Addendum 2: LDL as Primary Cause of CVD: Pro and Con

Issue Statement: Primary Root Causes and Solutions for Premature CVD and MI need to be Prioritised		
Hypothesis	**For**	**Against**
"Bad Cholesterol" or LDL (in and of itself) is a primary cause of CVD	COMPARATIVE/ASSOCIATIONAL evidence from prospective observational, epidemiological, ecological and other comparative studies indicates higher LDL, higher risk.	* Hazard ratios weak and inconsistent. * Framingham and many others show HR's disappear when HDL etc. taken into account * Many studies show significant HR only for very, very high LDL levels * Case-control generally no sig LDL difference between diseased and well - ratios dominate * Even in FH, severly premature CVD have same LDL as those aging healthily - nearly all studies of note show this phenomenon - also FH now beginning to be viewed as dependent more on clotting phenomena - and early disease FH are strongly marked by many parameters relative to healthy FH (LDL is ironically the one that fails to maintain itself) * In ~20 studies, calcification extent didn't correlate with LDL levels * In autopsies, atherosclerosis extent didn't correlate with LDL levels * Etc. etc. etc.
	MECHANISTIC evidence from scientific literature - but conflicting with better mechanistic edidence?	* LDL lipoproteins glycated, damaged or modified would make sense - but latter due to effect of other genuine causes * Hyperinsulin/IR/hyperglycemia dramatically stronger evidence base - and these stronger hypotheses in turn actually cause LDL dysfunction?
	EXPERIMENTAL evidence from various pharmaceutical RCT's which lower LDL - LDL drops in the population, event rates are lowered	* Examples of pharmaceutical RCT's which lower cholesterol greatly, yet increase in event rates observed e.g. CETPi * Some analyses show that event-reduction extent...does not correspond to LDL-lowering extent in individuals - very few papers available with this particular individual-level data though - unfortunately? * These analyses do show that the medication impacts on e.g. ferritin, CRP and other trial measures, DO actually track in dose-response fashion for individual's reduced risk rate

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