September 15th, 2025

[redacted]
Five Pillars of Productivity Inquiry
Productivity Commission
697 Collins Street
Docklands Vic 3008

Dear [redacted],

Re: "Delivering quality care more efficiently – Interim report"

We write to you in response to the Productivity Commission (PC) request for information and feedback on the interim report titled "Delivering quality care more efficiently. We wish to provide information specifically in relation to Section 3: A National framework to support government investment in prevention (the National Framework).

Firstly, we commend the PC for recognising the value of prevention, the insufficient levels of investment in preventive health and the limitations in the current approach to economic evaluation of preventive health interventions. We support the proposed recommendations and eagerly anticipate their adoption.

Please find attached our recent paper in PharmacoEconomics [Ademi, Rodda et al 2025] discussing many of the challenges raised in the report along with potential solutions. This may be useful in preparing the final report.

In addition, please consider the following comments and suggestions in response to the report:

Re: figure 3.1 (page 53):

- We suggest refining the definitions of prevention, expanding to include primordial prevention. Primordial prevention is focused on individuals without risk factors with an aim to prevent risk factors from developing in the first instance and can include policy, taxation, legislation or regulation to provide health-promoting environments. [Ademi, Rodda 2025][1] The report mentions intervention in 'areas like housing, education, justice and family support services' that would likely be best described as primordial prevention. Primary prevention then aims to reduce risk factors that are already present, in order to prevent the onset of disease.
- We argue that the economic evaluation of secondary and tertiary prevention interventions is sufficiently accommodated within current health technology assessment frameworks (Pharmaceutical Benefits Advisory Committee (PBAC), the Medical Services Advisory Committee (MSAC)), therefore the national framework to support government investment in prevention should be focused on primary and primordial prevention interventions.

On page 60:

- The difficulty in determining causality between the effect of prevention interventions on risk factors and outcomes is acknowledged. The PC cites ACE-Prevention (page 58); while historically relevant, it is outdated, and substantial new evidence supports a life-course approach to prevention. Novel methodologies can be applied in some cases to overcome this difficulty. For example, we draw the Commission's attention to

emerging causal evidence that quantifies outcomes based on the cumulative impact of risk factors, adopting a life-course perspective.[2] This modelling is based on mendelian randomisation (MR), a methodology that uses genetic variants to assess whether an exposure-outcome relationship is likely causal, and to estimate its effect.[3, 4] For example, data from MR studies have been used to evaluate the impact of long-term reductions in low density lipoprotein cholesterol on coronary heart disease within a cost-effectiveness analysis of screening for familial hypercholesterolaemia and primary prevention of CVD.[5, 6] This life course model based on MR evidence has also evaluated the cost-effectiveness of early intervention in CVD with antihypertenisves and lipid lowering treatment[7, 8] and for Lipoprotein(a) screening.[9] MR data is now recognised by The National Institute for Health and Care Excellence (NICE)[10] and we propose that the Prevention Framework Advisory Board (PFAB) consider this type of evidence when evaluating prevention interventions.

- We would like to bring attention to health equity concerns when establishing effectiveness of interventions (within the PFAB context). These concerns are particularly relevant for primary prevention interventions implemented at the individual level requiring individual agency where differences in effectiveness across social groups are more likely to occur.[11] Furthermore it is well established that underserved populations are underrepresented in clinical trials.[12, 13] PFAB decision making should actively consider presence of these potential biases. For example, the inclusion of real-world evidence (such as administrative datasets, registries or well conducted pragmatic clinical trials) may assist in understanding differential effectiveness among subpopulations of concern.[14]

Systematic measurement of health-related productivity and integration into decision making

Measurement of health-related productivity facilitates evaluation of the economic impacts of a disease or intervention on the ability of individuals to engage in productive activities. It is currently inconsistently integrated into HTA decision-making in Australia, for example through cost-effectiveness analysis conducted from the societal perspective. However, this approach characterises health-related productivity losses or gains as an indirect cost of disease, rather than an outcome. When considering prevention activities, health-related productivity is a vital outcome, as these policies and interventions by their nature tend to target healthy individuals at the peak of their productive lives.

We would like to draw the Commission's attention to our recent work developing the Productivity-Adjust Life Years (PALY) metric, which offers an innovative focus on productivity as a direct outcome of healthcare and preventative interventions.[15] The PALY is calculated by multiplying years of life lived by a 'productivity index' ranging from 0 (completely unproductive) to 1 (completely productive). This enables productivity consequences of ill-health to be measured as an outcome rather than as a cost at a population level over time using epidemiological modelling techniques. PALYs can therefore measure the societal impact of ill health in a standardised way, facilitating comparison across diseases, socioeconomic, demographic and geographic settings. This is supported by the application of the PALY metric in over 40 peer reviewed publications to date, spanning 18 countries and a broad range of both acute and chronic health conditions. We believe this metric can play an integral role when developing policies around prevention.

Furthermore, there is a work underway by our group presented at the Australian Health Economics Society about the population norms on how to capture health related productivity index for paid and unpaid work, in Australia and globally.

Lastly, to address the questions raised in Information request 3.1 (page 65)

When prioritising different proposals, how should factors such as overall net benefits, net fiscal effects, cost-effectiveness, equity, ease of implementation, timescale and the value of future benefits and costs be weighted? Are there existing frameworks that do this well?

We propose that equity should most definitely be considered within PFAB decision making for the following reasons:

- The Australian public hold concerns for health inequalities based on Indigenous status, income and geographic location, with the majority of society are willing to sacrifice gains in total population health in order to improve health for the worst off.[16] However, standard cost-effectiveness analysis does not reflect these preferences.
    - Structural interventions delivered at the population level (e.g. via taxation, legislation) are likely to be cost-effective and improve health equity while primary prevention interventions delivered at the individual level have potential to exacerbate health inequalities. [Ademi, Rodda][1] As such we suggest the following:
- The National Framework be focused on structural (primordial prevention) in order to best reduce health inequalities.
- If primary prevention programs implemented at the individual level are to be assessed (e.g. educational or behavioural interventions), a quantitative evaluation of the equity impacts should be included and considered by the PFAB.
- Distributional cost-effectiveness analysis (DCEA) would be a suitable method to evaluate the equity impacts of an intervention (who gains and who loses) within a cost-effectiveness analysis.[17] DCEA can be especially useful in public health and DCEA has been successfully applied to the evaluation of alternative approaches to implementation of health programs taking a targeted approach to improving equity.[18-20] For example, we are currently working on a DCEA evaluating various implementation strategies for an antenatal intervention to prevent gestational diabetes. [not yet published] This methodology has enabled us to identify that whilst the intervention is cost-effective no matter how it is delivered, subsidy for provision to women with a BMI$\geq$25kg/m^3 would generate a greater net health benefit, whilst provision to women only in the public hospital system would have the greatest impact on health equity. These findings were presented this week at the Australian Health Economics Society Conference, Canberra.
- The degree of aversion to health inequality estimated for the Australian population in regards to Indigenous status, socioeconomic status and geographic location [16] could be applied to weight the value of future benefits (and costs). We suggest this to be done with care and that various levels of inequality aversion be evaluated via scenario analyses.

Whilst the use of discounting within cost-effectiveness analysis has its place, it can be problematic in health economic models evaluating the long-term outcomes of prevention where costs are predominantly upfront and benefits take long periods to eventuate.
In these models with long time horizons (e.g. 50-60 years), discounting can have a significant impact, generating uncertainty, and potentially making prevention appear less cost-effective compared to interventions with short-term effects. [Ademi, Rodda][1] Therefore, we propose that costs and benefits of prevention interventions be discounted at lower rates than routinely adopted for the evaluation of acute treatments, namely the 5% discounting routinely used by

the PBAC and MSAC. A sensible approach would be to model scenarios where a 0%, 1.5% and 3% discounting rate is applied to evaluations assessed by the PFAB.

There is no consistent approach to the economic evaluation of prevention interventions and novel methods to better evaluate the equity and intersectoral impacts of prevention have only limited practical application to date. To overcome these challenges, significant resources will be required to conduct and rigorously review economic evaluations of prevention interventions. We propose that the PC report include consideration of health economics workforce capacity and increased funding of research into the health economic evaluation of prevention.

Should there be minimum cost-effectiveness and/or cost-benefit ratios and how should they be set?

We hold concerns that explicitly setting a cost-effectiveness or cost-benefit ratio threshold for prevention interventions may inadvertently lead to higher costs, with providers/sellers potentially gaming the system.[21] We suggest looking to the incremental cost-effectiveness ratios (ICERs) for prevention interventions in the published literature [22] to provide a historical reference point when determining an acceptable ICER for prevention interventions.

How should decision makers balance the need to assess early effectiveness of programs with the need to maintain consistent long-term funding for programs with long-term benefits?

To be effective, primary prevention requires sustainable and long-term investment that is removed from short political and budget cycles.[23] As such, we argue the National Framework should focus on the evaluation of long-term benefits where possible.

However, we acknowledge that the government may wish to have some early indication of whether the funded program is delivering as intended. Suitable indicators of early effectiveness may include:

- Uptake rates and whether these differ across social groups. More specifically what proportion of the target population have made initial engagement with the program, and how does the spread of these proportions across equity relevant groups compare to the distribution in the target population (i.e. a representation index [13]).
- Engagement or retention rates: the proportion of the target population that is completing the intervention and how does the spread of these proportions across equity relevant groups compare to the distribution in the target population (again using a representation index [13]).
- Costs of implementing and delivering the program, and the extent to which these deviate from the costings provided in the initial economic evaluation.

How could a diversification strategy be designed to ensure that prevention programs from different sectors and with benefits across different timeframes are funded?

As described in the interim report, the impacts of prevention are intersectoral and should be valued accordingly. Moving away from a focus on specific diseases towards a focus on risk factors, and acknowledging that risk factors are commonly interrelated may be helpful. For instance, interventions reducing obesity have wide ranging impacts on diabetes, cardiovascular disease and liver disease.

In terms of giving due consideration to investment across different sectors, the 'extended impact inventory framework' may help to estimate the net effects of an intervention for multiple sectors.[24] The method can illustrate trade-offs between sectors whilst providing an assessment of the allocation of benefits across individuals, thereby accommodating equity concerns as well.[24]

Thank-you for the opportunity to contribute to this long overdue and critical conversation about investment in prevention. We eagerly await the final report and subsequent government response.

Yours sincerely,

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References:

1. Ademi Z, Rodda SE, Vivoda K, Hennessy S, Fenton O, Ware JS, et al. Highlights from the Manifesto on the Health Economics of Cardiovascular Disease Prevention. Pharmacoeconomics. 2025 2025/09/08.
2. Morton JI, Liew D, Ademi Z. A Causal Model for Primary Prevention of Cardiovascular Disease: The Health Economic Model for the Primary Prevention of Cardiovascular Disease. Value Health. 2024;27(12):1743-52.
3. Ademi Z, Morton JI, Liew D, Nicholls SJ, Zoungas S, Ference BA. Integrating the Biology of Cardiovascular Disease into the Epidemiology of Economic Decision Modelling via Mendelian Randomisation. Pharmacoeconomics. 2022 2022/11/01;40(11):1033-42.
4. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018 Jul 12;362:k601.
5. Ademi Z, Norman R, Pang J, Sijbrands E, Watts GF, Hutten BA, et al. Cost-effectiveness and Return on Investment of a Nationwide Case-Finding Program for Familial Hypercholesterolemia in Children in the Netherlands. JAMA Pediatr. 2023 Jun 1;177(6):625-32.
6. Ademi Z, Norman R, Pang J, Liew D, Zoungas S, Sijbrands E, et al. Health economic evaluation of screening and treating children with familial hypercholesterolemia early in life: Many happy returns on investment? Atherosclerosis. 2020;304:1-8.
7. Morton JI, Marquina C, Lloyd M, Watts GF, Zoungas S, Liew D, et al. Lipid-Lowering Strategies for Primary Prevention of Coronary Heart Disease in the UK: A Cost-Effectiveness Analysis. Pharmacoeconomics. 2024 Jan;42(1):91-107.
8. Morton JI, Liew D, Watts GF, Zoungas S, Nicholls SJ, Reid CM, et al. Immediate Versus 5-Year Risk-Guided Initiation of Treatment for Primary Prevention of Cardiovascular Disease for Australians Aged 40 Years: A Health Economic Analysis. Pharmacoeconomics. 2025 Mar;43(3):331-49.
9. Morton J, Kronenberg F, Daccord M, Bedlington N, Geanta M, Silberzahn T, et al. Lp(a) testing for the primary prevention of cardiovascular disease in high-income countries: a cost-effectiveness analysis. Atherosclerosis. 2025.
10. National Institute for Health and Care Excellence. NICE real-world evidence framework. Corporate document. 2022 23 June 2022. Contract No.: Corporate document [ECD9]2022.
11. Lee JT, Lawson KD, Wan Y, Majeed A, Morris S, Soljak M, et al. Are cardiovascular disease risk assessment and management programmes cost effective? A systematic review of the evidence. Prev Med. 2017 2017/06/01/;99:49-57.
12. Versavel S, Subasinghe A, Johnson K, Golonski N, Muhlhausen J, Perry P, et al. Diversity, equity, and inclusion in clinical trials: A practical guide from the perspective of a trial sponsor. Contemp Clin Trials. 2023 2023/03/01/;126:107092.
13. Mishra SR, Tan AC, Waller K, Lindley RI, Webster AC. Conceptualizing, operationalizing, and utilizing equity, diversity, and inclusion in clinical trials: a scoping review. J Clin Epidemiol. 2025;179:111649-.
14. Pennington B, Cummins E, Chandler A, Fotheringham J. Challenges in Modelling the Cost Effectiveness of Pharmacotherapies for Obesity. Pharmacoeconomics. 2025 2025/07/28.
15. Ademi Z, Ackerman IN, Zomer E, Liew D. Productivity-Adjusted Life-Years: A New Metric for Quantifying Disease Burden. Pharmacoeconomics. 2021 2021/03/01;39(3):271-3.
16. Boujaoude M-A, Dalziel K, Cookson R, Devlin N, Carvalho N. Aversion to income, ethnic, and geographic related health inequality: Evidence from Australia. Soc Sci Med. 2025 2025/01/01/;364:117495.

17. Cookson R, Griffin S, Norheim OF, Culyer AJ, Chalkidou K. Distributional Cost-Effectiveness Analysis Comes of Age. Value Health. 2021 Jan;24(1):118-20.
18. Collins B, Kypridemos C, Cookson R, Parvulescu P, McHale P, Guzman-Castillo M, et al. Universal or targeted cardiovascular screening? Modelling study using a sector-specific distributional cost effectiveness analysis. Prev Med. 2020 Jan;130:105879.
19. Asaria M, Griffin S, Cookson R, Whyte S, Tappenden P. Distributional Cost-Effectiveness Analysis of Health Care Programmes – A Methodological Case Study of the UK Bowel Cancer Screening Programme. Health Econ. 2015;24(6):742-54.
20. Kypridemos C, Collins B, McHale P, Bromley H, Parvulescu P, Capewell S, et al. Future cost-effectiveness and equity of the NHS Health Check cardiovascular disease prevention programme: Microsimulation modelling using data from Liverpool, UK. PLoS Medicine / Public Library of Science. 2018 05;15(5):e1002573.
21. Sellars M, Carter SM, Lancsar E, Howard K, Coast J. Making recommendations to subsidize new health technologies in Australia: A qualitative study of decision-makers' perspectives on committee processes. Health Policy. 2024 2024/01/01/;139:104963.
22. Howse E CP, Rychetnik L, Wilson A. The value of prevention: An Evidence Check rapid review brokered by the Sax Institute for the Centre for Population Health. Sydney2021.
23. Wouterse B, Vasco SJ, and Hiligsmann M. Future directions for the economics of prevention. Expert Rev Pharmacoecon Outcomes Res. 2025;25(6):841-4.
24. Walker S, Griffin S, Asaria M, Tsuchiya A, Sculpher M. Striving for a Societal Perspective: A Framework for Economic Evaluations When Costs and Effects Fall on Multiple Sectors and Decision Makers. Appl Health Econ Health Policy. 2019 Oct;17(5):577-90.

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LEADING ARTICLE

Highlights from the Manifesto on the Health Economics of Cardiovascular Disease Prevention

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Abstract

Cardiovascular disease (CVD) is a major contributor to the health and economic burden of disease globally. In this paper we discuss the literature on the health economics of the prevention and early intervention in CVD. We reveal the large economic impact of CVD and provide the economic argument supporting the calls for early detection and diagnosis of CVD outlined in the Global Heart Hub's patient-led Manifesto for Change. Many challenges in conducting cost-effectiveness analyses of interventions for CVD prevention are identified, as well as the emerging statistical and economic methods to help overcome these issues. Lastly, we acknowledge the profound disparities in cardiovascular health faced by minority or underserved populations, and the important role that prevention and early intervention can play in improving health equity.

1 Introduction

Cardiovascular disease (CVD) is the leading cause of disease burden globally, and CVD prevalence and mortality are predicted to grow, with 35.6 million cardiovascular

Key Points for Decision Makers

Early cardiovascular disease (CVD) interventions have been found to be cost-effective from both healthcare and societal perspectives: Preventive strategies and timely diagnosis can reduce long-term healthcare costs and improve quality of life.

Innovative methods support better decisions: We propose that funders take a proactive rather than reactive approach to cardiovascular health and consider alternative forms of evidence and emerging real-world evidence techniques for health technology assessment in CVD prevention.

Equity-driven prevention enhances efficiency: Prioritising underserved populations through better data collection and targeted, intersectoral policies can reduce disparities and improve overall system outcomes.

This article includes only the health economic aspects of CVD prevention based on a narrative review and the Manifesto meeting.

Zanfina Ademi and Sheridan E. Rodda: Shared first authorship.

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Global Heart Hub Manifesto
https://globalhearthub.org/manifesto/

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deaths worldwide projected for 2050 [1, 2]. The economic impact of CVD is equally staggering and is predicted to increase substantially [3]. In 2021, the total cost of CVD to the European economy was €282 billion, or €630 per citizen [4].

This increasing health and cost burden of CVD is due to an ageing population, rising healthcare costs, the growing prevalence of CVD risk factors and persistent inequities in CVD, particularly in disenfranchised or underserved groups [3]. The predominant modifiable risk factors for CVD are elevated systolic blood pressure, dietary risks (diets high in sodium and low in whole grains) and elevated low-density lipoprotein cholesterol (LDL-C). (1) Looking forward, high body mass index (BMI) and high fasting plasma glucose are expected to increasingly contribute to CVD mortality and morbidity. (2) There is now increasing recognition of the important role played by non-modifiable risk factors, including genetic risk factors, and the opportunities these create for early identification of high-risk groups.

Equitable action in cardiovascular health is required, and the Global Heart Hub, an international alliance of heart patient organisations, has produced 'Achieving Early Detection and Diagnosis of Cardiovascular Disease: A Manifesto for Change', centred around patients and carers with lived experience of CVD supported by global stakeholders [5]. The Manifesto for Change sets priority actions to improve CVD outcomes, calling for early detection and diagnosis of CVD. In this paper, we discuss the core economic concepts behind CVD prevention based on a narrative review and we apply these concepts to manifesto actions to provide health economic evidence for decision making.

2 The Economic Argument for CVD Prevention

The economic impacts of a disease are typically classified into direct healthcare costs (e.g. hospital stays, medications, procedures), direct non-healthcare costs (e.g. transportation, home modifications, informal caregiving) and indirect costs (e.g. lost productivity due to illness or premature death). When considering healthcare funding from a societal perspective, the direct and indirect costs are combined. Recently, productivity-adjusted life years (PALYs) has been proposed as an outcome measure to capture the impact of prevention beyond healthcare [6].

Direct healthcare costs are the largest contributor to the overall cost of CVD, and these costs are increasing (government contribution, health insurance and out-of-pocket). Growth of direct healthcare costs is driven by inpatient care in coronary heart disease (CHD), particularly medical devices and long-term care for both CHD and cerebrovascular disease [4, 7]. Direct non-healthcare costs and productivity are also significant and should be considered by funders wanting a comprehensive understanding of the benefits of an intervention. Direct non-healthcare costs include informal care, which is unpaid care undertaken by family or friends acting as carers for people affected by CVD. Time spent providing informal care takes away from time spent in work or leisure and carries an opportunity cost. Informal care is not consistently considered in economic evaluations but can have an economic impact, especially for CVD [8, 9]. Furthermore, productivity losses arising from premature mortality and morbidity negatively impact the workforce and in turn the wider economy and society [10].

In the United States (US), the total cost of CVD was US $627 billion for 2020 (2.7% of gross domestic product) [3]. Of this total, 63% were direct costs (health and non-healthcare costs combined) while productivity contributed the remaining 37% (US $234 billion) [3]. For the United Kingdom (UK), CVD cost £29 billion in 2021/2022, of which 57% was for direct healthcare costs, 22% for informal care and 21% for productivity [7]. Similarly, in the European Union (EU), CVD costs were €155 billion in 2021 (€347 per person), of which 46% were due to direct healthcare costs, 37% for direct non-healthcare costs (mostly informal care) and 17% for productivity losses [4]. In Australia, a 10-year projection revealed that the cost of CVD was 140.65 billion Australian dollars (AU $), of which 55% was due to productivity losses [11]. Recognising these indirect and non-healthcare costs of CVD is crucial for policy-making. An understanding of the consequences of healthcare funding decisions in the health and non-healthcare sectors is required to support the case for prevention interventions.

There are four approaches to CVD prevention worth noting. Primordial prevention is focused on individuals without CVD risk, with an aim to prevent risk factors from developing in the first instance [12]. It targets the entire population by addressing the underlying social, economic and environmental conditions that contribute to disease [12]. Primordial prevention interventions can include policy, taxation, legislation or regulation to provide health-promoting environments [12, 13]. Primary prevention focuses on healthy individuals whom already have increased risk of disease and aims to prevent the onset of disease. This can include immunisation, public health interventions and specific programmes to reduce risk factors such as behavioural interventions for physical activity or smoking cessation [12].

Secondary prevention targets individuals with early disease or risk factors (many of whom may be asymptomatic), with a view to preventing progression to serious symptoms or events. Much of the literature classifies screening and risk factor management, such as blood pressure screening, as secondary prevention [12, 13]. However, identifying high-risk

individuals through early screening to prevent initial CVD events could also fall under primary prevention [14]. This reflects a shift toward earlier investment in prevention, aiming to address risks before disease develops. Lastly, tertiary prevention is focused on reducing disease severity, symptoms and sequalae among individuals with established disease, for example, rehabilitation programmes [12, 13].

Globally CVD generates a large burden of disease and economic costs. Primary prevention and early detection and diagnosis of CVD provides an opportunity for action. For example, control of systolic blood pressure to below 130 mmHg through behaviour modification in US adults with stage 1 hypertension (at low 10-year risk of CVD) could prevent 26,100 CVD events and 2900 deaths and avoid US $1.6 billion in healthcare costs over 10 years [15]. In Australia, healthcare costs arising from initial CVD events were largest for chronic management and treatment; however, decreasing CVD risk by 10% through primary prevention among the disease-free population could prevent 13,225 deaths and save AU $6.23 billion over 2020–2029 [11]. By intervening at these earlier stages, health and economic outcomes can be improved.

Despite these opportunities, government healthcare funding is disproportionately directed towards secondary and tertiary interventions, with minimal spending on public health [16, 17]. In many countries, healthcare funding decisions, generally made by governments or insurers, are informed by health technology assessments (HTAs) that evaluate evidence on the cost-effectiveness (CE), equity and legal aspects and budget impact of interventions. However, evaluating the CE of interventions for preventing CVD poses unique challenges.

3 The Challenge of Demonstrating Cost-Effectiveness for CVD Prevention

Randomised controlled trials (RCTs) are the gold standard for new intervention strategies, providing high-quality efficacy data utilised by HTA bodies worldwide. However, RCTs have limitations, particularly in the disease prevention context, mainly because RCTs rarely measure long-term outcomes, due to time and budget constraints on long-term follow-up [18]. Prevention interventions generally incur costs upfront, and the benefits may only be realised in the longer term; therefore, RCTs are unsuitable for measuring efficacy, as the long-term benefits can be underestimated [19]. Also, RCTs often do not provide the long-term cost information needed for CE analyses. Lastly, there are the well-known concerns in generalising benefits observed in RCTs to implementation in the target population, including differences in adherence or uptake, which can systematically over- or underestimate intervention benefits [19].

RCTs demonstrating the CE of public health interventions are not feasible or ethical; therefore, computational models based on observational data, often requiring multiple data sources and including many assumptions, are commonly used [20]. Health economic simulation models are useful to evaluate the short- and long-term costs and outcomes of preventive health interventions (i.e. interventions targeting lifestyle and pharmacological treatments). Nevertheless, the type of model chosen (Markov cohort or patient-level simulation), the underlying assumptions and the estimation of CVD risk within the model can make evaluation very challenging. The occurrence of CVD events depends on age, a variety of interrelated risk factors and the history of the individual (risk exposure over time). Currently, the majority of health economic evaluations of early detection strategies for CVD use Markov cohort state models [18]. While Markov models may be simpler to conduct than patient-level simulations, or discrete event simulations, requiring fewer inputs, they have limited ability to accommodate the impact of multiple risk factors or the clinical history of simulated individuals, due to their memoryless nature [18, 21]. Patient-level (micro)simulation models over longer time horizons may be more suitable for the evaluation of early detection strategies as they can reflect long-term clinical and treatment history [18].

Even when simulation models are used, pitfalls remain in estimating disease risk and treatment effects. The risk or probability of CVD events occurring (transition probabilities) within health economic models can be taken from age-specific estimates or by using CVD risk scores. The majority of studies evaluating new medications for the management of atherosclerotic CVD used health economic models based on instantaneous age-related risk estimates [22]. However, these estimates and risk scores rely heavily on age and gender and fail to consider the cumulative effect of modifiable risk factors and, as a consequence, can systematically underestimate the benefits of CVD prevention [19]. Furthermore, the treatment effects of interventions are frequently modelled using estimates from short-term RCTs, as capturing long-term outcomes of complex interventions targeting multiple risk factors in real-world populations is not feasible.

The growing availability of real-world evidence (RWE) or non-randomised studies from registries and electronic health record data can provide sources of event-rates, adherence and long-term outcomes. Some HTA bodies have developed frameworks for how RWE is to be used, but there is no universally accepted RWE framework [23, 24]. RWE may not be widely accepted by HTA agencies due to concerns including potential for bias and residual confounding, transportability of treatment effects from the RWE to the target population, underdeveloped data infrastructure to support access to detailed RWE and ingrained perceptions that RWE

is of low quality [25]. Looking forward, technologies for high unmet clinical need or for rare and ultra-rare diseases, such as advanced or gene therapy products, with specific and small patient populations, will benefit from the application of RWE [23]. For CVD prevention, RWE could supplement RCT data by generalising trial findings to other populations and to help confirm costs and effectiveness where RCTs have used surrogate endpoints (such as reductions in weight or systolic blood pressure) or provided short-term follow up [23]. Researchers and policymakers may need to reconsider what evidence is sufficient to evaluate public health and prevention interventions [26]. Capacity-building steps to support the integration of RWE into HTA include global and more standardised technical guidance from HTA agencies on the best practices for RWE, training and education for all HTA stakeholders that is multi-disciplinary (e.g. across genetics/phenotyping, study design, analytical methods) and resourcing and workforce planning to support the conduct and evaluation of RWE [23, 25, 27].

A novel method to provide RWE, mendelian randomisation (MR), has recently been applied to health economic models for CVD prevention. The National Institute for Health and Care Excellence (NICE) recognises natural experiments, including instrumental variable methods [24]. MR is one such approach, using genetic variants to assess whether an exposure-outcome relationship is likely causal and to estimate its effect. For example, the impact of long-term reductions in LDL-C on CHD derived from MR studies has been used to evaluate the CE of screening for familial hypercholesterolaemia (FH) [28, 29]. MR can address concerns with CVD risk estimation by considering the cumulative effects of risk factors and overcomes the aforementioned issues with RCTs by providing generalisable, long-term costs and outcome estimates in situations where an RCT is not feasible [19]. The details of MR are provided elsewhere [30], but briefly, MR leverages the random inheritance of alleles from parents to assign individuals, simulating a naturally occurring RCT that can assess causality between risk factor levels and disease risk using (biological) observational data. Outcome data derived from MR studies has been incorporated into the economic evaluation of numerous CVD screening and prevention strategies that found early diagnosis and proactive management more cost-effective than intervening at a later stage [29, 31–34]. However, MR is not a substitute for an RCT, and careful consideration should be given to the population within the MR versus the target population, differences in therapy to MR, the goals of the intervention when interpreting MR-based economic evaluations, and which MR estimate to use when multiple are available [19]. There are currently limited biological scenarios to which MR can be applied because it requires robust biological evidence from a dataset linking individual-level genetic, risk factor and outcome data. Requirements of MR include genetic variants or alleles that are associated with the risk factor of interest, no unmeasured confounders linking the alleles to the outcome, genetic variants that only affect the outcome through the risk factor and a risk factor with evidence supporting an irreversible cumulative effect on the outcome over time (e.g. systolic blood pressure, low-density lipoprotein, smoking and diabetes for CVD) [19, 30]. Some limitations of MR include off-target, unexpected or adverse effects of an intervention that occur via a pathway unrelated to the mechanism of action, which will not be identified via MR. Risk factors that vary by disease stage cannot be accounted for within MR effect estimates. We anticipate that MR may be used as an input for costs and outcomes (including via surrogate endpoints) within HTA submissions for CVD in the future. For instance, the causal effect of BMI on quality-adjusted life years (QALYs) and total healthcare costs has been established and applied to a CE analysis of theoretical obesity policy examples [35]. MR is an emerging field; the necessary evidence, guidelines and expertise to apply MR techniques are currently limited but hold great potential for HTAs.

Lastly, traditional health economic practices pose challenges to demonstrating the impact of CVD prevention. Economic models to evaluate long-term outcomes of prevention may need to run for up to 50–60 years, making the effect of discounting more pronounced and generating greater uncertainty. Discounting, a necessary method routinely applied in health economics, involves adjusting future costs and benefits to their current value to reflect decision makers' time preference for money or resources in the present over the future. Consequently, benefits arising further in the future (such as CVD events avoided through prevention) have reduced value, making prevention appear less favourable when compared to acute treatments. The choice of discount rate greatly impacts economic evaluations in CVD prevention, and higher rates can favour interventions focused on the short term at the expense of preventive treatments and future generations [17, 33]. Scenario analysis with various discounting rates may be used to illustrate the opportunity cost of investment to decision makers.

Compared to simple clinical interventions, models for public health interventions may face greater structural uncertainty. These interventions are complex and multi-component, occurring within dynamic systems and involve behavioural change and are therefore difficult to characterise with a simple model structure [36]. For example, there are often only short-term (6–12 month) data available, with little known about the extent to which this behaviour change is maintained [37]. Consequently, assumptions are made around health benefits far into the future, generating additional uncertainty around the CE that may not be acceptable to decision makers. Strategies utilising behavioural science including better consideration of the intervention content

and context, and incorporating internal and external influences on individual health-related behaviours, may help to inform long-term assumptions [37]. Innovation in health economic practices and HTA processes is needed to best seize the opportunity to prevent CVD.

Moving forward, we need innovative approaches to evaluating CE to better recognise the potential health and economic benefits of investing in cardiovascular health. The Global Heart Hub's Manifesto for Change [5] calls for increased investment in research assessing the CE or return on investment (ROI) to support changes in CVD prevention. Advances in health economic methods are emerging to overcome these challenges and better evaluate the potential impact of CVD prevention.

4 Intervene Early Through Detection of At-Risk Individuals

Despite the availability of pharmacological and lifestyle interventions to prevent CVD events, CVD is underdiagnosed and insufficiently treated [38–40]. The early diagnosis of CVD and identifying at-risk individuals in order to promptly initiate guideline-directed medical therapy are important aims of CVD prevention. Prevention can be delivered at an individual level, such as behavioural interventions for lifestyle change, or the population level, for example, high-risk screening. Furthermore, population-wide interventions can be universal or targeted at specific groups. Robust evidence to support the CE of screening programmes in CVD was previously found to be lacking, and opportunities to improve the quality and applicability of economic evaluations for CVD screening were identified [41, 42]. These include conducting economic evaluation alongside clinical trials to better capture costs and outcomes including uptake and adherence, including the impact on health inequalities, exploring targeted screening approaches and developing a single validated or reference simulation model to improve transferability of results for policymakers [18, 41, 42]. Despite these challenges, a recent review has found a wide variety of CVD early detection strategies to be cost-effective or cost saving [18]. These studies were heterogenous, with most using Markov cohort models, but few reported on productivity losses or indirect healthcare costs, and only one mentioned equity or distributional effects [18]. Population screening using 10-year CVD risk was cost saving in 67% of studies [18]; thus, improving detection of high-risk individuals and subsequent management of risk can prevent CVD events and may be cost saving. When compared to standard of care in the UK, a scenario where it was possible to detect all individuals with high-risk CVD was estimated to save £68 billion in healthcare costs and prevent 3.4 million CVD events, becoming cost saving by 10 years [38]. When maximum detection rates were combined with subsequent best practice treatment for the high-risk individuals, 5.2 million CVD events were avoided, with cost savings slightly reduced (due to the costs of preventive treatment) but becoming cost saving by 13 years [38].

Risk scores are used worldwide to identify people at high-risk of CVD, but there are issues with their implementation. Firstly, the uptake of CVD risk screening and adherence to preventive treatment guidelines is suboptimal [43–45]. Secondly, the risk scores used can underestimate risk of CVD events by taking a static approach measuring risk factors at a single point in time, rather than a life-course approach to their development [34, 46]. It is established that age, sex, diabetes, chronic kidney disease, genetic or hereditary factors and the cumulative impact (level and duration of exposure) of modifiable risk factors such as obesity, smoking, elevated LDL-C and elevated systolic blood pressure all influence CVD risk [46]. However, CVD risk scores in use may not reflect true population risks, particularly in minority and disenfranchised groups. The American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations, QRISK3, AusCVDRisk calculator and SCORE2 all estimate 5- or 10-year absolute risks at the current point in time, but do not consider the cumulative impact of risk factors earlier in life [33, 46–48]. The recent AHA PREVENT equations based on novel risk prediction algorithms apply a life-course perspective for age-related risk, enabling estimation of short-term and long-term CVD risk. Nonetheless, these equations do not integrate other known risk factors in a cumulative manner or include genetic biomarkers such as lipoprotein(a) [Lp(a)]. Accurate long-term risk prediction is critical, as some individuals with low short-term risk of CVD may have high long-term risk but are not identified by current CVD screening guidelines; thereby, individuals miss out on intervention earlier in the life course when preventive strategies have more benefit [33, 46].

The value of preventive treatment has been demonstrated using the simple intervention of statin medication for lipid (LDL-C) lowering. Early initiation of statin treatment in the UK, from 30 years of age, is highly cost-effective for preventing CHD and more cost-effective than commencing treatment later in life [31]. This potential benefit arising from early intervention is illustrated in Fig. 1.

Even if at-risk populations are identified, statin treatment may be insufficient, with patients failing to achieve LDL-C therapeutic goals [32]. In Australia, the lost therapeutic benefit from delayed intensive lipid-lowering treatment (high-dose statin alone or with ezetimibe) is substantial. Among a simulated cohort of 1000 individuals at moderate to high risk of CVD, compared to those not achieving LDL-C targets under standard of care (low- to moderate-intensity statin), treatment intensification prevented 29 CHD events and gained 0.02 years of life lived per person and 0.03 QALYs

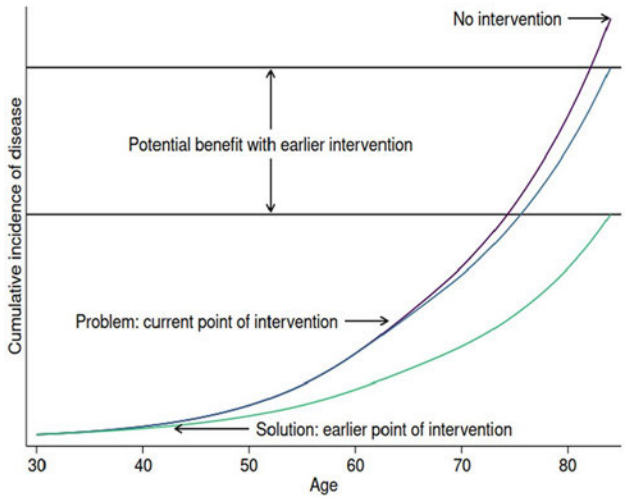

Fig. 1 Cumulative disease incidence by age with early vs later intervention. Modified from Morton and Ademi [31]

per person [32]. Treatment intensification was cost-effective (incremental cost-effectiveness ratio [ICER] AU $13,205 per QALY gained) and even more so when compared to a 5-year delay in treatment (ICER AU $7445) [32].

Recognising cumulative exposure to LDL-C, or 'cholesterol burden,' within CE studies is especially relevant when evaluating screening programmes for FH. Individuals with FH, a genetic condition of dysregulated LDL-C metabolism leading to elevated LDL-C levels from birth, experience this cholesterol burden acutely, having increased risk of premature death from CHD [49]. Detection of FH permits earlier lifestyle modification and pharmacological treatment to prevent CVD events. If cholesterol burden is underestimated or not included within the economic evaluation, more effective diagnostic and treatment policies may, incorrectly, not be recommended, particularly in younger individuals with FH [50]. Genetic screening for FH can be implemented universally (population-wide) or with a targeted approach called cascade screening (case finding through testing close relatives of known FH cases). Nationwide FH cascade screening of 10-year-olds (with subsequent preventive treatment) in the Netherlands was estimated to be cost saving from a societal perspective and likely cost-effective from a healthcare perspective (ICER €9220 per QALY), with a positive ROI of €8.37 per euro spent on the programme [29]. Similar modelling for Australia found FH cascade screening of 10-year-olds was cost saving from a healthcare perspective [28]. Studies taking a universal screening approach using opportunistic LDL-C testing of all children to indicate the need for further FH testing were also cost-effective [49]. Overall detection and management of FH in children via screening programmes is cost-effective from a healthcare and a societal perspective over multiple healthcare settings, but has not been widely adopted into policy [49]. Challenges remain in determining which screening strategy maximises benefit within the resource constraints of each setting.

Screening for Lp(a) is another potential avenue for detecting individuals at high risk of CVD. Lp(a) is an independent, causal risk factor for atherosclerotic CVD and aortic valve stenosis. As genetic polymorphism in apolipoprotein(a) drives increased Lp(a) levels, a single genetic test for adults is suitable for screening [51, 52]. Some have argued that Lp(a) measurement is unnecessary in the absence of an available treatment to specifically lower Lp(a) levels. However, when interpreted in combination with traditional CVD risk factors, Lp(a) testing can provide a more comprehensive, individualised risk assessment, managed with modification of other risk factors in the absence of a direct Lp(a)-reduction approach [53]. In patients with raised Lp(a) and a medium to large number of traditional CVD risk factors, overall CVD risk is underestimated markedly [54, 55].

These patients can miss opportunities for early and intensive treatment that would reduce global CVD risk even if Lp(a) remains unchanged [54, 55]. European, Canadian and American clinical guidelines now recommend Lp(a) status be measured at least once for adults and the results interpreted in the context of existing risk factors and global CVD risk [51, 52, 56]. Moreover, the Brussels declaration advocates for inclusion of Lp(a) testing in the national cardiovascular plan [53]. Risk factors are then managed through intensive lifestyle and pharmacological interventions. In addition, evidence is emerging in the use of lipoprotein apheresis, and treatments addressing Lp(a) levels are in the clinical trial pipeline. Current CVD risk scores do not include Lp(a); therefore, Lp(a) screening presents an opportunity to make early intervention in cardiovascular health even more impactful. Preliminary findings from the first Lp(a) global summit organised through the FH Europe Foundation found Lp(a) testing was cost saving in high-income countries (HICs) [53], and a recent, international study showed that Lp(a) screening and treatment in HICs is cost saving [57]. Further research is required to support the implementation of Lp(a) screening.

Strategies for the detection and early intervention in CVD are predominantly cost-effective and almost a quarter are dominant (cost saving) [18]. Through the application of novel health economic methods and improved consideration of CVD risk, we have demonstrated that improved detection and early intervention in CVD can result in large health benefits and cost savings; however, these findings do not always translate into health policy. As such, based on this narrative review and the Manifesto for Change recommends implementing pathways that ensure early signs of CVD are detected and managed for all stages of life by taking a life-course approach, supported by investment in research on the ROI for early CVD detection and diagnosis.

5 Intervene Early Through CVD Risk Factor Reduction

There has been longstanding debate as to whether the 'high risk' or individual approach to prevention, identifying and treating individuals at high risk of CVD discussed above, or a 'mass' or population approach reducing the determinants of CVD risk across the population as a whole should be adopted [58]. The high-risk approach has been the focus of public health efforts in HICs, but multiple risk factor screening is less commonly implemented in low- and middle-income countries (LMICs) with limited healthcare resources [58, 59]. Drawbacks to a high-risk screening approach are many and varied. In addition to the aforementioned issues with accurately assessing CVD risk, screening programmes alone are ineffective in preventing stroke and CVD events unless linked with suitable behavioural and pharmacological treatment, and even when uptake and treatment are adequate, the impact on CVD is modest [58]. The pharmacological treatment used should also be cost-effective. The CE of antihypertensives and statins is well established, but newer agents such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have not been found cost-effective as primary prevention [60]. Since we can now identify and control many of the underlying causes of CVD (such as tobacco use, excessive sugar and salt intake, inadequate fruit and vegetable intake, physical inactivity and harmful alcohol use), traditional thinking would indicate a renewed focus on reducing exposure to risk factors at the population level, in combination with CVD risk screening [58, 61].

There is limited research on the CE or ROI for these public health strategies. Only a minority of health economic evaluations for the primary prevention of CVD examine health promotion and public health interventions compared to secondary interventions, and consequently primary prevention and public health are underutilised and underfunded [17, 58]. This can be due to commercial or political interests and difficulties in robustly demonstrating CE [20, 62]. Within existing economic evaluations of public health interventions, it is difficult to make firm conclusions on CE or make comparisons to guide funding decisions due to potential publication bias and poorly reported or inconsistent methodologies [17, 20]. Many studies use no intervention rather than current best practice as a comparator, which may overestimate CE [20]. Not all evaluations measure comparable outcomes such as QALYs, disability-adjusted life years or life years gained, and there is inconsistency in the types of costs included (healthcare vs societal perspective) and the discounting rates applied [40]. For instance, the majority of evaluations of public health interventions targeting physical activity and healthy diet took a healthcare perspective, yet a societal perspective is preferable in public health, where the costs and benefits are likely to be inter-sectoral [20]. Studies on primary prevention rarely considered additional costs arising from living longer (due to CVD events avoided), introducing bias whereby CE must be interpreted based only on estimated reductions in CVD costs [17, 18]. Furthermore, studies primarily focus on major CVD events (myocardial infarction and stroke), leaving us with limited understanding of the CE of CVDs more broadly [63]. Lastly, equity considerations, such as effectiveness among different communities or populations, or distributional effects or impacts on health inequalities went mostly unreported [18, 63].

Despite these limitations, the majority of public health interventions for CVD have demonstrated potential to be cost-effective and even cost saving [20, 64, 65]. Across simulation-based studies, structural and policy interventions including taxation on tobacco, alcohol and salt and sugar were the most impactful for preventing CVD burden (mortality and incidence) [63]. Notable examples have identified health benefits and healthcare cost savings attributed to the reduction of sugar-sweetened beverage intake via taxation in the US [66], and for population-wide salt restriction in China [67]. In the HIC setting, most public health interventions provide ROI, and upstream, population-wide structural interventions reducing exposure to risk factors through fiscal (taxation) or regulation methods provide greater ROI [62]. For instance, taxation of tobacco, alcohol and unhealthy foods, mandated limits on salt in foods, and health promotion to increase physical activity and intake of fruits and vegetables have been estimated to be cost saving or cost-effective [12, 64, 65]. In LMICs, evaluating the CE of prevention is critical, as they face a growing burden of non-communicable disease (NCDs), alongside the competing demands of communicable disease, all within weaker healthcare infrastructure and tighter budgetary constraints [68–70]. Making global CE comparisons is challenging, with LMICs facing additional barriers to evaluating CE for primary prevention. CE thresholds differ vastly to those in HICs, vary widely by country and may not be established, relying instead on rules of thumb based on gross domestic product, which may lead to inappropriate decisions [69, 70]. For studies reporting QALYs, country-specific utilities are non-existent, with a reliance upon utilities derived from HICs [59, 69]. Similarly, CVD risks and treatment effects used within models are often taken from HICs, due to limited local RCT data [68, 69]. Studies on the CE of CVD prevention in LMICs are limited. The few studies for primordial or primary prevention predominantly focused on tobacco (mass media, taxation and legislation), salt (mass media, reformulation and labelling) and population screening for high-risk individuals, and all were very cost-effective or cost saving [69, 70]. There is a pressing need for studies in LMICs evaluating non-pharmacological and

population-level interventions that include equity impacts [68, 70].

While there may be little financial or political incentive to invest in preventive services, for younger people in particular, there is potential for well-conducted health economic research and advocacy to promote change in public policy [3, 62]. For example, in CVD prevention, expanding outcomes beyond QALYs to include PALYs captures patient-centred impacts, such as time spent at work or on daily activities that resonate in real-world settings [6, 71]. Underfunding of public health can occur because it sits within the healthcare budget but has benefits that accrue in other sectors that are not well accounted for. Capturing these broader non-health sector benefits and better understanding what goals or metrics are relevant to payers may support funding of primary prevention [72]. When resource allocation is accomplished through the government, this can involve multiple decision makers, each with their own objectives and remits [73]. Economic approaches to capture intersectoral impacts of policies including the often used 'societal perspective' may not include all costs, outcomes and opportunity costs across relevant sectors, involve many implicit value judgements and lack transparency in how their results inform choices made by (potentially multiple different) decision makers [73]. Novel approaches such as the 'extended impact inventory framework' are emerging that can be applied to CE analysis or cost–benefit analysis [73]. The framework involves estimating the net effect of an intervention (including opportunity costs) within all relevant dimensions (or sectors) such as health, education and crime, for example. This can evaluate both the current allocation across individuals (to address equity concerns for example) and provides the intervention effects across sectors to illustrate any potential trade-offs for consideration by intersectoral decision makers. Naturally, this approach also requires many normative judgements as to the selection of dimensions and their relative social value [73].

To promote action on CVD primary prevention we propose the following: better incorporation of equity into economic evaluations (see below), development of standardised guidance or best practice recommendations for the evaluation of primary prevention interventions that includes discounting, perspective and costs included, and the adoption of models and frameworks that move beyond major CVD events and report metrics relevant to payers, including intersectoral costs and benefits.

6 Intervene Early for Health Equity

Health inequities are differences (or inequalities) in health outcomes seen systematically across socioeconomic, geographic or demographic groups that are avoidable and unfair [74]. While healthcare policy and medical technology have evolved over time, this has not necessarily resulted in reduced inequalities in health, making health equity a concern for HTA globally [75]. Within healthcare decision-making, an equity-efficiency trade-off can exist where priority may be given to maximising health of the total population irrespective of how health is distributed (efficiency) or to prioritising health gains in particular individuals or groups (equity). Debate continues on how best to manage this conflict, but society does hold equity concerns in relation to the illness severity, age, race or ethnicity, socioeconomic status and geographic location of the individual [76–78]. Equity is commonly mentioned in HTA agency guidelines but rarely considered in an explicit manner, with decision-making in many countries based more on efficiency (as QALYs, for example) rather than equity [79].

The majority of deaths globally are attributable to NCDs (predominantly comprising CVD, as well as cancer, chronic respiratory disease and diabetes) [80], and NCDs account for much of the socioeconomic inequalities in all-cause mortality seen within and between countries [81, 82]. CVD in particular has the largest absolute and relative socioeconomic inequality in disease burden, when comparing across EU countries [81]. Inequalities in CVD outcomes across certain populations are well documented, with poorer outcomes reported in minority ethnic, immigrant or indigenous groups, in some rural or regional communities and in people of lower socioeconomic position [83–85]. For example, rates of myocardial infarction and CVD mortality are increasing among young women, and CVD in women is systematically underdiagnosed and undertreated [39]. Non-Hispanic black adult Americans have a higher prevalence of many CVDs and associated risk factors than white Americans [84]. Lastly, in Australia, indigenous populations are 2.1 times more likely than non-indigenous adults to have CVD, and people living in remote and very remote areas have a CVD death rate 1.4 times that seen in major cities [85]. Moreover, intersection of these socio-demographic characteristics can compound inequalities, with some communities facing overlapping gender, ethnic and socioeconomic-related disparities [39, 85, 86].

Inequity in CVD outcomes also has an economic impact. In Australia, bringing the health status of the most socioeconomically disadvantaged populations up to the same level as those least disadvantaged is estimated to save AU $704 million in healthcare costs and AU $3844 million in lost learnings over 2021–2030 [87]. For countries without universal

healthcare access, the costs of CVD-related healthcare may further increase disparities, resulting in intergenerational economic losses [3].

The social determinants of health (SDOH) are the conditions in which people are born, live, learn, work, play, worship and age, and the wider forces and systems shaping the conditions of daily life [88, 89]. These factors greatly impact CVD outcomes through psychosocial and biological pathways, particularly among marginalised communities through discrimination, stigmatisation and social exclusion [89]. Consequently, action to improve equity of CVD outcomes means addressing the structural determinants of health equity (i.e. access to healthcare and education, occupation and income, built, social and economic environment) that influence lived experience [89].

Many preventive public health policies using structural, fiscal, regulatory and educational mechanisms and preventative treatment or screening programmes improve health outcomes whilst also improving equity [90]. However, CVD prevention programmes delivered at the individual level require some degree of agency from individuals and may be more likely to generate or widen inequalities compared to population level strategies [41]. Therefore, depending on engagement and uptake, some interventions may worsen inequalities, indicating a need to evaluate the equity impacts of interventions as well as CE [90, 91]. Methods for conducting equity-informative CE analysis are emerging and have been applied to the evaluation of CVD prevention [64, 92]. For a population-wide individual CVD risk screening programme in the UK, universal implementation was unlikely to be cost-effective or equitable; a targeted approach delivered to the most socioeconomically deprived groups had potential to become cost-effective and equity improving in the future, but an approach combining targeted risk screening and structural public health interventions was estimated to be most cost-effective and deliver larger improvements in equity [91].

Opportunities to promote health equity within CVD prevention include: improving the measurement of the SDOH in research, incorporating the SDOH into CVD risk scoring, tailoring prevention programmes to community needs and priorities, designing interventions that address the upstream SDOH, greater incorporation of equity concerns into HTA processes and evaluating interventions using mixed methods to incorporate the lived experience of marginalised communities [79, 89]. A range of global initiatives, including but not limited to, the Global Heart Hub manifesto and FH Europe Foundation [53], have highlighted the need to address disparities in CVD detection and diagnosis through data collection to better monitor inequalities; implement policies addressing disparities that are targeted to local needs; and take an intersectoral approach that addresses the SDOH to facilitate equity of access.

7 Conclusion

The economic case for early intervention in CVD prevention is clear. Interventions that impact CVD prevention may improve health outcomes and can save money in the long term. The challenge that remains is to determine the optimal balance between interventions for early detection or CVD risk management, and primordial prevention through population-wide approaches tackling the upstream determinants of CVD. These questions should be explored by modelling long-term outcomes using a life-course approach and analysis of the equity impacts alongside CE.

This narrative review and Global Heart Hub's manifesto highlights the importance of equity in improving the lives of people living with CVD through early diagnosis and intervention, thereby preventing CVD events, reducing health inequities and limiting future economic burden to society. This can be achieved through:

- Reconsidering how we evaluate the CE of disease prevention in terms of accurate lifetime risk, discounting and the use of novel methods (MR and equity-informed analysis).
- Research to further grow the evidence base for CVD prevention that involves people with lived experience of CVD, including those from marginalised groups.
- Translating the economic evidence into practice by advocating for intersectoral policies for CVD prevention that address the SDOH.

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Declarations

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References

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76:2982–3021.
2. Chong B, Jayabaskaran J, Jauhari SM, et al. Global burden of cardiovascular diseases: projections from 2025 to 2050. Eur J Prev Cardiol. 2024. https://doi.org/10.1093/eurjpc/zwae281.
3. Kazi DS, Elkind MSV, Deutsch A, et al. Forecasting the economic burden of cardiovascular disease and stroke in the United States through 2050: a presidential advisory from the American Heart Association. Circulation. 2024;150:e89–101.
4. Luengo-Fernandez R, Walli-Attaei M, Gray A, et al. Economic burden of cardiovascular diseases in the European Union: a population-based cost study. Eur Heart J. 2023;44:4752–67.
5. Pinto FJ, Harding E, Fenton O. A manifesto from Global Heart Hub for early detection and diagnosis of cardiovascular disease. Eur Heart J. 2024;46:339–40.
6. Ademi Z, Ackerman IN, Zomer E, et al. Productivity-adjusted life-years: a new metric for quantifying disease burden. Pharmacoeconomics. 2021;39:271–3.
7. Shih K, Herz N, Sheikh A, et al. Economic burden of cardiovascular disease in the United Kingdom (UK). Eur Heart J Qual Care Clin Outcomes. 2025;11(5):678–90.
8. Krol M, Papenburg J, van Exel J. Does including informal care in economic evaluations matter? A systematic review of inclusion and impact of informal care in cost-effectiveness studies. Pharmacoeconomics. 2015;33:123–35.
9. Espinola N, Pichon-Riviere A, Casarini A, et al. Making visible the cost of informal caregivers' time in Latin America: a case study for major cardiovascular, cancer and respiratory diseases in eight countries. BMC Public Health. 2023;23:28.
10. Luengo-Fernandez R, Little M, Gray A, et al. Cardiovascular disease burden due to productivity losses in European Society of Cardiology countries. Eur Heart J Qual Care Clin Outcomes. 2024;10:36–44.
11. Marquina C, Talic S, Vargas-Torres S, et al. Future burden of cardiovascular disease in Australia: impact on health and economic outcomes between 2020 and 2029. Eur J Prev Cardiol. 2021;29:1212–9.
12. Howse E CP, Rychetnik L, Wilson A. The value of prevention: an evidence check rapid review brokered by the Sax Institute for the Centre for Population Health. Sydney. https://preventioncentre.org.au/resources/the-value-of-prevention/. Accessed: 27/23/2025.
13. AbdulRaheem Y. Unveiling the significance and challenges of integrating prevention levels in healthcare practice. J Prim Care Community Health. 2023;14:1–6.
14. Pandian JD, Gall SL, Kate MP, et al. Prevention of stroke: a global perspective. Lancet. 2018;392:1269–78.
15. Sims KD, Wei PC, Penko JM, et al. Projected impact of non-pharmacologic management of stage 1 hypertension among lower-risk US adults. medRxiv. 2023.
16. Shiell A, Garvey K, Kavanagh S, et al. How do we fund public health in Australia? How should we? Aust NZ J Public Health. 2024;48:100187.
17. Schwappach DLB, Boluarte TA, Suhrcke M. The economics of primary prevention of cardiovascular disease—a systematic review of economic evaluations. Cost Eff Resour Alloc. 2007;5:5.
18. Oude Wolcherink MJ, Behr CM, Pouwels X, et al. Health economic research assessing the value of early detection of cardiovascular disease: a systematic review. Pharmacoeconomics. 2023;41:1183–203.
19. Ademi Z, Morton JI, Liew D, et al. Integrating the biology of cardiovascular disease into the epidemiology of economic decision modelling via Mendelian randomisation. Pharmacoeconomics. 2022;40:1033–42.
20. Gebreslassie M, Sampaio F, Nystrand C, et al. Economic evaluations of public health interventions for physical activity and healthy diet: a systematic review. Prev Med. 2020;136:106100.
21. Briggs ACK, Sculpher M. Decision modelling for health economic evaluation. New York: Oxford University Press; 2006.
22. Marquina C, Zomer E, Vargas-Torres S, et al. Novel treatment strategies for secondary prevention of cardiovascular disease: a systematic review of cost-effectiveness. Pharmacoeconomics. 2020;38:1095–113.
23. Pratt N VC, Camacho X, Donnolley N, Pearson S. Optimising the availability and use of real world data and real world evidence to support health technology assessment in Australia. The University of New South Wales. Sydney. https://www.health.gov.au/resources/publications/hta-policy-and-methods-review-optimising-the-availability-and-use-of-real-world-data-and-real-world-evidence-to-support-health-technology-assessment?language=en. Accessed: 7/8/2025.
24. National Institute for Health and Care Excellence. NICE real-world evidence framework. Corporate document. 2022. 23 June 2022. Contract No.: Corporate document [ECD9]. https://www.nice.org.uk/corporate/ecd9. Accessed: 7/8/2025.
25. Gomes M, Turner AJ, Sammon C, et al. Acceptability of using real-world data to estimate relative treatment effects in health technology assessments: barriers and future steps. Value Health. 2024;27:623–32.
26. Ogilvie D, Adams J, Bauman A, et al. Using natural experimental studies to guide public health action: turning the evidence-based medicine paradigm on its head. J Epidemiol Community Health. 2020;74:203.
27. Claire R, Elvidge J, Hanif S, et al. Advancing the use of real world evidence in health technology assessment: insights from a multi-stakeholder workshop. Front Pharmacol. 2023;14:1289365.
28. Ademi Z, Norman R, Pang J, et al. Health economic evaluation of screening and treating children with familial hypercholesterolemia early in life: many happy returns on investment? Atherosclerosis. 2020;304:1–8.
29. Ademi Z, Norman R, Pang J, et al. Cost-effectiveness and return on investment of a nationwide case-finding program for familial

hypercholesterolemia in children in the Netherlands. JAMA Pediatr. 2023;177:625–32.
30. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601.
31. Morton JI, Marquina C, Lloyd M, et al. Lipid-lowering strategies for primary prevention of coronary heart disease in the UK: a cost-effectiveness analysis. Pharmacoeconomics. 2024;42:91–107.
32. Marquina C, Morton J, Zomer E, et al. Lost therapeutic benefit of delayed low-density lipoprotein cholesterol control in statin-treated patients and cost-effectiveness analysis of lipid-lowering intensification. Value Health. 2023;26:498–507.
33. Morton JI, Liew D, Watts GF, et al. Immediate versus 5-year risk-guided initiation of treatment for primary prevention of cardiovascular disease for Australians aged 40 years: a health economic analysis. Pharmacoeconomics. 2025;43:331–49.
34. Morton JI, Liew D, Ademi Z. A causal model for primary prevention of cardiovascular disease: the health economic model for the primary prevention of cardiovascular disease. Value Health. 2024;27:1743–52.
35. Harrison S, Dixon P, Jones HE, et al. Long-term cost-effectiveness of interventions for obesity: a Mendelian randomisation study. PLoS Med. 2021;18:e1003725.
36. Squires H, Chilcott J, Akehurst R, et al. A systematic literature review of the key challenges for developing the structure of public health economic models. Int J Public Health. 2016;61:289–98.
37. Squires H, Kelly MP, Gilbert N, et al. The PHEM-B toolbox of methods for incorporating the influences on behaviour into public health economic models. BMC Public Health. 2024;24:2794.
38. Thomas C, Brennan A, Goka E, et al. What are the cost-savings and health benefits of improving detection and management for six high cardiovascular risk conditions in England? An economic evaluation. BMJ Open. 2020;10:e037486.
39. Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease commission: reducing the global burden by 2030. Lancet. 2021;397:2385–438.
40. Ademi Z, Liew D, Chew D, et al. Drug treatment and cost of cardiovascular disease in Australia. Cardiovasc Ther. 2009;27:164–72.
41. Lee JT, Lawson KD, Wan Y, et al. Are cardiovascular disease risk assessment and management programmes cost effective? A systematic review of the evidence. Prev Med. 2017;99:49–57.
42. Hiligsmann M, Wyers CE, Mayer S, et al. A systematic review of economic evaluations of screening programmes for cardiometabolic diseases. Eur J Public Health. 2016;27:621–31.
43. Nieuwlaat R, Schwalm J-D, Khatib R, et al. Why are we failing to implement effective therapies in cardiovascular disease? Eur Heart J. 2013;34:1262–9.
44. Hespe CM, Campain A, Webster R, et al. Implementing cardiovascular disease preventive care guidelines in general practice: an opportunity missed. Med J Aust. 2020;213:327–8.
45. Finnikin S, Ryan R, Marshall T. Statin initiations and QRISK2 scoring in UK general practice: a THIN database study. Br J Gen Pract. 2017;67:e881–7.
46. Khan SS, Coresh J, Pencina MJ, et al. Novel prediction equations for absolute risk assessment of total cardiovascular disease incorporating cardiovascular-kidney-metabolic health: a scientific statement from the American Heart Association. Circulation. 2023;148:1982–2004.
47. SCORE2 working group ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42:2439–54.
48. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099.
49. Marquina C, Morton JI, Ademi Z. Health economics of detection and treatment of children with familial hypercholesterolemia: to screen or not to screen is no longer the question. Curr Opin Endocrinol Diabetes Obes. 2024;31:84–9.
50. Faria R, Saramago P, Cox E, et al. How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis. Atherosclerosis. 2023;367:40–7.
51. Koschinsky ML, Bajaj A, Boffa MB, et al. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. J Clin Lipidol. 2024;18:e308–19.
52. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022;43:3925–46.
53. Kronenberg F, Bedlington N, Ademi Z, et al. The Brussels International Declaration on Lipoprotein(a) testing and management. Atherosclerosis. 2025. https://doi.org/10.1016/j.atherosclerosis.2025.119218.
54. Kronenberg F, Mora S, Stroes ESG, et al. Frequent questions and responses on the 2022 lipoprotein(a) consensus statement of the European Atherosclerosis Society. Atherosclerosis. 2023;374:107–20.
55. Kronenberg F. Lipoprotein(a): from causality to treatment. Curr Atheroscler Rep. 2024;26:75–82.
56. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. Can J Cardiol. 2021;37:1129–50.
57. Morton J, Kronenberg F, Daccord M, et al. Lp(a) testing for the primary prevention of cardiovascular disease in high-income countries: a cost-effectiveness analysis. Atherosclerosis. 2025. https://doi.org/10.1016/j.atherosclerosis.2025.120447.
58. Feigin VL, Brainin M, Norrving B, et al. What is the best mix of population-wide and high-risk targeted strategies of primary stroke and cardiovascular disease prevention? J Am Heart Assoc. 2020;9:e014494.
59. Win ZM, Mao W, Traill T, et al. Cost-effectiveness and budget impact analysis of screening and preventive interventions for cardiovascular disease in Myanmar: an economic modelling study. Lancet Reg Health Southeast Asia. 2024;26:100394.
60. Korman M, Wisløff T. Modelling the cost-effectiveness of PCSK9 inhibitors vs. ezetimibe through LDL-C reductions in a Norwegian setting. Eur Heart J Cardiovasc Pharmacother. 2018;4:15–22.
61. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14:32–8.
62. Masters R, Anwar E, Collins B, et al. Return on investment of public health interventions: a systematic review. J Epidemiol Community Health. 2017;71:827.
63. Uthman OA, Court R, Anjorin S, et al. The potential impact of policies and structural interventions in reducing cardiovascular disease and mortality: a systematic review of simulation-based studies. Health Technol Assess. 2023;29(37):1–32.
64. Kypridemos C, Allen K, Hickey GL, et al. Cardiovascular screening to reduce the burden from cardiovascular disease: microsimulation study to quantify policy options. BMJ. 2016;353:i2793.
65. Vos T CR, Barendregt J, Mihalopoulos C, Veerman JL, Magnus A, Cobiac L, Bertram MY, Wallace AL. Assessing cost-effectiveness in prevention (ACE–Prevention): final report. Melbourne. https://public-health.uq.edu.au/files/571/ACE-Prevention_final_report.pdf. Accessed: 28/3/25.
66. Mekonnen TA, Odden MC, Coxson PG, et al. Health benefits of reducing sugar-sweetened beverage intake in high risk populations of California: results from the cardiovascular disease (CVD) policy model. PLoS ONE. 2013;8:e81723.

67. Wang M, Moran AE, Liu J, et al. Projected impact of salt restriction on prevention of cardiovascular disease in China: a modeling study. PLoS ONE. 2016;11:e0146820.
68. Oguta JO, Breeze P, Wambiya E, et al. Application of decision analytic modelling to cardiovascular disease prevention in sub-Saharan Africa: a systematic review. Commun Med. 2025;5:46.
69. Singh K, Chandrasekaran AM, Bhaumik S, et al. Cost-effectiveness of interventions to control cardiovascular diseases and diabetes mellitus in South Asia: a systematic review. BMJ Open. 2018;8:e017809.
70. Aminde LN, Takah NF, Zapata-Diomedi B, et al. Primary and secondary prevention interventions for cardiovascular disease in low-income and middle-income countries: a systematic review of economic evaluations. Cost Eff Resour Alloc. 2018;16:22.
71. Abushanab D, Marquina C, Morton JI, et al. Projecting the health and economic burden of cardiovascular disease among people with type 2 diabetes, 2022–2031. Pharmacoeconomics. 2023;41:719–32.
72. Wouterse B, Vasco SJ, Hiligsmann M. Future directions for the economics of prevention. Expert Rev Pharmacoecon Outcomes Res. 2025;25:841–4.
73. Walker S, Griffin S, Asaria M, et al. Striving for a societal perspective: a framework for economic evaluations when costs and effects fall on multiple sectors and decision makers. Appl Health Econ Health Policy. 2019;17:577–90.
74. McCartney G, Popham F, McMaster R, et al. Defining health and health inequalities. Public Health. 2019;172:22–30.
75. Ward T, Mujica-Mota RE, Spencer AE, et al. Incorporating equity concerns in cost-effectiveness analyses: a systematic literature review. Pharmacoeconomics. 2022;40:45–64.
76. Bobinac A, van Exel NJ, Rutten FF, et al. Inquiry into the relationship between equity weights and the value of the QALY. Value Health. 2012;15:1119–26.
77. Whitty JA, Lancsar E, Rixon K, et al. A systematic review of stated preference studies reporting public preferences for healthcare priority setting. Patient. 2014;7:365–86.
78. Whitty JA, Ratcliffe J, Chen G, et al. Australian public preferences for the funding of new health technologies: a comparison of discrete choice and profile case best-worst scaling methods. Med Decis Mak. 2014;34:638–54.
79. Saygın Avşar T, Yang X, Lorgelly P. Equity in national healthcare economic evaluation guidelines: essential or extraneous? Soc Sci Med. 2024;357:117220.
80. World Health Organization (WHO). Noncommunicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. WHO Accessed: 30/6/2025.
81. Andrade CAS, Mahrouseh N, Gabrani J, et al. Inequalities in the burden of non-communicable diseases across European countries: a systematic analysis of the Global Burden of Disease 2019 study. Int J Equity Health. 2023;22:140.
82. Di Cesare M, Khang Y-H, Asaria P, et al. Inequalities in non-communicable diseases and effective responses. Lancet. 2013;381:585–97.
83. Højstrup S, Thomsen JH, Prescott E. Disparities in cardiovascular disease and treatment in the Nordic countries. Lancet Reg Health Eur. 2023;33:100699. https://doi.org/10.1016/j.lanepe.2023.100699
84. Minhas AMK, Talha KM, Abramov D, et al. Racial and ethnic disparities in cardiovascular disease—analysis across major US national databases. J Natl Med Assoc. 2024;116:258–70.
85. Australian Institute of Health and Welfare. Heart, stroke and vascular disease: Australian facts. Canberra. https://www.aihw.gov.au/getmedia/72332e75-5907-442c-bf45-5de6761a5986/heart-stroke-and-vascular-disease-australian-facts.pdf?v=20240617080258&inline=true. Accessed: 22/08/2024.
86. Lee C, Park S, Boylan JM. Cardiovascular health at the intersection of race and gender: identifying life-course processes to reduce health disparities. J Gerontol B Psychol Sci Soc Sci. 2021;76:1127–39.
87. Hastings K, Marquina C, Morton J, et al. Projected new-onset cardiovascular disease by socioeconomic group in Australia. Pharmacoeconomics. 2022;40:449–60.
88. World Health Organization. Social determinants of health. World Health Organization (WHO). https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1. Accessed: 30/3/2025.
89. Powell-Wiley TM, Baumer Y, Baah FO, et al. Social determinants of cardiovascular disease. Circ Res. 2022;130:782–99.
90. Thomson K, Hillier-Brown F, Todd A, et al. The effects of public health policies on health inequalities in high-income countries: an umbrella review. BMC Public Health. 2018;18:869.
91. Kypridemos C, Collins B, McHale P, et al. Future cost-effectiveness and equity of the NHS health check cardiovascular disease prevention programme: microsimulation modelling using data from Liverpool, UK. PLoS Med. 2018;15:e1002573.
92. Avancena ALV, Prosser LA. Examining equity effects of health interventions in cost-effectiveness analysis: a systematic review. Value Health. 2021;24:136–43.

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Methodology

A Causal Model for Primary Prevention of Cardiovascular Disease: The Health Economic Model for the Primary Prevention of Cardiovascular Disease

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ABSTRACT

Objectives: Our objective was to design and develop an open-source model capable of simulating interventions for primary prevention of cardiovascular disease (CVD) that incorporated the cumulative effects of risk factors (eg, cholesterol years or blood-pressure years) to enhance health economic modeling in settings which clinical trials are not possible.

Methods: We reviewed the literature to design the model structure by selecting the most important causal risk factors for CVD—low-density lipoprotein-cholesterol (LDL-C), systolic blood pressure (SBP), smoking, diabetes, and lipoprotein (a) (Lp(a))—and most common CVDs—myocardial infarction and stroke. The epidemiological basis of the model involves the simulation of risk factor trajectories, which are used to modify CVD risk via causal effect estimates derived from Mendelian randomization. LDL-C, SBP, Lp(a), and smoking all have cumulative impacts on CVD risk, which were incorporated into the health economic model. The data for the model were primarily sourced from the UK Biobank study. We calibrated the model using clinical trial data and validated the model against the observed UK Biobank data. Finally, we performed an example health economic analysis to demonstrate the utility of the model. The model is open source.

Results: The model performed well in all validation tests. It was able to produce interpretable and plausible (consistent with expectations of the existing literature) results from an example health economic analysis.

Conclusions: We have constructed an open-source health economic model capable of incorporating the cumulative effect of LDL-C (ie, cholesterol years), SBP (SBP-years), Lp(a), and smoking on lifetime CVD risk.

Keywords: cardiovascular disease, causal modeling, health economic analysis, primary prevention.

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Highlights

- Many health economic models for cardiovascular disease (CVD) are based on randomized clinical trials; however, because they do not incorporate the cumulative effect of changes in risk factors, they may underestimate the benefit of therapies as the time horizon of the studies increases. No health economic models have incorporated the cumulative effect of risk factors on the risk for incident CVD.
- Herein, we outline the construction of a health economic model that incorporates the cumulative and causal effects of low-density lipoprotein-cholesterol, systolic blood pressure, smoking, diabetes, and lipoprotein (a) (Lp(a)) on the risk of myocardial infarction and stroke. We describe the rationale behind the novel model structure, how we incorporated causal effects of key cardiovascular risk factors, and calibrated and tested the model against real-world data. We also provide all syntax necessary for model construction.
- This model has potential in public health and clinical decision making when a clinical trial for the intervention simulated is not possible or practical, which is the case for most long-term studies on the primary prevention of CVD. It can assess the cost-effectiveness of complex interventions for CVD prevention and identify individuals in whom long-term targeted CVD prevention is cost-effective.

Introduction

Although most health economic models for cardiovascular disease (CVD) adopt a lifetime perspective, the effect estimates underlying treatment effects are predominantly based on short-term randomized clinical trials (RCTs).[1,2] However, several major risk factors for CVD—low-density lipoprotein-cholesterol (LDL-C), systolic blood pressure (SBP), smoking, and diabetes—have cumulative effects on the risk for CVD.[3–5] Therefore, it is likely that using RCT-based efficacy estimates will substantially underestimate the benefits of risk factor control when a model time horizon is substantially longer than the trial period, because the benefits of risk factor control should increase with time (if people remain adherent). This limitation risks misallocation of resources and forgoing the potential benefits of early intervention for the primary prevention of CVD.

Nevertheless, RCTs remain the gold standard for causal evidence and observational studies provide less reliable estimates of the effects of risk factor modification. We recently proposed that when an RCT that would produce the results required to inform a health economic model is not possible or practical (such as when the time horizon is too long or cost is too high, as in primary prevention of CVD), health economic models should be based on causal effects derived from Mendelian randomization analyses.[6] Briefly, this is because Mendelian randomization, when combined with knowledge of disease pathophysiology and other forms of epidemiological evidence, can

allow for causal inference from observational data, which can be used for the design of health economic models that incorporate the long-term, cumulative effects of risk factors (eg, cholesterol years or blood-pressure years) on the risk for CVD.

This approach was then illustrated via a study that assessed the cost-effectiveness of lipid-lowering strategies for primary prevention of coronary heart disease initiated at ages 30, 40, 50, and 60 years and showed that earlier lowering of LDL-C is a more cost-effective strategy than late intervention.[7] However, this model did not include risk factors other than LDL-C and thus could not simulate interventions that did not lower LDL-C (ie, most lifestyle interventions) or target treatment via absolute risk of CVD. Therefore, there remains a requirement for a health economic model that reliably incorporates the cumulative effects of modifiable risk factors on CVD risk.

Here, we outline the construction of such a health economic model, which incorporates the causal effects of LDL-C, SBP, smoking, diabetes, and lipoprotein (a) (Lp(a)) on the risk of myocardial infarction (MI) and stroke. We describe the rationale behind the novel model structure, how we incorporated causal effects of key cardiovascular risk factors, and calibrated and tested the model against real-world data. Further, in an online protocol, we provide all syntax necessary for model construction (ie, the model is open source).

Methods

A more detailed explanation of the models' construction, as well as all syntax, is available in the protocol, available at https://shop.monash.edu/primary-prevention-cardiovascular-disease-health-economic-model.html. All analyses were conducted in Stata, Version 17.0 (StataCorp).

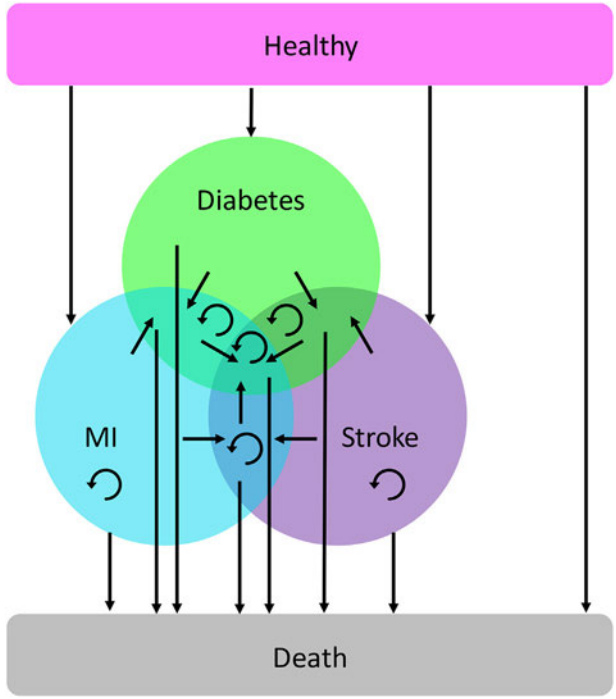
Choice of Model Structure

The model includes 2 CVDs—MI and stroke (stratified by ischemic and hemorrhagic subtype)—and 5 modifiable risk factors—LDL-C, SBP, Lp(a), diabetes, and smoking. These CVDs were selected because they are responsible for the majority of the burden of CVD,[8] and because the causal structure of these CVDs, particularly MI, has been studied at length.[9] LDL-C, SBP, diabetes, and smoking were included because they are the modifiable causal risk factors in both the Framingham risk score and pooled cohort equation[10,11]; Lp(a) was included because it is causal for both MI and stroke and is an important risk factor for CVD in a subset of the population with very high Lp(a).[12-14]

The model has the following living health states: no CVD or diabetes; MI, stroke, and diabetes; and all combinations thereof (diabetes constitutes both a health state and a risk factor for MI and stroke). Thus, there were a total of 9 health states: No diabetes or CVD; MI; stroke; MI and stroke; diabetes; diabetes and MI; diabetes and stroke; diabetes, MI, and stroke; and dead (Fig. 1). Further, the model tracks recurrent MI and stroke. From any living health state an individual in the model can transition to death, which is the only absorbing state in the model.

Because the included risk factors (smoking in particular) are associated with diseases other than CVD that may cause death (and thus become a competing risk for CVD), we reviewed evidence from Mendelian randomization studies that examined the association between each risk factor and cause of death that was responsible for at least 1% of all deaths in the UK Biobank cohort. This led to the inclusion of several cause-specific mortality rates in the model. A detailed description of the literature reviewed for inclusion of each risk factor and outcome association is provided in the protocol, pp.5-47, Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010 summarizes the included associations, and Figure 1 shows the model structure.

Figure 1. Model structure. Straight arrows represent transitions between states; circular arrows repeat events (MI or stroke) within a health state.



MI indicates myocardial infarction.

Overview of Approach to Incorporation of Causal Effects of Risk Factors

For LDL-C, SBP, Lp(a), and smoking, the effect of these risk factors on CVD risk is proportional to both magnitude of exposure (ie, absolute levels of the risk factor) and duration of exposure (ie, time spent exposed to the risk factor).[3,5,15] This is essentially the concept of cholesterol years, blood-pressure years, or smoking-pack years.[16] Results from Mendelian randomization can quantify the effect of exposure to the risk factor over the lifetime but cannot provide an age- or exposure-specific estimate of effect. Thus, the key assumption underlying the relationship of LDL-C, Lp(a), and SBP with CVD risk is that CVD risk is proportional to the time-weighted mean cumulative level of the risk factor at a given age. For smoking, the cumulative impact is captured using the lifetime smoking index (LSI),[17] which incorporates the nonlinear effects of duration of smoking, time since cessation of smoking, and number of cigarettes smoked per day. The effects of the risk factors are incorporated into the model using the following formula:

$$R_a = R \times M^{(x-\mu)}$$

in which R_a is the adjusted age and sex-specific rate of CVD, R the age- and sex-specific rate of CVD for the whole population, M the measure of association from a Mendelian randomization study, x the time-weighted mean cumulative level of the risk factor (or LSI) for the individual in the simulation, and μ the time-weighted mean cumulative level of the risk factor (or LSI) across the

population used to derive the age- and sex-specific rate for the whole population.

Thus, this formula provides an estimate of the age-specific rate of CVD for an individual based on their exposure to risk factors over the lifetime. To estimate the time-weighted mean cumulative level of the risk factor (or LSI) at any age, the risk factor trajectory over the lifetime needs to be simulated. The approach to this for each risk factor is outlined below.

For diabetes, incorporating duration of exposure and magnitude of exposure (ie, to elevated glucose) was deemed impractical for this model (discussed in the protocol, p.19); thus, the effect of diabetes on the risk of CVD was incorporated using the following formula:

$$R_{DM} = R_{NoDM} \times M$$

in which R_{DM} is the age and sex-specific rate of CVD in people with diabetes, R the age and sex-specific rate of CVD in people without diabetes, and M the measure of association from a Mendelian randomization study (a rate ratio in this instance).

Simulation of Risk Factor Trajectories

As described above, there are 2 risk factor trajectories that are captured in this model—the risk factor trajectories among UK Biobank participants (μ, above) and the risk factor trajectories for the model population (x, above). Importantly, the simulation of risk factor trajectories in the UK Biobank population is designed to recapitulate the values used in the estimation of transition probabilities (thereby incorporating the effects of any lipid or blood pressure lowering therapies in the UK Biobank population). For the UK Biobank population, which recruited people (mostly) between the ages of 40 and 69 years,[18] we used generalized linear models, stratified by sex, to estimate age and sex-specific value of each risk factor for people between ages 40 and 69 years. For all risk factors, we used these models to project the risk factor values from ages 70 to 84 years, assuming the trajectory of risk factor values would continue linearly from age 69 to 84 years. For diabetes and the LSI, we used these models to estimate the values from ages 30 to 39 years, assuming a linear trajectory from 30 to 40 years. For LDL-C, Lp(a), and SBP, to estimate values before age 40, we made the following assumptions. For LDL-C, we assumed that mean LDL-C was 0.75 mmol/L at birth,[19] increases linearly to 2 mmol/L by age[5,20] and then increases linearly to age 40 years. For Lp(a), we assumed that the value was constant from birth to age 40 years.[21] For SBP, we assumed that mean SBP was 85 mm Hg at birth and increases linearly to 118 mm Hg by age 17 years,[22] then increases linearly to age 40 years. Once each risk factor was simulated, we then calculated the time-weighted mean cumulative level of the risk factor (time weighting is outlined in the calibration section below). For the model population, risk factor trajectories can be specified at any age and do not necessarily need to follow these assumptions, although for all examples we present, we followed these assumptions. Moreover, any level and timing of nonadherence can be specified by modifying the risk factor trajectories of the simulated population.

Estimation of Transition Probabilities

The incidence of CVD (both fatal and nonfatal) and mortality rates in people without CVD were estimated using age-period cohort models.[23] For these models, we followed individuals from date of first assessment in the UK Biobank until the first of MI, stroke, death, or end of follow-up for CVD models or followed until death or end of follow-up for mortality models. Risk time and events were then tabulated into 0.5-year intervals by age and period, stratified by sex. Poisson models were then fit on these data, with spline effects of current age, period (calendar time), and cohort (period minus age), with log-link, and person-years of follow-up as the exposure (separately by sex). These models were then used to predict incidence and cause-specific mortality rates in single-year intervals with the prediction year set at 2016 (the mid-point of follow-up). The resulting transition probabilities are shown in Appendix Figures 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010. The incidence of type 2 diabetes was modeled using data from Pal et al[24] via Poisson regression with spline effects of age, stratified by sex (Appendix Fig. 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010). These transition probabilities are the "unadjusted" transition probabilities (population mean transition probabilities hereafter) on which risk factors exert their effects in the model (via the formula described above and the effects listed in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010).

To estimate the incidence of recurrent events and death after an incident CVD event, we used Poisson models with spline effects of age and binary effects of prior MI and stroke, stratified by sex. The resulting transition probabilities are shown in Appendix Figure 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010. Because the focus of this model is primary prevention of CVD, the incidence of recurrent events and death after CVD were not sensitive to risk factors other than age and sex in this model.

Construction of the Microsimulation Model

After estimation of population mean transition probabilities and risk factor trajectories in the UK Biobank sample, there are 5 steps for the model itself. First, select the population(s) and intervention(s) to be tested. Second, simulate modifiable risk factor trajectories based on the selected population(s) and intervention(s) (details below). Third, using these risk factor trajectories, calculate transition probabilities for the primary prevention population adjusted for risk factor values for use in the model. Fourth, perform the microsimulation (details below). Finally, calculate desired results.

In this instance, unlike the simulation of risk factor trajectories for the UK Biobank, in which the trajectories are meant to match the population so that the population mean transition probabilities accurately reflect the risk factor values in the UK Biobank cohort, the risk factor trajectories can be specified in detail with any trajectory possible. Nevertheless, it is more realistic to use similar assumptions to those described above. Simulation of modifiable risk factor trajectories for the model is the point for interventions to act; thus, the effect and timing of the intervention must be decided before simulation of risk factor trajectories. These risk factor trajectories are then used in concert with the population mean transition probabilities and risk factor trajectories in the UK Biobank sample to calculate adjusted transition probabilities, using the formulas described above.

The model is a microsimulation model, the structure of which has been described above. The model can be populated with any age, sex, and starting health states. Transitions between states are determined by converting all incidence rates for leaving a health state into transition probabilities, then "stacking" these transition probabilities so that they measure continuously from 0 to 1 (for example, if the probability of developing type 2 diabetes, MI, stroke, and death is 0.1, 0.15, 0.1, and 0.2, respectively, then the stacked probabilities range from 0.0-0.1, 0.1-0.25, 0.25-0.35, 0.35-0.55, and 0.55-1.0 for type 2 diabetes, MI, stroke, death, and remaining in the health state), then a random number between

0 and 1 is selected, and whichever interval this number falls in dictates the health state the individual moves to in that cycle. An example of this process is shown in Appendix Figure 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010. Thus, individuals are at risk for only 1 event each cycle.

The model advances in 0.1-year cycles and saves each cycle, tracking the current health state (no CVD or diabetes, prior MI, prior stroke, type 2 diabetes, or combinations thereof, and death), and number of MIs and strokes. Once run, the saved cycles can be used to calculate desired results.

Calibration of the Model

The relationship of LDL-C and SBP with CVD risk is unlikely to be linear. For example, under the assumption that LDL-C is cumulative and causal for coronary heart disease (CHD),[25] and given that the relative risk for CHD of a 1 mmol/L reduction in LDL-C over the lifetime (mean age 65 years) is 0.48,[3] it would not be possible to show a relative risk for CHD of a 1 mmol/L reduction in LDL-C over approximately 5 years in RCTs of 0.77.[26] Therefore, it is likely that LDL-C in more recent years has more relevance for CHD risk than less recent years, meaning that for the model to accurately recapitulate reality, the effect of LDL-C should be time weighted. Similarly, the relative risk for CHD per 10 mmHg reduction in SBP over the lifetime (mean age 65 years) is 0.57,[3] whereas the relative risk for CHD per 5 mmHg reduction in SBP over 4 years in clinical trials is 0.92,[27] again, indicating that SBP in more recent years is more important than less recent years.

Therefore, we calibrated the model using clinical trial data to define the time-weighting functions for LDL-C and SBP. For this, we simulated clinical trials using the model across several weighting functions and selected the functions that most accurately recapitulated the composite CVD outcome over the short term. For LDL-C, this function was characterized by the following formula:

$$w = \left(\frac{x-3}{3}\right)^{-2}$$

in which w is the weighting factor, and x is years before the age at which the cumulative LDL-C is being calculated.

For SBP, the formula was:

$$w = \left(\frac{x-2.1}{2.1}\right)^{-2}$$

Additionally, because we assumed that the pathophysiology of Lp(a) on CVD risk is similar to LDL-C, we used the same time-weighting function for Lp(a) as for LDL-C.

Model Tests

To test the model, we conducted 4 tests. First, to test the structure of the model and estimation of transition probabilities, we aimed to recapitulate the first 14 years of follow-up in the UK Biobank study. To do this, we populated the model with the UK Biobank population at baseline and simulated 3 different risk factor trajectories following first assessment (as follow-up changes in medication use and risk factors were not available for most participants). Second, we subjected the model to absurdity tests. That is, we tested if the model would give the expected results at extreme values of risk factor inputs. Third, we conducted one-way sensitivity analyses to determine which of the model inputs the model was most sensitive to, across a range of individuals. All inputs to the epidemiologic basis of the model are shown in Appendix Tables 2 to 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010. Fourth, we conducted a probabilistic sensitivity analysis by varying all model inputs in 1000 Monte Carlo simulations to estimate the overall uncertainty in the epidemiological outputs of the model.

Health Economic Analysis

Finally, to demonstrate the utility of the model, we conducted a full health economic analysis. We used the model to estimate the cost-effectiveness of initiation of 20 mg of atorvastatin and 5 mg of rampiril for primary prevention of CVD at age 40 years compared with initiating these therapies at age 60 years. That is, early vs late intervention to control risk factors. We tested this strategy on 3 individuals (each simulated 10 000 times): (1) a person with an LDL-C of 3.5 mmol/L, SBP of 150 mmHg, and Lp(a) of 20 mg/dL, nonsmoker, and without diabetes at age 40 years; (2) a person with an LDL-C of 3.5 mmol/L, SBP of 150 mmHg, and Lp(a) of 200 mg/dL, current smoker who has smoked 20 cigarettes per day since age 18 years, and with diabetes at age 40 years; and (3) a person with an LDL-C of 4.5 mmol/L, SBP of 170 mmHg, and Lp(a) of 20 mg/dL, nonsmoker, and without diabetes at age 40 years. All analyses were stratified by sex (ie, 6 individuals total). The confidence intervals for each result were derived from probabilistic sensitivity analyses with 1000 Monte Carlo simulations (ie, 1000 probabilistic simulations over each of the 10 000 replicated individuals), as described above.

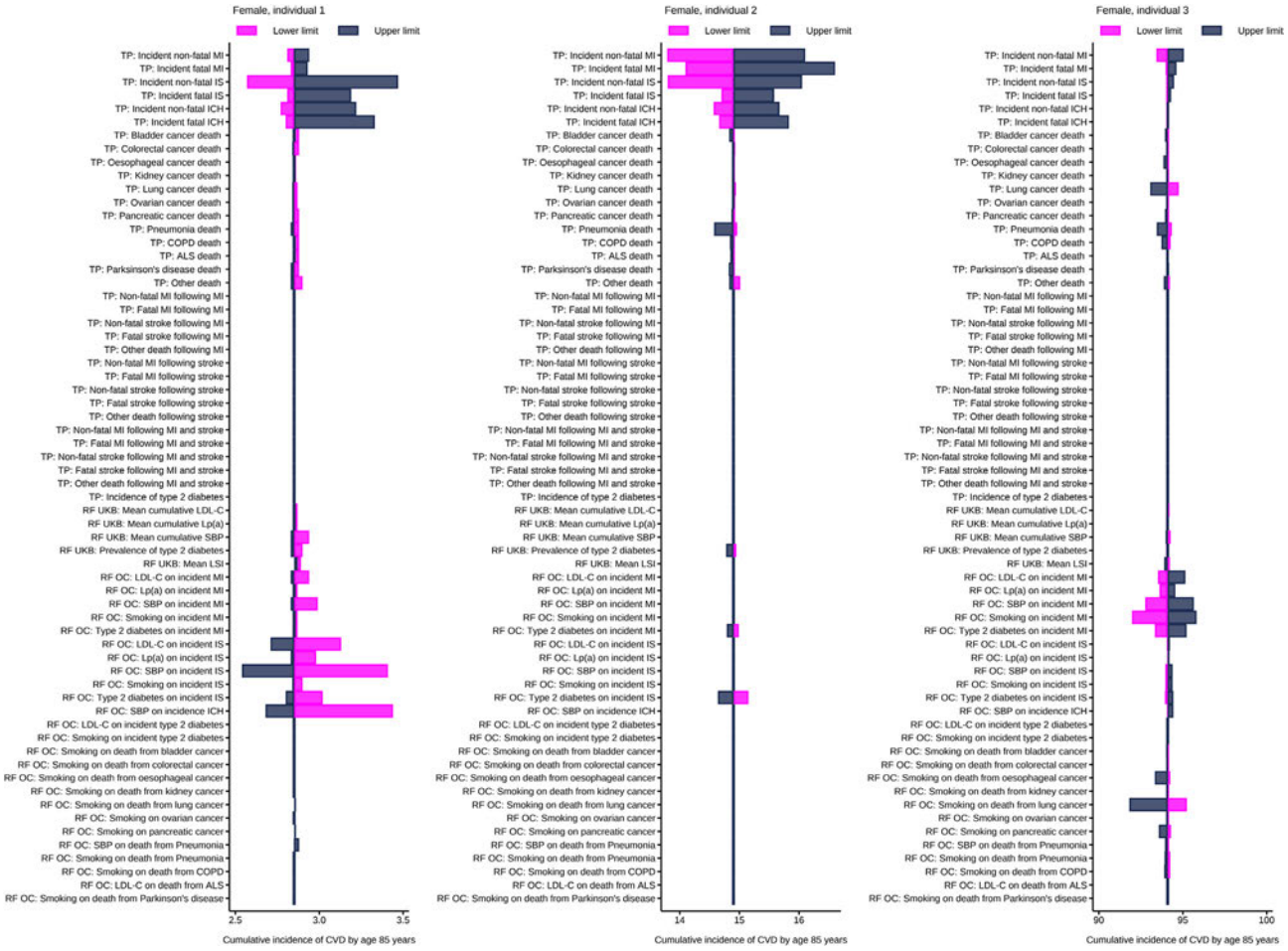
Briefly, the model inputs in addition to those described above were as follows. The effect of atorvastatin 20 mg was to lower LDL-C by 42.3% (42.0, 42.6)[28]; the effect of rampiril 5 mg was to lower SBP by 6.29 mmHg (3.32, 9.26)[29]; the annual costs of atorvastatin 20 mg and ramipril 5 mg were $176.41 and $173.22, respectively[30]; utility values for people without CVD or diabetes were age and sex-specific and derived from an Australian population study[31]; utilities for CVD and diabetes were derived from systematic reviews[32-34]; healthcare costs (acute and chronic costs of diabetes, MI, and stroke, and medication costs) were derived from the most recent Australian studies (Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010).[35,36] All costs were inflated to 2022 Australian dollars (AUD). We used 5% annual discounting in the base-case analysis.[37] We conducted one-way and probabilistic sensitivity analyses, with the primary outcome the incremental cost-effectiveness ratio (ICER) for initiation of therapy at 40 vs 60 years, from the Australian healthcare perspective. More detail on the full health economic analysis is available in the protocol, including scenario analyses where the lipid-lowering agent was changed from atorvastatin 20 mg to evolocumab 420 mg, lower levels of adherence were simulated, and the discounting rate was varied from 5% to 4%, 3%, 2%, 1%, and 0%. We did not use Mendelian randomization to derive effects of disease on utilities or costs because such studies are scant.[38]

Results

Model Validation

The model structure was able to accurately recapitulate the observed results in the UK Biobank study (Appendix Fig. 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010). Similarly, the model performed as expected at extreme values of risk factor inputs (Appendix Fig. 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010). The lifetime risk of CVD in the model was most sensitive to transition probabilities from no CVD to CVD, and the effect of risk factors on outcomes; nevertheless, no single input had a major effect on this outcome (Fig. 2). For the cumulative

Figure 2. Tornado diagrams for one-way sensitivity analyses. These show the cumulative incidence of CVD by age 85 years at the lower and upper bounds of the confidence intervals for each model input. Inputs are broken into 3 categories: TP, transition probabilities; RF UKB, risk factor values in the UK Biobank; RF OC, effect of risk factors on outcomes. The 3 individuals have the following risk factor values: (1) LDL-C of 1.5 mmol/L, SBP of 120 mm Hg, and Lp(a) of 0 mg/dL at age 40 years, never smokes, never develops diabetes; (2) mean value of all risk factors for the UK Biobank population at every age; (3) LDL-C of 5.0 mmol/L, SBP of 170 mm Hg, and Lp(a) of 100 mg/dL at age 40 years, pack-a-day smoker since age 18 years, diabetes from age 30 years.



CVD indicates cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure.

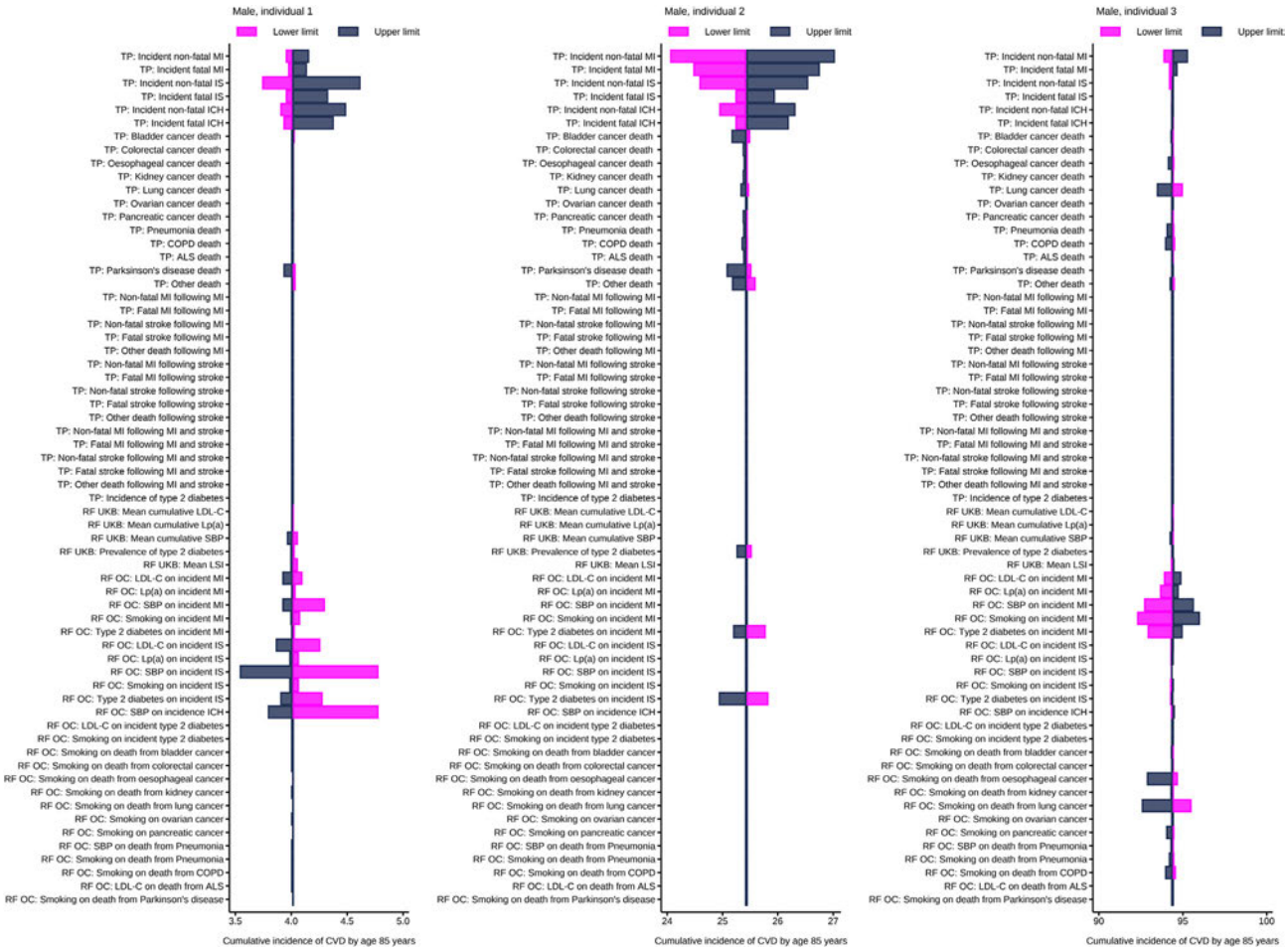
incidence of all-cause mortality, certain rarer causes of death (bladder cancer, Parkinson's disease, and pneumonia) had major effects in one-way sensitivity analyses, owing to the high uncertainty in the estimation of their rate in the UK Biobank sample (Appendix Fig. 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.07.010). Nevertheless, the probabilistic sensitivity analysis showed a reasonable level of uncertainty for all epidemiological outputs of the model (Fig. 3).

Example Health Economic Analysis

In females, the model suggested that initiation of atorvastatin 20 mg and ramipril 5 mg at age 40 years would lead to a lifetime risk of MI of 4.2% (95% CI: 3.3, 5.3), 17.1% (11.7, 25.6), and 19.2% (15.2, 24.3) for individuals 1, 2, and 3, respectively, compared with 7.4% (6.3, 8.9), 33.3% (24.2, 45.7), and 37.6% (30.5, 45.5) for intervention at age 60 years, respectively; estimates for males were 8.0% (6.6, 9.6), 26.2% (19.0, 36.6), and 28.7% (23.8, 34.2) for individuals 1, 2, and 3, respectively, at age 40 years, compared with 12.9% (11.3, 14.6), 46.5% (36.3, 59.0), and 48.5% (41.7, 55.6) for age 60 years, respectively (Table 1). Reductions in the lifetime risk of stroke were much smaller than those observed for MI (Table 1).

For health economic outcomes, intervention at age 40 vs 60 years was projected to lead to a gain in quality-adjusted life-years of 341 (−249, 821), 1154 (235, 2116), and 4547 (3111, 6443) for females 1, 2, and 3, respectively; corresponding estimates for males were 634 (−226, 1259), 1165 (−75, 2286), and 5614 (3933, 7458). For individual 1 in both females and males, earlier (vs later) intervention cost approximately AU$4000 and AU$3600 per person, respectively, whereas earlier intervention was cost-saving for individuals 2 and 3. Earlier (vs later) intervention was not cost-effective in individual 1 in either females or males (because they are at low CVD risk), but most simulations showed the intervention was dominant (beneficial and cost-saving) in individuals 2 and 3 (Fig. 4). Earlier intervention was not cost-effective when the lipid-lowering agent to evolocumab; ICERs were similar to the base-case when lower adherence was simulated; and ICERs improved with lower discounting rates.

Figure 2. (*continued*).



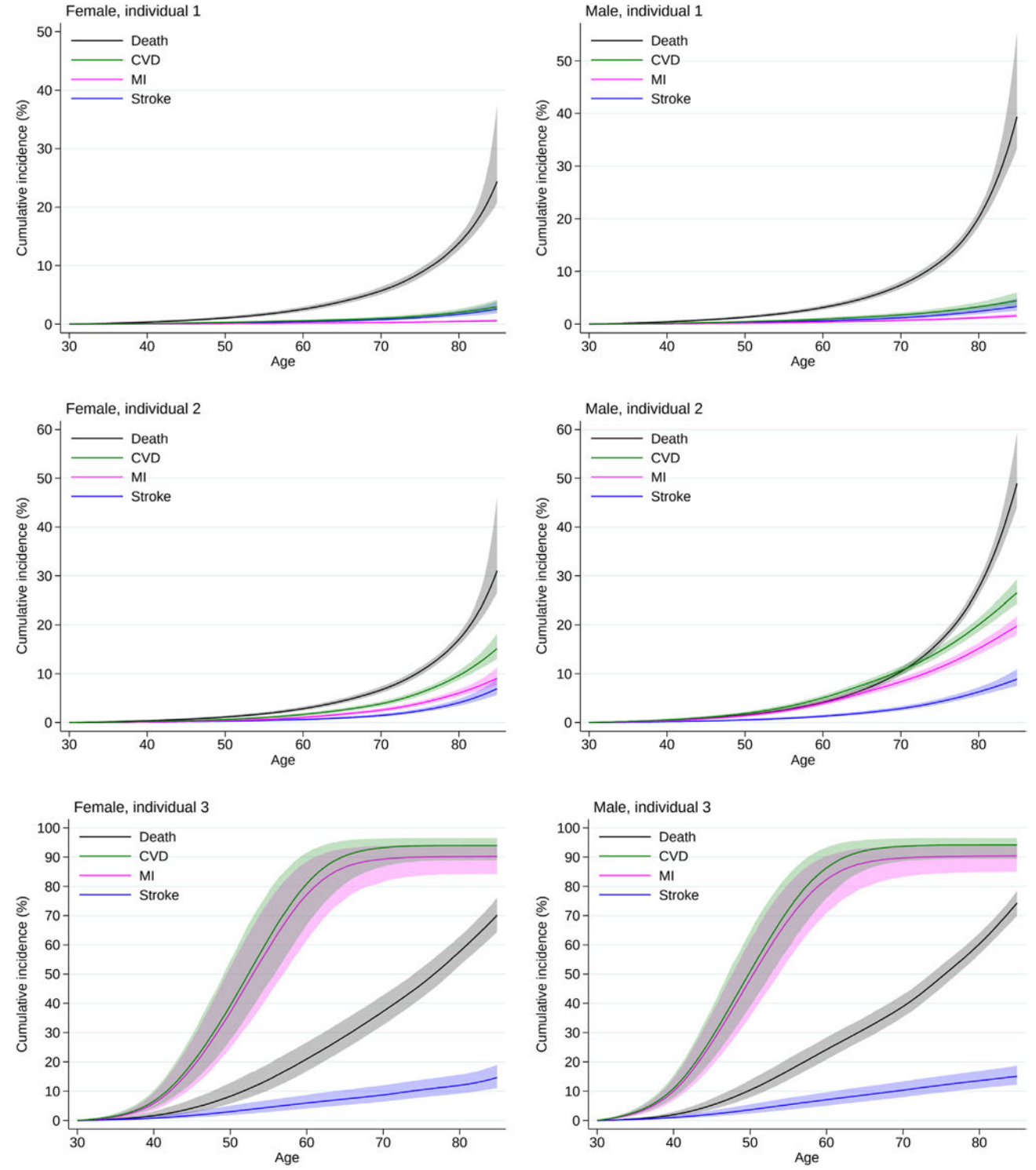
Discussion

We have designed and developed a novel health economic model that simulates risk factor trajectories over the life course and uses these to project CVD (MI and stroke) outcomes and associated healthcare costs, based on data from Mendelian randomization and calibrated using RCTs. The model can be populated with any individual (characterized by the models' risk factors) and simulate any modification to the risk factors over any length of time between ages 30 and 84, with risk proportional to the cumulative level of the risk factors, essentially quantifying the concept of cholesterol years, blood-pressure years, and smoking-pack years. This model has potential in public health and clinical decision making when a clinical trial for the intervention simulated is not possible or practical, which is the case for most long-term studies on the primary prevention of CVD. It can assess the cost-effectiveness of complex interventions for CVD prevention and identify individuals in whom long-term targeted CVD prevention is cost-effective.

The model performed well on the model validation tests and was calibrated using clinical trial data. Additionally, it is mostly based on well-known disease biology in terms of the relationship between the included risk factors and risk for CVD. The utility of the model was demonstrated in an example health economic analysis, in which it was clearly shown that for higher-risk individuals, early control of risk factors is an effective and dominant (cost-saving) approach to the prevention of CVD. A major advantage of the model is that transition probabilities (and hence, the entire model population) can be personalized to any individual, even if someone with those characteristics was not present in the UK Biobank sample on which the model is based. Thus, the model also has the potential to generate personalized estimates of the lifetime risk and health outcomes of CVD and link these to tailored treatment recommendations.

Nevertheless, the model has several limitations that are worth outlining. First, the epidemiological structure of the model is not that of a randomized trial. Although the effect estimates for interventions are based on causal data from Mendelian randomization, there were a number of assumptions underlying their incorporation in the model. Second, we did not perform a complete systematic review for each effect estimate incorporated. Third, the allelic variation in risk factors, and thus the variation underlying Mendelian randomization, is usually smaller than clinical interventions. For example, reductions in LDL-C with lipid-lowering therapy can exceed 50%,[28] whereas the variation attributable to most alleles is in the range of 0% to 5% per allele.[3] Therefore, the effect estimates in the model rely on extrapolating effects beyond the range they were estimated under. Fourth, we have not included only Mendelian randomization as our source of evidence—selection of each source of evidence was

Figure 3. Cumulative incidence (and 95% confidence intervals) of CVD, MI, stroke, and death for 3 individuals from a probabilistic sensitivity analysis. The 3 individuals have the following risk factor values: (1) LDL-C of 1.5 mmol/L, SBP of 120 mm Hg, and Lp(a) of 0 mg/dL at age 40 years, never smokes, never develops diabetes; (2) mean value of all risk factors for the UK Biobank population at every age; (3) LDL-C of 5.0 mmol/L, SBP of 170 mm Hg, and Lp(a) of 100 mg/dL at age 40 years, pack-a-day smoker since age 18 years, diabetes from age 30 years.



CVD indicates cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; SBP, systolic blood pressure.

Table 1. Probabilistic sensitivity analysis results. 1000 probabilistic iterations over 10 000 iterations of each individual, from age 40 to 84 years.

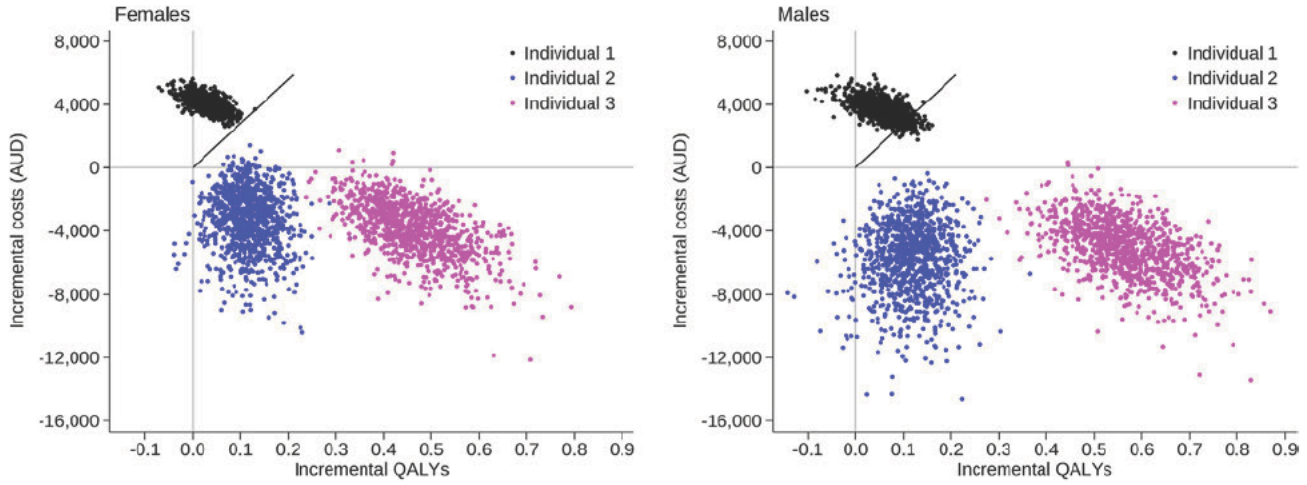
Sex	Individual	Outcome	Intervention at 60	Intervention at 40	Difference
Female	1	Incident MI (N)	741 (629, 887)	420 (330, 531)	−320 (−396, −255)
		Incident stroke (N)	679 (546, 875)	641 (497, 846)	−39 (−89, 9)
		Diabetes (N)	2882 (2660, 3149)	3293 (2831, 3832)	410 (148, 700)
		Deaths	2870 (2516, 4252)	2718 (2367, 4185)	−145 (−208, −73)
		Total MIs (N)	940 (788, 1127)	507 (399, 640)	−432 (−544, −336)
		Total strokes (N)	919 (731, 1172)	863 (670, 1128)	−57 (−137, 20)
		Total YLL	176 828 (176 216, 177 390)	177 468 (176 853, 178 001)	631 (303, 1010)
		Total QALY	152 443 (150 018, 154 606)	152 772 (150 271, 155 045)	341 (−249, 821)
		Total healthcare costs (AU$)	91 812 526 (80 859 671, 103 677 936)	131 972 016 (118 665 579, 148 708 682)	40 291 138 (31 557 401, 50 586 549)
		ICER			88 987 (−1 269 563, 1 185 971)
	2	Incident MI (N)	3326 (2417, 4571)	1707 (1174, 2561)	−1624 (−2131, −1162)
		Incident stroke (N)	1427 (992, 2012)	1336 (864, 2015)	−80 (−207, 63)
		Diabetes (N)	10 000 (10 000, 10 000)	10 000 (10 000, 10 000)	0 (0, 0)
		Deaths	8272 (7415, 8826)	8698 (7635, 9233)	389 (145, 611)
		Total MIs (N)	4406 (3154, 6036)	2181 (1492, 3256)	−2232 (−3002, −1581)
		Total strokes (N)	2062 (1424, 2955)	1920 (1250, 2934)	−118 (−302, 99)
		Total YLL	158 535 (152 711, 162 583)	159 420 (153 052, 163 783)	842 (−510, 2090)
		Total QALY	108 839 (92 990, 121 879)	109 967 (94 094, 123 188)	1154 (235, 2116)
		Total healthcare costs (AU$)	749 278 270 (626 969 350, 879 123 104)	717 667 286 (595 409 106, 47 388 596)	−30 995 777 (−73 432 444, −144 278)
		ICER			−26 339 (−130 549, 1172)
	3	Incident MI (N)	3756 (3054, 4550)	1924 (1518, 2432)	−1820 (−2249, −1453)
		Incident stroke (N)	1192 (948, 1528)	1132 (887, 1490)	−56 (−166, 50)
		Diabetes (N)	2112 (1931, 2314)	2662 (2517, 2794)	548 (266, 788)
		Deaths	4300 (3848, 5303)	3530 (3119, 4812)	−733 (−1005, −425)
		Total MIs (N)	4856 (3899, 5968)	2331 (1826, 2979)	−2519 (−3163, −1993)
		Total strokes (N)	1621 (1277, 2095)	1529 (1178, 2023)	−91 (−244, 62)
		Total YLL	172 088 (169 912, 173 522)	175 726 (174 683, 176 467)	3618 (2579, 5196)
		Total QALY	146 282 (142 965, 149 076)	150 883 (148 278, 153 094)	4547 (3111, 6443)
		Total healthcare costs (AU$)	199 200 759 (158 919 779, 250 420 418)	161 553 505 (144 984 800, 180 906 033)	−37 705 058 (−74 692 252, −8 450 138)
		ICER			−8215 (−14 858, −2463)
Male	1	Incident MI (N)	1286 (1127, 1463)	802 (658, 959)	−481 (−573, −405)
		Incident stroke (N)	852 (713, 1040)	811 (652, 1000)	−44 (−99, 6)
		Diabetes (N)	3566 (3184, 3962)	4061 (3407, 4773)	488 (193, 823)
		Deaths	4445 (3940, 5733)	4279 (3755, 5634)	−158 (−232, −70)
		Total MIs (N)	1657 (1452, 1879)	985 (800, 1177)	−671 (−800, −553)
		Total strokes (N)	1090 (908, 1330)	1027 (832, 1276)	−63 (−147, 17)
		Total YLL	174 579 (173 893, 175 253)	175 527 (174 789, 176 109)	947 (532, 1366)
		Total QALY	154 422 (152 015, 156 581)	154 988 (152 385, 157 426)	634 (−226, 1259)
		Total healthcare costs (AU$)	123 163 154 (108 514 409, 139 656 499)	159 064 386 (139 042 078, 182 905 921)	35 817 692 (24 522 204, 49 755 219)
		ICER			50 128 (−471 117, 517 545)
	2	Incident MI (N)	4646 (3626, 5897)	2620 (1904, 3658)	−2010 (−2449, −1565)
		Incident stroke (N)	1558 (1160, 2083)	1501 (1012, 2122)	−53 (−195, 105)
		Diabetes (N)	10 000 (10 000, 10 000)	10 000 (10 000, 10 000)	0 (0, 0)
		Deaths	8329 (7880, 8721)	8812 (8306, 9197)	472 (308, 646)
		Total MIs (N)	6382 (4955, 8094)	3467 (2511, 4882)	−2888 (−3597, −2233)
		Total strokes (N)	2138 (1555, 2927)	2078 (1385, 2943)	−60 (−270, 185)
		Total YLL	154 184 (148 416, 157 967)	154 717 (147 333, 159 139)	533 (−1241, 1999)
		Total QALY	108 713 (92 567, 122 095)	109 955 (93 616, 123 223)	1165 (−75, 2286)
		Total healthcare costs (AU$)	793 942 947 (675 001 057, 926 011 832)	735 970 112 (614 791 404, 858 981 294)	−56 428 180 (−106 479 981, −18 963 624)
		ICER			−45 606 (−251 864, 125 846)
	3	Incident MI (N)	4846 (4171, 5556)	2868 (2377, 3418)	−1968 (−2341, −1653)
		Incident stroke (N)	1333 (1111, 1650)	1328 (1077, 1696)	−4 (−107, 117)
		Diabetes (N)	2791 (2613, 2955)	3476 (3105, 3841)	685 (339, 1024)
		Deaths	5700 (5249, 6400)	5090 (4614, 6029)	−598 (−815, −301)
		Total MIs (N)	6460 (5534, 7498)	3568 (2947, 4289)	−2860 (−3408, −2409)
		Total strokes (N)	1710 (1409, 2139)	1696 (1365, 2170)	−15 (−153, 159)
		Total YLL	168 550 (166 784, 170 071)	173 024 (171 978, 173 942)	4473 (3386, 5834)
		Total QALY	146 454 (143 438, 149 091)	152 081 (149 545, 154 336)	5614 (3933, 7458)
		Total healthcare costs (AU$)	253 658 008 (210 340 508, 307 453 979)	203 654 815 (181 606 568, 230 026 400)	−50 043 708 (−86 995 324, −18 817 104)
		ICER			−8915 (−14 730, −3622)

The 3 individuals have the following risk factor values at age 40 years: 1. LDL-C of 3.5 mmol/L, SBP of 150 mm Hg, Lp(a) of 20 mg/dL, nonsmoker, no diabetes; 2. LDL-C of 3.5 mmol/L, SBP of 150 mm Hg, Lp(a) of 200 mg/dL, pack-a-day smoker since age 18 years, diabetes; 3. LDL-C of 4.5 mmol/L, SBP of 170 mmHg, Lp(a) of 20 mg/dL, nonsmoker, no diabetes.
ICER indicates incremental cost-effectiveness ratio; MI, myocardial infarction; QALYs, quality-adjusted life-years; YLL, years of life lived.

contextual and based on a range of considerations; there is not yet a guideline for when/how to include Mendelian randomization in health economic modeling, which is an area for future research.

Fifth, we calibrated the model using a combination of Mendelian randomization and clinical trial data, assuming that more recent values of LDL-C, Lp(a), and SBP were more relevant than values in the past when estimating the cumulative values of these risk factors, which is not consistent with some observational evidence.[39] Nevertheless, lack of weighting would only further enhance the importance of early risk factor control, making our model conservative with respect to earlier intervention. Sixth, the UK Biobank population underlying the model was affected by a "healthy volunteer" selection bias,[40] meaning risk estimates here may underestimate the risk in other populations. Although this is conservative, it does limit the generalizability of the model. Similarly, the UK Biobank population and most Mendelian randomization estimates come from predominately European

Figure 4. Probabilistic sensitivity analysis simulations presented in a common cost-effectiveness plane for 3 individuals for initiation of therapy at 40 vs 60 years of age, by sex. The 3 individuals have the following risk factor values at age 40 years: 1. LDL-C of 3.5 mmol/L, SBP of 150 mm Hg, Lp(a) of 20 mg/dL, nonsmoker, no diabetes; 2. LDL-C of 3.5 mmol/L, SBP of 150 mm Hg, Lp(a) of 200 mg/dL, pack-a-day smoker since age 18 years, diabetes; 3. LDL-C of 4.5 mmol/L, SBP of 170 mmHg, Lp(a) of 20 mg/dL, nonsmoker, no diabetes.



LDL-C indicates low-density lipoprotein-cholesterol; QALYs indicates quality-adjusted life-years; SBP, systolic blood pressure.

populations; thus, studies of higher-risk populations may need a modified version of the model. Seventh, several of the Mendelian randomization effect estimates included in the model had a high degree of uncertainty and/or had not been replicated at the time of model construction. Eighth, the underlying disease pathophysiology for every risk factor and outcome was not explicitly considered—the relationship between risk factors and risk for CVD was the biological relationship upon which the model was based. Therefore, certain conclusions from the model, particularly those not related to CVD, should be interpreted with caution. Ninth, we only included 5 modifiable risk factors in the model. Other risk factors influence CVD risk (such as inflammation[41] and stress[42]) and incorporation of other risk factors into future iterations of this model, or similar models, is an area for further study. Similarly, although MI and stroke are responsible for the majority of the burden of CVD,[8] we still have only included 2 cardiovascular outcomes (ie, only MI and stroke, out of all possible CVDs) in the model; inclusion of further CVDs is also warranted in future. Tenth, our risk factor trajectories for the mean of the UK Biobank sample required extrapolation out the sample range, which will have introduced error. Similarly, calculating trajectories in this assumes their values will remain stationary at a given age over calendar time, which is unlikely.[43] Eleventh, our simulation of risk factor trajectories in the UK Biobank population was designed to recapitulate the values used in the estimation of transition probabilities and will therefore include both people taking and not taking medications; recalibration of these values in settings where more or less people are taking medications may be required. Finally, our model was designed to capture the impact of interventions for primary prevention of CVD; thus, we did not attempt to integrate the effect of risk factors on recurrent CVD events.

In conclusion, when testing long-term interventions for primary prevention of CVD, a setting in which clinical trials are not practical, we propose one solution as being the use of health economic models based on cumulative risk factor trajectory modeling and Mendelian randomization. We have outlined construction of a novel model and have made all model syntax available to allow its use in health economic analysis.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2024.07.010.

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

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REFERENCES

1. Marquina C, Zomer E, Vargas-Torres S, et al. Novel treatment strategies for secondary prevention of cardiovascular disease: a systematic review of cost-effectiveness. *Pharmacoeconomics*. 2020;38(10):1095–1113.
2. Richman IB, Fairley M, Jørgensen ME, Schuler A, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of intensive blood pressure management. *JAMA Cardiol*. 2016;1(8):872–879.
3. Ference BA, Bhatt DL, Catapano AL, et al. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. *JAMA*. 2019;322(14):1381–1391.
4. Morton JI, Lazzarini PA, Polkinghorne KR, Carstensen B, Magliano DJ, Shaw JE. The association of attained age, age at diagnosis, and duration of type 2 diabetes with the long-term risk for major diabetes-related complications. *Diabetes Res Clin Pract*. 2022;190:110022.
5. Pope CA, Brook RD, Burnett RT, Dockery DW. How is cardiovascular disease mortality risk affected by duration and intensity of fine particulate matter exposure? An integration of the epidemiologic evidence. *Air Qual Atmos Health*. 2011;4(1):5–14.
6. Ademi Z, Morton JI, Liew D, Nicholls SJ, Zoungas S, Ference BA. Integrating the biology of cardiovascular disease into the epidemiology of economic decision modelling via Mendelian randomisation. *Pharmacoeconomics*. 2022;40(11):1033–1042.
7. Morton JI, Marquina C, Lloyd M, et al. Lipid-lowering strategies for primary prevention of coronary heart disease in the UK: a cost-effectiveness analysis. *Pharmacoeconomics*. 2024;42(1):91–107.
8. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982–3021.
9. Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis : current view and future perspective on lipoprotein modification treatment. *Neth Heart J*. 2017;25(4):231–242.
10. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837–1847.
11. Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S49–S73.
12. Lamina C, Kronenberg F, Lp(a)-GWAS-Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. *JAMA Cardiol*. 2019;4(6):575–579.
13. Larsson SC, Gill D, Mason AM, et al. Lipoprotein(a) in Alzheimer, atherosclerotic, cerebrovascular, thrombotic, and valvular disease: Mendelian randomization investigation. *Circulation*. 2020;141(22):1826–1828.
14. Welsh P, Welsh C, Celis-Morales CA, et al. Lipoprotein(a) and cardiovascular disease: prediction, attributable risk fraction, and estimating benefits from novel interventions. *Eur J Prev Cardiol*. 2022;28(18):1991–2000.
15. Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. *JAMA Cardiol*. 2018;3(7):619–627.
16. Shapiro Michael D, Bhatt Deepak L. "Cholesterol-years" for ASCVD risk prediction and treatment. *J Am Coll Cardiol*. 2020;76(13):1517–1520.
17. Wootton RE, Richmond RC, Stuijfzand BG, et al. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol Med*. 2020;50(14):2435–2443.
18. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLOS Med*. 2015;12(3):e1001779.
19. Descamps OS, Bruniaux M, Guilmot PF, Tonglet R, Heller FR. Lipoprotein concentrations in newborns are associated with allelic variations in their mothers. *Atherosclerosis*. 2004;172(2):287–298.
20. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. *JAMA*. 2012;308(6):591–600.
21. Wang XL, Wilcken DE, Dudman NP. Early expression of the apolipoprotein (a) gene: relationships between infants' and their parents' serum apolipoprotein (a) levels. *Pediatrics*. 1992;89(3):401–406.
22. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report):555–576.
23. Carstensen B. Age–period–cohort models for the Lexis diagram. *Stat Med*. 2007;26(15):3018–3045.
24. Pal K, Horsfall L, Sharma M, Nazareth I, Petersen I. Time trends in the incidence of clinically diagnosed type 2 diabetes and pre-diabetes in the UK 2009-2018: a retrospective cohort study. *BMJ Open Diabetes Res Care*. 2021;9(1):e001989.
25. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459–2472.
26. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267–1278.
27. Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397(10285):1625–1636.
28. Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. *Cochrane Database Syst Rev*. 2015;2015(3):Cd008226.
29. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. *Cochrane Database Syst Rev*. 2008;2008(4):Cd003823.
30. The pharmaceutical benefits scheme. PBS and RPBS section 85 date of supply data. The Pharmaceutical Benefits Scheme. https://www.pbs.gov.au/info/statistics/dos-and-dop/dos-and-dop. Accessed February 15, 2023.
31. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes*. 2016;14(1):133.
32. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value Health*. 2014;17(4):462–470.
33. Betts MB, Rane P, Bergrath E, et al. Utility value estimates in cardiovascular disease and the effect of changing elicitation methods: a systematic literature review. *Health Qual Life Outcomes*. 2020;18(1):251.
34. Joundi RA, Adekanye J, Leung AA, et al. Health state utility values in people with stroke: a systematic review and meta-analysis. *J Am Heart Assoc*. 2022;11(13):e024296.
35. Cobiac LJ, Magnus A, Barendregt JJ, Carter R, Vos T. Improving the cost-effectiveness of cardiovascular disease prevention in Australia: a modelling study. *BMC Public Health*. 2012;12:398.
36. Lee CM, Colagiuri R, Magliano DJ, et al. The cost of diabetes in adults in Australia. *Diabetes Res Clin Pract*. 2013;99(3):385–390.
37. Department of Health. The pharmaceutical benefits advisory committee (PBAC) guidelines. https://pbac.pbs.gov.au. Accessed September 28, 2021.
38. Dixon P, Harrison S, Hollingworth W, Davies NM, Davey Smith G. Estimating the causal effect of liability to disease on healthcare costs using Mendelian Randomization. *Econ Hum Biol*. 2022;46:101154.
39. Boshuizen HC, Lanti M, Menotti A, et al. Effects of past and recent blood pressure and cholesterol level on coronary heart disease and stroke mortality, accounting for measurement error. *Am J Epidemiol*. 2007;165(4):398–409.
40. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026–1034.
41. Swerdlow DI, Holmes MV, Kuchenbaecker KB, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis. *Lancet*. 2012;379(9822):1214–1224.
42. Crawford AA, Bankier S, Altmaier E, et al. Variation in the SERPINA6/SERPINA1 locus alters morning plasma cortisol, hepatic corticosteroid binding globulin expression, gene expression in peripheral tissues, and risk of cardiovascular disease. *J Hum Genet*. 2021;66(6):625–636.
43. Carroll MD, Kit BK, Lacher DA, Shero ST, Mussolino ME. Trends in lipids and lipoproteins in US adults, 1988-2010. *JAMA*. 2012;308(15):1545–1554.

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

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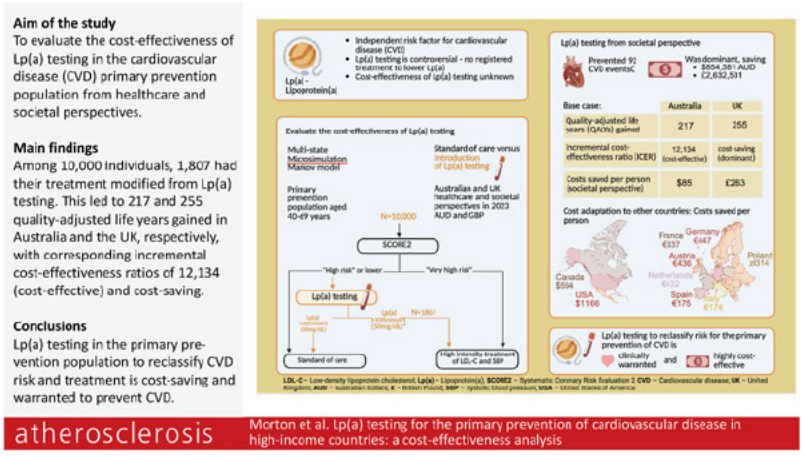
HIGHLIGHTS

- 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

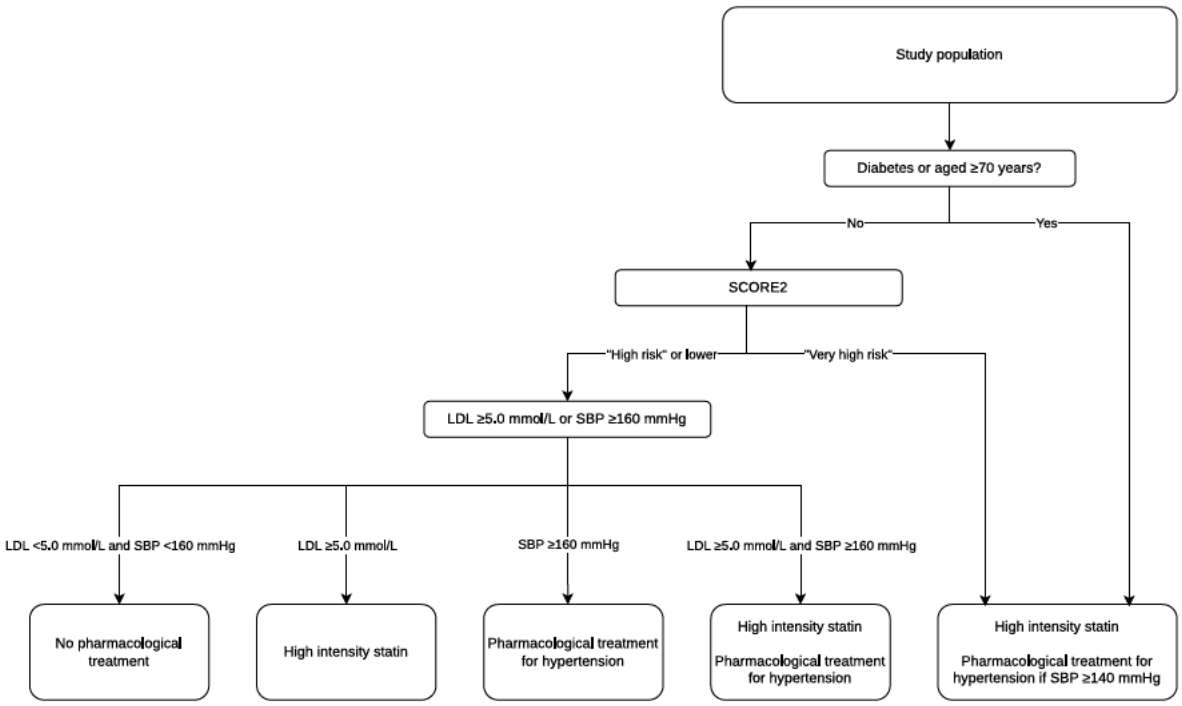


Fig. 1. Schematic of the control scenario.

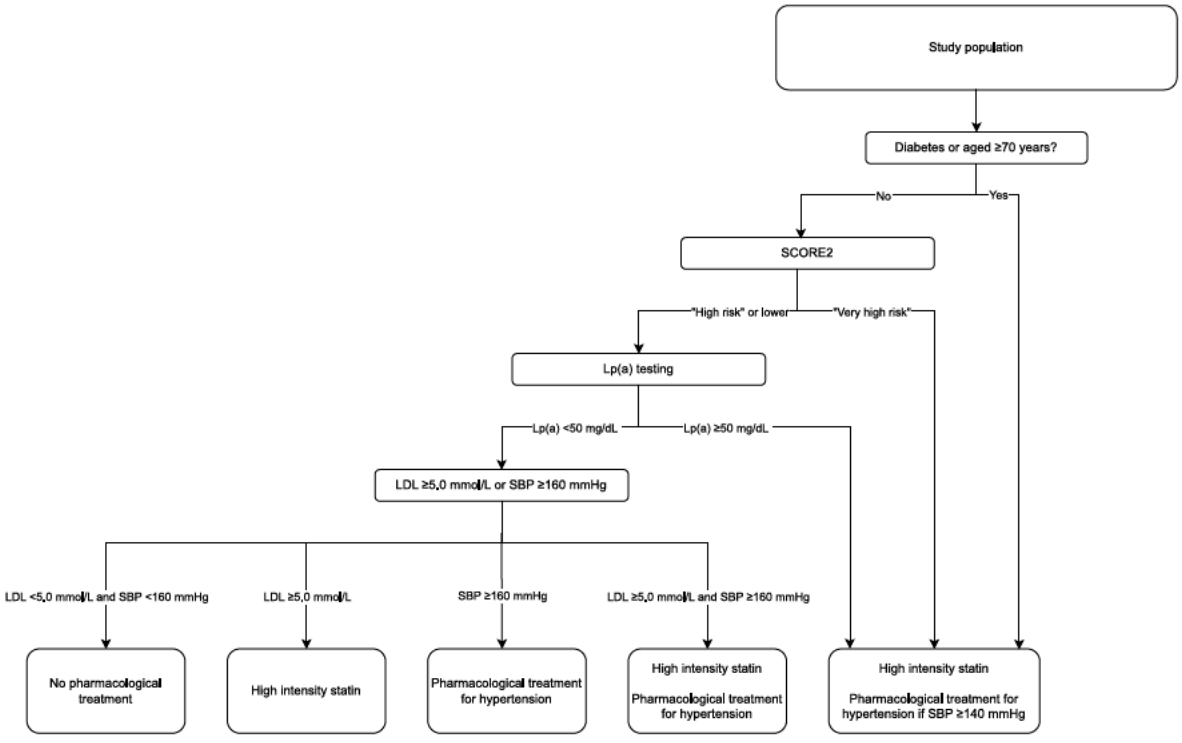


Fig. 2. Schematic of the intervention scenario.

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

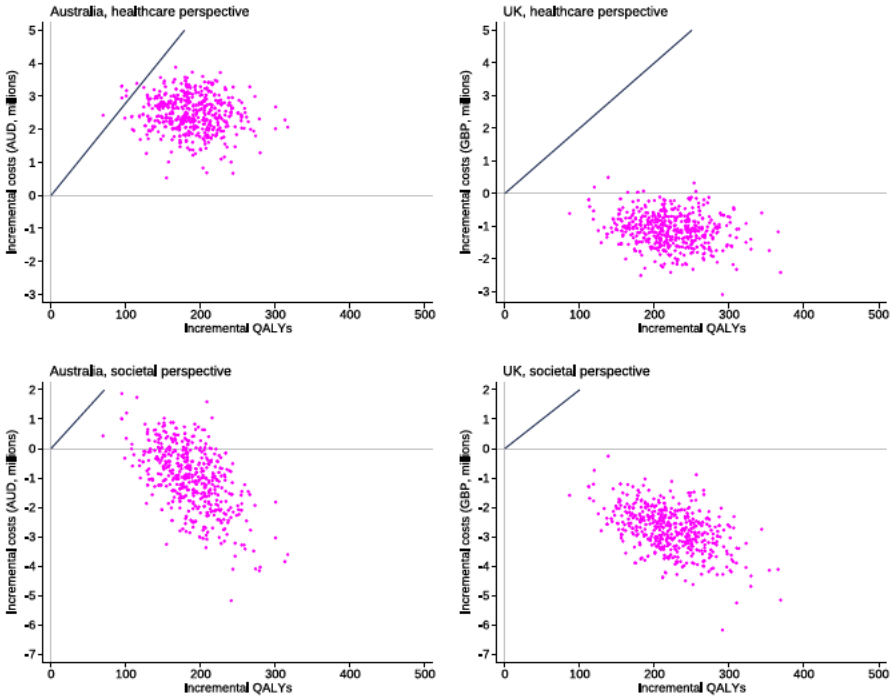


Fig. 3. Results of the probabilistic sensitivity analysis for Lp(a) testing (intervention) compared to standard of care (control) in a common cost-effectiveness plane for each country. The cost-effectiveness plane shows incremental quality adjusted life years (QALYs) for the intervention compared to 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/

References

[1] Kronenberg Florian, Mora Samia, Stroes Erik SG, Ference Brian A, Arsenault Benoit J, Berglund Lars, Dweck Marc R, Koschinsky Marlys, Lambert Gilles, Mach Francois, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022;43(39):3925–46.

[2] Børge G Nordestgaard, Langsted Anne. Lipoprotein (a) and cardiovascular disease. Lancet 2024;404(10459):1255–64.

[3] Boerwinkle Eric, Leffert Carla C, Lin Jingping, Lackner Carolin, Chiesa Giulia, Hobbs Helen H, et al. Apolipoprotein (a) gene accounts for greater than 90% of the variation in plasma lipoprotein (a) concentrations. J Clin Investig 1992;90(1):52–60.

[4] Coassin Stefan, Kronenberg Florian. Lipoprotein (a) beyond the kringle IV repeat poly- morphism: the complexity of genetic variation in the LPA gene. Atherosclerosis 2022;349:17–35.

[5] **The European Society of Cardiology. European commission announces EU Cardiovascular health plan. Available at:** https://www.escardio.org/The-ESC/Press-Office/Press-releases/eu-health-ministers-adopt-landmark-council-conclusions-on-cardiovascular-health. **[Accessed 28 February 2025].**

[6] Visseren Frank LJ, Mach François, Smulders Yvo M, Carballo David, Koskinas Konstantinos C, Bäck Maria, Benetos Athanase, Biffi Alessandro, Boavida Jose-Manuel, Capo- danno Davide, et al. ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the european society of cardiology and 12 medical societies with the special contribution of the european association of preventive cardiology (EAPC). Eur Heart J 2021;42(34):3227–337. 2021.

[7] Roth Gregory A, Mensah George A, Johnson Catherine O, Addolorato Giovanni, Am- mirati Enrico, Baddour Larry M, Barengo Nöel C, Beaton Andrea Z, Benjamin Emelia J, Benziger Catherine P, et al. Global burden of cardiovascular