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INVITED EDITORIAL

Linear reverse risk of HDL-C levels for predicting cardiovascular disease: it is not that straightforward!

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The residual risk of cardiovascular disease is ~50–60% despite intensive LDL-cholesterol lowering with statins and ezetimibe, prompting investigation into therapies that elevate HDL-cholesterol.[1–3] Earlier studies suggested that the risk of atherosclerotic disease has a linear relationship with HDL-C levels. One meta-analysis reported that for every 1 mg/dL increase in HDL-C there is a 2% decrease in risk of coronary heart disease in men and 3% decrease in women.[4] Based on an elderly cohort of the Framingham Heart Study, it was[5] estimated that every change of 10 mg/dL in HDL-C is associated with a 50% change in risk.[6] Given this strong inverse linear relationship between cardiovascular risk and HDL levels, the New Zealand guidelines group[7] incorporated HDL-C levels in the assessment of cardiovascular risk. However, attempts to increase HDL-C with pharmacotherapy has not been associated with improved outcomes,[8] particularly in patients whom significant risk reduction has already been achieved with LDL-C lowering.[9] Cholesterol ester transfer protein inhibitors have either neutral, very small or negative, effects on cardiovascular outcomes.[10–13] Similarly, studies of niacin and fibrates have had disparate outcomes.[5,8,14,15] Newer treatments, including anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies have resulted in modest increases in HDL-C levels—up to 7.6% in one meta-analysis of 25 trials—but with more dramatic reductions of over 50% in LDL-C levels driving decreased major cardiovascular events in some studies.[16] In addition, studies utilizing Mendelian randomization have shown no direct relation between genetically determined HDL-C concentrations and cardiovascular events.[17–19] While low HDL-C levels in the absence of hypertriglyceridaemia have been associated with increased cardiovascular risk and primary lipid disorders such as ApoA-I deficiency, they may be reflective of underlying disease states, certain medication use (i.e. anabolic steroids, fibrates), impact of type of exercise (aerobic vs. isometric),[20] and malignancy.[21] On the other end of the spectrum, there are reports suggesting that very high HDL-C levels adversely impacts survival.[22,23] Emerging evidence suggests that the relationship between cardiovascular risk and HDL-C levels is not linear and may even be U-shaped.[22]

It has been argued that this so-called HDL paradox stems from a progressive mistaken discernment between HDL and HDL-C.[24] These authors contend that the 1975 Gofman–Miller[25–27] hypothesis stating that 'a reduction in plasma-HDL may impair the normal clearance of cholesterol from the arterial wall and thereby accelerate the development of atherosclerosis' refers to HDL particle number. But given that HDL particle number could not be measured, HDL concentration became the surrogate measurement and subsequently as a result of widespread public acceptance clinical HDL concentration became commonplace. As a result, with time, clinicians and clinical investigators began to pursue ways in which HDL concentration could be elevated to reduce cardiovascular risk.

In their paper Zhong *et al.*[28] report a meta-analysis of 37 prospective cohort studies, involving 3 524 505 participants and more than 612 027 deaths, to evaluate the association between HDL-C levels and mortality. They found HDL-C level was found to be associated with mortality from all causes, cardiovascular disease (CVD), and cancer in a J-shaped dose–response pattern, with the lowest risk observed at HDL-C levels of 1.40–1.50 mmol/L, 1.75–1.85 mmol/L, and 1.65–1.75 mmol/L, respectively. Compared with HDL-C level of 1.45 mmol/L, the pooled hazard ratios (HRs) for all-cause mortality were 1.12 [95% confidence interval (CI) 1.04–1.21] and 1.47 (95% CI 1.39–55) for each 1 mmol/L increase and decrease in HDL-C levels, respectively. Moreover, the pooled HRs for all-cause mortality were 1.21 (95% CI 1.09–1.36) and 1.36 (95% CI 1.21–1.53) for the highest and the lowest categories of HDL-C levels, respectively. Therefore, HDL-C level is associated mortality from all causes, CVD, and cancer in a J-shaped dose–response manner, that is, both extremely high and low HDL-C levels are associated with an increased risk of mortality. The findings of this meta-analysis are supported by the fact that other studies have also shown that individuals with very high HDL

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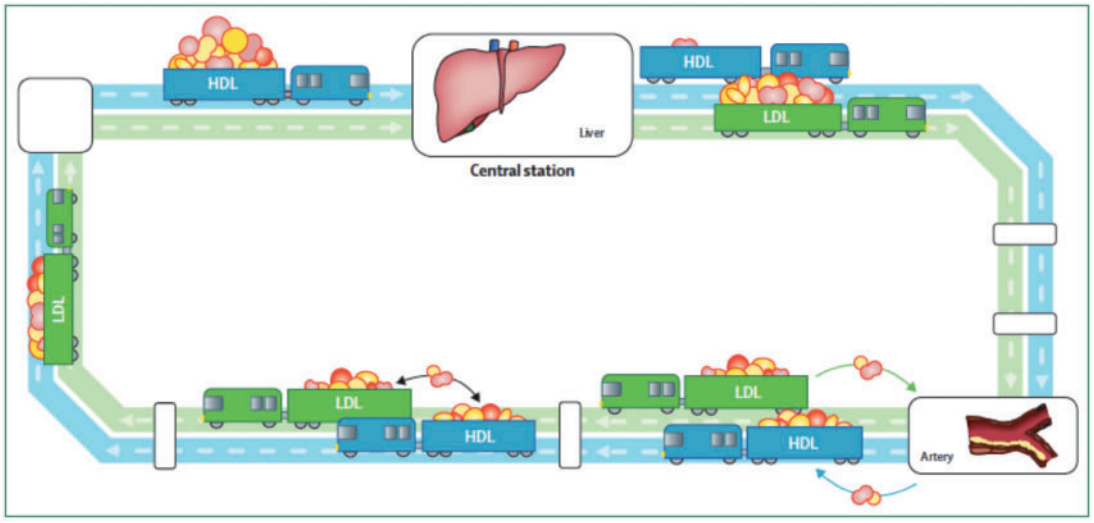

Figure 1 Schematic representation of lipid transport as a metro system. The HDL transport system (blue line) can be likened to a series of heterogeneous protein trains carrying a diverse group of lipid passengers (different lipid species indicated by various shapes and colours of passengers) through the circulatory system. As HDL trains travel through the circulatory system, lipid passengers embark and disembark at various stations [peripheral tissues (white rectangles and square)]. Lipid passengers can also move between circulating cells and lipoproteins [including LDLs (on the green line) and very low density lipoprotein (VLDLs) (not shown)]. The net direction of lipid movement associated with HDL is uptake from peripheral tissues and transport to the liver, which in arteries prevents proatherogenic lipid accumulation. In this analogy, the liver is the central station, where most lipid passengers disembark and previously lipid-laden HDL trains can be recycled and recirculated. The liver is also a hub of HDL production, forming nascent HDL particles that are lipid-poor and avid acceptors of peripheral lipids.[24]

cholesterol[22,23] or high ratio of HDL cholesterol to particle number[29] have increased morbidity and mortality burden of atherosclerosis. To explain these results Xiang and Kingwell[24] and Feng *et al.*[30] argue that HDL-C is essentially a snapshot, a static measure, of the dynamic process of HDL particle transport and nor does it reflect particle function[24] (*Figure 1*). Feng *et al.* proposed that the reserve remnant cholesterol transport hypothesis wherein HDL acquires triglyceride-rich lipoproteins upon lipolysis with subsequent transport of remnant-derived cholesterol to the liver in a pathway which originates in the intestine with secretion of ApoA-1 on chylomicrons followed by transport to plasma via lymph. To assess this hypothesis they developed a novel *in vitro* fluorescent assay to evaluate the capacity of HDL to acquire free cholesterol from triglyceride-rich lipoproteins during lipolysis by lipoprotein lipase. They applied this assay to several groups of subjects with markedly different HDL-C levels. Their findings revealed that decrease free cholesterol transfer from triglyceride-rich lipoproteins to HDL in subjects with both low and extremely high HDL-C. These investigators conclude that these findings are probably a link between HDL-associated cardiovascular risk to triglyceride metabolism and account for U-shape relationship of HDL-C and cardiovascular disease. These findings are in important advance in the dynamics of HDL-C transport. The next step would be to determine whether this assay can predict linear cardiovascular risk. The fact that much is yet to be learnt about HDL-C transport should not be viewed as a drawback, instead it heralds a golden opportunity for life scientists and clinical investigators to work closely together to expand our understanding of this complex phenomenon. Recent advancements in 'omics' including at the molecular gene level (genomics: the study of genes and their function), the protein level (proteomics: the study of proteins), the transcript level (transcriptomic: the study of all RNA molecules, including non-coding RNAs), and the metabolic level (metabolomics: the study of molecules involved in cellular metabolism) raise the possibility that more accurate biomarkers of HDL-C transport system, such as the novel assay developed by Feng *et al.*,[30] rather than HDL-C test could be developed. These include HDL particle number, functionally significant structural components and function, as well as cholesterol efflux capacity (the first step in reverse cholesterol transport) with the hope that they could more accurately predict future cardiovascular risk, and to guide and monitor therapy. Until then, HDL-C remains a useful risk marker to predict cardiovascular risk but with the caveat that the association is curvilinear—that is, it is not straightforward!

Conflict of interest: none declared.

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