Original article

Association between lipid markers in childhood/ adolescence and cardiovascular events in adulthood: A systematic review

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ABSTRACT

Introduction. The association between lipid markers in childhood/adolescence and the incidence of clinical cardiovascular events in adulthood has been little explored in the bibliography. The objective of this systematic review was to analyze available evidence on this topic.

Population and methods. This systematic review was conducted in accordance with the PRISMA guidelines. A comprehensive bibliographic search was done to find studies assessing the association between lipid levels in childhood and the incidence of cardiovascular events in adulthood. There were no language or geographic restrictions.

Results. A total of 5 observational studies (all prospective cohorts) including 43 540 patients were identified and considered eligible for this study. Four studies assessed triglyceride levels; all reported a significant association between this lipid marker in childhood and cardiovascular events in adulthood. A study reported the same association with total cholesterol level, while another showed the predictive value of lipoprotein (a) for the same clinical outcome. Only one study assessed high-density lipoprotein cholesterol (HDL-C), but it did not find an association with the endpoint of interest. The analysis of low-density lipoprotein cholesterol (LDL-C) showed contradictory results, although the association was significant in the studies with a larger sample size and a higher number of events during follow-up.

Conclusion. According to this review, alterations in lipid markers in childhood and adolescence are associated with a higher cardiovascular risk in early and middle adulthood.

Keywords: dyslipidemia; child; adolescent; cardiovascular disease; adult.

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INTRODUCTION

Atherosclerosis is the main pathophysiological substrate of cardiovascular disease (CVD) and the main cause of morbidity and mortality in developed countries.[1] Although the atherosclerotic process progresses over time, the first changes in the arterial wall may be observed early in life.[2]

It is not uncommon to find cardiovascular risk factors, including dyslipidemia, in children and adolescents.[3,4] Moreover, multiple prospective studies have associated the presence of certain cardiovascular risk factors in childhood with the onset of subclinical atheromatosis in adulthood, such as carotid artery intima-media thickening, carotid plaques, or coronary artery calcification.[5–8] However, beyond analyzing some CVD surrogates, accurately determining the association between risk factors in childhood and clinical cardiovascular events in adulthood is extremely complex and, therefore, much less explored in the bibliography.

Despite these limitations, some studies have assessed the association between conventional lipid markers in childhood, such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, with the incidence of cardiovascular events in adulthood.[9–12] Likewise, recent reports have described an association between cardiovascular events in adulthood and lipoprotein (a) [Lp(a)] levels in childhood.[13] It is important to note that these studies assessed samples from the general population, and not from subgroups with primary lipid disorders (e.g., familial hypercholesterolemia), in which the unfavorable cardiovascular prognosis has been well established.[14,15]

A previous systematic review[16] assessed the association between cardiovascular risk factors in childhood and the occurrence of atherosclerotic events in adulthood, although it analyzed most of the subgenerational CVD risk factors and did not include the latest and most relevant studies published to date.[11,12]

The objective of this systematic review was to analyze the association between lipid markers in childhood/adolescence and the incidence of cardiovascular events in early and middle adulthood.

POPULATION AND METHODS

This systematic review was registered in PROSPERO and conducted in accordance with the PRISMA recommendations.[17]

A systematic bibliographic search was done to identify studies assessing the association between lipid levels in childhood/adolescence and the development of cardiovascular events in adulthood. Two independent reviewers searched the following electronic databases: PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane Controlled Trials using the following terms: total cholesterol, LDL-C, HDL-C, triglycerides, dyslipidemia, risk factors, and lipoprotein (a) in childhood, combined with the following terms: cardiovascular events, acute myocardial infarction, stroke, peripheral artery disease, coronary heart disease, coronary artery revascularization, and cardiovascular death in adulthood.

All observational cohort studies that assessed the relationship between lipid levels in childhood/adolescence and cardiovascular events in adulthood were included. No cross-sectional or case-control studies were included. There were no language or geographic restrictions.

Assessed endpoints were the clinical cardiovascular events in adulthood reported in the included studies. Effect size and 95% confidence interval (CI) values for these endpoints were reported as odds ratio (OR) or hazard ratio (HR), as indicated in the original publications.

The risk of bias was assessed using the Cochrane Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-1) tool.[18] This tool assesses 7 domains and categorizes studies as having a low, moderate, serious, or critical risk of bias. Discrepancies between reviewers were solved through the intervention of an additional third reviewer.

It was not possible to conduct a quantitative analysis (meta-analysis) due to the different lipid markers and cutoff points analyzed, the type of cardiovascular events reported, and the different measures of association described.

RESULTS

A total of 5 observational studies (all prospective cohorts) including 43 540 patients were identified and considered eligible for this study.[9-13] *Figure 1* shows the flow chart of the selection process.

Figure 2 shows the quality of selected studies in terms of bias assessment. The characteristics of the studies included in this review are presented in *Table 1*.

Triglycerides

The Princeton Follow-up Study (PFS) followed a group of 808 children with baseline triglyceride measurements obtained between 1973 and 1976 for 22 to 31 years (1998–2003).[9] Throughout follow-up, 19 individuals developed cardiovascular events (mean age: 31.7 years). Triglyceride levels in childhood were independently associated (adjusted for age, sex, and race) with an increased risk for a cardiovascular event in adulthood (HR: 5.35, 95% CI: 1.69–20.0 per 1 unit on the logarithmic scale). A second publication based on the PFS reported the 26-year follow-up of a group of 909 children with baseline lipid profile measurements obtained between 1973 and 1978.[10] In the multivariate analysis, a high triglyceride level (> 110 mg/dL) in childhood was the only independent explanatory variable for developing CVD in adulthood (adjusted OR: 5.85, 95% CI: 2.33–14.7). A third report by Morrison et al. from the same study analyzed the predictive value of combined lipid markers in childhood and adulthood.[11] Thus, 770 children aged 5 to 20 years were followed-up for 26 years. The incidence of cardiovascular events was 1% in the group with normal triglyceride levels at both visits (childhood and adulthood); 1.9% in subjects with high triglyceride levels (> 110 mg/dL) in childhood, but normal in adulthood; 2.9% in the group with normal triglyceride levels in childhood, but high in adulthood; and 14.6% in subjects with high triglyceride levels at both visits ($p < 0.0001$). Individuals who showed high triglyceride levels in both stages of life were almost 6 times more at risk for a cardiovascular event compared to the rest of the groups (adjusted OR: 6.06, 95% CI: 2.20–16.7).

Lastly, a prospective study with participants from the International Childhood Cardiovascular Cohort Consortium (7 cohorts started between the 1970s and 1990s) assessed whether triglyceride levels in childhood (3 to 19 years old) were associated with cardiovascular events in adulthood (mean follow-up of 35 years).[12] Lipid values at each visit during childhood and adolescence were "normalized" to a Z-score,

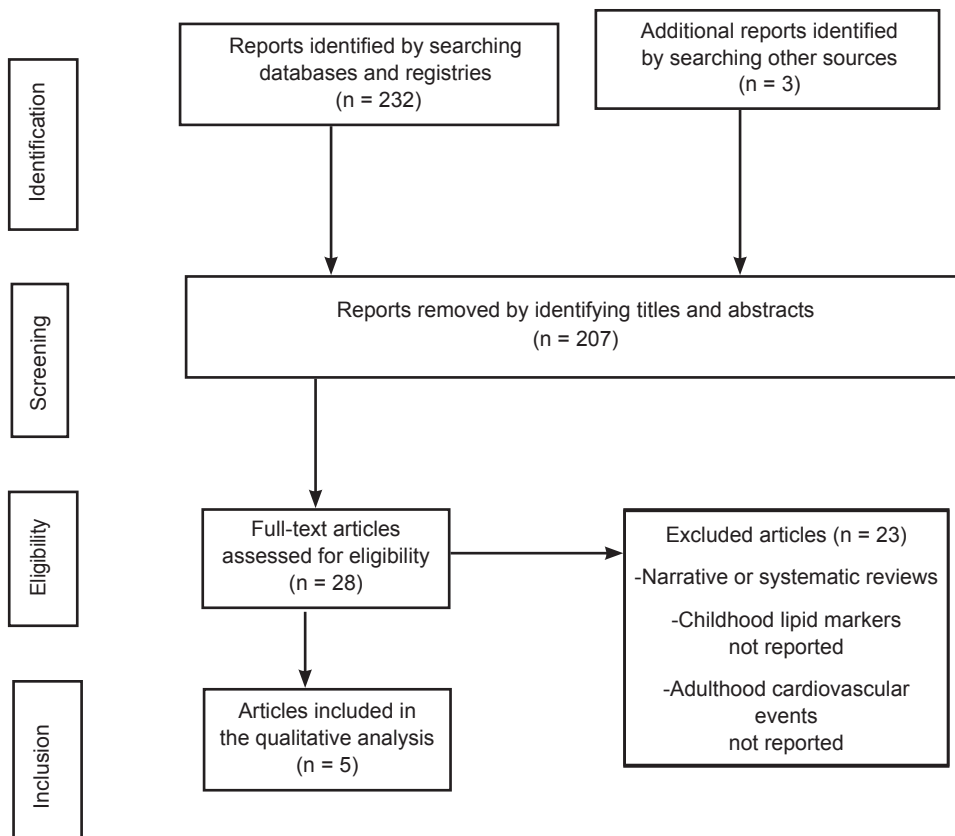**FIGURE 1.** Flow chart of the study selection process for this review

FIGURE 2. Assessment of bias in included studies

TABLE 1. Characteristics of the studies included in this systematic review

Study (year)	n	Baseline population	Follow-up	Lipid markers assessed	Events assessed
Morrison et al. (2009)[9]	808	Children with a mean age of 12.3 ± 3.8 years; 52% were males.	22–31 years old Mean age at follow-up 38.5 years.	TG	CV events (AMI, stroke, PAD or coronary artery revascularization).
Morrison et al. (2012)[10]	909	Children aged 6 to 18 years. Mean age 12.3 ± 3.4 years; 46% were males.	26 years. Mean age at follow-up 38 years.	TG LDL-C HDL-C	CV events (AMI, stroke, PAD or coronary artery revascularization).
Morrison et al. (2012)[11]	770	Children aged 5 to 20 years. Mean age 12.4 ± 3.4 years; 46% were males.	26 years. Mean age at follow-up 38 years.	TG LDL-C	CV events (AMI, stroke, PAD or coronary artery revascularization).
Jacobs et al. (2022)[12]	38 589	Children aged 3 to 19 years. Mean age 11.8 ± 3.1 years; 49.7% were males.	35 years. Mean age at follow-up 47 years.	Total cholesterol TG	Fatal and non-fatal CV events (AMI, stroke, ITA, CHF, PAD, chest angina, AAA, carotid surgery, or coronary artery revascularization).
Raitakari et al. (2023)[13]	2464	Children and adults aged 9 to 24 years.	Median age at follow-up 47 years.	Lp(a) LDL-C	Fatal and non-fatal CV events.

AAA: abdominal aortic aneurysm; ITA: ischemic transient attack; LDL-C: low-density lipoprotein cholesterol;
HDL-C: high-density lipoprotein cholesterol; CV: cardiovascular; PAD: peripheral artery disease; AMI: acute myocardial infarction;
CHF: congestive heart failure; Lp(a): lipoprotein(a); TG: triglycerides.

estimated based on the mean values for the overall population (stratified by age and sex). The Z-scores were then averaged to obtain a single value per person. In total, 319 fatal cardiovascular events that occurred among 38 589 study participants were analyzed. The HR for a fatal cardiovascular event was 1.50 per unit in the triglyceride Z-score (95% CI: 1.33–1.70). Likewise, the dichotomous analysis of the lipid variable showed that children and adolescents with high triglyceride levels (> 100 and > 130 mg/dL, respectively) had an HR of 2.75 for developing a fatal cardiovascular event (95% CI: 1.71–4.42). In addition, 779 fatal and non-fatal cardiovascular events that occurred among the 20 656 participants who were assessed for this event were analyzed. In this case, the HR was 1.45 per unit in the Z-score (95% CI: 1.34–1.56) and 2.47 when the triglyceride level was analyzed dichotomously (95% CI: 1.89–3.24).

Total cholesterol and low-density lipoprotein cholesterol

The aforementioned study by Jacobs et al. also analyzed the relationship between total cholesterol in childhood and cardiovascular events in adulthood.[12] In this case, the HRs for fatal cardiovascular events and for the combination of fatal and non-fatal events were 1.30 (95% CI: 1.14–1.47) and 1.31 (95% CI: 1.22–1.42) per unit in the Z-score, respectively. Likewise, high cholesterol levels (> 200 mg/dL) in childhood were associated with an HR of 2.20 (95% CI: 1.44–3.37) and 2.13 (95% CI: 1.60–2.83) for fatal cardiovascular events or for the combination of fatal and non-fatal events, respectively.

A secondary analysis of the Cardiovascular Risk in Young Finns Study (YFS) showed that LDL-C levels in young people (aged 9–24 years) were significantly associated in a multivariate analysis with the occurrence of cardiovascular events in adulthood (median age: 47 years).[13] In this case, the HR associated with the primary endpoint was 1.26 (95% CI: 1.06–1.47) per standard deviation. In contrast to that study, 2 publications using data from the PFS failed to demonstrate a significant association between increased LDL-C levels (> 110 mg/dL) in childhood and clinical events in adulthood.[10,11]

High-density lipoprotein cholesterol

The only study included in this review that analyzed HDL-C levels did not show a significant association between such lipid marker in childhood and cardiovascular events in adulthood.[10] The reported OR for CVD associated with low HDL-C levels (< 50 mg/dL in women and < 40 mg/dL in men) was 1.03 (95% CI: 0.37–2.88).

Lipoprotein (a)

Recently, an analysis of the YFS showed that Lp(a) levels measured in individuals ages 9 to 24 years were associated with an increased incidence of cardiovascular events in adults.[13] On that occasion, 95 of the original 3596 participants had CVD during follow-up. The age- and sex-adjusted HRs for fatal and non-fatal CVD were 1.96 (95% CI: 1.35–2.57) and 1.25 (95% CI: 1.03–1.47) considering a cutoff point for Lp(a) > 30 mg/dL or per standard deviation, respectively. A multivariate analysis, which included an adjustment for other risk factors, showed similar results [Lp(a) > 30 mg/dL: HR: 1.77 (95% CI: 1.17–2.37)].

Interestingly, the results observed in the YFS were replicated in the Bogalusa Heart Study (BHS) database. In this case, in an age- and sex-adjusted model, subjects aged 8 to 17 years exposed to high levels of Lp(a) showed 2.5 times the risk of developing CVD in adulthood compared to unexposed individuals.

DISCUSSION

This systematic review assessed the body of evidence currently available on the association between lipid levels in childhood/adolescence and cardiovascular events in adulthood and found a significant association in most cases.

A few decades ago, the BHS demonstrated that high lipid levels in childhood were the best predictors that those same markers would remain high during the follow-up period.[19] In addition, that study revealed an association between lipid levels in childhood and the presence of early atherosclerotic lesions in the aorta and coronary arteries.[20]

When we assess the relationship between lipid markers in the earliest stages of life and clinical cardiovascular events in adulthood, the information available is scarce. Limitations related to the extensive follow-up required to assess such an association and the low incidence of events in young adults (need for a large sample size to achieve adequate statistical power) explain this situation in part.

Evidence based on epidemiological and genetic data supports the association among increased triglyceride levels, triglyceride-

rich lipoproteins, and CVD.[21] Four of the 5 studies included in this review reported a significant association between triglyceride levels in childhood and cardiovascular events in adulthood.[9–12] According to these studies, in most cases, high triglyceride levels in childhood remain high into adulthood. All studies adjusted the result for body mass index, a variable commonly associated with such lipid alteration.[22] In addition, a study revealed that high triglyceride levels were common in the parents and siblings of studied children, which evidences a family involvement.[10]

According to a Mendelian randomization study, prolonged exposure to low LDL-C levels early in life is associated with a lower probability of a cardiovascular event over time.[23] Likewise, the very high LDL-C values observed in familial hypercholesterolemia considerably affect cardiovascular prognosis.[14,15] Three studies included in this review analyzed LDL-C levels and one of them, total cholesterol levels. The 2 studies with the highest number of events reported a significant association,[12,13] whereas the studies with the fewest events showed conflicting results.[10,11] The latter results may be attributed to the lipid-lowering treatment received by young adults with higher LDL-C levels or to the fact that only 19 events were analyzed (low statistical power). Likewise, this last argument could explain the lack of association between HDL-C and CVD observed in the only study that assessed such marker.[10] However, the relationship between HDL-C and cardiovascular risk in adults remains a matter of debate at present.[24]

Lastly, the association between Lp(a) levels in adulthood and increased occurrence of vascular events is well documented.[25] The current recommendations for adults suggest measuring Lp(a) at least once in a lifetime as part of cardiovascular risk stratification.[26] However, a systematic measurement is not indicated in children. Some recommendations suggest measuring Lp(a) in pediatric patients with familial hypercholesterolemia, a family history of premature CVD, high Lp(a) levels in the family, or stroke of unknown cause.[27,28] In this regard, data from one of the studies analyzed in this review provide new evidence that could be considered in future recommendations.[13] According to this study, an early identification of a high Lp(a) level predicts an increased risk of CVD in adults.

The findings of this review reinforce the need for early screening for risk factors in general, and lipid disorders in particular. The possibility of detecting extremely relevant conditions in an early manner, such as familial hypercholesterolemia, is a clear advantage of this strategy.[29] However, intervening in the habits of the family and child may also be relevant in the presence of less marked dyslipidemias.[30]

Screening for dyslipidemia only in those children or adolescents with a family history of early CVD or dyslipidemia seems insufficient. Such approach hinders the possibility of making a diagnosis in many cases and, more seriously, makes the early management of affected children impossible. Considering this fact and the physiological variations of the lipid profile during development, recent recommendations advise universal screening at 2 points in life: between 6 and 11 years of age and between 17 and 21 years of age.[31]

It is important to emphasize that lipid values should be assessed in the primary care setting, i.e. by the pediatrician, and referral to a specialist should be reserved for selected cases. The basic lipid profile should include total cholesterol, triglyceride, HDL-C, and LDL-C measurements. Given the analytical and biological variability, it is recommended to confirm results with a second measurement before making a definitive diagnosis, in the case of pathological results.

This systematic review poses certain limitations. First of all, only a few studies were included. Secondly, we were not able to perform a meta-analysis due to the high clinical heterogeneity, the different lipid cutoff points used, and the different endpoints reported. Finally, the studies included in this review were observational. Therefore, the presence of biases and confounding factors is to be expected. Despite its limitations, this systematic review analyzed all the evidence published to date on this topic.

CONCLUSION

This review strongly suggests that alterations in lipid markers in childhood and adolescence are associated with a higher risk for CVD in early and middle adulthood. This includes traditional lipid markers (total cholesterol, triglycerides, and LDL-C) as well as novel lipid markers [Lp(a)]. An early detection of these markers during childhood would allow to optimize cardiovascular risk stratification and, in some cases, provide interventions and modify risk factors in an early manner. ■

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