

Non-high-density lipoprotein (non-HDL) cholesterol in adolescence as a predictor of atherosclerotic cardiovascular diseases in adulthood

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Defined as the total cholesterol minus high-density lipoprotein (HDL), non-HDL cholesterol has been increasingly acknowledged as a measure of risk estimation for developing atherosclerotic cardiovascular diseases (ASCVD). Comprising of apolipoprotein B100-containing cholesterol (very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), and lipoprotein (a) (Lp(a))), and apolipoprotein B48-containing lipoproteins (chylomicrons and its remnants), elevated serum levels of non-HDL cholesterol in early adolescence has been strongly linked with the development of ASCVD in adulthood. This article reviews the evidence from longitudinal studies, which demonstrate the cumulative risk of ASCVD in relation to the elevated levels of non-HDL cholesterol earlier in life.

Keywords

High-density lipoprotein; HDL; Non-HDL; Low-density lipoprotein; LDL; Atherosclerotic cardiovascular diseases; ASCVD

1. Introduction

A growing body of knowledge has shown biological signs of atherosclerosis in the arteries of adolescents and children as young as 2 years old [1–3]. The progression of the so-called subclinical atherosclerosis has been associated with ASCVD in adulthood. Although clinical manifestations of ASCVD is rare in such a young age, early modification of the underlying risk factors poses a pivotal role in the prevention of cardiovascular diseases in adulthood.

From an epidemiologic standpoint, the risk factors for the development of ASCVD can be divided into modifiable (anthropometric parameters, metabolic derangements, and sedentary lifestyle) and non-modifiable components (age, race/ethnicity, and familial/genetic predisposition) [4].

From a clinical standpoint, susceptible individuals for developing ASCVD can be stratified into high-risk, moderate-risk, and low-risk [5].

Dyslipidemia is a medical condition characterized by the disorders in lipid metabolism. It has been considered, for a long time, a risk factor for ASCVD with cholesterol-lowering agents constituting the mainstay of tertiary, secondary, and recently primary prevention.

Non-high-density lipoprotein cholesterol (non-HDL-C) is calculated as the total serum cholesterol minus the level of high-density lipoprotein (HDL). This measures all the atherogenic lipoproteins in plasma including apolipoprotein B100-containing cholesterol (VLDL, LDL, IDL, and Lp(a)) as well as apolipoprotein B48-containing lipoproteins (chylomicrons and its remnants) [6, 7]. Recent studies have started to embrace the inclusiveness of non-HDL cholesterol levels in estimating the risk of developing ASCVD, especially over the course of a lifetime [5, 6, 8, 9]. This article aims to review the evidence from longitudinal studies on the existing link between non-HDL cholesterol levels in early life with the development of ASCVD in adulthood.

2. Attention to non-HDL cholesterol in ASCVD risk reduction

The risk reduction in individuals with established ASCVD or at a high risk of developing one starts with lifestyle modification, which aims at promoting a healthy diet and more physical activity. The 2018 Guideline on the Management of Blood Cholesterol by the American Heart Association and American College of Cardiology recommended that a maximally-tolerated statin therapy should aim to lower the

serum level of LDL by $\geq 50\%$ [10]. However, there has been not much of an emphasis on the measurement of non-HDL-c in this setting nor any interest in its specific treatment. In contrast, the 2001 Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) had specifically provided stratified goals for non-HDL cholesterol based on a 10-year risk of ASCVD and the number of risk factors [6]: a non-HDL level-c < 130 mg/dL in those with a 10-year ASCVD risk $> 20\%$, non-HDL-c < 160 mg/dL in those with multiple risk factors and a 10-year risk $\leq 20\%$, and a non-HDL-c < 190 mg/dL in those with $\leq 0-1$ risk factor. Similarly, the 2019 guidelines by the European Society of Cardiology recommended a non-HDL-c < 85 mg/dL in patients at a very high risk of CVD, a level < 100 mg/dL for high-risk patients, and a level < 130 mg/dL in those with a moderate risk for ASCVD [11].

One of the reasons for focusing on non-HDL cholesterol as a better predictor of ASCVD is our growing knowledge of the atherogenicity of triglyceride-rich lipoproteins (TRL) and their remnants [12–14]. Commonly measured as triglyceride/HDL ratio, higher levels of triglyceride compared to lower levels of HDL has been a reliable indicator of metabolic syndrome, which is characterized by insulin resistance and accelerated atherosclerosis [13]. Such a pro-atherosclerotic state is strongly seen in those with hypertriglyceridemia despite being treated with maximally-tolerated statins [14]. As non-HDL cholesterol measures all the atherogenic lipoprotein particles, including triglyceride-rich lipoprotein, it is a more inclusive predictor of the lifelong risk of ASCVD [15]. However, the relationship between plaque characteristics and serum levels of lipoprotein is complex and difficult to ascertain using a single blood biomarkers.

3. Non-HDL cholesterol and atherosclerosis

The pathophysiology of atherosclerotic plaque formation in relation to non-HDL cholesterol is similar to other atherogenic lipid particle. The atherosclerosis process, as a result of elevated non-HDL cholesterol, starts with the retention of lipoproteins within the arterial wall [16]. Such a response-to-retention mechanism is central to the early development of atherosclerosis [17].

Progressive retention of atherogenic lipoprotein particles triggers an inflammatory response, which further causes endothelial dysfunction [16–18]. Such an activated/pro-inflammatory state set the stage, within the arterial wall, for active uptake of more lipid particles by upregulated macrophages. On the other hand, chemical modification of deposited lipids, through oxidative stress or hyperglycosylation, attracts more inflammatory cells, which in turn, accelerates lipid deposit and retention.

Although sub-endothelial fatty streaks rarely elicit clinical symptoms, once the lipid-laden macrophages (foam cells) extends toward the smooth muscle of the arterial wall (media),

atherosclerosis will be more likely to become symptomatic. Such a fatty streak owes its growth to the apoB-containing lipoproteins, which include all the cholesterol particles except HDL, and triglyceride-rich remnants. The oxidative stress, which results in oxidative modification of these atherogenic lipoprotein particles, accelerates the process of foam cell formation and atherosclerotic plaque expansion by recruiting more inflammatory cells and highly-active uptake of a larger amount of atherogenic particles. It is not surprising to expect that circulating antioxidants play a counteracting role to protect against plaque growth and stabilization [19].

The atherogenic effect of circulating lipoproteins in the development of ASCVD has been more robustly measured by prospective longitudinal studies. In a population-based cohort of 589 individuals, Armstrong *et al.* [9] found that coronary artery calcification score in mid-adulthood (33 to 45 years old) was significantly associated with non-HDL cholesterol in adolescence, young-adulthood, and mid-adulthood; however, the earlier rise of non-HDL cholesterol, i.e., in adolescence, had the strongest link with the development of coronary artery calcification, a finding in the favor of cumulative risk of exposure to non-HDL cholesterol since early age in life. Another longitudinal data analysis from 4 prospective cohorts of 4,582 children aged 3 to 19 years revealed that dyslipidemia at early adolescence increases the relative risk of carotid intima-media thickness in adulthood by 29% [20].

The effect of genetic and heritable risk factors on adult ASCVD has been investigated by different studies [21, 22]. Beekman *et al.* [21] used the data of twins from three different ethnicities to assess the intermediating phenotypes leading to established cardiovascular diseases. The study estimated the heritability likelihood of serum levels of apolipoproteins and lipid particles to range between 0.48 and 0.87. In another genome-wide association study, Buscot *et al.* [22] evaluated the relationship between polygenic genetic risk score and LDL, HDL, and triglyceride across different time points from adolescence to the adulthood. The weighted genetic risk scores used the 38 single-nucleotide polymorphisms (SNPs) for HDL, 14 SNPs for LDL, and 24 SNPs for triglyceride, and assessed its association with the serum levels of apolipoproteins at 8 different time-points from 1980 to 2011. Although the scoring system could not predict, with a high confidence, the occurrence of developmental trajectories but it could anticipate the serum levels of HDL, LDL, and triglyceride levels at all ages.

In contrast to non-HDL cholesterol, the descriptor/mature HDL is a composition of heterogeneous macromolecules with varying diameters and density, which can be further divided into sub-classes of HDL₂₋₄ [23, 24]. The anti-atherosclerotic role of HDL has been extensively investigated by experimental, clinical, and epidemiological studies, and is contributed to removing extra cholesterol from the foam cells, inhibiting the oxidation of LDL, and limiting the inflammatory process underlying the ASCVD [23–26]. In an autopsy study of tissue specimens obtained

Table 1. Studies evaluating the longitudinal effect of lipoprotein levels in early life and atherosclerotic cardiovascular diseases in adulthood.

Author/Year	Sample size	Risk factor	Measure of association	Type of ASCVD	Follow-up	Conclusion
Armstrong MK, <i>et al.</i> /2021 [9]	589	Non-HDLc	Cumulative odds ratio, 95% CI: 1.5 (1.14–1.92)	Coronary artery calcification	28 years	Non-HDLc at all life stages are associated with ASCVD
Juonala M, <i>et al.</i> /2020 [20]	4582	Non-HDLc	Relative risk, 95% CI: 1.29 (1.07–1.55)	Carotid intima-media thickness	26 years	Elevated non-HDLc increases the risk of carotid artery atherosclerosis
Magnussen CG, <i>et al.</i> /2009 [27]	1711	LDL and HDL cholesterol	Relative risks from 1.6 to 2.5	Carotid artery intima-media thickness	21 years	Pediatric dyslipidemia especially in obese/overweight predicts CIMT in adulthood
Raitakari OT, <i>et al.</i> /2003 [29]	2229	LDL, HDL, TG, and LDL/HDL ratio	Regression coefficient for different lipid profiles	Common carotid artery intima-media thickness	21 years	Lipid profile in 12–18 years of age predicts carotid intima-media thickness in adulthood
Mahoney LT, <i>et al.</i> /1996 [28]	197	LDL, HDL, TG, and LDL/HDL ratio	Average serum levels of lipoproteins	Coronary artery calcification	21 years	Higher serum levels of atherogenic lipoproteins are associated with coronary artery calcification from childhood to adulthood, more in males than in females

HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TG, Triglyceride; CI, Confidence interval; ASCVD, Atherosclerotic cardiovascular diseases; Non-HDLc, Non-HDL cholesterol; CIMT, Carotid intima-media thickness.

from 3000 individuals between the age of 15 to 34 years, who had died due to lethal accidents, homicide, or suicide, McGill *et al.* [26] reported that the extent of atherosclerotic plaque lesions across the cardiovascular system, in the right coronary artery and abdominal aorta, was strongly associated with the serum levels of non-HDL cholesterol but inversely related with the HDL cholesterol concentration.

The observations of experimental studies on the tissue specimens obtained from adolescence and topographic imaging points out the gradual development of ASCVD, initially as a fatty streak, which later progresses to the fibrous plaque and raised lesions [24–26]. Although published studies in the literature have tried to connect the circulating atherogenic biomarkers such as HDL and non-HDL cholesterol with atherosclerotic lesions at different time points in life, to the best our knowledge, no study has feasibly measured the average level of atherogenic lipoprotein particles in relation to the cumulative risk of ASCVD from childhood to adulthood.

4. The linkage between non-HDL cholesterol and atherosclerosis in epidemiological studies

The atherosclerotic lesions start to appear over the endothelial lining of medium-to-large arteries decades before ASCVD becomes clinically evident. Although rapid progression of atherosclerotic plaque buildup occurs during mid-adolescence to early adulthood, autopsies have shown signs of atherosclerosis in coronary artery and aorta of children as young as 2 years of age [3, 27].

As the primary target for ASCVD risk reduction, LDL-C is often considered a measure of efficacy for the treatment of adult dyslipidemia [10]. However, as the growing evi-

dence is acknowledging the robustness of non-HDL cholesterol in ASCVD risk estimation [28], attentions have shifted to this non-expensive and readily available laboratory parameter. One of the reasons that non-HDL cholesterol has received an increasing endorsement as a strong predictor of ASCVD is its comprehensiveness in quantifying atherogenic particles including LDL and non-LDL atherogenic lipoproteins. Such an inclusive risk predictability, even at a small level, will cumulatively translate into a significant value over the course of an individual's life.

A meta-analysis of individual data from 8 randomized clinical trials encompassing 62,154 persons aimed to evaluate the strength of relationship between lipid profile and major cardiovascular events [29]. Of these, 38,153 patients were on statin therapy and were followed up for 1 year in terms of fatal and non-fatal myocardial infarction and stroke, any coronary artery disease-related event, and hospitalization for unstable angina. The study found that the adjusted hazard ratio for major cardiovascular events, per 1-standard deviation increase in the serum level of lipid profile components, was 1.16 for non-HDL cholesterol, 1.14 for apolipoprotein B, and 1.13 for LDL cholesterol, and significantly stronger for non-HDL cholesterol than for both of LDL cholesterol and apolipoprotein B. This adds to the beneficial utility of non-HDL cholesterol in prediction of major cardiovascular events among adults taking statins.

Table 1 summarizes the findings of longitudinal studies on the atherogenic effects of dyslipidemia in early life, measured by different endpoints, on development of ASCVD in adulthood. Although the importance of non-HDL cholesterol in risk stratification of individuals at the risk of ASCVD development or its progression is not a new concept [29], few longitudinal studies have estimated the predictive util-

ity of non-HDL cholesterol in early life with the measures of atherosclerosis in adulthood. In fact, available studies have evaluated the relationship between well-established atherogenic lipoproteins such as LDL, triglyceride, or LDL/HDL ratio with the development of calcification, intima-media thickness, or atherosclerosis of coronary or carotid arteries [30–33]. As emphasized by two previous studies [9, 20], non-HDL cholesterol levels in adolescence are strongly associated with ASCVD in adulthood and should be used more widely as a measure of risk prediction and treatment efficacy for primary, secondary, and tertiary prevention purposes.

5. Conclusions

A growing body of knowledge is endorsing the robustness of non-HDL cholesterol in risk stratification of population, especially adolescents, at the risk of developing ASCVD or its progression. Non-HDL cholesterol constitutes all the apoB-containing lipoprotein particles except HDL, which also includes triglyceride-rich remnants. This inclusive prediction measure becomes cumulatively associated with ASCVD, over the course of a time, from adolescence to adulthood.

Author contributions

SS developed the research question, performed the literature review, and drafted the manuscript. WI and AAS participated in the literature review and drafting the manuscript. NF and SG contributed to the literature review, data extraction, and scientific writing. SohK, ET, and SiaK critically reviewed the manuscript and revised it for any scientific and technical errors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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