

YOU CAN'T TREAT WHAT YOU DON'T TEST:
IMPLEMENTATION OF LIPOPROTEIN(a) TESTING AND EVIDENCE-BASED
TREATMENT PLAN FOR MIDLIFE WOMEN IN A WELLNESS CLINIC

by

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A scholarly project submitted in partial fulfillment
of the requirements for the degree

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DEDICATION

For Carsen and Birdie—everything I do, I do reaching toward the women you will become. You are my reason for rising, my reason for returning, and the most meaningful work of my life.

To my husband, who gave me the gift of space to grow without ever letting me feel alone in it. Your love held us all steady.

And to my parents, who taught me what it means to believe in someone completely and without condition—I hope I have made you proud.

This work is proof that we can do hard things.

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ABSTRACT

Background: Lipoprotein(a) [Lp(a)] is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) when present in elevated levels (>50 mg/dL) and existing in 20-30% of the general population, yet fewer than 1% of U.S. adults have ever been screened. Lp(a) accelerates arterial plaque formation at six times the rate of a typical LDL particle and is 70–90% genetically determined, though hormonally modulated. Lp(a) demonstrates an inverse relationship with estrogen, such that supplementation after ovarian failure may lower concentrations by up to 30%—representing a relationship of particular relevance for midlife women, whose progressive estrogen decline eliminates endogenous arterial protection and accelerates ASCVD risk, particularly when baseline Lp(a) is already elevated. **Purpose:** This quality improvement project implemented standardized Lp(a) screening and individualized, evidence-based treatment planning in a wellness clinic primarily serving peri- and menopausal women receiving bioidentical hormone replacement therapy. **Methods:** Grounded in the Johns Hopkins Evidence-Based Practice Model and guided by iterative Plan-Do-Study-Act cycles, Lp(a) testing was integrated into the clinic's existing laboratory order set over eight weeks. Patients with Lp(a) >50 mg/dL received individualized education addressing diet, physical activity, supplementation, hormonal optimization, and self-advocacy for further risk stratification. **Results:** All 17 eligible patients were screened (100%; exceeding the 90% SMARTIE target) and all four patients with Lp(a) >50mg/dL received education (100%; meeting 100% SMARTIE target), plus one additional patient with a borderline elevation of 41.1mg/dL, consistent with the testing laboratory's flagging threshold of >30mg/dL. The sample was predominantly female (70.6%; M age = 44.6 years). Lp(a) was right-skewed (Mdn = 11.3 mg/dL; IQR: 8.3 – 41.1), with no statistically significant correlations observed between Lp(a) and other biomarkers, reinforcing the particle's independent metabolic pathway from other lipids. **Conclusion:** Routine Lp(a) screening is feasible and clinically meaningful in hormone management settings. A 23.5% prevalence among eligible patients (consistent with general population-level findings) underscores the urgency of universal screening and offers a replicable integration model.

Keywords: lipoprotein(a), Lp(a), *LPA*, cardiovascular risk, menopausal women, BHRT, ASCVD prevention

CHAPTER ONE

REVIEW OF THE LITERATURE

Introduction

Atherosclerotic cardiovascular disease (ASCVD) has been the leading cause of death in the United States (U.S.) for more than a century, claiming more lives than cancer and fatal accidents combined (Centers for Disease Control and Prevention, 2024). ASCVD is not a sudden event, but a progressive condition that takes foothold in a patient's vasculature silently over decades, long before patients and clinicians recognize symptoms (Mendieta et al., 2023). New research is increasingly suggesting earlier and tighter risk factor control, and some experts are proposing that the medical community should move away from the traditional 10-year risk stratification to a 30-year model (An et al., 2023; Ridker et al., 2024). While clinicians routinely assess standard lipid parameters, as well as providing education on modifiable risk factors, an important and genetically mediated risk factor, lipoprotein(a) [Lp(a)], is frequently overlooked (Laffin & Nissen, 2024). Lp(a) is a low-density lipoprotein (LDL)-like particle that has emerged as an established, causal, and genetically-determined risk factor for ASCVD, calcific aortic valvular stenosis (CAVD), ischemic stroke, and peripheral artery disease (PAD) (Bess et al., 2024). While most of the population has low or undetectable concentrations of Lp(a), up to 30% of the population has excessive Lp(a), as defined by >50 mg/dL or >125 nmol/L (Laffin & Nissen, 2024).

Synthesized in the liver, Lp(a) particles are approximately 70-90% genetically determined and only minimally influenced by standard lipid-modifying factors (Razavi et al., 2025). As a result, the American College of Cardiology (ACC) and the American Heart Association (AHA) recommend testing any individual with a family history of ASCVD or elevated Lp(a) or familial hypercholesteremia (FH) in their 2018 ACC/AHA guidelines (American Heart Association, 2023). However, and more in-line with the current science, the National Lipid Association (NLA), Canadian Cardiovascular Society's (CCS) and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommend testing every individual over the age of five once in their lifetime inside of steady states (Koschinsky et al., 2024; Mach et al., 2019; Pearson et al., 2021). This highlights a major lag-point and practice inconsistency within US practice as compared to the rest of the developed world. Regrettably, less than 1% of the total population in the U.S. has ever been tested for this once-in-a-lifetime lab value (Razavi et al., 2025), and still only around 4% of the U.S. population with established ASCVD have been tested (Shah et al., 2024), leaving much to be desired for primary prevention of this deadly lipoprotein. This gap represents a critical missed opportunity for both primary and secondary prevention of ASCVD and coronary artery disease (CAD) in the US.

Background and Significance

Structurally, an Lp(a) particle is similar to that of a conventional LDL particle, comprised of a lipid core and a single apolipoprotein(B) (ApoB) molecule; however, the central difference is that Lp(a) is covalently bound to the plasminogen-like protein, apolipoprotein(a) [Apo(a)], that attaches itself to the lipid via a single disulfide bridge (Telyuk et al., 2022). Apo(a) is highly polymorphic, containing large individual ranges of copies of Kringle IV (KIV) type 2 repeats,

which determines the size of the Lp(a) particles and contributes to their atherogenicity; the less KIV type 2 repeats, the smaller the isoform, the higher the serum concentration of Lp(a) a patient has (Laffin & Nissen, 2024). The KIV type 2 segments, termed for their famous Scandinavian pastry namesake, demonstrate an increased propensity to becoming lodged into the endothelium (Simantiris et al., 2023). Lp(a) promotes atherosclerosis and inflammation by direct arterial intima penetration by way of its unique structure, then by attracting macrophages to the site of adherence, smooth muscle propagation then takes hold, causing pro-inflammatory cytokine release, teed up by the oxidized phospholipids that the molecule carries; all of these events then lead to lipid deposition, calcification and gross endothelial dysfunction (Bess et al., 2024).

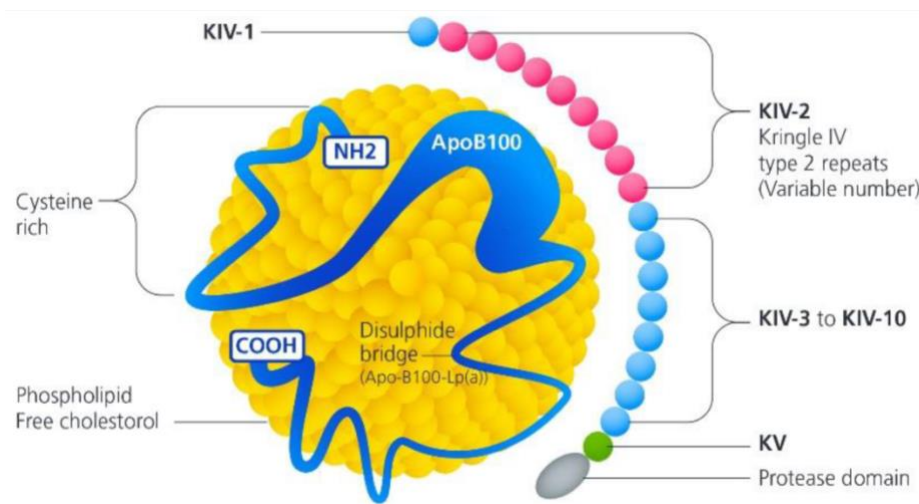


Figure 1: Structure of a Lp(a) particle. Adapted from Telyuk et al. (2022)

Studies have shown that elevated Lp(a) is associated a two to four-fold risk of CAVD, ASCVD, PAD and ischemic stroke within a person's lifetime as compared to someone with low Lp(a) (Clarke et al., 2009). The large variance in risk is largely explained by the number of the aforementioned KIV type 2 repeats within the Lp(a) particle, determining serum concentrations

ranging anywhere from undetectable levels to over >1000 mg/dL (Boffa & Koschinsky, 2024); this attribute contributes to the wide phenotypic variability within this genetic mutation.

Unfortunately, there are no targeted U.S. Food and Drug Administration (FDA)-approved medications to lower Lp(a), as is for other LDL particles such as statins. In fact, Lp(a) can rise in the presence of statin therapy (Bess et al., 2024); however, optimizing other modifiable risk factors such as: a favorable lipid profile, adhering to a nutritious diet, regular physical activity and hormone optimization, patients can mitigate the risks associated with Lp(a) thus lowering the risk of all-cause mortality (Bess et al., 2024). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the only class of medication that have been shown to reduce Lp(a) by up to 30%; unfortunately, many experts have not found this to be substantial enough to offset potential risk (Bess et al., 2024). Positively, according to the *EPIC-Norfolk* study, funded by the University of Cambridge, if a patient within the highest quartile of serum Lp(a) optimizes all other modifiable risk factors, they can reduce their risk by approximately 75%, which is far from negligible (Perrot et al., 2017).

In contrast, Lp(a) is an acute phase reactant, meaning its serum values are up-regulated or down-regulated in the presence of underlying pathologies (Dzobo et al., 2022). Chiefly, Lp(a) is highly responsive to inflammation and hormonal imbalance (Enkhmaa & Berglund 2022). Recent work by Kraaijenhof et al. (2025) demonstrate that concomitantly elevated high-sensitivity c-reactive protein (hs-CRP) in addition to elevated Lp(a) markedly increases the risk of ASCVD. This highlights the augmented risk of Lp(a) in the presence of existing endothelial inflammation. In alignment with these findings, the ACC has released guidance on testing hs-CRP in all patients due to its predictive factor for ASCVD and is now seen as on par, if not a

better indicator of heart disease than serum LDL cholesterol (ACC, 2025). However, having a low hs-CRP in the event of cooccurring high Lp(a) does not absolve a patient from risk (Ridker et al., 2024). Small et al. (2024) note that high Lp(a) was associated with increased cardiovascular risk regardless of hs-CRP. One point remains true: Lp(a) is a major, independent, causal risk factor and should be aggressively tested and treated.

Undertesting and Clinical Awareness Gaps

Statistics estimating the population presence of Lp(a) range anywhere from 20-30% (Kelsey et al., 2023; Laffin & Nissen, 2024) highlighting the gap in knowledge of how many patients this gene mutation affects. Kelsey et al. (2023) uncovered that across 11 health systems, only 0.06% of patients were screened for elevated Lp(a) levels, and the authors hypothesize that providers may not be testing for Lp(a) due lack of knowledge, lack of awareness of testing guidelines, and lack of confidence to interpret the results if they are aware of this lipoprotein. Although lipoprotein(a) was discovered in 1963 by the Norwegian physician Kare Berg (Boffa & Koschinsky, 2024), the medical community was unsure of the lipids true significance and cardiovascular impact until 2009, when the landmark mendelian randomization study written by Clarke et al. (2009) was published in the New England Journal of Medicine; the authors revealed that high Lp(a) was a highly influential marker for ASCVD. Lipoprotein(a)'s causal designation and conflicting testing guidelines compound the confusion in regard to standardized testing. For example, in Germany, where Lp(a) testing is encouraged to be performed on all patients at least once, their rates of testing hover at approximately 5%, and while still low, are roughly five times that of the U.S. (Kamstrup et al, 2024). To summarize, the significance of this problem lies within the opportunity to improve cardiovascular prevention, through widespread testing and

aggressive management of other risk factors, even in the absence of Lp(a)-lowering medications. By increasing Lp(a) testing in adults, we can better identify high-risk individuals and more accurately stratify their risk and tailor their care.

Current Treatment Criteria

Currently, there is no targeted pharmacological therapy for elevated Lp(a), making some clinicians hesitant to test for something they cannot directly treat (Bess et al., 2024). Presently, recommendations for reducing Lp(a) include modifying all other risk factors to optimize cardiovascular health including but not limited to: statin therapy, ezetimibe, PCSK9 inhibitors (when clinically indicated to lower overall ApoB burden), and diet and lifestyle optimization, in addition to performing coronary artery calcium scans in patients above 35 years old (American Heart Association, 2023). However, there are several targeted therapy trials that are now in phase 3, and will likely be available for secondary prevention (but not primary prevention) sometime in 2026 (Bess et al., 2024). According to mendelian randomization studies, for a medication to have a clinical benefit, meaning lower instances of adverse cardiac events, it would have to lower Lp(a) by 50mg/dl or 105 nmol/L to be effective (Kamstrup et al., 2024). Niacin, or vitamin B3, shows evidence that it lowers Lp(a) by 23%; however, despite these favorable biochemical changes, it failed to show efficacy in lowering morbidity and mortality for patients at risk of cardiovascular disease (Bess et al., 2024). The disconnect found between the biochemical lowering of Lp(a) and the absence of clinical benefit underscores the intricacy of residual cardiovascular risk and highlights the significance of understanding the mechanistic underpinnings of Lp(a)-mediated risk. This is particularly noteworthy in relation to physiological

factors, such as genetics, hormonal, and immunometabolic mediators that govern Lp(a) concentrations.

Hormonal Influence of Lp(a)

Interestingly, a number of studies have noted an intersection between hormonal status and Lp(a) regulation, suggesting that certain hormones have an inverse relationship with Lp(a). Bess et al. (2024) discuss how exogenous administration of androgens, estrogens and progestins modify Lp(a)—exogenous testosterone lowers Lp(a) around 20% in men, and hormone replacement therapy (HRT) with estradiol with or without progestins lower Lp(a) by 20-30% in women. These reductions in Lp(a) are consistent with the effects observed with the only currently available class of medications shown to lower Lp(a)—PCSK9 inhibitors. Additionally, menopausal women with elevated Lp(a) experience greater reductions in serum concentrations after HRT, compared to those with lower initial levels, highlighting the intrinsic hormonal regulation of Lp(a) (Gregersen et al., 2019; Nudy et al., 2025; Suk Danik et al., 2008; Taskinen et al., 1999). Concentrations of Lp(a) are, on average, 17% higher in women than in men after the age of 50, which corresponds with the onset of menopause. According to Nordestgaard & Langsted (2024), women who have Lp(a) measured prior to menopause should have it reassessed approximately five years after turning 50. Aljawini et al. (2023) found that Lp(a) has an average increase by 0.41 units for every year of age in postmenopausal women, further confirming the presumed hormonal reactivity of Lp(a) throughout the lifespan. Additionally, at the level of the menstrual cycle, Ricci et al. (2001) demonstrated that Lp(a) concentrations fluctuate across menstruation and decline further during ovarian stimulation with recombinant FSH, providing early evidence that even short-term shifts in estrogenic tone modulate Lp(a) expression.

Beyond sex hormones, thyroid function has also been shown to influence Lp(a) concentrations. Thyroid hormones are known to influence serum lipid concentrations by the key enzyme regulation involved in lipid metabolism (Lwin et al., 2024). Both hyper and hypothyroidism are associated with up or downregulation of Lp(a), respectively (Lwin et al., 2024). Interestingly, several studies have outlined the connection of hypothyroidism and excess Lp(a) (Yetkin et al., 2015; Lwin et al., 2024; Zhong et al., 2025) and that treatment with thyroid replacement consistently decreases serum Lp(a). This relationship is thought to reflect thyroid hormone-mediated regulation of hepatic apolipoprotein synthesis and LDL receptor activity, emphasizing the broader impact of endocrine imbalance on cardiovascular risk (Zhong et al., 2025). Furthermore, patient's with autoimmune thyroiditis (Hashimoto's) have been found to have the most consistently high Lp(a) concentrations, even in a euthyroid state (Yetkin et al., 2015), possibly also pointing to autoinflammatory mediators of Lp(a).

Although hormonal interventions can produce measurable reductions in Lp(a), it is important to reiterate that approximately 70-90% of serum concentrations are genetically-determined (Razavi et al., 2025). Hormonal modulation may therefore influence phenotypic expression of Lp(a), but cannot fully overcome inherited predisposition. Proposed mechanisms include hormone-mediated changes in hepatic synthesis of apolipoprotein(a), alterations in catabolic rates of Lp(a), and modulation of inflammatory signaling pathways that indirectly affect Lp(a) production (Dzobo et al., 2022; Zhong et al., 2025). Additionally, transient elevations in Lp(a) have been reported during periods of significant hormonal fluctuation—such as pregnancy, perimenopause, hypogonadism and untreated autoimmune thyroiditis—suggesting

that physiologic shifts in endocrine function can alter Lp(a) expression (Enkhmaa & Berglund 2022).

Physiologically, the incidence of adverse ASCVD events occurs, on average, 10 years later in women than it does in men and myocardial infarction (MI) and sudden cardiac death by 20 years (Hodis & Mack, 2022). This shift in timelines appears to be correlated to the loss of endogenous hormones, namely estrogen and progesterone, which are cardioprotective by way of reducing oxidative stress, improving vasodilation and supporting broad endothelial protection (Hodis & Mack, 2022). Corral et al. (2025) highlight that from menarche, and during the reproductive age—sans pregnancy—Lp(a) remains stable until perimenopause. The trajectory of ovarian failure follows a predictable pattern: progesterone is the earliest hormone to decline in perimenopause, while estradiol diminishes more substantially when the ovaries near complete failure. With the onset of menopause, and the resulting hypo-hormonal state, this represents a profound and well-documented, reduction in endothelial protection, and overall ASCVD risk surges (Hall, 2015). As illustrated in Figure 2, the decline in estrogen during the menopausal transition precipitates a cascade of interconnected cardiovascular risk factors, including rising Lp(a), hyperlipidemia, hypertension, and accelerated coronary artery calcification (D'Costa et al., 2025). This highlights the important window for exogenous hormone replacement in women nearing or at menopause from the approach of maintaining cardiovascular health.

Collectively, these findings underscore the influence of hormonal status on Lp(a) regulation and highlight the need for systematic screening for all patients, but especially those who are at high-risk, have autoimmune thyroiditis or menopausal women undergoing hormonal replacement therapy (HRT). Contemporary literature evaluating the longitudinal effects of HRT

on Lp(a) remains limited, characterizing an important gap in the current clinical knowledge and a compelling opportunity for further analysis.

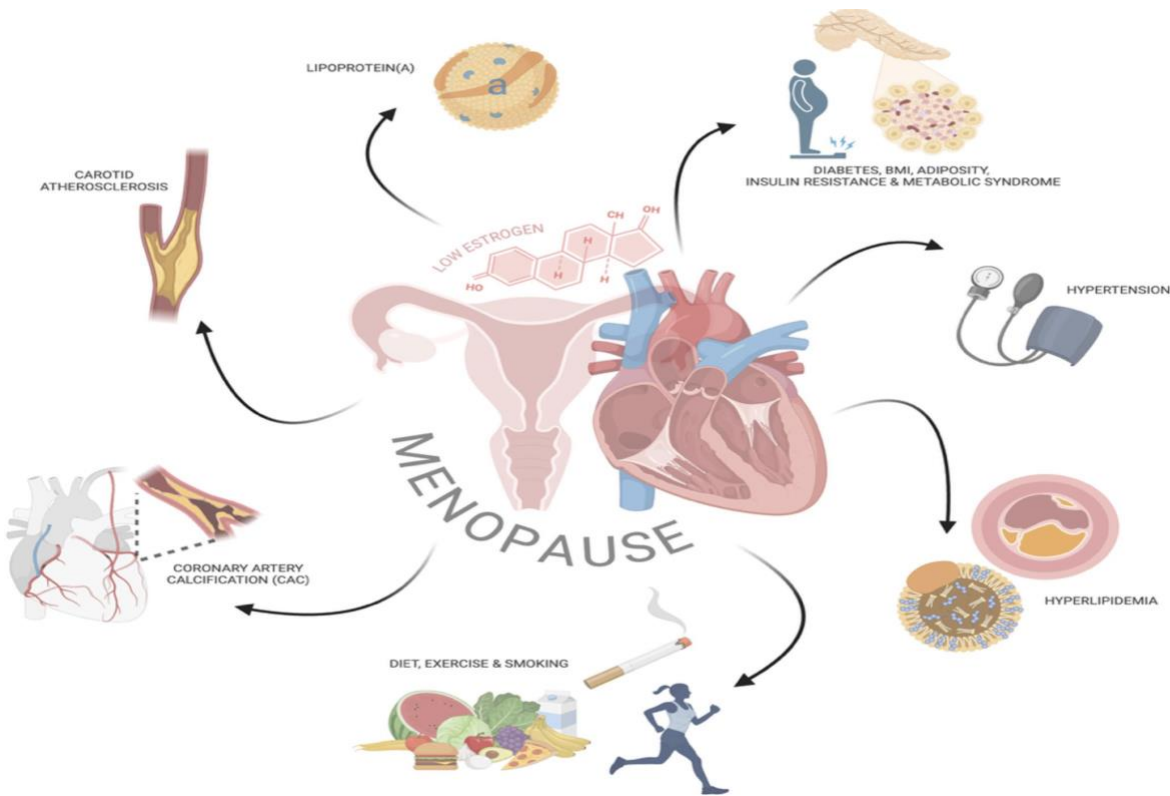


Figure 2. Cardiovascular risk factors associated with the menopausal transition, including Lp(a) elevation, hyperlipidemia, hypertension, insulin resistance, coronary artery calcification, and carotid atherosclerosis, mediated by declining estrogen. Adapted from D'Costa et al. (2025)

Methods

Overview of Selected Studies

The formal search strategy outlined below was preceded by an extended period of literature appraisal conducted over several weeks during which the author participated in broad reading across the Lp(a), hormonal modulation and cardiovascular prevention literature to refine the clinical question for this scoping review. In September of 2025, this scoping review appraised

evidence-based and peer reviewed literature, focusing on the endocrine-lipid interface of thyroid and sex hormones on Lipoprotein(a). Articles from 1996-2025 are included (articles over six years old are used for foundational purposes) and were located through PubMed, Web of Science, the Montana State University Library database, and Google Scholar. The Polit-Beck Hierarchy of Evidence was used to evaluate literature quality. The initial search yielded 6,909 articles that were then narrowed to 100 through scholarly discernment and project focus, these studies were then appraised using the inclusion criteria through article assessment.

Approximately 85 studies were omitted due misalignment with inclusion criteria. Fifteen articles were included in this scoping review of the evidence: three systematic review and meta-analyses, two quasi-experimental (non-randomized interventional), and ten observational studies. 11 of 15 studies were published in the last six years, and the four older studies remained for foundational mechanistic purposes.

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram was utilized for study extraction (Appendix A). Search ranges initially ranged from 1996 - 2025, but after foundational studies were identified, so as not to exclude the significant *Women's Health Initiative* (WHI) or *Women's Health Study* (WHS), search criteria only included 2015-2025. Keywords included: Lipoprotein(a) OR "Lp(a)"; Thyroid OR "Hashimoto*"; hormon* NOT "growth" NOT "GH"; hormone replacement therapy OR "HRT"; NOT dementia. The American College of Cardiology and American Heart Association were also used for data collection.

Eligibility

Inclusion criteria incorporated studies published in English with any person over the age of 5 (when Lp(a) reaches baseline serum levels), examining Lp(a) through the lifespan, and its relationship to hormones—specifically thyroid and sex hormones. In addition, precedent was given to studies mentioning menopause, HRT, bioidentical hormone replacement therapy (BHRT), or thyroid replacement. After foundational studies, the search narrowed to after 2015, and those published after 2020 were given the most favor. Exclusion criteria included any studies that mentioned growth hormones (GH), dementia, and studies done in the setting of genetic abnormalities.

Quality Assessment

To ensure quality assessment of the 15 articles included in this scoping review, the following information was isolated and evaluated: conceptual framework, design/method, sample/setting, major variables, measurement, data analysis, findings and strength of evidence. The quality of the compiled evidence for this review is as follows: three systematic reviews and meta analyses (Level I), two quasi-experimental, non-randomized controlled intervention (Level III), and ten observational studies (cohort or cross-sectional) (Level IV). The levels of evidence are based on the Polit & Beck (2022) hierarchy of evidence.

Results

Literature Search and Characteristics

This scoping review explored the hormonal and endocrine influence on Lp(a) levels and their associated cardiovascular risk implications in adults; the review process is outlined in

Appendix A. Fifteen peer-reviewed studies were included in this synthesis, representing a mixture of cross-sectional, cohort, quasi-experimental, and systematic review designs (Aljawini et al., 2023; Anagnostis et al., 2017; Chang et al., 2022; Freaney et al., 2021; Honigberg et al., 2022; Liao et al., 2024; Lwin et al., 2024; Nie et al., 2022; Razavi et al., 2025; Ricci et al., 2001; Simony et al., 2022; Suk Danik et al., 2008; Taskinen et al., 1996; Yurtseven et al., 2024; Zhong et al., 2025). Sample sizes across studies varied widely—from small studies with 120 participants (Taskinen et al., 1996), to large population-based cohorts exceeding 20,000 participants (Simony et al., 2022; Razavi et al., 2025).

The included studies collectively represented a broad geographic scope, spanning populations in North America, Europe, the Middle East, and Asia. Six of the studies were conducted in postmenopausal women (Aljawini et al., 2023; Anagnostis et al., 2017; Honigberg et al., 2022; Liao et al., 2024; Nie et al., 2022; Suk Danik et al., 2008), while four focused on mixed-sex adult samples (Chang et al., 2022; Simony et al., 2022; Yurtseven et al., 2024; Zhong et al., 2025) and one assessed premature menopause as an independent cardiovascular risk enhancer in women aged 40-65 (Freaney et al., 2021). One study examined hormone-driven physiologic or interventional effects (Taskinen et al., 1996), and one article focused on the prevalence of Lp(a) testing within a large diverse U.S. population, revealing persistent under-screening (Razavi et al., 2025). One study examined Lp(a) fluctuations across the natural menstrual cycle and during ovarian stimulation in reproductive-age women (Ricci et al., 2001), and one assessed the effect of thyroid dysfunction on Lp(a) concentrations in mixed-sex adults (Lwin et al., 2024).

Study designs varied across levels of evidence, with three systematic reviews or meta-analyses (Anagnostis et al., 2017; Liao et al., 2024; Nie et al., 2022), two quasi-experimental trials (Ricci et al., 2001; Taskinen et al., 1996), and ten cohort studies (Aljawini et al., 2023; Chang et al., 2022; Freaney et al., 2021; Honigberg et al., 2022; Lwin et al., 2024; Razavi et al., 2025; Simony et al., 2022; Suk Danik et al., 2008; Yurtseven et al., 2024; Zhong et al., 2025). Participant demographics included predominantly middle-aged to older adults, with mean ages ranging from 45 to 68 years in most studies. Female representation was substantial, with 12 of the 15 studies exclusively or primarily composed of women, and 11 of those focused on peri- or postmenopausal populations.

Synthesis of the Literature

Hormonal correlations with Lp(a) Across three decades of work, the literature supports a meaningful relationship between endocrine behavior and circulating Lp(a). Early interventional and cohort studies that showed estrogenic states tend to lower Lp(a), whereas menopause is associated with higher Lp(a) concentrations (Aljawini et al., 2023; Anagnostis et al., 2017; Freaney et al., 2021; Honigberg et al., 2022; Liao et al., 2024; Suk Danik et al., 2008). In postmenopausal women, both transdermal estradiol and oral estrogen-progestin reduced Lp(a) (Taskinen et al., 1996). In the foundational *Women's Health Study (WHS)*, Suk Danik et al. (2008), reported that HRT was associated with a reduced risk of ASCVD among women receiving therapy compared to non-users. In contrast, Honigberg et al. (2022) found that HRT did not have an impact on elevated Lp(a)-associated risk, although the study did show lower Lp(a) values for HRT users than non-users; the authors hypothesize that before, HRT was a marker of

health-seeking behavior, and that it has largely fallen out of favor in regular primary care, leading to women who only experience severe vasomotor symptoms seek HRT treatment.

Empirically, we know that Lp(a) increases in the postmenopausal phase for women (Aljawini et al., 2023; Anagnostis et al., 2017; Freaney et al., 2021; Honigberg et al., 2022; Liao et al., 2024; Suk Danik et al., 2008) and we also know that ASCVD risk significantly increases at the same time (Bess et al., 2024), making it logical to extrapolate that the two may be interconnected. Furthermore, large cohorts demonstrate sex and age-dependent gradients in Lp(a)-related morbidity and mortality (Simony et al., 2022), prompting some discussion for sex-specific thresholds (Yurtseven et al., 2024).

Importantly, the estrogen-Lp(a) signal is not limited to classic hormone replacement therapy. Liao et al. (2024) synthesized randomized trials of Raloxifene—a selective estrogen receptor modulator (SERM)—and found a statistically significant reduction in Lp(a) alongside other favorable lipoprotein shifts. This extends the estrogenic pattern beyond replacement therapy to selective receptor modulation, suggesting that hepatic or vascular estrogen-receptor signaling may contribute to Lp(a) regulation.

Beyond gonadal hormones, the thyroid axis also matters: a systematic review indicates that restoring euthyroidism generally lowers Lp(a) (Lwin et al., 2024). Zhong et al. (2025) highlight the relationship between type II diabetes and the reduction of thyroid hormone sensitivity that correlates with higher Lp(a) despite “normal” lab values. Together, these findings frame Lp(a) as responsive—within limits—to a broader hormonal and metabolic context.

Ultimately, contemporary studies underscore that while HRT can modify the Lp(a)-ASCVD relationship, the magnitude of effect varies across therapy type and baseline risk

(Honigberg et al., 2022). Collectively, the evidence supports multihormonal influence on Lp(a) (estrogenic states, SERMs, and thyroid signaling) with consistent biochemical effects (Liao et al., 2024; Lwin et al., 2024; Nie et al., 2022; Ricci et al., 2001; Suk Danik et al., 2008; Zhong et al., 2025). These nuances strengthen the case for individualized risk assessment, particularly in HRT settings, with consideration to menopausal status and thyroid health, may together refine cardiovascular risk management.

Interventions and Management Strategies Interventions aimed at modulating hormone status have demonstrated modest but consistent effects on Lp(a). Meta-analyses by Anagnostis et al. (2017), Nie et al. (2022) and Liao et al. (2024) confirmed that estrogen-based HRT, tibolone and Raloxifene, significantly lower Lp(a) concentrations across multiple trials. Taskinen et al. (1996) also observed that both cyclic transdermal and continuous estrogen–progestin regimens reduced Lp(a) levels. These findings are further supported by Ricci et al. (2001), whose observation of Lp(a) fluctuations across the menstrual cycle provides additional evidence that short-term estrogenic variation modulates Lp(a) expression. Current management therefore emphasizes lifestyle optimization, control of other lipid fractions (e.g., ApoB, LDL-C), and emerging Lp(a)-targeted therapies now in phase 3 development (Bess et al., 2024).

Emerging Therapies and Future Directions Novel therapeutic strategies targeting Lp(a) synthesis are currently in late-stage clinical development. Antisense oligonucleotides (pelacarsen) and small interfering RNA agents (olpasiran, zerlasiran) have demonstrated reductions in Lp(a) of up to 80–90% in phase 2 trials (Bess et al., 2024). Kamstrup et al. (2024) emphasize that future research should focus on harmonizing assay methods, defining risk thresholds by sex and ethnicity, and determining whether pharmacologic Lp(a)-lowering

translates into improved cardiovascular outcomes. Current guidelines from the AHA and ACC (2023) note that these agents may become available for secondary prevention by 2026. This emerging therapeutic landscape adds weight to the need for proactive screening and patient identification now, before widespread implementation.

Discussion and Conclusion

The body of evidence demonstrates that hormonal status plays a substantial role in modulating lipoprotein(a) concentrations, thereby influencing atherosclerotic cardiovascular disease (ASCVD) risk. Across decades of investigation, the relationship between sex hormones, thyroid hormones, and Lp(a) has emerged as both biologically plausible and clinically significant. Collectively, the data show that hormone replacement therapy and other estrogenic states consistently lower Lp(a) by approximately 20–30% (Taskinen et al., 1996; Suk Danik et al., 2008; Nie et al., 2022; Anagnostis et al., 2017). Conversely, menopause, thyroid dysfunction, and advancing age are associated with Lp(a) elevation and a corresponding rise in cardiovascular risk (Aljawini et al., 2023; Lwin et al., 2024; Zhong et al., 2025).

Despite these hormonal influences, approximately 70–90% of an individual's Lp(a) level remains genetically determined (Razavi et al., 2025). Therefore, hormone therapy may modulate risk phenotype but cannot override inherited predisposition. It is important to recognize that there is a notable difference in Lp(a) lowering and translation to clinical benefit, as in the case with Niacin (Bess et al., 2024) and in the debatable findings of Honigberg et al. (2022). Nonetheless, until there are targeted therapies to lower both—it's imperative that all other risk factors be optimized, such as in the case with documented cardiovascular-protective hormone replacement therapy when appropriate. Current clinical guidelines acknowledge Lp(a) as a causal risk factor,

yet remain inconsistent on universal testing, resulting in under-identification of high-risk individuals—particularly women in the perimenopausal and postmenopausal years, when Lp(a) concentrations rise. This represents a missed opportunity for targeted cardiovascular risk mitigation within hormone replacement therapy practices.

CHAPTER TWO

QUALITY IMPROVEMENT PROPOSAL

Introduction

Lipoprotein(a) [Lp(a)] is an established, causal, and genetically inherited risk factor for ASCVD. When high levels are present in the blood, categorized by $>50\text{mg/dL}$ or $>125\text{nmol/L}$, it yields a two to four-fold increase of disease-causing atherosclerosis than that of a typical LDL particle, with a positive association seen between risk and serum levels in a step-wise fashion (Boffa & Koschinsky, 2024; Clarke et al., 2009). Although Lp(a) was discovered over 60 years ago, it was only recognized as a causal risk-factor in 2009 through landmark Mendelian randomization studies (Clarke et al., 2009). Despite this, recommendations for testing remain inconsistent across professional societies. For example, the American College of Cardiology (ACC) and American Heart Association (AHA) recommend testing in high-risk individuals, while the National Lipid Association (NLA), European Atherosclerosis Society (EAS) and the Canadian Cardiovascular Society (CCS) recommend testing at least once in a person's life (Mach et al., 2019; Wilson et al., 2019). Partially due to these discrepancies, testing for Lp(a) in the United States continues to be exceedingly low, with $<1\%$ of the population being tested despite high levels of Lp(a) being present in up to 30% of the general population (Razavi et al., 2025; Shah et al., 2024). While there is no data on Lp(a) testing specific to Montana, the testing rate of Lp(a) at the proposed project site, a wellness clinic primarily serving peri- and menopausal women, is also $<1\%$ (Posada, personal communication, August 26, 2025).

Synthesized in the liver, Lp(a) is largely untouched by traditional modifiable risk factors due to serum levels being dominated (70-90%) by genetics (Bess et al., 2024). Traditional lifestyle modifiers such as optimal diet, physical activity, and traditional lipid-modulating medications, such as statin therapy remain largely ineffective at lessening Lp(a) (Bess et al., 2024). While there are several novel treatments on the horizon, such as RNA-based therapies, there is no FDA-approved medication that lowers high levels of this highly atherogenic particle (Boffa & Koschinsky, 2024). Even still, these therapies will likely not be available for primary prevention at first introduction.

Beyond genetics, evidence highlights that hormonal status, systemic inflammation, and diet (to an extent) can assist in modulating serum Lp(a) levels (Honigberg et al., 2022; Lwin et al., 2024) and the implementation of an overall ideal modifiable cardiovascular risk profile can reduce the overall risk of all-cause mortality up to 75% in individuals with high Lp(a) concentrations (Kraaijenhof et al., 2025). These factors are particularly relevant to women's cardiovascular health, as Lp(a) concentrations rise substantially after menopause—paralleling the loss of estrogen's vasoprotective and lipid-modulating effects—at the same time that cardiovascular morbidity and mortality accelerate (Bess et al., 2024; Hodis & Mack, 2022; Suk Danik et al., 2008). In fact, cumulative data across RCT's and meta-analyses over decades of research reinforce the statistical significance of statin therapy lowering all-cause mortality in men, but not in women for primary CHD prevention, highlighting importance sex differences in therapy (Hodis & Mack, 2022). Therefore, the menopausal transition represents a critical convergence point where both hormonal decline and Lp(a) elevation amplify cardiovascular risk—a pattern often overlooked in traditional medical models.

Cumulatively, lack of testing for Lp(a), coupled with limited therapeutic options and insufficient understanding of non-genetic modifiers, such as inflammation, hormones and diet, underscore the importance of tailoring care for this patient subset, which represents nearly one third of the global population, but especially for menopausal women whom are already experiencing increase ASCVD risk. Identifying and addressing this largely overlooked risk factor, particularly in the setting of hormonal medicine, signifies a distinct opportunity for advancing care and improving outcomes for this at-risk population.

Problem and Aim Statement

This Doctorate of Nursing Practice (DNP) quality improvement (QI) project problem is a lack of standardized, routine screening for Lp(a) both in the primary care and within specialty settings. This practice gap is particularly relevant in a wellness clinic that primarily serves peri- and menopausal women due to the heightened cardiovascular risk that is parallel to menopause and female aging. Unfortunately, most patients and practitioners lack structured treatment plans for individuals with elevated Lp(a) due to limited clinical guidance and absence of specific Lp(a)-lowering medications.

The aim of this project is to implement a tailored treatment plan for patients with elevated serum Lp(a) (>50mg/dL) that emphasizes reducing aggregate cardiovascular risk through targeted anti-inflammatory dietary choices, guidance on structured physical activity, evidence-based supplementation, and hormonal optimization through exogenous therapy when appropriate. Additionally, this projects aims to equip patients with the knowledge of self-advocacy tools to pursue further risk stratification with their primary care providers (PCPs) or any collaborative practitioners for themselves and their family members.

Context

As previously mentioned, less than 1% of the population in the U.S. is tested for serum Lp(a) levels (Razavi et al., 2025) and only 4% of those with established ASCVD are tested (Shah et al., 2024). According to the NLA, every person should be tested for high levels of this established, causal risk factor (Koschinsky et al., 2024). Additionally, women of peri- and menopausal age are especially vulnerable to adverse cardiovascular events due to the rapid and significant loss of vaso-protective estrogen and progesterone with a co-occurring rise in Lp(a), underlining the risk of elevated baseline Lp(a) lying largely dormant until exposed by the hormonal shifts characteristic of mid-life (Hodis & Mack, 2022). Discussions with the site representative (primary stakeholder) yielded effective conversations on the importance of ASCVD prevention within this population and the hormonal modulators at play together with the importance of timing within the administration of exogenous hormones (Hodis & Mack, 2022). It was agreed by both parties that Lp(a) testing is an important biomarker for ASCVD risk stratification and thus serum levels will be collected with each set of baseline labs for the purposes of this project, and a tailored treatment plan will be implemented for patients with elevated serum Lp(a).

This quality improvement project will take place in a high plains medical aesthetic and wellness clinic in a metropolitan area. Primarily, the clinic as a whole focuses on skin health, aesthetics, and wellness, with the latter arm of the clinic being the center for this quality improvement project. The patient profile of this clinic primarily consists of female adults in midlife.

Stakeholders for this project include:

- Clinic owner/medical director/nurse practitioner (NP)/site representative: operates the clinic, and whom serves as both the clinical lead and organizational decision-maker in this project. Their role is essential for authorizing practice changes, integrating new screening tools into the current workflow and ensuring alignment with the clinic's mission of preventative, safe, and patient-centered care.
- Patients (pre, peri, and menopausal women): direct beneficiaries of the project who will receive screening, education and individualized treatment plans.
- Collaborating providers: with the permission of the patient, PCPs (if the patient is established with one) will become essential for patients with extremely high Lp(a) ($>100\text{mg/dL}$). Patients will receive tailored education and resources to help them engage in informed conversations with their PCP's regarding advanced cardiovascular risk assessment options, such as coronary artery calcium scans (CAC) and genetic testing, where appropriate.

Quality Improvement Framework

The Johns Hopkins Evidence-Based Practice Model (JH-EBP) serves as the conceptual framework for the development, implementation and execution for the planned practice change with the addition of the Plan, Do, Study Act (PDSA) cycle to expand the evidence to implementation. JH-EBP theoretical model was selected because it provides a structured, systematic process for translating evidence into clinical practice, emphasizing interdisciplinary collaboration, stakeholder engagement and patient-centered care (Dang & Dearholt, 2018).

Within the JH-EBP model, there lies three phases: practice question, evidence, and translation (PET), which work together to ensure the clinical initiatives are clinically relevant, evidence informed and implementable in real-world settings (Dang & Dearholt, 2018).

- Practice Question: The identified problem is a lack of standardized Lp(a) screening and intervention for peri- and postmenopausal women receiving BHRT in a wellness clinic. The primary stakeholder (owner and NP of the practice site), validated the relevance of implementing a standardized screening protocol and structured education strategy.
- Evidence: The previous synthesis of the literature and national guidelines from the NLA support a once-in-a-lifetime testing of Lp(a) and cardiovascular risk mitigation strategies in those with elevated levels. This evidence informed the tailored intervention plan that includes screening, individualized education and support for guidance for shared decision-making with primary care providers.
- Translation: The intervention will be implemented and evaluated through structured workflows, brief patient education sessions, and documentation processes. Outcome tracking will evaluate screening rates, patient engagement and workflow adherence. To enhance implementation fidelity, the Plan-Do-Study-Act (PDSA) model will be embedded into the implementation portion of the QI project during the 8-week timeframe to refine education delivery and optimize workflow efficiency.

Plan-Do-Study-Act Process

(P)lan: The primary stakeholder agreed that Lp(a) is a critical biomarker that should be integrated into wellness assessments for all patients, but especially for peri- and menopausal women. Prior to project launch, Lp(a) was added to all baseline labs. The DNP student developed

patient-facing educational materials and an evidence-based management plan that includes diet, physical activity, supplement, hormonal roles and self-advocacy strategies.

(D)o: Upon Institutional Review Board (IRB) approval, either the site representative or the DNP student will deliver a brief (15 minute) patient education to follow up on laboratory results, should the patient's Lp(a) level come back elevated in collaboration with the NP. Patients will receive educational handouts, including recommendations for engaging their PCP about further cardiovascular risk stratification options such as coronary artery calcium scans (CAC) or genetic testing, where appropriate. Furthermore, all patients will be offered the choice to opt-out of their unidentifiable data being used for this QI project.

(S)tudy: The DNP student will gather feedback on workflow clarity, time burden, and patient response. If SMARTIE goals are not met, the student will investigate and adjust the QI project as necessary.

(A)ct: Based on these findings, the DNP student and stakeholder will adjust the education and documentation workflow for the second cycle to improve adherence and consistency. Any modifications will be documented and approved by the NP stakeholder and potentially MSU's IRB.

The above implementations and outcomes are expected to be successful based on the literature and national guidelines. The proposed intervention presents a minimal time burden, as it integrates seamlessly into the current workflow and presents a low budget-to-benefit ratio incurred by the patient with their baseline lab findings. The proposed implementation for this project is meant to have the lowest possible barrier to ensure the highest fidelity. The DNP student will implement and synthesize findings, saving the stakeholders time throughout this

project. Following the 8-week implementation, Lp(a) testing with baseline labs will continue, and educational materials will remain in the clinic library. As a long-term goal, Lp(a) labs will be incorporated into the patients one-year follow up testing to support long-term goals and longitudinal change to support individualized cardiovascular risk management. This sustainability plan ensures that the implementation does not solely rely on the DNP student for practice change, but that it becomes seamlessly embedded into the clinic's workflow.

Methods

Implementation Summary

Over an eight week timeframe, this quality improvement project aims to screen 90% of peri- and menopausal patients receiving BHRT at a wellness clinic for Lp(a), ideally prior to the start of their hormone replacement/lifestyle regimen. Project interventions include screening all patients whom are having baseline or yearly labs drawn, with particular attention to Lp(a) in women (who have never been screened) with baseline labs. Patients who have elevated Lp(a) (>50mg/dL) will receive specialized diet, movement, supplement, and hormonal education as they relate to mitigating residual cardiovascular risk associated with elevated Lp(a). Additionally, high-risk clients will receive support and advocacy guidance regarding this elevated lab in a good-faith effort to bridge the gap between their PCP, who may not have much knowledge of this test and its implications to the patient's overall wellbeing. Two PDSA cycles will be completed throughout the 8-week QI implementation period with a minimum of one more cycle during the follow-up 12-month period leading up to the one year Lp(a) recheck.

Intervention & Implementation

Stakeholders and this author prioritized screening peri- and menopausal women at the clinic due to the compounded risk of developing ASCVD in the menopausal transition period. The medical literature published surrounding Lp(a) testing and peri- and menopausal hormonal modulation strongly supports the compounding risk mitigation of ASCVD and aggressive modifiable risk factor implementation (Aljawini et al., 2023; Anagnostis et al., 2017; Bess et al., 2024; Boffa et al., 2024; Chang et al., 2022; Corral et al., 2024; Driesenga et al., 2025; Enkhmaa et al., 2022; Hodis & Mack, 2022; Honigberg et al., 2022; Liao et al., 2024; Nie et al., 2022; Nudy et al., 2025; Simony et al., 2022). This screening process aligns with the NLA's recommendation for Lp(a) testing and will attempt to delineate a specific risk-mitigation lifestyle plan and appropriate hormonal modulation for this population in lieu of a targeted medication. Specifically, this plan will involve Lp(a) screening for all patients with baseline labs, and for patients with elevated levels, they will receive specific education on Lp(a) along with diet, exercise, supplement, self-advocacy and hormonal modulation strategies.

Timeline and Budget

This project will take place between January and February 2026 (see Figure 3). The budget is minimal for the stakeholder clinic, as it will involve printing packets for an estimated 20-30% of patients with elevated Lp(a), consistent with general population estimates (Laffin & Nissen, 2024). The project coordinator (PC) will be donating an estimated 270 hours to this QI project, saving the clinic approximately \$8,100 with a conservative hourly wage of \$30/hr. The Lp(a) test itself cost approximately \$40, representing a modest expense given its potential to inform lifelong cardiovascular risk prevention strategies.

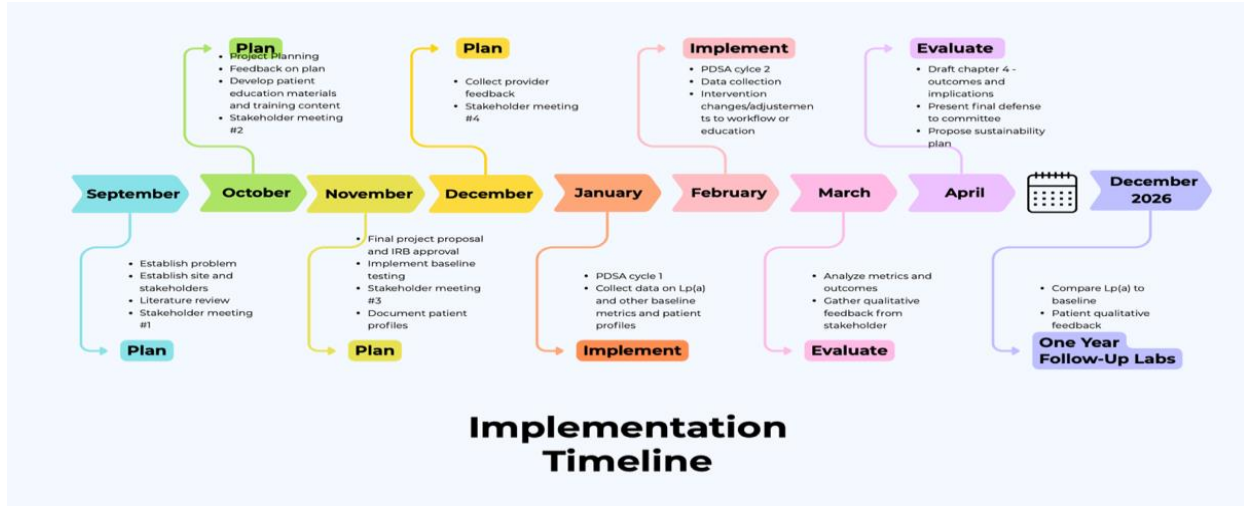


Figure 3. Implementation Timeline

Workflow

The clinic's existing workflow will be minimally altered for the purpose of this QI project. A sign will be placed in the exam room explaining that participation is voluntary (Appendix B). Additionally, screening for Lp(a) will be built into the structured order sets for BHRT patients, making testing automatic once a full panel of baseline or yearly labs is ordered. Furthermore, education for patients with elevated Lp(a) will be presented to them at their lab "Findings" follow-up appointment at the end of the appointment so as to not disturb the NP's current education workflow, or whenever is most convenient for the NP. An estimated 15 minutes will be planned for education with hope that with practice and streamlining this information, may soon be cut down to approximately 5-7 minutes. See Appendix C for education information that will be presented to the patient in the event of an elevated Lp(a) lab finding.

Challenges

Challenges that are expected with this project include the QI timeline and length for data collection, eight weeks is a short timeframe and this project will take place over/close to the holiday season, which can make data collection difficult logistically. Additionally, some patients seen in this integrative clinic express heightened caution regarding how their personal health information is used and shared. Early in the planning process, the primary stakeholder noted that a portion of the clinic's population has concerns about government access to medical data. Within an integrative care setting, where patients may seek alternatives to traditional allopathic medicine, these privacy sensitivities may be more prevalent and warrant intentional reassurance and transparent communication throughout the project

The third anticipated issue is lack of patients with high Lp(a). Although it has been well established that 20-30% of the general population has elevated Lp(a), it is more common in African American, and South Asian populations than it is in those of Caucasian descent (Bess et al., 2024), which reflects the majority demographic makeup of this clinic's patient population.

Evaluation and Analysis

The evaluation and analysis process for this QI project will be directly aligned with the projects SMARTIE goals and overall aim of improving cardiovascular risk identification, education, and risk mitigation. The structured goals will guide the outcomes of the interventions. Data will be collected via the clinic's EHR and the PC will conduct bi-weekly data audits during the implementation phases in January and February.

Quantitative data, including Lp(a) serum levels, testing rates, patient education completion, and one-year follow-up Lp(a) data will be evaluated using descriptive and inferential

statistics. Chi-squared analyses will be used to assess pre- and post-implementation completion rates, while paired sample t-tests will be utilized to evaluate laboratory markers before and after the implementations, relevant only to the long-term SMARTIE goal. Qualitative data provided from both provider and patient feedback will be organized thematically based on value metrics such as knowledge, advocacy and engagement. Findings from each SMARTIE goal will inform ongoing process improvements and guide future recommendations.

Table 1. SMARTIE Goal #1 (Short-term)

SMARTIE Goal #1		
90% of peri- and menopausal women receiving care at the clinic will complete Lp(a) testing by February 15 th 2026		
Data to be Collected	Collection Process	Planned Data Analysis
<ul style="list-style-type: none"> - Number of eligible peri- and postmenopausal BHRT patients seen during the implementation period (denominator). - Number of those who completed Lp(a) testing (numerator). - Provider completion rate (%) of ordered and resulted labs. 	<ul style="list-style-type: none"> - Data will be extracted biweekly from the electronic health record (EHR) by the project lead. - Lab completion status will be recorded in an Excel with no patient identifiers - The DNP student will verify completeness monthly and reconcile discrepancies. 	<ul style="list-style-type: none"> - Calculate percentage of eligible patients tested (numerator/denominator ×100).

Table 2. SMARTIE Goal #2 (Medium-term)

SMARTIE Goal #2		
By February of 2026, 100% of patient's with high Lp(a) (>50mg/dL) will receive individualized education and advocacy training focused on hormonal balance, cardiovascular risk and lifestyle modification strategies.		
Data to be Collected	Collection Process	Planned Data Analysis
<ul style="list-style-type: none"> - Total number of patients identified with elevated Lp(a) during the implementation period (denominator). - Number of those receiving documented education and counseling (numerator). 	<ul style="list-style-type: none"> The project coordinator (PC) and clinical providers will document completion of education sessions within the EHR visit note. 	<ul style="list-style-type: none"> The PC will calculate the education reach rate (numerator + denominator×100).

- Short (two question survey will be administered before and after the education.		
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Table 3. SMARTIE Goal #3 (Long-term)

SMARTIE Goal #3		
By May 2026, >80% of patients who received specialized education for Lp(a) will have their labs redrawn to assess lifestyle and hormonal interventions to assess changes in Lp(a) and associated cardiometabolic biomarkers.		
Data to be Collected	Collection Process	Planned Data Analysis
<ul style="list-style-type: none"> - Baseline and 12-month Lp(a) values - Secondary biomarkers (ApoB, LDL-C, HDL, hs-CRP, thyroid function) - Percentage of patients completing one-year follow-up testing 	<ul style="list-style-type: none"> - Follow-up lab results extracted from EHR by the PC - Data verified by clinic NP/primary stakeholder - Stored in an Excel sheet with patient identifiers removed. 	The PC will conduct a paired sample t-test to evaluate change in biomarkers from baseline to follow-up. A bar graph or box plot will visually display pre- and post-intervention Lp(a) values.

Safety & Confidentiality

Before conducting this QI project Montana State University's IRB will conduct an ethical review of this project proposal and approval will be obtained from the primary stakeholder and owner of the clinic. No site-specific review was required as the organization does not have an IRB board. All providers are required by the Health Insurance Portability and Accountability Act (HIPAA) law to ensure patient confidentiality. Patient data from the EHR will include age, lab values (Lp(a), hs-CRP, lipid panel) with date, BHRT treatment regimen, BMI, smoking status, ASCVD history, statin use, menopausal status and education completion. Data will be de-identified by deleting patient name, date of birth (DOB), medical record number (MRN), phone numbers, and emails; additionally, the PC will assign each patient a QI project code such as A001, A002 etc. and actual patient identifiers will not be stored. Storage of protected health information (PHI) will be done on a password protected, encrypted folder that does not have access to a cloud and is only available offline. There will be a form, Appendix B, displayed in the

exam room at the clinic outlining that participation in this QI project is purely voluntary and the option to not participate is always available, and this will be verbalized to patients as well with review of their Lp(a) lab value.

Conclusion

Lipoprotein(a) is a highly atherogenic particle with the potential to cause considerable risks of morbidity and mortality for those with high levels, and is present in up to 30% of the general population (Laffin & Nissen, 2024). Despite clear recommendations from the National Lipid Association (NLA) (Koschinsky et al., 2019), Lp(a) remains profoundly undertested in the U.S. (Razavi et al., 2025). This practice gap is especially consequential for peri- and menopausal women who are already facing rising cardiovascular risk due to the loss of vasoprotective sex hormones and overall less than optimal lipid profiles (Anagnostis et al., 2017; Bess et al., 2024; Hodis & Mack, 2022). Within this context, failure to identify elevated Lp(a) represents a missed opportunity for risk stratification and ASCVD prevention.

This QI project will attempt to further elucidate the relationship between exogenous sex hormone optimization and their relationship to Lp(a) levels by implementing standardized Lp(a) testing in peri- and menopausal women receiving BHRT in a wellness clinic. Grounded in the evidence and medical literature surrounding Lp(a), patients with elevated serum Lp(a) levels will receive targeted diet, lifestyle, hormonal interaction, supplement and self-advocacy strategies to implement while they are receiving BHRT. This project is further strengthened by stakeholder engagement, a defined workflow, and a focus on feasibility in a self-pay, largely female patient population.

Use of the JH-EBP model with subsequent PDSA cycles provide a structured framework for the proposed project and translating evidence into practice. The methods, SMARTIE goals, and evaluation strategies described in this chapter are designed to generate actionable data on screening rates, education, and early biomarker trends, with the hope that these risk-mitigation strategies reduce morbidity and mortality in the clinic's patient population. Subsequent chapters will present the results of the proposed intervention and discuss implications for future quality improvement projects surrounding Lp(a).

CHAPTER THREE

QUALITY IMPROVEMENT MANUSCRIPT

Contribution of Authors and Co-Authors

Manuscript in Chapter 3

Author: Amethyst Jade Lewis RN, BSN

Contributions: Investigation of clinical problem, reviewer of existing and emerging literature, development of implementation, creation of evidence-based treatment plan, collaborator with site representative and clinic staff, collection of data and analysis, writing of original manuscript, and dissemination of project findings.

Co-Author: Dr. Julie H. Alexander-Ruff

Contributions: Served as project committee chair, providing scholarly oversight, methodological guidance, and critical review of the manuscript throughout all stages of project development and writing.

Co-Author: Dr. Lindsey Davis

Contributions: Served as project committee second reader, providing critical review and feedback on manuscript content, structure, and scholarly rigor.

Manuscript Information

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- ☒ Prepared for submission to a peer-reviewed journal
- ☐ Officially submitted to a peer-reviewed journal
- ☐ Accepted by a peer-reviewed journal
- ☐ Published in a peer-reviewed journal

Clinical Problem

Despite cardiovascular disease remaining the leading cause of death in the United States, lipoprotein(a) [Lp(a)]—a well-established, independent, and causal risk factor for atherosclerotic cardiovascular disease (ASCVD)—continues to be excluded from standard lipid panels and is measured in fewer than 5% of eligible patients, even among those with established ASCVD (Albena & Mehta, 2023; Laffin & Nissen, 2024; Razavi et al., 2025; Shah et al., 2024). The clinical significance of Lp(a) lies in its atherogenicity: on a per-particle basis, Lp(a) is estimated to be six times more atherogenic than low-density lipoprotein (LDL) (D'Costa et al., 2025), and elevated levels (>50 mg/dL) are present in up to 30% of the general population, with risk directly correlated with degree of elevation (D'Costa et al., 2025; Laffin & Nissen, 2024). While Lp(a) concentrations remain largely stable across the lifespan (Razavi et al., 2025), this stability is disputed by one significant hormonal inflection point affecting half the world's population: menopause. Lp(a) concentrations are known to rise from the premenopausal period through ovarian failure, with an average increase of approximately 25% across the menopausal transition (Aljawini et al., 2023; Anagnostis et al., 2017; D'Costa et al., 2025; Freaney et al., 2021; Honigberg et al., 2022). Whether this rise independently accelerates CVD progression has not been definitively established and may be confounded by generalized aging; however, Lp(a)'s causal role in atherosclerosis is well-documented (Bess et al., 2024; Boffa & Koschinsky, 2024), and the overall risk of ASCVD is unequivocally elevated in the postmenopausal period (D'Costa et al., 2025).

Mechanistically, menopause introduces an assemblage of hormonal, metabolic and physiologic shifts—there is broad lipid dysregulation—including elevations in total cholesterol

(10-14%), LDL (14-19%), and apolipoprotein-B [ApoB] (8-15%), that are independent of aging alone (D'Costa et al., 2025). Additionally, menopause is associated with elevated Coronary Artery Calcium (CAC) scores, reflecting greater subclinical atherosclerotic burden and indicator of advanced, calcified plaque (D'Costa et al., 2025). For Lp(a) specifically, exogenous hormone therapy lowers Lp(a) by up to 30% (Anagnostis et al., 2017), further cementing the molecule's hormonal modulation. Furthermore, the evidence surrounding the use of hormone replacement therapy (HRT) significantly reducing risk of all-cause mortality and cardiovascular morbidity, is profound. Hodis & Mack (2022) extensively outline that HRT, when started before the age of 60 or within 10 years of menopause, significantly reduces all-cause mortality and the incidence of cardiovascular disease (CVD) in addition to the benefits to quality of life. The authors go on to further elucidate that the timing of HRT for women is important for the prevention and amelioration of tissue damage associated with aging (Hodis & Mack, 2022), highlighting the urgency of appropriate testing and treatment for midlife women. Unfortunately, recent estimates place HRT use at only 4.7% for menopausal treatment in the U.S. (Yang & Toriola, 2024).

The aforementioned evidence highlights the critical gap in testing for Lp(a) in peri- and menopausal women, confounded by the sharp rise in Lp(a) and generalized ASCVD risk associated with menopause's massive hormonal shift. Referencing the title of this project: we cannot treat what we don't test—this project arose from the urgency with which we need to properly treat midlife women; the persistence of unscreened, and unaddressed Lp(a) elevation in a population already experiencing accelerated ASCVD risk represents a modifiable gap in care, particularly when safe and effective risk-mitigation strategies, including hormone optimization when appropriate, are available. The following review of the literature examines the molecular

basis of Lp(a)'s atherogenicity, its modulation during menopausal transition, and the evidence supporting standardized screening in peri- and menopausal women.

Review of the Literature

Three key themes emerged from the literature review over the preceding months during this project. They are: Lp(a) biology and ASCVD risk; Lp(a), inflammation and the endothelium; Lp(a) and menopause, a dynamic risk factor.

Lp(a) Biology and ASCVD Risk

The molecular structure of Lp(a) is highly homologous to plasminogen (PLG), likely due to where the LPA gene is located on chromosome 6, adjacent to PLG and likely arose from its duplication, further explaining the Kringle IV (KIV) type 2 repeats, that make Lp(a) so atherogenic, but do not share the same enzymatic dissolution (Kronenberg, 2022; Yun et al., 2026). The number of KIV type 2 repeats is inversely correlated with Lp(a) particle size and directly correlated with plasma concentrations— individuals with shorter apolipoprotein(a) [Apo(a)] isoforms produce more Lp(a) particles per unit of LPA gene transcription and consequently carry higher atherogenic burden (Kronenberg, 2022). In fact, the LPA gene harbors one of the most structurally variable reputations in the entire human genome, with KIV type 2 copy numbers varying greatly between individuals, and contributing to the greater than 1,000-fold variations between individuals (Kronenberg, 2022). This genetic architecture is why serum Lp(a) concentrations are 70-90% heritable and largely resistant to traditional diet, lifestyle modifications, and statins, like other lipids are, the latter of which paradoxically raises Lp(a)

while lowering ApoB burden (Tsimikas et al., 2022). Elevated levels of Lp(a) are defined as $>50\text{mg/dL}$ or $>125\text{nmol/L}$.

Lp(a), Inflammation and the Endothelium

The atherogenicity of Lp(a) is not solely a function of the particle, but is also a result of the pro-inflammatory phospholipids that naturally attach themselves to the particle, named oxidized phospholipids (OxPL), specifically, the OxPL that attach to ApoB (OxPL-ApoB) located on the LDL portion of the Lp(a); these particles serve as a link between a lipids and endothelial inflammation (Tsimikas et al., 2024). OxPL-ApoB aids in Lp(a)'s ability to obtain direct arterial intima penetration, which then attracts macrophages to the site of injury, causing foam cell formation, cytokine release (via interleukin (IL)-1 β , IL-6, IL-8, and tumor necrosis factor- α) and finally producing an atherosclerotic plaque with a necrotic core (Tsimikas et al., 2020; Ugovsek & Sebestjen, 2021). Arterial inflammation has become a foundation of contemporary cardiovascular risk assessment, and hs-CRP has emerged as its most clinically accessible biomarker. Importantly, hs-CRP and Lp(a) are mechanistically independent, and within the literature, elevated hs-CRP ($>2\text{mg/L}$) does not predict elevated Lp(a), and low hs-CRP does not exclude elevated serum Lp(a). This independence is not a limitation of either biomarker, but rather an example of their biologically independent pathways. Still, Zhang et al. (2021) demonstrated in a cohort of nearly 4,700 participants over a mean of 13.6 years, that the simultaneous elevation of Lp(a) and hs-CRP ($>2\text{mg/dL}$) conferred disproportionate cardiovascular hazard through convergent but non-redundant pathways. Remarkably, Zhang et al. (2021) further established that without simultaneously elevated hs-CRP, elevated serum Lp(a) did not transmit to increased CVD risk. Ridker et al. (2024) further expanded on this concept by

assessing hs-CRP and Lp(a) over the span of 30 years in perimenopausal women reinforcing Lp(a) as an independent marker for risk while also acknowledging that co-occurring elevated levels of hs-CRP exacerbated the atherosclerotic effects of Lp(a). Moreover, recent work by Nomura et al. (2025) reinforced all of the previous findings while including the addition of another marker for inflammation—homocysteine (tHcy), ruling that in order for Lp(a) to engage its atherogenic effects, it also had to be accompanied by elevated levels of hs-CRP or tHcy.

These landmark studies collectively reinforce a three-component framework of atherogenesis in which coronary atherosclerotic plaque formation requires the convergence of systemic inflammation, atherogenic lipoproteins, and endothelial injury—whether mechanical, as in the case of hypertension, or chemical, as in tobacco exposure (Ross, 1999; Libby et al., 2002). This framework represents a meaningful evolution beyond the historically dominant lipid-centric model of atherogenesis, repositioning inflammation not as a downstream consequence of lipid accumulation but as an independent, co-equal driver of plaque initiation and progression, especially when confronted with compromised endothelial integrity (Ridker et al., 2024; Zhang et al., 2021; Nomura et al., 2025). These findings are further affirmed by the 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia (Blumenthal et al., 2026), which for the first time in the United States, formally recommends universal, once-in-a-lifetime Lp(a) measurement in all adults and explicitly elevates hs-CRP as a clinically meaningful risk-enhancing factor in the comprehensive assessment of ASCVD risk.

Lp(a) and Menopause, A Dynamic Risk Factor

The conventional clinical framework characterizes Lp(a) as biologically static after the age of 5, and genetically fixed and unresponsive to lifestyle or most pharmacologic interventions— a characterization that has historically been used to justify infrequent or one time testing (Razavi et al., 2025). However, this framework inadequately accounts for the documented physiological modulation of Lp(a) across the menopausal transition. A 2023 systematic review and meta-analysis (Anagnostis et al.) of 4,686 premenopausal and 8,274 postmenopausal women identified a statistically significant rise in Lp(a) from pre- to post-menopause with some cohorts identifying menopausal status as the single strongest independent predictor of Lp(a) levels in women, with some cohorts finding that the transition from pre- to post-menopause superseded age, BMI, and traditional lipid parameters. The proposed mechanisms centers on estrogen's suppressive effect on LPA gene transcription in the liver: endogenous estrogen down-regulates Lp(a) production at the level of gene expression and the progressive estrogen decline of perimenopause may progressively unmask a woman's full genetic Lp(a) set point (Corral et al., 2025). Whether this represents a true biological increase in Lp(a) production or the removal of a suppressive hormonal effect on an otherwise genetically fixed value remains under investigation, but the clinical implication is the same: a woman's Lp(a) in perimenopause may be meaningfully higher than the value she carried pre-menopausally, and a single lifetime measurement in her 30's, likely does not reflect her cardiovascular risk in her 50's.

Exogenous hormone therapy further muddies Lp(a) interpretation in this population. Oral estrogen formulations reduce Lp(a) by approximately 27% through hepatic first-pass metabolism, and its effect on LPA gene transcription that occurs in the liver, while transdermal estrogen, which bypasses hepatic first-pass processing, exerts a much less meaningful effect on

Lp(a) levels (Bess et al., 2024; Boffa & Koschinsky, 2024). Theoretically, a value obtained after months of oral estradiol may underestimate a patient's true genetic set point by as much as 30%, potentially miscategorizing a high risk patient as low or intermediate risk. Measuring Lp(a) at HRT initiation prior to or coinciding with therapy should be a prerequisite for clinically meaningful risk assessment for cardiovascular disease. The 2026 Guideline on the Management of Dyslipidemia's (Blumenthal et al., 2026) landmark endorsement of universal Lp(a) screening for all adults, validates this project's central clinical logic—but their silence on the perimenopausal transition as a repeat measurement point represents the most consequential remaining gap between the current guideline language and the biology of the population this project serves.

Conceptual Framework

The Johns Hopkins Evidence-Based Practice Model (JH-EBP) served as the conceptual framework for the development, implementation and execution for this Quality Improvement (QI) project, with the addition of the Plan, Do, Study Act (PDSA) cycles that facilitated iterative, small scale testing of practice changes through a structured sequence of planning, implementing, evaluating and refining (Dang & Dearholt, 2018). JH-EBP was chosen because it offers a structured and systematic approach to translating research evidence into clinical practice while promoting interdisciplinary collaboration, stakeholder engagement, and patient-centered care (Dang & Dearholt, 2018).

Project Aim

The aim of this QI project was to implement a standardized Lp(a) screening protocol in a high plains wellness clinic primarily serving midlife peri- and menopausal women receiving HRT, with the goals of achieving a >90% screening completion rate, documenting the prevalence of elevated (>50 mg/dL) in this population, and generating a scalable clinical blueprint for mitigating risk associated with Lp(a).

Methods

Context

The project site was a high plains wellness clinic serving a predominantly peri- and menopausal female clientele, with bioidentical hormone replacement therapy (BHRT) as the primary treatment modality. Clinic visits were structured around general wellness and hormonal optimization, with standardized laboratory panels used to guide and monitor therapy. Prior to this project, no standardized protocol existed for Lp(a) measurement; conventional lipid panels and hs-CRP were obtained routinely, but Lp(a) was ordered at the discretion of the provider and infrequently captured. This gap was identified as both clinically significant and operationally addressable, given that the BHRT initiation visit represents a natural, high yield point for cardiovascular risk baseline assessment and midlife women. The analytic sample consisted of n = 17 patients seen during the implementation window of December 15, 2025 through February 10, 2026.

Intervention

The intervention consisted of the addition of Lp(a) into the clinic's standardized BHRT laboratory panel for all eligible patients presenting during the implementation window. Provider education was delivered in a brief in-service format prior to implementation covering Lp(a) risk thresholds, clinical interpretation in the context of BHRT route of administration, and referral indications for patients with elevated values.

A brief patient-facing educational handout (Appendix C) was developed and distributed at lab "Findings" appointments to patients with elevated levels of Lp(a). The handout contextualizes Lp(a) as an independent cardiovascular risk factor and contextualizes the significance of the result within the patient's overall cardiometabolic profile. Additionally, it highlights the importance of screening, diet, exercise, evidence-based supplements and lifestyle modifications in the setting of elevated Lp(a) and supports patient self-advocacy regarding this underrecognized biomarker. Most importantly, the handout frames Lp(a) as a single component of overall cardiovascular risk and highlights findings from the *EPIC-Norfolk* study, demonstrating that optimization of modifiable cardiovascular risk factors may offset up to 75% of the excess risk associated with elevated Lp(a) (Perrot et al., 2017). Although the primary SMARTIE threshold for individualized education was defined as >50 mg/dL, patient's with values in the borderline range (30-50mg/dL), also received education, consistent with the laboratory's flagging threshold of >30 mg/dL, which aligns with the 1.2-fold increased ASCVD risk identified at this level (Blumenthal et al., 2026). During the implementation period, the handout was revised by the approval of MSU's IRB, to replace the recommendation for flaxseed with high-quality omega-3 fish oil supplementation—reflecting updated evidence supporting

marine-derived omega-3 fatty acids as the more clinically substantiated dietary intervention in the context of cardiometabolic risk reduction (Ward et al., 2023).

Measures

Three SMARTIE goals guided data collection and outcome evaluation across the implementation period. The primary outcome measure was Lp(a) screening completion rate, defined as the percentage of eligible peri- and menopausal BHRT patients with a resulted Lp(a) value by February 15, 2026, with a target of >90%. Data were extracted biweekly from the electronic health record by the project coordinator, recorded in a de-identified Excel spreadsheet, and verified monthly for completeness. Secondary outcome measures included education and advocacy reach among patients identified with elevated Lp(a) (>50 mg/dL) and longitudinal biomarker reassessment at follow-up. Patient and provider feedback, where collected, was intended to be organized thematically around the value metrics of knowledge, advocacy, and engagement. Due to the project starting earlier than originally anticipated due to more favorable data collection timing, formal patient feedback was not collected within the implementation window and is addressed further in the “Limitations” section. Exploratory measures included Spearman rank correlations examining the relationships between Lp(a) & hs-CRP, Lp(a) & LDL-C, and Lp(a) & age were also analyzed across the sample.

Ethical Considerations

This project was reviewed and approved by the Montana State University Institutional Review Board (IRB) prior to initiation. All data were collected and stored in a de-identified format with no protected health information (PHI) retained in the analytic dataset. Furthermore, data were stored securely in an encrypted folder on a password-protected device accessible only

to the project coordinator, and unable to be synced with any cloud software. Summarized data only were used for project reporting and dissemination and destroyed upon project completion. Additionally, a sign was clearly displayed in the clinic's waiting room outlining patient's ability to voluntarily withdraw from this QI project at any time for any reason. Patient participation did not alter the clinical care received, and no experimental interventions were introduced.

Analysis

Descriptive statistics were used to calculate screening completion rates and Lp(a) prevalence within the sample. Spearman rank correlation coefficients were calculated for each of the three exploratory biomarker pairs, with a significant threshold of $p < 0.05$. Spearman's rank correlation was selected as the appropriate non-parametric method given the small sample size ($n = 17$) and the non-normal distribution of Lp(a) values in the general population. Statistical analyses were conducted using Python (Python Software Foundation, 2024) with the SciPy statistical library (Virtanen et al., 2020) and NumPy (Harris et al., 2020), with analytical support provided by Claude (Anthropic, 2026).

Results

Screening Completion

Lp(a) screening was completed in 100% of eligible patients ($n = 17$) during the December 15, 2025 through February 10, 2026 implementation window, exceeding the 90% SMARTIE target. Successful integration of Lp(a) into the standard BHRT laboratory panel, combined with the pre-implementation provider education supported full protocol adherence across the implementation period.

Education Completion

Education was completed for 100% of patients with Lp(a) exceeding 50 mg/dL ($n = 4$), meeting the 100% SMARTIE target. One additional patient with a borderline Lp(a) of 41.1 mg/dL also received individualized education, consistent with the clinic's laboratory flagging threshold of >30 mg/dL and the stepwise ASCVD risk profile associated with Lp(a) elevation (Blumenthal et al., 2026).

Sample Characteristics

Of the 33 patients who underwent laboratory testing during the eight-week implementation period, 17 had Lp(a) drawn as part of a full baseline panel and comprised the analytic sample. The remaining 16 patients received focused laboratory panels consistent with their established treatment plans (e.g., testosterone monitoring for patients on androgen therapy) and were not eligible for inclusion per project criteria.

The analytic sample ($n = 17$) consisted of 12 females (70.6%) and 5 males (29.4%). Mean age was 44.6 years ($SD = 6.9$, median = 43.0, $IQR = 41.0\text{--}51.0$, range 30–56). Among the 12 female patients, menopausal status was determined from provider charting based on laboratory values, clinical symptoms, and last menstrual period and was distributed as follows: 4 menopausal (33.3%), 6 perimenopausal (50.0%), 2 premenopausal (16.7%). Five patients were initiating care at the time of the project; 12 were established patients. One patient was on statin therapy (rosuvastatin 10 mg); no patients were on PCSK9 inhibitors or ezetimibe. Regarding smoking status, 15 patients were never-smokers, one reported current chewing tobacco use, one reported active vaping. No patients had a formal CAD or ASCVD history on record; however,

two patients had prior coronary artery calcium (CAC) imaging on file, one with a score of 0 and one with a score of 4 in the left anterior descending artery (LAD) with an Lp(a) of 77.4mg/dL.

Lp(a) Prevalence

Lp(a) values demonstrated a right-skewed distribution (mean = 32.7 mg/dL, SD = 39.7, median = 11.3 mg/dL, IQR = 8.3–41.1, range 6.0–143.5), consistent with the known population-level distribution of this biomarker. Four patients (23.5%) met the threshold for elevated Lp(a) (>50 mg/dL), of whom three were female and one was male; one additional patient (5.9%) returned a borderline value of 41.1 mg/dL in the 30–50 mg/dL range; and 12 patients (70.6%) had values <30 mg/dL. Mean LDL-C was 119.6 mg/dL (SD = 31.0, median = 117.0, IQR = 102.0–136.0). Mean HDL-C was 68.1 mg/dL (SD = 22.5, median = 63.0, IQR = 52.0–83.0). Mean triglycerides were 102.2 mg/dL (SD = 55.6, median = 71.0, IQR = 63.0–127.0), reflecting notable right skew driven by two patients with values above 174 mg/dL; hs-CRP was available for 16 of 17 patients—one patient had a “not-resulted” value and was excluded from hs-CRP correlational analysis. Among those with available values, mean hs-CRP was 1.6 mg/L (SD = 1.8, median = 0.9, IQR = 0.5–1.9, range 0.2–6.0). The majority (62.5%, n = 10) had hs-CRP values below 1.0 mg/L, while 4 patients (25.0%) exceeded the elevated inflammatory, clinically-significant threshold of >2.0 mg/L that is correlated with increased risk of ASCVD (Nomura et al., 2025; Ridker et al., 2024; Zhang et al., 2021) .

Correlational Analysis

Spearman correlation analysis was selected given the non-normal, right-skewed distribution of Lp(a) values and the small sample size. Correlations were run between Lp(a) and hs-CRP, age, LDL-C, HDL-C, triglycerides, and total cholesterol. No statistically significant

correlations were identified between Lp(a) and any of the examined variables. Lp(a) and hs-CRP demonstrated no meaningful association ($r = -0.110$, $p = 0.685$, $n = 16$), consistent with the current literature supporting their roles as independent rather than correlated cardiovascular risk factors (Kraaijenhof et al., 2025; Simantiris et al., 2023; see Figure 4).

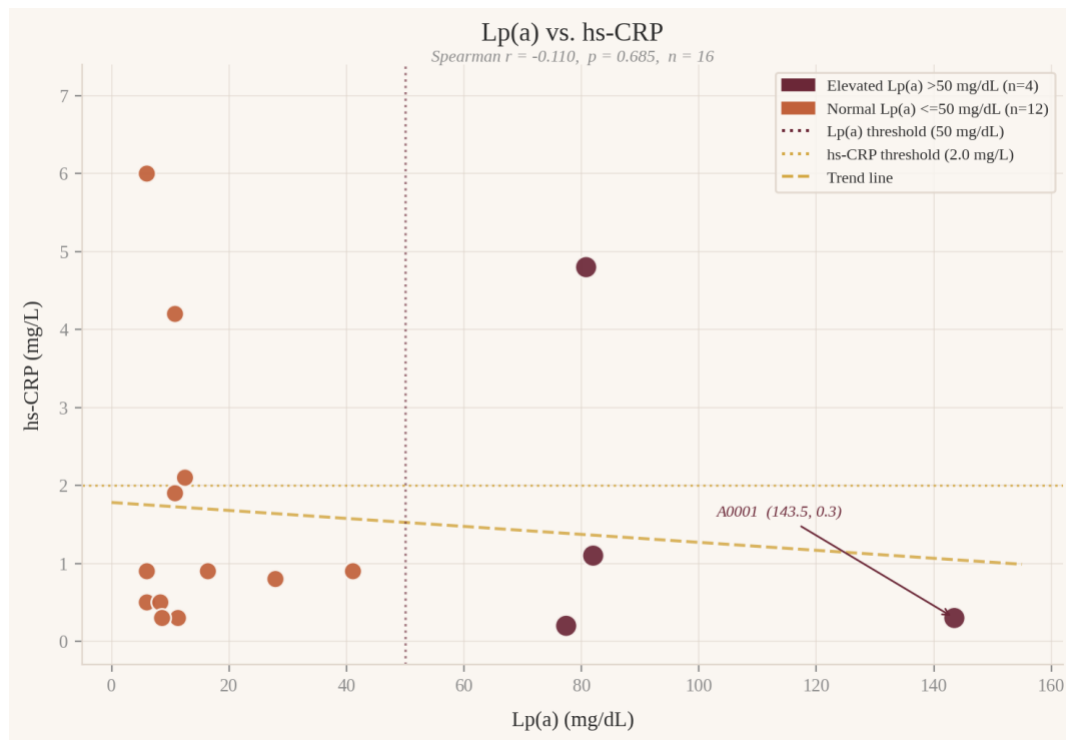


Figure 4. Scatter plot of Lp(a) (mg/dL) versus hs-CRP (mg/L); Spearman $r = -0.110$, $p = 0.685$, $n = 16$. Generated with analytical support from Claude (Anthropic, 2026)

A weak inverse trend was observed between Lp(a) and age ($r = -0.430$, $p = 0.085$), with the elevated Lp(a) subgroup ($n = 4$) having a younger mean age (39.2 years) compared to the non-elevated Lp(a) group (46.3 years); however, this did not reach statistical significance and should be interpreted cautiously given the sample size. No significant associations were found between Lp(a) and LDL-C ($r = 0.166$, $p = 0.525$), HDL-C ($r = -0.063$, $p = 0.810$), triglycerides ($r = -0.117$, $p = 0.656$), or total cholesterol ($r = 0.032$, $p = 0.903$). These findings are consistent with

the well-established genetic independence of Lp(a) from standard lipid fractions (Bess et al., 2024; Razavi et al., 2025). The absence of significant correlations across all variables is likely attributable to the limited statistical power inherent in a small QI sample and should not be interpreted as broad evidence of clinical relationship. The distribution of Lp(a) values is illustrated in Appendix D, and a summary of Spearman correlational coefficients between Lp(a) and six biomarkers can be found in Appendix E.

Discussion

Guidelines Alignment

When this project was in its infancy, a central flaw identified in Chapter One was the misalignment among U.S. cardiovascular societies regarding Lp(a) screening as the guidance lagged far behind international bodies and the mounting evidence base. Over the course of this project's implementation, that tension was formally resolved. The 2026 multi-society Guideline on the Management of Dyslipidemia (Blumenthal et al., 2026) retired the 2018 blood cholesterol guidelines and, for the first time in U.S. clinical history, recommended universal Lp(a) measurement in all adults. The guideline's deliberate retitling to "Dyslipidemia" signals that Lp(a) is no longer an afterthought, it is a distinct, causal, and actionable target. The evidence was never absent; the field has simply, at last, caught up.

The Gender Gap in Guidelines

Despite this progress, the 2026 guideline's once-in-a-lifetime framework reflects a consequential blind spot: it does not completely address Lp(a)'s known physiological modulation across women's reproductive lifespan. Menopause, pregnancy, and the postpartum period are

each documented windows of Lp(a) fluidity—with elevated Lp(a) associated with preeclampsia, gestational diabetes, and intrauterine growth restriction (Corral et al., 2025), yet none are recognized in the current screening guidance as indications for repeat measurement. This omission is not incidental. It reflects the broader pattern of medical paternalism that has historically defaulted to male-patterned disease trajectories as the clinical standard, leaving women's hormonal biology systematically under-addressed in cardiovascular risk frameworks (Brown et al., 2022). Strides are being made, but a guideline that recommends universal screening while remaining silent on the population most hormonally vulnerable to Lp(a) elevation has not gone far enough.

Challenging the “Genetically Static” Narrative: Clinical Observations

Two de-identified clinical observations challenge the current models in place on Lp(a) modifiability. In personal observation, a male patient with baseline Lp(a) of 478 nmol/L demonstrated a reduction to 232 nmol/L over four months following initiation of a PCSK9 inhibitor, and testosterone therapy in the setting of hypogonadism—a magnitude exceeding what pharmacologic PCSK9 inhibition alone would predict. During a second observation, a postmenopausal female patient initiated on oral estradiol, oral micronized progesterone, and topical testosterone, without any traditional lipid-lowering medications, demonstrated an Lp(a) reduction from 176mg/dL to 116 mg/dL over five months, again exceeding what oral estrogen alone would be expected to produce. While these are clinical observations, not controlled findings, and causal inference is not appropriate, they are consistent with the biological plausible argument that hormonal setting modulates Lp(a) expression in ways the current literature has not

fully characterized. They represent exactly the kind of harbinger that should motivate further investigation.

Inflammation as the Unifying Mechanism

The non-significant Lp(a) and hs-CRP correlation in this sample is not evidence of failure, but is confirmation that these markers measure distinct constructs requiring independent assessment. Lp(a) drives vascular inflammation directly through its OxPL-mediated endothelial injury, foam cell formation, and cytokine release, while hs-CRP reflects the systemic inflammatory burden that amplifies those effects (Tsimikas et al., 2017). Zhang et al. (2021), Ridker et al. (2024), and Nomura et al. (2025) collectively establish that co-elevation of Lp(a) and inflammatory markers confers disproportionate cardiovascular hazard through convergent, non-redundant pathways. Inflammation is not a downstream consequence of lipid accumulation—it is a co-equal driver, and in the perimenopausal woman, its rise as a major risk factor is inseparable from the purpose this project was designed to address, which is improving longevity and vitality for midlife women who have been left behind by modern medicine.

Limitations

The results of this project should be interpreted in the context of several limitations. The analytic sample of $n = 17$ limits statistical power and the generalizability of findings to broader peri- and menopausal populations. The planned patient education survey was not administered due to IRB and operational constraints, preventing assessment of patient-reported outcomes related to Lp(a) screening receipt and health behavior response; this represents a documentation and systems gap rather than a project failure and is a priority for future implementation cycles. The cross-sectional design captures a single Lp(a) measurement, which cannot characterize

longitudinal Lp(a) trajectory across the menopausal transition; this is precisely the limitation that motivates the recommendation for baseline measurement at HRT initiation and repeat testing at clinically significant hormonal inflection points as well as yearly follow-up labs as outlined in Chapter Two. Additionally, HRT administration was not systematically controlled in the correlational analysis; patients receiving HRT at the time of measurement may have had pharmacologically suppressed Lp(a) values, introducing the possibility of measurement bias that could underestimate the true prevalence of elevated Lp(a) in the sample. Missing hs-CRP data for one participant further reduced the available sample for that specific correlation, reflecting a documentation systems gap consistent with real-world QI implementation. The stable clinical context of a single integrative wellness clinic may also limit the external applicability of the screening protocol to settings with different patient populations or workflow structures. Stakeholder availability was also periodically constrained by unforeseen personal circumstances during the implementation period, resulting in the cancellation of some pre-scheduled site representative meetings; this reflects a common and underappreciated challenge in real-world quality improvement, where implementation fidelity is inherently dependent on the availability and bandwidth of key personnel outside of the project coordinator's control. Finally, the implementation period coincided with the holiday season, which likely contributed to reduced patient volume and constrained data collection.

Recommendations

Future implementations of Lp(a) screening in clinics serving midlife peri- and menopausal women should obtain serum Lp(a) prior to the initiation of any HRT, bioidentical or synthetic, to capture the most clinically informative baseline value and avoid pharmacologic

suppression that may misclassify a patient's true cardiovascular risk category. Given that Lp(a) has been reliably shown to rise across the menopausal transition, a post-menopausal measurement is recommended in addition to the pre-treatment baseline, consistent with guidance from Aljawini et al. (2023), supporting reassessment at hormonally significant inflection points. Co-assessment of hs-CRP alongside Lp(a) at each screening encounter is further recommended to capture the inflammatory context in which elevated Lp(a) operates, given the additive, and potentially synergistic, cardiovascular risk conferred by their co-occurrence (Kraaijenhof et al., 2025).

Despite Blumenthal et al.'s (2026) recognition of Lp(a) as a causal risk factor and growing consensus supporting at least once-in-a-lifetime testing, the AHA's PREVENT risk calculator—released in 2023 as the updated standard for primary prevention risk stratification—does not include Lp(a) as a scored variable (Khan et al., 2024). This structural inconsistency leaves clinicians encouraged to test for Lp(a) without an integrated tool for incorporating the result into routine risk estimation. Until calculators reflect the current evidence base, clinicians are encouraged to apply Lp(a) results qualitatively within shared decision-making frameworks rather than awaiting algorithmic guidance that does not yet exist.

Conclusion

This quality improvement project demonstrated that standardized Lp(a) screening is feasible, clinically meaningful, and readily compatible into the routine care of peri- and menopausal women receiving HRT; achieving 100% screening completion of eligible patients and identifying clinically elevated Lp(a) in nearly one quarter of the female sample, highlights what a standard lipid panel would have left entirely undetected. The concurrent publication by

Blumenthal et al. (2026) formally validates the clinical premise on which this project was built, marking a turning point in cardiovascular prevention within the U.S. Yet the collective silence on retesting outside of hormonally-driven Lp(a) inflection points—the perimenopausal transition, pregnancy and postpartum—conditions that exclusively affect women, represent the most consequential remaining gap between guideline language and the biology of the population this project was designed to serve. The convergence of rising Lp(a), escalating inflammatory burden, and the loss of hormonally-mediated endothelial protection in the perimenopausal window creates a cardiovascular risk environment that is greater than the sum of its parts—and one that begins with a single lab order. We cannot treat what we don't test, and in midlife women, the window to establish a meaningful baseline is narrower, and more consequential, than current guidelines have yet to acknowledge.

CHAPTER FOUR

ADVANCED NURSING ESSENTIALS REFLECTION

Introduction

While the Doctor of Nursing Practice (DNP) Program has provided extensive scholarly, professional, and clinical preparation for my transition into the provider role, it has also offered a deeper glance in to the broader academic and professional landscape of healthcare practice. As my didactic learning, clinical rotations, and QI manuscript work as the program progressed, I realized that learning extended beyond clinical competence, and into the workings of evidence appraisal, leadership, and ethical responsibility.

As the saying goes, “the further you get from shore, the deeper the water gets”, and when reflecting on my education I have realized that advanced nursing practice requires comfort with uncertainty, accountability, and nuance. The DNP is not an endpoint, but a threshold—one that requires graduates to step forward into a healthcare climate marked by competing narratives, misinformation, and skepticism toward expertise. Grounded in nursing science, evidence-based practice, and patient-centered values, the DNP-prepared nurse enters this arena prepared not only to deliver care, but to lead, to advocate, and to uphold the integrity of the profession.

To that end, the patient remains at the center of nursing practice. Our pursuit of better answers, our willingness to listen to concerns, fears, and questions, and our commitment to translating complex medical systems into compassionate, understandable care are what make the profession scientific and deeply human. This chapter is a reflection of my time at Montana State

University (MSU) in the DNP program and the education and expertise I have gained during the last four years.

Domain One: Knowledge for Nursing Practice:

The first domain of nursing emphasizes the integration of liberal arts and the sciences, focusing on the critical appraisal of scientific literature and the nurse's ability to apply that evidence in practice (AACN, 2021). While the DNP student is trained to rigorously evaluate literature and apply scientific and medical knowledge, it remains essential to the core of nursing that this work is carried out through a human-centered lens.

Over the course of the DNP program, my understanding of information, knowledge, and evidence underwent a conceptual shift. While I gained technical skills in my Evidence-Based Practice courses such as rapidly appraising literature and identifying methodological shortcomings, more importantly my approach to clinical decision-making evolved from guideline adherence towards synthesis of emerging evidence. Essentially, while the foundation I was taught in my courses allowed me to interpret the literature, what I gained overall is and was much more valuable—evaluating areas of clinical practice where evidence may be incomplete, conflicting, or extrapolated from populations that do not reflect the entire patient profile that nurse practitioners (NPs) serve.

This shift became particularly relevant within my doctoral project focused on implementation of standardized Lipoprotein(a) screening as evidenced by the absence of routine screening in primary care. I saw this as not only a gap in practice, but a broader problem in the translation of the emerging science surrounding genetically-mediated cardiovascular risk into routine patient care. Additionally, in the setting of long-term health, it was obvious through my

understanding and the literature that the 10-year risk stratification has become somewhat outdated when faced with the pathophysiology of atherosclerotic cardiovascular disease (ASCVD). Ultimately, applying evidence in this context required moving beyond the pigeonholed risk calculators, towards a more integrative understanding of the interplay between hormonal health, endothelial dysfunction, inflammation, and lipid burden across the lifespan.

In rural and medically underserved areas such as Montana, where access to rare subspecialties like lipidology or even cardiology services are limited, the ability of primary care clinicians to critically evaluate and implement emerging evidence becomes essential. This domain has strengthened my role as a lifelong learner and enhanced my ability to apply evidence and evolving knowledge in a way that is both clinically meaningful and lacking in our communities.

Domain Two: Person-Centered Care:

At the core of nursing is the patient. Per the AACN (2021), person-centered care “focuses on the individual within multiple complicated contexts... [it] is holistic, individualized, just, respectful, compassionate...”. One of the foundational skills I have refined throughout this program is the ability to connect with patients across the lifespan and bridge gaps for them within the health care system and in the social experience of seeking care.

Patients should feel respected, heard, and included as active participants in their care. Advanced nursing practice requires not only the delivery of information, but the ability to translate complex medical concepts such as cardiometabolic risk, genetic predisposition, or preventative treatment strategies into language that is both understandable and actionable. Shared decision making becomes particularly important in preventative care settings, where risk

modification may not produce immediately tangible outcomes but carries significant long term implications for morbidity and mortality.

Through my clinical experiences, including rotations in medical genetics and primary care, I came to understand that some of the most impactful moments in patient care occur not through technical knowledge alone, but through conversations that address uncertainty, fear and familial implications of disease. Advanced practice nursing uniquely positions clinicians to support patients and families through these moments by combining clinical expertise with empathy and advocacy. For me, it was the very real and raw conversations that were had with not only the patients, but their families who were often privy to these conversations. It is our unique ability as advanced practice nurses to hold people— their emotions, questions, concerns and given them our knowledge from education, but also our compassion and support.

Domain Ten: Personal, Professional, and Leadership Development:

Domain 10 reflects the integration of personal health, resilience, and well-being as well as how these factors contribute to lifelong learning and the development of leadership capacity (AACN, 2021). Throughout this program, my experiences have reinforced the idea that clinicians cannot sustainably care for others without also attending to their own health and well-being. Patients often look to their health care providers not only for clinical expertise, but also for guidance in navigating their own health behaviors and risks.

Directly prior to this manuscript's work, I was personally confronted with the discovery that I have elevated lipoprotein(a), and thus I am at an increased likelihood of developing ASCVD within my lifetime. Processing this finding required me to reconcile my clinical knowledge with my own perceived vulnerability, and ultimately reshaped how I communicate

cardiovascular risk to patients. Learning to reframe an unfavorable lab value as a risk indicator, rather than a definitive diagnosis, while navigating this reality myself, fostered a level of understanding and perspective that could not have been replicated through coursework alone.

MSU's emphasis on inquiry and discovery prompted my initial exploration of this often under recognized biomarker which has since become a central component of my developing clinical practice. This experience strengthened my ability to guide patients through risk-based decision-making with greater transparency and compassion, particularly as I prepare to care for individuals in our rural state who may benefit from earlier identification and prevention-focused cardiometabolic care.

Additionally, over the course of the DNP program, my understanding of implementation of evidence into practice evolved from the singular clinical perspective to that of a systems-level thinker. Throughout the program, and particularly through this dissertation, my clinical coursework, and advanced assessment courses, I have learned to take complicated subjects and nuanced science and put them into measurable clinical practice changes aimed at improving overall health and advanced cardiovascular risk assessment. What was once considered an emerging, or rarely assessed laboratory value, tested by fewer than 1% of clinicians in the United States, became a structured implementation with a measurable and actionable component of preventative care through science.

This type of translation from idea to intervention reflects the role of the DNP-prepared nurse as both clinician and leader. By integrating implementation strategies such as standardized screening protocols and population-level risk identification, advanced practice nurses can

influence care delivery beyond the individual patient encounter and into the broader clinical environment.

Practicing in a world increasingly shaped by misinformation represents an ongoing challenge for clinicians entering practice today. It is imperative that we remain grounded in scientific evidence while also advocating for the ethical application of emerging therapies. Within areas such as women's hormone health where symptoms are frequently minimized or treatment approaches influenced by outdated or misinterpreted data, the responsibility to provide informed, evidence-based care becomes particularly significant.

Occasionally, professional development demands participation even in the presence of imperfect knowledge. Transitioning from RN to NP and the accountability associated with this has required growth in professional confidence, interprofessional collaboration, and readiness to engage with nuanced decision-making. The ability to acknowledge knowledge gaps while actively seeking evidence based solutions has been a defining component of my doctoral education period as I move forward into practice, I am reassured by the knowledge that my time within this program has prepared me not only to deliver safe patient care but to advocate for patients and contribute meaningfully to the advancement of preventative medicine within my community.

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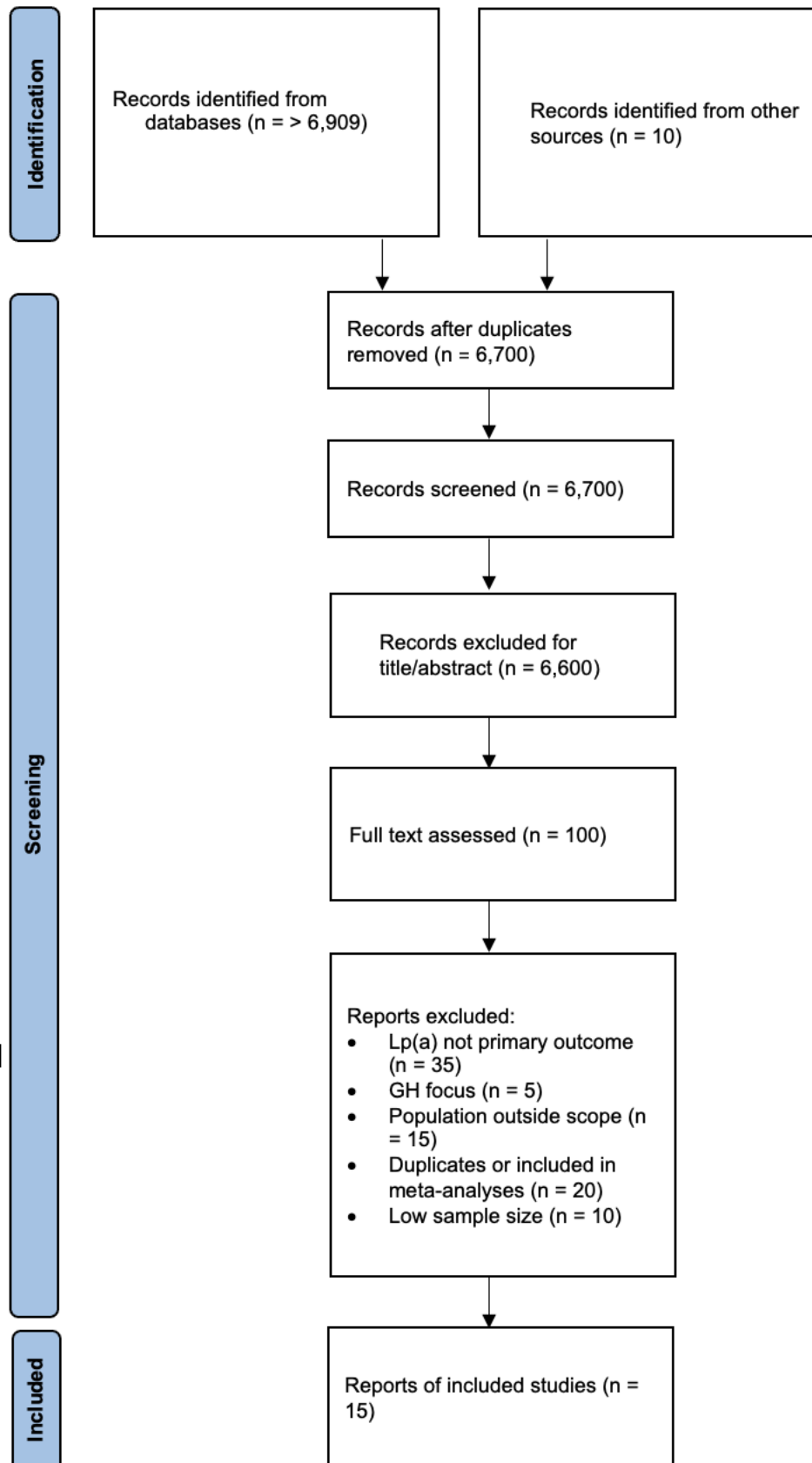
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APPENDICES

APPENDIX A

PRISMA FLOW DIAGRAM



APPENDIX B

PATIENT PARTICIPATION AND OPT OUT INFORMATION

Patient Participation and Opt-out Information

At our clinic, we are always working to provide the most advanced, evidence-based and personalized care to our patients to support your long-term health. As part of this commitment, we are participating in a quality improvement project focused on improving cardiovascular risk screening and education.

This project is being implemented by DNP-FNP student, Amethyst Lewis on behalf of Montana State University and includes the routine collection of Lipoprotein(a) or Lp(a) lab results (already included in your baseline labs), along with brief education to help you better understand your cardiovascular health and advocate for additional care when needed.

Your information will remain confidential and de-identified if used for quality improvement evaluation. **Participation involves no additional costs and no change to your clinical care.**

Participation in this project is completely voluntary and you may choose to opt-out at any time without affecting your care in any way. If you choose to opt-out, please notify Britt, or any member of the clinical team.

Thank you for your time,

Amethyst Jade Lewis, DNP-FNP Student
Amethyst.ganson@student.msu.edu

APPENDIX C

PATIENT EDUCATION HANDOUT

Lipoprotein(a) and Your Health: A Preventative Guide

What is Lipoprotein(a) or Lp(a)?

- Lp(a), pronounced “L-P-little-A”, is a type of cholesterol made by your liver
- Everyone has some Lp(a) in their blood, but up to 30% of the general population has “high” levels ($> 50\text{mg/dL}$), and this can increase your chances for cardiovascular disease such as heart attack or stroke
- Lp(a) is inherited and runs in families, your level is typically an average of your parents’ levels
- Lp(a) is different than LDL, or the more typical type of “bad” cholesterol in that it does not respond much to traditional medications or lifestyle interventions

Why this matters:

- High Lp(a) doesn’t mean something is wrong today
- This is a long-term risk marker and will help us guide us on your health journey
- Knowing your Lp(a) **before** it causes issues puts you in a great position for making good long-term decisions about your heart and vascular health

So, what can we do?

According to a long-term population based study in the United Kingdom (the *EPIC-Norfolk* study), when a patient optimizes their modifiable cardiovascular risk factors, such as health-promoting diet and lifestyle behaviors, they may reduce their cardiovascular risk up to 75%, in spite of high Lp(a) (Perrot et al., 2017). This means, we can do things now to protect you from future disease—this is great news.

What you can do to lower risk

Nutrition:

Focus on anti-inflammatory, heart healthy eating:

- Prioritize vegetables, fruits, high-quality protein, whole grains, nuts, seeds, & beans
- Certain natural fats lower Lp(a)—such as those found in nuts, and naturally-raised grass-fed animal proteins that are also higher in omega-3 fatty acids
- Fatty fish (sardines, salmon and mackerel) also provide large amounts of heart-protective omega-3 fats
- Limit processed foods, added sugars, and trans fats
- Strict vegetarian diets have shown some Lp(a)-lowering effects, but they can lack notable amounts of important macronutrients, such as proteins and fats. Whatever your eating style, incorporate nitrate-rich vegetables such as arugula, spinach, and beets which support healthy blood vessel function
- Olive oil is rich in monounsaturated fats and is one of the most studied parts of a heart-healthy diet. Try to incorporate this into recipes when you can. Importantly, choose freshly bottled, EVOO with an ideal polyphenol content of at least 250mg/kg, when available

In short – eat real, whole foods as often as possible

Exercise & Movement:

- Generally, the best movement is that of which you'll do. Find something you enjoy and do it 4+ times/week, recommended at 150 minutes per week minimum
- Outside of preferred activities, intense physical exercise has been shown to have significant reductions on Lp(a); this can generally look like doing an activity that is recognized by barely being about to speak in full sentences but not out of breath; this is known as zone 2 & 3 workouts in the fitness realm
- Weight lifting or resistance training 4x/week is also great for cardiovascular health and longevity in general

Targeted Supplements:

Use high-quality, third-party tested products

- CoQ10: supports cholesterol processing in the liver
- High-quality fish oils that are high in EPA can reduce arterial inflammation and improve Lp(a) levels
- Curcumin (from turmeric): offers anti-inflammatory benefits that modestly reduce Lp(a)
- L-carnitine: an amino acid that supports mitochondrial health, can reduce Lp(a) by up to 20%. Also naturally found in red meat, fish, poultry and dairy

It's important to note that all supplements should be third-party verified for purity and accuracy of contents.

Hormone Health and Lp(a):

- Because Lp(a) is made in the liver, a healthy metabolism and balanced hormones may help support lower levels; many high-quality studies support this
- Hormones such as progesterone, estradiol, testosterone and thyroid help maintain the lining of your blood vessels (the endothelium) and protect against plaque formation
- Supporting hormonal balance in general can be a very important part of long-term cardiovascular and health protection

Family Health and Screening

- Since Lp(a) is genetically inherited, first-degree family members (fathers, mothers, children, siblings) should also consider being tested
- A one-time blood test can help guide prevention across generations
- For patients >35, a coronary artery calcium scan (CAC) should be discussed with your PCP. This test would show you if you already have advanced, calcified plaque in your vessels. We recommend low-dose CT scanners to achieve this, if you choose to have this done.

Self-Advocacy in Your Healthcare Journey

Because Lp(a) is a newer and rapidly evolving area of cardiovascular medicine, **many healthcare providers are still becoming familiar with how to interpret and manage elevated levels**. This means you may sometimes encounter clinicians who are unsure what steps to take next—or who may not routinely screen for Lp(a) at all.

Your awareness is a powerful tool.

Here in our clinic, we use the latest evidence to guide your long-term prevention plan. However, when you are seeing providers outside this setting, you may need to **advocate for yourself and your family**. This can include:

- **Sharing your Lp(a) results** with new providers
- **Asking whether they are familiar with current guidelines** from the ACC/AHA, NLA, ASPC, or EAS
- Asking your PCP if Aspirin therapy would be right for you
- **Requesting appropriate follow-up testing**, such as advanced lipid panels or a low-dose Coronary Artery Calcium (CAC) scan when indicated
- **Discussing your family history** and encouraging screening for first-degree relatives
- **Bringing this handout** to visits as a reference point

You should never feel uncomfortable asking questions like:

“Given my elevated Lp(a), how can we reduce my overall cardiovascular risk?”

If a provider is unsure, that’s okay—Lp(a) science is advancing quickly. What matters most is that you remain informed, proactive, and empowered. We are here to support you, guide your care, and help equip you with the tools you need to navigate conversations confidently across all of your healthcare encounters.

Sources

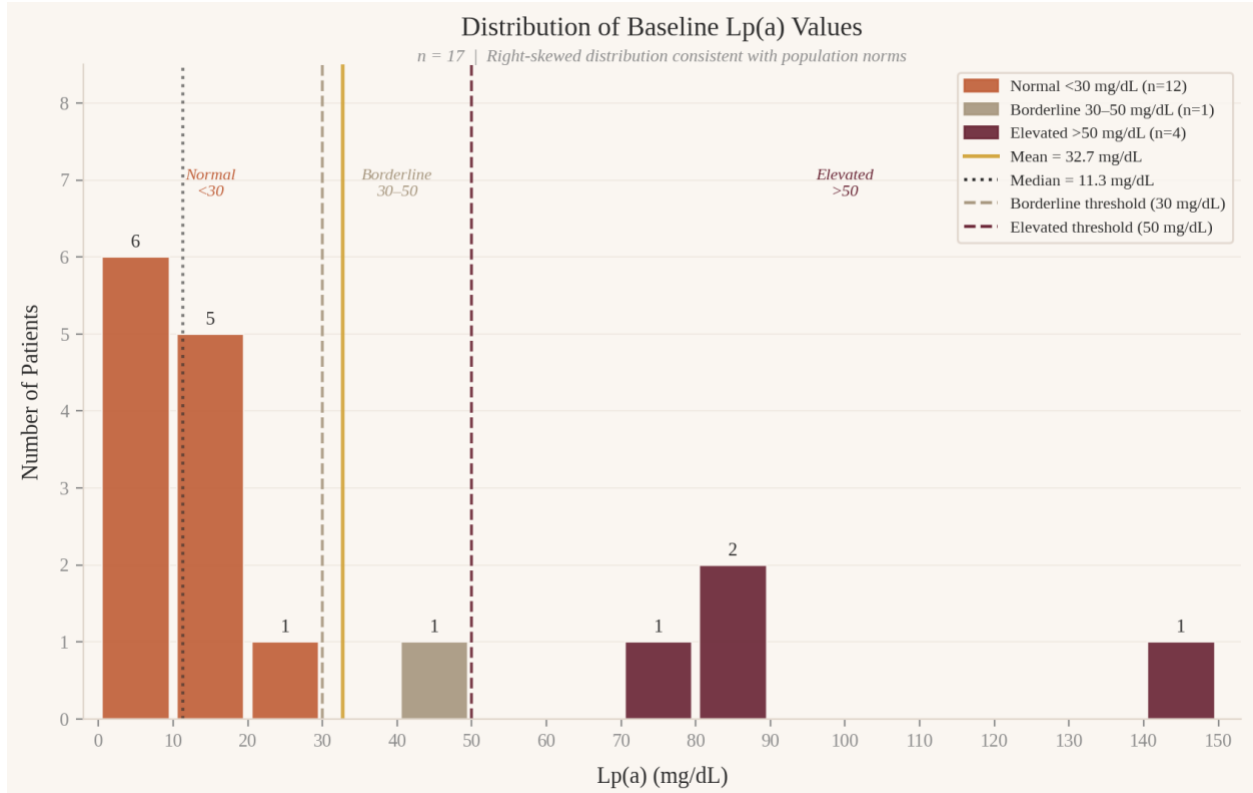
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APPENDIX D

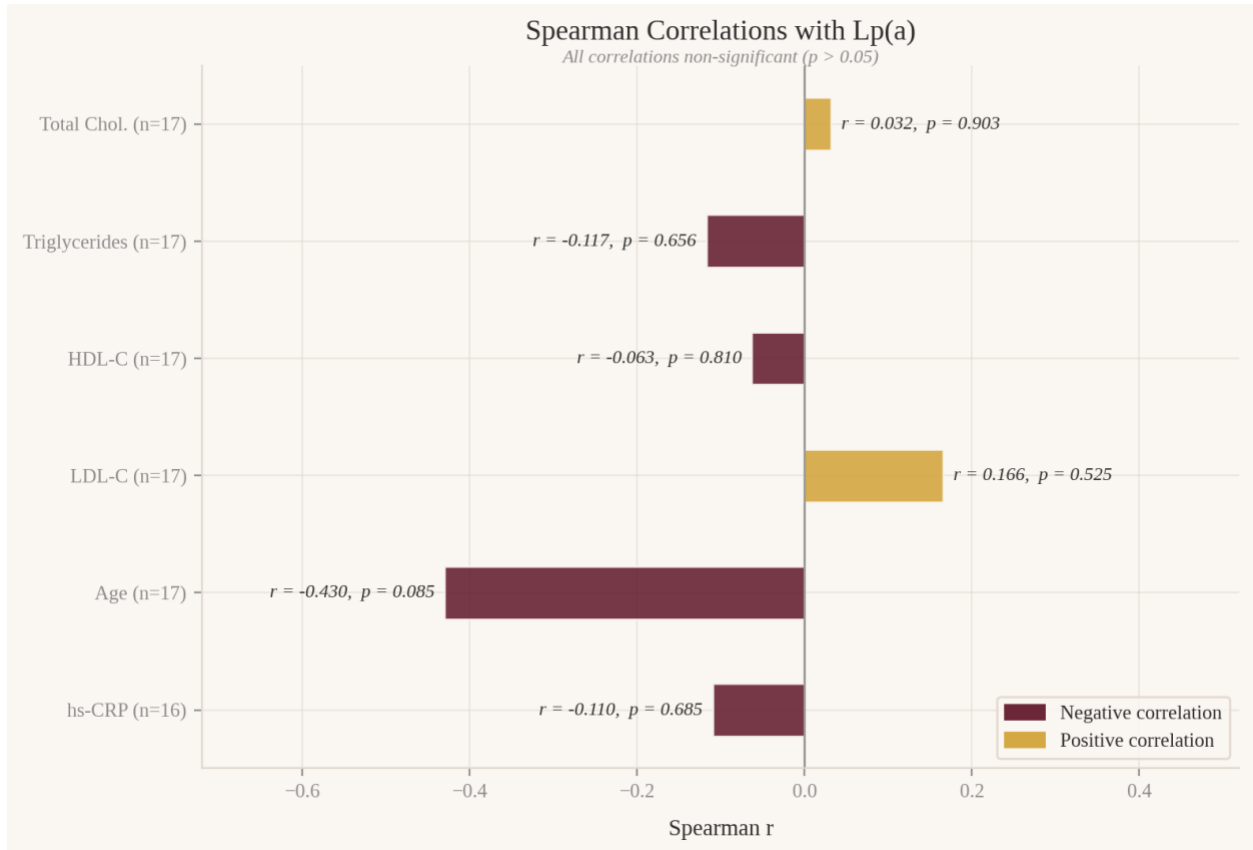
DISTRIBUTION OF BASELINE LP(a) VALUES



Appendix D. Frequency distribution of baseline Lp(a) values (mg/dL) across the analytic sample ($n = 17$). Bars are colored by clinical zone: terracotta = normal (<30 mg/dL, $n = 12$); taupe = borderline (30–50 mg/dL, $n = 1$); burgundy = elevated (>50 mg/dL, $n = 4$). Generated at the instruction of the author with analytical support from Claude (Anthropic, 2026).

APPENDIX E

SPEARMAN CORRELATION COEFFICIENTS



Appendix E. Summary of Spearman correlation coefficients between baseline Lp(a) and six clinical variables ($n = 16\text{--}17$). Burgundy bars indicate negative correlations; gold bars indicate positive correlations. All correlations were non-significant ($p > 0.05$). Generated at the instruction of the author with analytical support from Claude (Anthropic, 2026).