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Title: Long-term cardiovascular risks and statin treatment impact on socioeconomic inequalities: microsimulation model

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Abstract (249 words)

Background

UK cardiovascular disease (CVD) incidence and mortality have declined in recent decades but socioeconomic inequalities persist.

Aims

We present a new CVD model and project health outcomes and impact of guideline-recommended statin treatment across quintiles of socioeconomic deprivation in UK.

Design and Setting

Lifetime microsimulation model developed using 117,896 participants in 16 statin trials and 501,854 UK Biobank (UKB) participants and quality of life data from national health surveys.

Method

We developed a CVD microsimulation model using risk equations for myocardial infarction, stroke, coronary revascularisation, cancer, vascular and nonvascular death, estimated using trial data. We calibrated and further developed this model in the UKB cohort, including further characteristics and a diabetes risk equation, and validated the model in UKB and Whitehall II cohorts. We used the model to predict CVD incidence, life expectancy, quality-adjusted life years (QALYs) and impact of UK guideline-recommended statin treatment across quintiles of socioeconomic deprivation.

Results

Age, sex, socioeconomic deprivation, smoking, hypertension, diabetes and cardiovascular events were key CVD risk determinants. Model-predicted event rates corresponded well to observed rates across participant categories. The model projected strong gradients in remaining life expectancy, with 4-to-5 years (5-to-8 QALYs) gaps between the least and most socioeconomically deprived quintiles. Guideline-recommended statin treatment was projected to increase QALYs with larger gains in quintiles of higher deprivation.

Conclusions

The study demonstrated the potential of guideline-recommended statin treatment to reduce socioeconomic inequalities. This CVD model is a novel resource for individualised long-term projections of health outcomes and effects of CVD treatments.

Keywords: Cardiovascular disease; Markov microsimulation model; Individual patient characteristics; socioeconomic status; inequality.

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How this fits in

This study presents a new CVD microsimulation policy model that enables individualised lifetime predictions of disease risks, survival, and quality of life (available at https://livedataoxford.shinyapps.io/shiny_ctt_ukb_model/).

The model quantified gaps at middle age of 4-to-5 years in life expectancy (5-to-8 quality of life-adjusted life years) across quintiles of socioeconomic deprivation in UK. We report that guideline-recommended statin treatment has a good potential to reduce health inequalities. Strengthening statin use would lead to larger benefits and larger reductions in health inequalities.

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Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally.(1) In the UK, despite declines in age-standardised CVD mortality and morbidity over the last decades, CVD remains a significant burden for the health system.(2) Regional and socioeconomic inequalities persist, with slower improvements in the most deprived areas(3, 4) and increasing gaps in life expectancy at birth between the least and the most deprived quintiles from 5-7 to 6-8 years from 2001 to 2017.(3)

Disease policy models use epidemiological evidence to model key disease stages and relationships and project the health status of individuals and populations.(5) Unlike CVD risk equations, such as QRISK(6) or SCORE(7), which estimate risk of a particular CVD outcome over a fixed period (typically 5 or 10 years), policy models can project long-term risks, accounting for competing risks and enable estimation of long-term quality-of-life-adjusted survival and costs, providing useful predictions for clinical and policy decision making. Policy models are often developed using summary data,(8, 9) which do not allow reliable assessment of outcomes in distinct patients. In recent years, however, an increasing number of CVD policy models, developed using individual participant data (IPD), have emerged.(10-15) These models, however, often used older data,(13-15) limiting their usefulness for contemporary policy analysis. While the use of newer data to recalibrate CVD risk equations has been shown to improve their performance in contemporary populations,(16, 17) we are not aware of efforts to update policy models, which are structurally more complex, using newer data.

We present a new individual-based CVD microsimulation policy model, developed using IPD from trials and a large contemporary UK population cohort. We employ the model to assess health outcomes across UK quintiles of socioeconomic deprivation and the impact of guideline-recommended statin therapy to reduce CVD risk on socioeconomic inequalities.

Method

The CVD microsimulation policy model structure

This CVD policy model is a microsimulation model of the progression of CVD and key competing events. The model (see schematic in **Supplementary Figure 1**) includes seven events, namely first occurrences of myocardial infarction (MI), stroke, coronary revascularisation (including percutaneous coronary intervention and coronary artery bypass grafting), incident cancer, incident diabetes, vascular death and nonvascular death. Parametric proportional hazards risk equations inform the risk of these events. The model inputs are individuals' characteristics of age, sex, ethnicity, body mass index (BMI), smoking status, blood pressure, lipids, haemoglobin A1C (HbA1c) and creatinine levels, previous CVD history, treated hypertension, diabetes and cancer history, mental illness, physical activity, diet quality and socioeconomic deprivation (based on Townsend Score) (see details in **supplementary Table S1 and supplementary methods 1)**.

The model projects disease events and health-related quality of life (QoL) annually until death or 110 years of age using each individual's characteristics. In each annual cycle, the

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occurrences of events are simulated in a random order. Individual's age and history of events are updated annually and inform the subsequent events' risks in a time-dependent manner.

Estimation and calibration of model risk equations

The risk equations underlying the CVD policy model were developed using Cholesterol Treatment Trialists' (CTT) Collaboration and the UK Biobank (UKB) IPD. First, Cox proportional hazards risk equations were estimated for model endpoints except incident diabetes (unavailable in CTT data provided for this study) using 117,896 individuals from 16 randomised statin trials in CTT.(18) Second, data from the 501,854 participants aged 40 to 70 years, recruited in the UKB between 2006 and 2010 throughout the UK and their follow-up information until 31st March 2017(19) was used to calibrate the risk equations and develop a de novo incident diabetes risk equation. Separate parametric risk equations were fitted for individuals without and with CVD history, with the exception of the incident diabetes and incident cancer equations that were fitted across all participants. Parameter uncertainty was assessed using bootstrapping.(20) See **Supplementary methods 2** for further details.

Model validation

The model was validated by comparing the model-simulated cumulative incidences of each endpoint with the observed cumulative incidences, overall, and in participant categories. This included validating the UKB-calibrated model in the UKB cohort and among Whitehall II participants (N = 6761; 10 years follow-up; external validation) (see **Supplementary methods 2 and 3**).

Health-related quality of life

Health-related QoL associated with participant characteristics and disease histories was estimated using a linear regression model of EuroQoL-5 Dimension (EQ-5D) utility using pooled 2006, 2011 and 2017 Health Survey for England (HSE) participant data. QoL utility ranges from −0.594 for the worst health state to 1 for full health where 0 is equivalent to death in the EQ-5D-3L used in 2006 and 2011.(21) The EQ-5D-5L, used in HSE 2017 was mapped into EQ-5D-3L(22) prior to pooling. The QoL model was integrated into the CVD model to annually predict individuals' QoL.

Model applications

We used the CVD microsimulation model to perform lifelong projections for all UKB participants using their baseline characteristics. We executed 500 microsimulations for each individual to minimise the Monte Carlo uncertainty, and probabilistic sensitivity analyses using 500 and 1000 bootstrap coefficient sets for individuals without and with CVD history at entry, respectively. We summarised the results in categories of UKB participants by CVD history, age, sex and estimated 10-year CVD risk (QRISK 3 score(6)).

We used this model to assess the remaining life years and QALYs and the effects of statin treatment as recommended by the UK National Institute for Health and Care Excellence (NICE) guidance(8) across quintiles of socioeconomic deprivation under the scenarios of full statin coverage and real-world use of statin treatment as observed in UKB in 2015-2016 (see **Supplementary methods 2** and **Supplementary methods 4**). 10-year, 20-year and lifetime projections of life years and QALYs for UKB participants were standardised to mid-2020 UK

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population distribution by sex, age and socioeconomic quintile (based on the Index of Multiple Deprivation) (for details see **Supplementary methods 2**).

Software and computing

All analyses were performed using R 4.2.1. The model simulation utilised Queen Mary University of London's Apocrita High Performance Computing (HPC) facility, supported by QMUL Research-IT.(23)

Stakeholder involvement

The project was guided by multidisciplinary project management and steering groups, including primary care and specialist clinicians, lay persons, trialists, statisticians and health economists. Three lay persons were involved as members of these groups, helping refine methodology and approaches to presenting study findings.

Results

Summary of the CTT and UKB data

In CTT trials, 68,018 participants without and 49,878 with CVD history were followed, over 3.9 and 4.6 years on average, respectively. In UKB, 444,576 participants without and 57,278 with CVD history were followed for 8.1 and 7.9 years on average, respectively. Their characteristics are summarised in **Table 1**. The details of contributing trials and the numbers of events during follow-up are summarised in **supplementary Tables S2** and **S3**.

Risk equations

MI was strongly associated with an increased risk of stroke, and MI and stroke were associated with an increased risk of vascular death, with increases greatest in the years of these events. Coronary revascularisation was associated with a reduced risk of vascular death. Duration since diabetes diagnosis was associated with increased risks of all cardiovascular events and, in those without diagnosed diabetes, higher HbA1c levels were associated with increased risks of all cardiovascular events. These patterns were similar between people without and with CVD history though magnitudes differed (**Figure 1 and supplementary Tables S4-6**).

Age, male sex, smoking, treated hypertension, unhealthy diet and lower physical activity were strongly associated with an increased risk of cardiovascular events. Greater socioeconomic deprivation was associated with a higher risk of stroke, incident diabetes, vascular and nonvascular death (**supplementary Tables S4-6**).

Model validation

In the internal validation of the model based on CTT risk equations, the model-predicted cumulative incidence rates closely matched the observed rates (**supplementary Figure S2**). External validation of the model based on CTT risk equations in the UKB cohort indicated the need for calibration to improve the accuracy of predictions. After calibration, there was good correspondence between cumulative incidence rates predicted by the model and the observed rates in the UKB for all endpoints across follow-up years in categories of

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participants (**Figure 2 & supplementary Figure S3-4**). The UKB-calibrated model demonstrated a good overall performance in the external Whitehall II cohort (**Figure 2**).

Effects of CVD events on quality of life

CVD was a key determinant of quality of life. MI was associated with a decrement in EQ-5D utility of 0.10 (95%CI 0.03-0.16) in the year of event and 0.07 (0.04-0.10) in subsequent years. Stroke was associated with a decrement of 0.09 (0.04-0.13) in the year of event and 0.13 (0.11-0.16) in subsequent years. Diabetes was associated with a decrement of 0.04 (0.03-0.06) in the first 10 years from diagnosis and 0.08 (0.06-0.10) in subsequent years. Cancer affecting daily life was associated with a decrement in quality of life of 0.13 (0.11-0.14) (**supplementary Table S7**). For use in the CVD microsimulation model, the cancer-related utility decrement was revised to 0.03 informed from the literature(24-26) to reflect any cancer history.

Long-term projections of survival and QALYs

The differences in CVD risk between individuals of different age, sex and cardiovascular risk were reflected in their model predicted survival and QALYs (**Figure 3)**. For individuals in the same age and sex category, shorter life expectancy and fewer QALYs were predicted for people with CVD history or higher 10-year CVD risk. Men had shorter life expectancy but more QALYs as a proportion of their life expectancy than women. The projected remaining life expectancy (from age at entry) ranged between 19.5 (95%CI 18.7-20.4) and 38.9 (37.3-40.2) years [12.2 (11.7-12.8)-33.0 (31.8-34.0) QALYs] for men, and 25.2 (24.2-25.9) and 42.1 (40.3-43.7) years [14.7 (14.0-15.5)-33.0 (31.8-34.0) QALYs] for women. Being in the highest 10-year CVD risk category (≥20%) or having CVD history was associated with up to 10 years lower life expectancy and 14 less QALYs, compared to those in the same age group with the lowest risk (see summary of parameter uncertainty in **supplementary Tables S8-10** and the events' accumulation in **Figure S5**).

Health outcomes across quintiles of socioeconomic deprivation

There were moderate gradients at 10 years in the predicted years of life and QALYs across the quintiles of socioeconomic deprivation (**Figure 4**). Over a longer duration, the gradients in the predicted survival and QALYs increased. Over a lifetime, individuals in the most socioeconomically deprived quintile had 4 to 5 years shorter life expectancy (5 to 8 less QALYs) than those in the least deprived quintile.

Benefits from statin therapy across quintiles of socioeconomic deprivation

UKB participants in more socioeconomically deprived quintiles were more likely to be at higher CVD risk and, therefore, meet statin treatment criteria, and gained more benefit. For instance, compared to no use of statin therapy, if all people in their 50s recommended statin therapy were initiating and taking it over their lifetime, 703 and 360 life years (399 and 170 QALYs) gained were projected per 1000 men and women, respectively, in the most deprived quintile, compared to 406 and 94 life years (277 and 55 QALYs) gained in the least deprived (**Figure 5**). In scenario analysis, the real-world use of statin treatment among eligible participants ranged from about 40% in the least to 45% in the most deprived quintile and, while treatment benefits were proportionately reduced, larger benefits were projected in quintiles with higher socioeconomic deprivation (**Figure S6**).

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Model web interface and prediction for a typical individual

The CVD microsimulation model interface and user guide are available at https://livedataoxford.shinyapps.io/shiny_ctt_ukb_model/. The model interface enables users to project outcome for one or a group of patients. To illustrate its use, the model predicted 5.2% 10-year and 40% lifetime cumulative incidence of major vascular event (MI, stroke, coronary revascularisation or vascular death), 28 years further lifespan, and 23 QALYs over the lifetime for a 60-year old white man, non-smoker, overweight (BMI level 25-30 kg/m^2), in quintile 3 of socioeconomic deprivation, with moderate physical activities, a healthy diet, an LDL cholesterol of 3.6 mmol/L, an HDL cholesterol of 1 mmol/L, creatinine of 82 umol/L, blood pressure of 140/80 mmHg, HbA1c of 40 mmol/mol, not on antihypertensive or statin treatment, without histories of CVD, severe mental illness, cancer or diabetes and with 12.6% estimated 10-year CVD risk (QRISK3). For UKB participants without CVD at entry, **Figure S7** presents model-predicted 10-year risks of major vascular event against QRISK3 10-year CVD risks.

Discussion

Summary

This study presents a new CVD microsimulation policy model that enables individualised lifetime predictions of disease risks, survival, and quality of life. The model demonstrated good predictive accuracy across diverse patient categories of the UK population. The model quantified gaps at middle age of 4-to-5 years in life expectancy (corresponding to 5-to-8 QALYs) across quintiles of socioeconomic deprivation in UK and demonstrated good potential of guideline-recommended statin treatment to reduce these gaps.

Strengths and limitations

The main strengths of this CVD model are in its use of rich contemporary individual participant data including a larger set of characteristics and disease endpoints than other previous studies. First, the model has the advantage of reflecting contemporary CVD trends in the UK, being derived from a large current UK population cohort. Second, it includes a rich set of individual characteristics of high policy interest, including socioeconomic deprivation, physical activity and diet quality. Third, the microsimulation framework can track individuals' history and multiple interacting comorbidities.(27) Fourth, the model includes incident diabetes and cancer as key competing disease risks to better reflect overall health and enable inclusion of a broader range of effects. Finally, the model can inform assessments of the net effects and cost-effectiveness of therapies.

The CVD model has some limitations. The UK Biobank is a cohort of people healthier than the general UK population, with underrepresentation of more socioeconomically deprived categories.(28) Notwithstanding this, the model projections for different individuals using their characteristics are likely generalisable to similar individuals in the general population. To enhance generalisability of our findings, we standardised our results to the 2020 UK population by age, sex and socioeconomic deprivation. Moreover, the oldest individuals during UKB follow-up were in their 80s and further research is needed to assess the model performance among the elderly.

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Comparison with existing literature

The inequalities in health outcomes associated with socioeconomic deprivation at age 40-70 years reported in the present study are expectedly smaller than the previous estimates of 6-8 years estimated at birth(3) but echo studies suggesting that socioeconomic deprivation remains an important health determinant.(29-31) We also quantify and report larger gradient in inequalities when quality of life is considered in addition to individuals' survival. Similar to recent studies(32-35), we note that the use of statin treatment was not worse among the more socioeconomically disadvantaged categories.

Implications for practice

The CVD microsimulation model could help inform strategies for CVD management including assessments of their cost-effectiveness across UK population categories and impact on health inequalities.

We report that guideline-recommended statin treatment has a good potential to reduce inequalities in health across socioeconomic status though the reductions are larger for differences in life expectancy than for QALYs, underlining the need for multifaceted action to tackle health disparities. Strengthening statin use would lead to larger benefits and larger reductions in health inequalities.

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Conflict of interest: AK reports receiving grants for his institution from Abbott, Amgen, and Mylan; consulting fees from AstraZeneca; honoraria from Sanofi and Pfizer; and is a Data Safety Monitoring Board member of the Kowa PROMINENT trial. JA reports receiving a grant to their research institution from Novartis for the ORION 4 trial of inclisiran. JS reports receiving grants for his institution from Abbvie, Astra Zeneca, Bayer, Bristol Myers Squibb, Pfizer, and Roche. All other authors declare no competing interests.

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Data Availability Statement: Requests for individual patient data from trials contributing into the Cholesterol Treatment Trialists' Collaboration should be made directly to the data custodians of each trial (see Cholesterol Treatment Trialists' data policy on https://www.cttcollaboration.org/. Other data underlining this work may be obtained from third parties (UK Biobank https://www.ukbiobank.ac.uk/; Whitehall II study www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii) and are not publicly available. Researchers can apply to use the UK Biobank resource and Whitehall II study data. The R code of the CVD microsimulation model (License: MIT License) is available at http://www.herc.ox.ac.uk/downloads/supportingmaterial and from https://github.com/RunguoWu/UK_CVD_model (available on manuscript acceptance).

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References

1. WHO. Cardiovascular diseases (CVDs)2022 03/08/2022. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Bhatnagar P, Wickramasinghe K, Wilkins E, et al. Trends in the epidemiology of cardiovascular disease in the UK. Heart. 2016;102(24):1945-52.
3. Marmot M, Allen J, Boyce T, et al. Health equity in England: the Marmot review 10 years on. Institute of Health Equity; 2020.
4. Asaria P, Fortunato L, Fecht D, et al. Trends and inequalities in cardiovascular disease mortality across 7932 English electoral wards, 1982–2006: Bayesian spatial analysis. Int J Epidemiol. 2012;41(6):1737-49.
5. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
6. 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.
7. SCORE2 working group and 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(25):2439-54.
8. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2014 27/05/2023. Available from: https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-243786637.
9. Constanti M, Floyd CN, Glover M, et al. Cost-effectiveness of initiating pharmacological treatment in stage one hypertension based on 10-year cardiovascular disease risk: a Markov modeling study. Hypertension. 2021;77(2):682-91.
10. Lewsey JD, Lawson KD, Ford I, et al. A cardiovascular disease policy model that predicts life expectancy taking into account socioeconomic deprivation. Heart. 2015;101(3):201-8.
11. Asaria M, Walker S, Palmer S, et al. Using electronic health records to predict costs and outcomes in stable coronary artery disease. Heart. 2016;102(10):755-62.
12. Kypridemos C, Guzman-Castillo M, Hyseni L, et al. Estimated reductions in cardiovascular and gastric cancer disease burden through salt policies in England: an IMPACTNCD microsimulation study. BMJ Open. 2017;7(1):e013791.
13. Pandya A, Sy S, Cho S, et al. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. JAMA. 2015;314(2):142-50.
14. Heart Protection Study Collaborative Group. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20 536 people. BMJ. 2006;333(7579):1145.
15. Nijhuis RL, Stijnen T, Peeters A, et al. Apparent and Internal validity of a Monte Carlo–Markov model for cardiovascular disease in a cohort follow-up study. Med Decis Making. 2006;26(2):134-44.
16. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J. 2019;40(7):621-31.
17. Wallisch C, Heinze G, Rinner C, et al. Re-estimation improved the performance of two Framingham cardiovascular risk equations and the Pooled Cohort equations: a nationwide registry analysis. Sci Rep. 2020;10(1):1-11.
18. Downs J, Gotto A, Clearfield M, et al. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. Am J Cardiol. 1995;75(16).
19. 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.

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20. Gray AM, Clarke PM, Wolstenholme JL, et al. Applied methods of cost-effectiveness analysis in healthcare: OUP Oxford; 2010.
21. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.
22. Hernandez Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. Pharmacoeconomics. 2023;41(2):199-207.
23. King T, Butcher S, Zalewski L. Apocrita - High Performance Computing Cluster for Queen Mary University of London. 2017.
24. Wu M, Brazier JE, Kearns B, et al. Examining the impact of 11 long-standing health conditions on health-related quality of life using the EQ-5D in a general population sample. Eur J Health Econ. 2015;16(2):141-51.
25. Tsiplova K, Pullenayegum E, Cooke T, et al. EQ-5D-derived health utilities and minimally important differences for chronic health conditions: 2011 Commonwealth Fund Survey of Sicker Adults in Canada. Qual Life Res. 2016;25(12):3009-16.
26. Keng MJ, Leal J, Bowman L, et al. Decrements in health-related quality of life associated with adverse events in people with diabetes. Diabetes Obes Metab. 2021.
27. Kuntz K, Sainfort F, Butler M, et al. Decision and simulation modeling in systematic reviews [Internet]. 2013 11/08/2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK127482/.
28. 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):1026-34.
29. Singh GK. Area deprivation and widening inequalities in US mortality, 1969-1998. Am J Public Health. 2003;93(7):1137-43.
30. Woods LM, Rachet B, Riga M, et al. Geographical variation in life expectancy at birth in England and Wales is largely explained by deprivation. J Epidemiol Community Health. 2005;59(2):115-20.
31. Seaman R, Riffe T, Leyland AH, et al. The increasing lifespan variation gradient by area-level deprivation: A decomposition analysis of Scotland 1981-2011. Soc Sci Med. 2019;230:147-57.
32. Thalmann I, Preiss D, Schlackow I, et al. Population-wide cohort study of statin use for the secondary cardiovascular disease prevention in Scotland in 2009–2017. Heart. 2023;109(5):388-95.
33. Wu R, Rison SCG, Raisi-Estabragh Z, et al. Gaps in antihypertensive and statin treatments and benefits of optimisation: a modelling study in a 1 million ethnically diverse urban population in UK. BMJ Open. 2021;11(12):e052884.
34. Jones N, Fischbacher C, Guthrie B, et al. Factors associated with statin treatment for the primary prevention of cardiovascular disease in people within 2 years following diagnosis of diabetes in Scotland, 2006–2008. Diabet Med. 2014;31(6):640-6.
35. Boruzs K, Juhász A, Nagy C, et al. Relationship between statin utilization and socioeconomic deprivation in Hungary. Front Pharmacol. 2016;7:66.

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Figures and tables

Table 1: Baseline characteristics of study participants

	CTT Collaboration		UK Biobank	
	Without CVD history	**With CVD history**	**Without CVD history**	**With CVD history**
N	68,018	49,878	444,576	57,278
Age, years	62.3 (9.2)	62.7 (9.1)	56 (8.1)	60.4 (7.0)
Sex, male (%)	43,972 (65%)	39,085 (78%)	194,996 (44%)	33,734 (59%)
Ethnicity				
White	49,170 (72%)	38,901 (78%)	420,409 (95%)	54,488 (95%)
Black	6,110 (9.0%)	1,226 (2.5%)	7,268 (1.6%)	770 (1.3%)
South Asian	NA	NA	6,946 (1.6%)	1,053 (1.8%)
Other*	12,738 (19%)	9,751 (20%)	9,953 (2.2%)	967 (1.7%)
Smoking status				
Non-smoker	54,145 (80%)§	40,324 (81%)§	250,261 (56%)	25,137 (44%)
Ex-smoker	NA	NA	148,312 (33%)	25,211 (44%)
Current smoker	13,873 (20%)	9,554 (19%)	46,003 (10%)	6,930 (12%)
BMI (kg/m^2)				
<18.5	670 (0.99%)	251 (0.50%)	2,370 (0.53%)	256 (0.45%)
18.5-25	19,963 (29%)	15,023 (30%)	149,300 (34%)	13,415 (23%)
25-30	28,598 (42%)	23,711 (48%)	189,650 (43%)	24,241 (42%)
30-35	13,532 (20%)	8,487 (17%)	74,714 (17%)	13,222 (23%)
35-40	3,708 (5.5%)	1,806 (3.6%)	20,662 (4.6%)	4,328 (7.6%)
40+	1,547 (2.3%)	600 (1.2%)	7,880 (1.8%)	1,816 (3.2%)
LDL cholesterol (mmol/L)	3.5 (0.89)	3.8 (0.85)	3.6 (0.82)	3.1 (0.87)
HDL cholesterol (mmol/L)	1.3 (0.38)	1.1 (0.31)	1.5 (0.37)	1.3 (0.36)
HbA1c (mmol/mol)	NA	NA	35.8 (6.2)	38.6 (8.7)
Creatinine (umol/L)	91 (24)	98 (23)	71 (15)	77 (19)
Systolic Blood Pressure (mmHg)	142 (20)	139 (22)	138 (19)	139 (19)
Diastolic Blood Pressure (mmHg)	83 (11)	81 (11)	82 (10)	81 (10)
On hypertension treatment	35,478 (52%)	25,472 (51%)	71,930 (16%)	26,184 (46%)
Prior diabetes (any)	15,131 (22%)	7,949 (16%)	21,567 (4.9%)	8,171 (14%)
Prior Type 1 diabetes	NA	NA	2,741 (0.62%)	1,479 (2.6%)

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Prior cancer	32 (0.05%)	25 (0.05%)	32,713 (7.4%)	5,861 (10%)
Prior CVD				
MI only		24,866 (50%)		2,071 (3.6%)
Peripheral arterial disease only		3,186 (6.4%)		6,806 (12%)
Stroke only		3,875 (7.8%)		5,137 (9.0%)
Other coronary heart disease only†		9,631 (19%)		28,973 (51%)
Two or more		8,320 (17%)		14,291 (25%)
Townsend deprivation score¶				
Quintile 1 (least deprived)	NA	NA	166,141 (37%)	18,960 (33%)
Quintile 2	NA	NA	89,397 (20%)	10,957 (19%)
Quintile 3	NA	NA	72,626 (16%)	9,034 (16%)
Quintile 4	NA	NA	64,448 (14%)	9,178 (16%)
Quintile 5	NA	NA	51,964 (12%)	9,149 (16%)
Physical activity				
High level	NA	NA	145,206 (33%)	16,780 (29%)
Moderate level	NA	NA	146,156 (33%)	17,679 (31%)
Low level	NA	NA	65,932 (15%)	10,105 (18%)
Missing	NA	NA	87,282 (20%)	12,714 (22%)
History of severe mental illness	NA	NA	36,087 (8%)	6,324 (11%)
Unhealthy diet (incl. uncertain)	NA	NA	158,569 (36%)	21,705 (38%)

Mean (SD) or count (%). BMI, body mass index; CVD, cardiovascular disease; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, hemoglobin A1C; MI, myocardial infarction; NA, not available.

*Other ethnicity includes Chinese, Mixed, White and Black Caribbean, White and Black African, White and Asian, Any other mixed background and other ethnic group.

§Include ex-smokers.

†Other coronary heart disease includes acute rheumatic fever, chronic rheumatic heart diseases, hypertensive heart disease, angina pectoris, other acute ischaemic heart disease, chronic ischaemic heart disease, pulmonary heart disease and other form of heart disease.

¶Townsend score used to categorise UK Biobank participants into quintiles of socioeconomic deprivation using national cut-off values.

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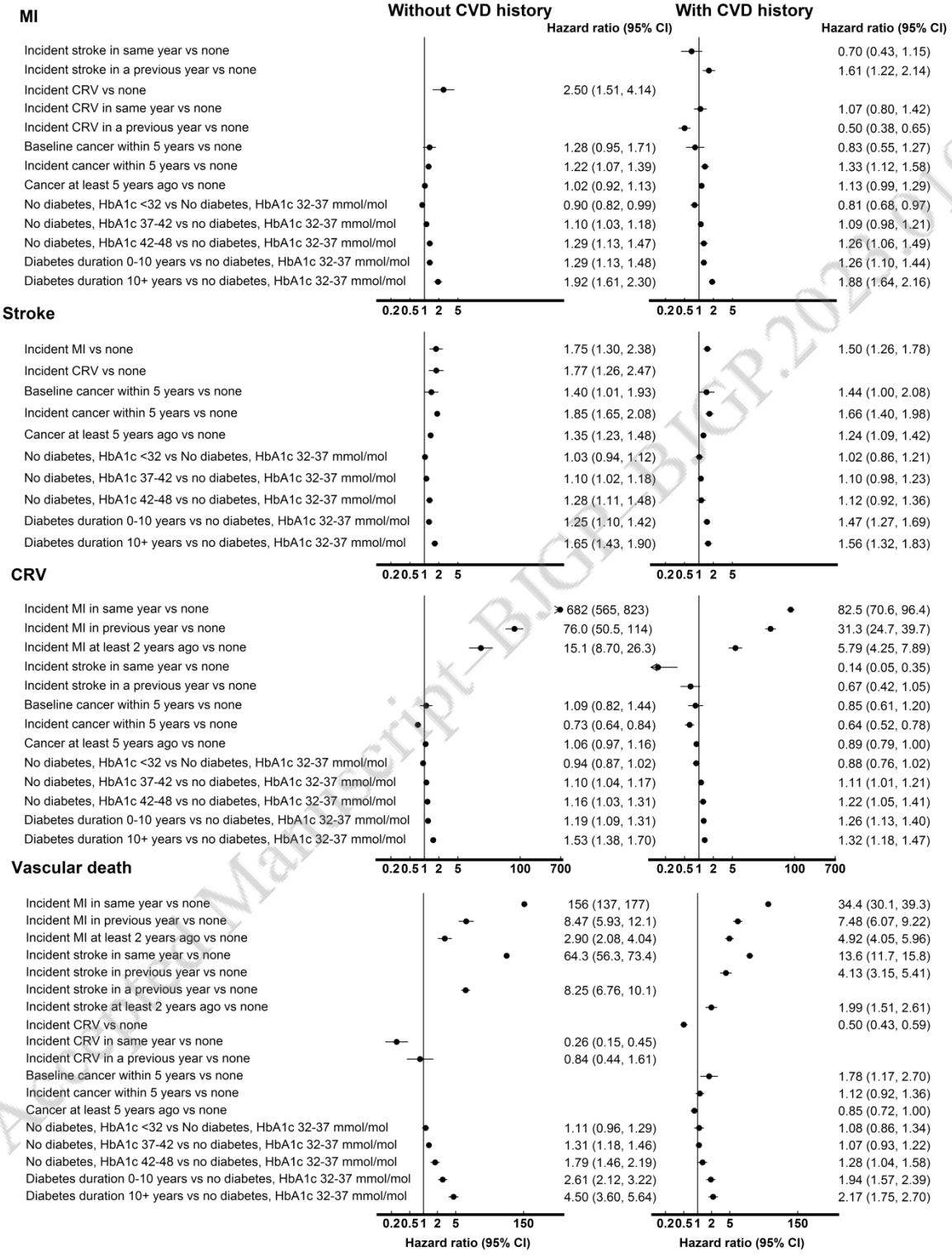
Figure 1: Risk of vascular endpoints associated with disease event histories



Adjusted for other individual characteristics at entry and current age. See **supplementary Tables S4, S5 and S6** for full details of the risk equations. CVD, cardiovascular disease; MI,

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myocardial infarction; CRV, coronary revascularisation; HR, hazard ratio; CI, confidence interval; HbA1c, haemoglobin A1C.

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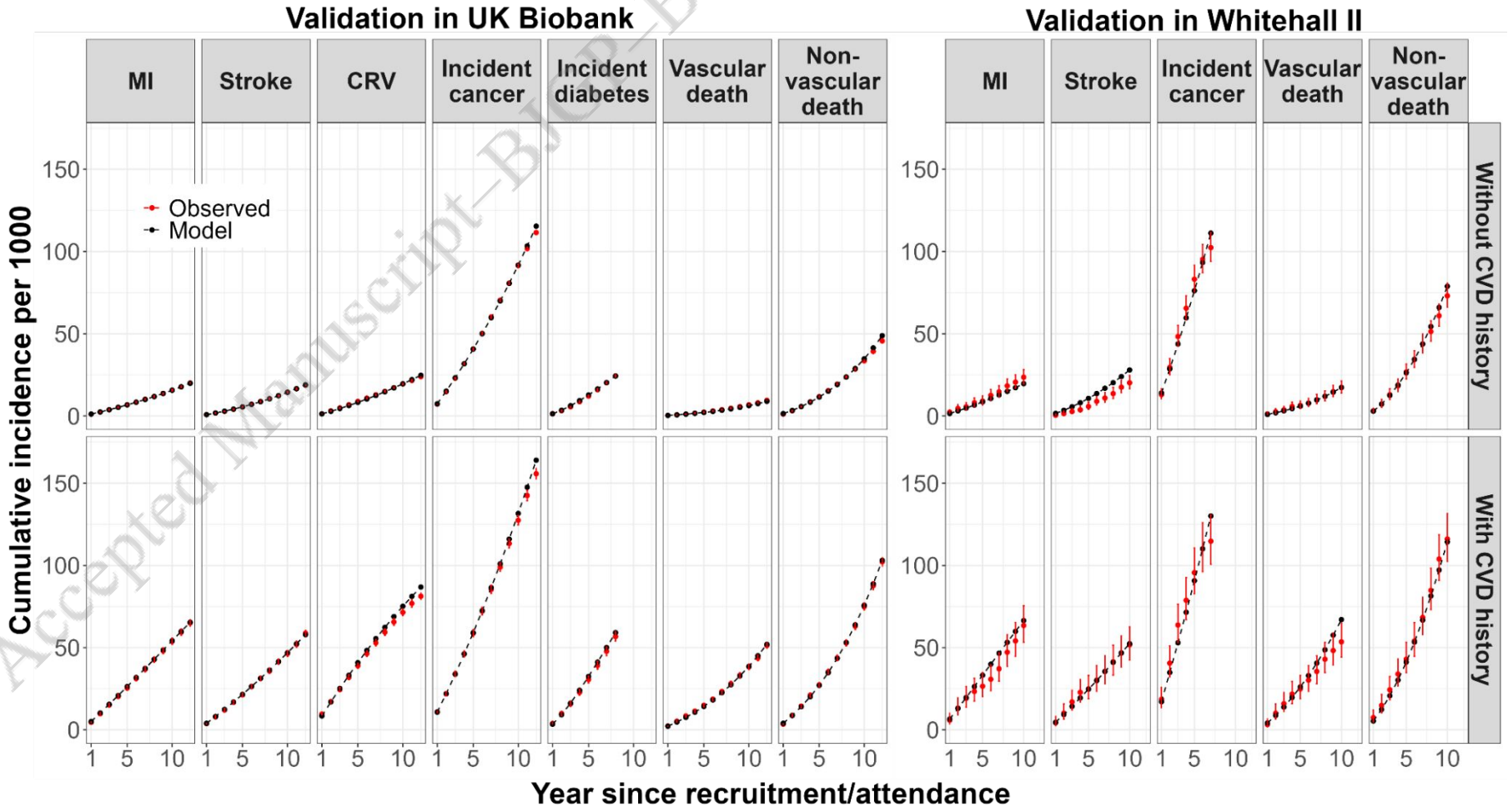
Figure 2: Validation of the CVD model in UK Biobank and Whitehall II Phase 9 participants



Validation covers 12 years in UK Biobank (8 years for incidence diabetes due to stopping follow-up earlier) and 10 years in Whitehall II Phase 9 data (7 years for incidence cancer due to stopping follow-up earlier). MI, myocardial infarction; CRV, coronary revascularisation.

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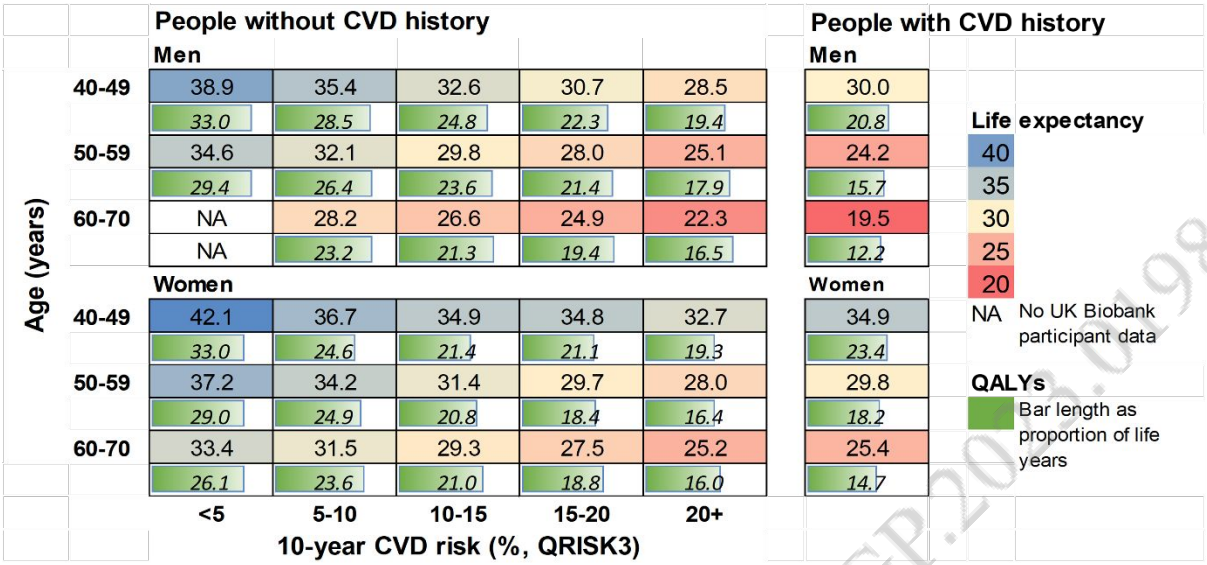
Figure 3: Predicted remaining life expectancy (years) and QALYs for UK Biobank participants



Predicted outcomes presented by CVD history, sex, age and, for people without CVD history, by 10-year CVD risk (QRISK3). CVD, cardiovascular disease; QALY, quality-adjusted life year.

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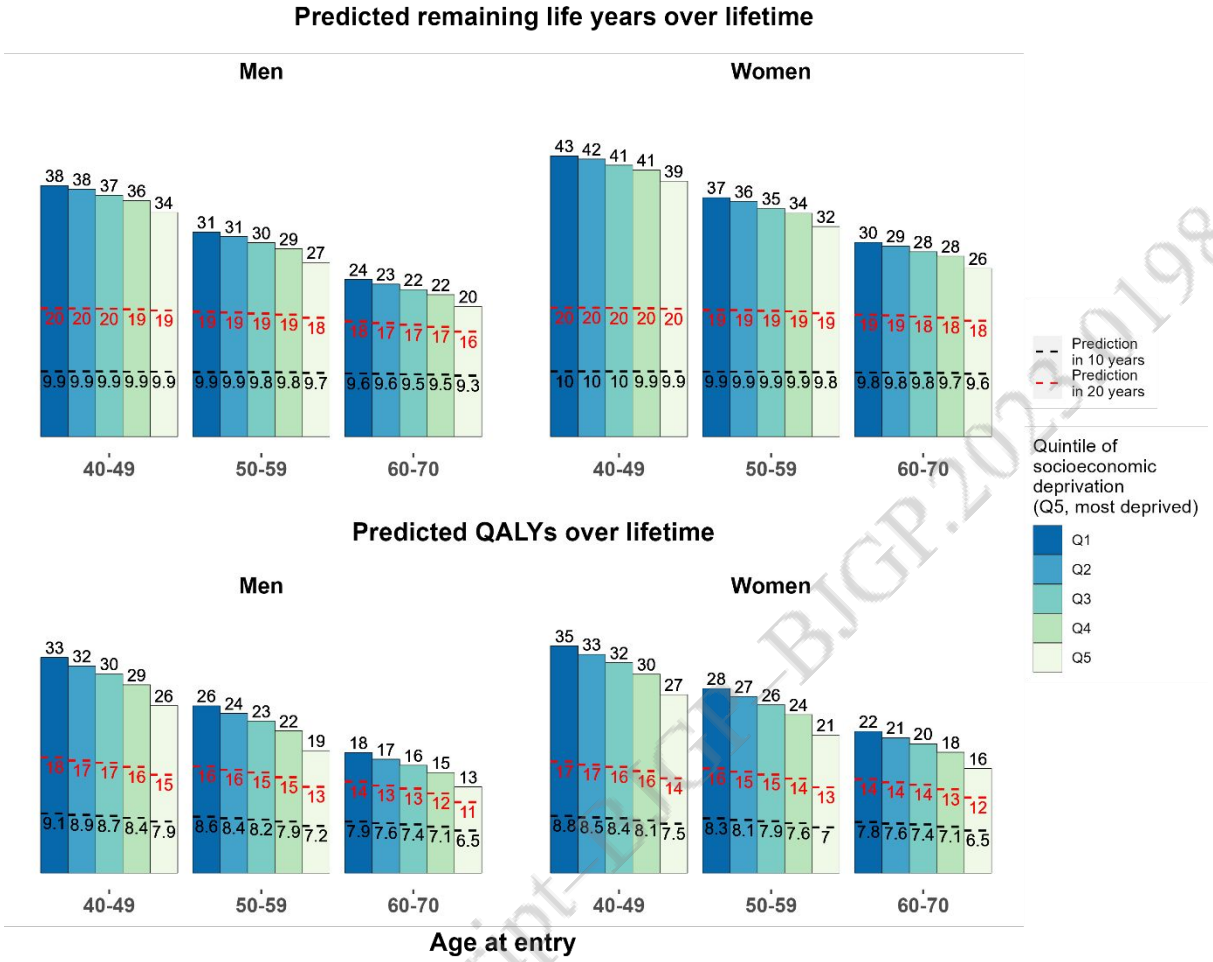
Figure 4: Predicted life years and QALYs in 10 years, 20 years and over lifetime, by sex, age and quintile of socioeconomic deprivation in UK



Predicted remaining life years and QALYs by age, sex, and socioeconomic deprivation quintiles (using Townsend score) at entry into UK Biobank were standardised to mid-2020 UK population distribution by age, sex and quintile of socioeconomic deprivation (using Index of Multiple Deprivation quintiles). The bars represent remaining life years or QALYs over lifetime and the areas under the black dotted lines and red dotted lines represent QALYs in 10 years and QALYs in 20 years, respectively. QALY, quality-adjusted life year.

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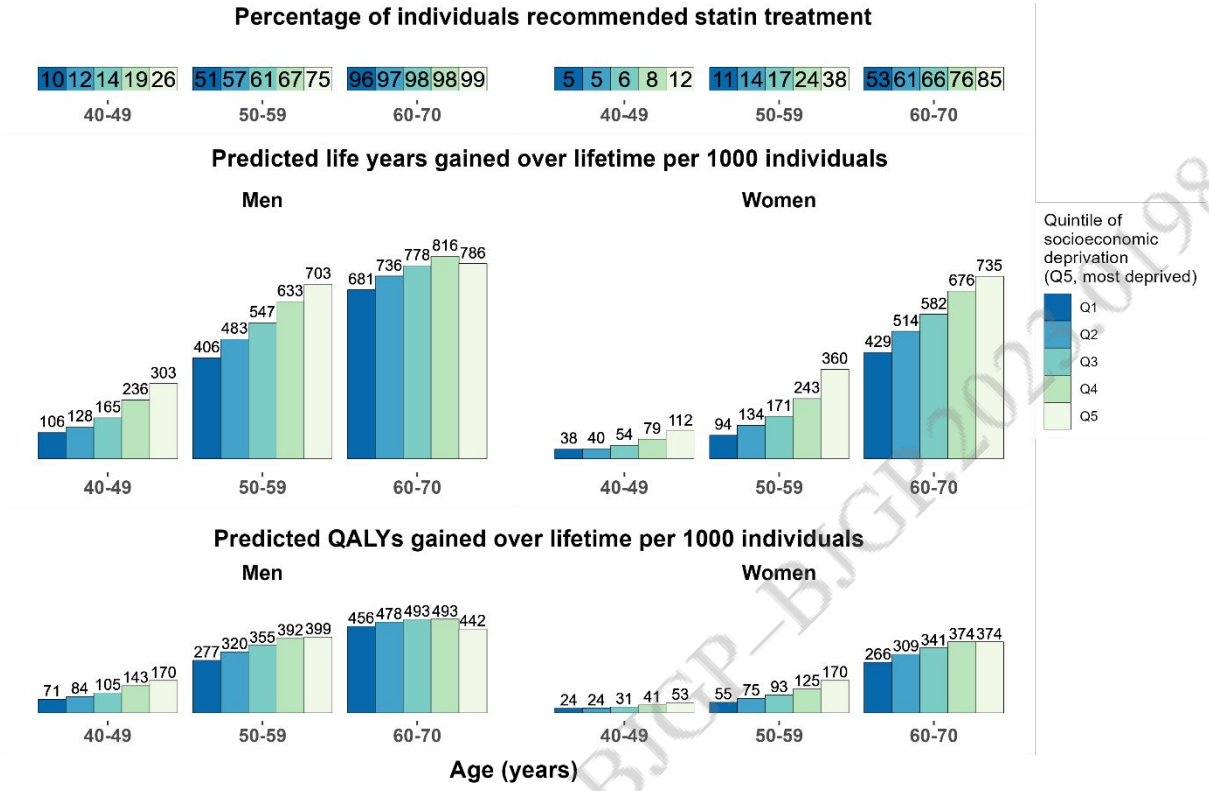
Figure 5: Predicted lifetime benefit from UK guideline-recommended statin therapy, by sex, age and quintile of socioeconomic deprivation in UK



Predicted life years and QALYs gained with full implementation of UK National Institute for Health and Care (NICE) guideline-recommended statin therapy at entry into UK Biobank were standardised to mid-2020 UK population distribution by age, sex and quintile of socioeconomic deprivation (using Index of Multiple Deprivation quintiles). Atorvastatin 20mg/day was used for individuals without CVD history but with a 10-year CVD risk≥10%, and/or type 1 diabetes, an estimated glomerular filtration rate (eGFR)<60mL/min/1.73^2, or albuminuria, and atorvastatin 80mg/day for individuals with CVD history (20mg to those with eGFR<60mL/min/1.73^2). The percentages of individuals meeting the criteria for statin treatment in categories of UK Biobank participants are reported at the top. The bars represent predicted life years and QALYs gained per 1000 individuals, assuming the percentage of individuals recommended statin therapy in UK population categories is the same as in the corresponding categories in UK Biobank. QALY, quality-adjusted life year.

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