Bale/Doneen Live Chat Session

Amy Doneen MSN, ARNP

October 9, 2013

5:30-6:30 pm PST

Outline for today's discussion

Red Flags:

Menopausal Hormone Therapy for Women

Disease/Inflammation:

Arterial Inflammation Precedes Calcification

Root Causes:

Lipo(a)

Vitamin D deficiency

Genetics:

MTHFR

Treatment:

STATINS and brain health

Vitamin A & E

Plavix and DES

Exercise

Testosterone and CVD – pros and cons

Cinnamon

Red Flags

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Post stopping Phases of the Women's Health Initiative Randomized Trials

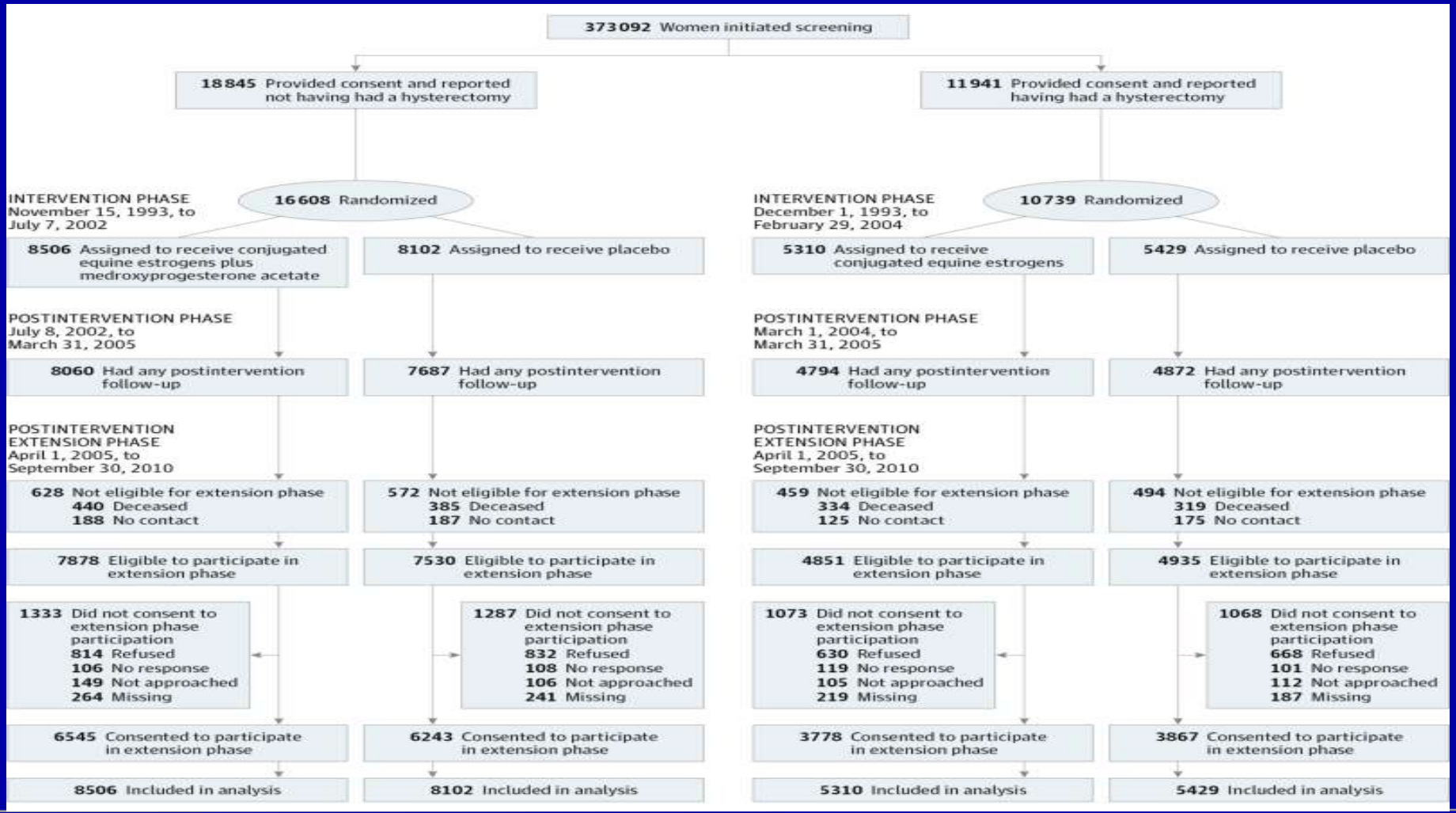
Women's Health Initiative Trials of Menopausal Hormone Therapy Through Extended Follow-up.

There were 342 306 women who were ineligible or unwilling to participate in the hormone therapy trials. The post intervention phase began on the day after participants were instructed to stop study medication use and continued through the original trial completion date.

During the extension phase, there was follow-up for those who provided additional consent (conjugated equine estrogens plus medroxyprogesterone acetate or placebo trial: 83% of those eligible and 2.8% dropped out; conjugated equine estrogens alone or placebo trial: 78% of those eligible and 3.0% dropped out).

JAMA. 2013;310(13):1353-1368

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Post stopping Phases of the Women's Health Initiative Randomized Trials



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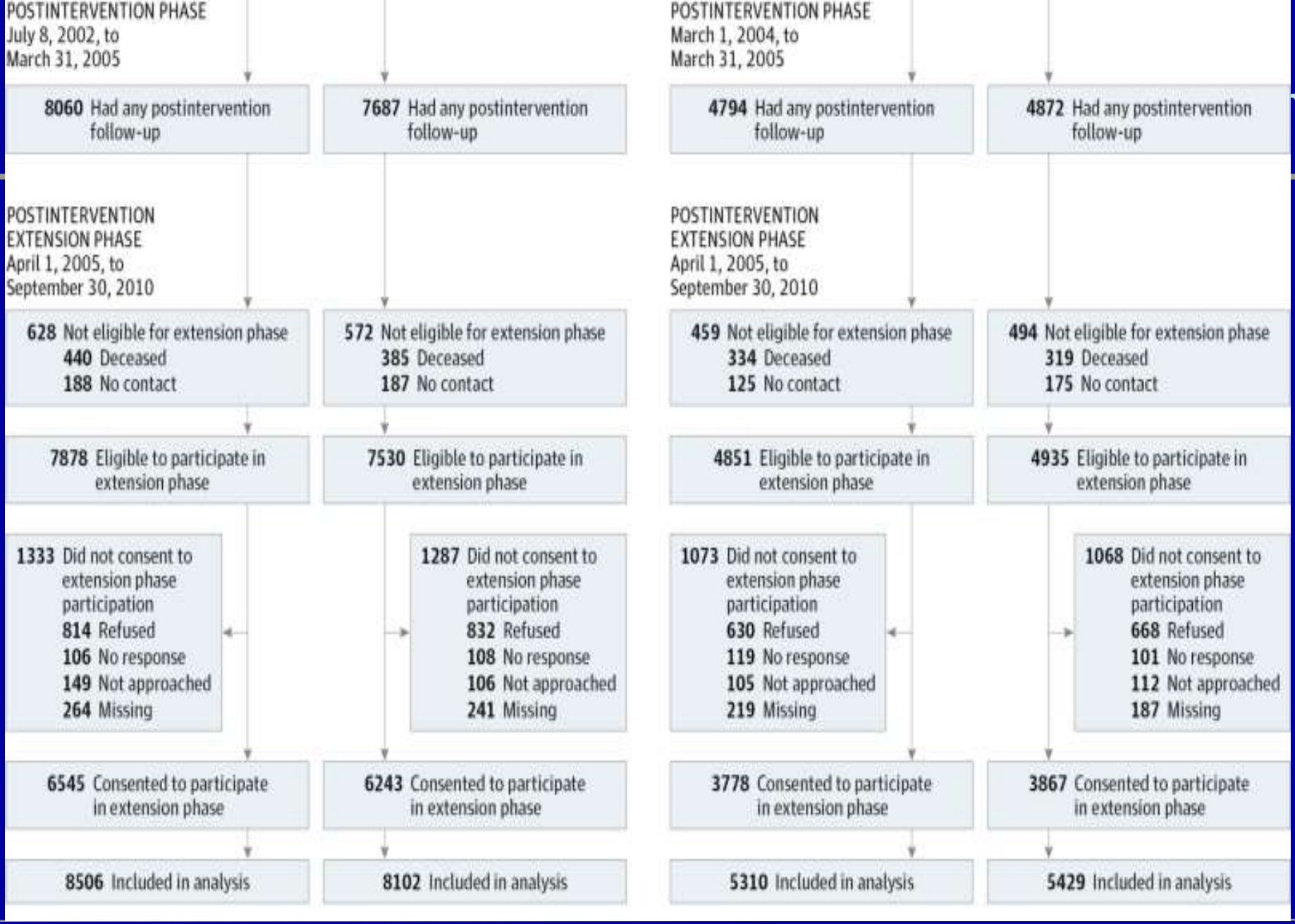

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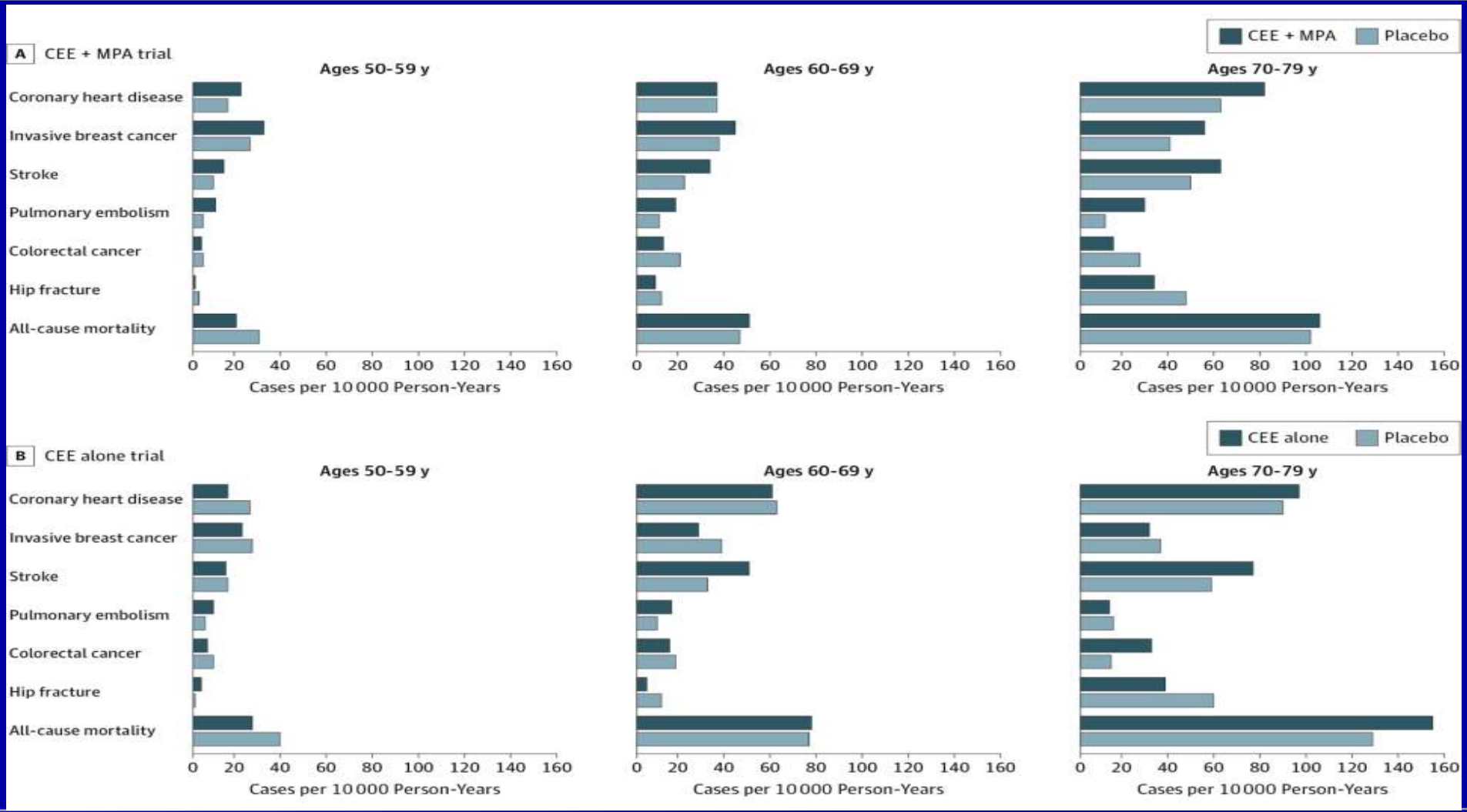

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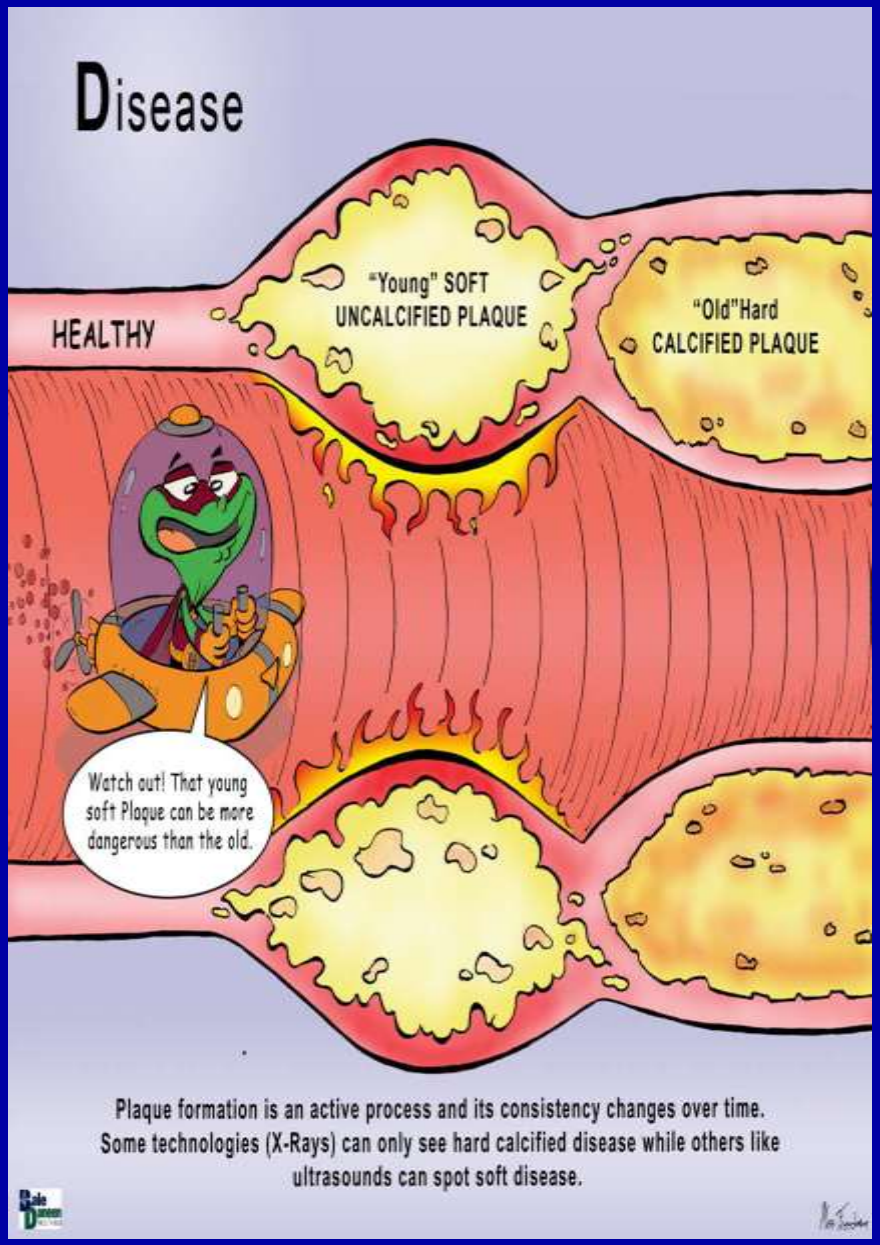


Arterial Inflammation Precedes Calcification

- 137 pts; age-61±13 yrs; 48.1% men; serial PET/CT scans 1–5 yrs apart; thoracic aorta focal arterial inflammation was prospectively (baseline) determined by PET/FDG

- A blinded investigator evaluated calcium deposition on the baseline and follow-up computed tomographic scans along the same standardized sections of the aorta.

- A vascular segment was classified as either with or without subsequent calcification.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

- Across all patients, subsequent Ca deposition was associated with the underlying inflammatory signal, measured as standardized uptake value with OR of 2.94 (95%CI- 1.27-6.89) or as TBG ratio with OR 2.59 (95% CI, 1.18-5.70) p values of 0.01 and 0.02 respectively – adjusted for CV risk factors.

- First-in-human evidence that arterial inflammation precedes subsequent Ca deposition.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

- Local FDG uptake was the strongest predictor of subsequent local calcification compared to traditional risk factors.

- Arterial segments that manifest any subsequent calcium deposition had higher inflammatory signals at baseline.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

- Presence of preexisting calcification was associated with lower arterial inflammation.
- Consistent with previous findings that vascular inflammation is lowest in densely calcified locations.
- It is reasonable to assume that inflammation and calcification represent different phases of atherosclerosis.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

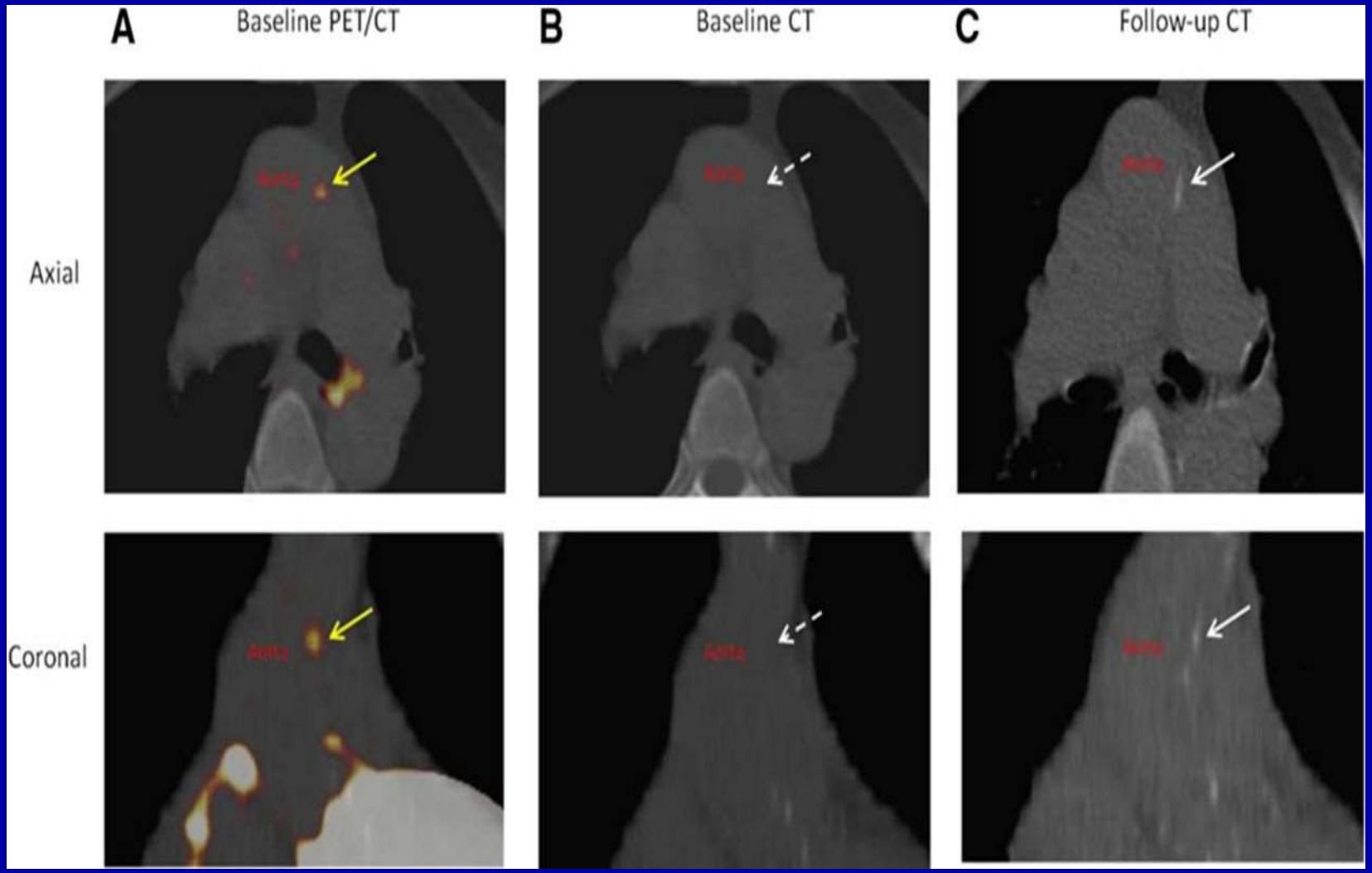
- Inflammation is an important driver of plaque progression.

- Human studies have shown that high aortic and carotid FDG uptake is related to subsequent risk of plaque rupture and clinical events.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

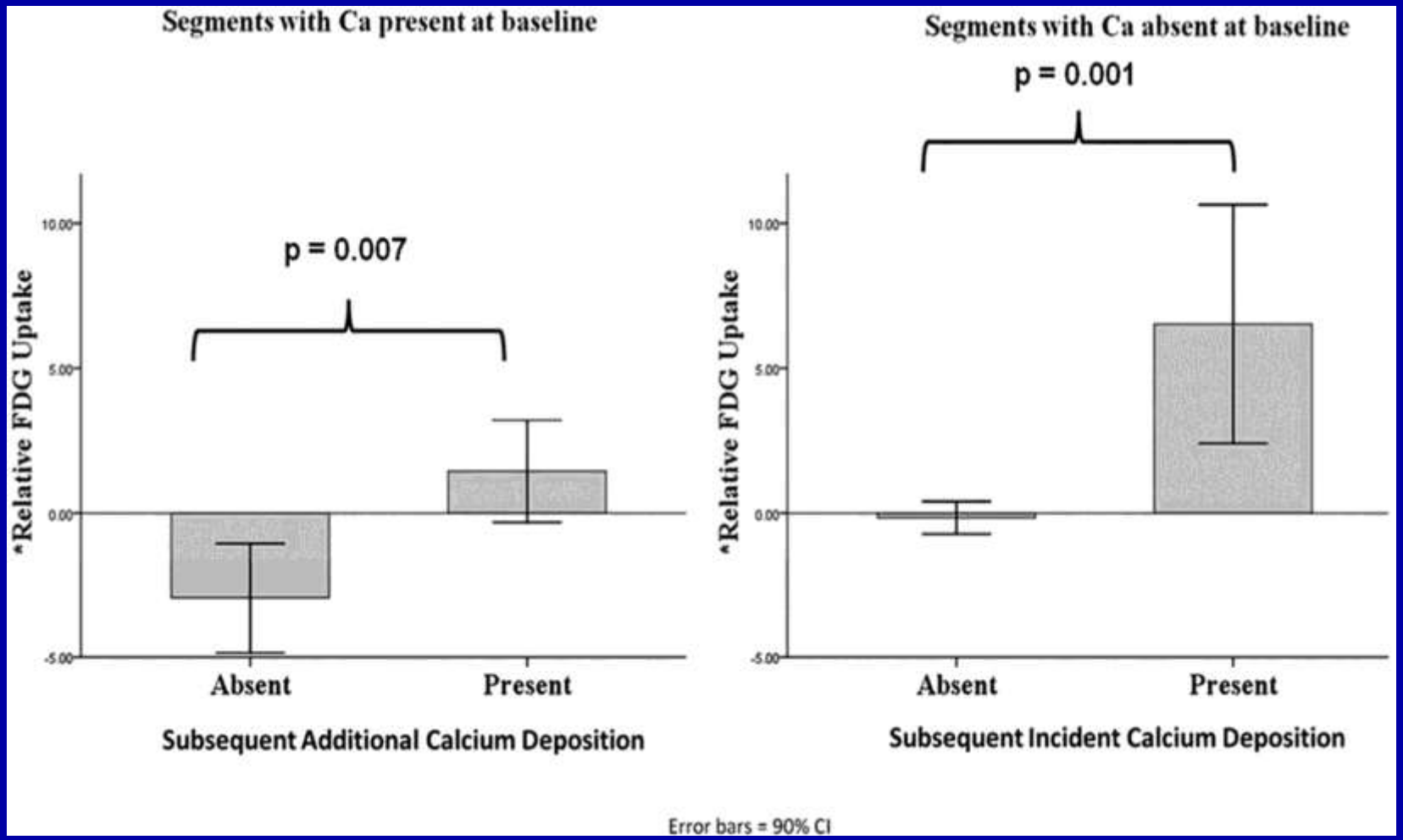
Baseline (PET) and sequential (CT) images of incident calcium deposition.



Abdelbaky A et al. Circ Cardiovasc Imaging 2013;6:747-754

Arterial Inflammation Precedes Calcification

Within-pt segmental arterial FDG uptake. *Percent difference between segment standardized uptake value (SUV) and mean SUV of the whole aorta.



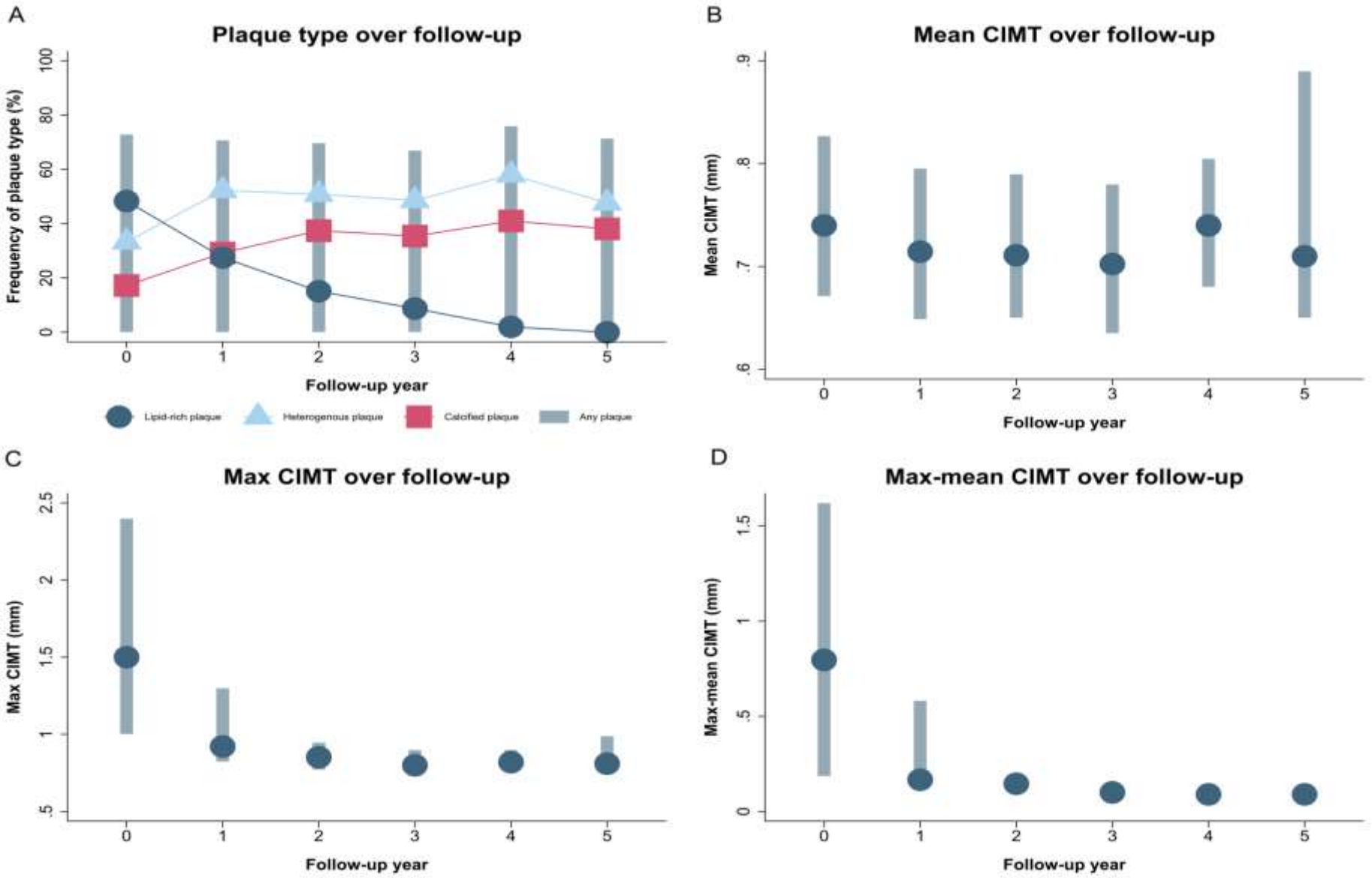
Abdelbaky A et al. Circ Cardiovasc Imaging 2013;6:747-754

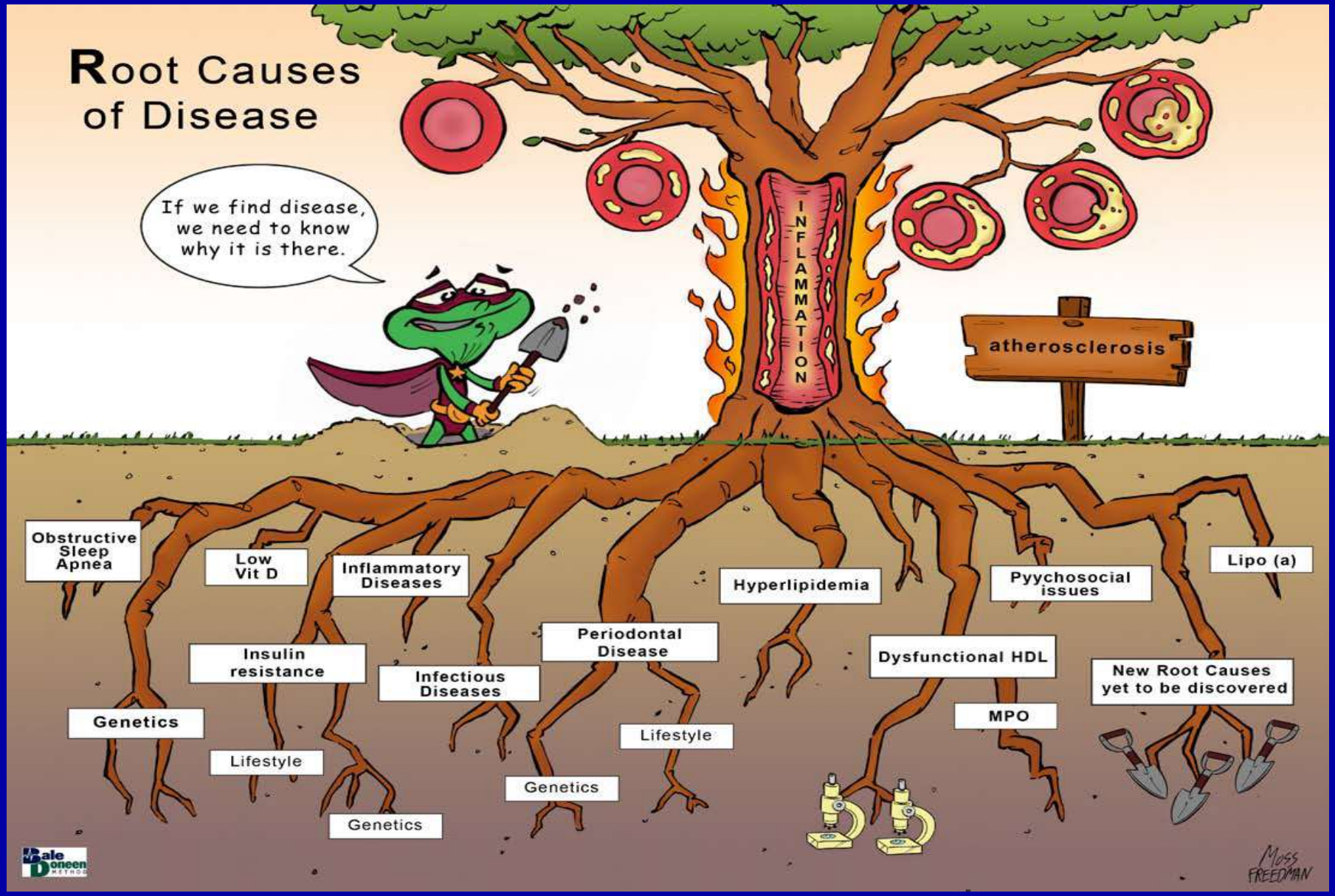
BD Method Thoughts

- Inflammation is the driver of disease and risk.
- Calcified plaque may or may not represent active inflammation.
- Un-calcified plaque should be considered ‘hot’ dangerous plaque.
- It takes the bio-markers of inflammation to clearly define risk when disease is identified with only calcified lesions.

Independent Effects of Risk Factors and Treatment on Carotid Intima-Media Thickness Progression in a Community Practice

Birju Patel, MPH, Michael Blaha, MD MPH, Amy Doneen, RN BSN MSN ARNP, Brad Bale, MD, Steven Jones, MD





Lipo (a)

Lipo (a) Baseline and One Year Follow-up Predict CV Risk in CAD Pts

- 7,863 post-MI pts; ~18% female; baseline and one year change in Lp (a) evaluated for predicting CV event risk; 6 yr. follow-up.

- The median conc. of Lp(a) at baseline was 13.9 (25th–75th percentiles, 6.6–44.05) mg/dL with the upper decile >73.7 mg/dL; none had values >90 mg/dL.

- Half the patients had values <13.9 mg/dL, which are 'normal'

Nestel, P. J., et. al. (2013). Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Baseline Predicts CV Risk in CAD Pts

- CHD events: Lp(a) >73.7 mg/dL
  HR- 1.24 (95%CI, 1.02-1.52)

- CVD events: Lp(a) >73.7 mg/dL
  HR- 1.21 (95%CI, 1.07-1.36)

- Non-fatal MI: Lp(a) 44.1-73.7 mg/dL
  HR- 1.28 (95%CI, 1.02-1.60)

Nestel, P. J., et. al. (2013) *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Baseline Predicts CV Risk in CAD Pts

- Lp(a) represents a significant risk factor for recurrent events.
- Substantially higher risk with Lp(a) values >73 mg/dL.
- Suggestions Lp(a) levels of >50 mg/dL should be considered a robust cutoff value CVD event risk.

Nestel, P. J., et. al. (2013) *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Change in One Year Follow-up Predict CV Risk in CAD Pts

- A relative change >13% from baseline to one yr is larger than can be accounted for by analytic variation.

- An increasing >13% relative to a decrease of >13% generated a significant increased risk

  HR for CV event- 1.21 (95%CI,1.06–1.39) P=0.005

  HR for CHD event- 1.21 (95%CI,1.05–1.39) P=0.009

Nestel, P. J., et. al. (2013). Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Change in One Year Follow-up Predict CV Risk in CAD Pts

- If lipo (a) increased by ≥3.4 mg/dL versus decreased by ≥2.4 mg/dL, 23% more likely to have CV event

  HR-1.23 (95% CI, 1.07–1.39) P=0.002

Nestel, P. J., et. al. (2013). Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Baseline and One Year Follow-up Predict CV Risk

- Study confirms a significant association between Lp(a) concentration and future CV events in patients with stable ischemic heart disease.

- Lp(a) as an important CVD risk factor is supported by this study.

Nestel, P. J., et. al. (2013) *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Baseline Predict CV Risk in CAD Pts.

Table 3. Baseline Plasma Lp(a) Concentration and Prediction of CHD and CVD Events

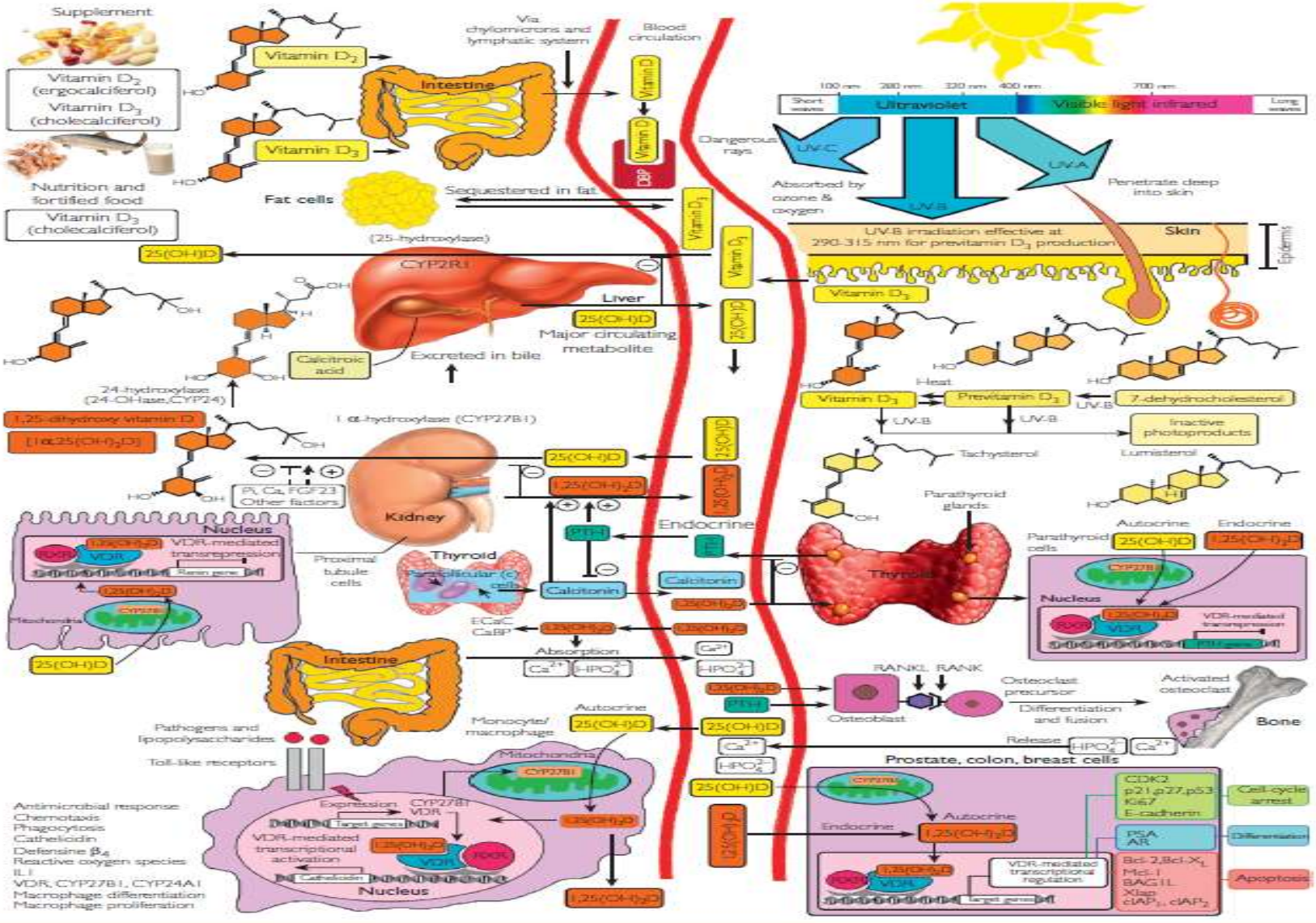
End Point	Variable	Baseline Lp(a) Concentration, mg/dL	Events, n/Total	5-Year Event Rate, %	HR (95% CI)*	*P* Value (Trend)
CHD events*	Lp(a)	≤13.9	544/3949	11.5	1	0.03
		13.9–44.1	260/1938	11.2	0.96 (0.83–1.12)	…
		44.1–73.7	172/1187	12.3	1.07 (0.90–1.27)	…
		>73.7	124/789	13.1	1.24 (1.02–1.52)	…
	Pravastatin	…	…	…	0.80 (0.71–0.90)	<0.001
Nonfatal MI	Lp(a)	≤13.9	291/3949	6.4	1	0.06
		13.9–44.1	150/1938	6.7	1.06 (0.87–1.30)	…
		44.1–73.7	110/1187	8.2	1.28 (1.02–1.60)	…
		>73.7	68/789	7.6	1.30 (0.99–1.70)	…
	Pravastatin	…	…	…	0.80 (0.68–0.94)	0.006
Unstable angina	Lp(a)	≤13.9	911/3949	20.8	1	0.09
		13.9–44.1	410/1938	19.2	0.90 (0.80–1.02)	…
		44.1–73.7	303/1187	22.6	1.07 (0.94–1.22)	…
		>73.7	205/789	24.9	1.14 (0.98–1.34)	…
	Pravastatin	…	…	…	0.88 (0.80–0.96)	0.006
Coronary revascularization	Lp(a)	≤13.9	546/3949	12.4	1	<0.001
		13.9–44.1	269/1938	12.2	1.04 (0.90–1.21)	…
		44.1–73.7	179/1187	13.1	1.09 (0.91–1.29)	…
		>73.7	145/789	16.8	1.45 (1.20–1.75)	…
	Pravastatin	…	…	…	0.83 (0.74–0.94)	0.003
Total CVD events†	Lp(a)	≤13.9	1508/3949	33.5	1	0.002
		13.9–44.1	712/1938	32.3	0.95 (0.87–1.04)	…
		44.1–73.7	481/1187	34.3	1.06 (0.96–1.18)	…
		>73.7	339/789	38.4	1.21 (1.07–1.36)	…
	Pravastatin	…	…	…	0.84 (0.78–0.90)	<0.001
Total CHD events‡	Lp(a)	≤13.9	1416/3949	31.5	1	<0.001
		13.9–44.1	653/1938	29.9	0.93 (0.85–1.02)	…
		44.1–73.7	454/1187	32.7	1.06 (0.96–1.18)	…
		>73.7	324/789	36.9	1.23 (1.09–1.40)	…
	Pravastatin	…	…	…	0.85 (0.79–0.92)	<0.001

HRs and 95% CIs are adjusted for baseline variables: treatment, sex, stroke, diabetes mellitus, smoking, hypertension, total cholesterol, apolipoprotein B, apolipoprotein A1, HDL-c, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin use at baseline. CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; Lp(a), lipoprotein(a); and MI, myocardial infarction.

Nestel, P. J., et. al. (2013) *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

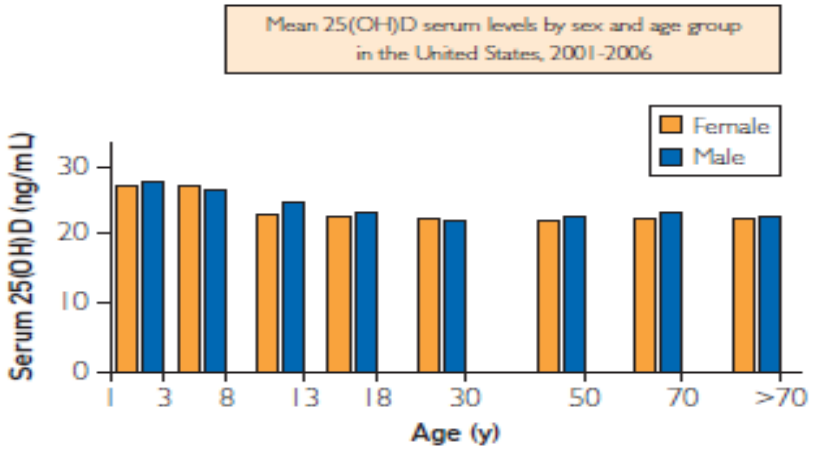
Vitamin D

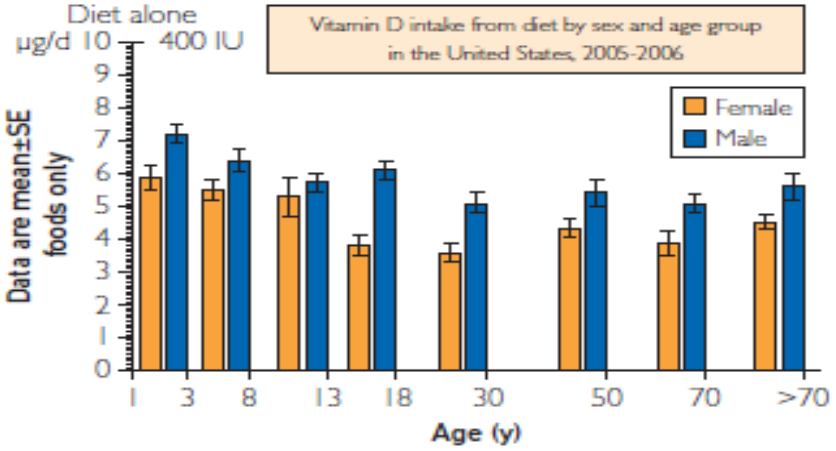
Vitamin D Deficiency



Hossein-nezhad, A., et al. Vitamin D for health. Mayoclinicproceedings. July 2013. 88(7):720-753

Vitamin D Deficiency





Institute of Medicine[62] recommendations	RDA (IU/d)	600		400[b]		600		800
	UL (IU/d)[a]	4000		1000	1500	2500	3000	4000
The Endocrine Practice Guideline Committee recommendations for patients at risk for vitamin D deficiency[60]	Daily allowance (IU/d)	600–1000[a] 1500–2000[c]		400–1000		600–1000		1500–2000
	UL (IU/d)[a]	10,000		2000		4000		10,000

[a] UL indicates level above which there is risk of adverse events. The UL is not intended as a target intake.
[b] Reflects AI reference value rather than RDA. RDAs have not been established for infants.
[c] Mother's requirement 4000-6000 (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

Hossein-nezhad, A., et al. Vitamin D for health. Mayoclinicproceedings. July 2013. 88(7):720-753

Bale Doneen METHOD

Vitamin D Deficiency

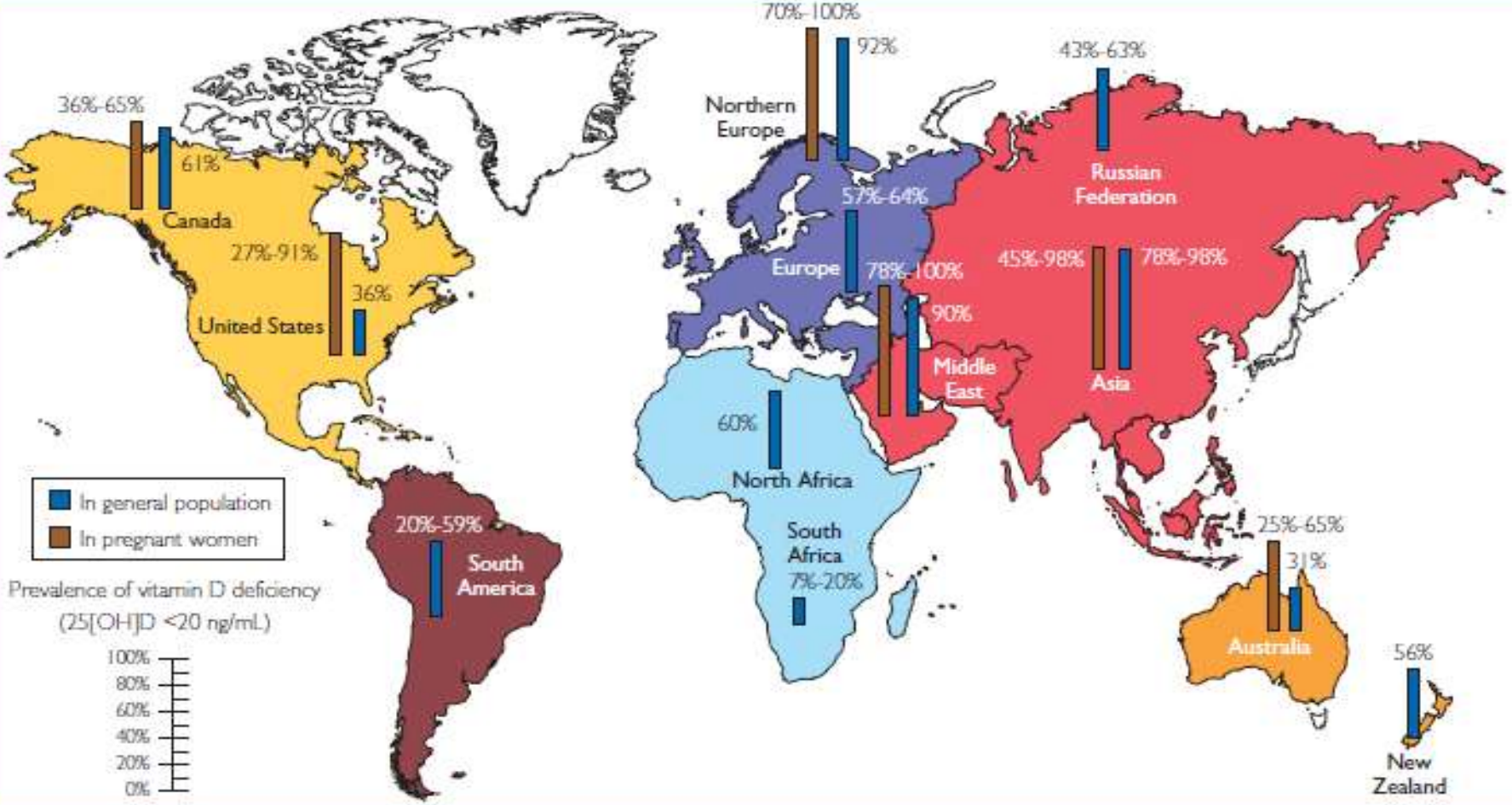


FIGURE 5. Reported incidence of vitamin D deficiency defined as a 25-hydroxyvitamin D (25[OH]D) level below 20 ng/mL around the globe in pregnant women and the general population. To convert 25(OH)D values to nmol/L, multiply by 2.496. Copyright Holick 2013, reproduced with permission.

Hossein-nezhad, A., et al. Vitamin D for health. Mayoclinicproceedings. July 2013. 88(7):720-753

Vitamin D Deficiency
Cardiovascular Disorders and T2 DM

Vitamin D deficiency found to be related to:

1. Coronary artery calcifications
2. Influence the activity/expression of macropahges and lymphocytoctes in atherosclerotic plaques – promoting chronic inflammation in the artery wall
3. Inhibit foam cell formation and promoted angiogenesis in endothelial colony forming cells in vitro – due to in vascular endothelial growth factor expression and pro-matrix MMP-2
4. Elevation in PTH levels, which have been linked to IR and increases in acute phase proteins.

Hossein-nezhad, A., et al. Vitamin D for health. Mayoclinicproceedings. July 2013. 88(7):720-753

Vitamin D Deficiency
Cardiovascular Disorders and T2 DM

In FRS offspring (1739 patients), mean age 59, 55% women, without previous CV event, followed 5.4 years – 120 experienced first CV event. Individuals with 25(OH)D of ≤15 ng/mL HR 1.62 compared to ≥ 15ng/mL.

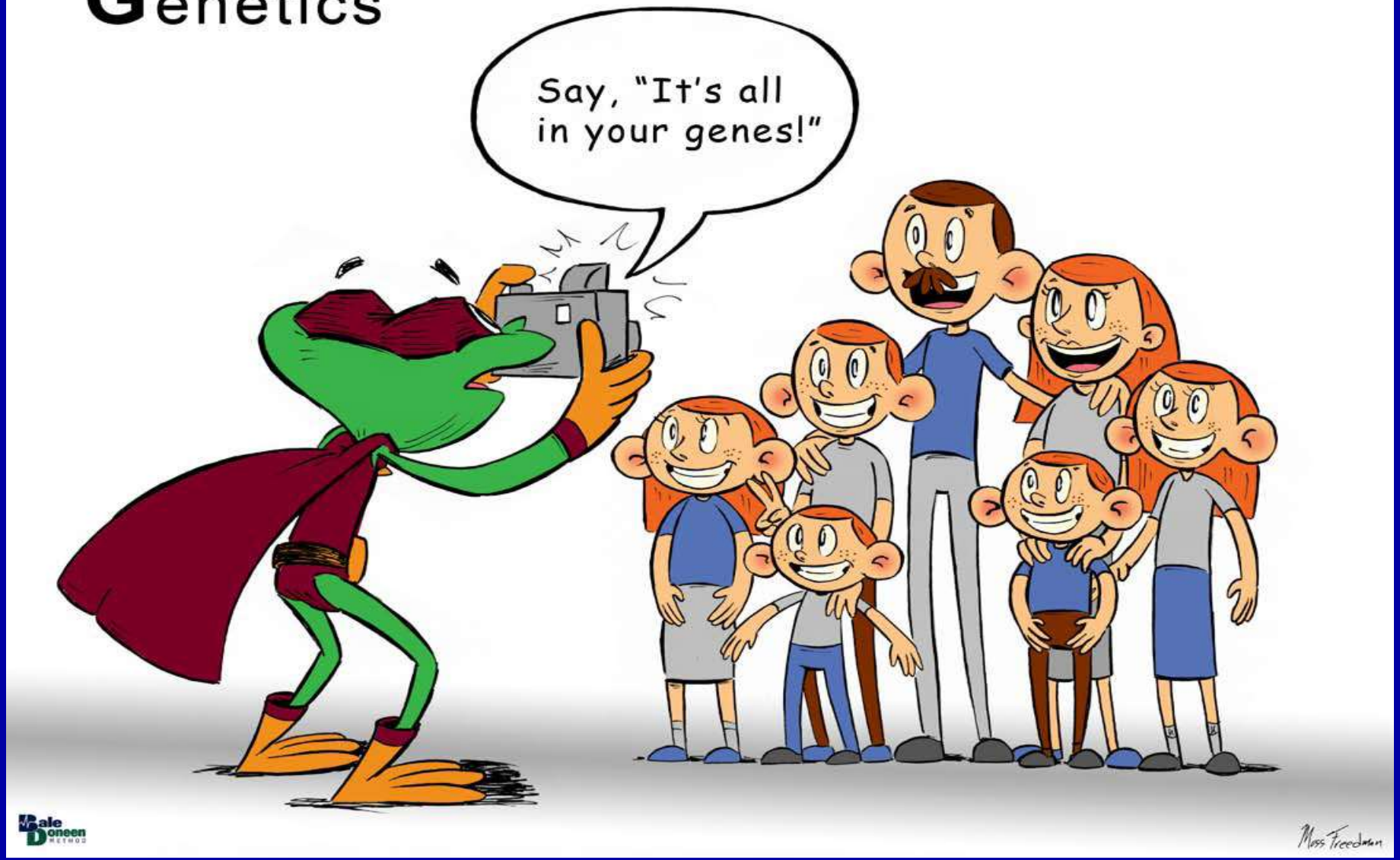
Effect evidence with HTN (HR, 2.13; 95% CI, 1.30-3.48) but not in those without HTN.

Observational studies show <30ng/mL was strongly related to metabolic syndrome and hypertension.

Strong inverse relationship between serum 25(OH)D and incidence of T2DM – combined RR 0.59 suggests risk of CM may be reduced by 41% (95% CI, 33%-48%) by having a serum Vit D level > 32 ng/mL compared with 19.5 at baseline.

Hossein-nezhad, A., et al. Vitamin D for health. Mayoclinicproceedings. July 2013. 88(7):720-753

Genetics



MTHFR Paradoxical Relationship to CV Risk

- Prospective cohort 5,925 pts; utilized Mendelian genetics to examine association of MTHFR-C677T-*TT* genotype on CV and all-cause mortality.

- Technique used genetic polymorphisms as a proxy which is less susceptible to confounding by behavioral or environmental exposures.

- This strengthens the ability to infer a causal influence.

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- MTHFR C677T-*TT* is a proxy for high homocysteine (hmcy) and lower folate concentrations

- *TT* genotype had a 2.2-lmol/L higher homocysteine and a 1.4-ng/mL lower folate concentration, respectively, than *CC* genotype.

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- After adjusting for ethnicity and other CVD risk factors *TT* genotype (positive for MTHFR) was associated with:

significantly lower CVD mortality

HR: 0.69 (95% CI:0.50-0.95)

not significant for all-cause mortality

HR: 0.79 (95% CI: 0.59-1.05)

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- Follow-up was from 1991 through 2006
- Mandatory folate fortification of flour took place ~ half way through the follow-up period (1/1/1998)

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- The inverse assoc. of *TT* was consistent across sex, race-ethnicity, use of supplements containing folic acid, serum folate deficiency status, CVD status at baseline, and CRP.

- *TT*'s assoc. with lower risk of CVD mortality was chiefly due to deaths occurring after the introduction of folic acid fortification & in deaths after age 50

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- In an 18-y follow-up of 12,239 middle-aged women living in the Netherlands, a population without folic acid fortification, the rate ratios for CVD mortality were 0.7 (95% CI: 0.5-0.9) for *CT;* 0.6 (95% CI: 0.4-1.0) for *TT*, compared with *CC*

- This is consistent with the current study.

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- Randomized trials have shown that lowering homocysteine for 5 yrs with folic acid and other B vitamins has no effect on the risk of CVD.

- Meta-analyses of published studies examining MTHFR-C677T variant's association with CVD risk have been conflicting.

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

- These findings suggest that the *TT* genotype of the MTHFR C677T is associated with a lower risk of CVD mortality, especially in a population with adequate folate intake.

Yang, Q., et. al. (2012). Prospective study of methylenetetrahydrofolate reductase (MTHFR) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

TABLE 2

Weighted allele and genotype frequencies and 95% CIs of MTHFR 677C→T by race-ethnicity per NHANES III DNA Data (1991–1994) Linked Mortality through 2006[1]

Polymorphism and race-ethnicity	No. of participants[2]	Allele frequency		Genotype frequency			*P* value (HWE)[3]
		C	*T*[2]	*CC*	*CT*	*TT*[2]	
		%	%	%	%	%	
Non-Hispanic white	2353	67.1 (64.7, 69.3)	33.0 (30.7, 35.3)[a]	45.6 (42.9, 48.3)	42.8 (40.8, 44.9)	11.6 (9.6, 14.0)[a]	0.107
Non-Hispanic black	1619	89.0 (88.0, 89.9)	11.0 (10.1, 12.0)[b]	79.4 (77.4, 81.3)	19.4 (17.5, 21.5)	1.2 (0.7, 2.0)[b]	0.891
Mexican American	1675	55.0 (53.0, 58.0)	45.2 (42.3, 47.1)[c]	30.1 (27.2, 33.1)	50.6 (48.4, 52.8)	19.4 (16.7, 22.3)[c]	0.732
Total	5925	69.0 (67.0, 71.0)	31.0 (29.0, 33.0)	49.0 (46.7, 51.4)	39.9 (38.3, 41.6)	11.0 (9.3, 13.0)	

[1] 95% CIs in parentheses. Means with different superscript letters are significantly different, $P < 0.001$ (Satterthwaite-adjusted *F* test; *P* value reflects the difference in allele frequency or genotype prevalence between race-ethnicity groups. Satterthwaite-adjusted *F* statistics were used to test for pairwise differences between race-ethnicity groups). HWE, Hardy-Weinberg equilibrium; MTHFR, methylenetetrahydrofolate reductase.

[2] Sample sizes are unweighted.

[3] Significance of the deviation of genotype frequencies.

Yang, Q., et. al. (2012). *Am J Clin Nutr, 95*(5), 1245-1253.

MTHFR Paradoxical Relationship to CV Risk

TABLE 6

Risks (HRs and 95% CIs) for all-cause and CVD mortality that occurred before or after folic acid fortification by *MTHFR C677T* genotype per NHANES III DNA Data (1991–1994) Linked Mortality through 2006[1]

Characteristic	Deaths before folic acid fortification (before 1 January 1998)				Deaths after folic acid fortification (after 1 January 1998)			
	CC	*CT*	*TT*	*P* value[2]	*CC*	*CT*	*TT*	*P* value[2]
All-cause mortality								
No. of cases[3]	167	112	41		446	353	92	
HR adjusted for sex and race-ethnicity only	1.0	0.76 (0.49, 1.17)	1.09 (0.66, 1.79)	0.723	1.0	0.97 (0.78, 1.21)	0.73 (0.48, 1.12)	0.141
Fully adjusted HR[4]	1.0	0.81 (0.56, 1.17)	0.99 (0.61, 1.60)	0.959	1.0	0.98 (0.79, 1.21)	0.71 (0.47, 1.08)	0.105
CVD mortality								
No. of cases	77	49	26		188	148	37	
HR adjusted for sex and race-ethnicity only	1.0	0.86 (0.54, 1.39)	1.61 (0.90, 2.89)	0.102	1.0	0.87 (0.65, 1.16)	0.49 (0.28, 0.87)	0.017
Fully adjusted HR[4]	1.0	0.93 (0.65, 1.35)	1.51 (0.84, 2.69)	0.157	1.0	0.81 (0.60, 1.10)	0.42 (0.22, 0.83)	0.015

[1] 95% CIs in parentheses. CVD, cardiovascular disease; MTHFR, methylenetetrahydrofolate reductase.

[2] Reflects the differences in HRs across *MTHFR* C677T genotype. Satterthwaite-adjusted *F* statistics were used to test for difference in HRs across *MTHFR* C677T genotype. All tests were 2-tailed.

[3] Sample sizes are unweighted.

[4] Adjusted for sex, race-ethnicity, smoking status, alcohol use, BMI, education attainments, use of dietary supplements, physical activity, hypertension, diabetes, total cholesterol, and C-reactive protein in the Cox proportional hazard models.

Yang, Q., et. al. (2012). *Am J Clin Nutr, 95*(5), 1245-1253.

Dale Doneen METHOD

MTHFR Paradoxical Relationship to CV Risk

Characteristics	MTHFR 677C→T			
	CC	*CT*	*TT*	*P* value[2]
All-cause mortality				
No. of cases[3]	613	465	133	
HR adjusted for sex and race-ethnicity only	1.0	0.96 (0.79, 1.16)	0.81 (0.59, 1.12)	0.198
Fully adjusted HR[4]	1.0	0.96 (0.79, 1.18)	0.79 (0.59, 1.05)	0.097
CVD mortality				
No. of cases[3]	265	197	63	
HR adjusted for sex and race-ethnicity only	1.0	0.91 (0.72, 1.15)	0.77 (0.56, 1.05)	0.099
Fully adjusted HR[4]	1.0	0.88 (0.68, 1.13)	0.69 (0.50, 0.95)	0.026
IHD mortality				
No. of cases[3]	134	96	32	
HR adjusted for sex and race-ethnicity only	1.0	0.83 (0.62, 1.12)	0.66 (0.37, 1.18)	0.143
Fully adjusted HR[4]	1.0	0.79 (0.58, 1.07)	0.57 (0.31, 1.05)	0.056
Stroke mortality				
No. of cases[3]	48	33	13	
HR adjusted for sex and race-ethnicity only	1.0	0.74 (0.46, 1.19)	1.11 (0.44, 2.81	0.811
Fully adjusted HR[4]	1.0	0.69 (0.40, 1.20)	0.90 (0.33, 2.45)	0.836
Other CVD mortality				
No. of cases[3]	83	68	18	
HR adjusted for sex and race-ethnicity only	1.0	1.17 (0.69, 1.96)	0.80 (0.35, 1.83)	0.574
Fully adjusted HR[4]	1.0	1.14 (0.72, 1.82)	0.76 (0.34, 1.68)	0.476
Cancer mortality				
No. of cases[3]	126	96	24	
HR adjusted for sex and race-ethnicity only	1.0	1.08 (0.74, 1.58)	0.85 (0.52, 1.40)	0.496
Fully adjusted HR[4]	1.0	1.09 (0.76, 1.55)	0.85 (0.54, 1.33)	0.454
Non-CVD and noncancer mortality				
No. of cases[3]	222	172	46	
HR adjusted for sex and race-ethnicity only	1.0	0.95 (0.68, 1.31)	0.84 (0.46, 1.55)	0.559
Fully adjusted HR[4]	1.0	0.98 (0.69, 1.41)	0.87 (0.47, 1.62)	0.652

[1] 95% CIs in parentheses. CVD, cardiovascular disease; IHD, ischemic heart disease; MTHFR, methylenetetrahydrofolate reductase.

[2] Reflects the differences in HRs across *MTHFR* C677T genotype. Satterthwaite-adjusted *F* statistics were used to test for difference in HRs across *MTHFR* C677T genotype. All tests were 2-tailed.

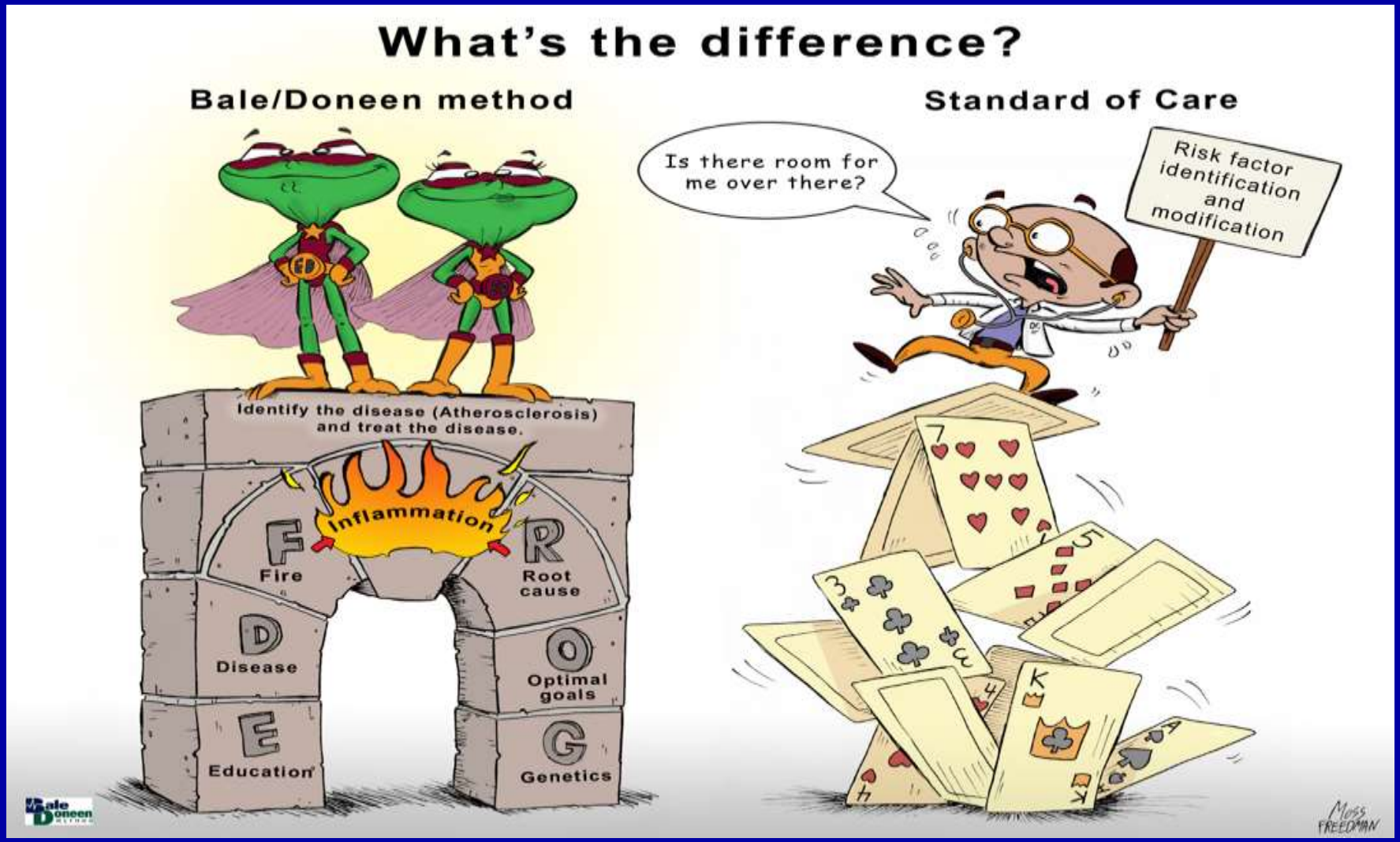
[3] Sample sizes are unweighted.

[4] Adjusted for sex, race-ethnicity, smoking status, alcohol use, BMI, education attainments, use of dietary supplements, physical activity, hypertension, diabetes, total cholesterol, and C-reactive protein in the Cox proportional hazard models.

Yang, Q., et. al. (2012). *Am J Clin Nutr, 95*(5), 1245-1253.

Dale Doneen METHOD

Treatment



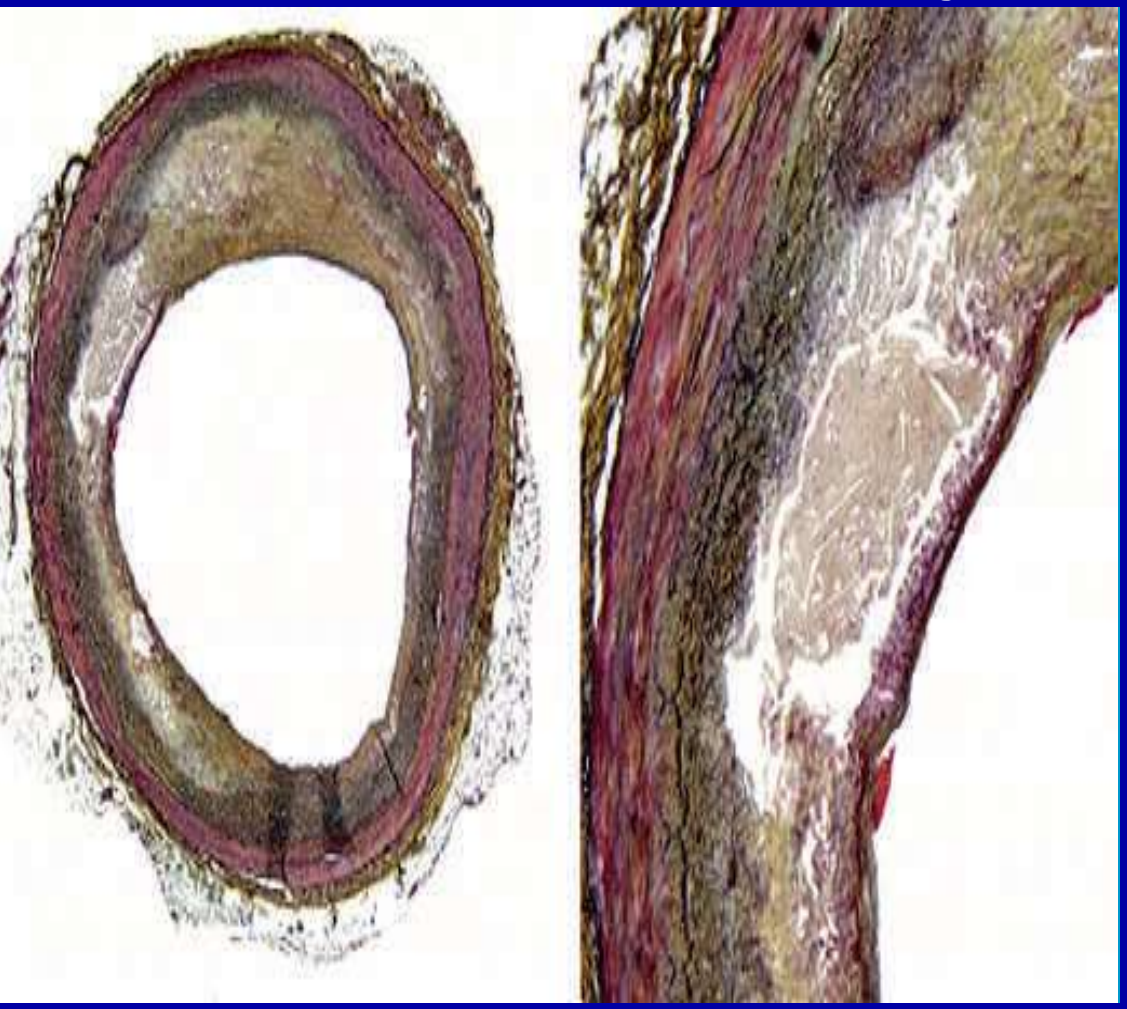
TREATMENT

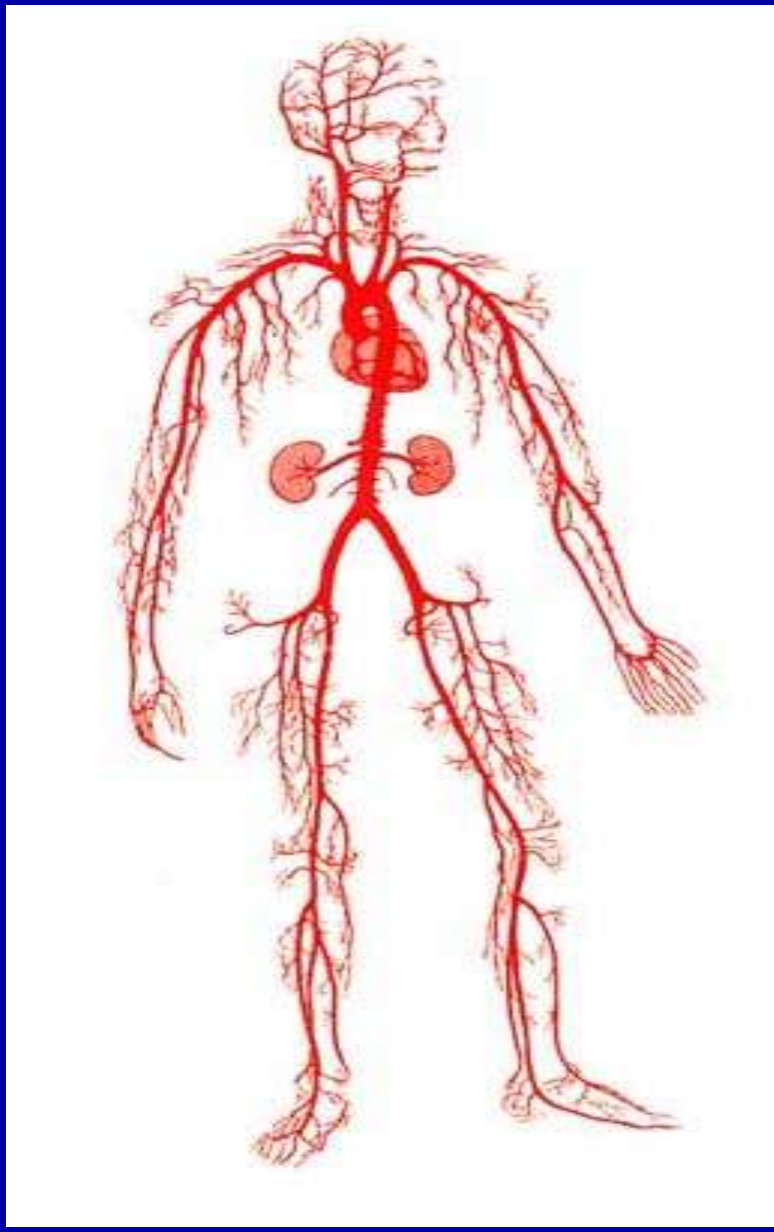
- STATINS and brain health
- Vitamin A and E
- Plavix and DES
- Exercise
- Testosterone and CVD – pros and cons
- Cinnamon

Vascular Health = Brain Health

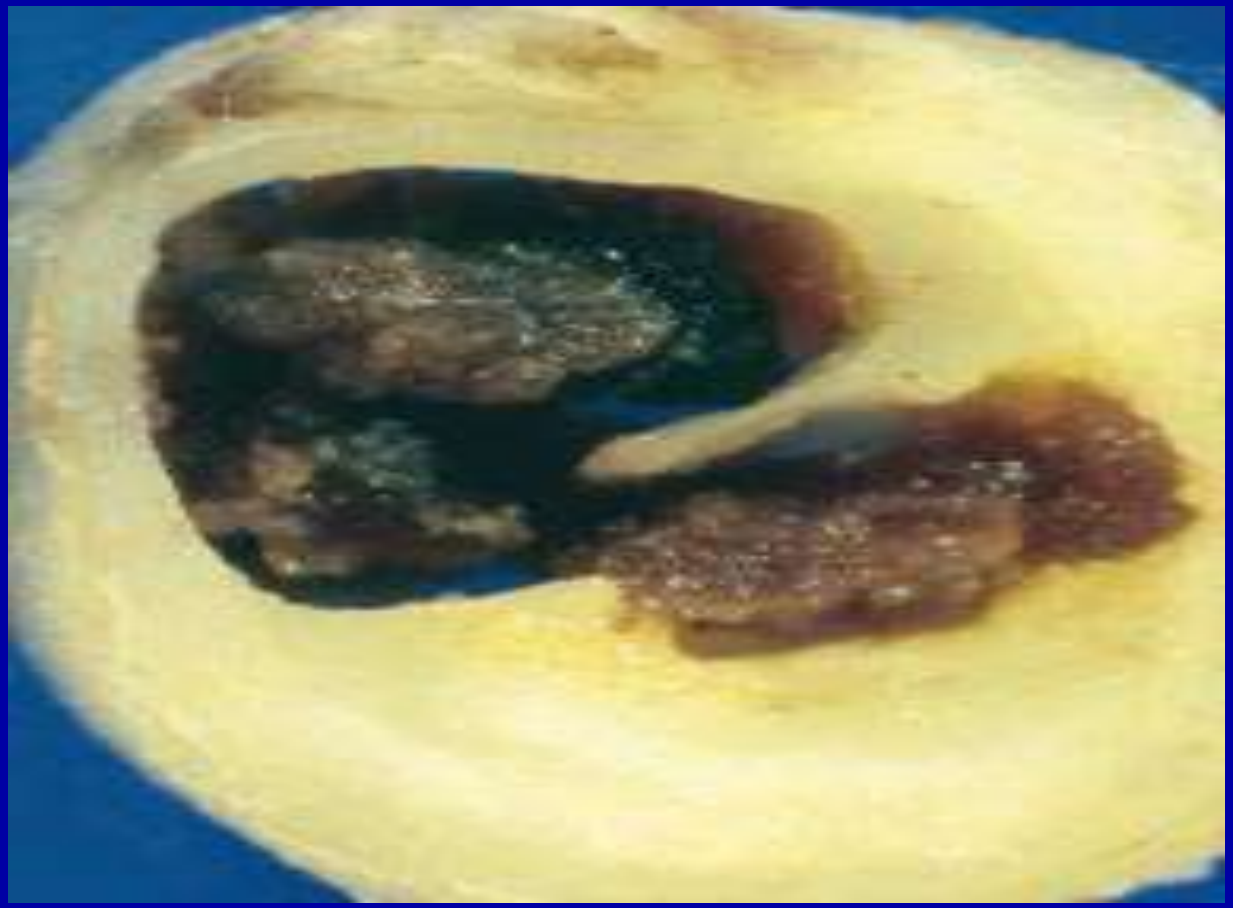
One Essential Element for Brain Health is Arterial Wellness

Atherosclerosis hides in the wall of the artery





Plaque Rupture = Thrombus = Blocked Artery

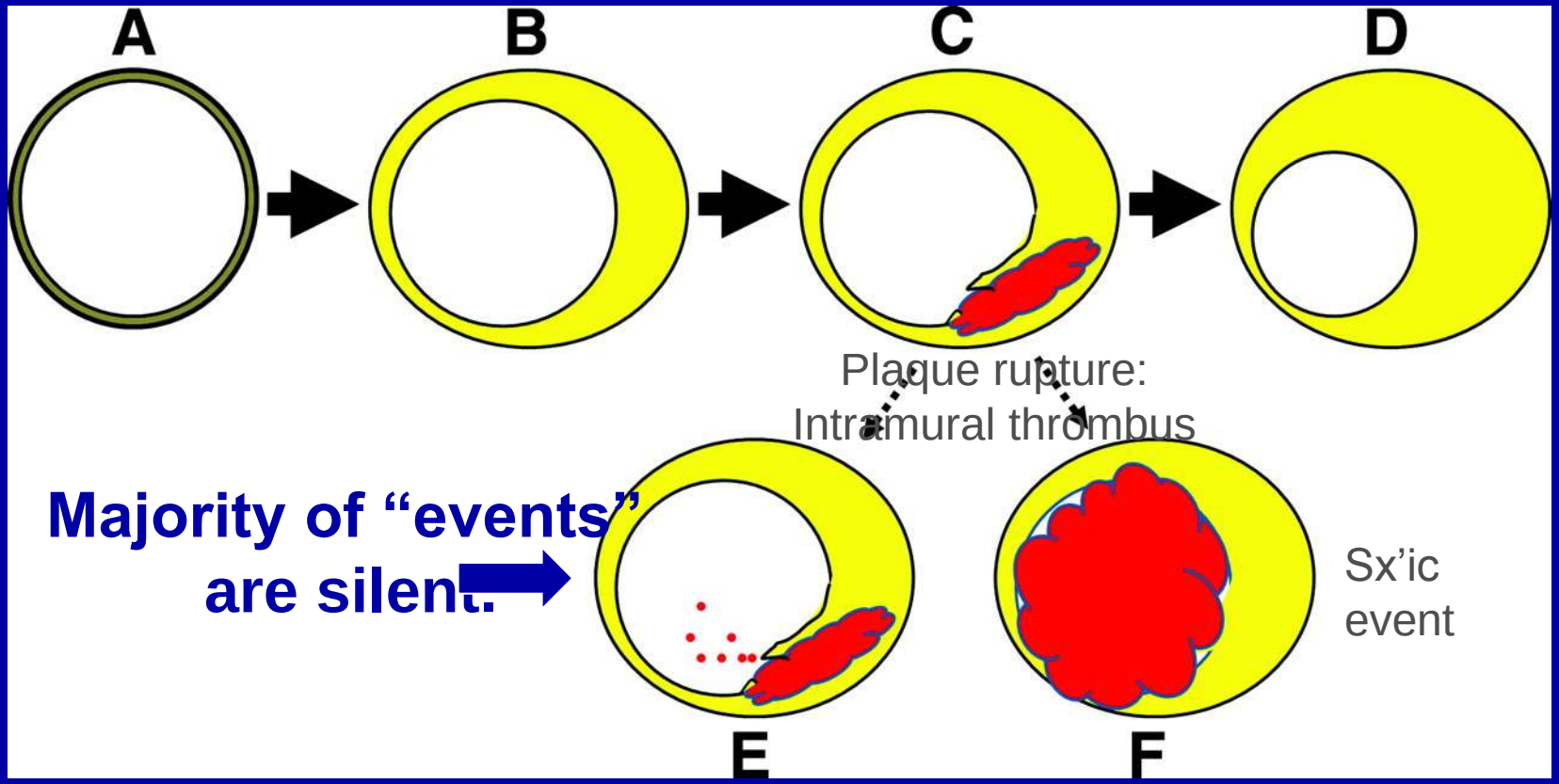


Thrombosis caused by disruption. The cap of the plaque has torn and thrombus within the lipid core extends into and occludes the lumen.

Michael J Davies *Heart 2000;**83:361–366***

Complexity of Coronary Events

The progression of coronary artery disease.



Arbab-Zadeh A et al. Circulation 3/6/2012;125:1147-1156

American Heart Association
Learn and Live

Dale Doneen Method

Blood Supply Critical for Brain!

- Brain is 2% of the human body, but it receives 25% of the cardiac output!

  "Think of the brain as a jet engine and the heart as the fuel tank"- Iadecola

- The brain's integrity depends on a continuous supply of oxygen and energy substrates delivered through blood flow (arterial health).

- Cerebrovascular disease (CVD) is an important cause of dementia

Iadecola, C., & Davisson, R. L. (2008). Hypertension and Cerebrovascular Dysfunction. *Cell Metab, 7*(6), 476-484.

Vascular Dementia (VaD)

Microvascular:

Cortical and subcortical micro-infarcts strongly related to cognitive impairment and predict poor outcome in the elderly with CVD

Small-vessel anomalies leading to micro-infarcts and diffuse white matter changes are common

Kalaria, R. N. (2012). Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. *Stroke, 43*(9), 2526-2534.

Statins

Statins May Enhance Brain Health

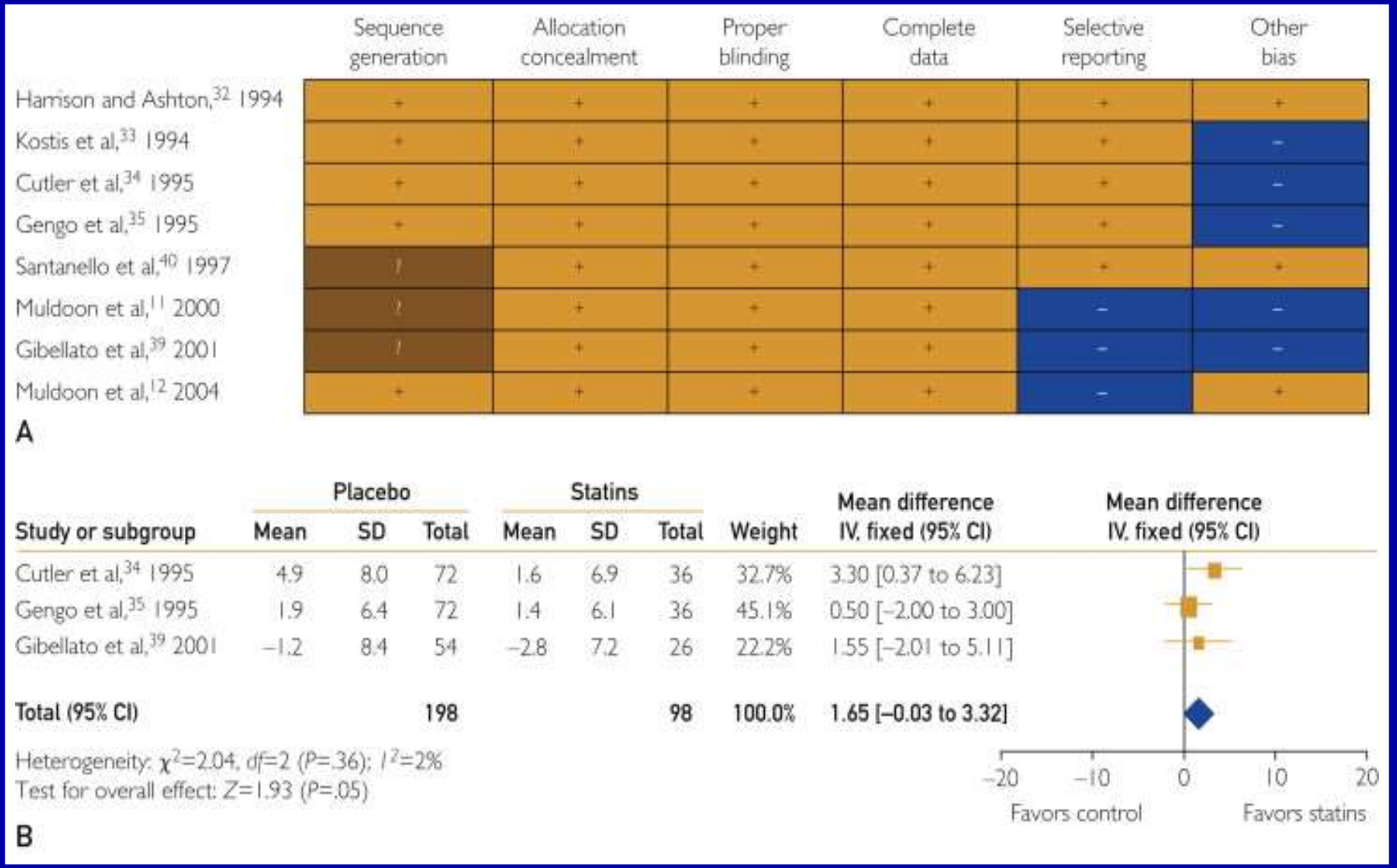
- >23,000 adults with no history of cognitive problems who took statins for more than a year; assess the long-term impact of statin use on cognition; mean exposure duration of 3 to 25 yrs.

- 29% reduction in incident dementia in statin-treated patients

HR-0.71 (95% CI, 0.61-0.82)

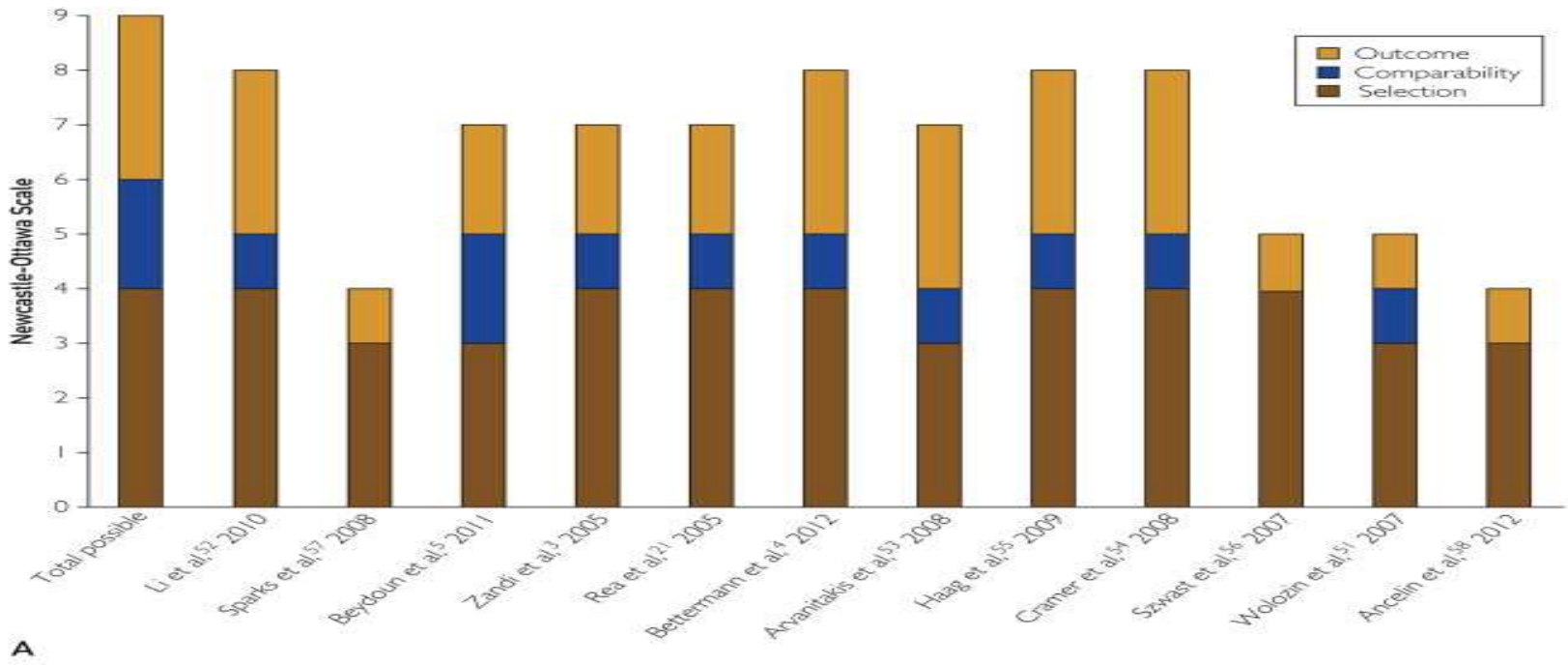
Swiger, K. J., et. al. (2013). Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. *Mayo Clinic Proceedings*. doi: 10.1016/j.mayocp.2013.07.013

First Year Difference in Cognition Not Significant



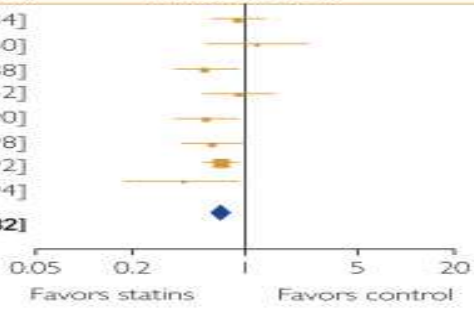
Swiger, K. J., et. al. (2013). Mayo Clinic Proceedings. doi: 10.1016/j.mayocp.2013.07.013

Long Term Benefit Significant for Statin Therapy



Study or subgroup	Log [hazard ratio]	Statins SE	Statins Total		Control Total	Control Weight	Hazard ratio IV, fixed (95% CI)
Rea et al,[21] 2005	−0.11	0.2	238		2560	14.9%	0.90 [0.61-1.34]
Zandi et al,[3] 2005	0.17	0.38	198		3110	4.1%	1.19 [0.56-2.50]
Cramer et al,[54] 2008	−0.58	0.23	452		1222	11.2%	0.56 [0.36-0.88]
Arvanitakis et al,[53] 2008	−0.09	0.26	119		810	8.8%	0.91 [0.55-1.52]
Haag et al,[55] 2009	−0.56	0.23		6992		11.2%	0.57 [0.36-0.90]
Li et al,[52] 2010	−0.47	0.23	775		2324	11.2%	0.63 [0.40-0.98]
Bettermann et al,[4] 2012	−0.34	0.13	776		2293	35.2%	0.71 [0.55-0.92]
Beydoun et al,[5] 2011	−0.89	0.42	109		1465	3.4%	0.41 [0.18-0.94]
Total (95% CI)			**2667**	23.443	**13.784**	**100.0%**	**0.71 [0.61-0.82]**

Heterogeneity: $\chi^2=8.20$, $df=7$ ($P=.32$); $I^2=15\%$
Test for overall effect: $Z=4.49$ ($P<.00001$)



B

Swiger, K. J., et. al. (2013). Mayo Clinic Proceedings.
doi: 10.1016/j.mayocp.2013.07.013

Statins May Enhance Brain Health

- Patients and healthcare providers can be reassured about concerns related to neurocognitive effects of statin therapy, and the evidence does not support a change to practice guidelines.

Swiger, K. J., et. al. (2013). Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. *Mayo Clinic Proceedings*. doi: 10.1016/j.mayocp.2013.07.013

Vitamin A & E

Vitamin E, A and Beta carotene Fail to Reduce Mortality Risk & May Increase Risk

- 296,707 pts; 68% ‘healthy’; mean age 63; 46% women; mean supplement rx 3 yrs;

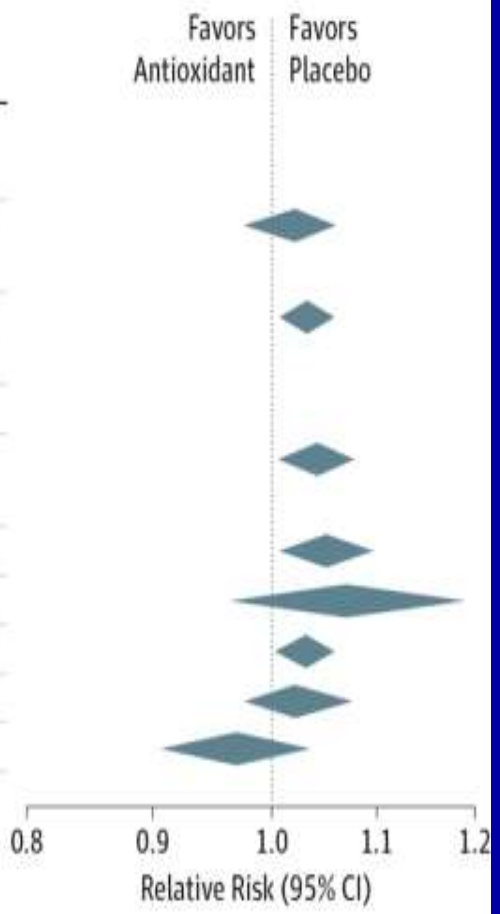
- Overall, the antioxidant supplements showed no significant mortality effect:

RR -1.02 (95% CI, 0.98-1.05)

Bjelakovic, G., Nikolova, D., & Gluud, C. (2013). Antioxidant supplements to prevent mortality. *JAMA*, *310*(11), 1178-1179.

Antioxidant Supplements to Prevent Mortality

Source	No. of Trials	No. of Participants	Antioxidants		Placebo		Relative Risk (95% CI)
			Deaths, No.	Participants, No.	Deaths, No.	Participants, No.	
Trials with both a low risk and a high risk of bias							
Trials assessing all selected antioxidant supplements	78	296707	21484	183749	11479	112958	1.02 (0.98-1.05)
Trials assessing all selected antioxidant supplements[a]	78	296707	21484	183749	11479	112958	1.03 (1.01-1.05)
Trials with a low risk of bias							
Trials assessing all selected antioxidant supplements	56	244056	18833	146320	10320	97736	1.04 (1.01-1.07)
Trials assessing beta carotene	26	173006	13202	96003	8556	77003	1.05 (1.01-1.09)
Trials assessing vitamin A	12	41144	3444	24596	2249	16548	1.07 (0.97-1.18)
Trials assessing vitamin E	46	171244	11689	97523	7561	73721	1.03 (1.00-1.05)
Trials assessing vitamin C	29	65942	3637	36659	2717	29283	1.02 (0.98-1.07)
Trials assessing selenium	17	62740	2670	39779	1468	22961	0.97 (0.91-1.03)



JAMA. 2013;310(11):1178-1179. doi:10.1001/jama.2013.277028

Vitamin E, A and Beta carotene Fail to Reduce Mortality Risk & May Increase Risk

- 56 trials with a low risk of bias showed 4% higher mortality with supplement use:

RR, 1.04 (95% CI, 1.01-1.07)

Bjelakovic, G., Nikolova, D., & Gluud, C. (2013). Antioxidant supplements to prevent mortality. *JAMA*, *310*(11), 1178-1179.

Vitamin E, A and Beta carotene Fail to Reduce Mortality Risk & May Increase Risk

- Results are consistent with the 2010 Dietary Guidelines for Americans and the NIH–sponsored State of-the-Science conference conclusion:

There is no evidence to support the use of multivitamin or mineral supplements.

Bjelakovic, G., Nikolova, D., & Gluud, C. (2013). Antioxidant supplements to prevent mortality. *JAMA*, *310*(11), 1178-1179.

Antiplatelet – Aspirin

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluting Stents

- Prospective trial 5,045 post drug eluding stent pts; after 12 mos. successful dual antiplatelet rx, randomized to dual or mono-ASA rx for 24 mos.

- End point: composite of cardiac death, MI or stroke.

- End point occurred in 57 aspirin-alone pts (2.4%) and 61 dual-therapy pts (2.6%)

  HR- 0.94 (95% CI, 0.66-1.35) P=0.75

Lee, C. W., et. al. (2013). Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation: A Randomized Controlled Trial. *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluting Stents

- The two groups did not differ significantly in terms of the individual risks of death from any cause.

- Major bleeding occurred in 24 (1.1%) and 34 (1.4%) of the aspirin-alone group and dual-therapy group pts, respectively

HR-0.71 (95% CI, 0.42-1.20) P=0.20

Lee, C. W., et. al. (2013). Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation: A Randomized Controlled Trial. *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluding Stents

Table 3. Baseline Characteristics of the Patients in Cohorts 1 and 2[a]

Characteristic	Cohort 1 (N=2701)	Cohort 2 (N=2344)	P value
No. of Patients			
Age—yr	62.5±10.0	62.3±10.1	0.48
Male sex	1883 (69.7%)	1615 (68.9%)	0.54
Diabetes mellitus	704 (26.1%)	714 (30.5%)	0.001
Hypertension	1540 (57.0%)	1362 (58.1%)	0.44
Current smoker	835 (30.9%)	580 (24.7%)	<0.001
Previous coronary angioplasty	336 (12.4%)	253 (10.8%)	0.07
Previous myocardial infarction	96 (3.6%)	99 (4.2%)	0.22
Previous stroke	102 (3.8%)	102 (4.4%)	0.30
Ejection fraction	59.3±9.4	59.4±8.7	0.69
Multivessel disease	1300 (48.1%)	1136 (48.5%)	0.81
Clinical indication at the index procedure			<0.001
Stable angina	1014 (37.5%)	953 (40.7%)	
Unstable angina	1102 (40.8%)	799 (34.1%)	
Non-ST-elevation myocardial infarction	289 (10.7%)	245 (10.5%)	
ST-elevation myocardial infarction	296 (11.0%)	332 (14.2%)	
Others	0	15 (0.6%)	

Lee, C. W., et. al. (2013). *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluding Stents

Discharge medication			
Aspirin	2692 (99.7%)	2333 (99.5%)	0.44
Clopidogrel	2696 (99.8%)	2327 (99.3%)	0.004
ACE inhibitor	1236 (45.8%)	1315 (56.1%)	<0..001
Beta-blocker	1786 (66.1%)	1522 (64.9%)	0.37
Calcium-channel blocker	1469 (54.4%)	978 (41.7%)	<0.001
Statin	2139 (79.2%)	2011 (85.8%)	<0.001

Lee, C. W., et. al. (2013). *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluding Stents

Left anterior descending artery	1781 (49.5%)	1768 (50.6%)	
Left circumflex artery	715 (19.9%)	651 (18.6%)	
Right coronary artery	976 (27.1%)	972 (27.8%)	
Left main coronary artery	112 (3.1%)	90 (2.6%)	
Graft	0	5 (0.1%)	
Others	11 (0.3%)	8 (0.2%)	
Multivessel intervention			
ACC-AHA lesion class B_2 or C	2838 (78.8%)	2734 (78.2%)	0.53
Bifurcation	477 (13.2%)	475 (13.6%)	0.67
Calcification	168 (4.7%)	172 (4·9%)	0.62
Total occlusion	407 (11.3%)	393 (11.2%)	0.94
Stents per lesion	1.3±0.5	1.2±0.5	0.003
Stent length per lesion	31.3±15.9	29.3±15.8	<0.001
Type of drug-eluting stent			0.25
Sirolimus	1566 (43.5%)	1551 (44.3%)	
Paclitaxel	738 (20.5%)	709 (20.3%)	
Zotarolimus	682 (18.9%)	664 (19.0%)	
Everolimus	427 (11.9%)	364 (10.4%)	
Others	190 (5.3%)	210 (6.0%)	

[a]Plus–minus values are means ±SD. ACC denotes American College of Cardiology, ACE angiotensin-converting enzyme, and AHA American Heart Association.

Lee, C. W., et. al. (2013). *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Mos with Drug Eluding Stents

End Point	Cumulative Event at 48 Mo, N (%)		Hazard Ratio (95% CI)[a]	P Value
	Aspirin Alone (N=1170)	Clopidogrel+ Aspirin (N=1174)		
Efficacy				
Cardiac death, myocardial infarction, or stroke (primary end point)	68 (5.3)	59 (4.5)	1.10 (0.79-1.55)	0.57
Death, myocardial infarction or stroke	81 (6.3)	77 (5.9)	1.02 (0.76-1.38)	0.90
Cardiac death or myocardial infarction	45 (3.5)	38 (2.8)	1.08 (0.71-1.64)	0.72
Death				
Death from any cause	37 (2.9)	46 (3.5)	0.76 (0.50-1.14)	0.19
Cardiac death	24 (1.9)	26 (2.0)	0.80 (0.47-1.38)	0.43
Myocardial infarction	26 (2.0)	16 (1.2)	1.60 (0.87-2.94)	0.13
Stroke				
Any stoke	26 (2.0)	26 (2.1)	0.97 (0.57-1.64)	0.91
Ischemic stroke	18 (1.4)	16 (1.3)	1.06 (0.56-2.02)	0.86
Stent thrombosis, definite	13 (1.0)	8 (0.6)	1.76 (0.74-4.20)	0.20
Repeat revascularization	87 (6.8)	92 (7.2)	0.95 (0.72-1.26)	0.73

Lee, C. W., et. al. (2013). *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluding Stents

TIMI major[b]	23 (1.8)	40 (3.2)	0.61 (0.38-0.99)	0.045
Fatal	1 (0.1)	2 (0.2)	0.50 (0.05-5.53)	0.57
Intracranial	2 (0.2)	9 (0.7)	0.22 (0.05–1.03)	0.054
Net clinical outcome				
Cardiac death, myocardial infarction, stroke, stent thrombosis, or	84 (6.69)	91 (7.0)	0.91 (0.69–1.21)	0.52
TIMI major bleeding				

[a]The hazard ratio throughout the entire treatment period is for the aspirin-alone group as compared to the dual-therapy group.

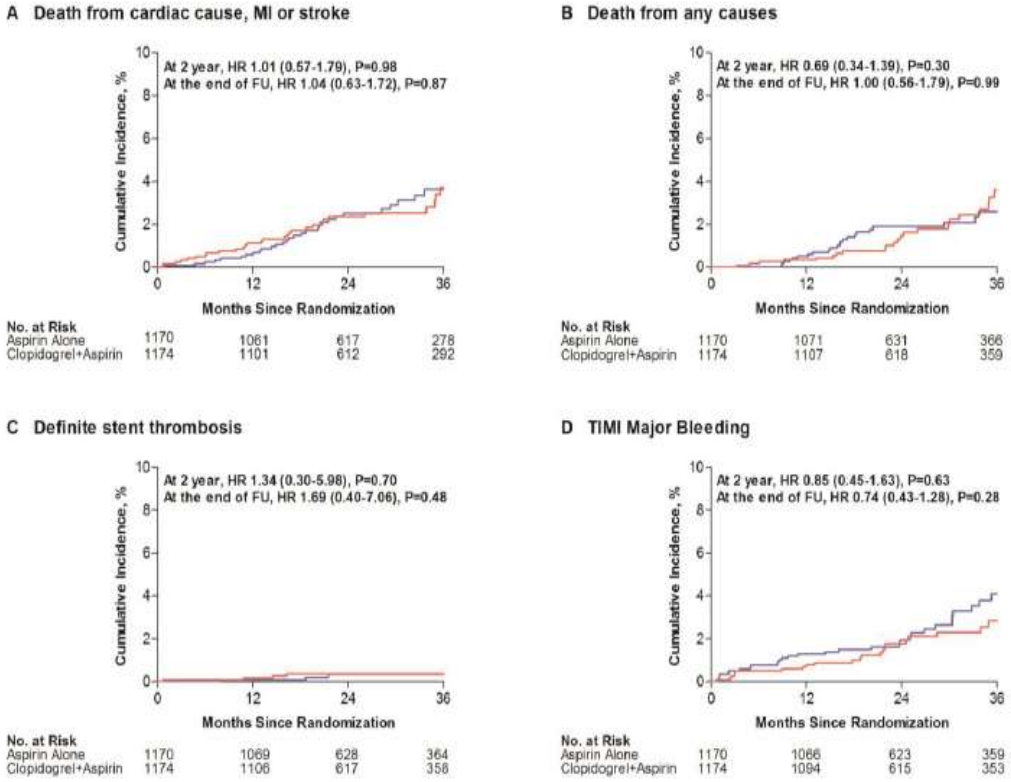
[b]Thrombolysis in Myocardial Infarction (TIMI) major bleeding refers to events that were adjudicated on the basis of previously used TIMI criteria.[4]

Lee, C. W., et. al. (2013). *Circulation*. doi: 10.1161/circulationaha.113.003303

Mono Antiplatelet Therapy Fine After 12 Months with Drug Eluding Stents

III. Supplementary Figure and Legends

Figure 1. Kaplan–Meier Estimates of Primary and Secondary End Points in Cohort 2. The cumulative incidences of the primary end point of death from cardiac causes, myocardial infarction, or stroke (A), death from any cause (B), definite stent thrombosis (C), and TIMI major bleeding (D) are shown. The dual-therapy group is shown in blue and aspirin-alone group in red.



Lee, C. W., et. al. (2013). *Circulation*. doi: 10.1161/circulationaha.113.003303

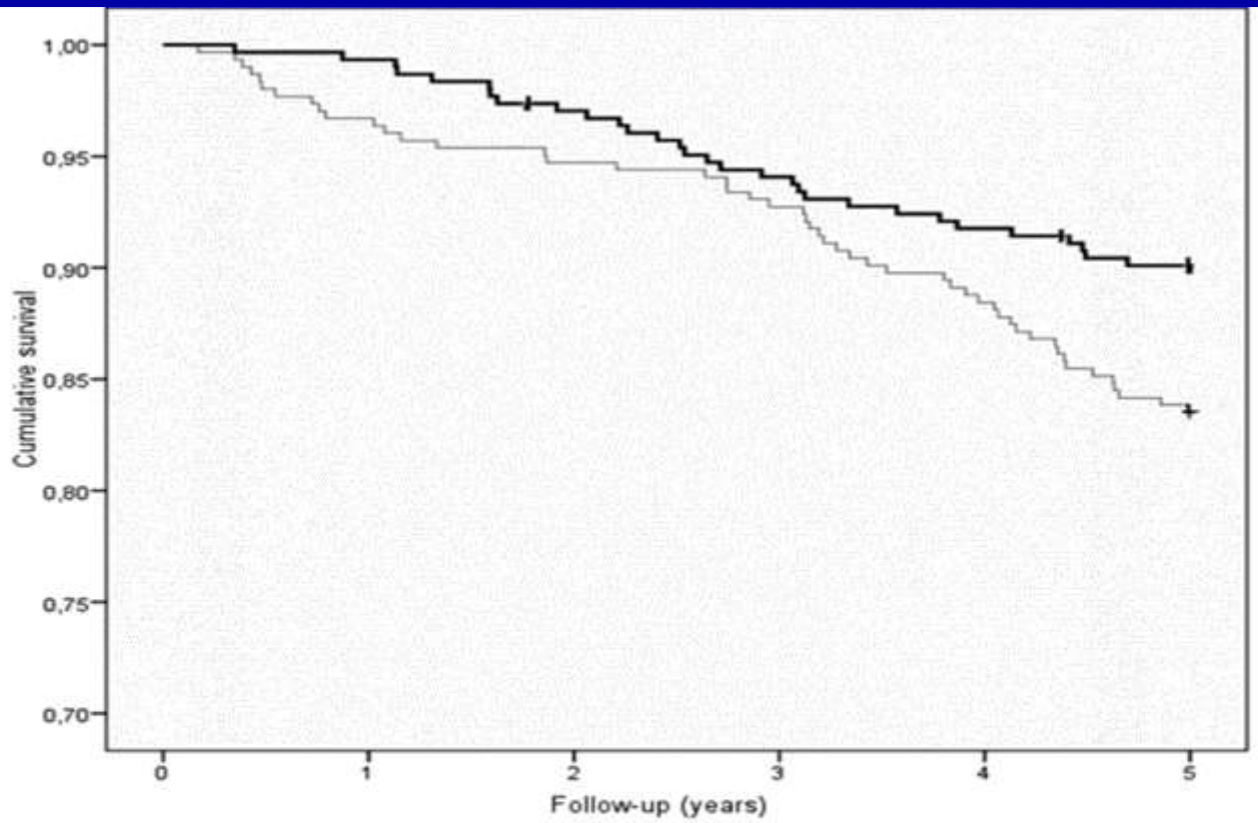
Exercise & Ischemic Heart Disease

Exercise Mediates the Association Between Positive Affect and 5-Year Mortality in Patients With Ischemic Heart Disease

Madelein T. Hoogwegt, Henneke Versteeg, Tina B. Hansen, Lau C. Thygesen, Susanne S. Pedersen, and Ann-Dorthe Zwisler

Circ Cardiovasc Qual Outcomes
Volume 6(5):559-566
September 17, 2013

Cumulative survival curve for all-cause mortality, stratified by the presence of high vs low positive affect.

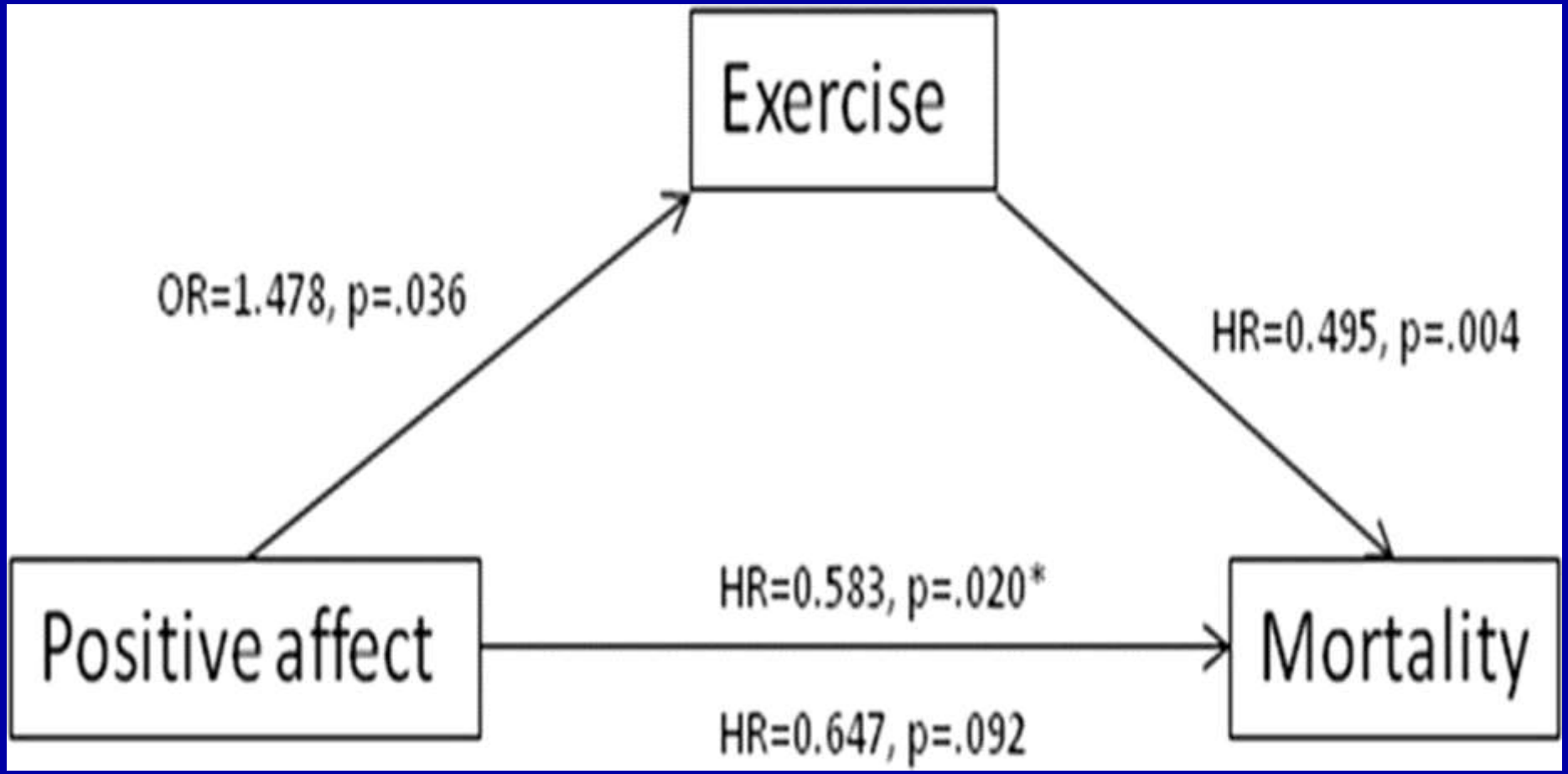


Number of patients at risk

	Baseline	1 year	2 years	3 years	4 years	5 years
Low positive affect	303	293	286	280	267	253
High positive affect	304	301	293	284	277	271
Total number of patients	607	594	579	564	544	524

Hoogwegt M et al. Circ Cardiovasc Qual Outcomes 2013;6:559-566

Final mediation model for positive affect, exercise, and mortality (adjusted model).



Hoogwegt M et al. Circ Cardiovasc Qual Outcomes 2013;6:559-566

Testosterone in Men

Beneficial and Adverse Effects of Testosterone on the Cardiovascular System in Men

Review – PubMed search from 1970-2013 with terms related to androgens in combination with CVD and testosterone of all levels.

Evidence Synthesis: Low T has been linked to increased BP, dyslipidemia, atherosclerosis, arrhythmia, thrombosis, endothelial dysfunction, & impaired left ventricular function. However, treatments with T to restore "normal concentrations" have not been proven to be beneficial with respect to CVD, nor have they shown specific adverse CV effects.

Conclusion: The exact relationship between T and CVD would support a cautious, restrained approach to T therapy in aging men, pending clarification of benefits and risks by adequately powered clinical trials of sufficient duration.

Ruige, J, Ouwens, M., et al. Beneficial and Adverse Effects of T on CVD. Endocrinol Metab 98: 0000-0000, 9/24/2013

Beneficial and Adverse Effects of Testosterone on the Cardiovascular System in Men

Summary of Prospective Observational Studies on T and Incident CVD in Healthy Men

First Author, Year (Ref.)	Age at Baseline, y	Duration, y	No. of Events/ Progression of Disease	Outcome	Abstract Conclusions of Authors
Price, 1997 (72)	55–74	5	40	AS	No support for sex hormones in the development of peripheral arterial disease
Hak, 2002 (73)	>55	7	28	AS	An independent inverse association between T and aortic atherosclerosis
Muller, 2004 (74)	77.2	4	195	AS	Low free T was related to IMT of the common carotid artery
Eller, 2005 (75)	50	4	95	AS	T was borderline significantly associated (negatively) with progression in IMT
Hougaku, 2006 (76)	68	11.8	206	AS	Adverse influence of low T on the CV system in men may be mediated in part via effects of T on vascular structure and function
Tivesten, 2006 (77)	58	3	313	AS	No association between total or free T and change in IMT
Cauley, 1987 (79)	46	6–8	163	MI	No relationship between sex hormones and risk of a heart attack
Philips, 1988 (80)	52–74	7	96	MI	No association between sex hormones and MI
Vikan, 2009 (81)	59.6	11.2	144	MI	No significant changes in risk for first-ever MI across different total or free T levels
Yeap, 2009 (53)	78.4	3.5	119	S	Lower total T predicts increased incidence of S or transient ischemic attack
Yarnell, 1993 (82)	45–59	5	153	IHD	No support for T as primary risk factor for IHD
Araujo, 2007 (83)	40 to 70	15.3	101	IHD	Little support for the hypothesis that endogenous sex steroid levels are associated with risk of premature death but further investigation of the relationship between sex steroids and mortality from ischemic heart disease may be warranted
Hautanen, 1994 (84)	48	5	62	CVD	T no coronary risk factor
Arnlöv, 2006 (85)	56	10	386	CVD	Serum T was not statistically significantly associated with incident CVD
Khaw, 2007 (86)	40 to 79	7	293	CVD	T inversely related to mortality due to CVD
Akishita, 2010 (87)	48	6	20	CVD	Low T is associated with CV events
Ohlsson, 2011 (88)	69–81	5	485	CV events	High T predicted a reduced risk of CV events
Menke, 2010 (89)	40	9	42	CM	Low T has a higher risk of CV mortality
Hyde, 2012 (90)	70–88	5.1	207	CM	Low T predicts mortality from CVD

Ruige, J, Ouwens, M., et al. Beneficial and Adverse Effects of T on CVD. Endocrinol Metab 98: 0000-0000, 9/24/2013

Bale Doneen METHOD

Beneficial and Adverse Effects of Testosterone on the Cardiovascular System in Men

Summary of T Trials; more than 100 participants & reporting CV Adverse Events

Author, Year (Ref.)	Age, y	Health Status/Low T (Y/N)	Duration, mo	T Dose	Randomization No., Placebo vs T	Lipids/BP After T	No. of Placebo vs T, CVD Events
Copenhagen Study Group, 1986 (1)	24–79	Alcoholic cirrhosis/N	28	Oral 600 mg/d	87:134	—	0:3, thrombosis
Snyder, 2001 (16)	>65	Y	36	Transdermal patch 6 mg/d	54:54	Lipids ↔	1:2, myocardial infarction; 2:2, CABG; 1:3, arrhythmia; 1:2, vascular events
Emmelot-Vonk, 2008 (15)	60–80	Y	6	Oral TU 160 mg/d	110:113	↓ HDL; ↑ BP ($P < .08$)	3:7, cardiovascular complaints
Legros, 2009 (14)	≥50	Y	12	Oral TU 80, 160, 240 mg/d	79:237	—	0:2, arrhythmia, cardiac arrest
Srinivas-Shankar, 2010 (7)	≥ 65	Frailty/Y	6	Transdermal gel 50 mg/d	132:130	Lipids ↔	1:0, myocardial infarction; 1:1, abdominal aneurysm; 0:2, pulmonary embolism, heart failure
Basaria, 2010 (6)	≥65	Limitations in mobility/Y	6	Transdermal gel 100 mg/d	103:106	—	1:2, syncope; 2:4, arrhythmia; 1:3, hypertension; 1:0, carotid-artery plaque; 0:5, coronary syndrome, chest pain, ischemia; 0:4, myocardial infarction, CABG, death due to myocardial infarction; 0:5, peripheral edema; 0:1, stroke; 0:1, heart failure
Kalinchenko, 2010 (11)	35–70	Metabolic syndrome/Y	7.5	Parenteral TU 1000 mg im at baseline, 6 and 18 wk	71:113	Lipids ↔	2:0, angina, myocardial infarction
Jones, 2011 (10)	≥40	Type 2 diabetes or metabolic syndrome/Y	12	Transdermal gel 60 mg/d	112:108	Lipids ↔; BP ↔	12:5[b]
Ho, 2011 (13)	≥40	Symptoms of T deficiency/Y	12	Parenteral TU 1000 mg im at baseline, 6, 18, 30, and 48 wk	60:60	—	1:1, died due to myocardial infarction; 1:1, chest pain
Kaufman, 2011 (12)	18–80	Y	6	Transdermal 1.62% gel 2.5 mg/d	40:234		0:11, vascular disorders

Ruige, J, Ouwens, M., et al. Beneficial and Adverse Effects of T on CVD. Endocrinol Metab 98: 0000-0000, 9/24/2013

Cinnamon

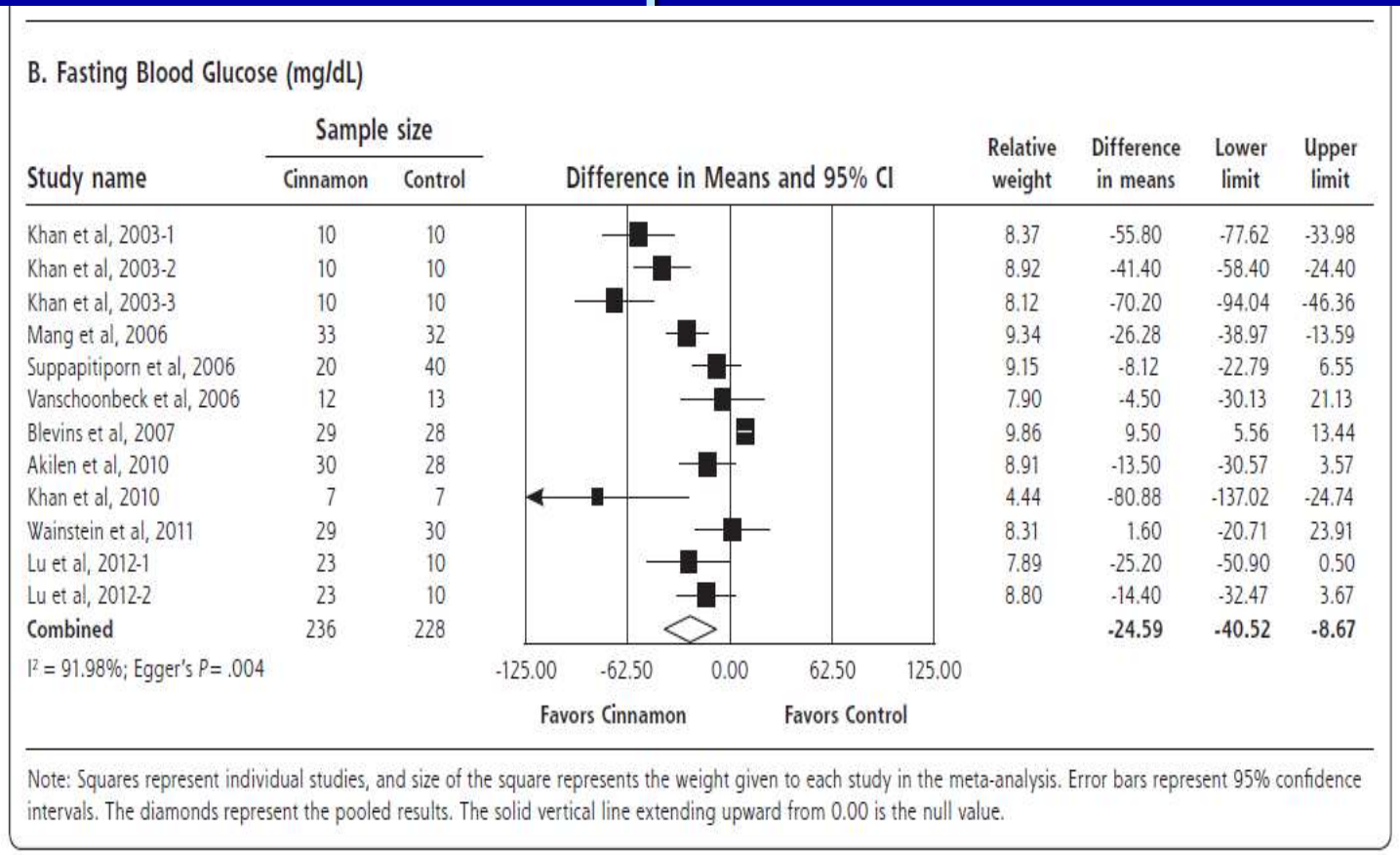
Cinnamon Reduces Glucose and Improves Lipids

- Meta-analysis of 10 RCTs; 543 diabetic pts; cinnamon 120 mg/d to 6 g/d for 4 to 18 wks

- Cinnamon showed statistically significant decrease in levels of fasting plasma glucose, TC, LDL-C, TG and increased HDL-C.

Allen, R. W., et. al. (2013). Cinnamon Use in Type 2 Diabetes: An Updated Systematic Review and Meta-Analysis. *Ann Fam Med, 11*(5), 452-459.

Cinnamon Reduces Glucose and Improves Lipids



B. Fasting Blood Glucose (mg/dL)

Study name	Sample size: Cinnamon	Sample size: Control	Relative weight	Difference in means	Lower limit	Upper limit
Khan et al, 2003-1	10	10	8.37	-55.80	-77.62	-33.98
Khan et al, 2003-2	10	10	8.92	-41.40	-58.40	-24.40
Khan et al, 2003-3	10	10	8.12	-70.20	-94.04	-46.36
Mang et al, 2006	33	32	9.34	-26.28	-38.97	-13.59
Suppapitiporn et al, 2006	20	40	9.15	-8.12	-22.79	6.55
Vanschoonbeck et al, 2006	12	13	7.90	-4.50	-30.13	21.13
Blevins et al, 2007	29	28	9.86	9.50	5.56	13.44
Akilen et al, 2010	30	28	8.91	-13.50	-30.57	3.57
Khan et al, 2010	7	7	4.44	-80.88	-137.02	-24.74
Wainstein et al, 2011	29	30	8.31	1.60	-20.71	23.91
Lu et al, 2012-1	23	10	7.89	-25.20	-50.90	0.50
Lu et al, 2012-2	23	10	8.80	-14.40	-32.47	3.67
Combined	236	228		**-24.59**	**-40.52**	**-8.67**

I^2 = 91.98%; Egger's P= .004

Note: Squares represent individual studies, and size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamonds represent the pooled results. The solid vertical line extending upward from 0.00 is the null value.

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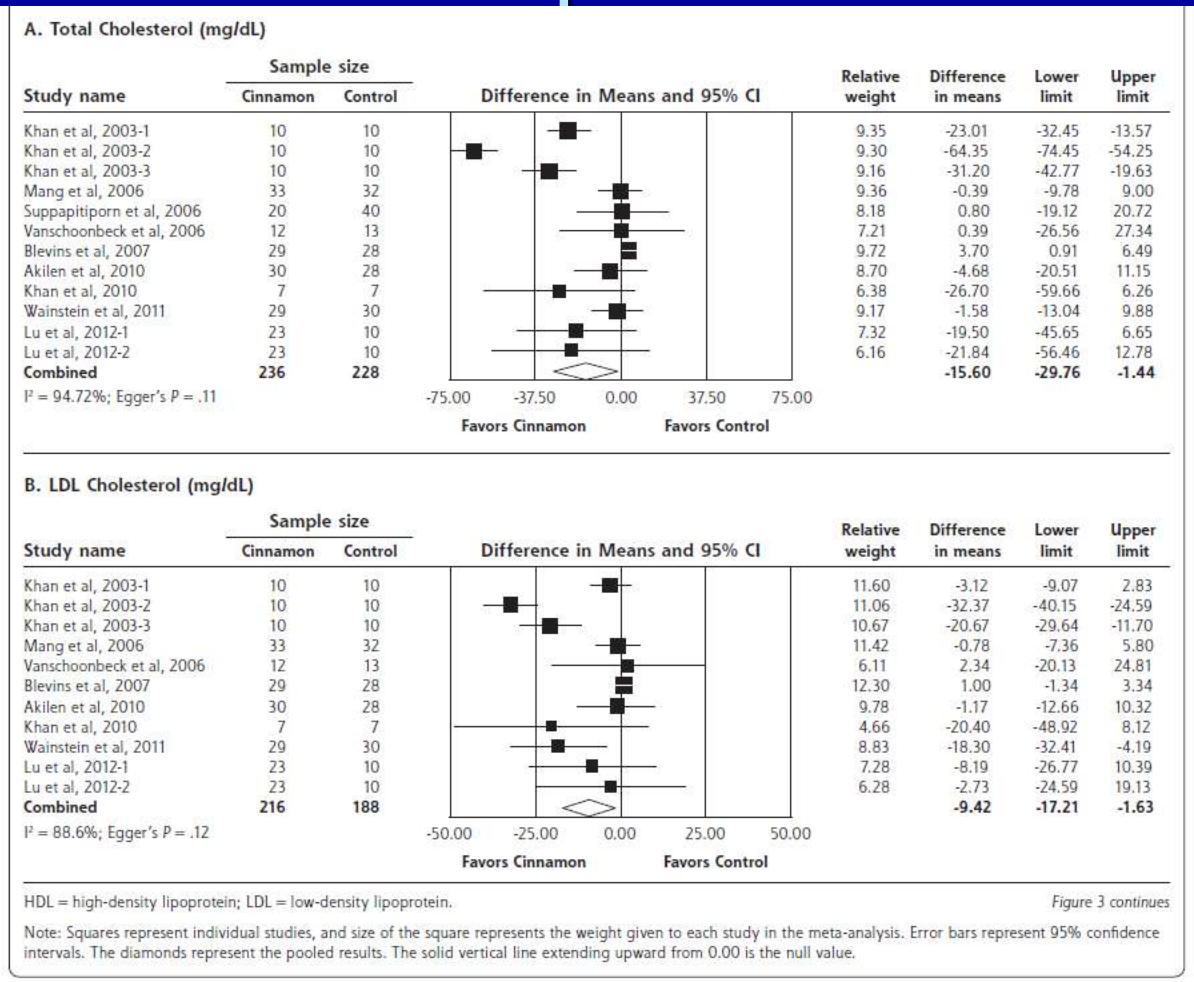
Cinnamon Reduces Glucose and Improves Lipids



A. Total Cholesterol (mg/dL)

Study name	Sample size: Cinnamon	Sample size: Control	Relative weight	Difference in means	Lower limit	Upper limit
Khan et al, 2003-1	10	10	9.35	-23.01	-32.45	-13.57
Khan et al, 2003-2	10	10	9.30	-64.35	-74.45	-54.25
Khan et al, 2003-3	10	10	9.16	-31.20	-42.77	-19.63
Mang et al, 2006	33	32	9.36	-0.39	-9.78	9.00
Suppapitiporn et al, 2006	20	40	8.18	0.80	-19.12	20.72
Vanschoonbeck et al, 2006	12	13	7.21	0.39	-26.56	27.34
Blevins et al, 2007	29	28	9.72	3.70	0.91	6.49
Akilen et al, 2010	30	28	8.70	-4.68	-20.51	11.15
Khan et al, 2010	7	7	6.38	-26.70	-59.66	6.26
Wainstein et al, 2011	29	30	9.17	-1.58	-13.04	9.88
Lu et al, 2012-1	23	10	7.32	-19.50	-45.65	6.65
Lu et al, 2012-2	23	10	6.16	-21.84	-56.46	12.78
Combined	**236**	**228**		**-15.60**	**-29.76**	**-1.44**

$I^2 = 94.72\%$; Egger's $P = .11$

Difference in Means and 95% CI: -75.00, -37.50, 0.00, 37.50, 75.00

Favors Cinnamon / Favors Control

B. LDL Cholesterol (mg/dL)

Study name	Sample size: Cinnamon	Sample size: Control	Relative weight	Difference in means	Lower limit	Upper limit
Khan et al, 2003-1	10	10	11.60	-3.12	-9.07	2.83
Khan et al, 2003-2	10	10	11.06	-32.37	-40.15	-24.59
Khan et al, 2003-3	10	10	10.67	-20.67	-29.64	-11.70
Mang et al, 2006	33	32	11.42	-0.78	-7.36	5.80
Vanschoonbeck et al, 2006	12	13	6.11	2.34	-20.13	24.81
Blevins et al, 2007	29	28	12.30	1.00	-1.34	3.34
Akilen et al, 2010	30	28	9.78	-1.17	-12.66	10.32
Khan et al, 2010	7	7	4.66	-20.40	-48.92	8.12
Wainstein et al, 2011	29	30	8.83	-18.30	-32.41	-4.19
Lu et al, 2012-1	23	10	7.28	-8.19	-26.77	10.39
Lu et al, 2012-2	23	10	6.28	-2.73	-24.59	19.13
Combined	**216**	**188**		**-9.42**	**-17.21**	**-1.63**

$I^2 = 88.6\%$; Egger's $P = .12$

Difference in Means and 95% CI: -50.00, -25.00, 0.00, 25.00, 50.00

Favors Cinnamon / Favors Control

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Figure 3 continues

Note: Squares represent individual studies, and size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamonds represent the pooled results. The solid vertical line extending upward from 0.00 is the null value.

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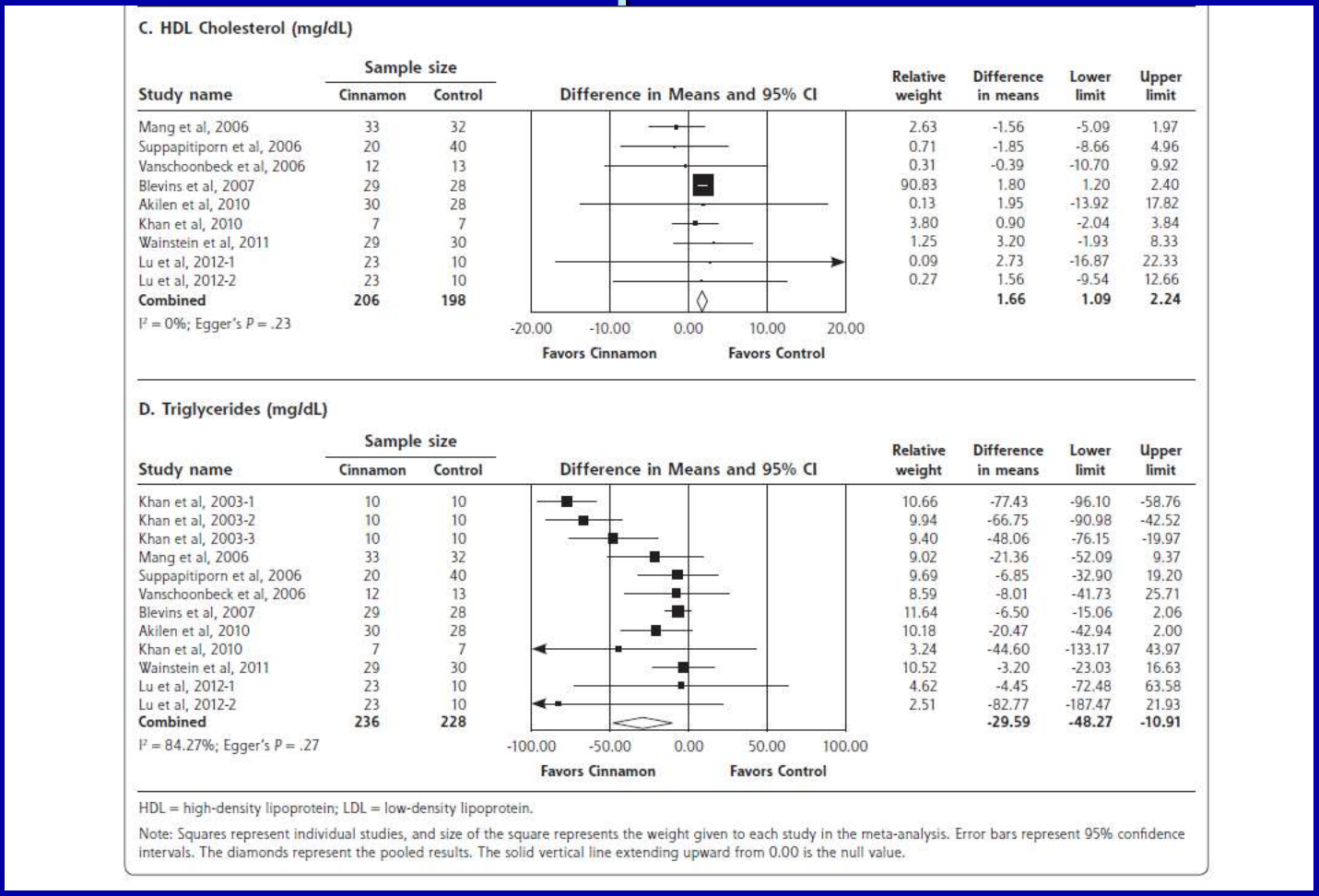
Cinnamon Reuces Glucose and Improves Lipids



C. HDL Cholesterol (mg/dL)

Study name	Sample size: Cinnamon	Sample size: Control	Relative weight	Difference in means	Lower limit	Upper limit
Mang et al, 2006	33	32	2.63	-1.56	-5.09	1.97
Suppapitiporn et al, 2006	20	40	0.71	-1.85	-8.66	4.96
Vanschoonbeck et al, 2006	12	13	0.31	-0.39	-10.70	9.92
Blevins et al, 2007	29	28	90.83	1.80	1.20	2.40
Akilen et al, 2010	30	28	0.13	1.95	-13.92	17.82
Khan et al, 2010	7	7	3.80	0.90	-2.04	3.84
Wainstein et al, 2011	29	30	1.25	3.20	-1.93	8.33
Lu et al, 2012-1	23	10	0.09	2.73	-16.87	22.33
Lu et al, 2012-2	23	10	0.27	1.56	-9.54	12.66
Combined	**206**	**198**		**1.66**	**1.09**	**2.24**

$I^2 = 0\%$; Egger's $P = .23$

Difference in Means and 95% CI

-20.00 -10.00 0.00 10.00 20.00

Favors Cinnamon Favors Control

D. Triglycerides (mg/dL)

Study name	Sample size: Cinnamon	Sample size: Control	Relative weight	Difference in means	Lower limit	Upper limit
Khan et al, 2003-1	10	10	10.66	-77.43	-96.10	-58.76
Khan et al, 2003-2	10	10	9.94	-66.75	-90.98	-42.52
Khan et al, 2003-3	10	10	9.40	-48.06	-76.15	-19.97
Mang et al, 2006	33	32	9.02	-21.36	-52.09	9.37
Suppapitiporn et al, 2006	20	40	9.69	-6.85	-32.90	19.20
Vanschoonbeck et al, 2006	12	13	8.59	-8.01	-41.73	25.71
Blevins et al, 2007	29	28	11.64	-6.50	-15.06	2.06
Akilen et al, 2010	30	28	10.18	-20.47	-42.94	2.00
Khan et al, 2010	7	7	3.24	-44.60	-133.17	43.97
Wainstein et al, 2011	29	30	10.52	-3.20	-23.03	16.63
Lu et al, 2012-1	23	10	4.62	-4.45	-72.48	63.58
Lu et al, 2012-2	23	10	2.51	-82.77	-187.47	21.93
Combined	**236**	**228**		**-29.59**	**-48.27**	**-10.91**

$I^2 = 84.27\%$; Egger's $P = .27$

Difference in Means and 95% CI

-100.00 -50.00 0.00 50.00 100.00

Favors Cinnamon Favors Control

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Note: Squares represent individual studies, and size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamonds represent the pooled results. The solid vertical line extending upward from 0.00 is the null value.

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Upcoming Events

October

10-12: Intern. Acad. of Biomedical Dentistry & Medicine – Houston

16-20: Bale/Doneen Reunion and CHL Symposium, – Dallas Ft. Worth

November

8-9: Bale/Doneen Preceptorship Program – Nashville, TN

13: Live Chat

December

11: Live Chat

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