Dyslipidemia
Statins, Niacin, and Diet

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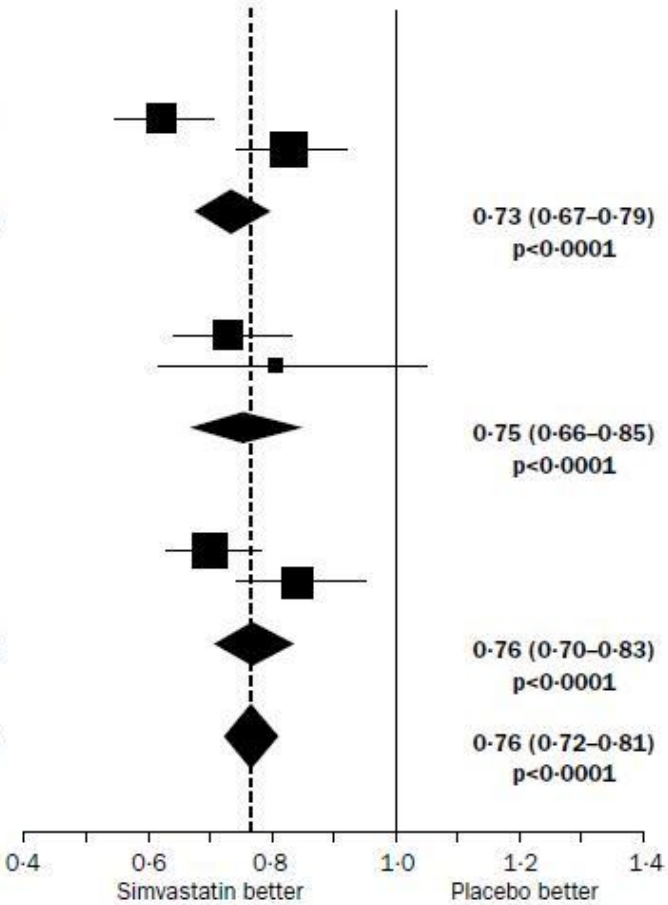
Quote 3: "The fact that an opinion has been widely held is no evidence whatever that it isn't utterly absurd. Indeed, in view of the silliness of the majority of mankind, a widespread belief is more likely to be foolish than sensible." Bertrand Russell.

MRC BHF Heart Protection Study

Lancet 360:7, 2002

- 20536 adults aged 40-80 with coronary/vascular disease, prior stroke, or type 2 diabetes, total cholesterol > 135 for 5 years
- Randomized (double blind) to placebo vs. simvastatin 40 mg
- Simvastatin 40 mg lowered LDL lowered by 38% from 143 to 89 mg dl^{-1}
- Major reductiones in MI, cardiovascular death, Stroke, and death

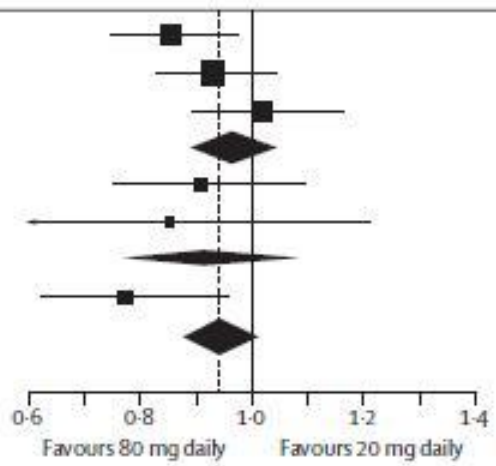
Type of major vascular event	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)	Event rate ratio (95% CI)
Coronary events			
Non-fatal MI	357 (3·5%)	574 (5·6%)	
Coronary death	587 (5·7%)	707 (6·9%)	
Subtotal: major coronary event	**898 (8·7%)**	**1212 (11·8%)**	**0·73 (0·67–0·79) p<0·0001**
Strokes			
Non-fatal stroke	366 (3·6%)	499 (4·9%)	
Fatal stroke	96 (0·9%)	119 (1·2%)	
Subtotal: any stroke	**444 (4·3%)**	**585 (5·7%)**	**0·75 (0·66–0·85) p<0·0001**
Revascularisations			
Coronary	513 (5·0%)	725 (7·1%)	
Non-coronary	450 (4·4%)	532 (5·2%)	
Subtotal: any revascularisation	**939 (9·1%)**	**1205 (11·7%)**	**0·76 (0·70–0·83) p<0·0001**
ANY MAJOR VASCULAR EVENT	**2033 (19·8%)**	**2585 (25·2%)**	**0·76 (0·72–0·81) p<0·0001**



SEARCH (1) Lancet 376:1658, 2010

- 12094 adults aged 18-80 with coronary disease
- Randomized (double blind) to simvastatin 20 vs. 80 mg
- LDL on 20 mg was 97, on 80 mg was 83 mg dl^{-1}

	Simvastatin allocation		Risk ratio (95% CI)	p value
	80 mg daily (n=6031)	20 mg daily (n=6033)		
Non-fatal MI	397 (6·6%)	463 (7·7%)		
Coronary revascularisation	570 (9·5%)	610 (10·1%)		
CHD death	447 (7·4%)	439 (7·3%)		
Major coronary event	**1189 (19·7%)**	**1225 (20·3%)**	0·96 (0·89–1·04)	0·37
Non-fatal stroke	209 (3·5%)	230 (3·8%)		
Fatal stroke	57 (0·9%)	67 (1·1%)		
Total stroke	**255 (4·2%)**	**279 (4·6%)**	0·91 (0·77–1·08)	0·30
Non-coronary revascularisation	144 (2·4%)	186 (3·1%)		
Major vascular event	**1477 (24·5%)**	**1553 (25·7%)**	0·94 (0·88–1·01)	0·10



- For Major Coronary Event (MI, revascularization, or CV death)
- RRR = 4 % (not significant) vs. 26 % in the HPS
- ARR = 0.6 % (not significant) vs. 3.1 %
- NNT = 167 (not significant) vs. 32

SEARCH (2) NEJM 359:789 (2008)

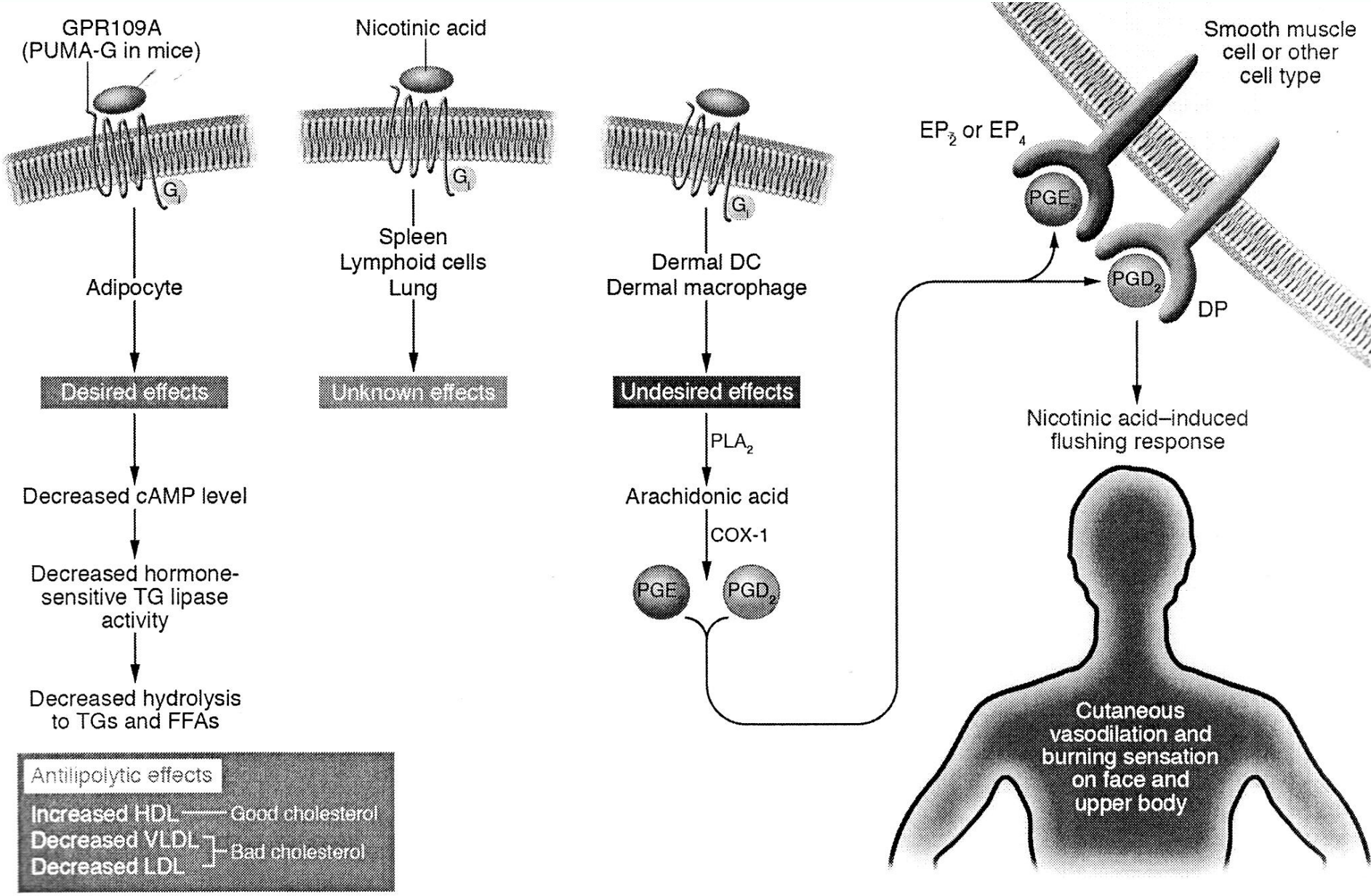
- 12064 patients with prior MI randomized 80 vs. 20 mg simvastatin daily
- Myopathy 0.13% with Simvastatin 20 mg and 1.62% with Simvastatin 80 mg
- Myopathy predictors with Simvastatin 80 mg
  - Amiodarone 8.8 (CI 4-18)
    - Not seen with 20 mg simvastatin & amiodarone
    - Recommend $\leq$ 20 mg simvastatin with amiodarone
  - Age > 65 2.3 (CI 1.3-4)
  - Creatinine > 1.0 2.5 (CI 1.4-5)
  - Ca antagonists 2.7 (CI 1.6-4)

SEARCH (3) NEJM 359:789 (2008)

- Genome scan of myopathy revealed linkage with SLC01B1 odds 4.3 (CI 2-7, p=0.001)
  - CC risk 18% (60% population risk from C)
  - CT risk 3%
  - TT risk 0.6%
- HPS (simvastatin 40) odds 2.6 (CI 1.3-5)
- SLC01B1 encodes the organic acid transporting peptide OATP1B1, people with C allele have higher serum statin levels.
- Summary: Big benefit with starting a statin, less benefit and more myopathy with increasing dose

Niacin & Flushing

JCI 115:3400 (2005)



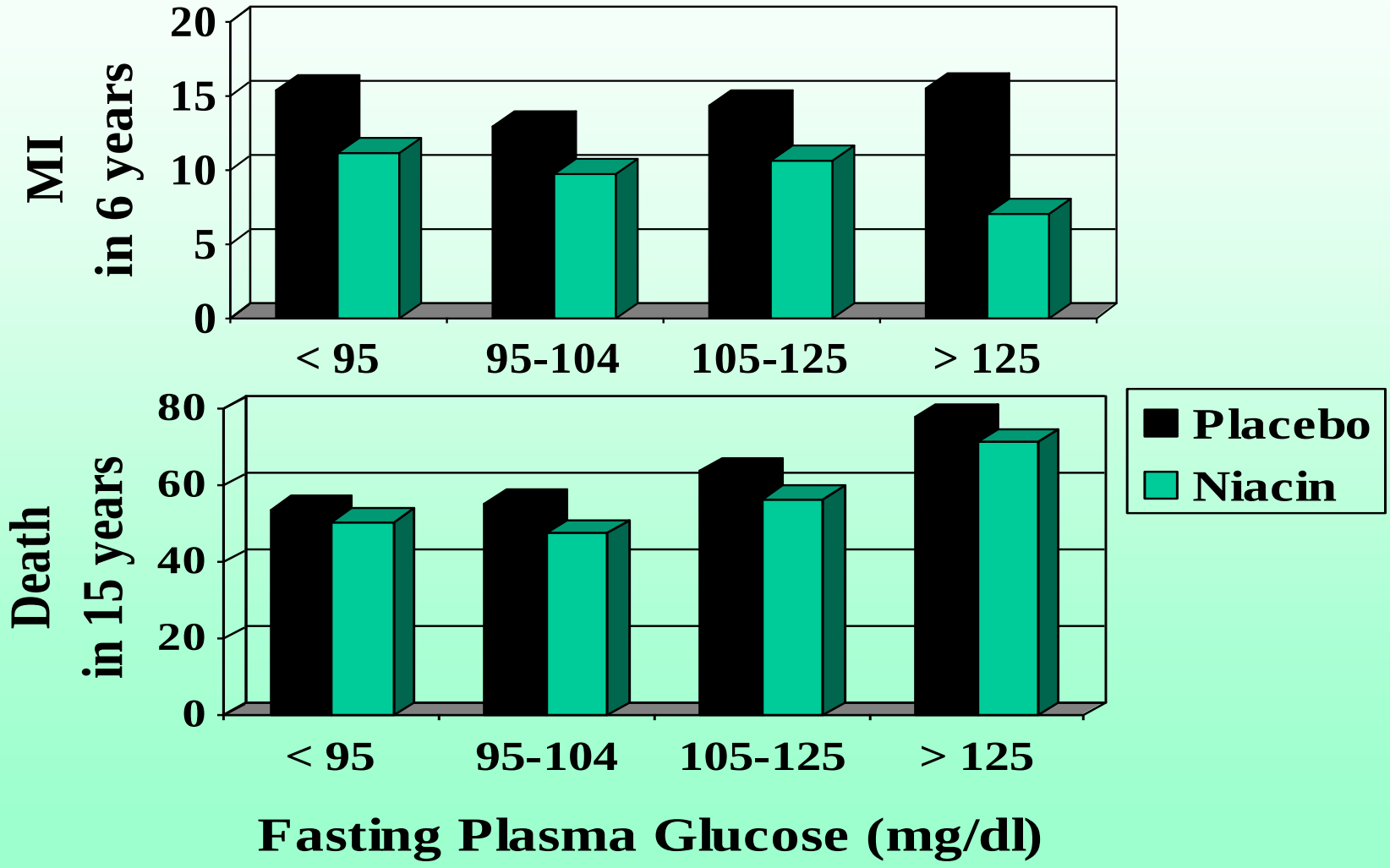
CDP Niacin JAMA 231:360, 1975

3908 post MI patients, aged 30-65 for 6.2 years
Randomization (double blind): Placebo vs. Niacin 3000 mg qd

Niacin better	NNT	RRR
MI	27 (18 to 67)**	26**
CV death	70 (25 to -62)	6
MI or CV death	22 (14 to 71)**	15**
CVA	37 (23 to 165)**	24**
All Death	97 (26 to -46)	4

CDP Niacin Reanalysis AJC 95:254, 2005

Overall for 6y MI P<0.005 15y Death P<0.005



AIM HIGH (NEJM, 11/2011)

- 3414 people (85% men) with known atherosclerosis already Rx with simvastatin 40-80 ± ezetimibe 10 to mean LDL 76, HDL 35
- Randomized Niacin IR 1500-2000 mg
  vs. placebo (50 mg niacin to cause flush)
  - On Rx HDL 44 (niacin) vs. 38 (placebo), increased 16%
  - On Rx LDL 65 (niacin) vs. 68 (placebo)
- By 3 years, 25% assigned to niacin were not taking it.
- Placebo patient took more ezetimibe (22 vs. 10%) and more were on 80 mg simvastatin (25 vs. 18%)
- Trial stopped at 3 years – RR 1.02 (0.87-1.21) primary endpoint
  RR 1.13 (0.90-1.42) Death, MI, CVA
- Implication – if LDL is low (60s), then no difference niacin vs intensification of LDL lowering with more statin + ezetimibe
- Given positive CDP niacin trial, there may be a role for niacin in people with higher LDL (> 90) and/or HDL < 30

THRIVE HPS2 (1) doi:10.1093/eurheart/eht055

- 25673 Europeans and Chinese with prior MI, prior CVA, PVD, or DM with angina
- All treaded with simvastatin 40 ± ezetimibe 10
  - LDL 63 and HDL 44 mg dl^{-1}
- Randomized placebo vs niacin 2 g plus PGD_2 blocker to reduce flushing
- Niacin reduced LDL 20% and increased HDL 17%
- Trial stopped for lack of benefit on MI/CVA, however, the data on MI/CVA was NOT published
- Implications – if LDL is low (60s) and HDL normal (40s), then no benefit of niacin added to statin/ezetimibe

THRIVE HPS2 (2) doi:10.1093/eurheart/eht055

- Niacin was associated with flushing and GI symptoms in all subject, well known prior niacin side effect
- However, more myopathy and abnormal liver function tests in Chinese – I suspect 2 g is too much niacin for Chinese

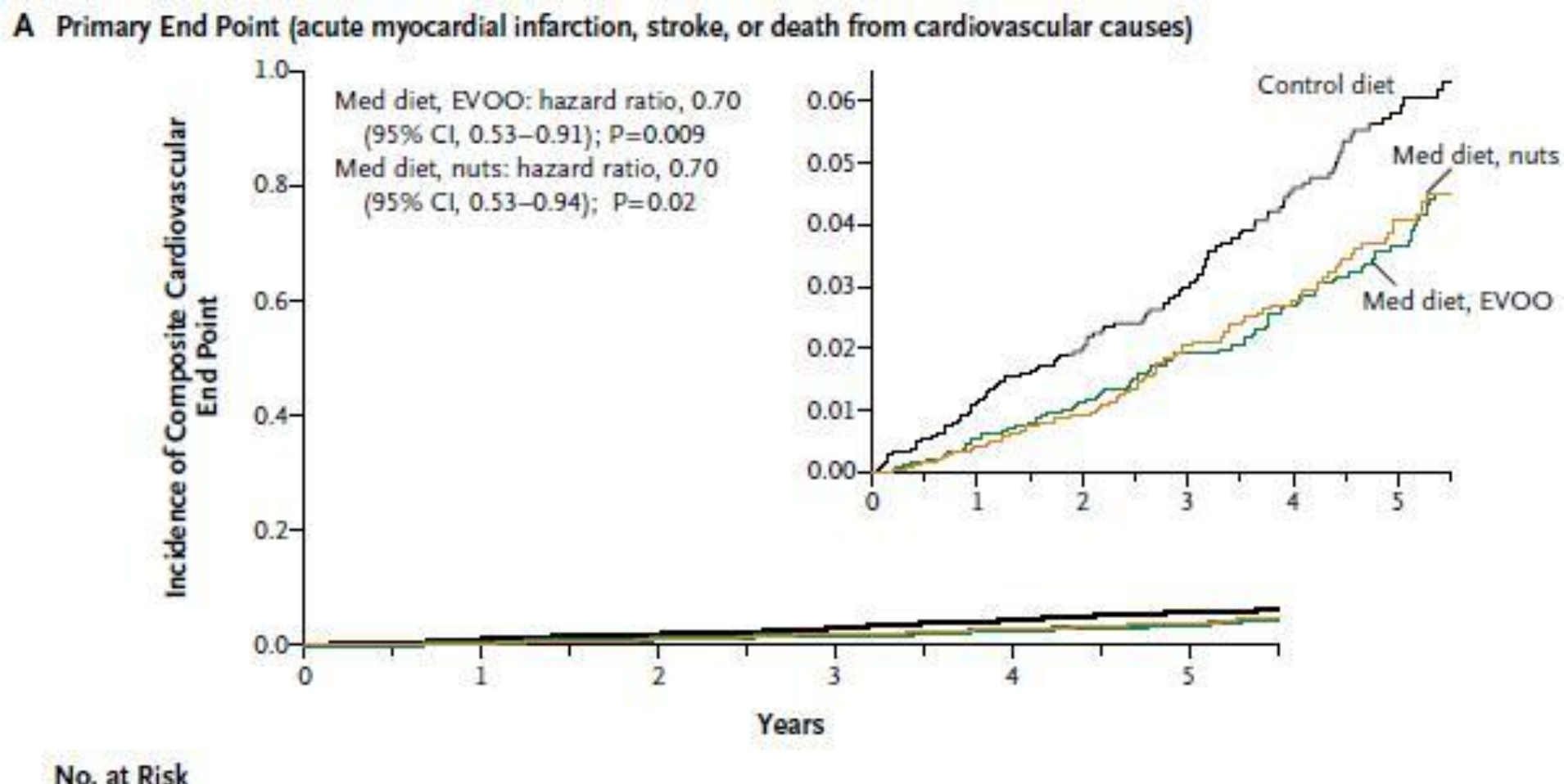
	Europeans		Chinese	
	Statin	Statin + Niacin	Statin	Statin + Niacin
Myopathy	0.02%	0.03%	0.06%	**0.32%**
LFTs >3x	0.14%	0.17%	0.16%	**0.46%**

PREDIMED (1) NEJM 368:1279 (2013)

- 7447 people, 57% female, aged 55-80, at high risk for CAD, but no known CAD, for 4.8 years
- Randomized to free unfiltered extra virgin olive oil (EVOO, 1 litre weekly) vs. free mixed nuts (50% walnuts, 25% almonds, 25% hazelnuts, 200 g weekly) vs. free nonfood gifts
- 15% smokers, 80% on BP meds, 57% on Lipid meds, 29% on antiplatelet, 39% on oral DM meds, 10% on insulin, 47% BMI > 30
  - similar in the three groups

PREDIMED (2) NEJM 368:1279 (2013)

- CV events significantly reduced with EVOO and Nuts
  - Stroke reduced more than MI or CV death
  - Mortality just missed with EVOO RRR 0.81 (0.63-1.05, p=0.11)



PREDIMED (3) NEJM 368:1279 (2013)

Similarities and Differences in Diet

- Differences
  - Olive oil > 4 tbsps daily, 94% in EVOO group, 80% in nuts, 59% control
  - Nuts > 4 servings weekly, 91% in nuts group, 42% in EVOO, 17% control
  - Vegetables > 2 servings daily, 74% in EVOO and nuts, 65% control
  - Fish > 3 servings weekly, 75% in EVOO and nuts, 66% control
  - Sofrito sauce > 2 servings weekly, 85% in EVOO and nuts, 65% control
    - Sofrito is tomato/onion/herbs simmered in EVOO
- Similarities
  - >95% use olive oil as main fat
  - 65% eat 3+ servings of fruit daily
  - 85% eat poultry more than red meat
  - >95% eat red/processed meat/butter/cream/margarine < 1 daily
  - >95% drink <1 soda daily

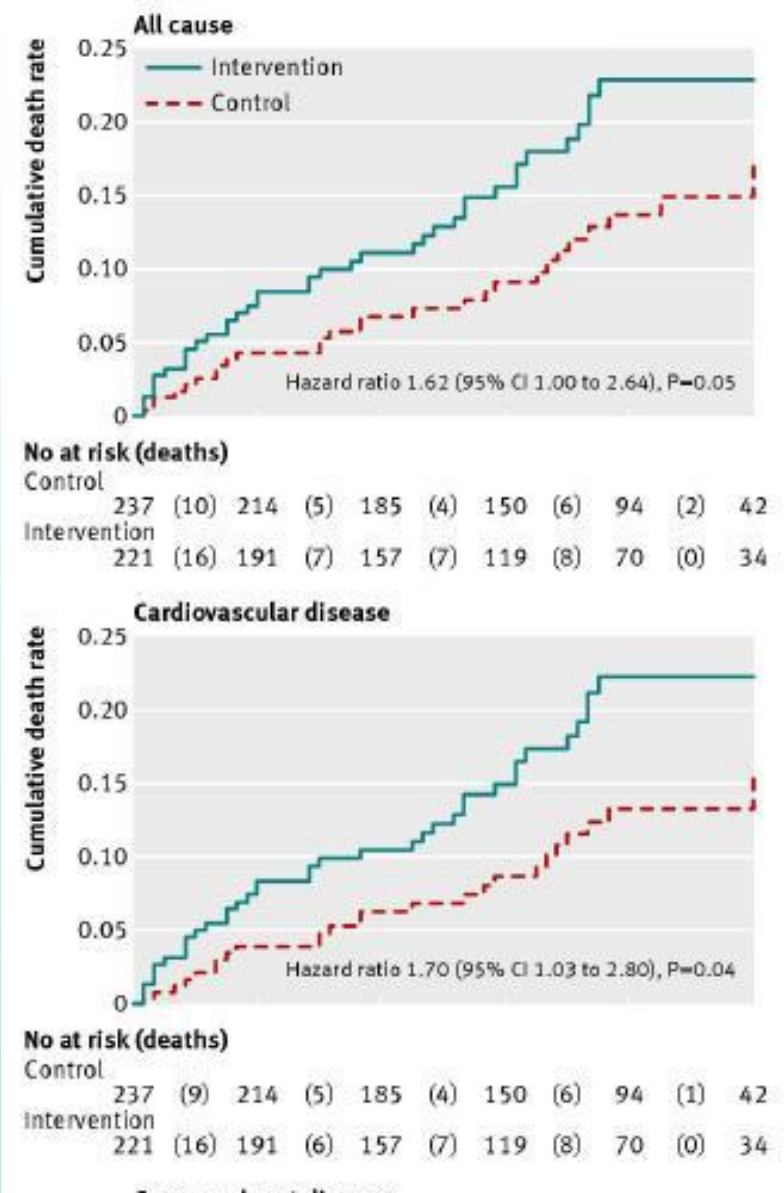
PREDIMED (4) AIM 145:1 2006

- In subgroups, the benefits of diet were greater for people with dyslipidemia, with hypertension, and with BMI>30 compare to those without and BMI <30.
- EVOO and Nuts significantly
  - Reduced SBP 6-7 mmHg
  - Reduced DBP 2 mmHg BP
  - Increased HDL 2-3 mg dl^{-1}
  - Reduced Fasting glucose 6-7 mg dl^{-1}
  - Reduced Fasting insulin 17-20 pmol l^{-1}
- EVOO alone significantly
  - Reduced CRP 0.5 mg l^{-1}
- No significant effect on Weight, BMI, waist circumference, LDL, or TG

Sydney Diet Heart Study (1) BMJ 346:e8707 (2013)

- 458 men aged 30-59 with recent Acute Coronary Syndrome for 3.3 years
- Trial performed 1966-73, new reanalysis
- Single blind control vs. advise to
  - increase omega 6 fat (safflower oil/margarine – given to subjects) from 6% to 15% of calories,
  - reduce saturated fat to <10%, and
  - reduce cholesterol to <300 mg/d
- Intervention group increased omega 6 by 7% of calories, decreased saturated fat by 5% of calories,
  decreased cholesterol by 130 mg daily
  No change in total fat, carbohydrate, protein, alcohol

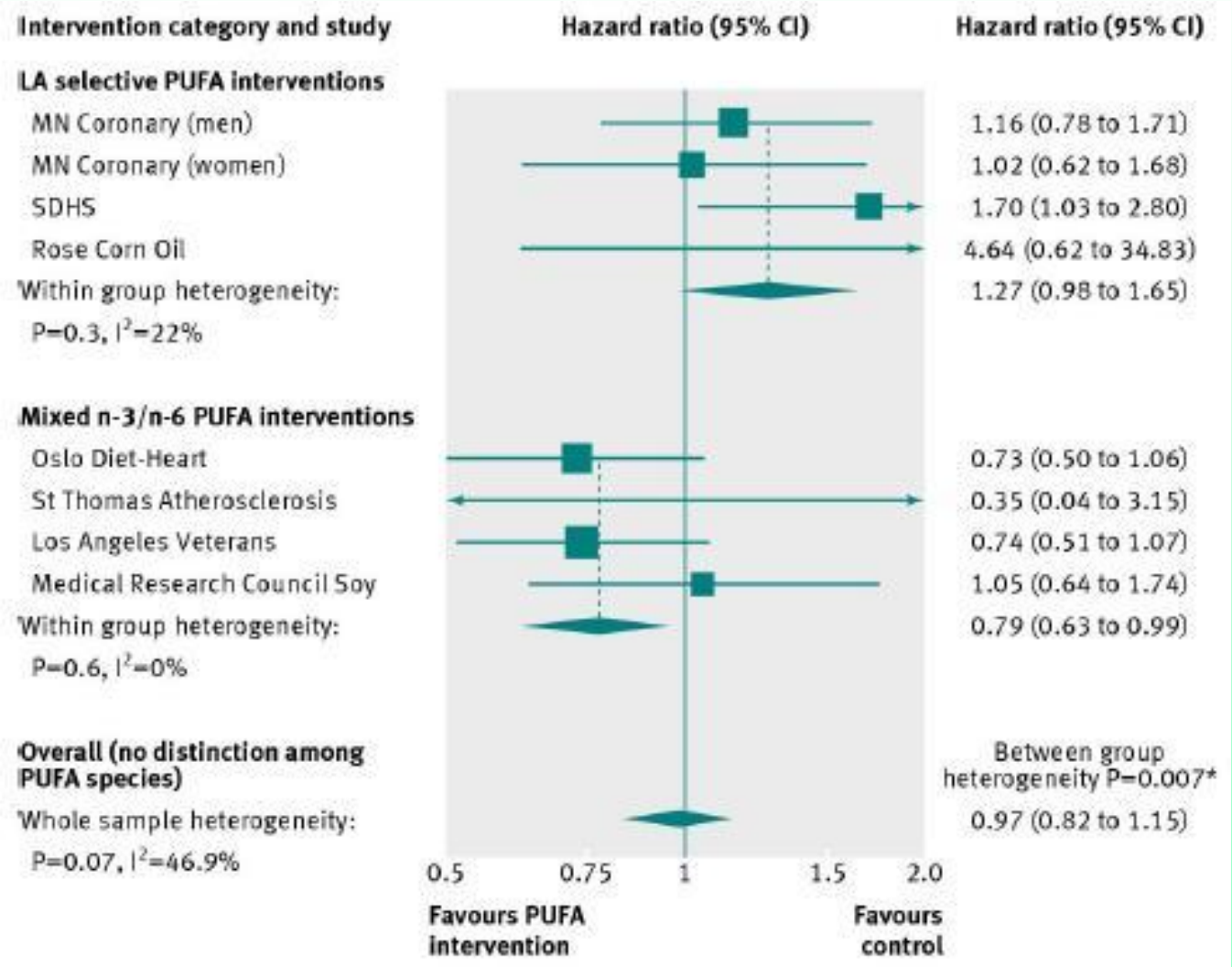
Sydney Diet Heart Study (2) BMJ 346:e8707 (2013)



- Significant increase in all cause, CV and CAD death
- CV death **INCREASED** 35% (12% to 63% CI) for each 5% increase in omega 6 calories
- CV death **DECREASED** 28% (5% to 46% CI) for each 5% increase in saturated fat calories

Sydney (3) Metaanalysis

BMJ 346:e8707, 2013



Nearly significant increase in Cardiovascular disease death with Omega 6 supplementation

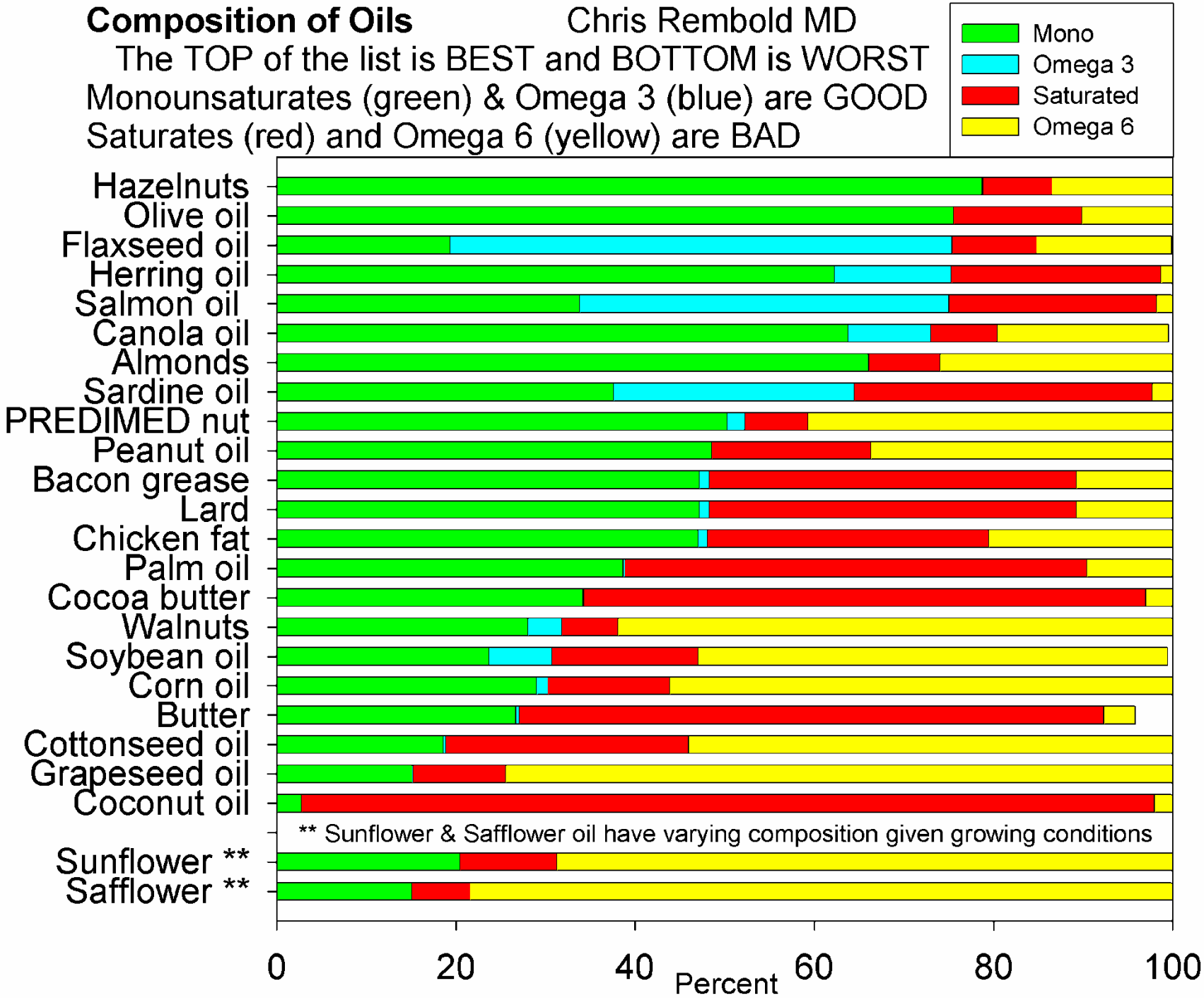
Significant decrease in Cardiovascular disease death with mixed Omega 3 and 6 supplementation

Composition of Oils Chris Rembold MD

The TOP of the list is BEST and BOTTOM is WORST

Monounsaturates (green) & Omega 3 (blue) are GOOD

Saturates (red) and Omega 6 (yellow) are BAD



Egg consumption and CAD

Rong BMJ 346:e8529, 2013

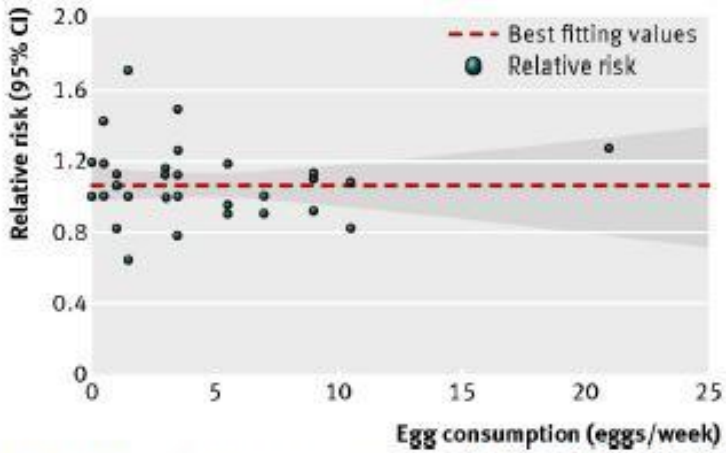


Fig 2 Dose-response analyses of egg consumption and risk of coronary heart disease

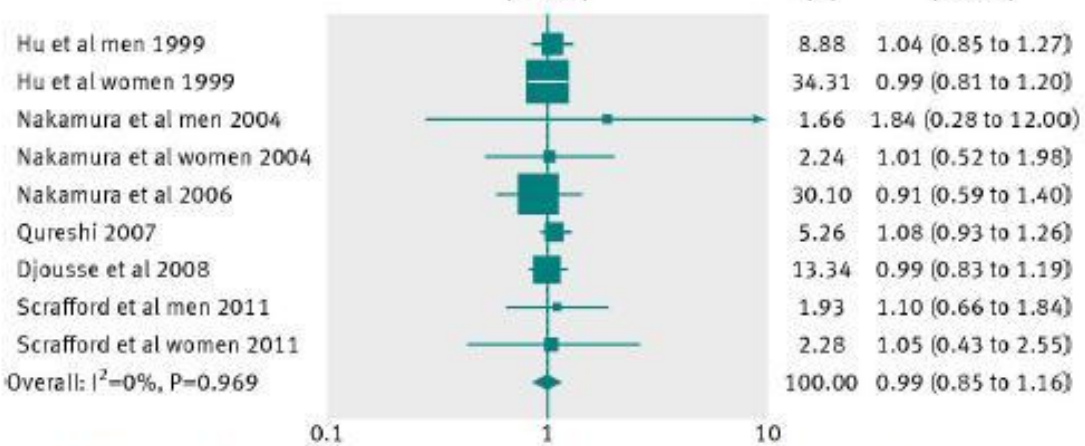
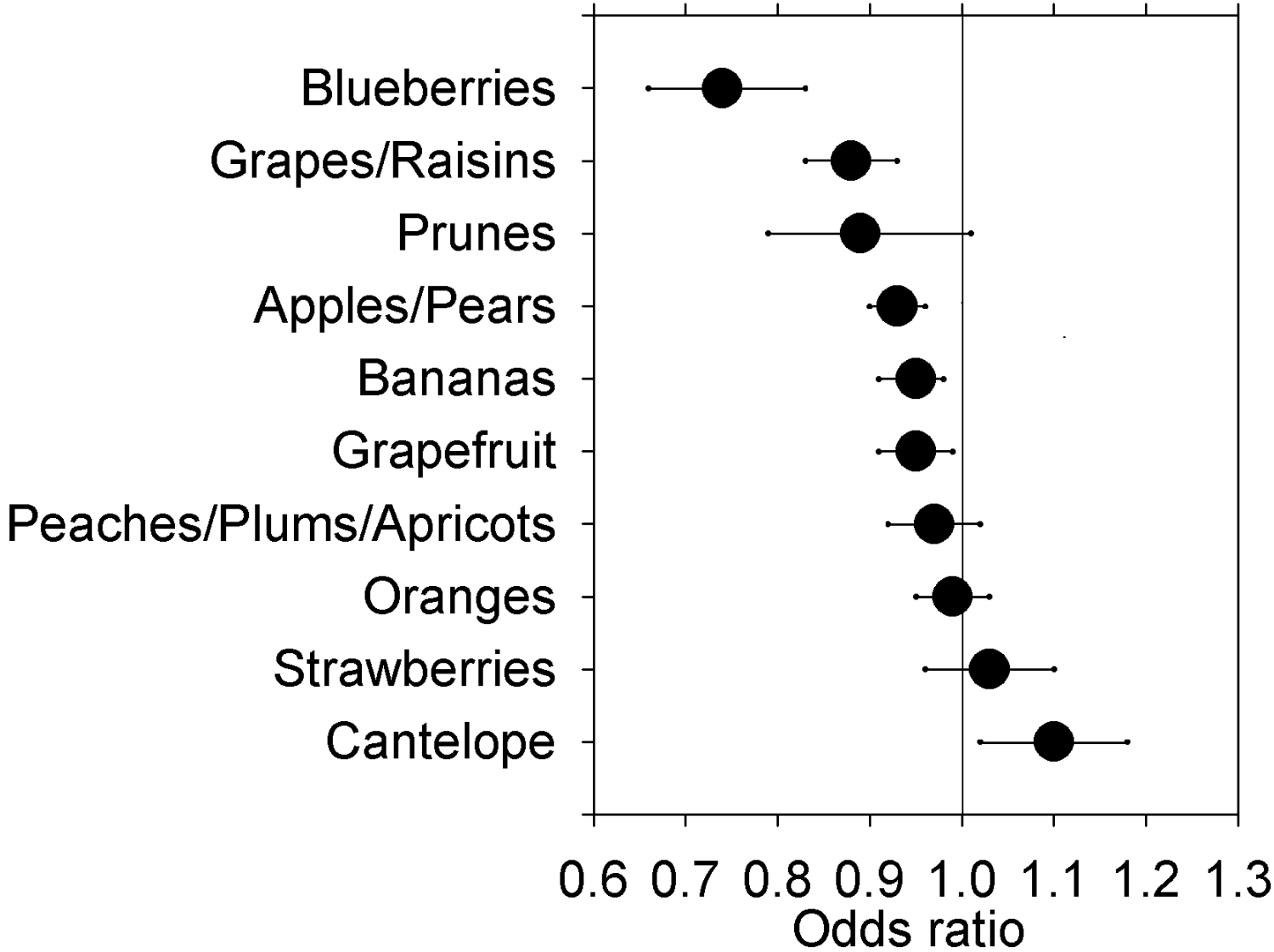


Fig 3 Forest plot of egg consumption and risk of coronary heart disease

- No effect of egg intake (cholesterol) on coronary artery disease

Risk of Type 2 Diabetes by fruit type intake
Nurses and Physicians Health Studies



Muraki, et al. BMJ 2013;347;f5001

Observational Studies in a Metaanalysis

The type of fruit intake predicts who will develop NIDDM

Blueberries, grapes, raisins, and prunes appear best

CAD Therapy proven to reduce Total Mortality

- Simvastatin (4S, HPS), Pravastatin (CARE, LIPID), Atorvastatin (CARDS), & Rosuvastatin (JUPITER)
- Niacin (CDP)
- ACE inhibitor (GISSI3, ISIS4)
- Fish oil (GISSI-Preventione – 1 g Lovaza - ?? 3 g OTC)
- Aspirin (81-648 mg - Antithrombotic Trialists Collaboration)
- With STEMI, thrombolysis or PCI
- With CHF: ACEI (SAVE), β-blocker (MERIT, SAVE), Spirononolactone (RALES), ICD