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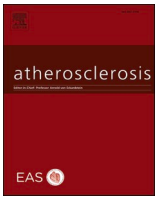

Lp(a) testing for the primary prevention of cardiovascular disease in high-income countries: a cost-effectiveness analysis

Jedidiah I. Morton [a,b,*], Florian Kronenberg [c], Magdalena Daccord [d], Nicola Bedlington [d], Marius Geanta [e], Tobias Silberzahn [d], Zhenyue Chen [f], Jean-Luc Eisele [g], Bogi Eliasen [h], Mariko Harada-Shiba [i], Marc Rijken [d], Albert Wiegman [d,j], George Thanassoulis [k], Pia R. Kamstrup [l,m], Iñaki Gutierrez-Ibarluzea [n], Pablo Coral [o], Raul D. Santos [p,q], Erik Stroes [j], Michal Vrablik [r], Gerald F. Watts [s,t], Christie M. Ballantyne [u], Samia Mora [v], Børge G. Nordestgaard [l,m], Kausik K. Ray [w], Stephen J. Nicholls [x], Zanfina Ademi [a,y,z,aa,**], On behalf of the Lp(a) International Taskforce (ITF) initiative

[a] *Health Economics and Policy Evaluation Research (HEPER) Group, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia*
[b] *Diabetes and Population Health, Baker Heart and Diabetes Institute, Melbourne, Australia*
[c] *Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Australia*
[d] *FH Europe Foundation, Amsterdam, the Netherlands*
[e] *Center for Innovation in Medicine, Bucharest, Romania*
[f] *Department of Cardiovascular Medicine, Shanghai Ruijin Hospital, Shanhai Jiaotong University School of Medicine, China*
[g] *World Heart Federation (WHF), Geneva, Switzerland*
[h] *Copenhagen Institute for Futures Studies, Copenhagen, Denmark*
[i] *Cardiovascular Center, Osaka Medical and Pharmaceutical University, Japan*
[j] *Department of Vascular Medicine, Amsterdam University Medical Centre, Amsterdam, the Netherlands*
[k] *MUHC Preventive and Genomic Cardiology, McGill University, Canada*
[l] *Department of Clinical Biochemistry, Copenhagen University Hospital – Herlev and Gentofte, Denmark*
[m] *Department of Clinical Medicine, University of Copenhagen, Denmark*
[n] *Ministry of Health, Basque Country, Spain*
[o] *FASTA University, Pharmacology Department, School of Medicine, Mar del Plata, Argentina*
[p] *Academic Research Organization, Hospital Israelita Albert Einstein, Sao Paulo, Brazil*
[q] *Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil*
[r] *Department of Internal Medicine, Department of Endocrinology and Metabolism, General University Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic*
[s] *Medical School, The University of Western Australia, Australia*
[t] *Departments of Internal Medicine and Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia*
[u] *Baylor College of Medicine, Houston, TX, USA*
[v] *Brigham and Women's Hospital, Harvard Medical School Boston, USA*
[w] *Department of Public Health and Primary Care, Imperial College London, London, United Kingdom*
[x] *Victorian Heart Institute, Monash University, Australia*
[y] *School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia*
[z] *Central Clinical School, Monash University, Melbourne, Australia*
[aa] *School of Pharmacy, University of Eastern Finland, Kuopio, Finland*

* Corresponding author. Health Economics and Policy Evaluation Research (HEPER) Group, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia.
** Corresponding author. Health Economics and Policy Evaluation Research (HEPER) Group, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia.
E-mail addresses: Jedidiah.Morton@monash.edu (J.I. Morton), Zanfina.Ademi@monash.edu (Z. Ademi).

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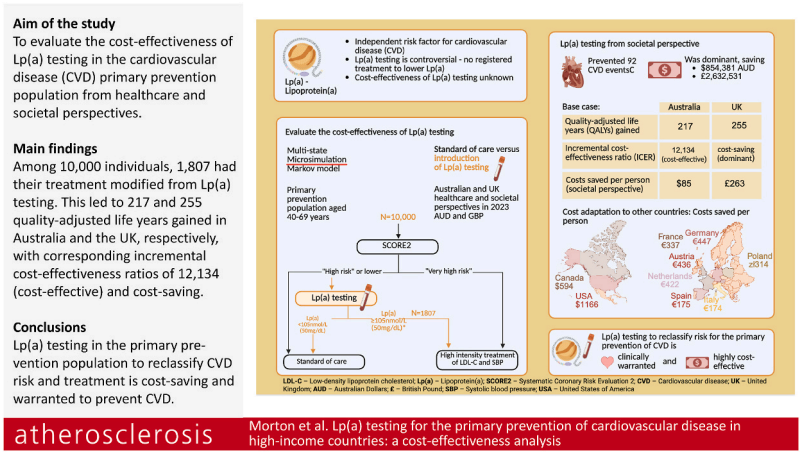
HIGHLIGHTS

- First cost-effectiveness study of routine Lp(a) testing for primary CVD prevention across multiple high-income countries.
- Lp(a) testing in primary prevention may reclassify CVD risk and be cost-saving from both healthcare and societal perspectives.
- Our model uses trial and real-world data, including Mendelian randomisation, to capture lifetime impact of elevated Lp(a) on CVD risk.
- Study introduces a novel open-access microsimulation model for the individual risk trajectory modelling over the life course.
- Findings support adding Lp(a) to CVD risk guidelines and funding models, improving equity and efficiency in prevention strategies.

GRAPHICAL ABSTRACT



ABSTRACT

Background and aims: Cost-effectiveness of Lipoprotein(a) [Lp(a)] testing is not established. We aimed to evaluate the cost-effectiveness of Lp(a) testing in the cardiovascular disease (CVD) primary prevention population from healthcare and societal perspectives.
Methods: We constructed and validated a multi-state microsimulation Markov model for a population of 10,000 individuals aged between 40 and 69 years without CVD, selected randomly from the UK Biobank. The model evaluated Lp(a) testing in individuals not initially classified as high-risk based on age, diabetes status, or the SCORE-2 algorithm. Those with an Lp(a) level ≥105 nmol/L (50 mg/dL) were treated as high risk (initiation of a statin plus blood pressure lowering). The Lp(a) testing intervention was compared to standard of care. The primary analyses were conducted from the Australian and UK healthcare perspectives in 2023AUD/GBP. A cost adaptation method estimated cost-effectiveness in multiple European countries, Canada, and the USA.
Results: Among 10,000 individuals, 1,807 had their treatment modified from Lp(a) testing. This led to 217 and 255 quality-adjusted life years gained in Australia and the UK, respectively, with corresponding incremental cost-effectiveness ratios of 12,134 (cost-effective) and −3,491 (cost-saving). From a societal perspective, Lp(a) testing saved $85 and £263 per person in Australia and the UK, respectively. Lp(a) testing was cost-saving among all countries tested in the cost adaptation analysis.
Conclusions: Lp(a) testing in the primary prevention population to reclassify CVD risk and treatment is cost-saving and warranted to prevent CVD.

1. Introduction

Lipoprotein(a) [Lp(a)] is an important risk factor for cardiovascular disease (CVD) [1,2]. Although the relationship between Lp(a) concentration and CVD risk is continuous [1], risk enhancing thresholds guide clinical practice. Depending on the threshold used to define "high" Lp(a), anywhere from ~10–20 % of individuals have high Lp(a) [1]. However, Lp(a) is not routinely measured in clinical practice at present. As a consequence, the overwhelming majority of individuals with high Lp(a) are unaware of their status and thus do not modify their CVD risk by initiating preventive measures. While highly effective treatments to lower Lp(a) are in a late stage of development [2], there are currently no clinically available options for lowering Lp(a) potently and selectively (beyond lipoprotein apheresis). Nevertheless, Lp(a) measurement can be used to reclassify risk and prompt more intensive management of other cardiovascular risk factors that might otherwise go untreated in an effort to lower overall cardiovascular risk without directly lowering Lp(a) [1]. Thus, widespread Lp(a) testing could be a useful way to improve the prevention of CVD in the population by identifying individuals at higher CVD risk than current risk scores estimate.

Lp(a) is a good screening candidate. More than >90 % of the concentration of Lp(a) is genetically determined [3,4], although genetic testing is not required to measure it. Hence, many guidelines recommend that Lp(a) needs to be measured only once in a lifetime in most people. The test cost is relatively inexpensive, ranging from a few dollars to approximately US$50, depending on the jurisdiction. These factors make Lp(a) screening followed by advice to modify treatment of other cardiovascular risk factors a potentially attractive option for CVD prevention.

However, while guidelines and society consensus statements have recommended the implementation of Lp(a) testing [1,2], to date, no studies have evaluated the cost-effectiveness of widespread Lp(a) testing, which is a key step in assessing the feasibility of implementing these recommendations. The feasibility of Lp(a) testing is especially important as European governments are currently developing cardiovascular health plans that could determine whether or not Lp(a) testing is made widely available [5].

Therefore, we have constructed a state-of-the-art health economic model to evaluate the cost-effectiveness of testing for Lp(a) in the primary prevention population, where testing is assumed to be followed by more intensive treatment of other cardiovascular risk factors in the population with high Lp(a), compared to current standard of care, as defined by the European guidelines for CVD prevention [6]. The primary analysis was conducted from the Australian and UK national healthcare system and societal perspectives, with secondary analyses adapting the results to other high-income countries in Europe and North America.

2. Methods

All analysis syntax and a more detailed explanations of the methods are available in an online protocol (available at: https://github.com/jimb0w/LPAtesting). All analyses were conducted in Stata, Version 17.0 (StataCorp, Texas, USA). We have completed this study in accordance with the CHEERS checklist (Appendix).

Table 1
Baseline characteristics for the model starting population.

	Females	Males	Overall
N	5,477	4,523	10,000
Age	58 (50, 63; 40, 69)	58 (50, 63; 40, 69)	58 (50, 63; 40, 69)
N (%) with diabetes	174 (3.2 %)	247 (5.5 %)	421 (4.2 %)
LDL-C (mmol/L)	3.7 (3.2, 4.3; 1.2, 9.0)	3.7 (3.2, 4.2; 1.1, 8.9)	3.7 (3.2, 4.3; 1.1, 9.0)
Lp(a) (nmol/L)	22.0 (8.3, 81.2; 0.2, 624.8)	17.7 (7.1, 70.6; 0.1, 487.8)	19.9 (7.8, 76.7; 0.1, 624.8)
N (%) with Lp(a) ≥105 nmol/L (50 mg/dL)	1,140 (20.8 %)	853 (18.9 %)	1,993 (19.9 %)
N (%) with Lp(a) ≥149 nmol/L (70 mg/dL)	742 (13.5 %)	510 (11.3 %)	1,252 (12.5 %)
N (%) with Lp(a) ≥192 nmol/L (90 mg/dL)	422 (7.7 %)	245 (5.4 %)	667 (6.7 %)
N (%) with Lp(a) ≥236 nmol/L (110 mg/dL)	250 (4.6 %)	137 (3.0 %)	387 (3.9 %)
SBP (mmHg)	134 (122, 150; 84, 225)	142 (130, 155; 96, 266)	138 (126, 152; 84, 266)
LSI	0.0 (0.0, 0.2; 0.0, 3.0)	0.0 (0.0, 0.6; 0.0, 3.3)	0.0 (0.0, 0.4; 0.0, 3.3)

Numeric variables are presented as median (25th centile, 75th centile; minimum, maximum). A conversion factor from nmol/L to mg/dL was applied according to Langsted et al., [68] as follows: (Lp(a) in nmol/L + 3.18)/2.18 = Lp(a) in mg/dL.
Abbreviations: LDL-C – Low density lipoprotein-cholesterol; Lp(a) – Lipoprotein (a); SBP – Systolic blood pressure; LSI – Lifetime smoking index.

2.1. Model overview

The model is represented schematically in Supplementary Fig. 1. We constructed a microsimulation model that ages people in 1-year cycles from the age they enter the model (40–69 years) to age 85 years. The model tracks the occurrence of cardiovascular events, both incident and recurrent. The cardiovascular events included in the model were myocardial infarction (MI) and stroke (ischemic and hemorrhagic), selected as the two most common forms of CVD [7].

Risk of MI and stroke in the primary prevention population was determined by age, sex, lowdensity lipoprotein-cholesterol (LDL-C) concentration, systolic blood pressure (SBP), Lp(a) concentration, diabetes, and smoking. The modifiable risk factors (other than Lp(a)) were selected as among the longest-standing and most evidenced-based causal risk factors for CVD [8,9].

The microsimulation model had the following health states: 1) No history of MI, stroke, or diabetes; 2) MI; 3) stroke; 4) diabetes; 5) MI and stroke; 6) MI and diabetes; 7) stroke and diabetes; 8) MI, stroke and diabetes; and 9) death. Repeat events (i.e., recurrent MI and stroke) were also tracked throughout the model time horizon.

The effects of LDL-C, SBP, Lp(a), and smoking on the risk of MI, stroke, and death from other causes was proportional to both magnitude and duration of exposure (i.e., the concept of cholesterol-years, pack-years, etc.). In line with our methodological framework [10–15], we assumed that risk of CVD was proportional to the cumulative exposure to a risk factor at a given age, an assumption which is supported by a substantial body of evidence [16–19]. Thus, the model adjusts the risk of CVD and death from other causes based on lifetime exposure to these risk factors. The effect of diabetes on the risk of MI, stroke, and death from other causes was binary.

The relationship between exposure to a risk factor and the risk of CVD or death was quantified using estimates from Mendelian randomisation studies [18–31]. The relationship of each risk factor with MI, stroke, and death from other causes is shown in Supplementary Table 1.

The risk of cardiovascular events and death from other causes after an individual had developed MI or stroke in the model was related to age, sex, prior MI status, and prior stroke status.

The model was validated using tests based on the AdViSHE tool [32] and calibrated using data from clinical trials. Results of the validation and calibration are presented in the online protocol.

2.2. Epidemiological inputs

The principal source of data for epidemiologic inputs to the model was the UK Biobank study [33]. The UK Biobank enrolled over 500,000 participants between 2006 and 2010, with follow-up data available until 2021. Epidemiologic inputs are summarised in Supplementary Table 2.

To estimate the incidence of MI (fatal and non-fatal), stroke (fatal and non-fatal), and mortality not due to coronary heart disease or stroke, prior to the development of MI or stroke, we used age-period-cohort models [34], which are described in full in the Supplementary Methods. The incidence of outcomes prior to the development of MI or stroke is shown in Supplementary Figs. 2–3. We followed a similar approach to estimate the incidence of MI, stroke, and mortality not due to coronary heart disease or stroke, following the development of MI or stroke (Supplementary Fig. 4). Because the UK Biobank does not contain reliable data on the incidence of diabetes, we derived the age and sex-specific incidence of diabetes from Pal et al., [35] as this study contained the most recent diabetes incidence data for the UK (Supplementary Fig. 5).

Data on risk factor trajectories were also mostly informed by data from the UK Biobank, but also necessitate several assumptions, which we drew from published literature. These assumptions and how the effect of risk factors on the incidence of outcomes was incorporated is explained in the Supplementary Methods.

2.3. Population, intervention, and control

The study population consisted of individuals without CVD (defined as prior MI and/or stroke), initially aged between 40 and 69 years. People aged 70 and above were excluded because they are considered high risk and are recommended treatment by current guidelines [6], meaning testing for Lp(a) with the goal of modifying traditional risk factors would not be appropriate.

People aged below 40 years were also excluded from the study population because they are not part of the Systemic Coronary Risk Estimation (SCORE2) algorithm and thus there are no risk treatment thresholds, are rarely recommended for pharmacological treatment in current guidelines [6], and were not present in the UK Biobank sample in sufficient numbers (as they were outside of the target recruitment population).

We populated our model with 10,000 randomly selected individuals from the UK Biobank study who were aged between 40 and 69, without prior CVD, who had information on their LDL-C, Lp(a), SBP, and high-density lipoprotein-cholesterol.

The standard of care (control) scenario was based on the European guidelines for CVD prevention [6]. The guidelines are designed to be individually specific; therefore, we simplified the guidelines to the following points for the purposes of the analyses. First, all individuals with diabetes received both a high intensity statin (regardless of baseline LDL-C because statins reduce CVD risk regardless of baseline LDL-C levels [36]) and pharmacological treatment for hypertension if they had an SBP of ≥140 mmHg. Second, all individuals without diabetes aged 40 and above were tested for CVD risk every 5 years using the updated SCORE2 algorithm [37]. Third, individuals deemed “Very high risk” from SCORE2 were treated with a high intensity statin (again, regardless of LDL-C) and received pharmacological anti-hypertensive treatment if they had an SBP of ≥140 mmHg; in the European guidelines, “Very high risk” thresholds are ≥7.5 % for individuals aged <50 years and ≥10 % for individuals aged 50–69 years. Fourth, individuals deemed ‘High risk” or lower were not pharmacologically treated unless they had an LDL-C level of ≥5.0 mmol/L or a SBP of ≥160 mmHg (varied to 3.0 mmol/L and 140 mmHg in scenario analyses; see below). And fifth, individuals become “Very high risk” once they reached age 70

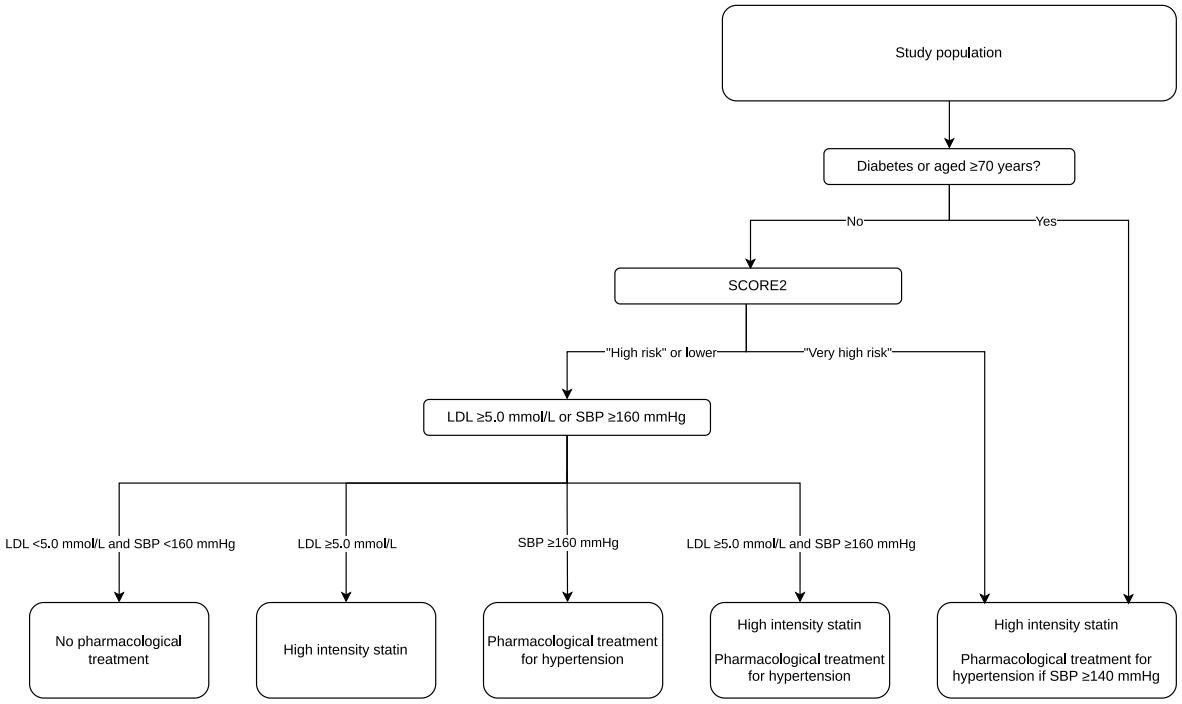


Fig. 1. Schematic of the control scenario.

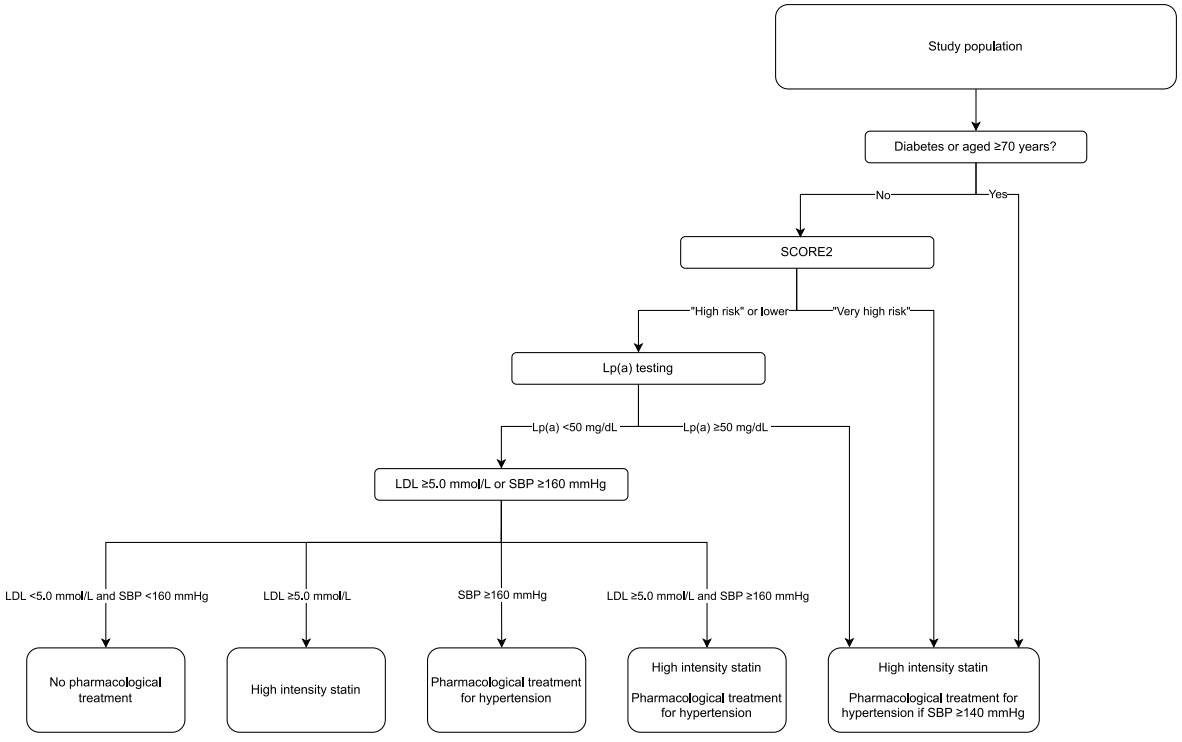


Fig. 2. Schematic of the intervention scenario.

years and received both a high intensity statin and pharmacological treatment for hypertension if they had an SBP of ≥140 mmHg. The standard of care scenario is represented schematically in Fig. 1.

We selected the high intensity statin in this study to be atorvastatin 80 mg once daily, with an LDL-C reduction of 51.7 % (95 %CI: 51.2 %, 52.2 %) [38]. Pharmacological therapy for lowering SBP was based on the most common medications used in the intensive arm of the SPRINT trial [39] – losartan 100 mg, chlortalidone 25 mg, and amlodipine 10 mg – leading to a 20 mmHg (±25 %) reduction in SBP. To match these clinical trials, we assumed conditions analagous to a clinical trial in the simulation of interventions: people either received treatment or they did not, and we assumed uptake and adherence was the same as these clinical trials.

The intervention scenario was identical to the standard of care scenario, except individuals classified as “High risk” or lower after risk estimation with SCORE2 received immediate further testing for Lp(a)

(Fig. 2). The result of this testing was to reclassify CVD risk based on Lp(a) levels – people with an Lp(a) of at least 105 nmol/L (50 mg/dL) were reclassified into the "Very high risk" category and treated as per everyone else in this category (i.e., a high intensity statin and pharmacological treatment for hypertension if they had an SBP of ≥140 mmHg). Lp(a) testing only occurred once at the age the person first reaches threshold for testing. In the control scenario, no Lp(a) testing occurred.

2.4. Health economic inputs

The primary analysis was based on the Australian and UK national healthcare systems and included both the healthcare and a societal perspective. All health economic inputs are shown in Supplementary Tables 3 and 4

Utilities measure quality of life and usually range from 0 (death) to 1 (perfect health) [40]. The utilities used in this study were derived from the EuroQol-five dimensions (EQ-5D) questionnaire [40] and a full explanation of their values and selection is available in the Supplementary Methods. The utilities for people without diabetes or CVD in Australia and the UK were derived from cross-sectional studies of the general populations (Supplementary Figs. 6–7) [41,42]. Utility values for each health state were derived from systematic reviews and/or cohort studies (Supplementary Methods).

All costs in the primary analysis were in 2023 Australian dollars ($, hereafter) and Great British pounds (£, hereafter), inflated (when necessary) using the Health Price Index [43] and NHS cost inflation index [44], for Australia and the UK, respectively. A full explanation of all cost inputs and their selection is available in the Supplementary Methods. Costs were derived preferentially from government costing reports and studies, followed by large cohort studies. The once-off cost of an Lp(a) test was set at $25 in Australia and £40 in the UK. This cost included the full cost to the healthcare system, not just the cost of the test itself. Indirect costs were estimated using the human capital approach (Supplementary Methods) [45]. We included costs due to lost earnings due to absenteeism, workforce dropout due to diabetes or CVD, and loss of future earnings due to death before retirement.

2.5. Outcomes

The model estimated: the number of people who received an Lp(a) test and the number of people who had their treatment modified in response to the Lp(a) test; the number of MIs, strokes, and deaths; years of life lived and quality-adjusted life years (QALYs) in each health state; the costs of Lp(a) testing; acute and chronic healthcare costs; and total indirect costs. The primary outcome was the incremental cost-effectiveness ratio (ICER), defined as the incremental healthcare costs divided by the incremental QALYs comparing the Lp(a) testing intervention to standard of care.

In the primary analysis, all health economic outcomes underwent discounting at 5 % in Australia and 3.5 % in the UK (per their respective guidelines [46,47]), and results were compared to the countries respective willingness-to-pay thresholds (as defined in guidelines) of $28,000 per QALY gained in Australia [48] and £20,000 to £30,000 per QALY in the UK [47]. If ICERs were below these values but still produced costs, results were considered cost-effective; if incremental costs were negative, the interventions were considered cost-saving. We stratified results by starting age group (40–49, 50–59, and 60–69) and sex.

2.6. Cost adaptation analyses

To provide an indication of the cost-effectiveness of Lp(a) testing in multiple other high-income countries, we used a cost adaptation method based on that reported by Ademi et al. [49,50] This method adapts all cost inputs to the model based on comparative differences between countries in per-capita healthcare spending, purchasing power parity, and mean annual income. These data were all derived from the Organization for Economic Cooperation and Development (OECD) [51–53]. We performed cost adaptation from both the healthcare system and societal perspectives for Austria, Canada, France, Germany, Italy, the Netherlands, Spain, Poland, and the USA, using the UK as the reference. The ICER derived through cost adaptation is only an estimation and does not represent the true ICER. It provides an approximate measure based on adjusted costs and assumptions, but it may not fully capture the actual cost-effectiveness in each country. These ICERs were compared to cost-effectiveness thresholds estimated by Pichon-Riviere et al. [54].

Table 2
Base case results for Lp(a) testing (intervention) compared to standard of care (control). Full results are shown Supplementary Tables 35 and 36.

Country	Outcome	Control	Intervention	Difference
Overall	Population size	10,000	10,000	0
	Lp(a) tests	0	9,098	9,098
	Treatment modified in response to Lp(a) test	0	1,807	1,807
	Incident MI (N)	677	617	−60
	Total MIs (N)	838	756	−82
	Incident stroke (N)	565	552	−13
	Total strokes (N)	702	692	−10
	Deaths (N)	3,727	3,701	−26
Australia	Chronic healthcare costs ($)	86,116,594	83,603,286	−2,513,308
	Acute event costs ($)	10,416,641	9,670,544	−746,097
	Medication costs ($)	42,395,294	48,062,287	5,666,993
	Lp(a) test costs ($)	0	227,450	227,450
	Total YLL	141,423	141,592	169
	Total QALY	118,161	118,378	217
	Total healthcare costs ($)	138,928,529	141,563,567	2,635,038
	Total indirect costs ($)	114,770,428	111,281,009	−3,489,419
	Total costs ($)	253,698,957	252,844,575	−854,381
	ICER ($ per QALY)			12,134
	SICER ($ per QALY)			−3,934
UK	Chronic healthcare costs (£)	74,655,129	73,040,742	−1,614,387
	Acute event costs (£)	2,751,321	2,609,579	−141,742
	Medication costs (£)	3,901,155	4,402,295	501,140
	Lp(a) test costs (£)	0	363,920	363,920
	Total YLL	164,453	164,670	217
	Total QALY	128,400	128,655	255
	Total healthcare costs (£)	81,307,605	80,416,536	−891,069
	Total indirect costs (£)	56,216,988	54,475,525	−1,741,463
	Total costs (£)	137,524,592	134,892,061	−2,632,531
	ICER (£ per QALY)			−3,491
	SICER (£ per QALY)			−10,314

The willingness-to-pay threshold was $28,000 per QALY gained in Australia [48] and £20,000 to £30,000 per QALY in the UK [47].
If ICERs were below these values but still produced costs, results were considered cost-effective; if incremental costs were negative, the interventions were considered cost-saving.
Abbreviations: MI – Myocardial infarction; YLL – Years of life lived; QALY – Quality-adjusted life years; ICER – Incremental cost-effectiveness ratio (defined as the incremental costs divided by the incremental QALYs for the intervention compared to control); SICER – Incremental cost-effectiveness ratio (societal perspective).

2.7. Sensitivity and scenario analyses

Results with the assumptions above are considered the "base case" – the most likely set of inputs. We conducted one-way sensitivity analyses by varying the model inputs between the lower and upper bounds shown in Supplementary Tables 1–4, presenting the results in Tornado diagrams. We conducted probabilistic sensitivity analyses using 500 Monte Carlo simulations based on the uncertainty in the model inputs. We used the probabilistic sensitivity analysis to compute 95 % uncertainty intervals by taking the 2.5th and 97.5th centiles of the simulation results.

Table 3
Cost adaptation results.

Country	Outcome	Control	Intervention	Difference
Austria	Total healthcare costs (2023 Euro)	115,968,289	114,697,365	−1,270,923
	Total indirect costs (2023 Euro)	99,788,351	96,697,156	−3,091,195
	Total costs (2023 Euro)	215,756,640	211,394,521	−4,362,118
	ICER (2023 Euro per QALY)			−4,979
	SICER (2023 Euro per QALY)			−17,090
Canada	Total healthcare costs (2023 CAD)	166,922,375	165,093,034	−1,829,341
	Total indirect costs (2023 CAD)	133,014,829	128,894,360	−4,120,469
	Total costs (2023 CAD)	299,937,204	293,987,394	−5,949,810
	ICER (2023 CAD per QALY)			−7,167
	SICER (2023 CAD per QALY)			−23,310
France	Total healthcare costs (2023 Euro)	101,157,140	100,048,535	−1,108,604
	Total indirect costs (2023 Euro)	73,312,382	71,041,346	−2,271,035
	Total costs (2023 Euro)	174,469,522	171,089,882	−3,379,640
	ICER (2023 Euro per QALY)			−4,343
	SICER (2023 Euro per QALY)			−13,241
Germany	Total healthcare costs (2023 Euro)	125,876,319	124,496,811	−1,379,508
	Total indirect costs (2023 Euro)	99,936,147	96,840,373	−3,095,774
	Total costs (2023 Euro)	225,812,465	221,337,184	−4,475,281
	ICER (2023 Euro per QALY)			−5,405
	SICER (2023 Euro per QALY)			−17,533
Italy	Total healthcare costs (2023 Euro)	58,629,741	57,987,204	−642,537
	Total indirect costs (2023 Euro)	35,544,620	34,443,536	−1,101,084
	Total costs (2023 Euro)	94,174,361	92,430,740	−1,743,621
	ICER (2023 Euro per QALY)			−2,517
	SICER (2023 Euro per QALY)			−6,831
The Netherlands	Total healthcare costs (2023 Euro)	111,861,747	110,635,829	−1,225,919
	Total indirect costs (2023 Euro)	96,843,024	93,843,068	−2,999,956
	Total costs (2023 Euro)	208,704,772	204,478,897	−4,225,875
	ICER (2023 Euro per QALY)			−4,803
	SICER (2023 Euro per QALY)			−16,556
Spain	Total healthcare costs (2023 Euro)	58,537,741	57,896,212	−641,529
	Total indirect costs (2023 Euro)	35,909,658	34,797,266	−1,112,392
	Total costs (2023 Euro)	94,447,398	92,693,478	−1,753,921
	ICER (2023 Euro per QALY)			−2,513
	SICER (2023 Euro per QALY)			−6,871
Poland	Total healthcare costs (2023 Zloty)	121,187,032	119,858,916	−1,328,117
	Total indirect costs (2023 Zloty)	58,502,346	56,690,089	−1,812,257
	Total costs (2023 Zloty)	179,689,378	176,549,004	−3,140,374
	ICER (2023 Zloty per QALY)			−5,203
	SICER (2023 Zloty per QALY)			−12,303
USA	Total healthcare costs (2023 USD)	285,907,091	282,773,769	−3,133,322
	Total indirect costs (2023 USD)	275,474,467	266,940,952	−8,533,515
	Total costs (2023 USD)	561,381,558	549,714,721	−11,666,837
	ICER (2023 USD per QALY)			−12,276
	SICER (2023 USD per QALY)			−45,708

Abbreviations: QALY – Quality-adjusted life years; ICER – Incremental cost-effectiveness ratio; SICER – Incremental cost-effectiveness ratio (societal perspective).

We also conducted nine scenario analyses. In the first three, we varied the Lp(a) threshold at which treatment occurs from 105 nmol/L (50 mg/dL) to 149 nmol/L (70 mg/dL), 192 nmol/L (90 mg/dL), and 236 nmol/L (110 mg/dL), respectively. The remaining six, and their results, are presented in the Supplementary Methods and Results.

3. Results

3.1. Overall

The characteristics of the random sample for 10,000 people from UK Biobank used in the model are shown in Table 1. The median LDL-C was 3.7 mmol/L (IQR: 3.2, 4.3) and SBP 138 mmHg (126, 152), and 19.9 % of the population had an Lp(a) ≥105 nmol/L (50 mg/dL) (range 0.1–624.8 nmol/L).

In the base case model, Lp(a) testing was performed on 9,098 of the 10,000 in the sample (Table 2; the Lp(a) testing subset in Fig. 2), and 1,807 (19.9 % of those tested) had their treatment recommendations for other risk factors modified in response (i.e., they initiated a statin as well as blood pressure lowering therapy if indicated). Among the model population, testing prevented 60 incident MIs, 13 incident strokes, and 26 deaths (Supplementary Fig. 8). This led to a gain in years of life lived of 169 in Australia and 217 in the UK and a gain in QALYs of 217 in Australia and 255 in the UK for the intervention compared to standard of care. Incremental QALYs exceeding years of life lived indicates improvements to quality of life in excess to simply quantity of life.

Lp(a) testing and subsequent treatment changes from risk reclassification saved $3,259,405 and £1,756,129 in healthcare costs for managing CVD, while causing an increase of $5,666,993 and £501,140 in medication costs and $227,450 and £363,920 in testing costs in Australia and the UK, respectively (Table 2). Overall, this resulted in a net cost of approximately $264 per person tested in Australia, whereas testing was cost saving in the UK, saving approximately £89 per person in the primary prevention population from a healthcare perspective. Lp(a) testing reduced indirect costs by approximately $349 and £174 per person, resulting in a total cost saving from the societal perspective of

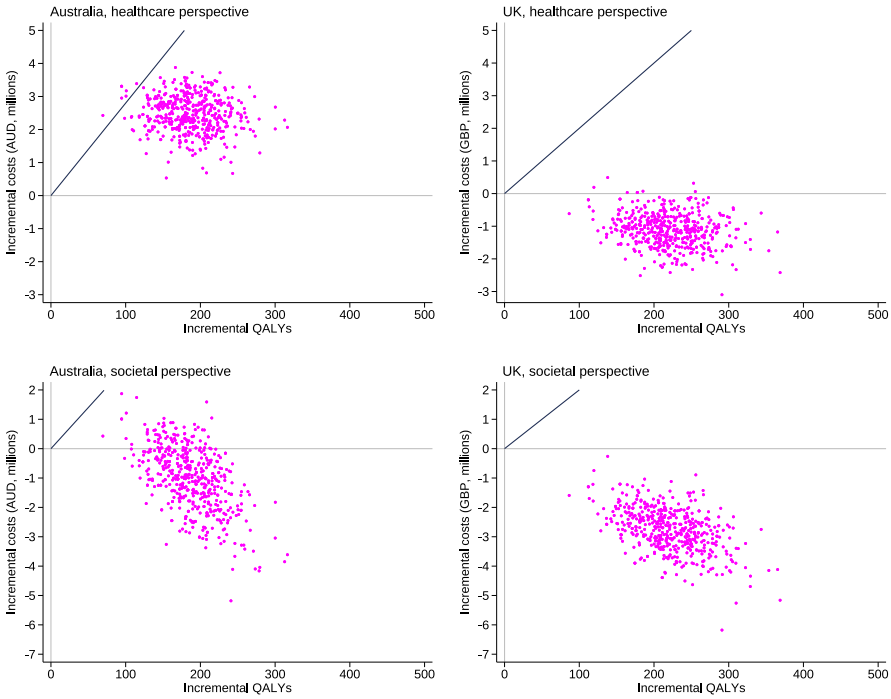


Fig. 3. Results of the probabilistic sensitivity analysis for Lp(a) testing (intervention) compared to standard of care (control) in a common cost-effectiveness plane for each country. The cost-effectiveness plane shows incremental quality adjusted life years (QALYs) for the intervention compared to the control along the x axis, and incremental costs along the y axis. Each dot represents a single simulation in which the input parameters were varied probabilistically to provide an estimate of the overall uncertainty of the results. The diagonal lines represent the willingness-to-pay thresholds for each country The willingness-to-pay threshold was $28,000 per QALY gained in Australia [48] and £20,000 in the UK [47]. Each dot in the plot represents an incremental cost-effectiveness ratio (defined as incremental costs divided by incremental QALYs). If an ICER (i.e., a single dot in the plot) was below the willingness-to-pay threshold (i.e., to the right of the line) but still produced costs (i.e., in the top right quadrant of the plane), results were considered cost-effective; if incremental costs were negative (i.e., the bottom right quadrant of the plane), the interventions were considered cost-saving.

$85 and £263 per person in Australia and the UK, respectively.

Lp(a) testing was cost-effective in Australia (ICER $12,134 per QALY; under the willingness-to-pay threshold of $28,000 per QALY in Australia) and cost-saving (dominant; i.e., the intervention led to a gain in QALYs and was cost saving) in the UK compared to standard of care in the primary prevention population from a healthcare perspective, and cost saving in both countries from the societal perspective. Age and sex stratified results are shown in Supplementary Tables 5–14.

3.2. Cost adaptation analyses

The results of the cost adaptation analysis for each country are shown in Table 3. Lp(a) testing would be cost-saving from the healthcare perspective in all countries simulated, with ICERs ranging from −2,513 Euro (2023) per QALY in Spain to −12,276 USD (2023) in the USA. Lp (a) testing was also cost-saving from the societal perspective in all countries, with cost savings of up to 1,167 USD (2023) per person in the USA (Table 3).

3.3. Sensitivity and scenario analyses

The results of the one-way sensitivity analyses are presented in Supplementary Fig. 9. No individual input had an impact on the ICER in either Australia or the UK.

The results of the probabilistic sensitivity analyses are presented in Fig. 3 and Supplementary Table 34. The intervention led to a QALY gain in all simulations in both Australia and the UK. From the healthcare perspective, the probability that Lp(a) testing was cost-effective and cost-saving was 99 % and 0 % in Australia and 100 % and 98 % in the UK, respectively; corresponding probabilities from the societal perspective were 100 % and 84 % in Australia and 100 % and 100 % in the UK.

The results of the scenario analyses are shown in Supplementary Tables 15–33. While the number of MIs and strokes prevented by risk reclassification decreased with an increasing threshold, all thresholds produced cost-saving and cost-effective ICERs.

4. Discussion

4.1. Main findings and interpretation

We have shown that testing for Lp(a) is cost saving in the primary prevention population aged between 40 and 69 years from the healthcare and societal perspectives in high-income countries, offering significant value for improving health outcomes and optimising resource allocation if implemented. This, while only a minority of those tested (approximately 20 % in our sample) will have their treatment modified in response to testing, because the benefits from preventing cardiovascular events by testing are still substantial owing to the high risk of CVD among the population with high Lp(a). These findings strongly support the implementation of Lp(a) testing to reduce CVD risk in the primary prevention populations across high income countries.

Finding cost-effective strategies to improve the prevention of CVD is a public health priority given that CVD remains a leading cause of morbidity and mortality worldwide [7]. While pharmacological control of two of the major CVD risk factors – LDL-C and SBP – has become a mainstay of CVD prevention, these medications come at a cost and have side effects, and thus a key issue has become effectively selecting people who will benefit from pharmacological treatments to control risk factors when there is not an overt clinical need for the therapies, as in the

primary prevention population without markedly elevated LDL-C or SBP [6]. Lp(a), as an important risk factor in a non-trivial minority (~10–20 % have concentrations above 105 nmol/L (50 mg/dL)) of the population, has the potential to be an important and cost-effective risk stratifier to address this critical clinical need, as shown by our findings.

However, despite calls from worldwide guidelines and society consensus statements for Lp(a) testing [1,2], Lp(a) is not routinely measured in clinical practice in most countries. One of the major reasons for this could be a prevailing opinion that Lp(a) should not be measured when no medication to lower Lp(a) is available, as reflected by a statement in the European guidelines for the prevention of CVD that "Lipoprotein(a) … provides limited additional value in terms of reclassification potential" [6]. This misjudgement has been rejected by numerous scientific statements [1,2,55] and guidelines [56,57] that recommend that other treatable risk factors should be treated more in-tensely in people with elevated Lp(a). Our results support this notion and oppose the paradigm that screening is only useful when the biomarker screened for is directly treatable. It is essential that guidelines be updated to reflect the most up-to-date healthcare recommendations.

The other reason Lp(a) has not been routinely measured in clinical practice in most countries may in part be due to the fact that the effectiveness and cost-effectiveness of Lp(a) testing had not yet been established – no other published study to date has investigated the cost-effectiveness of testing for Lp(a), with the exception of an abstract that indicated that Lp(a) testing was cost-effective [58]. Our work showing that Lp(a) testing is clinically warranted and cost-effective is therefore a critical addition to the growing body of evidence supporting the implementation of Lp(a) testing in clinical practice, even without a registered medication for Lp(a)-lowering itself.

In the cost adaptation analysis we demonstrated that population-based Lp(a) testing has the potential to be a cost-saving strategy in various healthcare systems. Specifically, the approach could be viable in countries such as Austria, Canada, France, Germany, Italy, Slovenia, Spain, the Netherlands, Poland and the US, based on their willingness-to-pay thresholds [54]. However, the calculated ICERs should be viewed as approximate estimates rather than precise country-specific outcomes, as this evaluation does not account for parameters unique to individual healthcare systems.

Our results were also robust to sensitivity and scenario analyses. In particular, when LDL- C or SBP lowering for all people not at very high CVD risk was initiated at a threshold of 3.0 mmol/L or 140 mmHg, and when we incorporated the increased risk of diabetes associated with statins [59], ICERs remained highly cost-effective in the UK for all three scenario analyses and in Australia for the latter two. These represent some of the most conservative assumptions we could have implemented, strengthening our conclusion that Lp(a) testing is cost-effective.

Thus, our results support widespread implementation of Lp(a) testing – a massive scaling up compared to current intermittent and sparse testing practices. We recommend that European and other governments include Lp(a) testing as part of their national cardiovascular health plans that are currently in development [5].

While beyond the scope of this work, it is worth noting that this scaling will present challenges, such as education of clinicians and patients, generating widespread Lp(a) testing capability and capacity, and ensuring that the scale-up does not exacerbate pre-existing health inequality. Indeed, just in Australia and the UK, based on the prevalence of CVD in the UK Biobank and population estimates [60,61], there are an estimated 8.5 and 26.5 million people, respectively, who would be recommended for an Lp(a) test based on our study. These factors have been discussed at length in the Brussels International Declaration on Lp (a) Testing and management [62]. Nevertheless, scaling up will also have benefits we have not accounted for, such as economies of scale (for example, Lp(a) testing will become much cheaper with a greater number of tests performed), aligning with the principle that people have the right to access important health information, implementation of more efficient screening strategies such as cascade screening, and preparing the screening infrastructure for when Lp(a) lowering medications are clinically available.

4.2. Strengths and limitations

Strengths of this study include that the model was based on a large population and effects of interventions on CVD were derived from real-world evidence (i.e. Mendelian randomisation) and lifetime risk factor trajectories, thereby including the cumulative, causal effects of risk factors on CVD risk.

Nevertheless, there are important limitations to the present study that warrant mention. First, the UK Biobank study has a "healthy volunteer" bias [63], meaning the CVD and mortality rates in the model may be underestimates. However, underestimating event risk would be conservative and thus our estimates of benefits of Lp(a) testing are likely underestimates due to this limitation, strengthening our conclusion that Lp(a) testing is likely cost saving. Second, the epidemiological structure of the model is not that of a randomised clinical trial, being based instead on causal data from Mendelian randomisation, meaning additional caution is required for interpretation of the results.

Third, the underlying event rates were all drawn from the UK and from a predominantly white population, which may not be representative of the breadth of countries for which results were presented in this analysis or other non-white populations; nevertheless the UK has a CVD mortality rate that is among the lowest in Europe [64], and non-white ethnicities have higher rates of CVD [65], again implying our results may underestimate the benefit of Lp(a) testing, except for countries and ethnicities with significantly lower CVD rates. Similarly, we only included high-income countries; studies specific to low and middle income countries will need to performed in the future. Fourth, many of the model inputs and assumptions, particularly the Mendelian randomisation inputs, had a high degree of uncertainty, although our results were robust to sensitivity analyses that would partly account for this.

Fifth, the model only included MI and stroke as the two most common CVDs, while other less common CVDs (such as peripheral artierial disease, aortic valve stenosis, and heart failure) would be impacted by Lp(a) testing, again implying our results may underestimate the benefits of Lp(a) testing. Sixth, because the SCORE-2 algorithm and, thus, current guidelines essentially only recommend pharmacological primary prevention of CVD from age 40 years, our starting population did not include people below this age. It is thus unclear whether Lp(a) testing would be cost-effective at a younger age, although cost effectiveness was greater at younger ages in the present study and earlier reclassification of risk and behaviour changes, lifestyle changes and treatment with statins would lower the lifetime risk of cardiovascular events [12]. Further studies are needed to determine the cost-effectiveness of Lp(a) testing at younger ages, particularly in an attempt to detect people with very high Lp(a) that may be at risk of a very early onset of CVD.

Seventh, modelling necessitates a loss of clinical nuance in the treatment of individuals in the model and reduces clinical practice to rigid practice points and assumptions. Indeed, we did not simulate lifestyle interventions as these are highly individual-specific and would be offered to people regardless of cardiovascular risk, although they may be intensified in people with high Lp(a), which is an area for future study. We endeavored to make conservative assumptions about treatment practices to strengthen the conclusions about cost-effectiveness. Finally, we did not include treatment side-effects in this study as these are rare [39,66] or a disutility associated with pill taking as it is insignificant [67].

5. Conclusion

Lp(a) testing to reclassify CVD risk in the primary prevention population aged between 40 and 69 years is a highly cost-effective way to prevent CVD. Implementation of Lp(a) testing is not only highly warranted from a clinical perspective, but is likely to come with a financial

return on investment when considered from the societal perspective. Our results support the immediate implementation of Lp(a) testing in primary prevention populations of high-income countries.

Patient and public involvement

Patients and advocates were actively involved in the research through FH Europe Foundation. Patients with elevated Lp(a) contributed from the outset as part of the Lp(a) International Task-force (ITF), participating in online and in-person meetings, including the ITF meeting during the ESC Congress (Amsterdam, 2023) and the ITF meeting during the EAS Congress (Lyon, 2024). A broader patient community was informed during the FH Europe Foundation Annual Network Meeting (Amsterdam, 2023).

Author contributions

JIM designed and constructed the model, performed the analysis and literature search, wrote the protocol, wrote the first draft of the manuscript, revised the manuscript, contributed to study design, and contributed to acquisition and interpretation of data. JIM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ZA is senior author and obtained funding, contributed to study design, design of the model, acquisition and interpretation of data, writing and revision of the manuscript, and supervision. All other authors contributed to study design, interpretation of data, and revision of the manuscript. All authors read and approved the final manuscript and JIM and ZA had final responsibility for the decision to submit for publication.

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Declaration of competing interest

FK has received honoraria for consulting or speaker activities from Novartis, Amgen, Silence Therapeutics and Roche. RDS has received honoraria related to consulting, speaker activities, and or research from Ach'e, Amgen, Amryt, Chiesi, Daiichi-Sankyo, Eli-Lilly, Esperion, Ionis, MSD, Novo-Nordisk, Novartis, PTC Therapeutics, Sanofi/Regeneron, Torrent, and Ultragenyx. TS has participated in an advisory board for Silence Therapeutics. GFW has received honoraria related to consulting, speaker activities, and or research from Amgen, Arrowhead, CSL Sequirus, Esperion, Ionis, Novo-Nordisk, Novartis, Sanofi/Regeneron. SJN has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Cyclarity, Eli Lilly, Esperion, Resverlogix, New Amsterdam Pharma, Novartis, InfraReDx and Sanofi-Regeneron and is also a consultant for Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron, Vaxxinity, CSL Sequiris and Novo Nordisk. BGN report consultancies/talks for AstraZeneca, Sanofi, Amgen, Amarin, Novartis, Novo Nordisk, Esperion, Abbott, Lilly, Arrowhead, and Marea. KKR has received research grants from Amarin, Amgen, Daiichi Sankyo, Merck Sharp & Dohme, Pfizer, Regeneron, and Sanofi, and is consultant for Abbott, Amarin, Amgen, AstraZeneca, Bayer, Biologix, Boehringer Ingelheim, Cargene Therapeutics, CRISPR, CSL Behring, Eli Lilly and Company, Esperion, Kowa Pharmaceuticals, NewAmsterdam Pharma, Novartis, Novo Nordisk, Pfizer, Regeneron, Resverlogix, Sanofi, Scribe Therapeutics, Silence Therapeutics, Vaxxinity, and Viatris, honoraria for lectures from Amarin, Amgen, Astra Zeneca, Biologix Pharma, Boehringer Ingelheim, Daiichi Sankyo, Esperion, Macleod, Novartis, Novo Nordisk, Sanofi, and Viatris, and stock options from New Amsterdam Pharma, Pemi 31, and SCRIBE Therapeutics. PRK has received lecture honoraria or consultancy fees from Physicians.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120447.

Data availability

Data from the UK Biobank study was used for this study. The dataset is accessible to researchers via https://www.ukbiobank.ac.uk/register-apply/

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