Journal of Clinical Lipidology (2024) 000, 1–9

Journal of Clinical Lipidology

Original Research

Association between very high HDL-C levels and mortality: A systematic review and meta-analysis

Isadora Mamede[1,*], Marcelo Antonio Pinheiro Braga[1], Otavio C. Martins[1], Anne E.O. Franchini, MD, Rodrigo B. Silveira Filho[1], Marcel C.F. Santos, MD

Faculty of Medicine, Federal University of Sao Joao del-Rei, Centro Oeste Campus, Divinopolis, Brazil (Dr Mamede); Faculty of Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil (Dr Braga); Faculty of Medicine, Federal University of Juiz de Fora, Juiz de Fora, Brazil (Dr Martins); Faculty of Medicine, President Tancredo de Almeida Neves University Center, Sao Joao del Rei, Brazil (Dr Franchini); Faculty of Medicine, Potiguar University, Natal, Brazil (Dr Silveira Filho); Department of Internal Medicine, University of Sao Paulo, Sao Paulo, Brazil (Dr Santos)

KEYWORDS
Cardiovascular disease;
Cardiovascular risk;
Cholesterol;
High-density lipoprotein;
Mortality

BACKGROUND: Recent research has raised questions about the assumed cardiovascular (CV) benefits of high-density lipoprotein cholesterol (HDL-C) and the potential for adverse outcomes with extremely high levels.

OBJECTIVE: We conducted a meta-analysis to investigate the association between very high HDL-C levels (≥80 mg/dL) and mortality outcomes in individuals without coronary artery disease (CAD).

METHODS: We systematically searched PubMed, Embase, and Cochrane databases for studies comparing very high HDL-C levels to normal levels (40–60 mg/dL) in CAD-free individuals. We assessed heterogeneity using I2 statistics with a random-effects model.

RESULTS: Our analysis included 1,004,584 individuals from 8 studies, of whom 133,646 (13.3 %) had very high HDL-C levels. All-cause mortality did not significantly differ between groups ($p = 0.55$), nor did cancer mortality ($p = 0.45$). Cardiovascular mortality showed no change in those with very high HDL-C (HR 1.05; 95 % CI 0.94–1.17; $p = 0.37$). Fatal and non-fatal coronary heart disease events were less frequent in the very high HDL-C group (HR 0.79; 95 % CI 0.73–0.86; $p < 0.00001$). Subgroup dose-response analysis revealed that very high HDL-C levels increased cardiovascular death in women above 116 mg/dL (HR 1.47; 95 % CI 1.01–2.15) and in men above 94 mg/dL (HR 1.29; 95 % CI 1.01–1.65) ($p\_nonlinearity < 0.01$).

CONCLUSIONS: These findings suggest that very high HDL-C levels are not protective against cardiovascular mortality and may, in fact, increase CV mortality risk specially in men.

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; EPCs, Endothelial progenitor cells; HDL-C, high-density lipoprotein cholesterol; HR, Hazard ratio; LDL-C, Low-density lipoprotein cholesterol; LLAs, Lipids-lowering agents; PROSPERO, International Prospective Register of Systematic Reviews; QUIPs, Quality In Prognosis Studies.

* Corresponding author at: 400 Sebastião Gonçalves Coelho Street, Chanadour district. Zip Code: 35501-296, Divinópolis, Brazil.
E-mail address: isamamede1@gmail.com (I. Mamede).
Submitted February 3, 2024. Accepted for publication June 10, 2024.
Social media: (I. Mamede)
[1] Medical Students.

https://doi.org/10.1016/j.jacl.2024.06.002

Please cite this article as: Mamede et al, Association between very high HDL-C levels and mortality: A systematic review and meta-analysis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.06.002

Introduction

High-density lipoprotein cholesterol (HDL-C) is responsible for transporting excess cholesterol from peripheral tissues and delivering it to the liver, so it can be excreted or reused, a process known as reverse cholesterol transport.[1] Historically, HDL-C has been considered a protective factor against cardiovascular (CV) events, particularly coronary heart disease (CHD), for its anti-atherogenic nature,[2] earning it the moniker "good cholesterol". However, attempts to reduce CV mortality by pharmacologically increasing HDL-C levels have proven unsuccessful.[3] Recent studies have also raised concerns about adverse outcomes associated with very high HDL-C levels.[4]

A prior meta-analysis[5] has been published evaluating the relation between HDL-C levels and mortality from all causes, cardiovascular disease (CVD) and cancer in the general population. This study included in the baseline characteristics people with a history of CHD, a very significant risk factor for both all-cause and cardiovascular mortality. Thus, a precise correlation cannot be made from the exposure to the outcomes. Furthermore, they only considered values above 100 mg/dL as a high HDL-C level in the mortality endpoint.

The present systematic review and meta-analysis aimed to determine the impact of very high levels of HDL-C (≥80 mg/dL) in mortality and CV events compared to normal levels (40–60 mg/dL) in patients without coronary heart disease.

Materials and methods

Search strategy and eligibility

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (Supplemental Methods 1 and 2).[6] Studies were included if they met the following eligibility criteria: 1) observational studies (case-control, prospective and retrospective cohort studies); 2) compare individuals with very high HDL-C (≥ 80 mg/dL) to those with HDL-C between 40 and 60 mg/dL; 3) enroll patients or general population free of coronary artery disease (CAD); 4) have a follow-up period of at least 5 years; and 5) report any of the outcomes of interest. We excluded duplicated studies or overlapping patient populations, as well as studies involving patients with a history of CAD, and those lacking adequate information on outcomes. This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023426606). Detailed search terms are available in Supplemental Methods 3. Article selection was undertaken independently by two reviewers (I.M. and M.A.P.B.). Disagreements were resolved by consensus.

Data source

Queries of literature were performed using electronic databases Embase, Cochrane Central Register of Controlled Trials, and Medline (PubMed). The search included all submitted articles until 16th May 2023 without restriction to submission date, type of study, or language. Systematic reviews and meta-analyses were also evaluated to identify other relevant studies that were eventually missing by using search terms.

Data extraction

Baseline characteristics reported in Tables 1 and 2 were independently extracted by two authors (I.M. and O.C.M.) and outcome data were independently extracted by four authors (I.M., M.A.P.B., R.B.S.F., and O.C.M.). Inconsistencies were resolved by discussion along with other two authors (M.C.F.S., and A.E.O.F.). Extracted data included (1) author; (2) study design; (3) number of patients; (4) sex distribution; (5) mean age; (6) mean body mass index (BMI); (7) proportion of patients with diabetes; (8) proportion of patients with hypertension; (9) proportion of smokers; (10) proportion of participants taking lipid-lowering agents (LLAs); (11) mean triglycerides levels; (12) mean total cholesterol levels; (13) mean Low-density lipoprotein cholesterol (LDL-C) levels; (14) mean HDL-C levels; (15) follow-up; (16) clinical outcomes; and (17) adverse events. Data were extracted and recorded on an Excel template.

Quality assessment

Based on the Quality In Prognosis Studies (QUIPs) tool,[7] two reviewers (I.M. and M.A.P.B.) independently assessed the quality of included studies. Each study was evaluated for a high, low, or moderate risk of bias across six domains: participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. Discrepancies were resolved through discussion. To assess for evidence of publication bias, funnel plots were used. Egger's regression test could not be performed due to the limited number of included studies ($n < 10$).

Data synthesis and statistical analyses

Primary endpoints were (1) all-cause mortality and (2) cardiovascular mortality, as per the individual articles' definitions (see Supplemental Methods 4). CV mortality en-

Please cite this article as: Mamede et al, Association between very high HDL-C levels and mortality: A systematic review and meta-analysis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.06.002

Table 1 Baseline characteristics of included studies.

Study	N VH/NL	Age[a],y VH/NL	Men,% VH/NL	BMI[a], kg/m^2 VH/NL	DM,% VH/NL	HTN,% VH/NL	Smoker[b],% VH/NL	Follow-up
Hamer 2018[13]	4259/16,141	50.1/45.5[c]	19.4/56.8[c]	24.8/27.4[c]	NA	NA	17.8/25.9[c]	326,016 p-y
Hirata 2018[14]	1922/23,793	55.1/57.3	40.1/48.9	21.3/23.4	4.0/4.7	32.1/37.2	20.4/26.8	126,481 p-y
Ko 2016[15]	43,896/326,888	58.3/57.2	14.8/48.8	NA	9.1/20.8	35.0/44.9	15.2/16.0	4.9 ± 0.4 y[a]
Kobayashi 2019[16]	11,646/34,102	46.1/45.7	17.0/70.4	NA	0.8/2.6	4.6/9.2	8.1/22.5	1746 (740–3113) d[a]
Liu 2022[17]	28,638/219,191	57.6/ 56.2	12.8/52.9	24.3/28.1	1.7/4.9	19.3/22.7	NA	9.0 y[a]
Madsen 2017[4]	25,629/41,294	60.6/56.2	21.5/58.3	23.9/27.7	2.6/5.0	NA	15.8/22.2	745,452 p-y
Wilkins 2014[18]	1508/11,871	58.4/57.4	16.3/46.8	24.1/26.9	3.2/6.5	17.7/22.2	27.3/30.7	307,245 p-y
Yang 2021[19]	16,148/197,658	57.8/58.9	35.8/54.4	22.8/24.3	8.7/14.2	35.2/42.8	11.9/17.7	6.0 (5.2–6.4) y[a]

BMI = Body Mass Index; *d* = days; DM = Diabetes mellitus; HTN = Hypertension; *y* = years; *N* = number of participants; NA = not available; NL = Normal high-density lipoprotein cholesterol group; p-*y* = person-years; VH = Very high-density lipoprotein cholesterol group;
[a]mean or median
[b]Current smoker.
[c]Includes individuals with CVD at baseline.

Table 2 Baseline lipid profile of included studies.

Study	TG[a], mg/dL VH/NL	TC[a], mg/dL VH/NL	LDL-C[a], mg/dL VH/NL	HDL-C[a], mg/dL VH/NL	Taking LLAs,% VH/NL
Hamer 2018[13]	NA	230.8/ 212.7[b]	NA	NA	NA
Hirata 2018[14]	NA	223.0/202.6	NA	88.2/ 49.5	NA
Ko 2016[15]	78.4/ 137.2	222.3/ 199.4	114.9/121.8	91.8/ 50.2	NA
Kobayashi 2019[16]	60.8/ 119.9	104.2/ 122.5	NA	NA	2.6/ 77.9
Liu 2022[17]	92.7/ 165.1	248.3/ 218.7	138.6/140.4	89.6/ 50.2	NA
Madsen 2017[4]	90.2/ 156.9	NA	117.2/130.1	90.6/ 48.7	10.0/ 11.7
Wilkins 2014[18]	104.2/ 159.1	223.7/ 215.6	113.3/140.5	92.2/ 49.7	NA
Yang 2021[19]	85.1/ 130.3	219.9/ 198.7	113.1/121.1	87.9/ 48.7	18.2/ 16.4

HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LLA = Lipid-lowering agent; NA = not available; NL = Normal high-density lipoprotein cholesterol group; TG = Triglycerides; TC = total cholesterol; VH = Very high-density lipoprotein cholesterol group.
[a]mean or median.
[b]Includes individuals with CVD at baseline.

compassed death from heart diseases, essential hypertension, hypertensive renal disease, cerebrovascular diseases, and peripheral vascular disease. Secondary endpoints were (1) cancer mortality and (2) Coronary heart disease events, with CHD events defined in accordance with each article's specifications (see Supplemental Methods 5). Hazard ratio (HR) was used as a common measure to assess association between HDL-C levels and adverse outcomes. Multivariate adjusted HR values were employed to control for covariates such as age, sex, body mass index (BMI), smoking, alcohol intake, hypertension, non-HDL-C cholesterol, and use of LLAs (see Supplemental Methods 6). We assessed statistical heterogeneity using Hedges Q statistic and I^2 statistic, with significance set at $p < 0.10$ and $I^2 \geq 25.0$ %.

For studies whose authors reported risk estimates stratified by different quantiles of HDL-C and had reference groups different from 40 to 60 mg/dL group, Orsini's[8] method was used to convert reference groups. If studies reported risk estimates by sex or quantiles of HDL-C, a fixed-effects model was used to pool the stratum data for the main analysis, provided the reference category was identical in subgroups. A random-effects model was employed to combine hazard ratios and 95 % CIs. Subsequently, we generated forest plots for each of the endpoints.

Dichotomous variables were reported as percentages, while continuous variables were reported as mean and standard deviation or median (interquartile range). In cases where baseline characteristics were provided as median and interquartile range, the method provided by Wan et al.[9] was used to convert them to mean and standard deviation. For studies that reported mean and standard deviation from independent non-overlapping groups, Cochrane Handbook for Systematic Reviews of Interventions'[10] formulae for combining summary statistics across two groups was utilized.

We conducted subgroup analyses to investigate how sex might influence the relationship between HDL-C levels and mortality. We conducted a dose-response meta-analysis to examine sex differences on mortality, and used this method as a sensitivity analysis to explore the link between CHD events and HDL-C levels. Given the uncertainty regarding the shape of the dose-response curve, we initially explored both linear and non-linear patterns (quadratic and restricted cubic spline mode), opting for the model with the lowest Akaike's information criterion (AIC).[11] Ultimately, quadratic model was selected and a pnon-linearity was obtained.

We established criteria to determine dose values when only ranges were available: if the smallest dose group be-

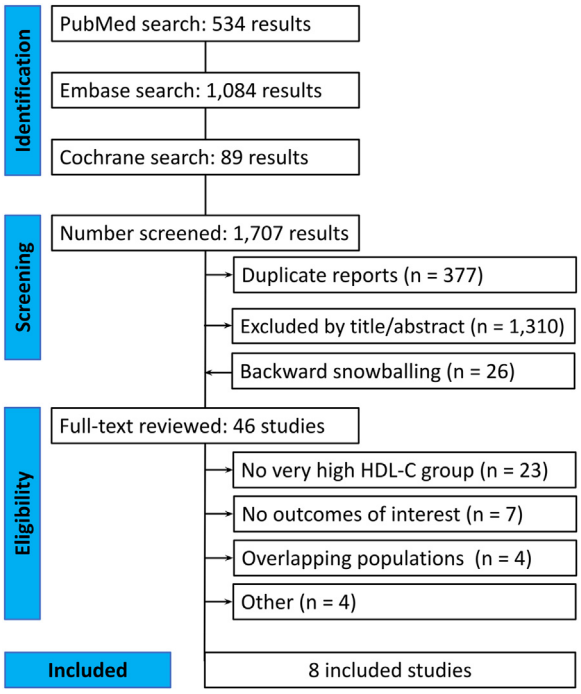

Fig. 1 PRISMA Flow Diagram of study screening and selection. The search across Embase, PubMed, and Cochrane yielded 1707 studies; 46 underwent full-text review based on inclusion and exclusion criteria. Ultimately, 8 studies were included in the meta-analysis.

gan with an open range, we set the dose as the median of that group, assuming a starting point of zero. For closed dose group ranges, we set the dose as the median. If the largest dose group ended with an open range, we calculated the dose by adding the difference between the median of the previous dose group and its starting value to the beginning value of the last group.[12]

Additional sensitivity analyses were conducted to assess the robustness of our findings. These included investigating heterogeneity and the reliability of aggregated results through fixed-effects models, various exclusion criteria, and stepwise omission of individual studies. Due to limited data on other outcomes, these analyses primarily focused on all-cause and CV mortality.

All data analyses were carried out using Review Manager 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R software version 4.3.2 (R Foundation, Viena, Austria) was used for the dose-response analysis.

Results

Initially, 1707 citations were identified, with an additional 26 from backward snowballing. After excluding duplicates, 1330 articles remained. We excluded 1310 based on title and abstract and another 38 after full-text evaluation (Fig. 1). Ultimately, 8 studies were included,[4,13–19] involving 1004,584 individuals, including 133,646 (13.3 %) with HDL-C levels $\geq$ 80 mg/dL. Baseline characteristics and lipid profiles are in Tables 1 and Table 2. Detailed breakdowns for men and women are available in the supplementary materials (Supplemental Table 1 and Supplemental Table 2 for baseline characteristics, and Supplemental Table 3 and Supplemental Table 4 for lipid profiles).

All-cause mortality

The analysis revealed no significant difference in all-cause mortality between individuals with very high and normal HDL-C levels (HR 1.03; 95 % CI 0.94–1.13; $p = 0.55$; I^2 71 %; Fig. 2A). Subgroup analysis by gender also revealed no significant variations, but no further increase in protection, for HDL-C levels $\geq$ 80 mg/dL among men (HR 0.97; 95 % CI 0.87–1.08 for 80 mg/dL; Fig. 2B) or for HDL-C levels $\geq$ 90 mg/dL women (HR 0.94; 95 % CI 0.82–1.07; Fig. 2C) (all pnon-linearity < 0.01).

Cardiovascular mortality

The examination of cardiovascular mortality revealed no significant distinctions among individuals with very high HDL-C levels compared to those with normal HDL-C levels (HR 1.05; 95 % CI 0.94–1.17; $p = 0.37$; I^2 44 %; Fig. 3A). However, in a dose-response meta-analysis stratifying by gender revealed a significantly elevated CV mortality in men with HDL-C levels above 94 mg/dL (HR 1.29; 95 % CI 1.01–1.65; Fig. 3B), while in women such significancy appeared for women values above 116 mg/dL (HR 1.47; 95 % CI 1.01–2.15; Fig. 3C) (all pnon-linearity < 0.01).

Secondary outcomes

CHD events were less frequent in the very high HDL-C group (HR 0.79; 95 % CI 0.73–0.86; $p < 0.00001$; I^2 0 %; Fig. 4). Albeit, a dose-response analysis demonstrated no further protection for HDL-C values over 126 mg/dL (HR 0.55; 95 % CI 0.29–1.01; Supplemental Fig. 1). Moreover, there were no significant differences in cancer mortality between groups, whether analyzed in men (HR 1.02; 95 % CI 0.81–1.29; $p = 0.85$; I^2 65 %; Supplemental Fig. 2), women (HR 0.86; 95 % CI 0.64–1.15; $p = 0.30$; I^2 86 %; Supplemental Fig. 2), or the overall population (HR 0.93; 95 % CI 0.77–1.12; $p = 0.45$; I^2 80 %; Supplemental Fig. 2).

Quality assessment

Quality assessment using the QUIPs tool indicated no studies at high risk of bias (Supplemental Figure 3). Four studies had an overall moderate risk of bias: one due to insufficient information on prognostic factor measurement method, two due to inadequate outcome measurement, and one due to confounding factors. There was no definitive evidence of publication bias in the funnel plot for CV mortality (Supplemental Figure 4). Nevertheless, the funnel plot for all-cause mortality showed an asymmetrical inverted shape (Supplemental Figure 5).

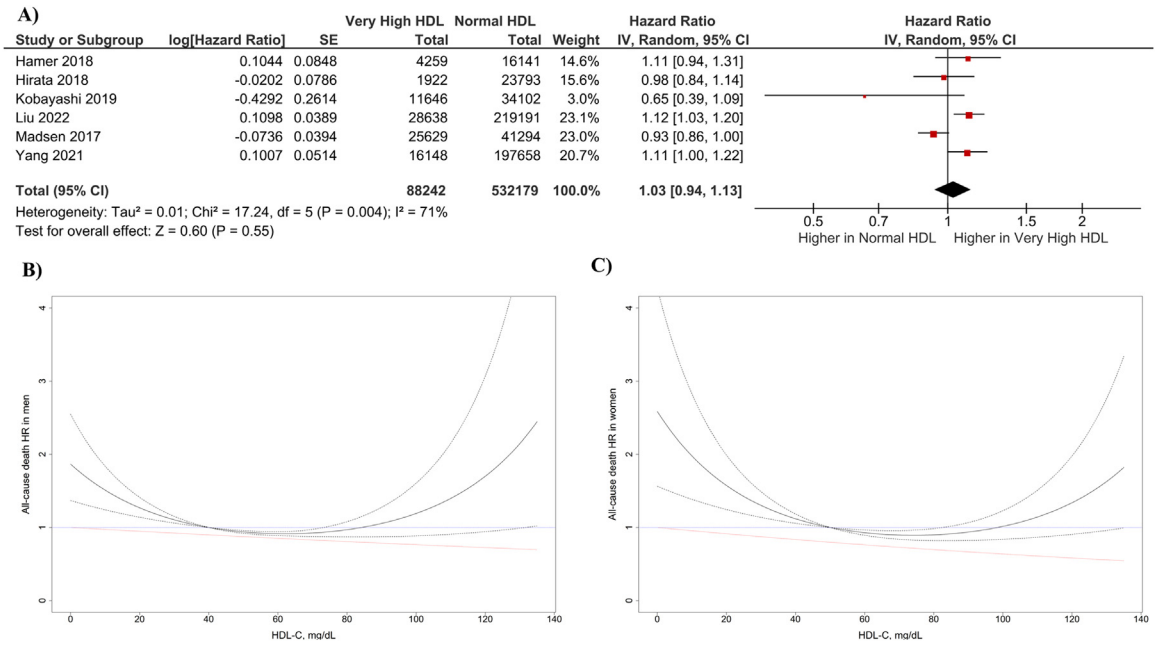

Fig. 2 All-cause mortality between Very high and Normal HDL-C groups. A) Forest plot illustrating all-cause mortality in relation to HDL-C levels across six studies within the entire cohort. There is no significant all-cause mortality difference between very high and normal HDL-C levels ($p = 0.55$). B) Gender-specific analysis involving five studies reveals no statistically significant association in men C) or in women. HDL = High-density lipoprotein cholesterol.

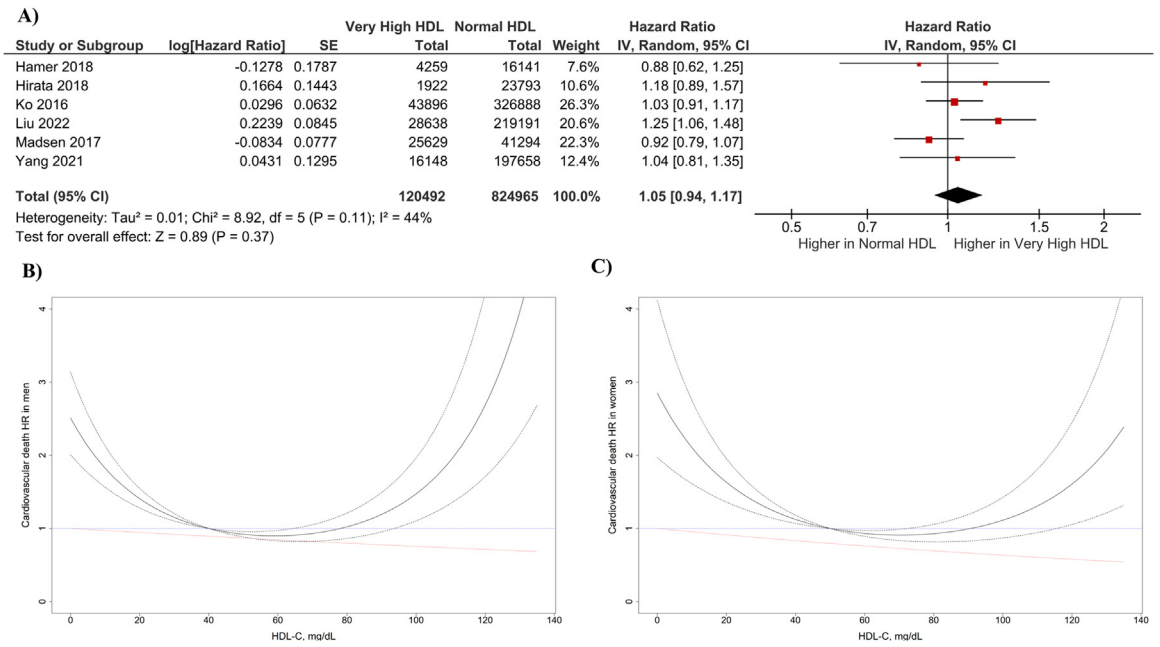

Fig. 3 Cardiovascular mortality in Very high HDL-C vs. Normal HDL-C levels. A) Forest plot depicting the link between cardiovascular mortality and HDL-C levels across six studies within the entire cohort. No distinction exists in cardiovascular death outcomes between very high and normal HDL-C levels ($p = 0.37$). B) Gender-specific analysis across five studies also indicates a higher risk of fatal cardiovascular outcomes in men with very high HDL-C ($\geq$ 94 mg/dL),C) and in women ($\geq$ 116 mg/dL). HDL = High-density lipoprotein cholesterol.

Discussion

Recent advances in observational data have enabled researchers to explore potential non-linear relationships between HDL-C levels and all-cause mortality. This exploration indicates that both low and high levels of HDL-C may have adverse effects. The initial two studies with such data were published in 2016.[15,20] Our meta-analysis reveals that, in comparison to normal HDL-C levels, very high levels are not associated with increased all-cause mortality in the general population. However, significant gender-specific disparities emerge. Among women, only very high HDL-C levels

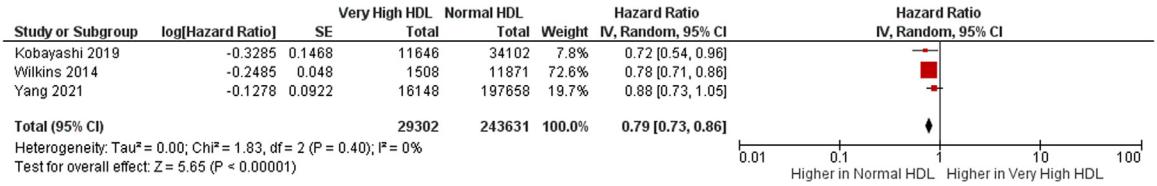

Fig. 4 Risk of coronary heart disease events in Very high HDL-C vs. Normal HDL-C. Forest plot displaying the risk of coronary heart disease events connected to HDL-C levels across three studies. HDL-C levels ≥ 80 mg/dL significantly protect against CHD events ($p < 0.00001$). HDL = High-density lipoprotein cholesterol.

≥ 116 mg/dL increase cardiovascular mortality compared to normal levels. In contrast, men with HDL-C levels exceeding 94 mg/dL face a 29 % increased risk of cardiovascular mortality.

All-cause mortality

In our analysis of six studies, no significant association was found between HDL-C levels above 80 mg/dL and increased all-cause mortality. A previous dose-response meta-analysis[5] reported a non-linear inverse association between HDL-C levels and all-cause mortality, suggesting a J-shaped curve. Their analysis included patients with a history of CAD at baseline, a recognized high-risk population. Furthermore, mortality was only observed in individuals with HDL-C levels above 100 mg/dL. In contrast, such an effect did not manifest within our study.

Significant heterogeneity was present in our data, with sensitivity analyses (Supplemental Table 5) suggesting a study[17] with moderate risk of bias due to incomplete information on prognostic factor measurement as a possible source.

Additionally, the funnel plot analysis revealed mild visual asymmetry, suggesting potential bias. However, this asymmetry might result from heterogeneity between studies rather than publication bias.[21] Limited study numbers can mislead visual assessments of funnel plots, lacking the statistical power to distinguish between publication bias and genuine heterogeneity. Therefore, it is important not to hastily conclude that the asymmetry indicates publication bias,[22] as true between-study heterogeneity is likely the underlying cause.

Cardiovascular risk

Literature findings on cardiovascular risk are conflicting. While some studies have not demonstrated an association between higher HDL-C levels and CV mortality,[14,15,19] others suggested an increased risk, particularly in men.[4,17] However, very high HDL-C levels have shown a protective effect against fatal and non-fatal CHD events.[16,18,19]

HDL particles, with cholesterol at their core and surrounded by phospholipids, free cholesterol, and various apolipoproteins such as Apolipoprotein A-I (apoA1) and apoA2, are crucial for lipid metabolism and cardiovascular health. They help maintaining blood vessels integrity and prevent the formation of atherosclerotic plaques, which are implicated in cardiovascular diseases like heart attacks and strokes, often triggered by oxidized LDL cholesterol. Beyond cholesterol transport, HDL-C facilitates reverse cholesterol transport, reduces inflammation, combats oxidative stress, and supports endothelial cell health. Moreover, HDL particles have vasodilatory, anti-clotting, and immune-modulating properties.[23] However, while an increase in HDL concentration may enhance these protective functions, any dysfunction in its structure can compromise its activities.

Our analysis indicates that very high HDL-C levels (between ≥80 mg/dL and <126 mg/dL) offer protection against fatal and non-fatal CHD events combined but not against cardiovascular mortality, especially in men. Notably, they not only fail to provide further protection in women and men at these levels when stratified by sex, but also increase risk in men and women when above 94 mg/dL and 116 mg/dL, respectively. Intriguingly, this risk escalates with even higher HDL-C levels, as corroborated by our dose-response analysis. This implies that factors beyond fatal CHD events, such as cerebrovascular incidents and increased carotid intima-media thickness (a predictor for CV risk), may contribute to the nonprotection observed in CV mortality.

Indeed, studies have found associations between elevated HDL-C levels and ischemic[14,24] and/or hemorrhagic[25] cerebrovascular events, which are not included in the CHD outcome, as it only considers heart related occurrences. This may be a contributing factor to the disparities between CHD events and CV mortality.

Furthermore, the relationship between HDL-C and CVD is complex and controversial, partly due to the diverse array of HDL subspecies, each with varying surface proteins impacting thrombosis, inflammation, immunity, and lipid metabolism. While some HDL subspecies offer protection against CVD, others may contribute to adverse cardiovascular outcomes. For instance, HDL containing complement C3 or alpha-2-Macroglobulin is associated with a higher risk of CVD, whereas HDL containing apoC1 or apoE is linked to a lower risk.[26]

Notably, the studies by Kobayashi[16] and Wilkins[18] only evaluated CHD occurrence and were thus included in the CHD events analysis, while Yang's study[19] overlapped between both outcomes. Moreover, none of the articles evaluated HDL subspecies, leaving the intricate interplay between HDL subspecies as another possible contributing factor to the contradictory findings observed in studies exploring the association between HDL-C and CHD risk.

Regarding gender disparities, hormonal variations may play a significant role. For instance, a study revealed that el-

evating HDL-C levels before the final menstrual period was associated with reduced progression in Carotid Intima-Media Thickness, whereas increasing HDL-C during menopause was linked to greater progression. This suggests that HDL particles may undergo changes in their anti-atherogenic properties during the menopausal transition, potentially influenced by complement C3 protein levels, which tend to be higher in postmenopausal women compared to premenopausal women.[27]

In addition, in individuals with notably high levels of HDL, the content of HDL phospholipids and cholesterol efflux capacity (CEC) play significant roles in the development of CAD and the occurrence of CHD events, with findings pointing towards reduced CEC and phospholipids content in patients with very high HDL and CAD.[28] The clinical importance of HDL CEC has been underscored by numerous studies, which have demonstrated an inverse correlation between CEC and the prevalence of atherosclerosis, as well as the incidence of cardiovascular events. Importantly, this relationship has been observed independently of plasma HDL-C levels.[29] Thus, it is plausible to consider that variations in phospholipid content and CEC among the studies included in the analysis may contribute to the observed differences in cardiovascular mortality and CHD event outcomes.

The mechanisms underlying the discovery that very high HDL-C levels were linked to an increased mortality remain unclear. One possibility is that relying solely on a basic assessment of HDL-C levels might be insufficient. It is believed that measuring the functional activity of HDL could offer a more effective approach to predicting mortality risk,[30] as in individuals with very high HDL-C levels, there is a likelihood that both the structure and functionality of high-density lipoprotein are compromised, leading to dysfunctional high-density lipoprotein that might pose harm rather than providing benefits.[31]

The reverse remnant-cholesterol transport hypothesis further elucidates the relationship between plasma HDL-C levels and cardiovascular disease, proposing that hindered transfer of free cholesterol from triglyceride-rich lipoprotein remnants to HDL impedes cholesterol transport to the liver. This impairment is evident in individuals with both low and very high HDL-C levels.[32]

Endothelial dysfunction and injury, pivotal in atherosclerotic lesion, contribute to cardiovascular disease progression. Although HDL supports endothelial progenitor cells (EPCs), elevated HDL levels can impair EPCs and angiogenesis via Rho-associated kinase pathways, diminishing HDL's protective effects. This has been further associated with HDL dysfunction particles. Thus, these pathological mechanisms corroborate that serum levels of HDL alone do not fully capture cholesterol flux.[33]

Examining HDL subclasses could provide valuable insights. For example, Martin et al.[34] analyzed HDL2-C (larger, more buoyant) and HDL3-C (smaller, denser) subclasses in two cohorts for secondary prevention. Individuals with lower HDL3-C had an over 50 % increased risk of mortality and myocardial infarction, highlighting the potential value of subclassifying HDL. We hypothesize that elevated HDL-C levels could serve as a compensatory mechanism aimed at mitigating the potential adverse effects of impaired HDL function, thereby attempting to maintain its overall action in the body.

Moreover, there are various factors known to elevate HDL concentrations, including chronic alcoholism, oral estrogen replacement therapy, regular aerobic exercise, and medication regimens involving niacin, statins, or fibrates.[35] Although the studies cited are predominantly observational in nature, efforts were made to adjust statistical analyses for these factors. Additionally, elevated HDL-C levels may be attributed to specific genetic variants associated with adverse health outcomes. Mutations in genes involved in HDL metabolism, such as APOA1,[36] Scavenger receptor class B type I (SCARB1),[37] Lipase C (LIPC),[38] and Cholesteryl Ester Transfer Protein (CETP),[39] can disrupt the synthesis, maturation, and functionality of HDL particles, impacting their atheroprotective properties.

For instance, apoA1 overproduction resulting from APOA1 mutations is associated with reduced cardiovascular risk, despite elevated HDL-C. Conversely, the SCARB1 (P376L) SNP, linked to significantly elevated HDL-C levels, paradoxically increases the risk of CHD, potentially due to compromised reverse cholesterol transport.

Therefore, future studies should consider women age and menopause status when evaluating HDL. Furthermore, further research is needed in the development and standardization of methodologies for fractionating HDLs based on their functional and genetic properties. This would enable a more comprehensive investigation into the potential role of very high HDL-C levels in mortality risk and contribute to the advancement of targeted therapies. Although the association between HDL CEC, HDL phospholipid content and cardiovascular outcomes is now established, fewer therapeutic trials interpolating theses three factors have obtained success. Currently, development of infusion preparations of apoA1 to improve CEC is under investigation.[40]

Finally, it is important to highlight the need for gender-specific definitions for normal and elevated HDL-C, as seen in individuals studies.[4,18] In our dose-response analysis, 40 mg/dL served as the reference for men, and 50 mg/dL for women. Extremely high levels were identified as 94 mg/dL for men and 116 mg/dL for women.

Despite the presence of moderate heterogeneity concerning cardiovascular mortality, our sensitivity analyses (Supplemental Table 6) have drawn attention to the potential contribution of study,[17] characterized by a moderate risk of bias due to insufficient information regarding the measurement method of the prognostic factor.

Cancer death

Aligned with individual studies,[4,15,19] our analysis did not find an association between very high HDL-C levels and cancer mortality, even in subgroup analyses by sex.

Please cite this article as: Mamede et al, Association between very high HDL-C levels and mortality: A systematic review and meta-analysis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.06.002

These findings suggest that elevated levels of HDL-C do not serve as either a protective or a risk factor for cancer-related mortality.

Limitations

Firstly, our findings were derived from study-level data, which precluded us from conducting an analysis of competing risk for cause-specific mortality to evaluate its potential impact on the results or implementing individual-level adjustments or stratification of the outcomes.

Secondly, while we extracted the most adjusted risk estimates for our analyses, residual confounding may still have influenced our pooled outcomes. Factors such as the presence of familial hypercholesterolemia or the use of statins could have acted as confounding variables in the association between HDL-C and mortality. Additionally, another limitation of our study is the insufficient availability of major baseline biological and clinical characteristics (such as age, smoking status, presence of diseases, lipid levels and menopause status for women) across a significant portion of the included studies. This lack of data may have constrained our ability to thoroughly analyze and adjust for potential confounding. Moreover, our analysis was further hindered by the scarcity of studies that incorporated these variables into their adjustments, which could leave our results vulnerable to residual confounding effects.

Thirdly, we observed both funnel plot asymmetry and significant heterogeneity in the all-cause mortality outcome. These observations raise concerns about the potential for publication bias and the reliability of the pooled results. However, we identified heterogeneity as the possible source of such asymmetry and explored its sources through sensitivity analyses. Clinical and methodological heterogeneity is commonplace in meta-analyses, particularly those involving observational studies.[21] Lastly, it is important to note that our study encompassed a limited number of studies about HDL-C levels, cancer mortality, and CHD events. As a result, the associated outcomes should be interpreted with caution and necessitate validation through future large-scale studies.

Conclusions

In summary, individuals with very high HDL-C levels do not demonstrate reduced all-cause or cardiovascular mortality compared to those with normal levels. Nevertheless, significant gender-specific disparities exist, with men facing an increased risk of cardiovascular mortality at HDL-C above 94 mg/dL and women at 116 mg/dL. These findings hold substantial clinical significance, considering the routine use of HDL-C measurements for cardiovascular risk assessment. Further research is needed to investigate the interplay between HDL-modulating therapies and mortality risks associated with high HDL-C levels. Additionally, exploring HDL subclasses and genetic variants, as well as excluding patients with known dyslipidemia, may offer valuable insights into the intricate and multifaceted relationship between HDL-C and mortality risk.

Use of AI and AI-assisted technologies statement

During the preparation of this work the authors used no artificial intelligence tools.

Ethical statement

Ethical approval is not necessary for this study as it involves the retrieval and synthesis of data from already published studies.

Declaration of competing interest

None.

CRediT authorship contribution statement

Isadora Mamede: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Marcelo Antonio Pinheiro Braga:** Writing – review & editing, Methodology, Data curation. **Otavio C. Martins:** Writing – original draft, Methodology, Formal analysis. **Anne E.O. Franchini:** Writing – review & editing, Methodology, Data curation. **Rodrigo B. Silveira Filho:** Writing – original draft, Methodology, Data curation. **Marcel C.F. Santos:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization.

Funding

This study was conducted without securing specific grants from public, commercial, or for-profit funding agencies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2024.06.002.

References

1. Chiesa ST, Charakida M. High-density lipoprotein function and dysfunction in health and disease. *Cardiovasc Drugs Ther*. 2019;33:207–219.
2. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989;79:8–15.

3. Keene D, Price C, Shun-Shin MJ, et al. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117 411 patients. *BMJ*. 2014;349:g4379.
4. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J*. 2017;38:2478–2486.
5. Zhong G-C, Huang S-Q, Peng Y, et al. HDL-C is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose-response fashion: a pooled analysis of 37 prospective cohort studies. *Eur J Prev Cardiol*. 2020;27:1187–1203.
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
7. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158:280–286.
8. Orsini N. From floated to conventional confidence intervals for the relative risks based on published dose-response data. *Comput Methods Programs Biomed*. 2010;98:90–93.
9. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
10. Higgins JPT, Li T, Deeks JJ, eds. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook
11. Orsini N. *Nordic and Baltic Stata Users' Group Meeting 2019*. Model selection in dose-response meta-analysis of summarized data; 2020.
12. Shim SR, Lee J. Dose-response meta-analysis: application and practice using the R software. *Epidemiol Health*. 2019;41:e2019006.
13. Hamer M, O'Donovan G, Stamatakis E. High-density lipoprotein cholesterol and mortality: too much of a good thing? *Arterioscler Thromb Vasc Biol*. 2018;38:669–672.
14. Hirata A, Sugiyama D, Watanabe M, et al. Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: the EPOCH-JAPAN study. *J Clin Lipidol*. 2018;12 674-684.e5.
15. Ko DT, Alter DA, Guo H, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. *J Am Coll Cardiol*. 2016;68:2073–2083.
16. Kobayashi D, Noto H, Shimbo T, et al. Repeated measures of extremely high levels of high-density lipoprotein cholesterol and subsequent all-cause mortality and cardiovascular events: a longitudinal study. *Atherosclerosis*. 2019;288:17–25.
17. Liu C, Dhindsa D, Almuwaqqat Z, et al. Very high high-density lipoprotein cholesterol levels and cardiovascular mortality. *Am J Cardiol*. 2022;167:43–53.
18. Wilkins JT, Ning H, Stone NJ, et al. Coronary heart disease risks associated with high levels of HDL cholesterol. *J Am Heart Assoc*. 2014;3:e000519.
19. Yang Y, Han K, Park SH, et al. High-density lipoprotein cholesterol and the risk of myocardial infarction, stroke, and cause-specific mortality: a nationwide cohort study in Korea. *J Lipid Atheroscler*. 2021;10:74–87.
20. Bowe B, Xie Y, Xian H, et al. High density lipoprotein cholesterol and the risk of all-cause mortality among U.S. veterans. *Clin J Am Soc Nephrol*. 2016;11:1784–1793.
21. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ*. 1998;316:140–144.
22. Simmonds M. Quantifying the risk of error when interpreting funnel plots. *Syst Rev*. 2015;4:24.
23. Allard-Ratick M.P., Sandesara P., Quyyumi A.A. et al. Everything in moderation: investigating the U-Shaped link between HDL cholesterol and adverse outcomes. 2019.
24. Lu J, Han G, Liu X, et al. Association of high-density lipoprotein cholesterol with all-cause and cause-specific mortality in a Chinese population of 3.3 million adults: a prospective cohort study. *Lancet Reg Health West Pac*. 2024;42:100874.
25. Qie R, Liu L, Zhang D, et al. Dose-response association between high-density lipoprotein cholesterol and stroke: a systematic review and meta-analysis of prospective cohort studies. *Prev Chronic Dis*. 2021;18:E45.
26. Sacks FM, Liang L, Furtado JD, et al. Protein-defined Subspecies of HDLs (High-Density Lipoproteins) and differential risk of coronary heart disease in 4 prospective studies. *Arterioscler Thromb Vasc Biol*. 2020;40:2714–2727.
27. El Khoudary SR, Wang L, Brooks MM, et al. Increase HDL-C Level over the menopausal transition is associated with greater atherosclerotic progression. *J Clin Lipidol*. 2016;10:962–969.
28. Agarwala AP, Rodrigues A, Risman M, et al. High-density lipoprotein (HDL) phospholipid content and cholesterol efflux capacity are reduced in patients with very high HDL cholesterol and coronary disease. *Arterioscler Thromb Vasc Biol*. 2015;35:1515–1519.
29. Adorni MP, Ronda N, Bernini F, et al. High density lipoprotein cholesterol efflux capacity and atherosclerosis in cardiovascular disease: pathophysiological aspects and pharmacological perspectives. *Cells*. 2021;10:574.
30. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med*. 2011;364:127–135.
31. Barter PJ, Rye K-A. HDL cholesterol concentration or HDL function: which matters? *Eur Heart J*. 2017;38:2487–2489.
32. Kontush A. HDL and Reverse Remnant-Cholesterol Transport (RRT): relevance to cardiovascular disease. *Trends Mol Med*. 2020;26:1086–1100.
33. Huang C-Y, Lin F-Y, Shih C-M, et al. Moderate to high concentrations of high-density lipoprotein from healthy subjects paradoxically impair human endothelial progenitor cells and related angiogenesis by activating Rho-associated kinase pathways. *Arterioscler Thromb Vasc Biol*. 2012;32:2405–2417.
34. Martin SS, Khokhar AA, May HT, et al. HDL cholesterol subclasses, myocardial infarction, and mortality in secondary prevention: the Lipoprotein Investigators Collaborative. *Eur Heart J*. 2015;36:22–30.
35. Ginter E, Kajaba I. Danger of very high HDL levels. *BLL*. 2017;118:319–320.
36. Segrest JP, Li L, Anantharamaiah GM, et al. Structure and function of apolipoprotein A-I and high-density lipoprotein. *Curr Opin Lipidol*. 2000;11:105–115.
37. Zanoni P, Khetarpal SA, Larach DB, et al. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science*. 2016;351:1166–1171.
38. Andersen RV, Wittrup HH, Tybjaerg-Hansen A, et al. Hepatic lipase mutations,elevated high-density lipoprotein cholesterol, and increased risk of ischemic heart disease: the Copenhagen City Heart Study. *J Am Coll Cardiol*. 2003;41:1972–1982.
39. Agerholm-Larsen B, Nordestgaard BG, Steffensen R, et al. Elevated HDL cholesterol is a risk factor for ischemic heart disease in white women when caused by a common mutation in the cholesteryl ester transfer protein gene. *Circulation*. 2000;101:1907–1912.
40. A K, Cm G, Pm R, et al. ApoA-I infusion therapies following acute coronary syndrome: past, present, and future. *Curr Atheroscler Rep*. 2022;24. doi:10.1007/s11883-022-01025-7.