Wel of geen HDL-C in het cardiovasculaire risicoprofiel ?

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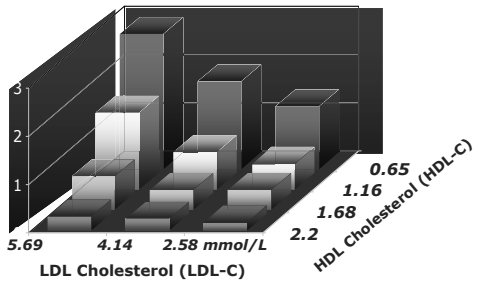
CVD Risk as a Function of LDL and HDL-C

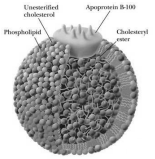
- (men aged 50-70 y) *Framingham Heart Study* -



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

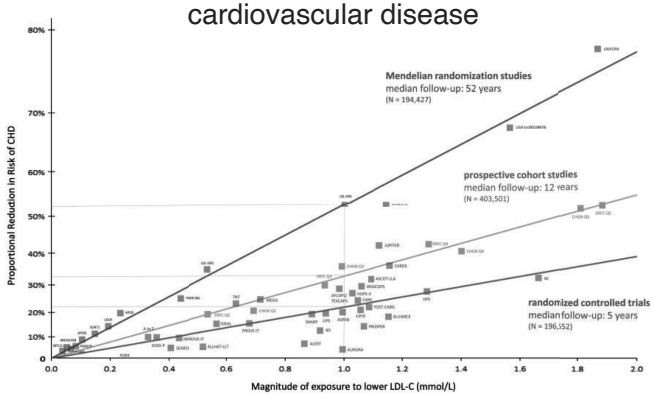


- LDL-cholesterol lowering irrespective of underlying mechanisms/intervention lowers CVD risk

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

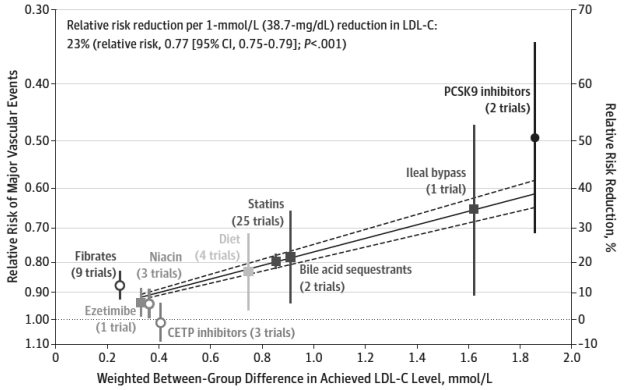
Ference BA et al. Eur Heart J. *2017;38;*:2459-2472

Low density lipoproteins cause atherosclerotic cardiovascular disease



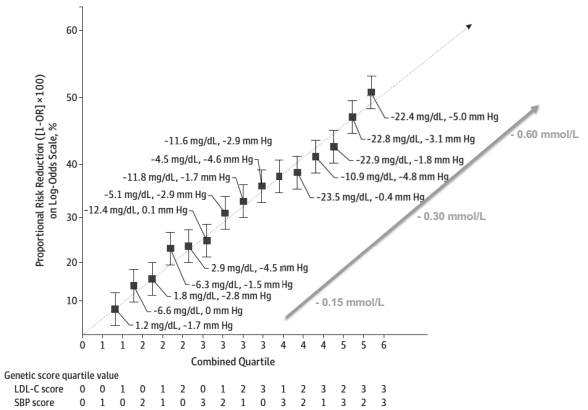
Ference BA et al. Eur Heart J. *2017;38;*:2459-2472

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

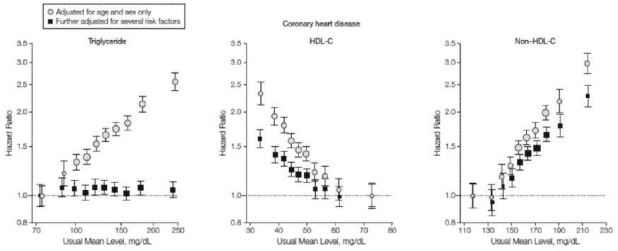


Ference BA et al. *JAMA. 2019;322;*:1381-1391

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

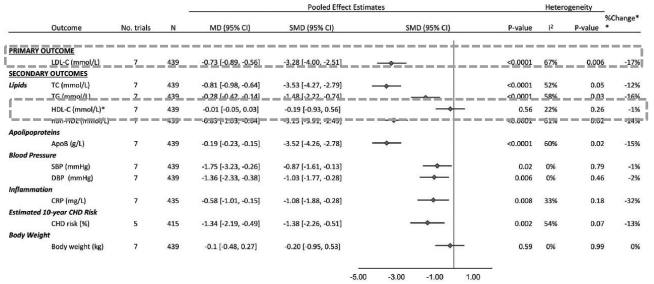


Data is based on 302430 subjects from 68 studies including 12785 cases

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

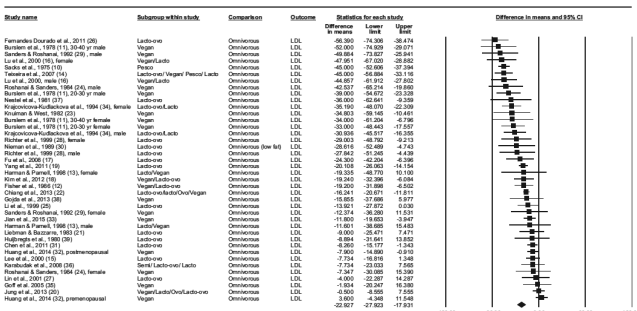
Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-analysis of Controlled Trials☆,☆☆

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,*]



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

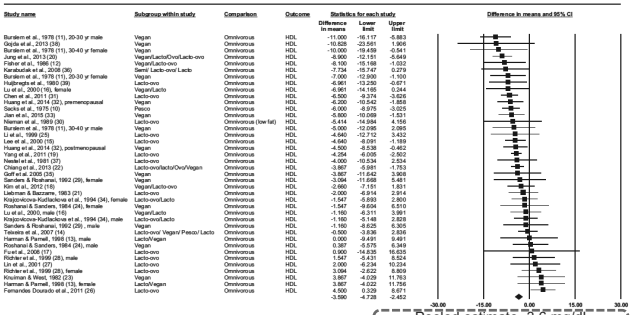
Association between plant-based diets and LDL cholesterol: a systematic review and meta-analysis



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



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

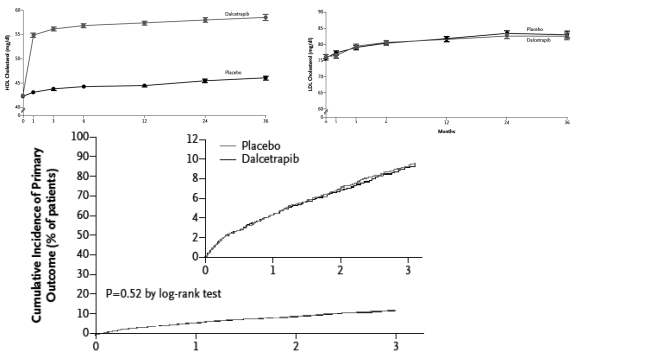
Table 3 The number of participants meeting metabolic syndrome (MetS) risk factors criteria at baseline and post-intervention

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.

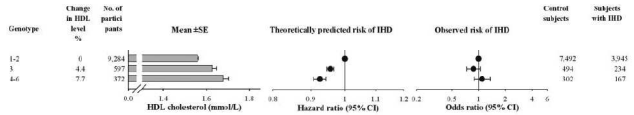
Kent et al. Nutrition & Metabolism 2013, 10:58

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



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

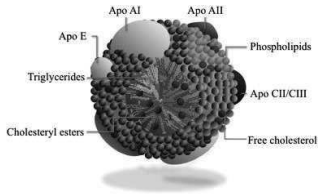
Genetically elevated HDL Cholesterol does not lower the risk of Ischemic Heart Disease



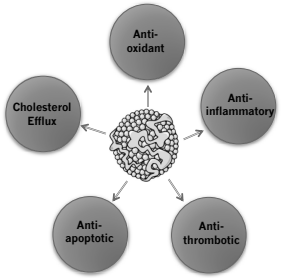
Haase et al. J Clin Endocrinol Metab 2010;95:e500-e510

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

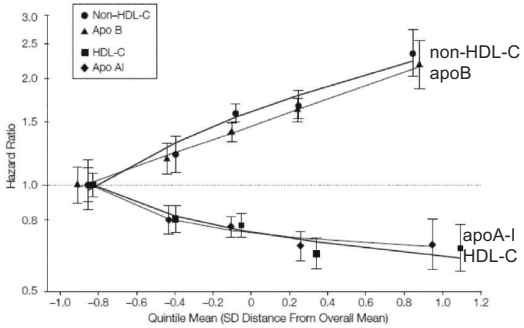
70% of the protein mass in HDL is ApoA-I



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



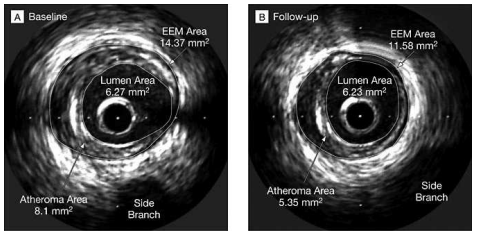
Cross-sectional, like HDL-C, ApoA-I is also a valid predictor for future CVD risk?



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

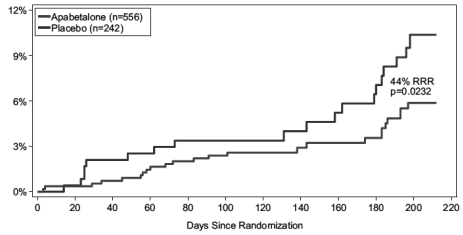
ApoA-I infusion has an acute effect on lesion regression

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

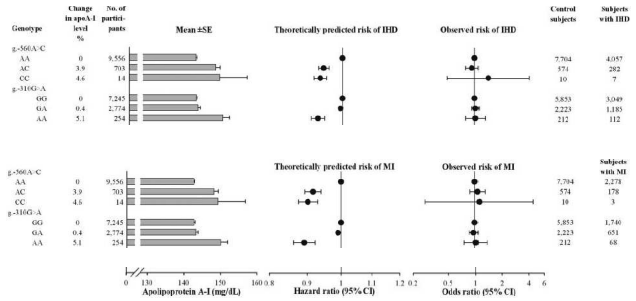


But also several negative outcome studies

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

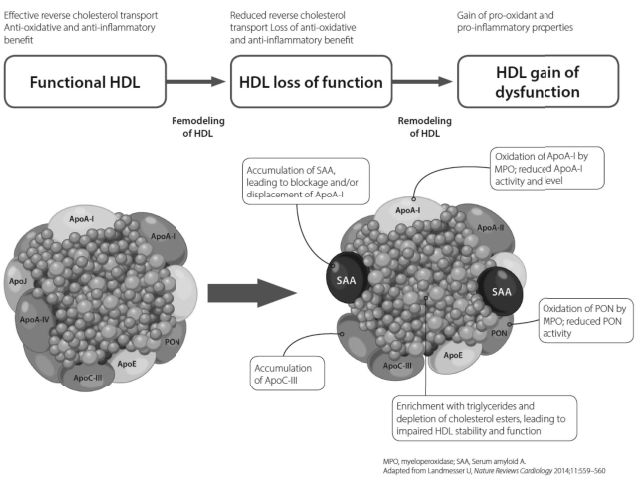
Copenhagen city heart study



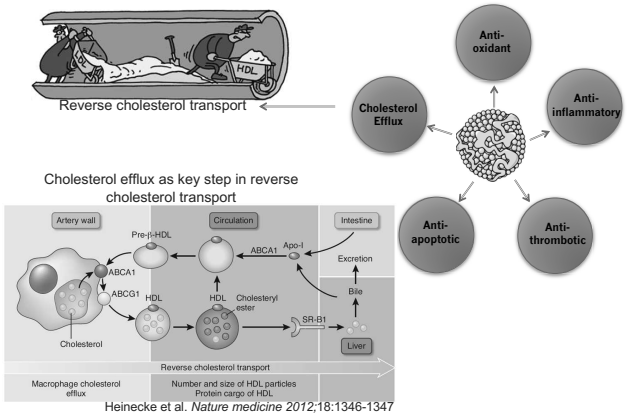
Haase et al. J Clin Endocrinol Metab 2010;95:e500-e510

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

HDL functionality?

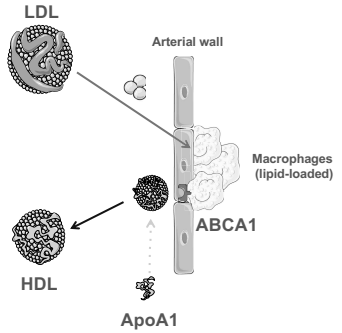


HDL functionality is the current paradigm

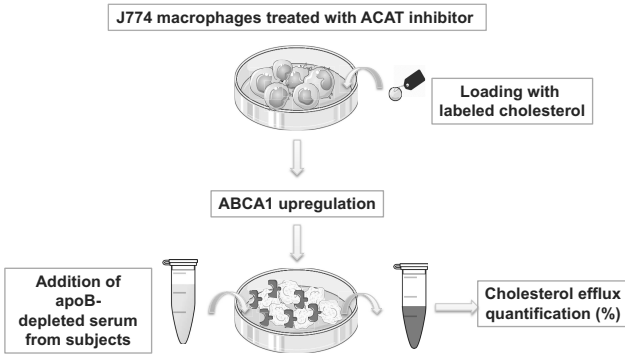


Heinecke et al. *Nature medicine 2012*;18:1346-1347

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

Cardiovascular Risk Factors	Odds Ratio (95% CI)	P Value
Diabetes	1.92 (1.26–2.93)	0.003
Hypertension	1.80 (1.31–2.47)	<0.001
Smoking	1.30 (0.95–1.73)	0.10
LDL cholesterol	1.01 (0.86–1.18)	0.93
HDL cholesterol	0.85 (0.70–1.03)	0.09
Efflux capacity	0.75 (0.63–0.90)	0.002

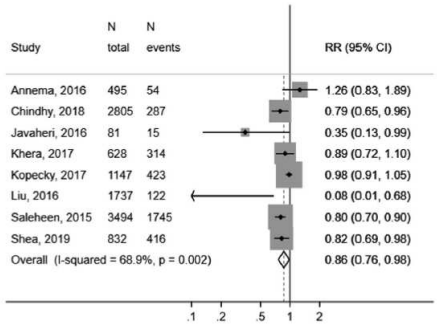
Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors [1]

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.

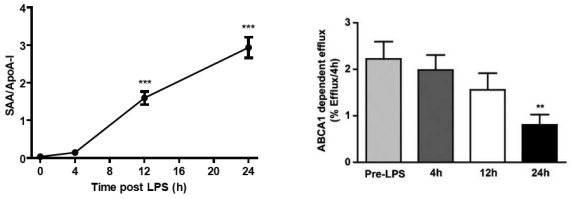
Khera AV., et al. N Engl J Med 2011;364:127-35

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



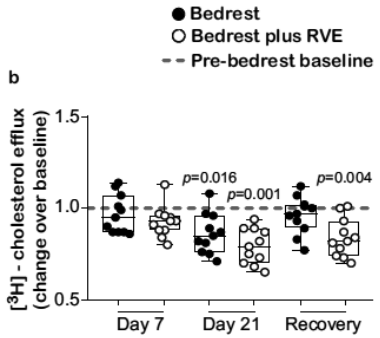
Soria-Florido et al. Atherosclerosis 2020;302:36-42

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



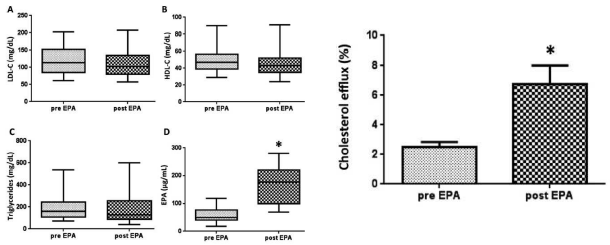
de la Llera Moyaa M. et al Atherosclerosis 2012;222:390-394

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 [0.37; 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

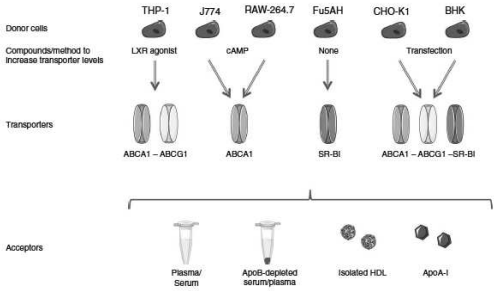
Interventions, not fully consistent but seems ok
but not yet to endpoints ??

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

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