and its Progression Among Older Adults: 10-Year Follow-up of MESA

- Longitudinal cohort study
- 5448 adults without clinically diagnosed CVD
- Baseline total calcium intake assessed from diet (food frequency questionnaire) and supplements (medication inventory), categorized into quintiles
- CAC assessment at baseline and 10 years later
- No BMD measurements
- RR of developing incident CAC over 10 years by quintile:
 - 1 reference
 - 2 0.95 (0.79-1.14)
 - 3 1.02 (0.85-1.23)
 - 4 0.86 (0.69-1.05)
 - 5 0.73 (0.57-0.93)

Calcium Intake from Diet and Supplements and the Risk of CAC and its Progression Among Older Adults: 10-Year Follow-up of MESA

- High total calcium intake was associated with decreased risk of incident atherosclerosis over long-term follow-up, particularly if achieved without supplement use
- Mean calcium intake in quintile 5 was > the upper limits of current recommendations, no increased risk of CAC progression was found, AND the highest quintile actually had decreased risk of incident CAC among those without prevalent CAC at baseline.
- After accounting for total calcium intake, calcium supplement use was associated with increased risk for incident CAC RR=1.22 (1.07-1.39)

Decreased Bone Mineral Density is an Independent Risk Predictor for the Development of Atherosclerosis: A Systematic Review and Meta-Analysis

- 25 studies involving 10,299 patients
- The incidence of ASVD was significantly increased in low BMD patients, compared to patients with normal BMD
 - OR 1.81, 95% CI (1.01-2.19), $p < 0.00001$
- After adjusting for age, sex, BMI, and other vascular risk factors, decreased BMD remained significantly associated with the incidence of ASVD
 - OR 2.96, 95% CI (2.25-3.88), $p < 0.00001$

Recent Publications



**CALCIUM SUPPLEMENTATION
AND
CARDIOVASCULAR RISK:
SYSTEMATIC REVIEWS 2012-
2015**

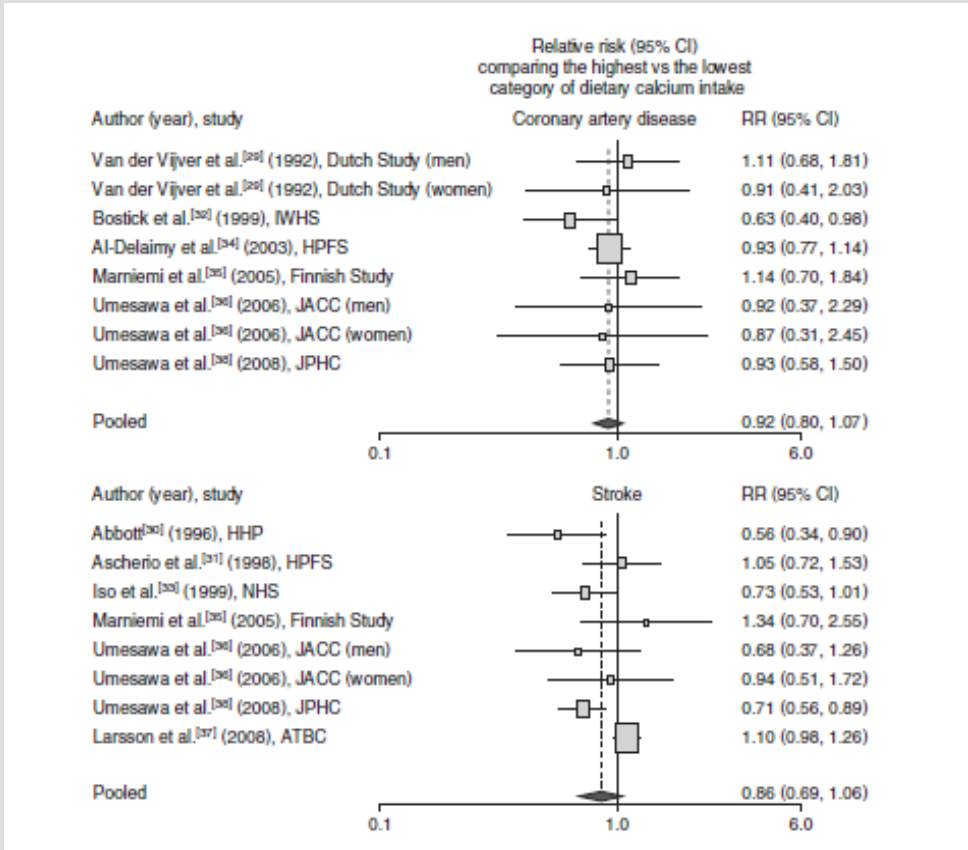
A Review of Calcium Supplements and Cardiovascular Disease Risk

Study	Primary Endpoint(s)	Follow-up	Outcome
Baron 1999	Colorectal adenoma	4 y	No difference in hosp cardiac events
Grant 2005	Fracture	2y-62mo	No difference in death rates
Brazier 2005	BMD	1 y	No difference in CV events
Prince 2006	Fracture	5 y	No difference in CHD
Jackson 2006	CHD & CVD mortality	7 y	No difference in total mortality
Lappe 2007	Fracture	4 y	No diff. in CV events
Hsia 2007	Fracture	7 y	No diff in CV events
Lewis 2011	Fracture	5 y	No diff in death or hosp
Ascherio 1998	Incident stroke	8 y	No difference
Bostick 1999	Ischemic HD mortality	8 y	No difference
Iso 1999	Stroke	14 y	No difference
Al-Delaimy 2003	Incident CHD	12 y	No difference
Pentti 2009	CHD		No difference
LaCroix 2009	CHD & CVD mortality	7 y	No difference
Lewis 2011	ASVD	9.5y (4.5 obs)	No difference
Wolfe 2011	MI	8 y	No difference

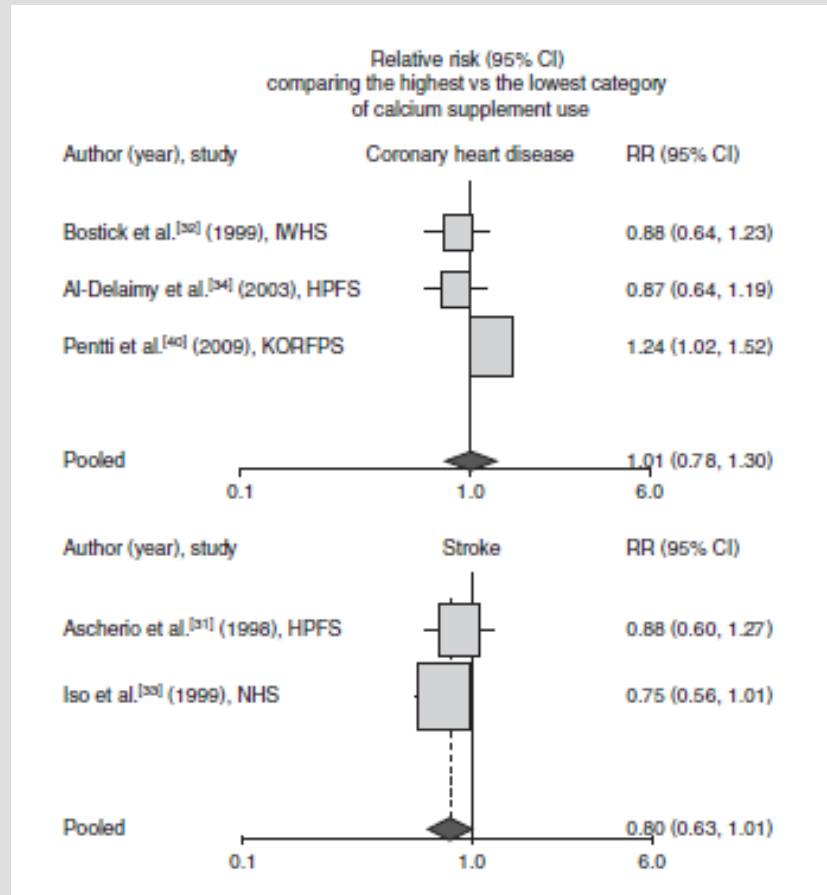
RCTs

Observational Studies

Calcium Intake and Risk of CV Disease: A Review of Prospective Studies and RCTs



Dietary calcium



Supplements

The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials



- Metanalysis of RCTs which compared calcium supplementation with or without vitamin D with placebo or no-treatment control groups
- Aim: to determine if calcium supplements increase all-cause mortality and coronary heart disease (CHD) risk including MI, angina and acute coronary syndrome, and chronic CHD verified by clinical review, hospital record, or death certificate in elderly women
- Mean cohort age >50 years
- Exclusion criteria:
 - Observational trials
 - Trials with a dose lower than 0.5 g of calcium per day
 - Mean cohort age <50
 - Trial duration <1 year
 - Trials where groups differed by factors that may be considered to mediate cardiovascular disease

The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials

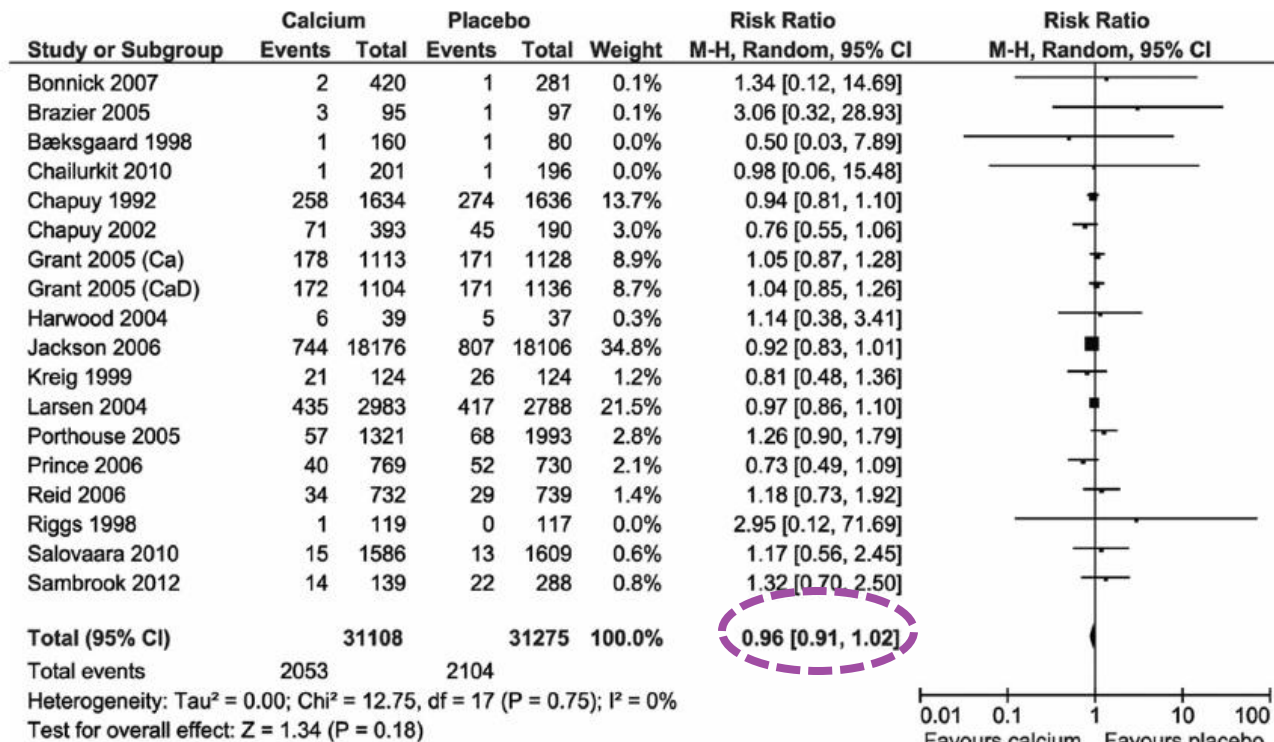


Fig. 3. Random-effects estimates of effect of calcium supplementation with or without vitamin D for the risk of all-cause mortality compared with no calcium. For Grant 2005, events were reported in those who received calcium versus placebo (Ca) and calcium plus vitamin D versus vitamin D only (CaD). M-H = Mantel-Haenszel. This method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.

The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials

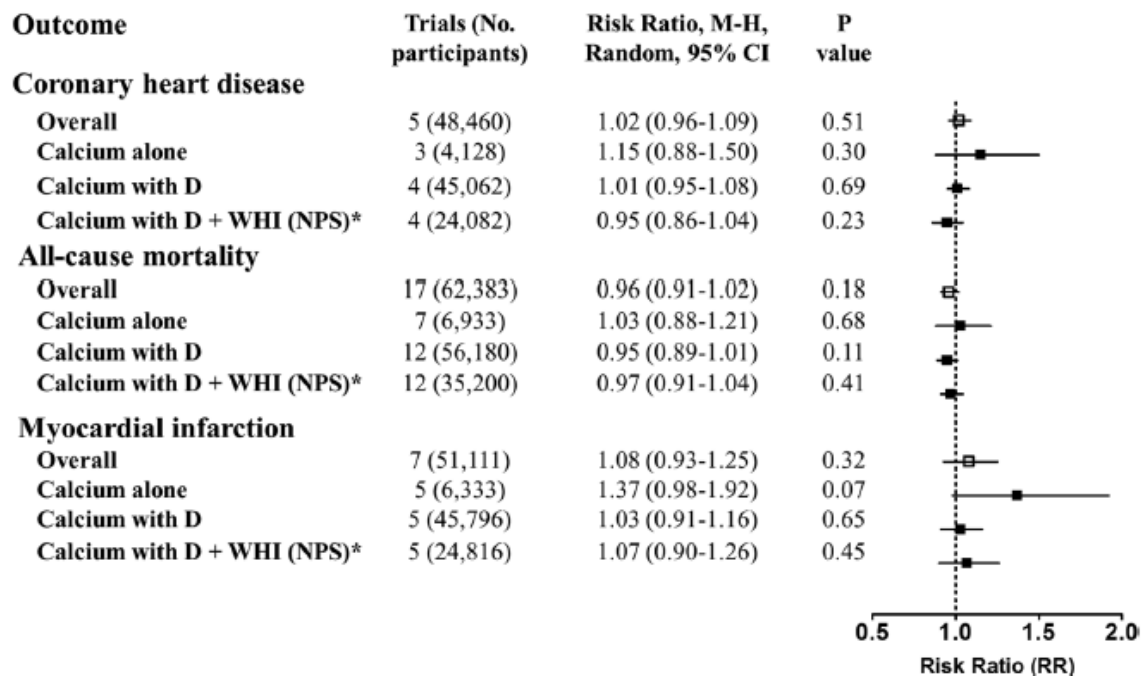


Fig. 5. Sensitivity analyses based on type of supplementation. * Post hoc subgroup analysis of the Women’s Health Initiative (WHI) in participants with no personal supplements at baseline (NPS) using the trial investigators’ internal data set.⁽²⁸⁾ M-H = Mantel-Haenszel. This method estimates the amount of between-study variation by comparing each study’s result with a Mantel-Haenszel fixed-effect meta-analysis result.

Appraisal of the Literature



Validity of Studies: Austin Bradford Hill Criteria for Causal Inference



- Biological plausibility
 - ✦ Little or no evidence of a link between increased calcium intake and the pathophysiological processes which contribute to CV disease
- Strength of association
 - ✦ $RR < 2.0$; considered weak and in a range where chance, bias, and/or confounding cannot be ruled out as explanations
- Biological gradient (dose–response relationship)
 - ✦ No dietary calcium/MI dose–response relationship in most studies
 - ✦ Subset analysis of WHI showed only women *not* taking personal supplements in addition to protocol calcium were at increased risk of CV events
 - removes any suggestion of a dose-response relationship .

Validity of Studies: Austin Bradford Hill Criteria for Causal Inference



- Consistency
 - ✦ Mixed results
 - ✦ 5 of the 11 trial-level studies in the Bolland paper recorded no MI and were therefore not included in the calculation of risk (eliminating 2400 person years on calcium supplements).
 - ✦ Results from prospective, observational studies have generally not favored an association between supplement use and adverse CV outcomes
- Hold over time
 - ✦ No correlation between trends in calcium supplement intake and heart disease
- Preferably confirmed by experiment
 - ✦ No impact of high calcium intake on cardiovascular function and the progression of CAD in Ossabaw swine

Lessons Learned: Randomized Controlled Trials



- True placebo-controlled randomization in a trial of a single, readily available nutrient such as calcium is difficult to achieve.
- Critical biological criteria needed for a RCT to be informative have generally not been met :
 - Use of a single form of the nutrient
 - Use of a low exposure control group
 - Adequacy of dose in the treatment group - the change in intake must be large enough to change nutrient status meaningfully
 - Demonstration/documentation of the change in nutrient status (not just altered intake/exposure), i.e., was a “therapeutic” blood level achieved
 - Optimization/standardization of co-nutrient status
- RCTs are ethically problematic as they require placing subjects at risk (if not of the disease outcome being tested, then of some other outcome)

Lessons Learned: Systematic Reviews



- Critical biological criteria needed for a systematic review to be informative are also difficult to meet
- Included studies must
 - meet the five individual study criteria
 - have the same basal nutrient status
 - use the same change in intake (dose)
 - have the same co-nutrient status
 - use the same form of the nutrient
- Any relaxation of these criteria can bias the result of the review

Combined Effort to Elucidate the Role of Calcium in Cardiovascular Disease

Calcium intake and CV disease risk:
Updated systematic review
and meta-analysis
Tufts University

Position statement :
National Osteoporosis Foundation (NOF) and
American Society for Preventive Cardiology (ASPC)

Calcium intake and CV disease risk: Updated systematic review and meta-analysis



Study Selection:

- Randomized trials and prospective cohort and nested case–control studies with data on dietary or supplemental intake of calcium, with or without vitamin D, and cardiovascular outcomes from 1966 to July 2016.
- 4 randomized and 27 observational studies included.
- Risk of bias was low for RCTs.

Calcium intake and CV disease risk: Updated systematic review and meta-analysis



- RCTs : No statistically significant differences in risks of CVD events/mortality between calcium +/- vitamin D compared to placebo.
- Cohort : No difference in CVD mortality and stroke.

Conclusion :

- No consistent dose-response relationships between total, dietary or supplemental calcium intake levels and CVD mortality
- Dose-response relationships with risks of total stroke or stroke mortality were highly inconsistent

Position statement:

National Osteoporosis Foundation (NOF) and
American Society for Preventive Cardiology (ASPC)



Lack of evidence linking calcium with or without
vitamin D supplementation to cardiovascular
disease in generally healthy adults

- The expert panel considered the findings of the updated evidence report provided by an independent review team at Tufts University.
- Also considered animal/mechanistic study which found no detectable effect of calcium on CAC
- Currently no established biological mechanism to support an association between calcium and cardiovascular disease.
- Official position statement adopted by the Boards of Directors of both societies July 2016.

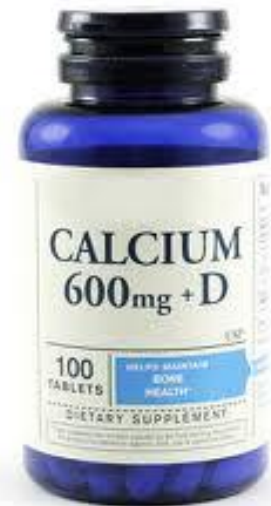
Position statement :

NOF and ASPC



- “There is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults.”
- “In light of the evidence available to date, calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d) should be considered safe from a cardiovascular standpoint.”

What Does This Mean In Clinical Practice?



Position statement : NOF and ASPC



- Obtaining calcium from food sources is preferred.
- Supplemental calcium can be safely used to make up any shortfall in dietary intake.
- Discontinuation of supplemental calcium for safety reasons is not necessary and may be detrimental to bone health in situations where intake from food is suboptimal
- Aim to reach, but not exceed, recommended intakes

Recommended Intake for Calcium



- Calcium intake includes dietary sources plus supplements, preferably in divided doses
 - Women
 - Age 50 & younger 1,000 mg daily
 - Age 51 & older 1,200 mg daily
 - Men
 - Age 70 & younger 1,000 mg daily
 - Age 71 & older 1,200 mg daily



INSTITUTE OF MEDICINE
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Vitamin D intake
recommendations
vary by society

Calcium Calculator



Product	Servings/day	Calcium	Total
Milk (8 oz)		x300	=
Yogurt (6 oz)		x300	=
Cheese (1 oz or 1 cubic inch)		x200	=
Fortified foods/juices		x80-1000*	=
Estimated total from other foods			= 250
Total daily calcium intake in mg			=

Step 1: Estimate calcium intake from calcium rich foods. (About 75-80% of calcium in American diets is from dairy products)

Step 2: Total from above + 250 mg for nondairy sources

*Calcium content of fortified foods varies