

Unfavorable Curves: Sex-Specific Lipid Metabolism and Lifelong Cardiovascular Risk

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Abstract

Background: Dysregulated lipid metabolism, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a major driver of cardiovascular disease (CVD). Sex differences in lipid biology and cumulative LDL-C influence disease onset and severity, yet clinical practice often relies on single time-point measurements.

Methods: This review synthesizes evidence from 84 studies exploring lipid metabolism, sex-specific risk, cumulative LDL-C exposure, and the efficacy of interventional therapies. Key studies of familial hypercholesterolemia (FH), longitudinal LDL-C trajectories, and major clinical trials of statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis were examined.

Results: Lifelong elevated LDL-C significantly increases CVD risk; Mendelian-randomization analyses indicate that early reductions confer a 3-fold greater benefit per unit LDL-C than interventions started later in life. Statins effectively lower LDL-C and reduce surrogate markers of atherosclerosis; combination therapy with ezetimibe or PCSK9 inhibitors provides additive benefits. HRT improves lipid profiles but carries cardiovascular and oncologic risks, limiting routine use. Lipoprotein apheresis offers substantial LDL-C and Lp(a) reduction in severe FH. Integration of cumulative lipid data into electronic health records and risk prediction models improves discrimination beyond traditional cross-sectional tools, with benefits for women whose risk trajectories are poorly represented by conventional methods.

Conclusions: Lifetime LDL-C exposure is a critical determinant of CVD risk. Early, sustained intervention tailored to sex and individual risk optimizes prevention. Translating cumulative lipid metrics into clinical practice offers a scalable approach to enhance risk stratification across the lifespan. Future research should address sex-specific responses to therapy and integration of cumulative lipid metrics into clinical practice.

Keywords: cardiovascular disease, sex-specific lipid metabolism, cumulative LDL exposure, estrogen, lipid regulation, menopause, sex hormones, atherogenesis



1. Introduction

The cardiovascular system sustains human life by maintaining the continuous circulation of oxygenated blood, nutrients, and metabolic substrates essential to systemic homeostasis; as a result, its failure—even transiently—carries severe physiological consequences (Chaudhry et al., 2022). Cardiovascular disease (CVD) encompasses a spectrum of disorders affecting the heart and its vasculature, most prominently coronary artery disease, cerebrovascular disease, and heart failure, and remains the leading global cause of death, accounting for approximately 17.9 million deaths annually or nearly one-third of all global mortality (Lopez et al., 2023; World Health Organization, 2019; Benjamin et al., 2018). It also constitutes an immense economic burden, generating an estimated \$237 billion in indirect annual costs and is projected to exceed \$368 billion by 2035 (Dunbar et al., 2018). Although the past half-century has seen remarkable advances in diagnostic imaging, pharmacological therapy, and surgical intervention that have improved acute outcomes, the overall prevalence of CVD continues to climb due to factors such as population aging, lifestyle-related risk factors, and widening health disparities (Zhou et al., 2022). The persistence of this burden thus highlights the need to interrogate the biological determinants that shape cardiovascular risk longitudinally across the lifespan, rather than at isolated moments in time.

Among these determinants, dysregulation of lipid metabolism has long been recognized as central to the pathogenesis of atherosclerotic disease (Steinbeck et al., 2025). Atherosclerosis—characterized by the accumulation of lipid-rich plaques within the arterial wall—develops gradually over decades and underlies most ischemic cardiovascular events (Pahwa & Jialal, 2023). While the cellular and molecular mechanisms governing plaque initiation and progression are well-established, with endothelial dysfunction, oxidative modification of low-density lipoprotein cholesterol (LDL-C) and chronic vascular inflammation primary among them, these processes are inherently time-dependent and modulated by systemic metabolic and hormonal states (Popa-Fotea et al., 2023). Consequently, lipid metabolism serves as both a mechanistic and epidemiological bridge between molecular pathophysiology and population-level CVD risk.

The risk of CVD demonstrates marked demographic heterogeneity. Men generally exhibit a higher incidence at younger ages, whereas the risk for women increases sharply following the onset of menopause, narrowing the sex gap in later decades (Merz & Cheng, 2016). The mechanistic basis of this disparity remains incompletely understood, though converging evidence implicates differences in lipid metabolism as a major driver (Robinson et al., 2022). Estrogen-mediated lipid regulation, characterized by enhanced hepatic LDL clearance and increased high-density lipoprotein cholesterol (HDL-C), is thought to contribute to the relative cardioprotection observed in premenopausal women (Palmisano et al., 2017). The postmenopausal decline in estrogen attenuates these effects, leading to adverse lipid shifts and accelerated atherosclerotic risk (Raj et al., 2023). By contrast, men, lacking this hormonal modulation, exhibit elevated LDL-C and reduced HDL-C levels throughout life, consistent with their earlier disease onset (Pérez-López et al., 2010). Although these sex differences are well-documented, their interaction with lifelong lipid exposure remains insufficiently characterized.

Cardiovascular risk is shaped not only by absolute lipid concentrations at a single point in time, but by cumulative exposure to atherogenic lipoproteins across the lifespan. Sex-specific lipid trajectories, particularly those shaped by hormonal transitions, may therefore exert disproportionate influence on lifetime cardiovascular risk that is not captured by conventional point-based risk estimates. Indeed, current clinical risk assessment frameworks rely predominantly on single time-point lipid measurements, which may inadequately capture the cumulative nature of atherogenic exposure. Such approaches can underestimate early-life risk, misclassify individuals with historically elevated cholesterol but later treatment, and obscure sex-specific trajectories shaped by hormonal transitions (Zhang et al., 2021; Seidemann et al., 2024).



Emerging evidence from Mendelian randomization studies and longitudinal cohorts suggests that the duration and timing of LDL-C exposure, rather than isolated values, are critical determinants of cardiovascular outcomes, with early reductions conferring disproportionately greater benefit than later intervention.

In this context, cumulative lipid burden may be conceptualized as the time-integrated exposure to circulating atherogenic lipoproteins, operationalized through metrics such as “cholesterol-years” or LDL years, serial aggregation of repeated lipid measurements, or genetic proxies for lifelong LDL-C elevation. However, the clinical implementation of such frameworks remains limited, and sex-specific validation is notably sparse.

Accordingly, this literature review synthesizes current evidence to evaluate cumulative lipid exposure as a determinant of cardiovascular risk across the lifespan, with particular attention to sex-specific biology. Rather than re-establishing known sex differences in lipid profiles, this review critically examines how cumulative LDL-C burden has been measured, where empirical support exists, and where significant gaps, especially regarding sex-stratified risk estimation, persist. By integrating mechanistic insights with epidemiological data, this review aims to clarify the translational potential of cumulative lipid metrics and to identify key methodological and evidentiary barriers that must be addressed to advance sex-specific cardiovascular prevention strategies.

2. Methods

Literature search strategy

A structured literature search was conducted to identify peer-reviewed studies examining the relationship between lipid metabolism, cholesterol regulation, sex-specific biological differences, and CVD risk. The primary database used was PubMed, with supplementary searches performed in Scopus and Google Scholar to ensure comprehensive coverage of both biomedical and biochemical research. Searches were limited to studies published in English between January 1990 and October 2025, reflecting the period during which modern lipid measurement techniques, large-scale epidemiological cohorts, and contemporary frameworks for cardiovascular risk assessment became widely established. No restrictions were placed on study geography.

Database-specific search strategies were developed using a combination of controlled vocabulary (e.g., Medical Subject Headings [MeSH] in PubMed) and free-text terms. Boolean operators were applied systematically, and truncation and phrase searching were used where appropriate. Search strategies were iteratively refined to optimize specificity, with consistent inclusion limits applied across databases. Reference lists of key review articles and landmark cohort studies were manually screened to identify additional relevant primary studies not found through electronic searches.

Search terms included, but were not limited to, combinations of the following keywords and Boolean operators: “cardiovascular disease” OR “atherosclerosis” AND “cholesterol” OR “lipids” OR “lipid metabolism” AND “sex differences” OR “gender differences” OR “menopause” OR “estrogen”. Additional terms such as “hormonal regulation”, “LDL-C”, “HDL-C”, “reverse cholesterol transport”, and “cumulative lipid burden” were incorporated in secondary searches to refine topic specificity. Reference lists of major reviews and landmark cohort studies were also manually screened to capture relevant primary research not indexed under these search terms.

Inclusion and exclusion criteria

Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies met one or more of the following criteria: large-scale epidemiological or longitudinal cohort studies examining serum lipid levels, aging, and cardiovascular outcomes in human populations; genetic or Mendelian randomization studies evaluating lifelong exposure and cardiovascular risk; mechanistic or biochemical studies elucidating pathways by which sex hormones influence lipid metabolism and atherogenesis; and review articles synthesizing lipid metabolism and CVD risk, included to contextualize primary findings.

Studies were excluded if they were from non-peer-reviewed sources, case reports, editorials, or conference abstracts; focused exclusively on animal or in vitro models without clear translational relevance to human lipid metabolism; or addressed metabolic disorders unrelated to cardiovascular lipid metabolism.

Screening and data extraction

The literature search yielded approximately 1,200 records across all databases. After removal of duplicates (~200), ~1000 records underwent title and abstract screening. Of these, ~850 articles were excluded based on relevance, leaving ~150 full-text articles assessed for eligibility. Following full-text review, 84 articles met inclusion criteria and were incorporated into the final qualitative synthesis.

Screening, eligibility assessment, and data extraction were performed by the author. Extracted data included study design, population characteristics, lipid metrics assessed (e.g., point-based LDL-C versus cumulative measures), duration of follow-up, sex-stratified analyses, and reported cardiovascular outcomes.

A PRISMA flow diagram summarizing the study selection process is provided in Figure 1.

Synthesis strategy

Included studies were grouped thematically according to whether they employed traditional point-based lipid measurements or cumulative lipid exposure metrics. Within these groups, evidence was further synthesized based on sex-specific analyses, age-related lipid trajectories, and cardiovascular outcomes. This approach enabled a direct comparison between conventional risk paradigms and emerging cumulative exposure frameworks.



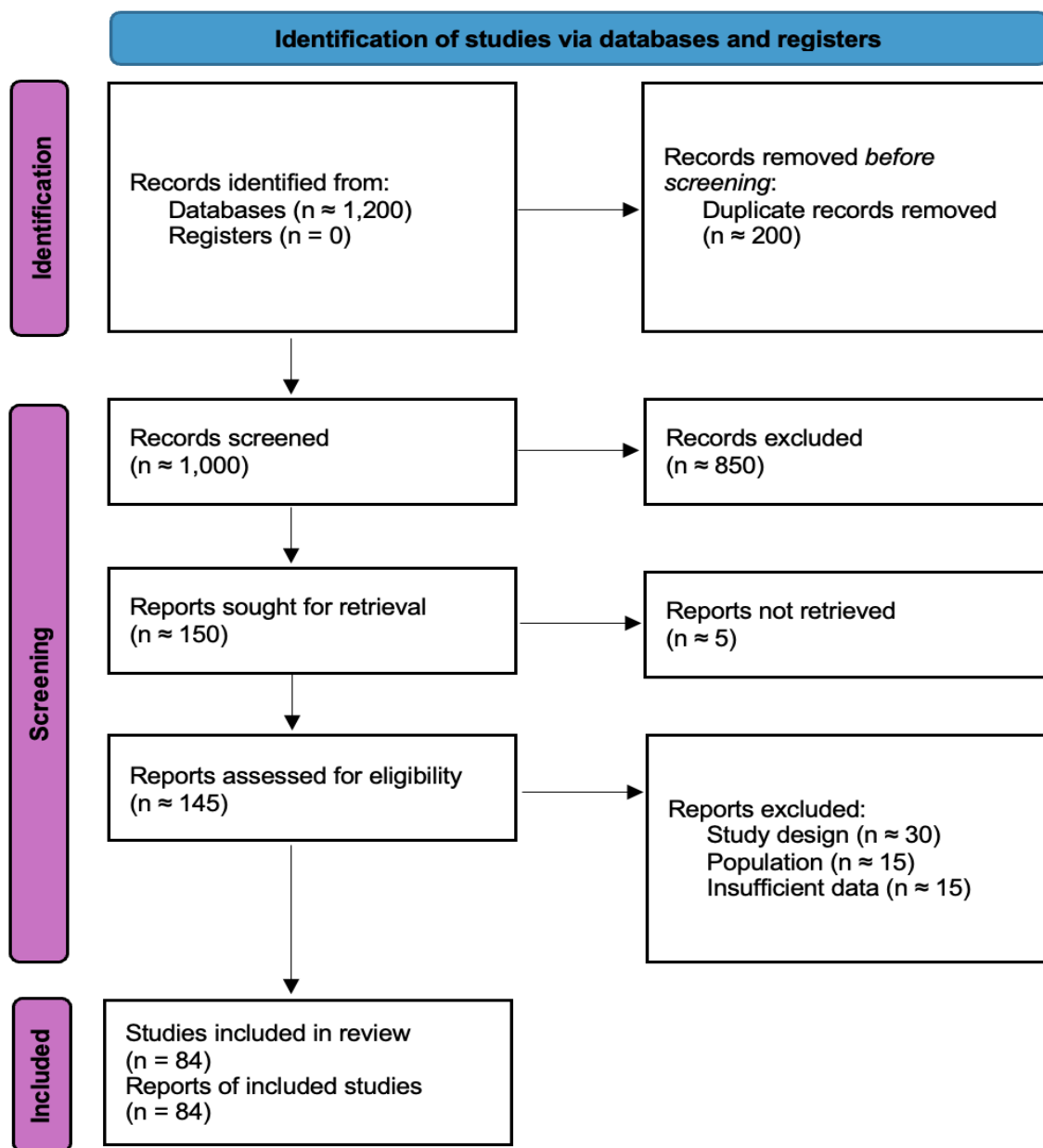


Figure 1: PRISMA flow diagram summarizing the literature search and study selection process.

Note: The literature search yielded approximately 1,200 records across databases, with ~200 duplicates removed. Title and abstract screening excluded ~850 articles, and 150 full-text articles were assessed for eligibility. Following full-text review, 84 studies were included in the final qualitative synthesis.

3. Results

Collectively, lipid biology is both a causal and modulatory factor in cardiovascular disease. Understanding how lipids circulate, modify, and accumulate within arterial walls is essential to contextualize both epidemiological trends and sex-based disparities in disease burden. Beyond the absolute concentrations of circulating lipoproteins, the cumulative exposure to atherogenic lipids over the lifespan is a central determinant of disease trajectory. This passage provides the biochemical context for understanding sex- and age-related heterogeneity in cardiovascular risk, which will be explored in greater depth in subsequent sections.

Lipid-driven atherosclerosis as a cumulative process

Lipid metabolism is central to the etiology of CVD, primarily through its influence on atherosclerotic plaque formation and progression. Atherosclerosis, the predominant pathological substrate underlying most ischemic cardiovascular events, is a progressive process initiated by endothelial dysfunction, in which the vascular endothelium loses its ability to regulate vascular tone and maintain barrier integrity (Park & Park, 2015). This impairment facilitates the subendothelial retention of apolipoprotein B-containing lipoproteins, primarily low-density lipoprotein cholesterol (LDL-C), which represents the principal atherogenic lipoprotein species (Tabas et al., 2007).

Upon infiltration into the arterial intima, LDL particles undergo oxidative and enzymatic modifications, producing oxidized LDL (oxLDL) (Jiang et al., 2022). OxLDL has multiple atherogenic properties, including upregulation of endothelial cell adhesion molecules, recruitment of circulating monocytes, and induction of pro-inflammatory signaling cascades (Poznyak et al., 2021). Monocytes differentiate into macrophages within the intima, engulfing oxLDL via scavenger receptors, and as lipid accumulation exceeds cellular processing capacity, macrophages transform into foam cells and form the fatty streak—the earliest visible lesion of atherosclerosis (Chistiakov et al., 2016; Ouyang et al., 2023).

Over time, smooth muscle cells migrate into the intima and deposit extracellular matrix, creating a fibrous cap over a lipid-rich necrotic core (Harman & Jørgensen, 2019). This plaque can remain stable for years, but oxidative stress and inflammatory activity promote thinning of the fibrous cap, increasing the likelihood of rupture, which subsequently exposes thrombogenic contents to circulating blood and precipitates acute coronary syndromes such as MI (Loftus, 2011). This process is thus inherently time dependent. More specifically, LDL particles that circulate for longer periods are more likely to undergo oxidative modification and arterial retention, increasing plaque burden incrementally over decades (Akyol et al., 2025). Consequently, atherosclerosis is fundamentally cumulative, with lifetime exposure to atherogenic lipoproteins representing a key determinant of disease severity (Almohtasib et al., 2024). Atherosclerosis thus reflects both the magnitude and duration of LDL-C exposure, supporting a cumulative exposure or a “cholesterol-years” model of development. This framework provides the mechanistic foundation for interpreting sex- and age-related heterogeneity in cardiovascular risk.

Figure 2 provides a schematic overview of the molecular pathways governing lipid metabolism.

The interactions between lipid species further modulate atherosclerotic risk. While LDL-C contributes directly to plaque formation, high-density lipoprotein cholesterol (HDL-C) mediates protective mechanisms through reverse cholesterol transport, whereby excess cholesterol is effluxed from peripheral tissues and transported to the liver for excretion (Ouimet



et al., 2019).

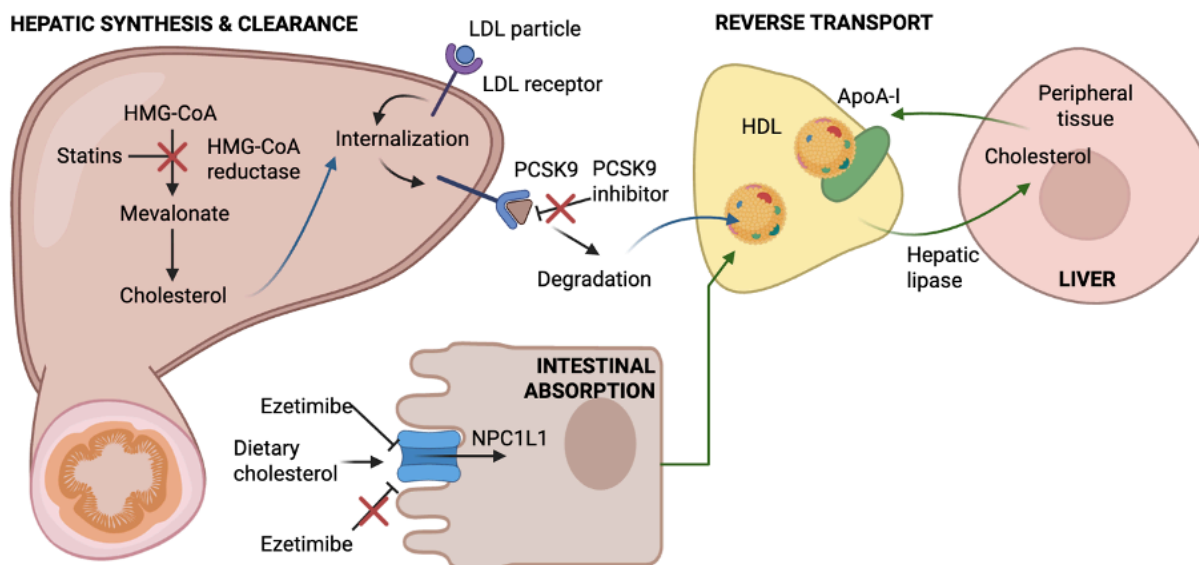


Figure 2: Molecular mechanisms of lipid metabolism and therapeutic intervention points.

Note: Simplified schematic illustrating hepatic cholesterol synthesis, intestinal absorption, LDL receptor-mediated clearance, and reverse cholesterol transport, highlighting targets of statins, ezetimibe, PCSK9 inhibitors, and hormone-mediated regulation. Created by author in BioRender.

Sex-specific lipid trajectories across the lifespan

Epidemiological data consistently demonstrate pronounced sex-based differences in both lipid metabolism and cardiovascular risk trajectories. Men generally exhibit higher LDL-C and triglyceride concentrations, coupled with lower HDL-C levels, beginning as early as adolescence (Russo et al., 2015). These differences correlate with earlier onset and greater lifetime incidence of atherosclerotic CVD (Rodgers et al., 2019). In contrast, premenopausal women typically maintain a more favorable lipid profile, characterized by lower LDL-C and elevated HDL-C levels, which correspond to their reduced risk of coronary events prior to menopause (Ryczkowska et al., 2022).

This divergence is largely attributed to the hormonal regulation of hepatic lipid processing. Androgen-dominant metabolic environments in males promote increased hepatic lipase activity, accelerating HDL catabolism and reducing HDL-C concentration (Herbst et al., 2003). Concurrently, reduced LDL receptor density in hepatocytes contributes to slower LDL clearance from the circulation; these features collectively produce an early-life metabolic phenotype conducive to lipid retention and vascular injury (Pirahanchi et al., 2023).

Figure 3 illustrates longitudinal lipid trajectories for men and women across adulthood.



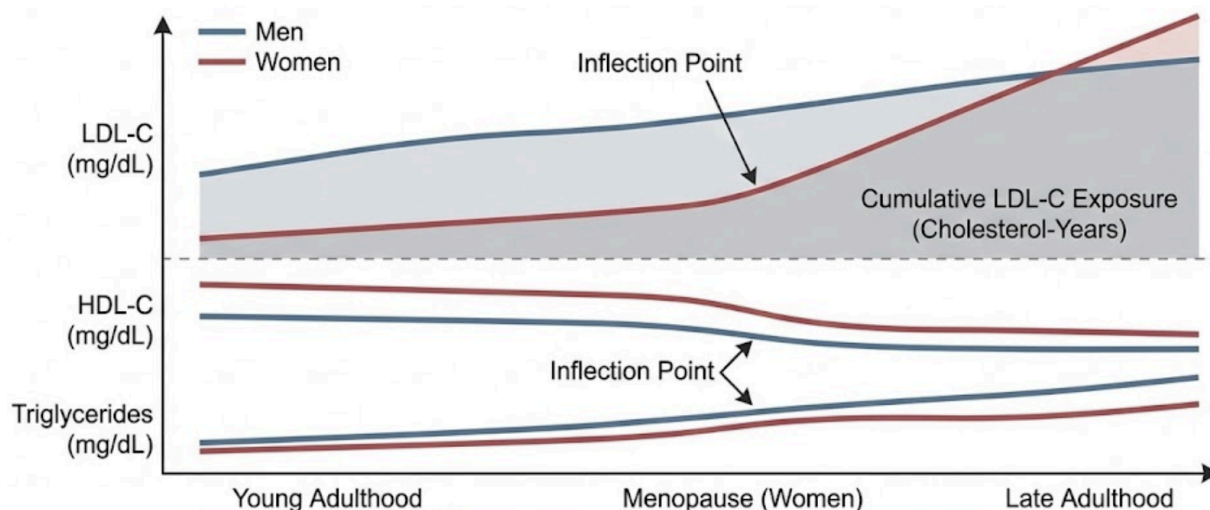


Figure 3: Sex-specific lipid trajectories and cumulative cardiovascular risk.

Note: Longitudinal trajectories of LDL-C, HDL-C, and triglycerides in men and women across adulthood. Inflection points highlight the midlife rise in LDL-C among women during the menopausal transition. Shaded areas indicate cumulative LDL exposure (“cholesterol-years”), illustrating differences in lifetime atherogenic burden and periods of elevated cardiovascular risk. Created by author in BioRender.

Sex hormones exert a considerable regulatory effect on lipid metabolism, contributing to observed demographic patterns in CVD incidence (Robinson et al., 2022). The onset of menopause represents a pivotal inflection point in female lipid physiology. Estrogen—the principal modulator of lipid homeostasis in women—exerts multifaceted effects on lipoprotein mechanisms, upregulating hepatic LDL receptor expression, facilitating LDL particle uptake and degradation, and promoting apolipoprotein A-I (ApoA-I) synthesis, the major protein constituent of HDL (Nii et al., 2016; Palmisano et al., 2018). These combined mechanisms confer a premenopausal cardioprotective lipid profile in women (Ryzkowska et al., 2022). Following menopause, declining estrogen levels attenuate these protective mechanisms; LDL-C increases, HDL-C decreases, and women’s cardiovascular risk rises sharply (Ryzkowska et al., 2022). By contrast, men lack this hormonal protection throughout life, which may explain their earlier onset of CVD (Rodgers et al., 2019). Moreover, estrogen stimulates the activity of ATP-binding cassette transporters (ABCA1 and ABCG1) involved in cholesterol efflux, thereby augmenting reverse cholesterol transport (Bao et al., 2023). These hormonal transitions shift women from a low cumulative LDL exposure trajectory toward a rapidly accelerating risk profile in midlife, narrowing the sex gap in atherosclerotic cardiovascular disease (ASCVD) incidence.

Beyond circulating estrogen, sex-specific lipid metabolism is modulated by androgens and progesterone. Androgens, which predominate in males, exert multiple pro-atherogenic effects, primarily through hepatic lipid regulation (Xu et al., 2022). Elevated androgens increase hepatic lipase activity, accelerating the catabolism of HDL particles and leading to smaller, less functional HDL that is less effective in reverse cholesterol transport (Kantor et al., 1985). Additionally, androgen exposure favors the production of small, dense LDL particles, which are more susceptible to oxidation, exhibit increased arterial

retention, and undergo atherogenic modification (Vekic et al., 2022). These molecular and structural alterations provide a mechanistic basis for the higher prevalence of early-onset cardiovascular disease observed in males.

In contrast, progesterone, a dominant female sex hormone during the luteal phase and pregnancy, influences lipid metabolism in a more nuanced manner. Progesterone modulates HDL functionality by altering particle composition and may affect the distribution of LDL subfractions, though the net cardiovascular impact remains less clearly defined (Corsini et al., 1988). Importantly, these effects are context-dependent, influenced by hormonal milieu, age, and concomitant estrogen exposure. Estrogen receptor signaling, mediated by ER α and ER β , plays a pivotal role in hepatocyte lipid handling, regulating transcription of key genes including LDL receptor, apolipoprotein A-I, and enzymes involved in cholesterol esterification and bile acid synthesis (Zhu et al., 2018). Additionally, estrogen modulates sterol regulatory element-binding protein (SREBP) pathways, which are central to endogenous cholesterol synthesis and intracellular lipid homeostasis (Sakai & Rawson, 2001). Collectively, these hormonal and intracellular mechanisms underlie the observed divergence in lipid profiles between males and females across the lifespan, contributing to delayed atherosclerotic development in premenopausal women and accelerated risk in men and postmenopausal women.

The effects of sex hormones extend beyond circulating lipoproteins to cellular processes in the vascular wall. Estrogen enhances endothelial nitric oxide synthase (eNOS) activity, promoting vasodilation and reducing oxidative stress, while androgens may favor pro-inflammatory cytokine expression and endothelial dysfunction (MacRitchie et al., 1997). These vascular effects amplify the consequences of sex-specific lipid profiles, reinforcing the higher baseline risk of atherogenesis in males and the protective effect of premenopausal estrogen in females.

In addition to conventional lipid fractions, lipoprotein(a) (Lp(a)) represents a genetically determined, highly atherogenic lipoprotein whose plasma concentration is largely stable throughout life and minimally influenced by diet, exercise, or conventional lipid-lowering therapies (Farzam et al., 2024). Structurally, Lp(a) consists of an LDL-like particle covalently bound to apolipoprotein(a), a glycoprotein homologous to plasminogen, which confers prothrombotic properties in addition to its atherogenic potential (Farzam et al., 2024). Elevated Lp(a) levels have been associated with accelerated coronary artery disease, calcific aortic valve disease, and heightened inflammatory signaling in the vascular endothelium (Wambua et al., 2025).

The clinical impact of Lp(a) appears to differ by sex and hormonal status. In premenopausal women, Lp(a)-related risk is partially mitigated by estrogen-mediated enhancement of LDL receptor expression and lipoprotein clearance (Corral et al., 2024). Postmenopausal women, however, experience a disproportionate increase in atherosclerotic cardiovascular disease (ASCVD) risk when Lp(a) levels are elevated, potentially due to the combined effects of increased LDL-C, loss of estrogen-driven hepatic clearance, and heightened inflammatory susceptibility in the vascular wall (Roeters van Lennep et al., 2023).

Consequently, these well-established sex differences have been reframed as divergent cumulative exposure trajectories shaped by hormonally timed inflection points rather than as static biological distinctions. Recent longitudinal analyses emphasize that cardiovascular risk divergence arises from differences in when and for how long individuals are exposed to atherogenic lipid environments, rather than from fixed sex-based lipid set points (Wilkins et al., 2024; Zheutlin et al., 2025). This temporal reframing has shifted the field away from cross-sectional lipid comparisons toward life-course modeling approaches that better capture the delayed but accelerated risk observed in postmenopausal women. Such findings



highlight the need to integrate sex, age, and duration of exposure into cardiovascular risk assessment rather than treating sex differences as isolated phenomena.

Longitudinal evidence of cumulative lipid burden

As endogenous estrogen production declines during the menopausal transition, these regulatory mechanisms wane, leading to measurable alterations in serum lipid composition (Patel et al., 2025). The extent and timing of these changes have been captured through large-scale prospective cohorts, including the Framingham Offspring Study (FOS) and the Study of Women's Health Across the Nation (SWAN) (Duncan et al., 2019; El Khoudary et al., 2019). More specifically, these cohorts provide empirical support for cumulative lipid exposure as a superior predictor of cardiovascular outcomes compared with single-point LDL measurements.

FOS, a longitudinal cohort initiated in 1971 to follow the descendants of the original Framingham Heart Study participants, provides some of the most comprehensive sex-stratified analyses of lipid trajectories and cardiovascular outcomes. Among 3,875 participants (54% women; mean age 48 years) followed between 1979 and 2014, investigators identified five distinct trajectories of total cholesterol (TC), LDL-C, and HDL-C across adulthood (Duncan et al., 2019). Importantly, women exhibited marked inflection points in LDL-C and HDL-C levels during midlife, consistent with the perimenopausal transition, where average LDL-C concentrations increased by approximately 10–15%, while HDL-C declined modestly—changes that paralleled reductions in circulating estradiol rather than chronological aging or body mass index (Ryckowska et al., 2022). This finding reinforces that timing and duration of exposure, rather than absolute midlife LDL-C alone, drive long-term risk.

Elevated lipid trajectories were strongly associated with future ASCVD and mortality. Participants maintaining LDL-C >155 mg/dL, TC >240 mg/dL, or non-HDL-C >180 mg/dL had over a twofold increase in ASCVD and all-cause mortality risk compared with those maintaining optimal lipid levels (HRASCVD = 5.09 [95% CI: 1.54–16.85]; HRdeath = 4.04 [1.84–8.89]) (Duncan et al., 2019). Conversely, persistently low HDL-C (<40 mg/dL) was associated with a nearly 4-fold higher ASCVD risk compared with concentrations >70 mg/dL (Duncan et al., 2019). These findings reinforce the concept of cholesterol-years—that is, cumulative exposure to atherogenic lipoproteins—as a more precise determinant of lifetime cardiovascular risk than any single lipid measurement (Wilkins et al., 2024). From a mechanistic perspective, these observations align with the decline in hepatic LDL receptor expression post-menopause, leading to reduced LDL clearance and prolonged lipoprotein residence time within circulation, thereby increasing the probability of oxidative modification and endothelial retention (P, 2025). FOS thus provides population-scale confirmation of the biochemical mechanisms previously discussed.

Complementing the Framingham data, SWAN—a multi-ethnic, prospective cohort initiated in 1994—has characterized the dynamic lipid changes across the menopausal transition in greater temporal resolution and demonstrated that the steepest increases in LDL-C occurred within a narrow window surrounding the final menstrual period, temporally aligned with estradiol decline. SWAN followed over 3,000 premenopausal women aged 42–52 from diverse ethnic backgrounds (Caucasian, African-American, Chinese, Japanese, and Hispanic) for over two decades, incorporating both hormonal and metabolic assessments at annual intervals (El Khoudary et al., 2019; Derby et al., 2009). Longitudinal analyses across the menopausal stages revealed that the steepest rise in LDL-C and total cholesterol levels occurred within a two-year window surrounding the final menstrual period (FMP), temporally coinciding with the estradiol nadir (El Khoudary et al., 2021).



These changes were most pronounced during early postmenopause, when estrogen depletion accelerates hepatic lipid remodeling (El Khoudary et al., 2021).

Mechanistically, SWAN's metabolic substudy highlighted that declining estrogen levels were associated with increased hepatic lipase activity and reduced ApoA-I concentrations, attenuating HDL particle maturation and impairing reverse cholesterol transport (Woodard et al., 2011). Additionally, small dense LDL particles became increasingly prevalent in the years following menopause, a pattern associated with heightened atherogenic potential due to their greater arterial wall penetrance and oxidative susceptibility (He et al., 2025). Importantly, SWAN's findings highlight menopause as a biologically discrete period of accelerated lipid remodeling that materially contributes to cumulative atherogenic burden.

Taken together, the Framingham and SWAN cohorts provide converging evidence that the menopausal transition represents a biologically distinct period of lipid remodeling with direct implications for cardiovascular risk. Framingham emphasizes the cumulative, long-term impacts of rising LDL-C post-menopause on clinical outcomes, while SWAN delineates the temporal and mechanistic sequence of lipid alterations accompanying hormonal declines; its inclusion of diverse populations underscores that, while hormonal decline is universal, its phenotypic lipid effects are modulated by race, diet, and genetic background.

When contextualized within the broader framework of lipid biology, these findings reinforce the notion that lifetime exposure to atherogenic lipoproteins—modulated by the hormonal milieu—is a principal determinant of CVD onset and severity. This cumulative exposure framework integrates both male and female trajectories: men experience a steady accrual of risk beginning early in adulthood due to persistently higher LDL-C levels, whereas women's risk accelerates sharply post-menopause as estrogen-mediated lipid regulation deteriorates. Such evidence provides a mechanistic and epidemiological rationale for sex-specific therapeutic approaches, discussed in subsequent sections, emphasizing the potential for early lipid intervention in premenopausal women to mitigate postmenopausal risk acceleration.

Empirical support for the cholesterol-years model

The primary aim of this review is to evaluate empirical evidence supporting cumulative lipid exposure models and to examine whether these approaches reveal sex-specific associations with cardiovascular outcomes beyond conventional point-based measurements. While relatively few studies explicitly operationalize cumulative cholesterol metrics, a growing body of longitudinal, genetic, and cohort-based evidence demonstrates that duration- and burden-based lipid exposure more accurately predicts cardiovascular risk, particularly when sex- and life-stage-specific trajectories are considered.

Indeed, while acute lipid measurements are standard clinical practice, growing evidence emphasizes that cumulative exposure to atherogenic lipoproteins, rather than isolated LDL-C levels, is the principal determinant of CVD risk (Zheutlin et al., 2025). Prolonged circulation of LDL particles increases the probability of their oxidative modification and subsequent arterial retention, accelerating atherogenesis (Maiolino et al., 2013). Indeed, accumulating epidemiological and genetic evidence supports a cholesterol-years model of atherogenesis in which the duration of exposure to atherogenic lipoproteins materially influences lifetime risk of coronary heart disease (CHD) (Zheutlin et al., 2025). In other words, genetic and modeling studies provide direct evidence that cumulative LDL exposure predicts cardiovascular outcomes more accurately than conventional point-based metrics.

Operationally, cumulative LDL exposure (“cholesterol-years”) is calculated by aggregating serial LDL-C measurements over



time, typically as the area under the LDL-C-time curve or as a time-weighted average of repeated values across adulthood (Ference et al., 2012). In genetic studies, this exposure is approximated through lifelong LDL-C differences conferred by specific variants, providing a proxy for sustained exposure independent of treatment or behaviour (Ference et al., 2012). In observational cohorts, cumulative burden has been modeled using repeated laboratory measurements collected at regular intervals, enabling estimation of total LDL exposure across decades (Zhang et al., 2021).

Mendelian-randomization meta-analyses by Ference et al. (2012) provide strong support for the cholesterol-years paradigm. Ference et al. (2012) integrated nonoverlapping data from 312,321 participants across nine polymorphisms affecting LDL-C regulation. Each mmol/L genetically lower LDL-C was associated with a 54.5% reduction in CHD risk (95% CI: 48.8–59.5%), reflecting a ~3-fold greater risk reduction per unit LDL-C than statin therapy initiated later in life ($p = 8.43 \times 10^{-19}$) (Ference et al., 2012). These results demonstrate that early and sustained reductions in LDL-C produce disproportionately larger cardiovascular benefits, supporting the notion that cumulative LDL exposure, rather than cross-sectional levels alone, governs atherosclerotic progression. Conceptually, these observations have been framed as the cholesterol-years or lifelong exposure model: the findings strongly support an area-under-the-curve model of LDL exposure across the lifespan that appears to predict disease more accurately than a single midlife measurement (Ference et al., 2012).

Complementing genetic findings, population-level analyses further corroborate this framework. Zhang et al. (2021) pooled data from four prospective cohorts (18,288 participants; 56.4% women; mean age 56.4 ± 3.7 years; median follow-up ≈ 16 years) (Zhang et al., 2021). Using cumulative LDL-C, time-weighted average (TWA), and LDL-C slope metrics, the study found that both cumulative LDL-C and TWA LDL-C were independently associated with incident CHD even after adjustment for the most recent midlife LDL-C and traditional CVD risk factors (Zhang et al., 2021). By contrast, the LDL-C slope alone was not significantly associated with CHD after accounting for midlife levels, reinforcing that the area under the LDL curve (cumulative burden) rather than transient changes in LDL-C is the critical metric (Zhang et al., 2021). Thus a lifelong lipid exposure model is translationally relevant once mechanistic insights from genetic studies are extended into population-level observations.

Navar-Boggan et al. (2015) provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥ 160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk. Although Navar-Boggan et al. (2015) did not stratify outcomes by sex, the findings are particularly salient when interpreted alongside sex-specific lipid trajectories observed in Framingham and SWAN, where women experience delayed but accelerated LDL



accumulation post-menopause. Together, these studies suggest that cumulative lipid exposure may systematically underestimate risk in women when assessed using midlife point measurements alone.

Further evidence comes from the Copenhagen General Population Study (CGPS) which enrolled 91,131 individuals between 2003 and 2015, with a mean follow-up of 7.7 years (Mortensen & Nordestgaard, 2020). During this period, 1,515 first myocardial infarctions (MI) and 3,389 atherosclerotic cardiovascular events occurred, where each 1.0 mmol/L increase in LDL-C was associated with a 34% higher risk of MI (HR: 1.34; 95% CI: 1.27–1.41) and a 16% higher risk of ASCVD overall (HR: 1.16; 95% CI: 1.12–1.21) (Mortensen & Nordestgaard, 2020). Notably, risk was amplified in older adults (aged 70–100 years) and in individuals with very high LDL-C (≥ 5.0 mmol/L), consistent with the notion that both absolute levels and cumulative exposure exacerbate atherosclerotic outcomes (Mortensen & Nordestgaard, 2020). Notably, the CGPS relies on single-point LDL-C measurements, which limits its ability to directly assess cumulative lipid exposure. However, its findings nevertheless align with cumulative risk models by demonstrating amplified risk at older ages, when lifetime LDL burden is greatest, but highlight the need for studies incorporating repeated measurements to more accurately quantify exposure over time.

Complementing these observational studies, population screening for heterozygous familial hypercholesterolemia (FH) demonstrates the extreme consequences of lifelong elevated LDL-C. FH, an autosomal dominant genetic disorder caused by mutations in genes critical for LDL clearance that impair hepatic LDL uptake, is characterized by markedly elevated plasma LDL-C concentrations from birth (Warden et al., 2024). Prevalence estimates range from 1/500 to 1/200 in Northern European populations, yet <1% of affected individuals are diagnosed in most countries (Nordestgaard et al., 2013). Individuals with untreated FH experience up to a 13-fold increased risk of CHD, suggesting that prolonged and substantial elevations in LDL-C from early life dramatically accelerate atherosclerosis (Nordestgaard et al., 2013). FH thus provides an application of the cholesterol-years paradigm: both the magnitude and duration of LDL-C elevation are critical determinants of cardiovascular risk, and the findings reinforce the mechanistic link between lifelong LDL burden and atherosclerotic disease.

Collectively, converging evidence from genetic, longitudinal, and clinical studies emphasizes that cardiovascular risk is not merely a function of LDL-C concentration at a single point in time, but rather of its cumulative exposure across the lifespan. Thus, early and sustained lipid control, rather than reactive prevention in midlife, yields disproportionately greater protection against lifetime cardiovascular risk. Table 1 synthesizes key studies comparing cumulative LDL metrics and traditional point-based measurements, illustrating the relative paucity but growing importance of longitudinal exposure modeling in cardiovascular risk assessment.

From a clinical standpoint, implementation is increasingly feasible as electronic health records now capture longitudinal lipid data across multiple life stages. While early-life measurements remain sparse in many populations, even partial cumulative estimates derived from adolescence or early adulthood onward may nevertheless capture a substantial proportion of lifetime atherogenic exposure (Zheutlin et al., 2025). Such partial cumulative modeling may substantially improve risk stratification as compared with single-point assessments, particularly in populations experiencing hormonally mediated lipid shifts. As longitudinal data availability continues to expand and cumulative exposure metrics become more readily integrated into existing cardiovascular risk calculators, cholesterol-years modeling represents a practical and scalable approach to refining lifetime cardiovascular risk assessment. The clinical performance and predictive value of longitudinal risk factor integration are discussed further in the subsection Emerging sex-specific strategies for mitigating cumulative lipid burden below, where emerging modeling approaches demonstrate improved discrimination and reclassification beyond traditional cross-sectional tools.

Table 1: Key studies comparing cumulative LDL exposure metrics with traditional point-based lipid measurements.

Note: Summary of major studies evaluating the relationship between cumulative LDL-C metrics (e.g., cholesterol-years, area under the LDL-C curve, time-weighted averages) and cardiovascular outcomes, with comparison to traditional single-point measurements. The table highlights population characteristics, lipid metrics assessed, comparators, outcomes, key findings, and clinical implications.

Study	Population	LDL Metric	Comparator	Outcome	Key Finding	Clinical Implication
Ference et al., 2012	Mendelian randomization meta-analysis, n > 300,000	Genetically mediated lifelong LDL reduction	Statin-era LDL reduction	CHD incidence	Lifelong LDL lowering yields ~3× greater risk reduction per mmol/L	Timing and duration of LDL exposure are critical
Zhang et al., 2021	4 pooled cohorts, n > 18,000; 56% women	Cumulative LDL-C (AUC), time-weighted average	Most recent LDL-C	Incident CHD	Cumulative and TWA LDL independently predicted CHD; LDL slope did not	Area-under-the-curve LDL more informative than point or slope
Navar-Boggan et al., 2015	Framingham Offspring Cohort; n=1,478; free of CVD to age 55	Duration of non-HDL-C ≥ 160 mg/dL ("years of exposure")	Single LDL/non-HDL at age 55	CHD incidence	CHD risk \uparrow dose-dependently with longer exposure (HR 1.39 per decade), independent of contemporaneous lipids	Duration of exposure captures risk missed by midlife measurements
CGPS (Mortensen & Nordestgaard, 2020)	Copenhagen General Population Study; n=91,131	Single LDL-C	—	MI, ASCVD	Higher LDL associated with higher risk, amplified at older ages	Highlights limitations of single-point LDL
Nordestgaard et al., 2013; Warden et al., 2024 (FH studies)	Population screening cohorts; heterozygous FH (~1/200-1/500 prevalence)	Lifelong genetically elevated LDL-C from birth	Non-FH population (normal LDL exposure)	CHD, MI	Untreated FH associated with up to 13-fold increased CHD risk due to lifelong LDL elevation	Demonstrates extreme consequences of cumulative LDL exposure; magnitude and duration determine risk

Therapeutic strategies and sex-specific limitations

Given the centrality of cumulative LDL-C exposure in atherosclerosis, therapeutic interventions aim to reduce circulating LDL-C levels, enhance clearance, or modify lipid metabolism to slow plaque progression.

Statins remain the first-line therapy for both primary and secondary prevention of CVD. Mechanistically, statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis in hepatocytes (Bansal & Cassagnol, 2023).



Reduced intracellular cholesterol triggers upregulation of LDL receptors on the liver surface, promoting the uptake of circulating LDL particles and lowering plasma LDL-C concentrations (Trapani et al., 2012). In children with heterozygous FH, statins have been shown to substantially reduce LDL-C levels and slow progression of atherosclerosis. A systematic review including nine randomized placebo-controlled trials (1,177 participants; median follow-up 24 weeks) found statin therapy reduced mean LDL-C by 32.15% (95% CI: 29.4–34.9%) and produced measurable improvements in brachial artery flow-mediated dilatation (2.7% higher; 95% CI: 0.42–4.98) and carotid intima-media thickness (CIMT) (mean change 0.01 mm lower) relative to placebo, both surrogate markers of atherosclerotic burden (Vuorio et al., 2019). Adverse events, including myopathy and changes in liver enzymes, were rare and comparable to placebo, supporting the safety of early statin initiation in pediatric populations (Vuorio et al., 2019).

Ezetimibe, an adjunct to statins, inhibits the NPC1L1 transporter in the intestinal brush border, reducing absorption of dietary and biliary cholesterol (Davis & Veltri, 2007). When combined with statins, ezetimibe provides additive LDL-C reductions (~15–20%) (Hammersley & Signy, 2017). The landmark IMPROVE-IT trial randomized high-risk post-MI patients with recent acute coronary syndrome to simvastatin 40 mg versus simvastatin 40 mg plus ezetimibe 10 mg daily (median follow-up 6 years) (Cannon et al., 2015). Combination therapy further reduced LDL-C (53.7 mg/dL vs 69.5 mg/dL; $p < 0.001$) and decreased major cardiovascular events at 7 years (absolute risk reduction 2.0%; HR: 0.936; 95% CI: 0.89–0.99) (Cannon et al., 2015). Subgroup analyses indicated greater benefit for patients with diabetes (5.5% absolute risk reduction; HR: 0.86) and for older adults aged ≥ 75 (HR: 0.80) highlighting ezetimibe's role in high-risk populations where further LDL-C lowering is required (Giugliano et al., 2018; Cannon et al., 2015). Meta-analyses of 27 trials (>21,000 participants) confirm that statin-ezetimibe combination therapy produces superior LDL-C reduction compared to statin monotherapy (mean additional reduction 15.1%) and maintains a favorable safety profile (Morrone et al., 2012).

PCSK9 inhibitors, including monoclonal antibodies evolocumab and alirocumab, preserve LDL receptor availability by preventing PCSK9-mediated receptor degradation, significantly enhancing hepatic LDL-C clearance (Jeswani et al., 2024). Clinical trials demonstrate 50–60% LDL-C reduction in patients with heterozygous FH, and reductions in major cardiovascular events of 15–20% (Tomlinson et al., 2021). For instance, the FOURIER trial reported a 59% LDL-C reduction with evolocumab, resulting in a 15% reduction in cardiovascular events; ODYSSEY Outcomes reported a 57% LDL-C reduction with alirocumab and a 15% reduction in adverse events (Jeswani et al., 2024). Inclisiran, a long-acting small interfering RNA (siRNA) targeting PCSK9, achieves similar LDL-C reductions (>50% for 6 months) with less frequent dosing (Jeswani et al., 2024). These therapies are generally well-tolerated, with injection site reactions being the most common adverse event (Jeswani et al., 2024).

Hormone replacement therapy (HRT) in postmenopausal women can partially restore premenopausal lipid profiles (Nie et al., 2022). Postmenopausal HRT has lipid-modifying effects by upregulating LDL receptors, enhancing HDL-C formation, and stimulating reverse cholesterol transport via ABCA1/ABCG1 transporters (Nie et al., 2022). A systematic review of 73 studies found that HRT significantly reduced LDL-C by 0.47 mmol/L (95% CI: -0.55 to -0.40), total cholesterol by 0.43 mmol/L, and Lp(a) by 49.46 mg/L relative to placebo (Nie et al., 2022). Moreover, the timing of HRT initiation relative to menopause is critical to its cardiovascular effects. Observational and trial data support a “timing hypothesis,” whereby initiation within ten years of menopause may confer modest cardiovascular protection, whereas later initiation may increase risks of stroke or coronary events (Hodis & Mack, 2022). Novel pharmacologic approaches, including selective estrogen receptor modulators (SERMs) and tissue-selective estrogen complexes (TSECs), aim to replicate lipid benefits while minimizing systemic risks, though large-scale cardiovascular outcome data remain limited (Pickar et al., 2018). By



selectively activating estrogen receptors in hepatic and vascular tissues while sparing breast and endometrial tissue, these agents aim to preserve favorable lipid profiles and reverse cholesterol transport without increasing oncologic risk (Martinkovich et al., 2014). Integration of these therapies with statins or PCSK9 inhibitors may offer synergistic LDL-C reduction in high-risk postmenopausal women, pending further study. Although HRT improves lipid profiles, its clinical use is constrained by increased risk of venous thromboembolism, stroke, and breast cancer, so it is typically reserved for symptomatic relief, with cardiovascular benefit considered secondary (Hodis & Mack, 2022).

In patients with severe or treatment-resistant dyslipidemia, particularly FH, lipoprotein apheresis provides immediate and potent LDL-C and Lp(a) reduction (Feingold, 2023). A multicenter study by von Dryander et al. demonstrated 55–70% reduction in LDL-C and Lp(a) per session. Corresponding reductions in cardiovascular event rates over two years were 54% for patients with isolated LDL elevation, 83% for elevated Lp(a), and 83.5% for combined LDL-C and Lp(a) elevations (von Dryander et al., 2013). Apheresis is intensive and resource-demanding, but offers a life-saving intervention for patients who cannot achieve lipid targets pharmacologically (Lui et al., 2014).

Limitations and gaps, however, remain in sex-specific and longitudinal assessment. Women remain underrepresented in clinical trials, limiting precise understanding of HRT or statin efficacy across different life stages, particularly during postmenopause (Witting et al., 2022). Longitudinal studies tracking cumulative LDL-C from childhood into adulthood remain scarce, limiting the ability to quantify lifetime exposure and optimize the timing of therapy. Despite these challenges, evidence from RCTs and observational studies consistently demonstrates that aggressive LDL-C reduction, especially when initiated early, significantly decreases the risk of cardiovascular events and mitigates cumulative lipid burden; consequently both magnitude and duration of LDL-C exposure are further confirmed to be central determinants of cardiovascular outcomes.

A summary of the discussed therapies is presented in Table 2.

Table 2: Therapeutic strategies targeting cumulative LDL-C exposure.

Note: Summary of lipid-lowering interventions, including statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis. The table highlights mechanisms of action, key efficacy data, relevant populations, and considerations.

Therapy	Mechanism of Action	Key Efficacy Data	Notes
Statins	Inhibit HMG-CoA reductase → ↓ cholesterol synthesis → ↑ hepatic LDL receptors → ↑ LDL-C clearance	Pediatric FH: LDL-C ↓ 32% (29–35%), CIMT regression 0.01 mm, flow-mediated dilation ↑ 2.7%	Primary & secondary prevention; early initiation maximizes benefit; safe in children/adolescents
Ezetimibe	Inhibits NPC1L1 → ↓ intestinal cholesterol absorption → additive LDL-C reduction	LDL-C ↓ ~15–20% when combined with statin IMPROVE-IT: 7-year MACE 32.7% vs 34.7% (ARR 2%, HR 0.936), greater benefit in ≥75 years & diabetics	Adjunct to statin therapy, especially when target LDL-C not achieved with statins alone
PCSK9 inhibitors	Monoclonal antibodies or siRNA block	LDL-C ↓ 50–60%	FH, statin-intolerant, high-risk ASCVD;

(Evolocumab, Alirocumab, Inclisiran)	PCSK9 → prevent LDL receptor degradation → ↑ LDL-C clearance	FOURIER: major CV events ↓ 15–20% ODYSSEY: LDL-C ↓ 57%, CV events ↓ 15%, safe & well-tolerated	Inclisiran allows long-acting dosing (every 6 months)
Hormone Replacement Therapy (HRT)	Estrogen ↑ LDL receptors, ↑ HDL formation, ↑ reverse cholesterol transport (ABCA1/ABCG1)	LDL-C ↓ 0.47 mmol/L, total cholesterol ↓ 0.43 mmol/L, Lp(a) ↓ 49.46 mmol/L	Postmenopausal women; used mainly for symptomatic relief; cardiovascular benefits secondary due to risks (VTE, stroke, breast cancer)
Lipoprotein apheresis	Mechanical removal of LDL-C and Lp(a) from plasma	LDL-C & Lp(a) 55–70% per session 2-year CV event reductions: isolated LDL ↑ 54%, isolated Lp(a) ↑ 83%, combined ↑ 83.5%	Severe or treatment-resistant FH; homozygous FH; high Lp(a); resource-intensive but highly effective

Emerging sex-specific strategies for mitigating cumulative lipid burden

Beyond conventional lipid-lowering therapies, emerging sex-specific strategies increasingly emphasize the timing and biological context of LDL-C exposure rather than absolute cholesterol thresholds alone. Indeed, this paradigm shift is particularly relevant for women, whose cardiovascular risk is disproportionately influenced by biological differences in lipid metabolism, hormonal transitions, and lifetime exposure trajectories.

Early trajectory-based intervention in women

One promising approach involves the earlier identification of adverse lipid trajectories in premenopausal women, even when absolute LDL-C levels remain below traditional treatment thresholds (Roeters van Lennep et al., 2023). Women often experience prolonged periods of moderate hyperlipidemia before menopause, during which cumulative LDL-C exposure accumulates (Jeong & Kim, 2022). Incorporating trajectory-based or cholesterol-years modeling into risk assessment may therefore justify the earlier initiation of LDL-lowering therapy in select women, particularly those with additional risk modifiers such as family history, pregnancy-related dyslipidemia, or polycystic ovary syndrome (O’Kelly et al., 2022). Such strategies aim to prevent decades of unrecognized exposure that manifest as accelerated risk after menopause.

Targeting menopause as a critical inflection point

Menopause represents a biologically distinct window during which LDL-C levels rise sharply. Accordingly, emerging strategies emphasize proactive lipid monitoring and intervention during the perimenopausal transition, rather than delaying treatment until overt hypercholesterolemia or clinical events occur (Fasero & Coronado, 2025). This life-stage-specific approach aligns with cumulative risk models by prioritizing prevention at a point when lipid trajectories diverge most rapidly between sexes.

Addressing Lp(a) and genetically mediated risk



Sex-specific approaches may also be particularly relevant for Lp(a). Novel antisense oligonucleotides and siRNA therapies targeting LPA transcription offer the potential to reduce Lp(a) independently of LDL-C, addressing a component of cumulative lipid risk that is largely resistant to lifestyle modification and pharmacotherapy (Tselepis, 2023). These agents may be especially beneficial in women whose risk escalates after estrogen withdrawal makes clear genetically mediated lipid abnormalities.

Integration of cumulative lipid metrics into clinical practice

Finally, emerging strategies increasingly emphasize integration rather than new drugs alone, and evidence supports the clinical feasibility and utility of incorporating cumulative and longitudinal lipid exposure into cardiovascular risk prediction models. Traditional tools such as the Pooled Cohort Equations (PCE) rely on cross-sectional risk factor measurements and may therefore underestimate lifetime risk, particularly in individuals with prolonged moderate dyslipidemia or hormonally mediated lipid shifts (Yu et al., 2023). Recent work by Yu et al. demonstrates that integrating longitudinal risk factor data substantially improves ASCVD risk prediction beyond conventional approaches. In a multicohort study of over 15,000 individuals followed for adjudicated ASCVD events, a deep learning model incorporating eight years of longitudinal risk factor data outperformed the PCE in discrimination (AUROC 0.815 vs. 0.792) and calibration, with a net reclassification index of 0.385. Notably, model inputs mirrored routinely collected clinical variables, underscoring the practicality of longitudinal implementation within existing electronic health record infrastructures. These findings provide empirical support for cumulative lipid burden modeling and suggest that risk prediction frameworks incorporating serial LDL-C exposure may more accurately capture lifetime atherogenic risk—particularly in women, whose cardiovascular risk trajectories are poorly reflected by single-point assessments. As longitudinal data capture becomes increasingly ubiquitous, integration of cumulative lipid metrics into risk calculators represents a scalable strategy to refine prevention and personalize lipid-lowering interventions across the lifespan.

4. Conclusion

Lipid metabolism is a central determinant of CVD, with cumulative exposure to atherogenic lipoproteins—particularly LDL-C—emerging as a more informative predictor of atherosclerotic burden than isolated midlife measurements. Epidemiological, genetic, and Mendelian-randomization studies consistently demonstrate that lifelong lower LDL-C, whether through inherited variants or early pharmacologic intervention, confers substantial and durable reductions in CHD risk. Sex-specific differences in lipid profiles, driven primarily by hormonal modulation, contribute to divergent CVD trajectories: men experience earlier elevations in LDL-C and greater early-life risk, whereas premenopausal women benefit from estrogen-mediated cardioprotection, which diminishes after menopause.

Importantly, empirical evidence supports the clinical relevance of assessing cumulative lipid exposure rather than relying solely on point-in-time measurements. Longitudinal analyses from the Framingham Offspring Cohort demonstrate that duration of moderate hyperlipidemia in early adulthood predicts future coronary heart disease in a dose-dependent manner, independent of contemporaneous lipid levels and traditional risk factors (Navar-Boggan et al., 2015). Notably, the majority of individuals with prolonged hyperlipidemia in early life would not have qualified for statin therapy under conventional 10-year risk-based guidelines, highlighting systematic underestimation of lifetime risk. Such findings emphasize the limitations of cross-sectional risk assessment and provide direct outcome-based support for cumulative lipid burden models.



Advances in data availability and analytic methods further corroborate the feasibility of translating lifetime lipid assessment into clinical practice. Recent work integrating longitudinal risk factor trajectories into deep learning-based prediction models demonstrate improved discrimination and risk reclassification for ASCVD compared with traditional pooled cohort equations (Yu et al., 2023). Because these models rely on routinely collected clinical variables, including serial cholesterol measurements, they offer a scalable framework for incorporating cumulative lipid exposure into individualized risk prediction. Together, these studies suggest that longitudinal lipid assessment can meaningfully improve risk stratification, particularly in populations whose lifetime risk is inadequately captured by conventional approaches.

Therapeutic interventions, including statins, ezetimibe, PCSK9 inhibitors, HRT, and lipoprotein apheresis, effectively target both the magnitude and duration of LDL-C exposure. Evidence highlights the importance of early initiation—particularly in high-risk populations such as children with FH—to reduce cumulative lipid burden and subsequent atherosclerotic events (van den Bosch et al., 2024). Despite such advancements, underrepresentation of women in clinical trials and limited longitudinal lipid-aging data remain key gaps, highlighting the need for sex-specific strategies and lifelong management approaches.

Collectively, these findings suggest a paradigm shift in cardiovascular prevention toward lifelong lipid management, emphasizing cumulative exposure rather than isolated thresholds. Incorporating longitudinal lipid trajectories into risk assessment frameworks has the potential to refine preventive strategies and advance precision medicine approaches tailored to sex, age, and lifetime CVD risk.

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Author Biography

Hannah (Kireina) Park is a young researcher from Vancouver, Canada, with interdisciplinary interests spanning chemistry, neurophilosophy, and cardiovascular medicine. Her work is driven by a central question at the intersection of molecular biology and clinical disease: how dysregulated biochemical processes give rise to complex cardiovascular pathology. She is particularly interested in lipid metabolism, cumulative risk modeling, and sex-based disparities in cardiovascular disease outcomes; her prior work, "Heart of the Matter: Age, Sex, and Chest Pain as Predictors of Cardiovascular Disease," has been published in *Curieux Academic Journal*.

Hannah approaches medicine through a chemical lens, viewing disease as the consequence of molecular systems operating



out of equilibrium, and believes that in this framework chemistry is causality. She thus plans to pursue chemistry at the university level while preparing for a future career in cardiac surgery, with long-term goals in translational cardiovascular research and patient-centered clinical care.

Mentor Contribution Statement

Daniel Sanghoon Kim, PhD, served as a research mentor for this manuscript. His role was advisory in nature and focused on oversight, methodological guidance, and editorial review. Dr. Kim provided high-level feedback on the conceptual framing of the literature review, including the organization of thematic sections and the integration of cumulative lipid exposure frameworks within the broader cardiovascular disease literature. During manuscript development, Dr. Kim reviewed draft versions of the paper and offered suggestions aimed at improving clarity and coherence. These contributions included recommendations on paragraph structure and transitions between sections; he additionally provided guidance on the presentation of results and figures to ensure alignment with established conventions in biomedical literature.

Dr. Kim did not generate original text, conduct the literature search, extract data, perform analyses, or draft any sections of the manuscript. All substantive writing, synthesis, and interpretation of the literature were completed independently by the author.

