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Cost-Effectiveness of Lipid-Lowering Treatments in Young Adults

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Abstract

Background: Raised low-density lipoprotein cholesterol (LDL-C) in young adulthood (ages 18–39 years) is associated with atherosclerotic cardiovascular disease (ASCVD) later in life. Most young adults with elevated LDL-C do not currently receive lipid-lowering treatment.

Objectives: We aimed to estimate the prevalence of elevated LDL-C in ASCVD-free U.S. young adults and the cost-effectiveness of lipid-lowering strategies for raised LDL-C in young adulthood compared with standard care.

Methods: Prevalence of raised LDL-C was examined in the U.S. National Health and Nutrition Examination Survey. The CVD Policy Model projected lifetime quality-adjusted life years (QALYs), healthcare costs, and incremental cost-effectiveness ratios (ICERs) for lipid-lowering strategies. Standard care was statin treatment for adults aged ≥40 years based on LDL-C, ASCVD risk, or diabetes plus young adults with LDL-C ≥190 mg/dL. Lipid-lowering incremental to standard care with moderate-intensity statins or intensive lifestyle interventions was simulated starting when young adult LDL-C was either ≥160 mg/dL or ≥130 mg/dL.

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Results: Around 27% of ASCVD-free young adults have LDL-C ≥130 mg/dL, and 9% have LDL-C ≥160 mg/dL. The model projected that young adult lipid-lowering with statins or lifestyle interventions would prevent lifetime ASCVD events and increase QALYs compared with standard care. ICERs were $31,000/QALY for statins in young adult men with LDL-C ≥130 mg/dL, and $106,000/QALY for statins in young adult women with LDL-C ≥130 mg/dL. Intensive lifestyle intervention was more costly and less effective than statin therapy.

Conclusion: Statin treatment for LDL-C ≥130 mg/dL is highly cost-effective in young adult men and intermediately cost-effective in young adult women.

CONDENSED ABSTRACT:

Raised low-density lipoprotein cholesterol (LDL-C) in young adulthood is associated with atherosclerotic cardiovascular disease (ASCVD) later in life. Most young adults with elevated LDL-C do not receive lipid-lowering treatment. We used the CVD Policy Model to estimate cost-effectiveness of lipid lowering with moderate-intensity statins or intensive lifestyle interventions for raised LDL-C in young adulthood compared with standard care. Statin treatment for LDL-C ≥130 mg/dL in young adulthood was projected to be highly cost-effective in men and intermediately cost-effective in women. Intensive lifestyle interventions were more costly and less effective than statins for young adult lipid lowering.

Keywords

Young adulthood; cholesterol; cardiovascular disease; statins; cost-effectiveness

Introduction

Raised low density-lipoprotein cholesterol (LDL-C) in young adulthood (ages 18 to 39 years) increases risk of atherosclerotic cardiovascular disease (ASCVD) later in life (1–3). At present, only a small proportion of young adults with raised LDL-C are recommended for lipid-lowering treatment.

HMG Co-A reductase inhibitors (‘statins’) substantially lower LDL-C, are cost-effective for primary ASCVD prevention in adults aged 40–74 years, and are available in low-cost, generic formulations (4,5). Intensive lifestyle interventions involving face-to-face or group-based behavioral counseling to improve diet, physical activity, or both, alongside regular primary care significantly reduce LDL-C, blood pressure, and body mass index (6).

The 2018 American College of Cardiology/American Heart Association (ACC/AHA) clinical guideline strongly recommended statins to prevent ASCVD in all adults with LDL-C ≥190 mg/dL, and those aged 40–74 years with 10-year ASCVD risk ≥7.5% or diabetes (7). The guideline recommended lifestyle modifications for all young adults with elevated LDL-C but restricted statin treatment to young adults with LDL-C ≥190 mg/dL. The United States Preventive Services Task Force has made no specific recommendation for the management of raised LDL-C in young adults (8).

Expanding statin or intensive lifestyle intervention eligibility for young adults could substantially improve population health (9). We compared the clinical and economic

impact of initiating lipid-lowering strategies for raised LDL-C in young adulthood to 2018 ACC/AHA guideline-recommended standard care using a mathematical model that simulated long-term ASCVD effects of LDL-C exposures and lipid-lowering interventions.

Methods

We obtained Columbia University Institutional Review Board approval to perform secondary analysis on individual participant data from National Institutes of Health observational cohort studies. All other data sources were publicly accessible or published summary data.

Number of Treatment-Eligible Young Adults

To project the number of U.S. young adults eligible for lipid-lowering therapies, we examined the age-stratified distribution of LDL-C (<100 mg/dL, 100–129 mg/dL, 130–159 mg/dL, 160–189 mg/dL, and ≥190 mg/dL) among ASCVD-free U.S. adults in the National Health and Nutrition Examination Survey (NHANES) 1999–2014, scaled to 2020 U.S. population estimates (10,11). We also examined self-reported cholesterol screening rates to contextualize awareness of raised LDL-C (Supplemental Appendix).

CVD Policy Model

A microsimulation version of the CVD Policy Model was developed in TreeAge Pro, version 2020 (TreeAge Software, Inc., Williamstown, Massachusetts). The model estimated lifetime health-related quality of life and direct healthcare costs (2020 USD) for LDL-C-reduction strategies in a nationally representative cohort of ASCVD-free U.S. young adults. The CVD Policy Model uses time-varying ASCVD risk factor exposures to simulate an individual's lifetime risk of ASCVD. As individuals progress through the model, they accumulate healthcare costs and quality-adjusted life years (QALYs; Supplemental Tables 1–5).

Individuals start the simulation without ASCVD and, each year, are at risk of coronary heart disease (CHD), stroke, combined CHD and stroke, and ASCVD or non-ASCVD death. Incident ASCVD and non-ASCVD mortality risks are estimated using competing risk survival models developed in the National Heart, Lung, and Blood Institute Pooled Cohorts Study (NHLBI-PCS) dataset (Supplemental Figure 1) (12–15).

Probabilities of first ASCVD event and probability of non-ASCVD mortality are operationalized in the model using logistic risk functions (Supplemental Table 1, Equation 1). Predictors include race (African American or non-African American), current age, LDL-C, high-density lipoprotein cholesterol, systolic blood pressure (SBP), body mass index, smoking status (current, former, never), cigarettes per day, diabetes status, and estimated glomerular filtration rate. Both LDL-C and SBP are incorporated in the risk functions as time-weighted averages (TWA) which are updated each year from age 18 to present. Individuals with higher lifetime exposure to LDL-C are at greater risk of experiencing CHD and stroke (Central Illustration). Interaction effects with age reduce the effect of the TWA variables over time.

Equation 1.

Logistic risk function predicting event k, incorporating underlying rate of event k in population (α), coefficients determining risk factor effect on risk (β), time-weighted average (TWA) LDL-C and SBP from age 18 to present, and remaining ASCVD risk factors (RFs)

$$rate_k = \frac{e^{(\alpha + \beta_{age} * AGE + \sum \beta_{RF} * RF + \beta_{SBP,TWA} * SBP_{TWA} + \beta_{LDL-C,TWA} * LDL-C_{TWA})}}{1 + e^{(\alpha + \beta_{age} * AGE + \sum \beta_{RF} * RF + \beta_{SBP,TWA} * SBP_{TWA} + \beta_{LDL-C,TWA} * LDL-C_{TWA})}}$$

Risk functions were recalibrated so that modeled event rates matched contemporary U.S. ASCVD incidence and total event, ASCVD-related mortality, and all-cause mortality rates (Supplemental Figure 2). Results were recalibrated with data from a previously validated, population simulation version of the CVD Policy Model and U.S. Centers for Disease Control and Prevention data. Recalibration was conducted separately for women and men.

Simulation Cohort

The simulated cohort was created by sampling ASCVD-free young adult participants from U.S. NHANES 1999–2014 exams. Participants were excluded if they reported a diagnosis of heart failure, stroke, or CHD. Lifetime (ages 18 to 89 years) ASCVD risk factor trajectories were assigned to each NHANES participant by randomly matching them 1:1 to NHLBI-PCS participants for whom trajectories were previously defined (Supplemental Table 6, Supplemental Figure 3) (1,13,14). We repeatedly sampled with replacement the NHANES-NHLBI-PCS matched participants to create 100 cohorts, each consisting of 250,000 young adult men and 250,000 young adult women.

Simulated Treatment Strategies

Every individual was simulated through the model from their age at NHANES observation until age 89 years or death. Lipid screening commenced at the start of the simulation and repeated every five years throughout an individual's life while untreated and without ASCVD. To avoid unnecessary inconvenience and testing costs for patients unlikely to require lipid management, screening was not continued for young adults with an LDL-C ≥10 mg/dL below the treatment initiation threshold at first screen. For these individuals, screening recommenced at age 40.

Lifetime ASCVD, survival, and cost-effectiveness outcomes were projected for different LDL-C treatment strategies. The reference 'standard care' strategy was defined according to the 2018 AHA/ACC guideline (Supplement) (16). Standard care was statin treatment for adults aged ≥40 years based on LDL-C, ASCVD risk, or diabetes plus young adults with LDL-C ≥190 mg/dL. Each young adult treatment strategy was supplemental to standard care.

Four treatment strategies were compared with standard care in the primary analysis. The first two initiated moderate-intensity statins in young adults with LDL-C ≥160 mg/dL or ≥130 mg/dL. The second two initiated intensive lifestyle modification in young adults with LDL-C ≥160 mg/dL or ≥130 mg/dL. All individuals were treated according to ACC/AHA 2018 guidelines after age 40 years. A secondary analysis included moderate intensity statins

plus intensive lifestyle intervention in young adults with LDL-C ≥160 mg/dL and LDL-C ≥130 mg/dL as a comparator.

Treatment Inputs

Treatment input parameters are outlined in Table 1.

For statin treatment strategies, the magnitude of clinical benefit was a function of the magnitude of LDL-C reduction. Moderate- and high-intensity statin therapy reduced LDL-C by 29% and 43%, respectively (17). For adults aged ≥40 years, we applied the relative risk (RR) of statins on ASCVD per 1.0 mmol/L (38.67 mg/dL) reduction in LDL-C from clinical trials (5). For young adults, lipid-lowering benefit was modelled through the counterfactual of lower ASCVD risk with lower time-weighted average LDL-C observed in longitudinal cohort data (13).

For lifestyle interventions, the magnitude of clinical benefit corresponded to LDL-C and SBP reductions (6). Intensive lifestyle interventions reduced LDL-C by 0.05 mmol/L (2.1 mg/dL) and SBP by 1.9 mm Hg, which were derived from a U.S. Preventive Services Task Force meta-analysis of behavioral counselling for ASCVD prevention (6). Lifestyle interventions also reduced risk of incident diabetes (RR 0.67) throughout the course of treatment.

Clinical benefit was greater for individuals receiving lipid-lowering in young adulthood because earlier intervention results in lower cumulative LDL-C exposure over the adult life course. To benchmark this assumption, we compared the simulated CHD RRs of young adult and later life LDL-C lowering with the RR of 0.78 per 17 mg/dL lifetime lower LDL-C observed in a Mendelian randomization study (PCSK9 R46L loss-of-function mutation, Supplemental Table 7) (18,19). As expected, the simulated RRs for CHD per 17 mg/dL of LDL-C lowering in young adulthood and in later life were higher, 0.86 and 0.92, respectively.

Adherence to statin therapy (i.e., proportion continuing with treatment beyond persistence observed in clinical trials) was assumed to be 67%, 53%, and 50% in the first, second, and subsequent years of treatment, respectively (20). Persistent statin users experienced slight increases in diabetes risk, annual pill-taking utility decrements, and follow-up physician visits (7,21,22). While statins are generally well-tolerated (23), costs were also included for minor and major statin-related adverse events which occurred in 4.7% and 0.006% of statin users, respectively (22). Based on expert opinion, treatment effect for intensive lifestyle interventions did not persist past five years. Low adherence or abbreviated treatment attenuated LDL-C reduction, side effect risks, and treatment-related costs. In a sensitivity analysis, we examined outcomes when the duration of treatment effect with full adherence was varied from 1 to 22 years.

The annual cost of statins was calculated as the median cost of statin therapy to all payers, including patient out-of-pocket costs, in the 2017 Medical Expenditure Panel Survey (Supplemental Table 8) (24). The cost of lifestyle intervention was the median cost of group therapy from a systematic review of economic evaluations of diet and physical activity

promotion programs for the prevention of type-2 diabetes (25). Few behavioral intervention studies extend beyond one year and optimal regularity of long-term behavioral visits with physicians has not been established. Based on expert opinion, we determined that patients receiving lifestyle modification treatment would incur costs for four annual cardiovascular prevention behavioral visits in years subsequent to treatment initiation.

Main Analysis

Primary model outcomes were lifetime QALYs gained, direct healthcare costs in 2020 U.S. dollars, and incremental cost-effectiveness ratios (ICERs), stratified by sex. The mean and 95% uncertainty interval (95% UI; i.e., the 2.5th to 97.5th percentile interval of the means) were calculated for model outcomes from 100 probabilistic simulations in which model inputs were sampled from pre-specified distributions. Strategies were classified as highly cost-effective (ICER <$50,000/QALY gained), intermediately cost-effective (ICER ≥$50,000/QALY but <$150,000/QALY gained), or not cost-effective (ICER ≥$150,000/QALY gained) in accordance with the ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures (26,27). We performed all analyses from a U.S. healthcare sector perspective, which includes all formal healthcare costs (i.e., treatment-related, ASCVD, and non-ASCVD healthcare costs) regardless of payer (e.g., patients, insurance companies, etc.). Future QALYs and costs were discounted 3.0% annually (28).

Sensitivity Analysis

One-way sensitivity analyses estimated the effect of changing the model inputs (Table 1) one at a time across the upper and lower uncertainty bounds while holding all other parameters constant (Supplement). In a further sensitivity analysis, we examined outcomes when the duration of treatment effect with full adherence was varied from 1 to 22 years.

This study followed the Consolidated Health Economic Evaluation Reporting Standards reporting guideline (Supplemental Table 9).

Results

Number of Treatment-Eligible Young Adults

An estimated 26.3 million (27%) U.S. young adults without ASCVD have LDL-C ≥130 mg/dL, and over 8.5 million (9%) have LDL-C ≥160 mg/dL (Figure 1, Table 2). Around half (56%) of young adults have had their cholesterol checked. In comparison, 87% of adults aged 40–74 years have had their cholesterol checked.

Main Cost-Effectiveness Analysis

Baseline characteristics of the simulation cohorts are provided in Supplemental Table 10. Compared to women, on average men had higher mean LDL-C, lower mean HDL-C, higher mean SBP, and higher smoking rates.

For both men and women, the simulated model projected that adding statin treatment for young adults with LDL-C ≥130 mg/dL to standard care would prevent the most ASCVD

events and gain the most QALYs in the population (Table 3, Figure 2, Supplemental Table 11).

For young adult men with LDL-C ≥160 mg/dL, statin therapy was estimated to produce an ICER of $13,200/QALY compared to standard care. Further expanding statin eligibility to young adult men with LDL-C ≥130 mg/dL was estimated to produce an ICER of $31,000/QALY compared with statins for LDL-C ≥160 mg/dL. For young adult women with LDL-C ≥160 mg/dL, the model projected that statins would produce an ICER of $51,500/QALY compared to standard care. Further expanding statin eligibility to young adult women with LDL-C ≥130 mg/dL produced an ICER of $106,000/QALY. Young adult lifestyle treatment strategies were all predicted to be more costly and less effective than statin treatment strategies (i.e., strictly dominated).

For men, statin therapy for individuals with LDL-C ≥130 mg/dL was projected to be the preferred strategy in 72% of probabilistic simulations at a cost-effectiveness threshold of $50,000/QALY. At a cost-effectiveness threshold of $50,000/QALY, standard care had the highest probability (51%) of being the preferred strategy for women (Supplemental Figure 4). At a higher cost-effectiveness threshold of $150,000/QALY, however, statin therapy with LDL-C ≥130 mg/dL was projected to be the preferred treatment strategy for both men (95%) and women (59%).

In the secondary analysis, the model projected that statins plus intensive lifestyle intervention for young adults with LDL-C ≥160 mg/dL had a higher ICER and less QALYs gained than statin therapy alone for both men and women (i.e., statins plus intensive lifestyle strategies were extendedly dominated) (Supplemental Table 12). Statins plus intensive lifestyle intervention for young adults with LDL-C ≥160 mg/dL were projected to produce ICERs of $59,300/QALY and $137,000/QALY compared to statin therapy alone for men and women, respectively.

Sensitivity Analysis

In sensitivity analyses, the cost-effectiveness of statin strategies was most sensitive to changes in the discount rate, statin efficacy, and magnitude of effect of cumulative exposure to LDL-C on CHD risk (Supplemental Figure 5). The cost-effectiveness of statin therapy could be improved for men and women by using low-price statin formulations, improving patient adherence, reducing required check-up visits for persistent statin users, and averting patient pill-taking disutility. Results for the intensive lifestyle interventions strategies were sensitive to changes in the effect of such interventions on young adult LDL-C, discount rate, and number of behavioral visits required in years subsequent to treatment initiation.

All treatments were projected to become more effective compared to standard care as duration of treatment effect increased (Supplemental Figure 6). Even when treatment effects were sustained for ≥10 years, statin treatment strategies were more cost-effective than intensive lifestyle interventions (Supplemental Figure 7).

Discussion

In this mathematical modelling study, early statin treatment starting in young adulthood at lower-than- current-guideline-recommended LDL-C thresholds was projected to prevent or delay ASCVD events and improve population health. Statin therapy was projected to be highly cost-effective for young adult men with LDL-C ≥130 mg/dL and intermediately cost-effective for young adult women with LDL-C ≥130 mg/dL. The advent of generic pricing has rendered statin treatment highly cost-effective for tens of millions of young adults with raised LDL-C. This result echoes previous findings regarding increased cost-effectiveness of statin therapy following price reductions (4,22,29).

To our knowledge, this is the first cost-effectiveness analysis of LDL-C treatment in young adults. Though the efficacy of young adult statin treatment has never been tested in clinical trials, the relationship between cumulative LDL-C exposure earlier in life and later life ASCVD has been established extensively in observational cohort studies. Cumulative exposure to high LDL-C in young adulthood and middle-age have both been shown to significantly increase risk of ASCVD in later life (3,13,30). When clinical trial evidence is unavailable, simulating decades-long “trials” is a feasible approach to estimating the effectiveness and cost-effectiveness of long-term statin treatment in young adults with raised LDL-C. Our benchmarking exercise found that the dose-response we estimated for young adult statin treatment lies between the observed effects of lifelong lower LDL-C (from a Mendelian randomization study comparing PCSK9 loss-of-function mutation carriers to non-carriers) and later-life LDL-C lowering (from randomized controlled trials of statin versus placebo).

Our NHANES analysis found that almost half of U.S. young adults have never had their cholesterol screened. This aligns with previous estimates of young adult LDL-C screening rates (31,32). In the U.S., many young adults lack health insurance; for those with employer-based or government insurance, lipid screening is not generally reimbursed. Insurance and payment reforms could incentivize young adult lipid screening and treatment. For example, Medicare could reimburse private insurers for treating raised LDL-C in young adults due to anticipated avoided ASCVD events and cost savings when these patients become Medicare eligible. Young adult lipid screening could be expanded efficiently by offering lower cost screening tests and engaging with community centers or using team-based care to introduce home, work site, or community-based lipid screening. Additionally, selectively screening young adults with obesity, diabetes, or genetic testing for family history consistent with familial hypercholesterolemia may increase screening and treatment among those at highest risk of ASCVD. However, before investing in expanded statin treatment to young adults, it is important to consider that our previous analysis found treating “borderline” risk adults aged ≥40 years (10-year ASCVD risk 5.0–7.4%) is even more cost-effective incremental to standard care than treating young adults with raised LDL-C (Supplemental Table 13) (4).

Greater cost-effectiveness of statin treatment for men has been observed in previous analyses (4). This differential cost-effectiveness occurred in our analysis because men are at greater lifetime risk of ASCVD than women (33) and young adult men are more likely to have elevated LDL-C than young adult women. Both LDL-C levels and cholesterol screening

rates vary across racial subgroups of U.S. young adults (Supplemental Table 14). Further research should establish the impact of young adult lipid-lowering screening and treatment strategies on racial disparities in health.

Study Limitations

Our results suggest that intensive intervention to lower LDL-C through individual lifestyle behavior change is not cost-effective. However, we did not evaluate the alternative of population-wide diet and lifestyle programs that have been highly effective in lowering LDL-C and improving population health (34). Alternative approaches that systematically optimize behavioral 'treatment packages' may help establish more cost-effective and sustainable behavioral treatments for LDL-C lowering (35,36).

Though young adult lipid-lowering could lead to lifetime health gains for eligible patients, there may be long-term statin-related adverse event risks that we have not accounted for. In middle-aged adults, long-term statins present a favorable profile when risks are weighed against benefits (37–39). Our analysis accounted for the risk of statin-induced diabetes, pill-taking disutility, and costs related to other major and minor statin-related adverse events. In sensitivity analyses, our results were robust to assumptions regarding the incidence and impact of statin-related adverse events. Nonetheless, we may have underestimated how intolerable daily pill-taking is for young adults. While there is limited evidence on statin adherence in ASCVD-free young adults, our estimate aligns with reported adherence rates in young adults with high LDL-C and individuals with who experienced 'extremely premature' ASCVD (40,41). Statin adherence rates may be lower in young adults compared with older adults and we explored alternative adherence rates in sensitivity analyses. A practical and more patient-centered approach to young adult lipid-lowering may require the development of once- or twice-yearly treatments (as seen with newer, experimental PCSK9 inhibitor agents) and making them low-cost.

Conclusions

Around one quarter of U.S. young adults have elevated LDL-C. This mathematical modelling study found that initiating statin treatment in young adults with LDL-C ≥130 mg/dL is highly cost-effective in men and intermediately cost-effective in women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures:

Dr Kazi reported receiving economic support from the Institute for Clinical and Economic Review outside the submitted work. Dr Moran reported receiving grants from the National Heart, Lung, and Blood Institute during the conduct of the study. No other disclosures were reported.

Role of the Funder/Sponsor:

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
CHD	Coronary Heart Disease
ICER	Incremental Cost-Effectiveness Ratio
INMB	Incremental Net Monetary Benefits
LDL-C	Low-Density Lipoprotein Cholesterol
NHLBI-PCS	National Heart, Lung, and Blood Institute Pooled Cohorts Study
NHANES	National Health and Nutrition Examination Survey
QALY	Quality-Adjusted Life Year
RR	Relative Risk
SBP	Systolic Blood Pressure
TWA	Time-Weighted Averages

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Clinical Perspectives

Competency in Systems-Based Practice: Treating elevated LDL-cholesterol (LDL-C) is intermediately cost-effective for young women and highly cost-effective for young men. Translational Outlook: Given the challenges and potential risks of beginning lifetime statin treatment in young adulthood, additional research is needed to develop efficacious and sustainable lifestyle interventions to lower LDL-C.

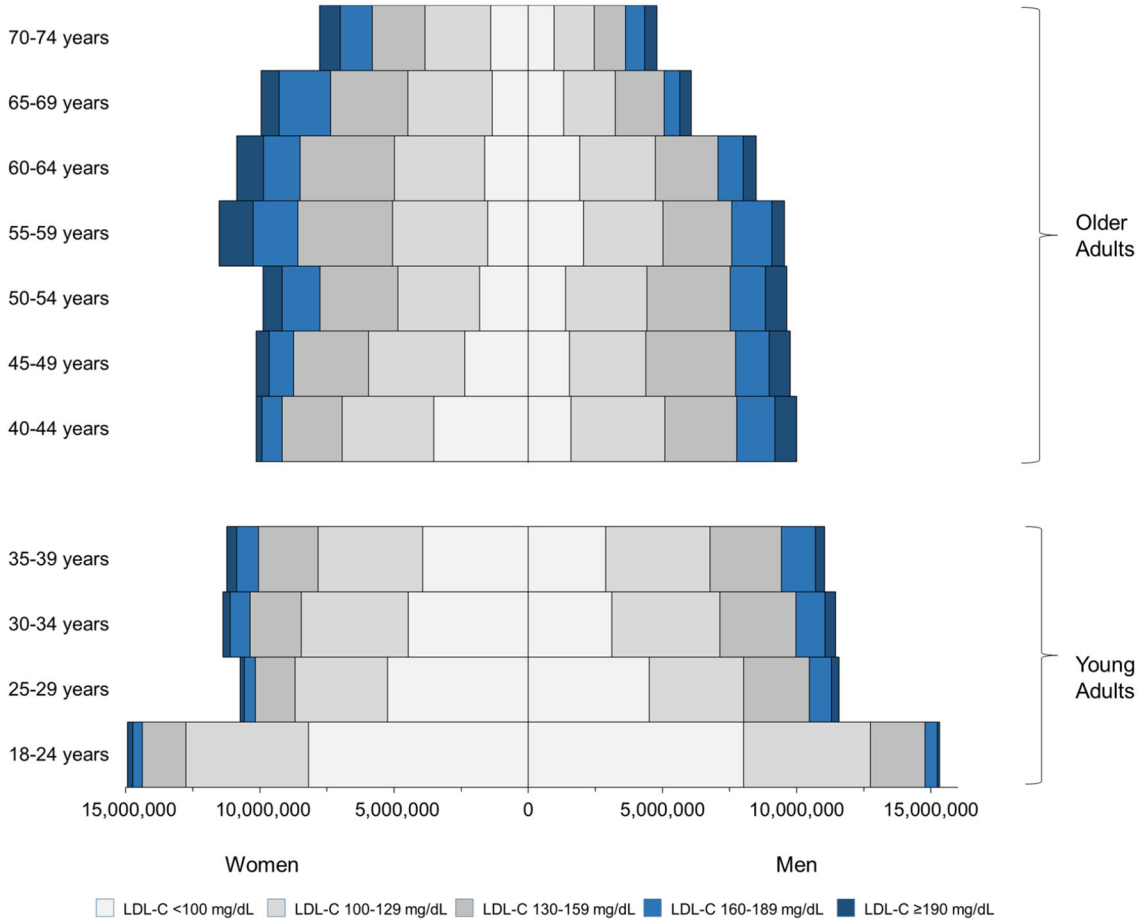
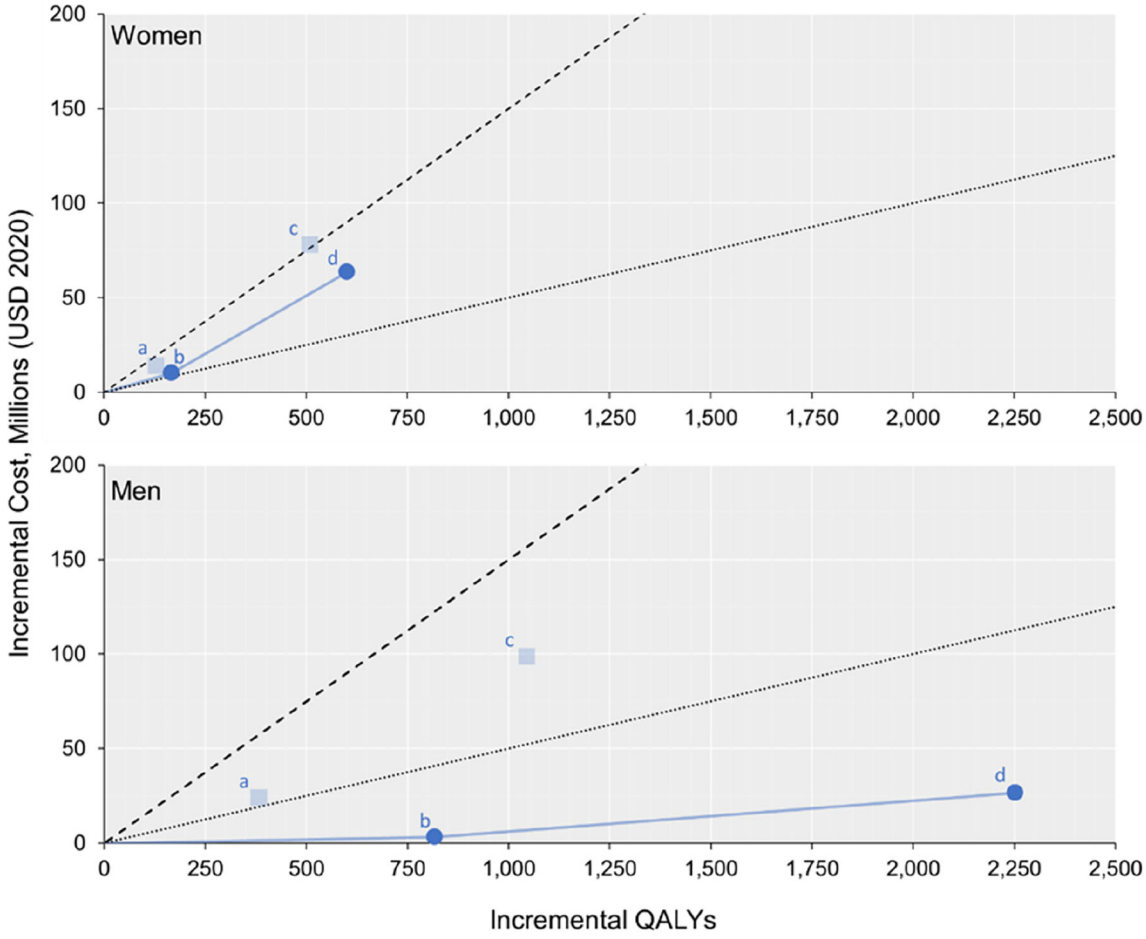


Figure 1. Distribution of untreated LDL-C in ASCVD-free, U.S. adults.

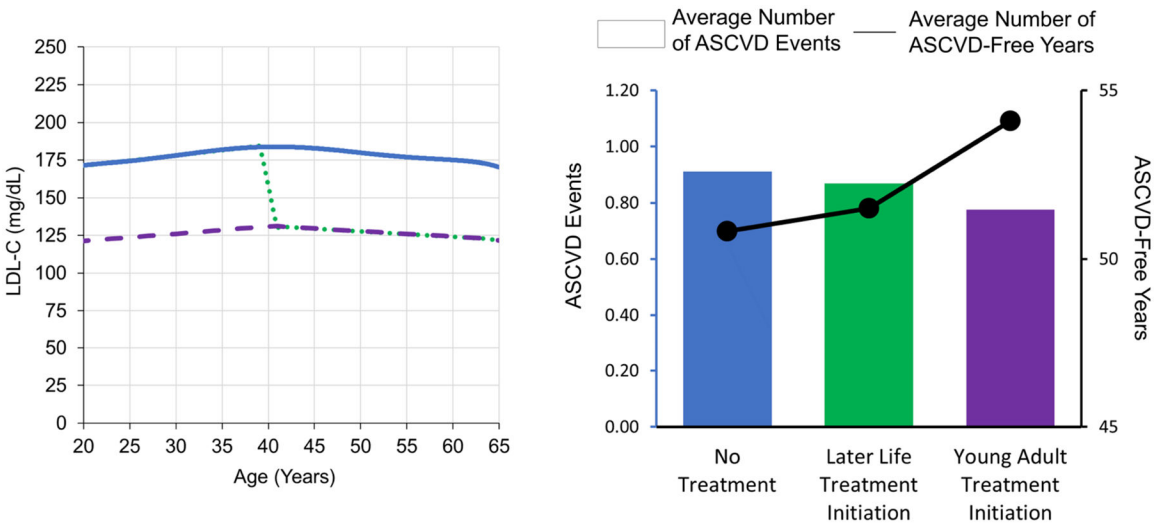
Analysis conducted in the National Health and Nutrition Examination Survey. LDL-C – low-density lipoprotein cholesterol. Notes: The LDL-C distribution was estimated from the 1999 to 2014 NHANES cycles and projected onto 2020 population estimates (method in Supplemental Methods; Table 2).To convert LDL-C from mg/dL to mmol/L, divide by 38.67.



a. Standard care + young adult LDL-C ≥160 mg/dL, lifestyle
b. Standard care + young adult LDL-C ≥160 mg/dL, statins
c. Standard care + young adult LDL-C ≥130 mg/dL, lifestyle
d. Standard care + young adult LDL-C ≥130 mg/dL, statins
– – – – – cost-effectiveness threshold: $150,000/QALY
····· cost-effectiveness threshold: $50,000/QALY

Figure 2. Cost-effectiveness plane for lipid-lowering strategies in U.S. young adults.

The transparent points illustrated indicate that the strategy costs more and is less effective than another strategy (i.e., strictly dominated). The solid blue lines represent strategies that are eligible to be considered the preferred treatment (i.e., the cost-effectiveness frontier, which comprises the non-dominated strategies ranked by increasing effectiveness). A strategy is considered cost-effective if the slope of the blue line connecting it to the next least effective strategy (i.e., the incremental cost-effectiveness ratio) is lower than the slope of the cost-effectiveness threshold line. The preferred strategy is defined as the treatment that results in the greatest QALY gains and is cost-effective. LDL-C - low-density lipoprotein cholesterol; QALYs – quality-adjusted life years. To convert LDL-C from mg/dL to mmol/L, divide by 38.67.



Central Illustration. Conceptual diagram, CVD Policy Model and time-weighted average risk factors.

Panel A (left): Potential LDL-C trajectories for a 20-year-old young adult with raised LDL-C (172 mg/dL) are shown: no treatment (blue), later life statin treatment (green), and lifetime statin treatment (purple). Panel B (right): Results are shown for 100,000 simulations of the three LDL-C trajectories in Panel A while holding other risk factors constant. Mean number of ASCVD events (left axis) was lower and mean ASCVD-free years (right axis) was greater with treatment initiation in young adulthood.

Table 1.

Simulation parameters

Parameter	Base case	Distribution for PSA	Lower Bound	Upper Bound	Source
RR per 1.0 mmol/L time-weighted average LDL-C reduction					
CHD	0.740	Beta	0.710	0.780	(13)
Stroke	0.900	Beta	0.810	0.990	(13)
RR per 1.0 mmol/L LDL-C reduction from statin therapy in adulthood					
CHD	0.760	Beta	0.730	0.790	(5)
Stroke	0.850	Beta	0.800	0.890	(5)
Statin LDL-C reduction (% change from baseline)					
Moderate-intensity	29.0	Beta	14.0	38.0	(17)
High-intensity	43.0	Beta	39.0	46.0	(17)
Statin-related adverse events					
Statin-induced diabetes, absolute annual risk increase (%)	0.500	Log-normal	0.000	1.00	(43)
Pill-taking disutility	0.002	Beta	0.000	0.004	(23)
Probability minor adverse event (%)	4.7	Beta	0.0	9.4	(23)
Probability major adverse event (%)	0.006	Beta	0.000	0.012	(23)
Cost minor adverse event ($)	178.53	Gamma	133.90	223.16	(23)
Cost major adverse event ($)	7,033.00	Gamma	5,274.75	8,791.25	(23)
Statin treatment adherence (%)					
Year 1	67.0	Beta	50.0	84.0	(21)
Year 2	53.0	Beta	40.0	66.0	(21)
Subsequent Years	50.0	Beta	38.0	63.0	(21)
Young adult intensive lifestyle intervention effects					
LDL-C reduction (mmol/L)	0.05	Beta	0.00	0.11	(18)
SBP reduction (mm Hg)	1.80	Beta	0.89	2.21	(18)
Relative risk incident diabetes	0.67	Beta	0.51	0.87	(18)
Duration of effect (years)	5.00	n/a	2.00	8.00	(18)
Annual intervention costs ($)					
Moderate-intensity (median; Medical Expenditure Panel Survey)	102.52	Gamma	41.18	163.85	(44)
High-intensity (median; Medical Expenditure Panel Survey)	151.34	Gamma	65.70	236.98	(44)
Statin dispensing fees	30.00	Gamma	0.00	60.00	Assumption
Group-based intensive lifestyle change intervention in primary care setting	512.83	Gamma	384.63	641.04	(26)
Checkup and screening visit costs ($ per visit)					
Checkup visit, on treatment	81.83	Gamma	59.96	99.93	(45)
Screening visit, no treatment	81.83	Gamma	59.96	99.93	(45)
Cardiovascular prevention behavioral visit (15 minutes)	33.07	Gamma	24.23	40.38	(45)
Other costs ($)					

Parameter	Base case	Distribution for PSA	Lower Bound	Upper Bound	Source
Lipid panel test	23.92	Gamma	17.94	29.89	(46)
Liver panel test	1.47	Gamma	1.10	1.84	(46)
Weighted statin-induced diabetes cost	9.75	Gamma	7.32	12.19	(46)
Office visit frequency					
Years between screening visits	5.00	n/a	4.00	6.00	(16)
Primary care check-up while on statin treatment (years)	1.25	Gamma	0.00	3.00	(16)
Behavioral visits in treatment years 2 to 5	4.00	Gamma	1.00	7.00	Assumption
Discount rate (%)					
Health	3.0	n/a	0.0	6.0	(29)
Costs	3.0	n/a	0.0	6.0	(29)

LDL-C – low-density lipoprotein cholesterol; PSA – probabilistic sensitivity analysis; RR – relative risk; SBP – Systolic blood pressure

Footnote: This table contains a list of the parameters employed to simulate cholesterol screening, statin therapy, and lifestyle interventions in our analysis. Probabilistic distributions are provided, which were used to stochastically sample these parameters. Lower and upper bounds are provided, which detail ranges employed in one-way sensitivity analyses.

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Table 2.

Prevalence of untreated LDL-C in ASCVD-free U.S. adults

	Total Number ASCVD-Free	Ever had LDL-C Screened? N (%, 95% UI)	LDL-C screened within 5 years N (%, 95% UI)	Number (%, 95% UI) in low-density lipoprotein cholesterol group				
				0–99 mg/dL	100–129 mg/dL	130–159 mg/dL	160–189 mg/dL	≥190 mg/dL
Women								
Young Adults (Aged 18–39)	47,904,000	26,747,000 (56, 95% UI: 54–58)	24,285,000 (51, 95% UI: 49–53)	20,905,000 (44, 95% UI: 41–46)	15,959,000 (33, 95% UI: 31–35)	7,510,000 (15, 95% UI: 14–17)	2,517,000 (5.3, 95% UI: 4.4–6.2)	1,013,000 (2.1, 95% UI: 1.5–2.8)
Older Adults (Aged 40–74)	63,366,000	55,345,000 (87, 95% UI: 86–88)	51,735,000 (82, 95% UI: 80–83)	12,829,000 (20, 95% UI: 19–22)	20,713,000 (33, 95% UI: 31–34)	17,659,000 (28, 95% UI: 26–30)	7,874,000 (12, 95% UI: 11–14)	4,291,000 (6.8, 95% UI: 5.9–7.8)
Men								
Young Adults (Aged 18–39)	49,385,000	23,100,000 (47, 95% UI: 44–49)	20,392,000 (41, 95% UI: 39–44)	17,951,000 (36, 95% UI: 34–49)	16,220,000 (33, 95% UI: 31–35)	10,232,000 (21, 95% UI: 19–23)	3,824,000 (7.7, 95% UI: 6.7–8.9)	1,158,000 (2.3, 95% UI: 1.7–3.2)
Older Adults (Aged 40–74)	58,091,000	48,613,000 (84, 95% UI: 82–85)	44,866,000 (77, 95% UI: 75–79)	10,341,000 (18, 95% UI: 16–19)	18,746,000 (32, 95% UI: 30–34)	17,344,000 (30, 95% UI: 28–32)	7,612,000 (13, 95% UI: 12–15)	4,048,000 (7.0, 95% UI: 5.9–8.1)
Combined								
Young Adults (Aged 18–39)	97,289,000	49,847,000 (51, 95% UI: 50–53)	44,677,000 (46, 95% UI: 44–48)	38,856,000 (40, 95% UI: 38–42)	32,179,000 (33, 95% UI: 31–35)	17,742,000 (18, 95% UI: 17–19)	6,341,000 (6.5, 95% UI: 5.8–7.3)	2,171,000 (2.2, 95% UI: 1.8–2.8)
Older Adults (Aged 40–74)	121,457,000	103,958,000 (86, 95% UI: 85–87)	96,601,000 (80, 95% UI: 78–81)	23,170,000 (19, 95% UI: 18–21)	39,459,000 (32, 95% UI: 31–34)	35,003,000 (29, 95% UI: 28–30)	15,486,000 (13, 95% UI: 12–14)	8,339,000 (6.9, 95% UI: 6.2–7.6)

Total number of ASCVD-free individuals was derived by combining ASCVD-free proportion of NHANES age-groups onto 2020 U.S.

Census Bureau population estimates (46). Proportion of untreated LDL-C levels were derived from cross-sectional analysis of NHANES 1999–2014, using fasting blood sampling weights to produce representative cohort. Uncertainty intervals were derived using the incomplete beta function with sample size based on the estimated variance of the proportion.

LDL-C – low-density lipoprotein cholesterol; 95% UI – 95% uncertainty interval

Table 3.

Incremental cost-effectiveness outcomes for lipid-lowering strategies in U.S. young adult men and young adult women

Policy	ASCVD Events Prevented (95% UI)	Discounted QALYs (95% UI)	Discounted total costs, thousands of 2020 $US (95% UI)	Incremental cost-effectiveness ratio ($/QALY)
Women				
Standard care *	Reference	Reference	Reference	Reference
Standard care + young adult LDL-C ≥160 mg/dL (lifestyle) **	32 (11–57)	130 (55–225)	13,800 (12,500–22,100)	Strictly Dominated
Standard care + young adult LDL-C ≥160 mg/dL (statins)	86 (38–150)	167 (2–424)	8,600 (2,580–17,100)	51,500
Standard care + young adult LDL-C ≥130 mg/dL (lifestyle) **	98 (43–165)	510 (256–778)	77,800 (39,300–131,000)	Strictly Dominated
Standard care + young adult LDL-C ≥130 mg/dL (statins)	412 (214–688)	601 (−174–1,590)	54,500 (24,800–101,000)	106,000
Men				
Standard care *	Reference	Reference	Reference	Reference
Standard care + young adult LDL-C ≥160 mg/dL (lifestyle) **	164 (90–244)	384 (215–639)	25,200 (13,400–43,500)	Strictly Dominated
Standard care + young adult LDL-C ≥160 mg/dL (statins)	491 (275–827)	817 (274–1,630)	10,800 (−3,190–28,300)	13,200
Standard care + young adult LDL-C ≥130 mg/dL (lifestyle) **	405 (255–594)	1,040 (643–1,530)	101,000 (53,000–179,000)	Strictly Dominated
Standard care + young adult LDL-C ≥130 mg/dL (statins)	1,530 (820–2,470)	2,250 (592–4,470)	55,200 (9,000–121,000)	31,000

Mean and 95% uncertainty interval (95% UI; i.e., the 2.5th to 97.5th percentile interval of the means) were calculated for model outcomes from 100 probabilistic simulations in which model inputs were sampled from pre-specified distributions.

* Treatment according to ACC/AHA 2018 guidelines; “standard care” strategy consisted of later life (age ≥40 years) statin treatment if clinical ASCVD, diabetes, LDL-C ≥190 mg/dl, or ten-year ASCVD risk ≥7.5% and young adult statin treatment if LDL-C ≥190 mg/dl.

** Individuals with LDL-C ≥190 mg/dL also received moderate-intensity statins

LDL-C – low-density lipoprotein cholesterol; UI = uncertainty interval based on probabilistic analysis. To convert LDL-C from mg/dL to mmol/L, divide by 38.67.

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