Wel of geen HDL-C in het cardiovasculaire risicoprofiel ?

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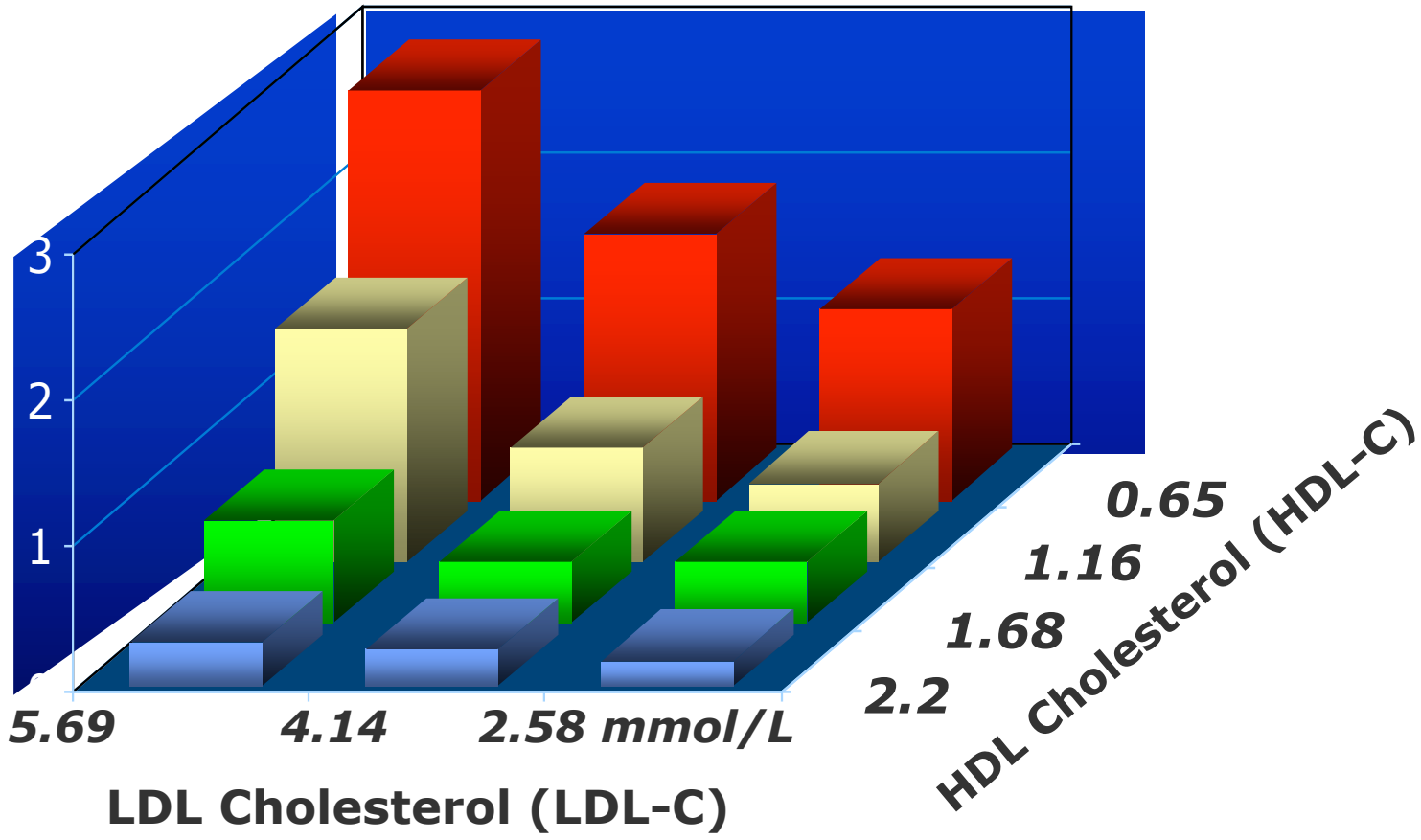
CVD Risk as a Function of LDL and HDL-C

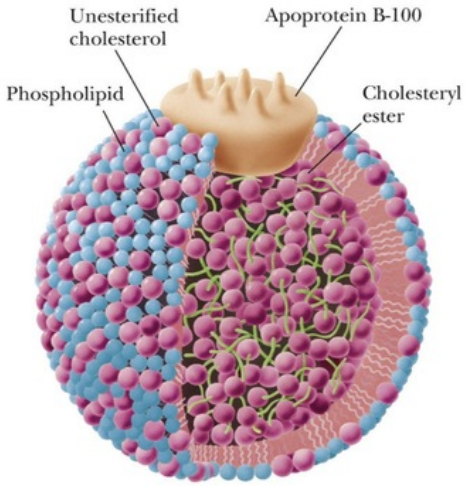
- (men aged 50-70 y) *Framingham Heart Study* -



Modified from Castelli WP. *Can J Cardiol* 1988;4:5A–10A.

Elevated serum LDL-cholesterol
- A causal risk factor of CVD -

- Causal relationship between LDL-cholesterol and CVD is supported by
  - genetic studies
  - epidemiological studies
  - Mendelian randomisation studies
  - randomized control trials

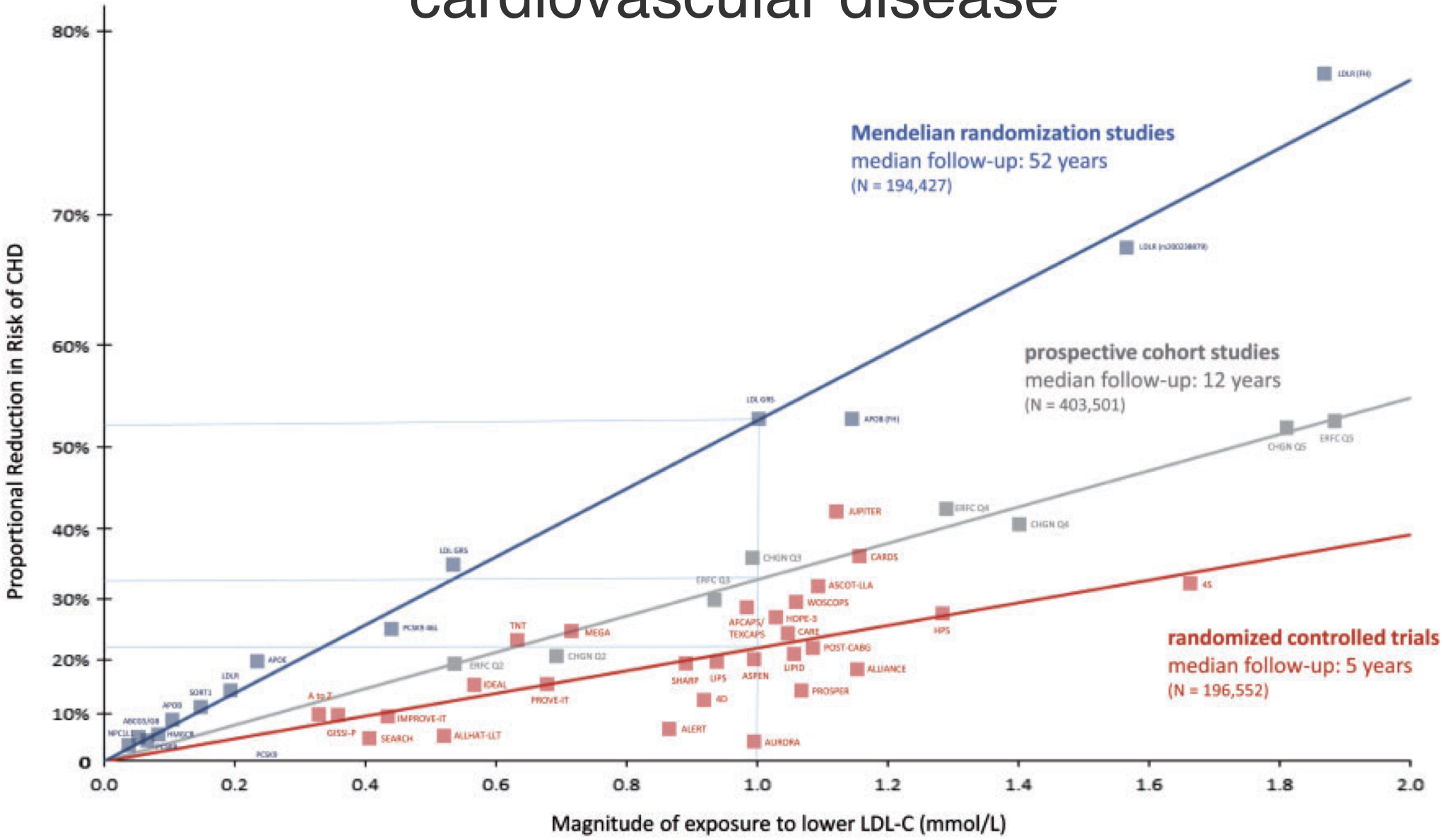


- LDL-cholesterol lowering irrespective of underlying mechanisms/intervention lowers CVD risk

Lowering LDL-cholesterol:
The *lower the better,* and the *earlier the better!*

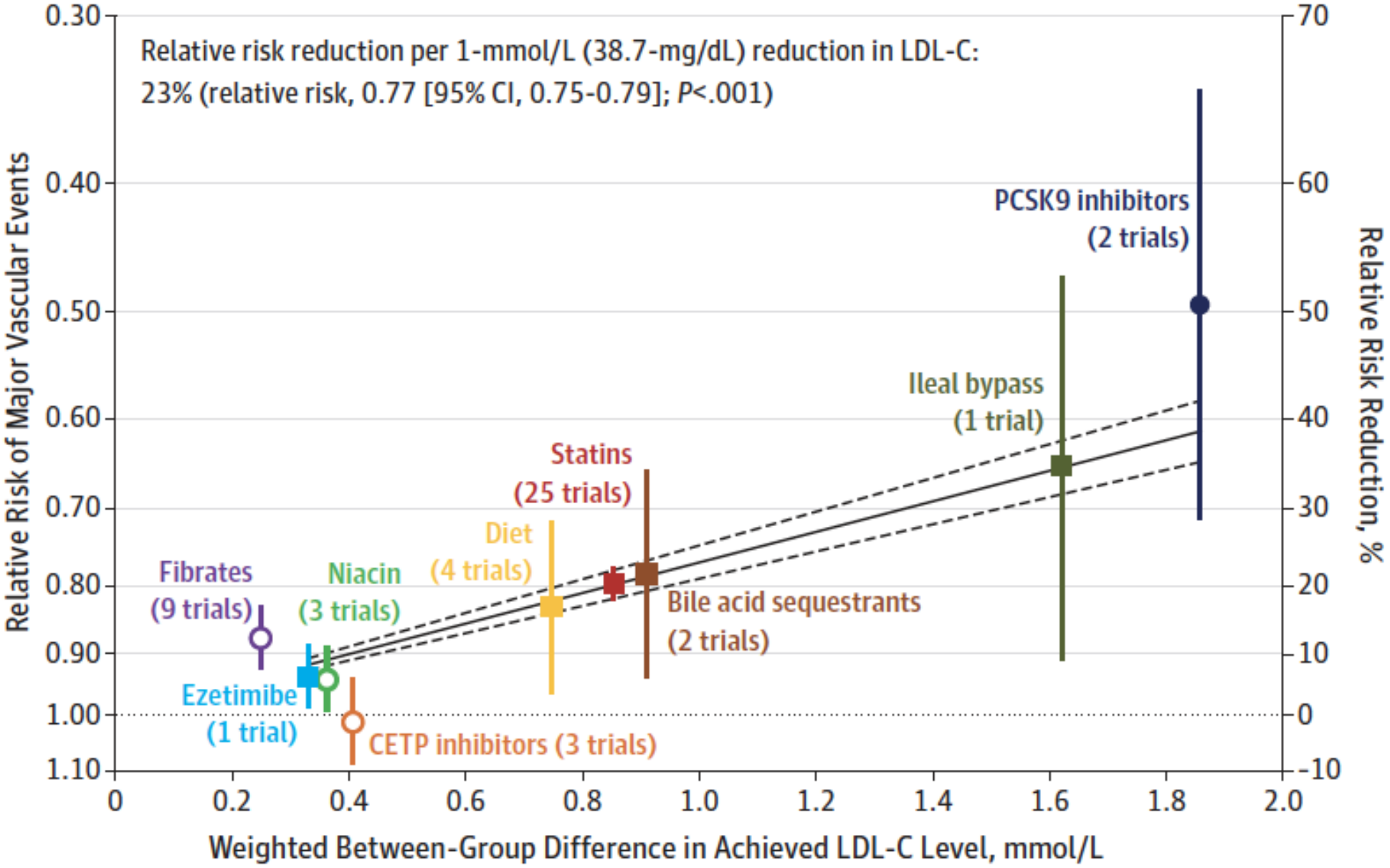
Ference BA et al. Eur Heart J. *2017;38;*.2459-2472

Low density lipoproteins cause atherosclerotic cardiovascular disease



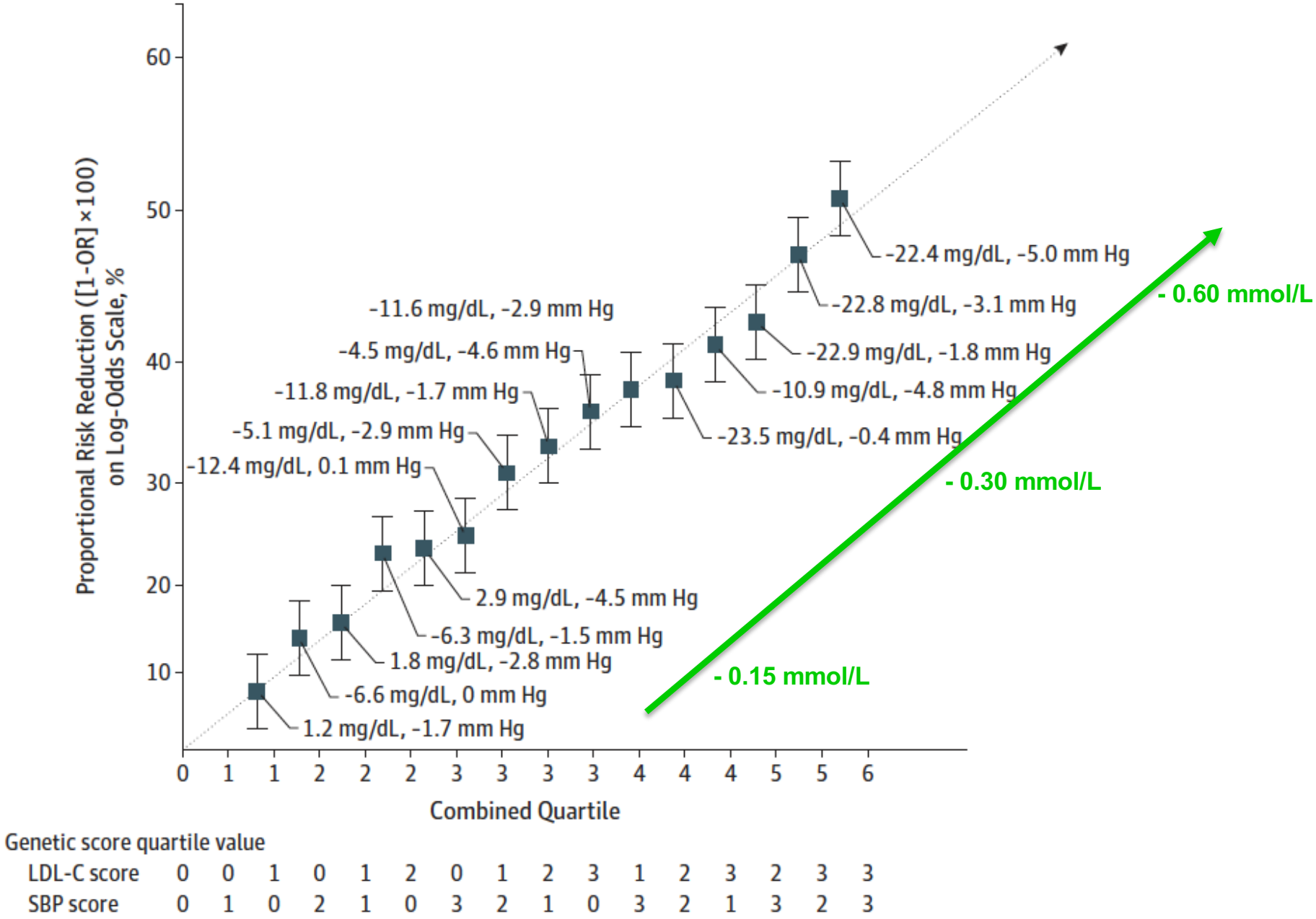
Ference BA et al. Eur Heart J. *2017;38;*.2459-2472

Both statin and non-statin interventions that lower LDL reduce relative risk for major vascular events



Silverman MG et al. JAMA. *2016;316;*.1289-1297

Figure 6. Dose-Dependent Associations and Meta-Regression Analysis for Combinations of Increasingly Lower LDL-C and Lower SBP on the Risk of Major Coronary Events



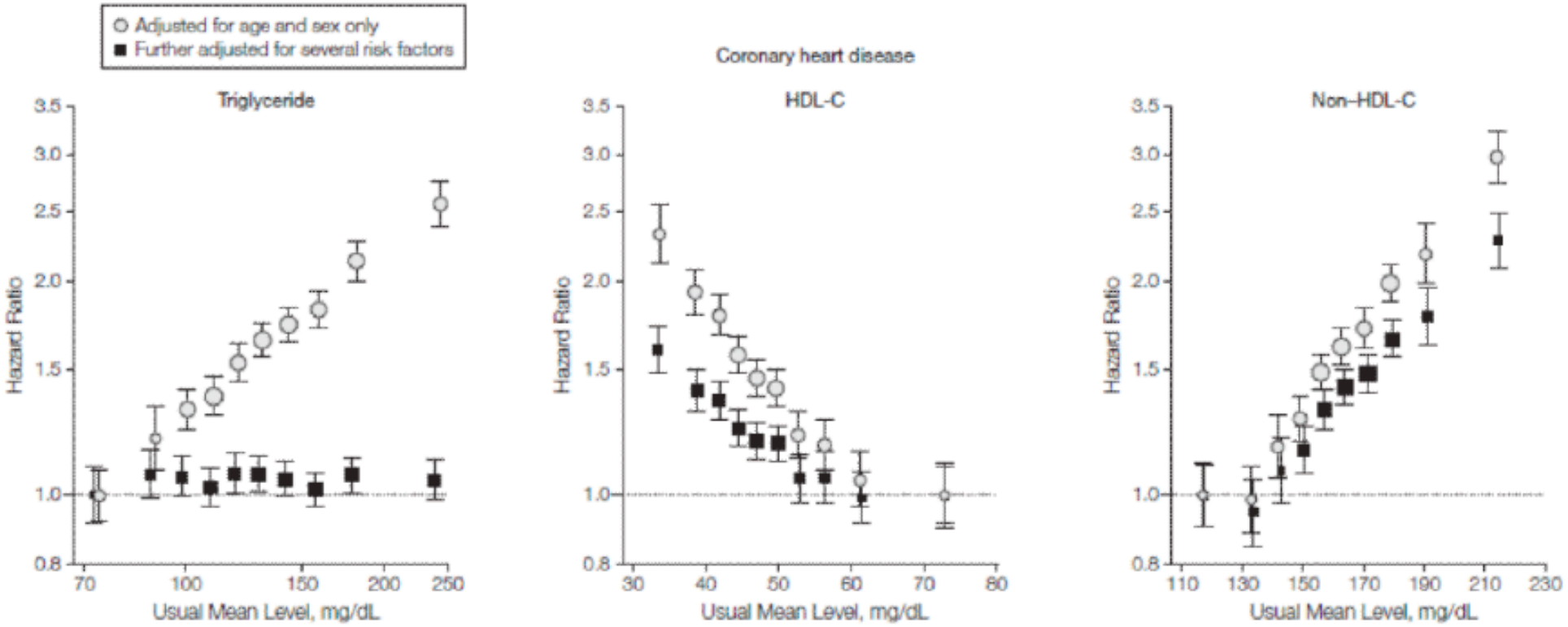
Genetic score quartile value																
LDL-C score	0	0	1	0	1	2	0	1	2	3	1	2	3	2	3	3
SBP score	0	1	0	2	1	0	3	2	1	0	3	2	1	3	2	3

Ference BA et al. *JAMA. 2019;322;*.1381-1391

What about HDL-c?

- Cross-sectional
- Interventions (nutrition / pharmacological)
- Genetics

Cross-sectional data
Harzard ratio's for coronary heart disease across quintiles of TAG, HDL-C and non-HDL-c concentrations



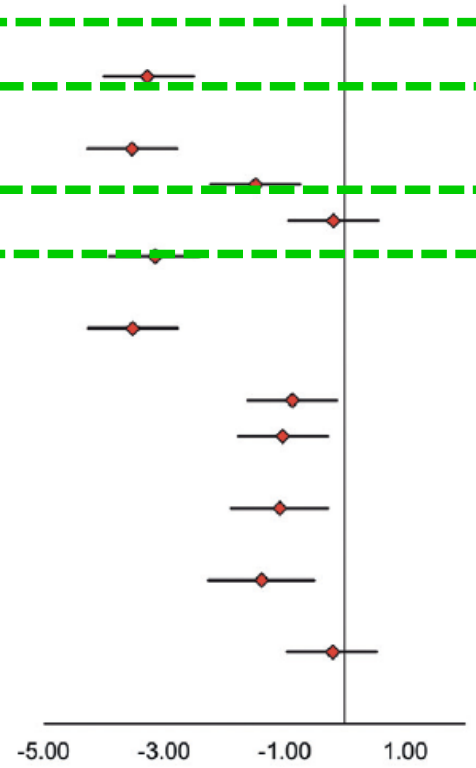
Data is based on 302430 subjects from 68 studies including 12785 cases

Emerging Risk Factor Collaboration, JAMA 2009;302:1993-2000

Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-analysis of Controlled Trials☆,☆☆

Laura Chiavaroli [a,b], Stephanie K. Nishi [a,b], Tauseef A. Khan [a,b], Catherine R. Braunstein [a,b], Andrea J. Glenn [a,b], Sonia Blanco Mejia [a,b], Dario Rahelić [f], Hana Kahleová [g,h], Jordi Salas-Salvadó [i,j], David J.A. Jenkins [a,b,c,d,e], Cyril W.C. Kendall [a,b,k,*], John L. Sievenpiper [a,b,d,e,*]

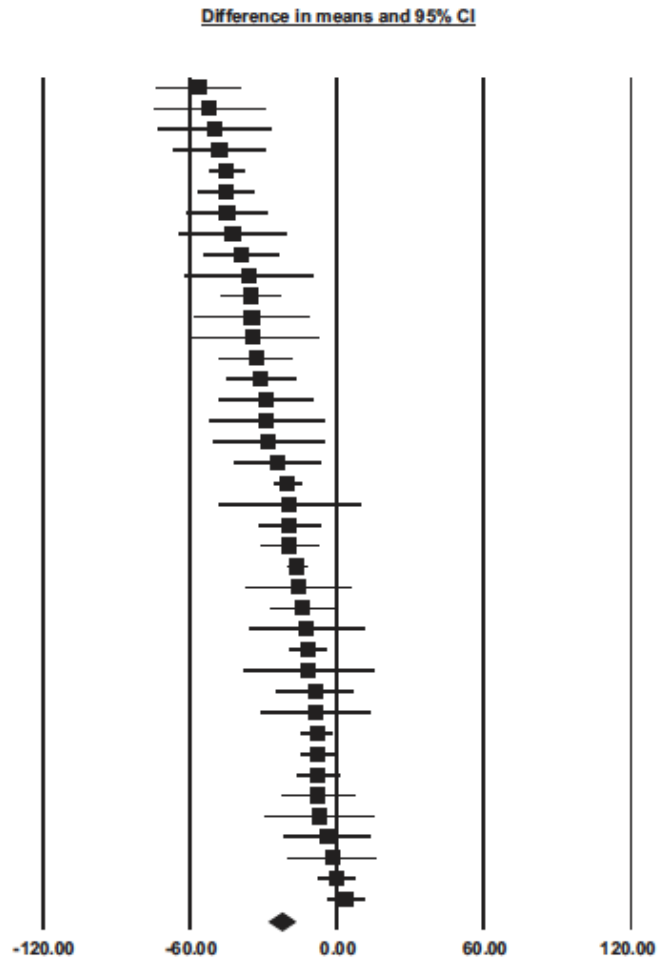
	Outcome	No. trials	N	Pooled Effect Estimates: MD (95% CI)	Pooled Effect Estimates: SMD (95% CI)	Heterogeneity: P-value	Heterogeneity: I^2	Heterogeneity: P-value	%Change*
PRIMARY OUTCOME									
	LDL-C (mmol/L)	7	439	-0.73 [-0.89, -0.56]	-3.28 [-4.00, -2.51]	<0.0001	67%	0.006	-17%
SECONDARY OUTCOMES									
Lipids	TC (mmol/L)	7	439	-0.81 [-0.98, -0.64]	-3.53 [-4.27, -2.79]	<0.0001	52%	0.05	-12%
	TG (mmol/L)	7	439	-0.28 [-0.42, -0.14]	-1.48 [-2.22, -0.74]	<0.0001	58%	0.03	-16%
	HDL-C (mmol/L)*	7	439	-0.01 [-0.05, 0.03]	-0.19 [-0.93, 0.56]	0.56	22%	0.26	-1%
	non-HDL (mmol/L)	7	439	-0.83 [-1.03, -0.64]	-3.15 [-3.91, -2.43]	<0.0001	61%	0.02	-14%
Apolipoproteins									
	ApoB (g/L)	7	439	-0.19 [-0.23, -0.15]	-3.52 [-4.26, -2.78]	<0.0001	60%	0.02	-15%
Blood Pressure									
	SBP (mmHg)	7	439	-1.75 [-3.23, -0.26]	-0.87 [-1.61, -0.13]	0.02	0%	0.79	-1%
	DBP (mmHg)	7	439	-1.36 [-2.33, -0.38]	-1.03 [-1.77, -0.28]	0.006	0%	0.46	-2%
Inflammation									
	CRP (mg/L)	7	435	-0.58 [-1.01, -0.15]	-1.08 [-1.88, -0.28]	0.008	33%	0.18	-32%
Estimated 10-year CHD Risk									
	CHD risk (%)	5	415	-1.34 [-2.19, -0.49]	-1.38 [-2.26, -0.51]	0.002	54%	0.07	-13%
Body Weight									
	Body weight (kg)	7	439	-0.1 [-0.48, 0.27]	-0.20 [-0.95, 0.53]	0.59	0%	0.99	0%



Chiavaroli et al. Prog Cardiovasc Dis. 2018;61:43-53

Association between plant-based diets and LDL cholesterol: a systematic review and meta-analysis

Study name	Subgroup within study	Comparison	Outcome	Statistics for each study: Difference in means	Lower limit	Upper limit
Fernandes Dourado et al., 2011 (26)	Lacto-ovo	Omnivorous	LDL	-56.390	-74.306	-38.474
Burslem et al., 1978 (11), 30-40 yr male	Vegan	Omnivorous	LDL	-52.000	-74.929	-29.071
Sanders & Roshanai, 1992 (29) , male	Vegan	Omnivorous	LDL	-49.884	-73.827	-25.941
Lu et al., 2000 (16), female	Vegan/Lacto	Omnivorous	LDL	-47.951	-67.020	-28.882
Sacks et al., 1975 (10)	Pesco	Omnivorous	LDL	-45.000	-52.606	-37.394
Teixeira et al., 2007 (14)	Lacto-ovo/ Vegan/ Pesco/ Lacto	Omnivorous	LDL	-45.000	-56.884	-33.116
Lu et al., 2000, male (16)	Vegan/Lacto	Omnivorous	LDL	-44.857	-61.912	-27.802
Roshanai & Sanders, 1984 (24), male	Vegan	Omnivorous	LDL	-42.537	-65.214	-19.860
Burslem et al., 1978 (11), 20-30 yr male	Vegan	Omnivorous	LDL	-39.000	-54.672	-23.328
Nestel et al., 1981 (37)	Lacto-ovo	Omnivorous	LDL	-36.000	-62.641	-9.359
Krajcovicova-Kudlackova et al., 1994 (34), female	Lacto-ovo/Lacto	Omnivorous	LDL	-35.190	-48.070	-22.309
Knuiman & West, 1982 (23)	Vegan	Omnivorous	LDL	-34.803	-59.145	-10.461
Burslem et al., 1978 (11), 30-40 yr female	Vegan	Omnivorous	LDL	-34.000	-61.204	-6.796
Burslem et al., 1978 (11), 20-30 yr female	Vegan	Omnivorous	LDL	-33.000	-48.443	-17.557
Krajcovicova-Kudlackova et al., 1994 (34), male	Lacto-ovo/Lacto	Omnivorous	LDL	-30.936	-45.517	-16.355
Richter et al., 1999 (28), female	Lacto-ovo	Omnivorous	LDL	-29.003	-48.792	-9.213
Nieman et al., 1989 (30)	Lacto-ovo	Omnivorous (low fat)	LDL	-28.616	-52.489	-4.743
Richter et al., 1999 (28), male	Lacto-ovo	Omnivorous	LDL	-27.842	-51.245	-4.439
Fu et al., 2008 (17)	Lacto-ovo	Omnivorous	LDL	-24.300	-42.204	-6.396
Yang et al., 2011 (19)	Lacto-ovo	Omnivorous	LDL	-20.108	-26.063	-14.154
Harman & Parnell, 1998 (13), female	Lacto/Vegan	Omnivorous	LDL	-19.335	-48.770	10.100
Kim et al., 2012 (18)	Vegan/Lacto-ovo	Omnivorous	LDL	-19.240	-32.396	-6.084
Fisher et al., 1986 (12)	Vegan/Lacto-ovo	Omnivorous	LDL	-19.200	-31.898	-6.502
Chiang et al., 2013 (22)	Lacto-ovo/lacto/Ovo/Vegan	Omnivorous	LDL	-16.241	-20.671	-11.811
Gojda et al., 2013 (38)	Vegan	Omnivorous	LDL	-15.855	-37.686	5.977
Li et al., 1999 (25)	Lacto-ovo	Omnivorous	LDL	-13.921	-27.872	0.030
Sanders & Roshanai, 1992 (29), female	Vegan	Omnivorous	LDL	-12.374	-36.280	11.531
Jian et al., 2015 (33)	Vegan	Omnivorous	LDL	-11.800	-19.653	-3.947
Harman & Parnell, 1998 (13), male	Lacto/Vegan	Omnivorous	LDL	-11.601	-38.685	15.483
Liebman & Bazzarre, 1983 (21)	Lacto-ovo	Omnivorous	LDL	-9.000	-25.471	7.471
Huijbregts et al., 1980 (39)	Lacto-ovo	Omnivorous	LDL	-8.894	-31.641	13.852
Chen et al., 2011 (31)	Lacto-ovo	Omnivorous	LDL	-8.260	-15.177	-1.343
Huang et al., 2014 (32), postmenopausal	Vegan	Omnivorous	LDL	-7.900	-14.890	-0.910
Lee et al., 2000 (15)	Lacto-ovo	Omnivorous	LDL	-7.734	-16.816	1.348
Karabudak et al., 2008 (36)	Semi/ Lacto-ovo/ Lacto	Omnivorous	LDL	-7.734	-23.033	7.565
Roshanai & Sanders, 1984 (24), female	Vegan	Omnivorous	LDL	-7.347	-30.085	15.390
Lin et al., 2001 (27)	Lacto-ovo	Omnivorous	LDL	-4.000	-22.287	14.287
Goff et al. 2005 (35)	Vegan	Omnivorous	LDL	-1.934	-20.247	16.380
Jung et al., 2013 (20)	Vegan/Lacto/Ovo/Lacto-ovo	Omnivorous	LDL	-0.500	-8.555	7.555
Huang et al., 2014 (32), premenopausal	Vegan	Omnivorous	LDL	3.600	-4.348	11.548
				-22.927	-27.923	-17.931

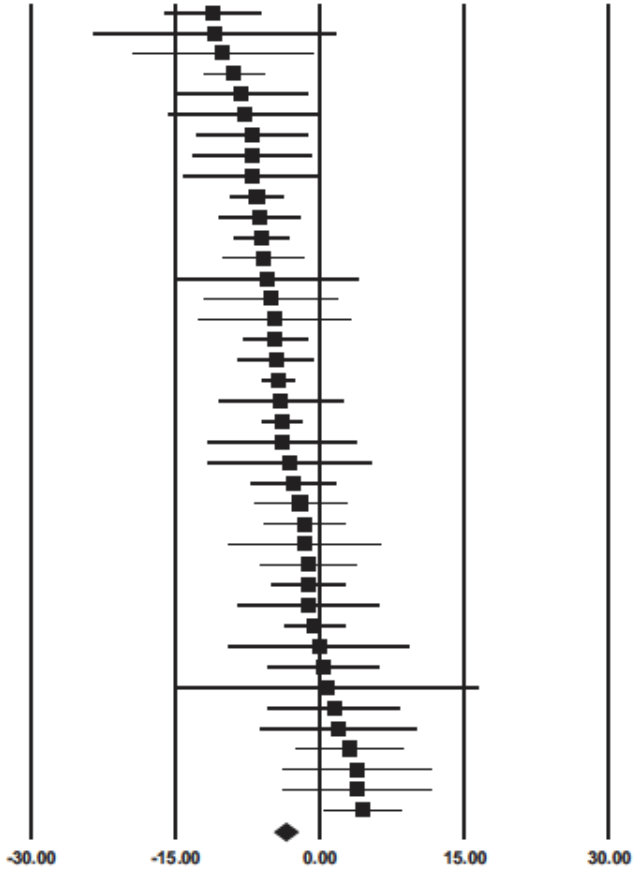


Pooled estimate -22.9 mg/dL (-0.6 mmol/L)
(95%CI -27.9 to -17,9 mg/dL); P<0.001

Yoko Yokoyama, et al. Nutrition Reviews 2017;75:683–698

Association between plant-based diets and HDL cholesterol: a systematic review and meta-analysis

Study name	Subgroup within study	Comparison	Outcome	Statistics for each study: Difference in means	Lower limit	Upper limit
Burslem et al., 1978 (11), 20-30 yr male	Vegan	Omnivorous	HDL	-11.000	-16.117	-5.883
Gojda et al., 2013 (38)	Vegan	Omnivorous	HDL	-10.828	-23.561	1.906
Burslem et al., 1978 (11), 30-40 yr female	Vegan	Omnivorous	HDL	-10.000	-19.459	-0.541
Jung et al., 2013 (20)	Vegan/Lacto/Ovo/Lacto-ovo	Omnivorous	HDL	-8.900	-12.151	-5.649
Fisher et al., 1986 (12)	Vegan/Lacto-ovo	Omnivorous	HDL	-8.100	-15.168	-1.032
Karabudak et al., 2008 (36)	Semi/ Lacto-ovo/ Lacto	Omnivorous	HDL	-7.734	-15.747	0.279
Burslem et al., 1978 (11), 20-30 yr female	Vegan	Omnivorous	HDL	-7.000	-12.900	-1.100
Huijbregts et al., 1980 (39)	Lacto-ovo	Omnivorous	HDL	-6.961	-13.250	-0.671
Lu et al., 2000 (16), female	Vegan/Lacto	Omnivorous	HDL	-6.961	-14.165	0.244
Chen et al., 2011 (31)	Lacto-ovo	Omnivorous	HDL	-6.500	-9.374	-3.626
Huang et al., 2014 (32), premenopausal	Vegan	Omnivorous	HDL	-6.200	-10.542	-1.858
Sacks et al., 1975 (10)	Pesco	Omnivorous	HDL	-6.000	-8.975	-3.025
Jian et al., 2015 (33)	Vegan	Omnivorous	HDL	-5.800	-10.069	-1.531
Nieman et al., 1989 (30)	Lacto-ovo	Omnivorous (low fat)	HDL	-5.414	-14.984	4.156
Burslem et al., 1978 (11), 30-40 yr male	Vegan	Omnivorous	HDL	-5.000	-12.095	2.095
Li et al., 1999 (25)	Lacto-ovo	Omnivorous	HDL	-4.640	-12.712	3.432
Lee et al., 2000 (15)	Lacto-ovo	Omnivorous	HDL	-4.640	-8.091	-1.189
Huang et al., 2014 (32), postmenopausal	Vegan	Omnivorous	HDL	-4.500	-8.538	-0.462
Yang et al., 2011 (19)	Lacto-ovo	Omnivorous	HDL	-4.254	-6.005	-2.502
Nestel et al., 1981 (37)	Lacto-ovo	Omnivorous	HDL	-4.000	-10.534	2.534
Chiang et al., 2013 (22)	Lacto-ovo/lacto/Ovo/Vegan	Omnivorous	HDL	-3.867	-5.981	-1.753
Goff et al. 2005 (35)	Vegan	Omnivorous	HDL	-3.867	-11.642	3.908
Sanders & Roshanai, 1992 (29), female	Vegan	Omnivorous	HDL	-3.094	-11.668	5.481
Kim et al., 2012 (18)	Vegan/Lacto-ovo	Omnivorous	HDL	-2.660	-7.151	1.831
Liebman & Bazzarre, 1983 (21)	Lacto-ovo	Omnivorous	HDL	-2.000	-6.914	2.914
Krajcovicova-Kudlackova et al., 1994 (34), female	Lacto-ovo/Lacto	Omnivorous	HDL	-1.547	-5.893	2.800
Roshanai & Sanders, 1984 (24), female	Vegan	Omnivorous	HDL	-1.547	-9.604	6.510
Lu et al., 2000, male (16)	Vegan/Lacto	Omnivorous	HDL	-1.160	-6.311	3.991
Krajcovicova-Kudlackova et al., 1994 (34), male	Lacto-ovo/Lacto	Omnivorous	HDL	-1.160	-5.148	2.828
Sanders & Roshanai, 1992 (29) , male	Vegan	Omnivorous	HDL	-1.160	-8.625	6.305
Teixeira et al., 2007 (14)	Lacto-ovo/ Vegan/ Pesco/ Lacto	Omnivorous	HDL	-0.500	-3.836	2.836
Harman & Parnell, 1998 (13), male	Lacto/Vegan	Omnivorous	HDL	0.000	-9.491	9.491
Roshanai & Sanders, 1984 (24), male	Vegan	Omnivorous	HDL	0.387	-5.575	6.349
Fu et al., 2008 (17)	Lacto-ovo	Omnivorous	HDL	0.900	-14.835	16.635
Richter et al., 1999 (28), male	Lacto-ovo	Omnivorous	HDL	1.547	-5.431	8.524
Lin et al., 2001 (27)	Lacto-ovo	Omnivorous	HDL	2.000	-6.234	10.234
Richter et al., 1999 (28), female	Lacto-ovo	Omnivorous	HDL	3.094	-2.622	8.809
Knuiman & West, 1982 (23)	Vegan	Omnivorous	HDL	3.867	-4.029	11.763
Harman & Parnell, 1998 (13), female	Lacto/Vegan	Omnivorous	HDL	3.867	-4.022	11.756
Fernandes Dourado et al., 2011 (26)	Lacto-ovo	Omnivorous	HDL	4.500	0.329	8.671
				-3.590	-4.728	-2.452



Pooled estimate -3.6 mg/dL (95%CI -4.7 to -2.5 mg/dL); P<0.001

Yoko Yokoyama, et al. Nutrition Reviews 2017;75:683–698

When people move towards a low-fat, plant-based diet, not only TC and LDL cholesterol, but also HDL levels decrease

Table 1 Mean changes in selected risk factors from baseline to 30 days

Factor	Participants (n)	Baseline		Post-intervention		Mean change	95% confidence interval	% change	t statistic	p value
		Mean	SD	Mean	SD					
SBP (mmHg)	4550	133.30	19.08	126.35	16.51	-6.95	-7.39, -6.51	-5.2	31.13	<0.001
DBP (mmHg)	4552	79.83	11.04	75.69	9.89	-4.14	-4.43, -3.85	-5.2	28.22	<0.001
BMI (kg/m^2)	4514	31.01	7.30	30.03	7.01	-0.98	-1.01, -0.96	-3.2	78.11	<0.001
TC (mg/dl)	4655	193.55	41.75	172.09	37.83	-21.46	-22.23, -20.69	-11.1	54.73	<0.001
HDL (mg/dl)	4654	54.84	25.76	50.07	23.16	-4.77	-5.03, -4.51	-8.7	36.56	<0.001
LDL (mg/dl)	4550	131.10	62.02	114.00	54.87	-17.10	-17.90, -16.30	-13.0	41.98	<0.001
TG (mg/dl)	4650	143.35	90.02	132.30	74.55	-11.05	-12.80, -9.31	-7.7	12.41	<0.001
FPG (mg/dl)	4587	101.29	28.94	94.86	20.99	-6.43	-6.96, -5.90	-6.3	23.99	<0.001

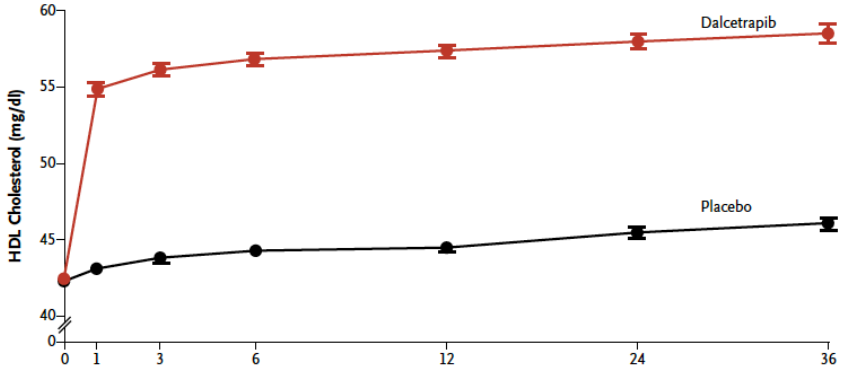
Table 3 The number of participants meeting metabolic syndrome (MetS) risk factors criteria at baseline and post-intervention

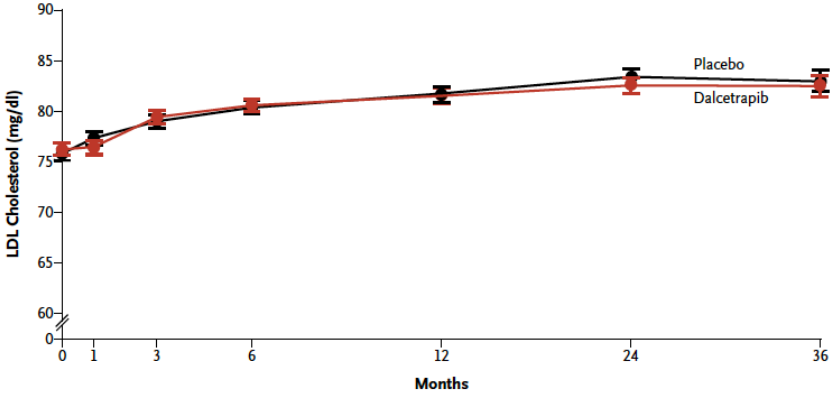
Risk factor	Baseline (N)	Post-program (N)	Improved MetS status* (N)	% improvement
BMI	2228	1951	+277	12.4%
BP	2761	1994	+767	27.8%
FPG	1618	1145	+472	29.2%
TG	1606	1426	+180	11.2%
HDL	2030	2640	- 610	-30.0%

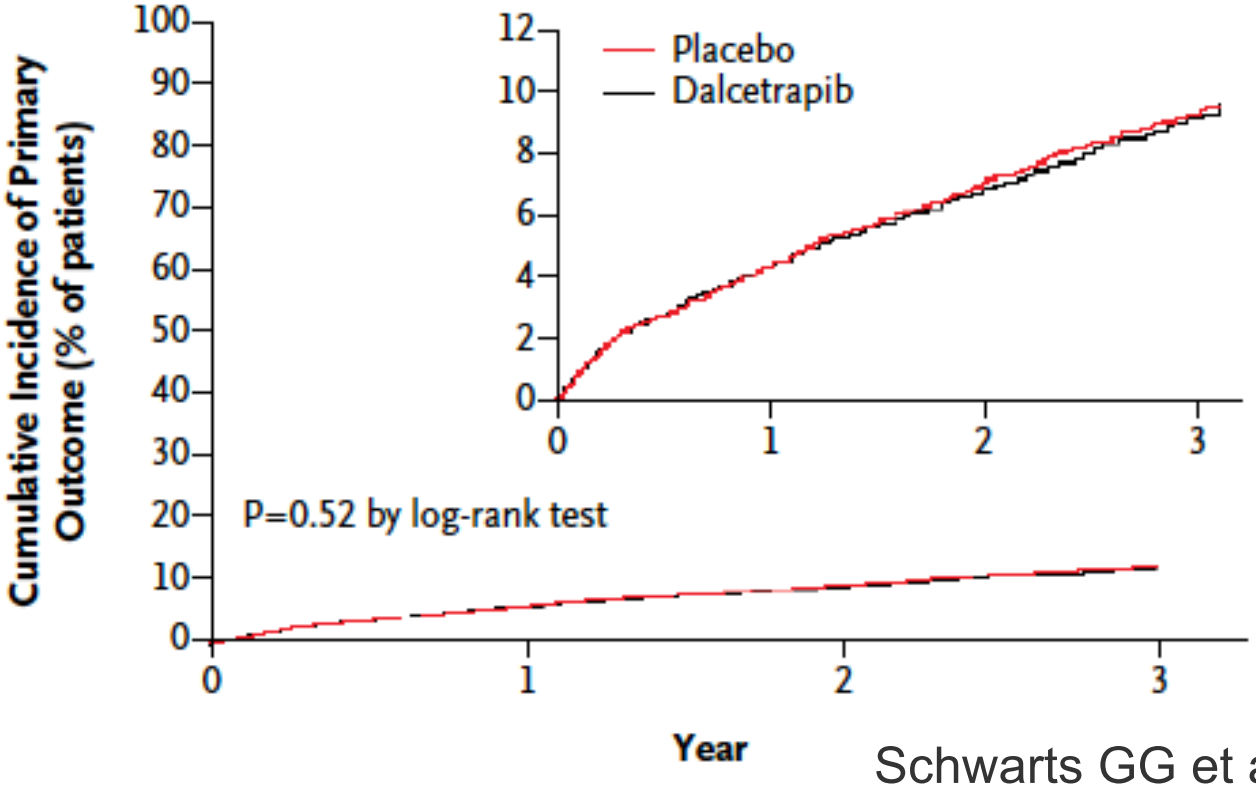
*Number of participants who improved their MetS status during the intervention for each of the five criteria.

Kent et al. Nutrition & Metabolism 2013, 10:58

30% increase in HDL-C via CETP inhibition (Dalcetrapid) does not lower death from CVD

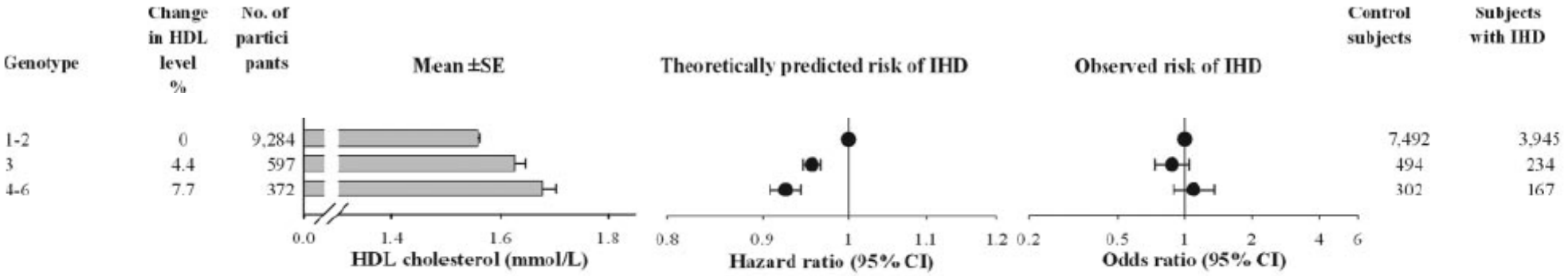






Schwarts GG et al NEJM 2012;367:2089-2099

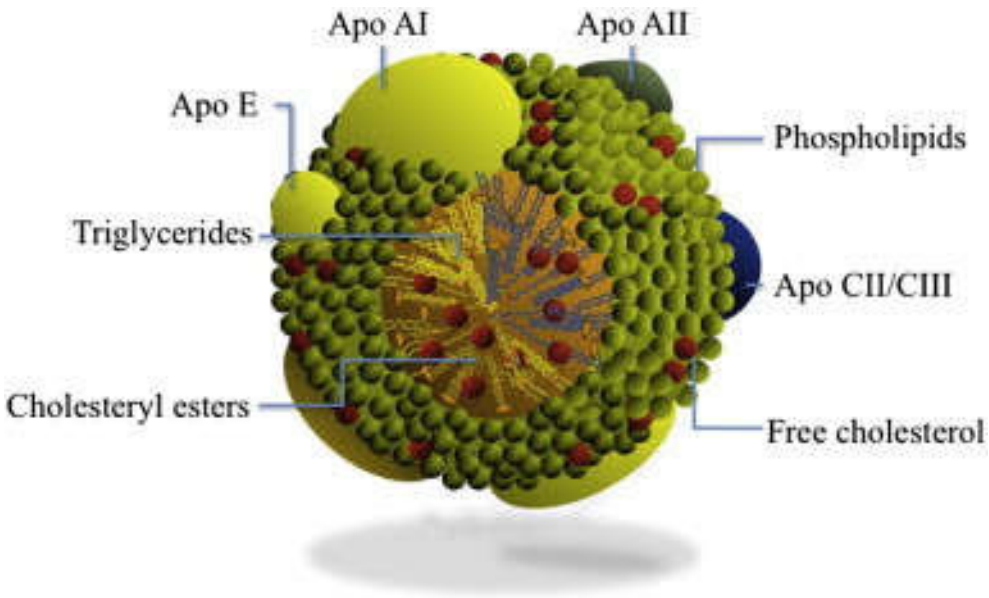
Genetically elevated HDL Cholesterol does not lower the risk of Ischemic Heart Disease



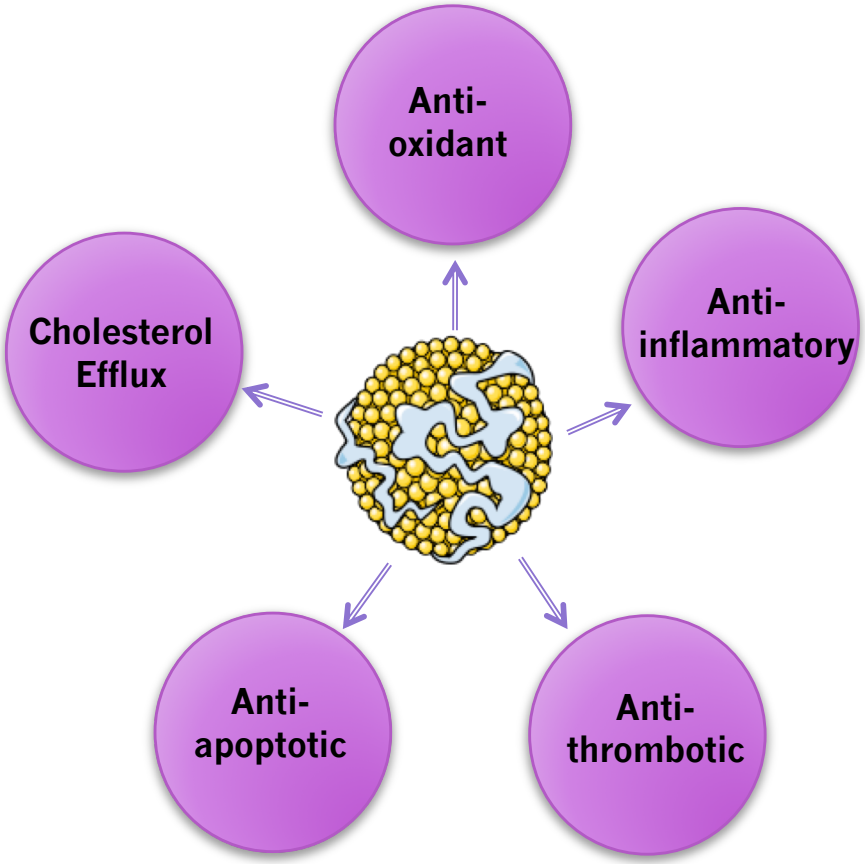
Haase et al. J Clin Endocrinol Metab 2010;95:e500-e510

So, is there an alternative explanation, in line with HDL-C ?

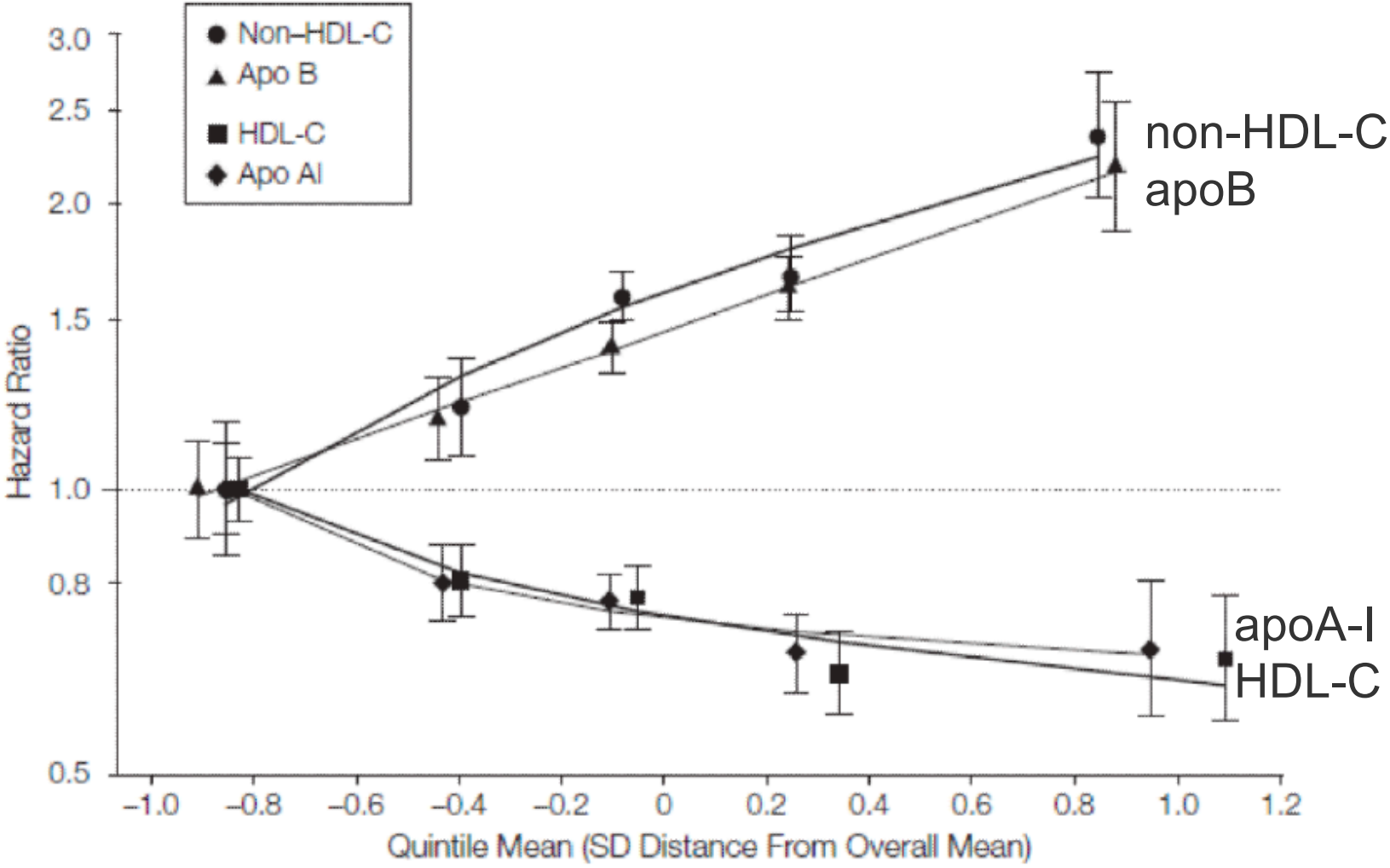
70% of the protein mass in HDL is ApoA-I



HDL has many anti-atherogenic functions (mainly linked to its main protein apoA-I)



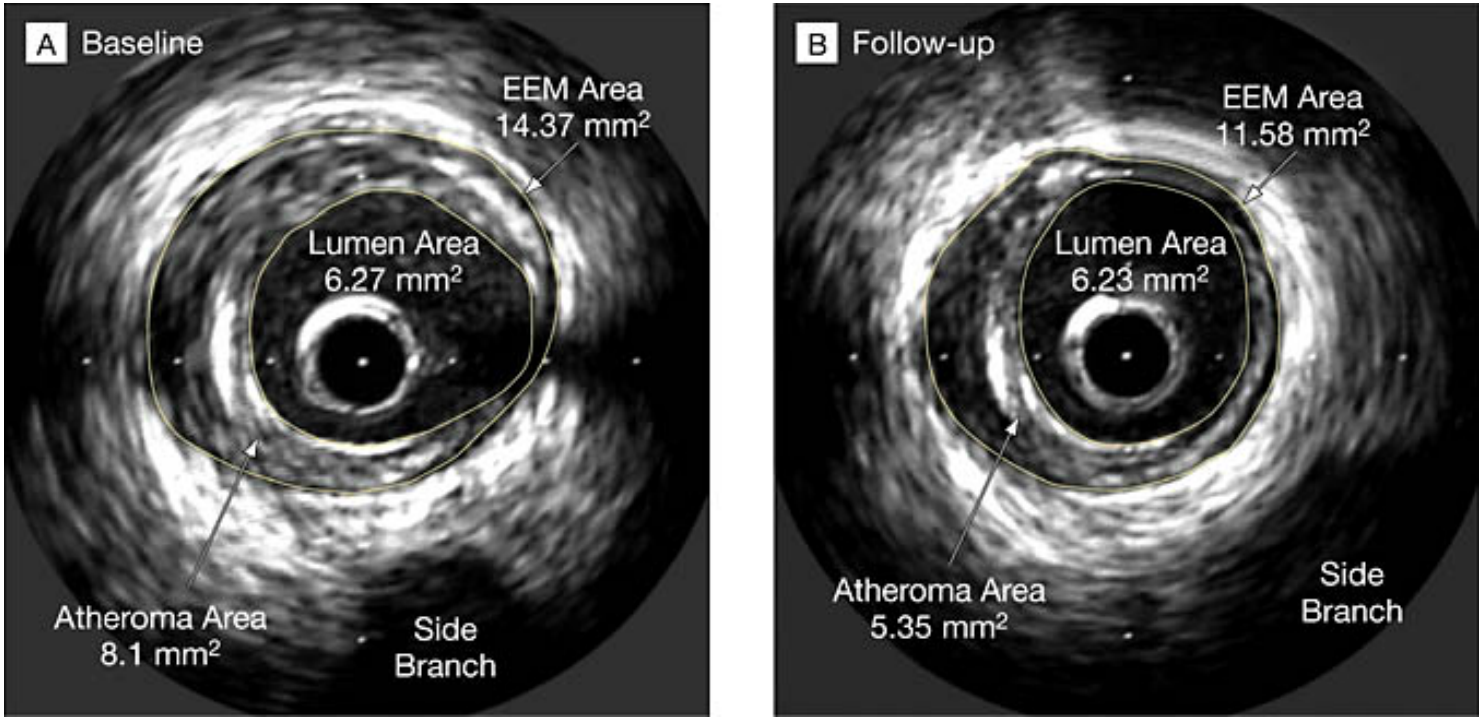
Cross-sectional, like HDL-C, ApoA-I is also a valid predictor for future CVD risk?



Emerging Risk Factor Collaboration, JAMA 2009;302:1993-2000

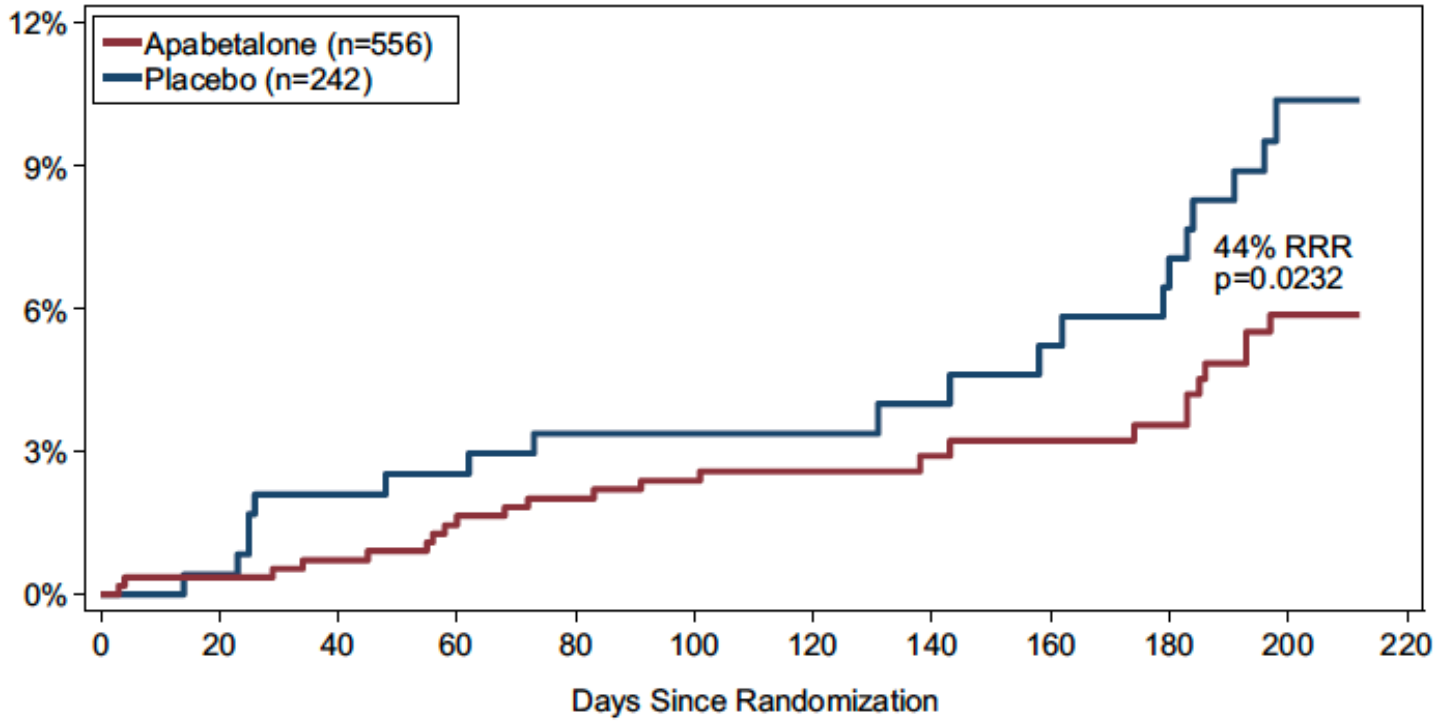
ApoA-I infusion has an acute effect on lesion regression

Example of Atheroma Regression in a Patient Who Received High-Dose ETC-216



Nissen, S. E. et al. JAMA 2003;290:2292-2300.

RVX208 stimulates apoA-I gene transcription, elevates apoA-I and lowers time to first event

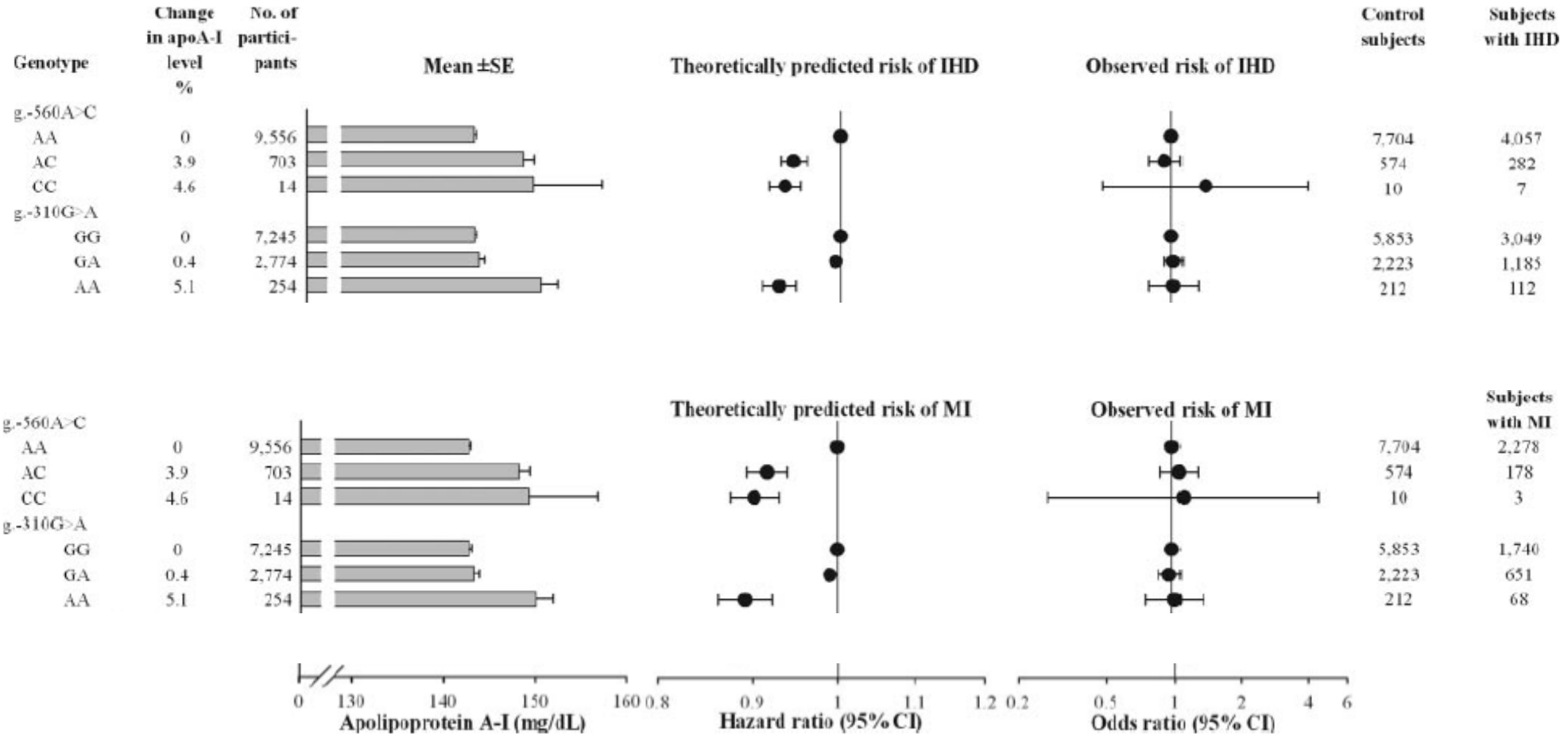


But also several negative outcome studies

Nicholls SJ et al, Am J Cardiovasc Drugs 2018;18:109-115

And genetic data does not confirm the causal role for apoA-I in CVD risk

Copenhagen city heart study



Haase et al. J Clin Endocrinol Metab 2010;95:e500-e510

So, is there an alternative explanation, in line with HDL-C and apoA-I ?

HDL functionality?

Effective reverse cholesterol transport Anti-oxidative and anti-inflammatory benefit

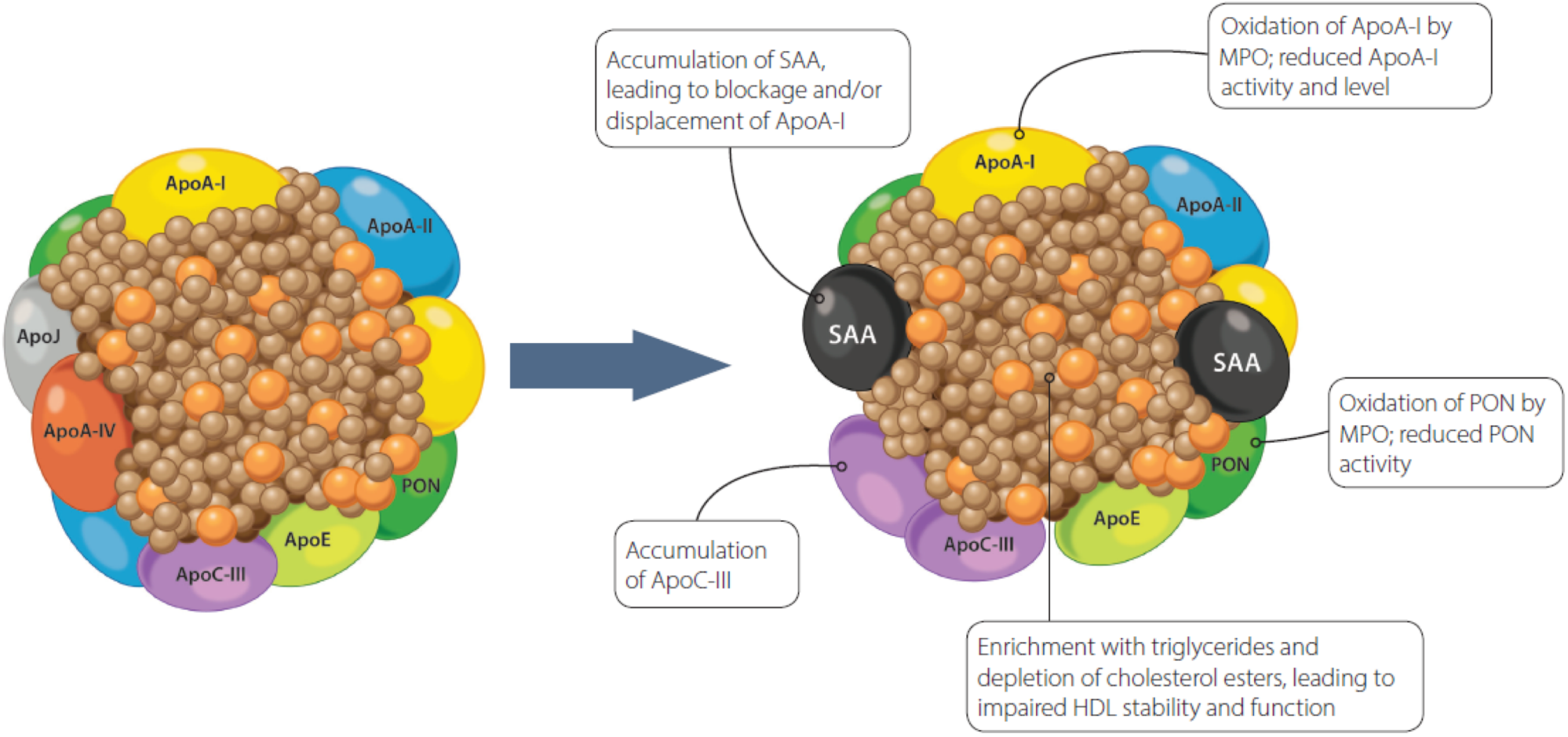
Reduced reverse cholesterol transport Loss of anti-oxidative and anti-inflammatory benefit

Gain of pro-oxidant and pro-inflammatory properties

Functional HDL → **HDL loss of function** → **HDL gain of dysfunction**

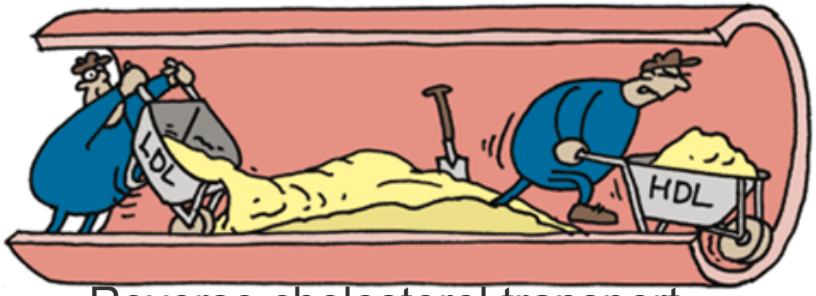
Remodeling of HDL

Remodeling of HDL

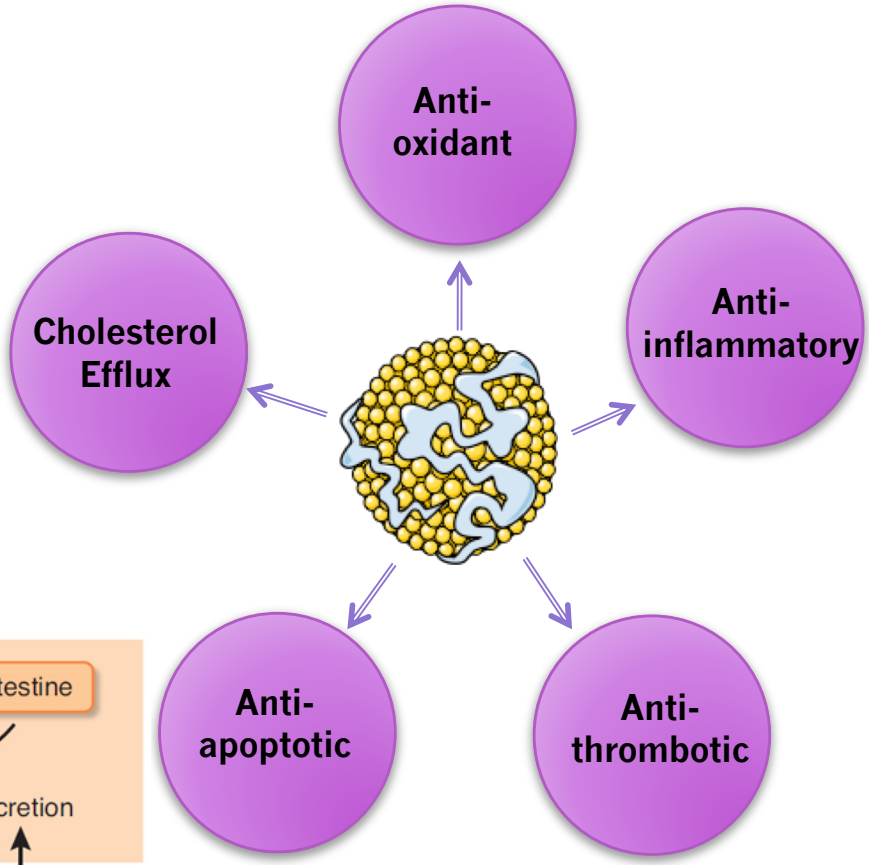


MPO, myeloperoxidase; SAA, Serum amyloid A.
Adapted from Landmesser U, *Nature Reviews Cardiology* 2014;11:559–560

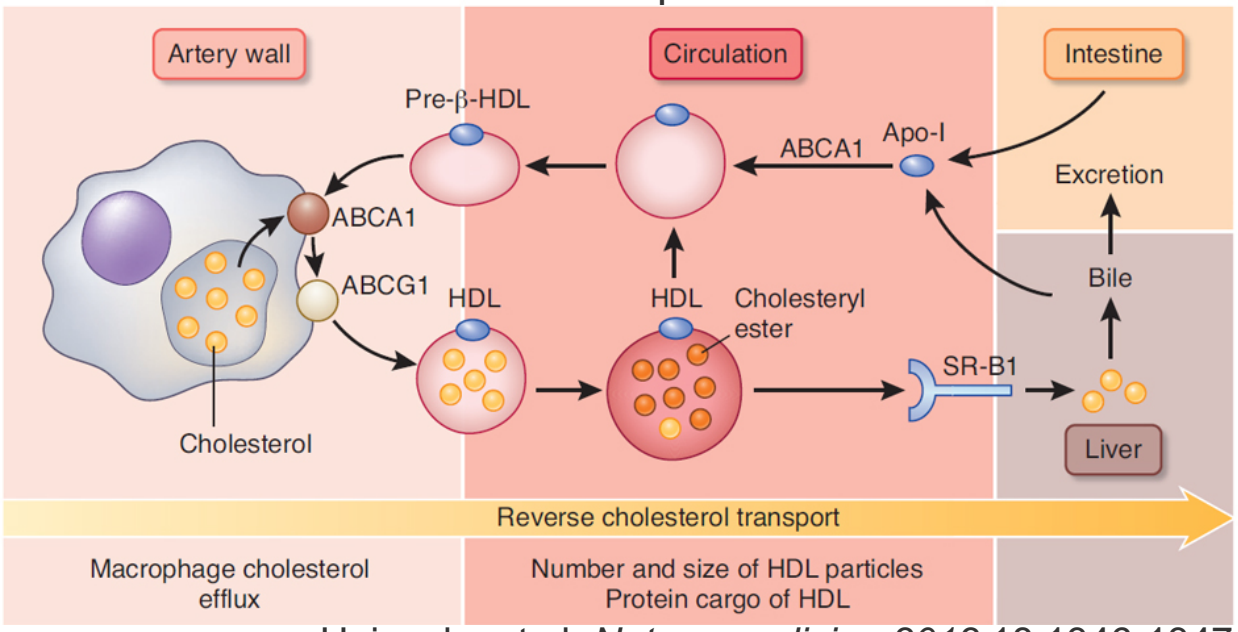
HDL functionality is the current paradigm



Reverse cholesterol transport

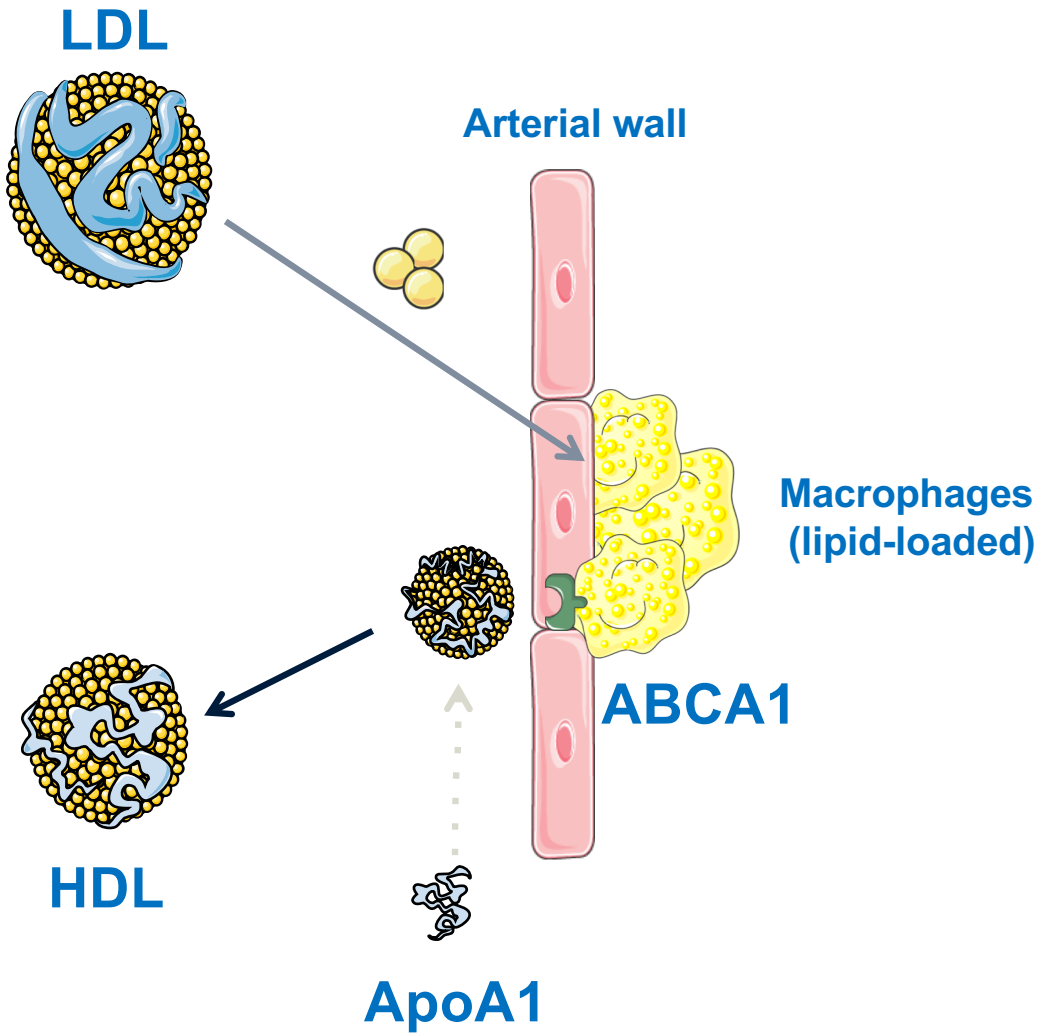


Cholesterol efflux as key step in reverse cholesterol transport

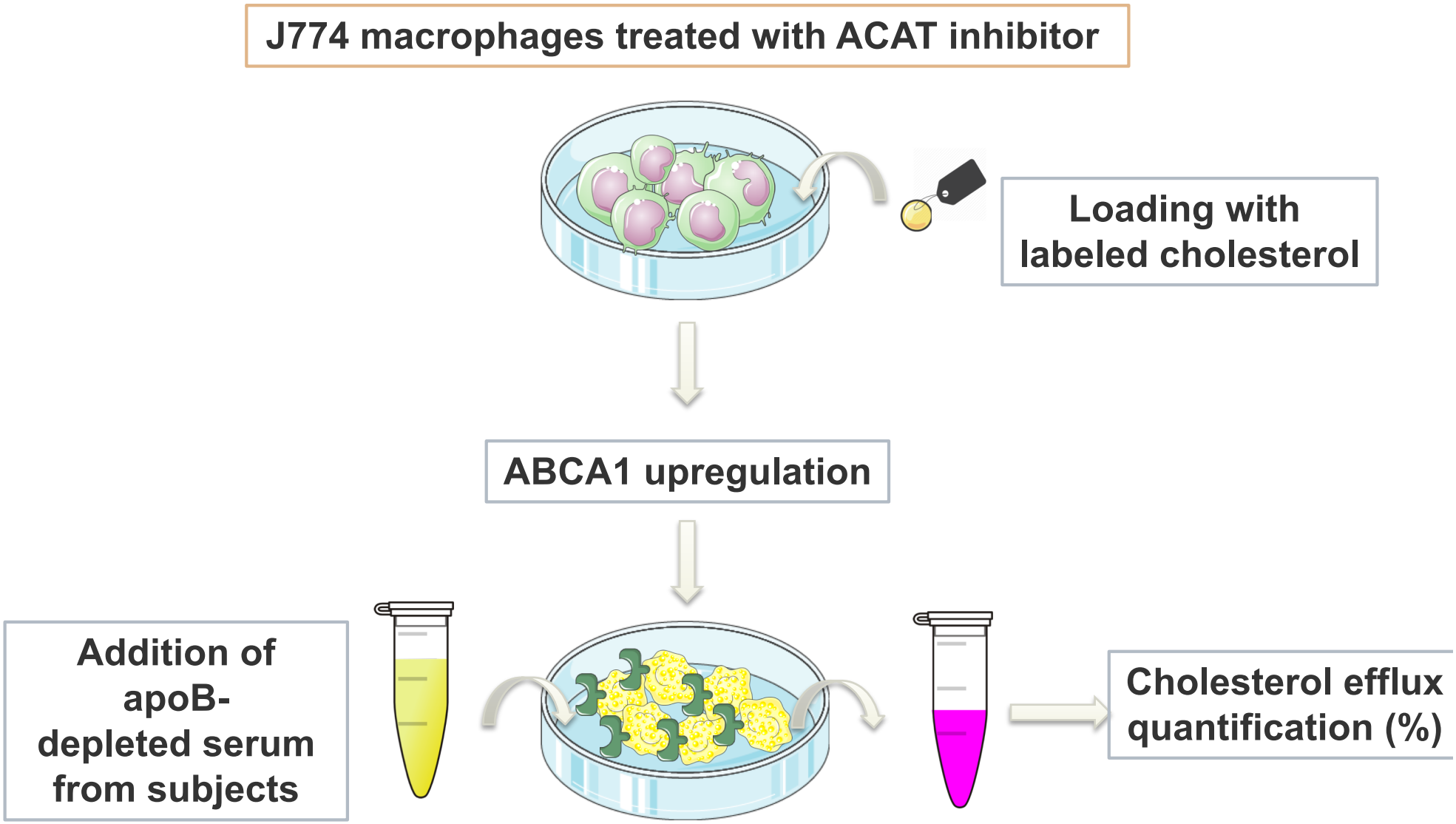


Heinecke et al. *Nature medicine 2012;*18:1346-1347

HDL functionality is often defined as "cholesterol efflux capacity"

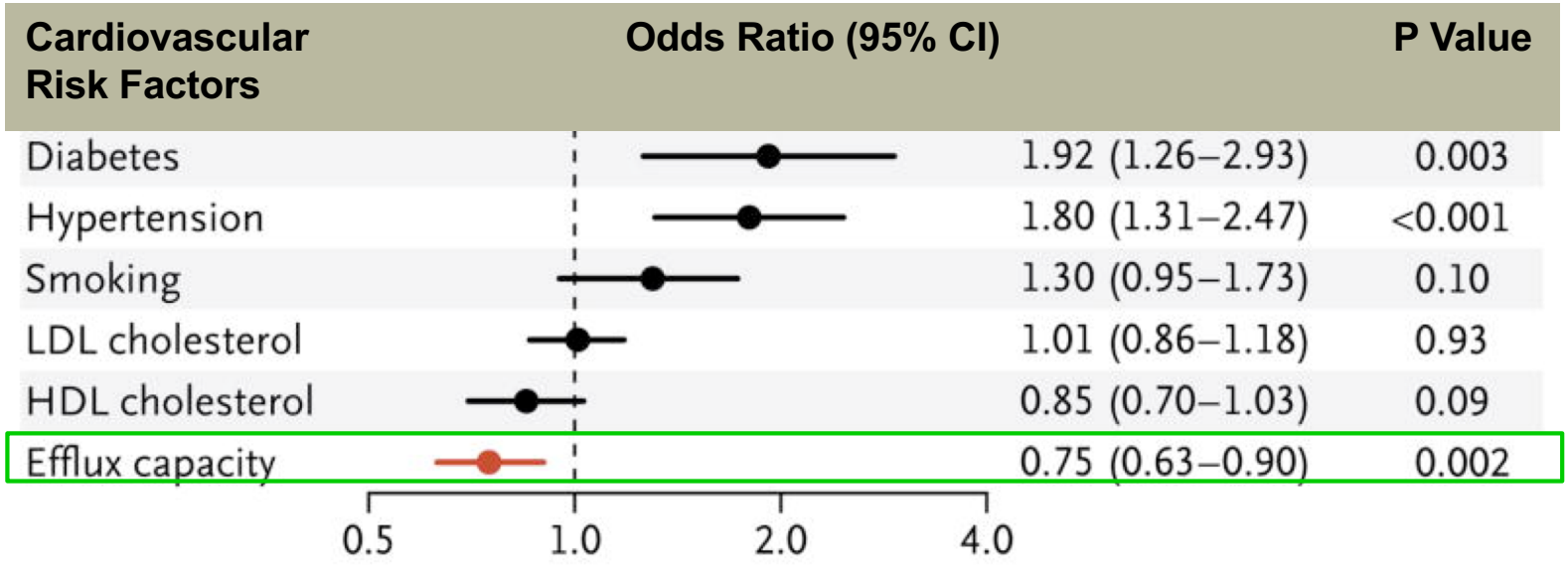


How can we measure cholesterol efflux capacity



Talbot et al. Prog Lipid Res 2018;69:21-32

Cholesterol efflux capacity is inversely associated with cardiovascular risk



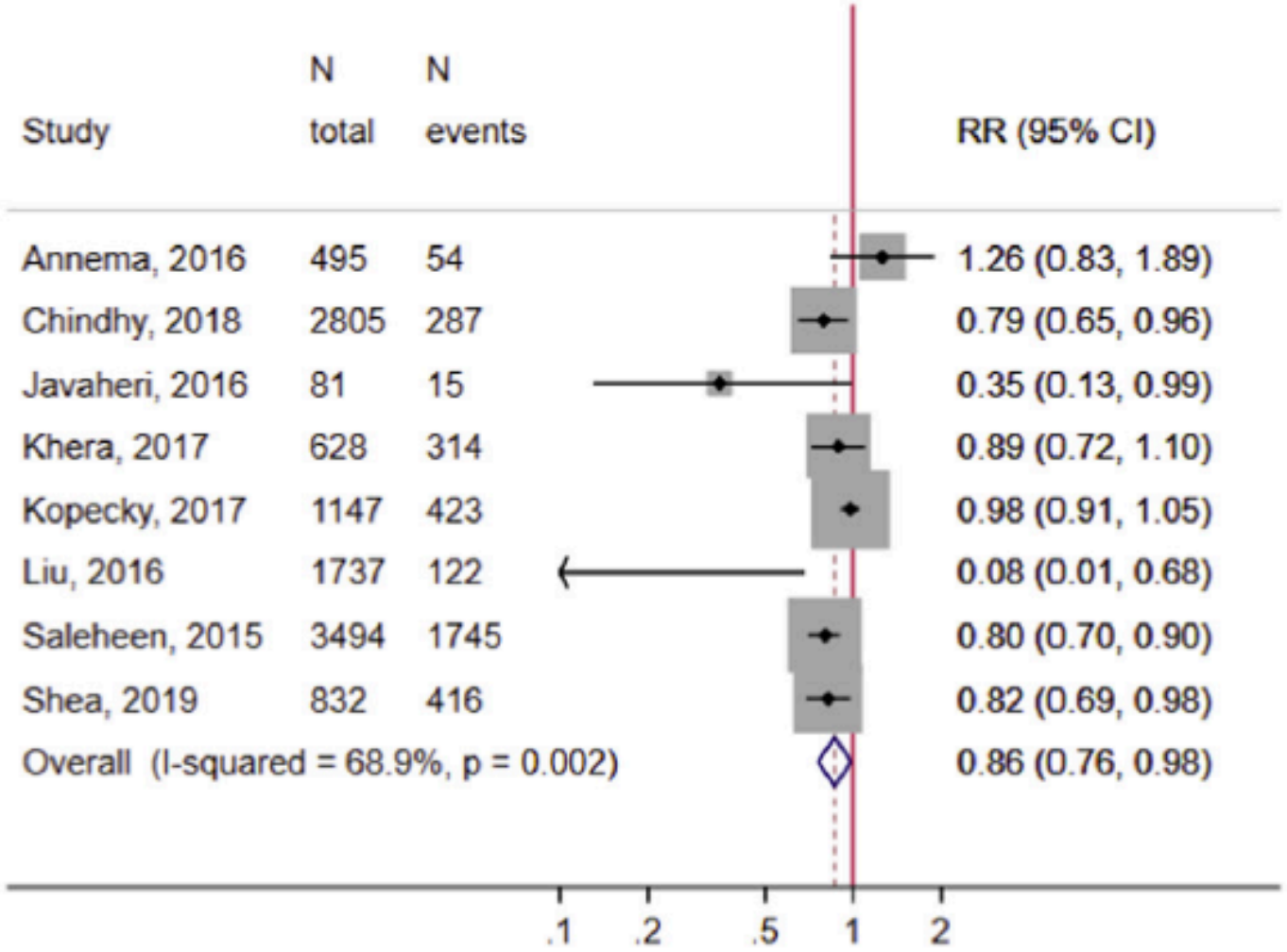
Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors (1)

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Improving HDL functionality may be more beneficial than simply increasing HDL-C concentrations.

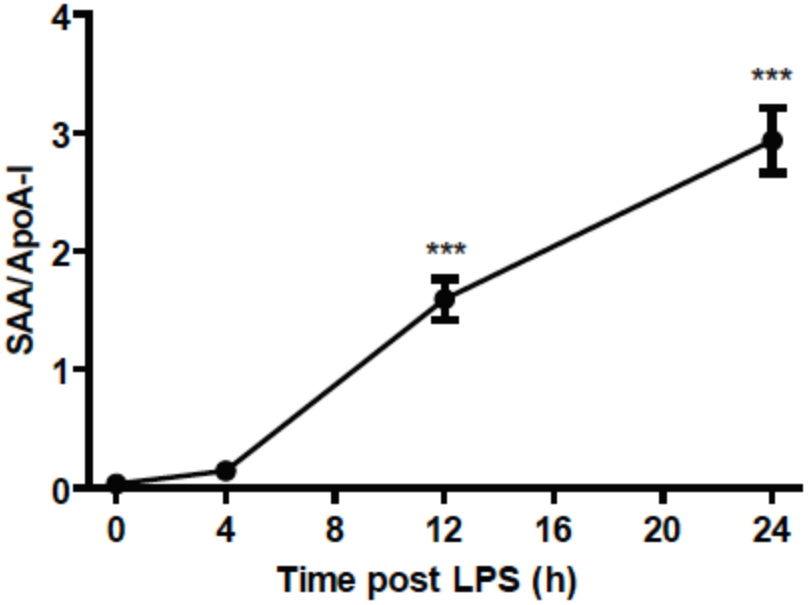
Khera AV., et al. N Engl J Med 2011;364:127-35

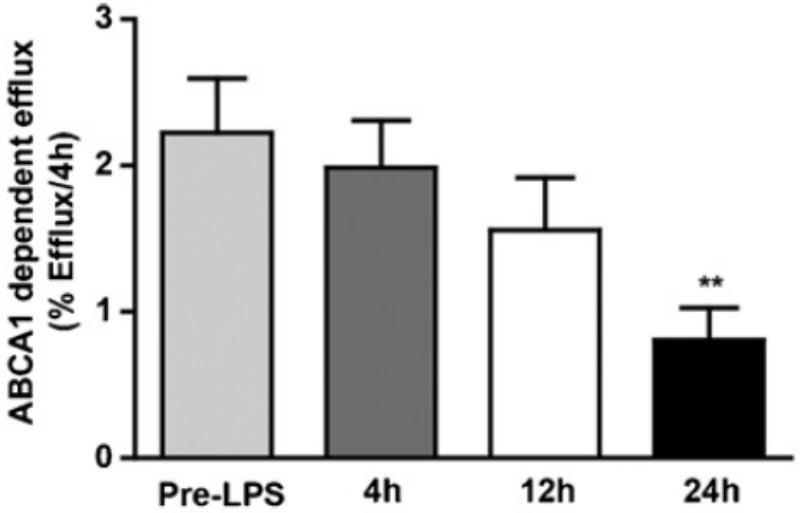
Meta-analysis shows an association between 1SD increase in CEC and major cardiovascular events (MACE) of 0.86



Soria-Florido et al. Atherosclerosis 2020;302:36-42

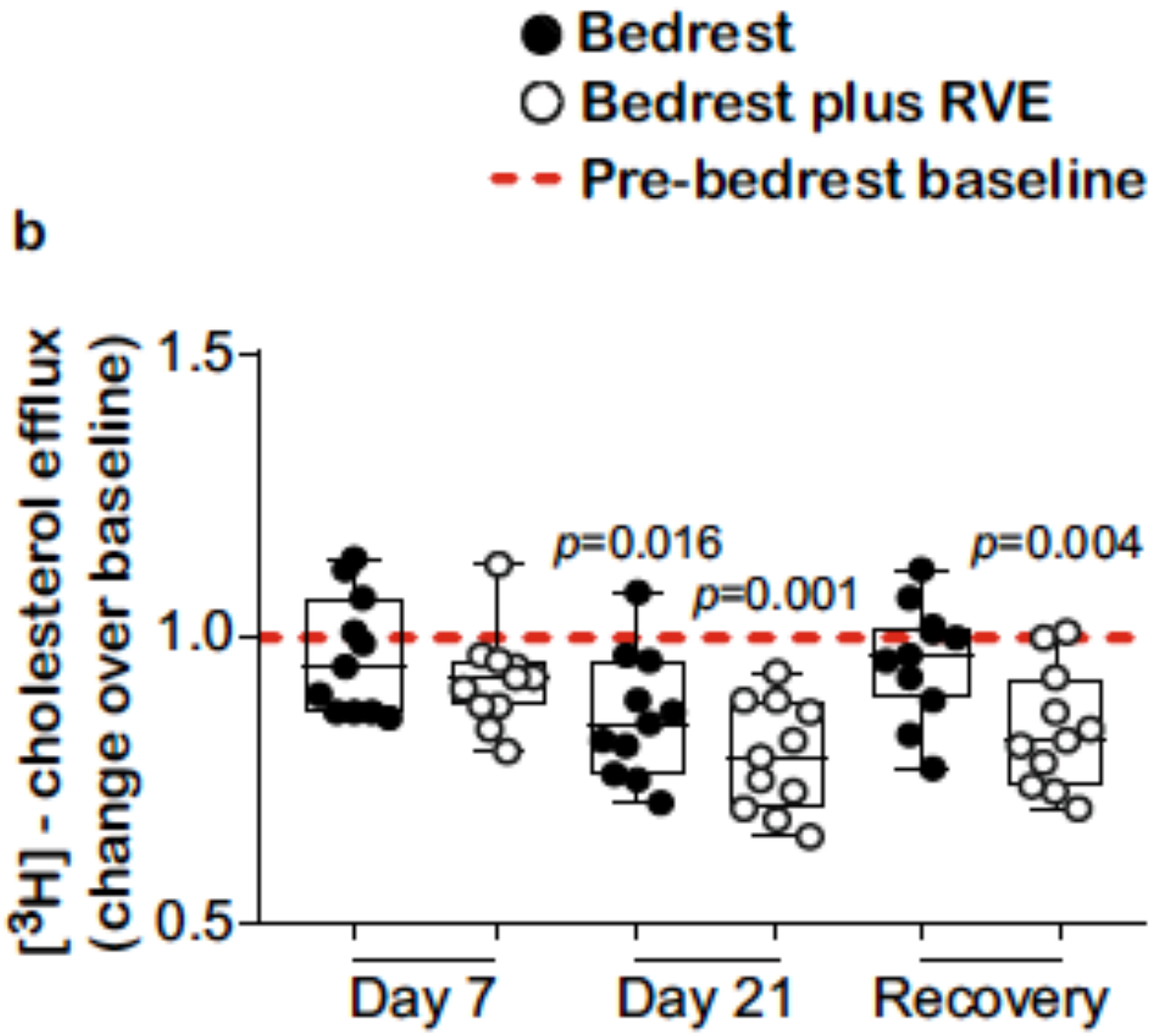
Inflammation (LPS infusion) changes HDL composition and lowers cholesterol efflux capacity





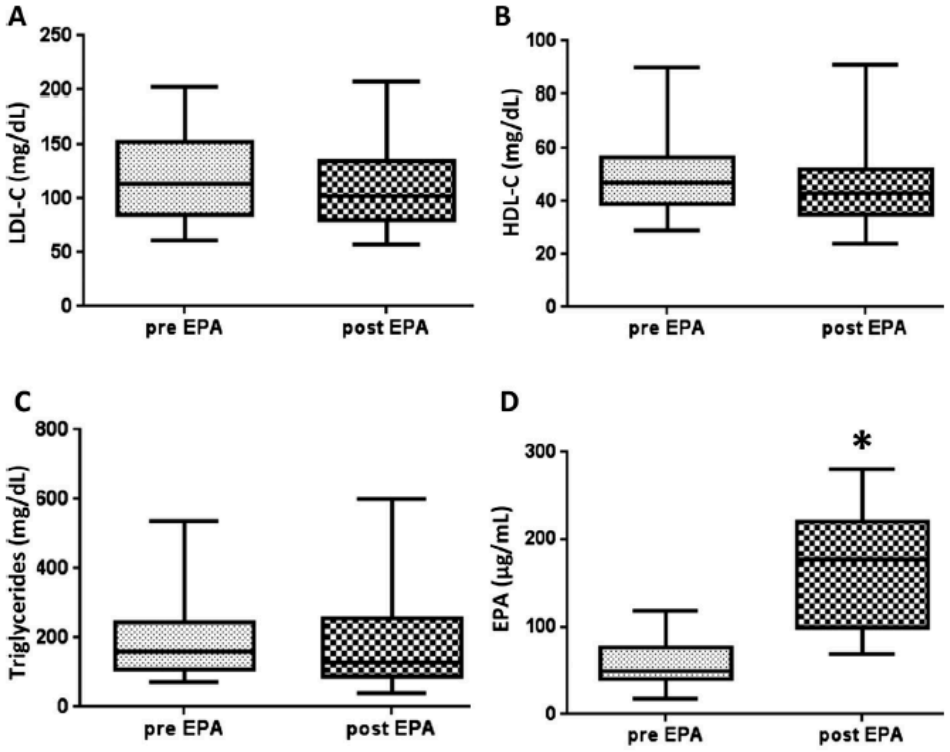
de la Llera Moyaa M. et al Atherosclerosis 2012;222:390-394

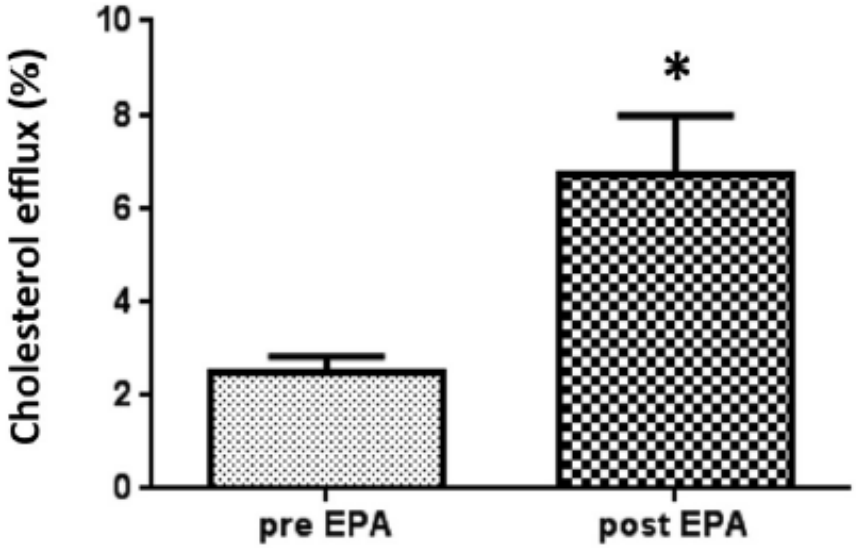
Physical inactivity lowers cholesterol efflux capacity



Trakaki. et al Sci Rep 2020;10:15001

4 weeks high dose EPA (1.8 g/d) improves cholesterol efflux capacity in dyslipidemic subjects





Tanaka. et al atherosclerosis 2014;237:577-583

Increased consumption of olive oil, nuts, legumes, whole grains and Fish promotes HDL functions in high CVD risk subjects

Table 1. Association between increases in the consumption of different food items and changes in HDL-related traits (in %).

Variables[a)]	↑ 10 g d^{-1} of virgin olive oil		↑ 30 g d^{-1} of nuts		↑ 25 g d^{-1} of legumes		↑ 25 g d^{-1} of whole grains		↑ 25 g d^{-1} of fish	
	Raw model	Adjusted model	Raw model	Adjusted model	Raw model	Adjusted model	Raw model	Adjusted model	Raw model	Adjusted model
Change in HDL cholesterol concentrations (%)	−0.057 [−0.70; 0.59]	0.005 [−0.76; 0.77]	1.43 [−1.03; 3.90]	1.66 [−1.31; 4.62]	3.13* [0.70; 5.58]	2.60* [0.18; 5.03]	0.25 [−0.40; 0.90]	0.26 [−0.39; 0.91]	−1.17* [−2.20; −0.15]	−1.14* [−2.21; −0.065]
Change in cholesterol efflux capacity (%)	0.54* [0.036; 1.03]	0.68* [0.084; 1.27]	2.03 [−0.043; 4.11]	1.36 [−1.32; 4.05]	0.59 [−1.50; 2.65]	0.82 [−1.31; 2.95]	0.53* [0.018; 1.05]	0.64* [0.12; 1.16]	−0.93* [−1.73; −0.12]	−1.11* [−1.96; −0.27]
Change in HDL capacity to esterify cholesterol (%)	0.33 [−1.01; 1.67]	−0.068 [−1.70; 1.57]	−3.90 [−9.84; 2.04]	−2.03 [−9.93; 5.85]	−0.13 [−7.00; 6.75]	0.78 [−6.55; 8.13]	−0.49 [−1.72; 0.74]	−0.35 [−1.63; 0.93]	−0.46 [−2.65; 1.73]	−0.36 [−2.75; 2.04]
Change in cholesteryl ester transfer protein activity (%)	0.003 [−0.76; 0.76]	0.54 [−0.40; 1.48]	0.63 [−2.75; 4.02]	0.37 [−4.29; 5.01]	−3.35 [−7.25; 0.53]	−4.80* [−9.03; −0.57]	0.26 [−0.45; 0.97]	0.24 [−0.52; 0.99]	−1.41* [−2.63; −0.18]	−1.63* [−3.00; −0.27]
Change in paraoxonase-1 antioxidant activity (%)	2.56* [0.62; 4.51]	2.09 [−0.33; 4.51]	3.48 [−5.37; 12.4]	12.2* [0.13; 24.2]	14.6* [4.25; 24.9]	11.7* [0.44; 22.8]	0.17 [−1.67; 2.01]	−0.13 [−2.08; 1.82]	3.18* [−0.003; 6.33]	3.93* [0.40; 7.45]
Change in HDL capacity to promote endothelial release of nitric oxide (%)	0.26 [−0.99; 1.51]	−0.28 [−1.79; 1.23]	2.07 [−2.69; 6.81]	−1.79 [−7.80; 4.20]	1.37 [−3.53; 6.25]	2.02 [−2.93; 6.95]	0.064 [−1.27; 1.40]	−0.28 [−1.65; 1.08]	1.29 [−0.70; 3.28]	1.88 [−0.19; 3.95]

Hernaez. et al Mol Nutr Food Res 2019;63:1800847

So far cholesterol efflux capacity seems valid

Cross sectional

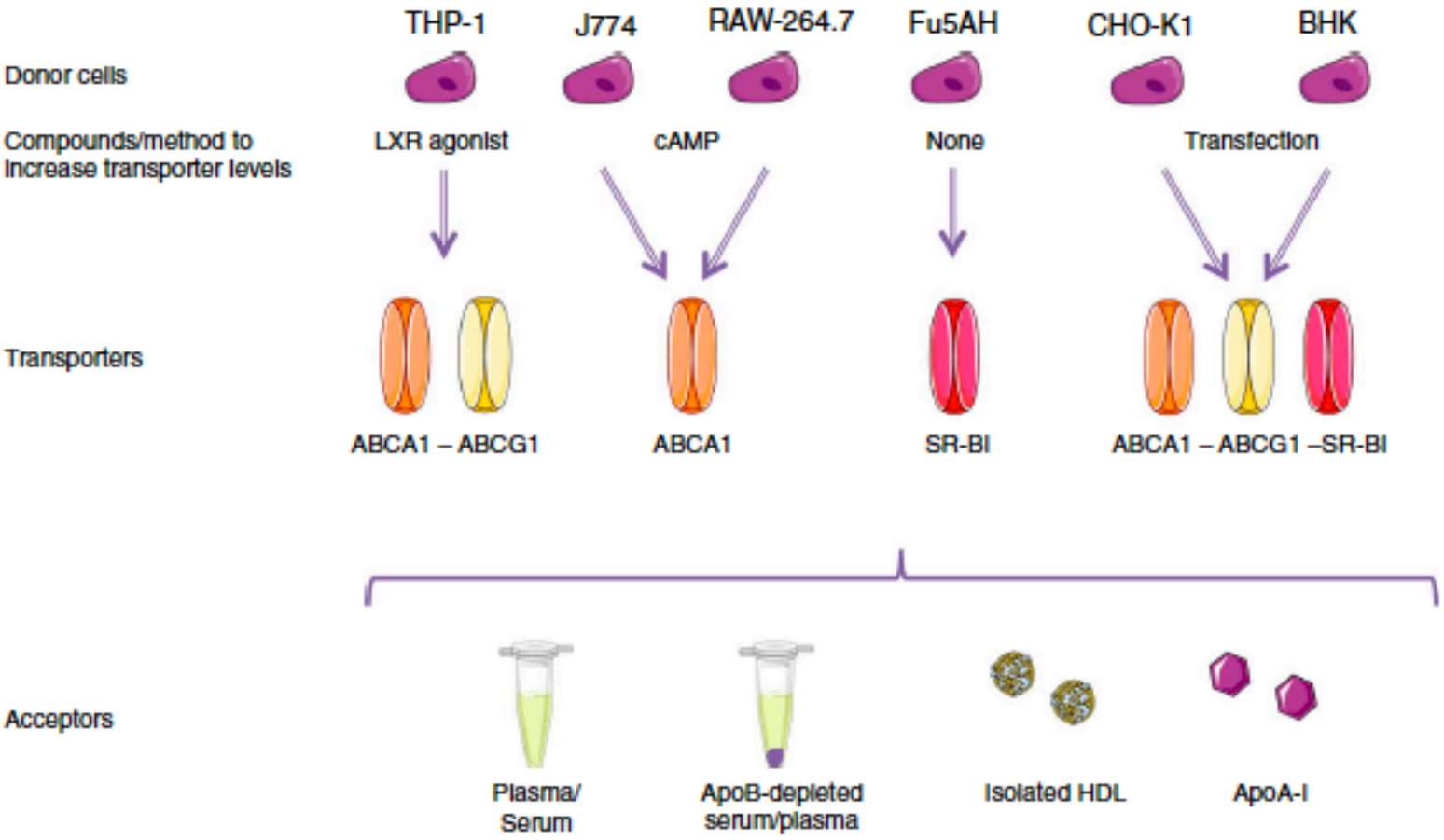
Interventions, not fully consistent but seems ok
but not yet to endpoints ??

Genetics (mendelian randomization), urgently needed ??

Two attention points:
Difficulty is the variation in assays between labs,
there is a clear need for standardization

Other HDL functionalities

Variation in methodology for cholesterol efflux capacity



Talbot et al. Prog Lipid Res 2018;69:21-32

Key messages

- Cross-sectional, serum **HDL-C** is a strong predictor for future CVD risk.
- Interventions that elevate HDL-C do not lower CVD events and also genetics do not support a causal role in CVD.
- Utilizing **apoA-I** (the major protein in HDL) instead of HDL-C also does not hold. Although it predicts cross-sectional CVD risk and elevations sometimes lower CVD events, genetics again do not support a causal role.
- Utilizing **HDL functionality** is nowadays the most valid paradigm. There are different definitions of HDL functionality, but **cholesterol efflux capacity** is most closely linked to its postulated function.
- Indeed cholesterol efflux capacity predicts CVD risk cross-sectional. It can be modified by pharmacological and lifestyle based interventions. But there are no studies yet that link a better cholesterol efflux capacity with endpoints and genetic studies are lacking.
- Attention points relate to the variation in cholesterol efflux assays, and maybe we have not choosen the right HDL functionality.

Wel of geen HDL-C in het cardiovasculaire risicoprofiel

Jogchum Plat

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