

Does High LDL-cholesterol Cause Cardiovascular Disease? *Letter to the Editor*

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We read with great interest the narrative review article written by Ravnskov *et al.* (1), who had already reiterated in published letters over the past decade their doubts and claims on both the validity of the 'cholesterol hypothesis' and the beneficial effects of statin treatment on risk of incident cardiovascular disease (CVD) events.

The authors claim in the final "Key issues" of their review article that (1) the hypothesis that high LDL-cholesterol levels cause atherosclerosis and CVD has been shown to be false by numerous observations and experiments; (2) the assertion that statin treatment is beneficial has been kept alive by individuals who have ignored the results from trials with negative outcomes and by using deceptive statistics; and (3) clinicians should abandon the use of statins and PCSK-9 inhibitors, and instead identify and target the actual causes of CVD.

As with most disagreements in life, there is some truth on both sides. CVD is a complex and multifactorial disease. So, how much the LDL-cholesterol is increased is important and furthermore increased LDL-cholesterol concentrations *per se* are not the only important issue. LDL-cholesterol needs to be incorporated into atherosclerotic plaques and that may happen for different reasons in different people. Some people are more resistant to the effects of their high LDL-cholesterol than others. That is why the concept of absolute risk is valuable. As clinicians, we would treat middle-aged patients with diabetes, who were smokers and who were hypertensive with a statin, even if their plasma LDL-cholesterol concentrations were considered fairly 'normal', because their absolute risk of CVD events would be considered high enough to intervene with a treatment (a statin) to attempt to lower that absolute risk. In contrast, most clinicians would not treat a teenager without familial hypercholesterolaemia with a modestly high LDL-cholesterol concentration because their absolute risk of CVD is low.

As we say in situations like this ...'the devil is in the detail'! We strongly believe that it is not sufficient to say 'a high LDL-cholesterol level always or never causes CVD events and mortality!'. Binary interpretations of the data in biology and medicine are far too simplistic an approach.

Reference list

1. Ravnskov U, de Lorgeril M, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, Kendrick M, Langsjoen PH, Mascitelli L, McCully KS, Okuyama H, Rosch PJ, Schersten T, Sultan S, Sundberg R. LDL-C does not cause cardiovascular disease: a comprehensive review of current literature. *Expert Rev Clin Pharmacol*. 2018 Sep 10. doi: 10.1080/17512433.2018.1519391. [Epub ahead of print]