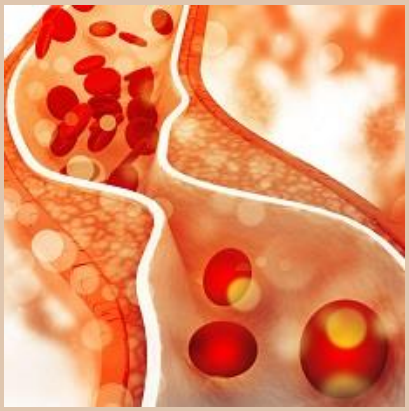
Time of Exposure Matters



Early cholesterol levels correlate with later-life events

Low-density lipoprotein cholesterol (LDL-C) has been determined to be a major modifiable risk factor for cardiovascular disease. We focus on LDL levels especially after cardiovascular events and use medications to lower cholesterol in these cases. But we also can use cholesterol-lowering medications for primary prevention, which is attempting to intervene before a health effect or even occurs. We have traditionally focused on lipid-lowering therapies later in life, from middle age on and after cardiac events. But should we be focusing on younger age groups for intervention? How much does cumulative exposure matter? Is a rise in LDL later in life more problematic than cumulative exposure?

This study included 18,288 participants from four studies: Atherosclerosis Risk in Communities Study, Coronary Artery Risk Development in Young Adults Study, Framingham Heart Study Offspring Cohort, and the Multi-Ethnic Study of Atherosclerosis. Included subjects had two or more LDL-C measures at least 2 years apart between the ages of 18 and 60 years, with at least one in middle age between 40 to 60 years. Participants were followed for a median of 16 years from their index visit at a median age of 56. The study found that greater exposures to cumulative LDL-C and time-weighted average LDL-C during young adulthood and middle age were associated with an increased risk of CHD, even after adjusting for the most recent LDL-C level during middle age.

Abstract

- **Importance:** Low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular disease (CVD). Most observational studies on the association between LDL-C and CVD have focused on LDL-C level at a single time point (usually in middle or older age), and few studies have characterized long-term exposures to LDL-C and their role in CVD risk.
- **Objective:** To evaluate the associations of cumulative exposure to LDL-C, time-weighted average (TWA) LDL-C, and the LDL-C slope change during young adulthood and middle age with incident CVD later in life.
- **Design, Setting, and Participants:** This cohort study analyzed pooled data from 4 prospective cohort studies in the US (Atherosclerosis Risk in Communities Study, Coronary Artery Risk Development in Young Adults Study, Framingham Heart Study Offspring Cohort, and Multi-Ethnic Study of Atherosclerosis). Participants were included if they had 2 or more LDL-C measures that were at least 2 years apart between ages 18 and 60 years, with at least 1 of the LDL-C measures occurring during middle age at 40 to 60 years. Data from 1971 to 2017 were collected and analyzed from September 25, 2020, to January 10, 2021.
- **Exposures:** Cumulative exposure to LDL-C, TWA LDL-C, and LDL-C slope from age 18 to 60 years.
- **Main Outcomes and Measures:** Incident coronary heart disease (CHD), ischemic stroke, and heart failure (HF).
- **Results:** A total of 18 288 participants were included in this study. These participants had a mean (SD) age of 56.4 (3.7) years and consisted of 10 309 women (56.4%). During a median follow-up of 16 years, 1165 CHD, 599 ischemic stroke, and 1145 HF events occurred. In multivariable Cox proportional hazards regression models that adjusted for the most recent LDL-C level measured during middle age and for other CVD risk factors, the hazard ratios for CHD were as follows: 1.57 (95% CI, 1.10-2.23; *P* for trend = .01) for cumulative LDL-C level, 1.69 (95% CI, 1.23-2.31; *P* for trend <.001) for TWA LDL-C level, and 0.88 (95% CI, 0.69-1.12; *P* for trend = .28) for LDL-C slope. No association was found between any of the LDL-C variables and ischemic stroke or HF.
- **Conclusions and Relevance:** This cohort study showed that cumulative LDL-C and TWA LDL-C during young adulthood and middle age were associated with the risk of incident CHD, independent of midlife LDL-C level. These findings suggest that past levels of LDL-C may inform strategies for primary prevention of CHD and that maintaining optimal LDL-C levels at an earlier age may reduce the lifetime risk of developing atherosclerotic CVD.

Low-density lipoprotein levels (LDL-C) are typically a focus in our cardiovascular treatment and prevention programs and the statin class used in the treatment of hyperlipidemia is the most prescribed group of medicines in the United States. This study focused on two aspects of LDL-C levels. The first is a rising LDL and the second is a persistently high LDL-C throughout life. The question the researchers wanted to answer was whether one was a greater risk factor than the other. They found that more cumulative exposure to higher LDL-C levels during young adulthood and middle age was associated with an increased risk of cardiovascular events. This finding fits with what we know from people who have a genetic predisposition to very high LDL-C levels (familial hypercholesterolemia) who go on to developed cardiovascular disease at a very young age. Previous studies have shown participants with long-term exposure in the highest LDL-C level group had 5 times the risk of CVD and 4 times the risk of total mortality compared with those in the optimal LDL-C level group (80-90 mg/dL).

The mechanism of this problem is that small LDL particles and certain lipoproteins freely enter and exit the endothelial barrier (inside of the blood vessels – especially coronary arteries), where they can interact with extracellular structures, such as proteoglycans, to become retained in the extracellular matrix. The LDL-C particles that are retained in the arterial wall are susceptible to various modifications, including oxidation. Oxidized LDL-C elicits an inflammatory response, which results in vascular injury and atheroma (soft fatty plaque) formation. With continued exposure to LDL-C, additional small LDL particles accumulate in the arterial wall, leading to the development of narrowed arteries hardened with plaque (atherosclerosis). Therefore, an individual's total atherosclerotic burden is believed to be associated with both the circulating LDL-C levels and the total duration of exposure.

It appears from this study that the risk of developing atherosclerotic plaques and coronary heart disease (CHD) events is associated with the cumulative exposure to LDL-C, so it is plausible that achieving optimal lipid levels early in life and maintaining those optimal levels throughout adulthood may prevent incident CHD events better than the current paradigm of deferring lowering LDL-C levels to later in life when atherosclerosis is likely already advanced.

The safest method of maintaining optimal LDL-C levels throughout life is to engage in healthy behaviors that lead to ideal cardiovascular health, through dietary changes, exercise, and not smoking. However, for many people, diet and other lifestyle modifications may not be sufficient to maintain optimal LDL-C levels throughout life. In these cases, pharmacological therapy to lower LDL-C levels earlier in life when atherosclerosis is less advanced may be a more successful way to reverse the disease course and prevent future CHD events. It is interesting because one issue is determining the threshold to treat. In this study, there is a suggestion that LDL-C of <100 is needed to avoid risk. One can make an argument that this is like smoking. We keep track of pack-years of smoking because we know that this cumulative exposure is associated with disease later in life. Perhaps, high lipid exposure may be the same. I tend to track triglyceride levels and triglyceride/HDL ratios as well to evaluate risk. This study didn't perform this calculation, but I would like to see how this correlates with long-term risk as well.

Zhang Y, Pletcher MJ, Vittinghoff E, et al. Association Between Cumulative Low-Density Lipoprotein Cholesterol Exposure During Young Adulthood and Middle Age and Risk of Cardiovascular Events. JAMA Cardiol. Published online September 22, 2021. doi:10.1001/jamacardio.2021.3508