Lifetime effects and cost-effectiveness of statin therapy for older people in the United Kingdom: a modelling study

SUPPLEMENTAL MATERIAL

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Supplemental Table 1: Proportional reductions in LDL cholesterol with statin regimens

	% reduction in LDL cholesterol[1]				
Dose (mg/day)	**5mg**	**10mg**	**20mg**	**40mg**	**80mg**
Fluvastatin	10%	15%	21%	27%	33%
Pravastatin	15%	20%	24%	29%	33%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

[1]Based on Law et al. (1)

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Supplemental Table 2: Baseline characteristics of UK Biobank and Whitehall II participants 70 years and older

	UK Biobank		Whitehall II	
	Participants without CVD	**Participants with prior CVD**	**Participants without CVD**	**Participants with prior CVD**
Number of participants	**13,772**	**4,349**	**1,247**	**754**
Age, years	72.4 (2.6)	72.7 (2.7)	73.6 (2.2)	73.8 (2.2)
Male sex	7009 (51%)	2874 (66%)	829 (66%)	515 (68%)
Ethnicity				
White	13532 (98%)	4259 (98%)	1154 (93%)	657 (87%)
Black	55 (0%)	13 (0%)		
South Asian	73 (1%)	37 (1%)	93 (7%)[2]	97 (13%)[2]
Others[1]	112 (1%)	40 (1%)		
Townsend socioeconomic deprivation				
Quintile 1 (least deprived)	6370 (46%)	1926 (44%)	0	0
Quintile 2	2958 (21%)	959 (22%)	108 (9%)	46 (6%)
Quintile 3	2032 (15%)	612 (14%)	847 (68%)	511 (68%)
Quintile 4	1483 (11%)	497 (11%)	291 (23%)	196 (26%)
Quintile 5	929 (7%)	355 (8%)	1 (0%)	1 (0%)
Smoking status				
Never	7870 (57%)	2112 (49%)	653 (52%)	374 (50%)
Former smoker	5508 (40%)	2110 (49%)	526 (42%)	334 (44%)
Current smoker	394 (3%)	127 (3%)	68 (5%)	46 (6%)
Physical activity				
High	4794 (35%)	1452 (33%)	463 (37%)	242 (32%)
Moderate	4779 (35%)	1501 (35%)	707 (57%)	433 (57%)
Low	1762 (13%)	641 (15%)	44 (4%)	47 (6%)
Missing	2437 (18%)	755 (17%)	33 (3%)	32 (4%)
Unhealthy diet (incl. uncertain)	3566 (26%)	1287 (30%)	797 (64%)	478 (63%)
BMI (kg/m^2)	27 (4)	27 (4.2)	27 (4.3)	28 (4.5)
<18.5	86 (1%)	20 (0%)	13 (1%)	4 (1%)
18.5-25	5187 (38%)	1263 (29%)	455 (36%)	215 (29%)
25-30	6138 (45%)	2054 (47%)	536 (43%)	326 (43%)
30-35	1892 (14%)	785 (18%)	192 (15%)	156 (21%)
35-40	384 (3%)	180 (4%)	38 (3%)	42 (6%)
40+	85 (1%)	47 (1%)	13 (1%)	11 (1%)
LDL-C (mmol/L)	3.7 (0.59)	3.3 (0.65)	3 (0.93)	2.6 (0.9)
HDL-C (mmol/L)	1.7 (0.3)	1.6 (0.3)	1.7 (0.42)	1.6 (0.43)
On statin treatment	3870 (28%)	2498 (57%)	419 (34%)	481 (64%)
Derived pre-treated LDL (mmol/L)[3]	4.2 (0.72)	4.4 (0.9)	3.4 (0.99)	3.7 (1.2)
Creatinine (umol/L)	77 (12)	81 (13)	88 (24)	96 (38)
Systolic BP (mmHg)	147 (18)	145 (18)	129 (16)	128 (17)
Diastolic BP (mmHg)	80 (10)	78 (10)	71 (10)	69 (10)
Treated hypertension	3593 (26%)	2098 (48%)	483 (39%)	533 (71%)
Prior diabetes	939 (7%)	578 (13%)	215 (17%)	204 (27%)

Prior cancer	1877 (14%)	680 (16%)	163 (13%)	94 (12%)
Severe mental illness	1192 (9%)	443 (10%)	14 (1%)	9 (1%)
Prior CVD history				
MI only		69 (2%)		34 (5%)
PAD only		354 (8%)		26 (3%)
Stroke only		315 (7%)		28 (4%)
Other CHD[4] only		2454 (56%)		456 (60%)
Two or more of MI, PAD, other CHD or stroke		1157 (27%)		210 (28%)

Values are mean (SD) or number (%). CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high density lipoprotein; LDL, low density lipoprotein; PAD, peripheral arterial disease; SD, standard deviation.

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

[2]Whitehall II only has two categories of ethnicity, White and non-White. We made the assumption that all non-White were South Asians, the second largest ethnicity group in the UK.

[3]Adjusted for use of statin treatment at baseline by statin type and dose.

[4]Other CHD 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.

Supplemental Table 3: Predicted incremental health outcomes, costs and cost-effectiveness of standard statin treatment compared to no statin, in categories by sex, prior cardiovascular disease and pre-treatment LDL cholesterol level

Sex	Men				Women			
CVD history and LDL-C levels	**Without CVD, LDL-C < 3.4**	**Without CVD, LDL-C 3.4-4.1**	**Without CVD, LDL-C ≥4.1**	**With prior CVD**	**Without CVD, LDL-C < 3.4**	**Without CVD, LDL-C 3.4-4.1**	**Without CVD, LDL-C ≥4.1**	**With prior CVD**
Incremental Life years (95% CI)	0.38 (0.3, 0.46)	0.59 (0.48, 0.71)	1.05 (0.87, 1.22)	0.65 (0.52, 0.81)	0.37 (0.29, 0.46)	0.52 (0.4, 0.64)	0.82 (0.65, 0.97)	0.72 (0.56, 0.9)
Incremental Life years, discounted (95% CI)	0.18 (0.15, 0.22)	0.28 (0.23, 0.33)	0.51 (0.43, 0.59)	0.35 (0.28, 0.43)	0.15 (0.12, 0.19)	0.21 (0.17, 0.26)	0.34 (0.27, 0.41)	0.33 (0.26, 0.41)
Incremental QALYs (95% CI)	0.25 (0.2, 0.31)	0.41 (0.33, 0.49)	0.7 (0.58, 0.82)	0.33 (0.25, 0.42)	0.24 (0.18, 0.29)	0.34 (0.26, 0.42)	0.51 (0.41, 0.61)	0.34 (0.26, 0.44)
Incremental QALYs, discounted (95% CI)	0.12 (0.1, 0.15)	0.2 (0.16, 0.24)	0.35 (0.29, 0.4)	0.18 (0.14, 0.23)	0.1 (0.08, 0.12)	0.14 (0.11, 0.18)	0.22 (0.18, 0.27)	0.16 (0.12, 0.21)
Incremental Hospital cost (95% CI)	280 (91, 466)	371 (99, 636)	885 (458, 1284)	-321 (-787, 187)	123 (-63, 322)	123 (-108, 376)	262 (-76, 600)	-172 (-685, 385)
Incremental Hospital cost, Discounted (95% CI)	-3 (-88, 84)	-37 (-158, 86)	54 (-144, 243)	-583 (-840, -305)	-35 (-111, 52)	-63 (-157, 41)	-79 (-213, 70)	-392 (-639, -122)
Incremental Primary care cost (95% CI)	250 (181, 318)	298 (212, 384)	610 (466, 747)	485 (320, 675)	255 (164, 340)	265 (172, 362)	475 (327, 609)	567 (363, 811)
Incremental Primary care cost, discounted (95% CI)	103 (71, 136)	112 (73, 152)	248 (180, 311)	225 (138, 326)	95 (58, 131)	92 (54, 132)	172 (115, 228)	222 (130, 331)
Statin cost (95% CI)	285 (276, 293)	297 (288, 307)	292 (282, 301)	248 (237, 260)	355 (345, 363)	365 (355, 373)	365 (354, 373)	329 (314, 344)
Statin cost, discounted (95% CI)	199 (195, 203)	205 (201, 210)	203 (199, 207)	180 (174, 185)	231 (227, 234)	236 (232, 239)	236 (232, 239)	219 (212, 225)
Statin Monitoring cost (95% CI)	74 (72, 76)	74 (72, 77)	79 (76, 82)	258 (249, 268)	73 (71, 76)	72 (69, 74)	74 (71, 77)	328 (315, 342)
Statin Monitoring cost, discounted (95% CI)	66 (65, 67)	66 (65, 67)	69 (68, 70)	199 (195, 204)	65 (64, 66)	64 (63, 65)	65 (64, 66)	233 (228, 239)

Incremental Total cost (£) (95% CI)	889 (638, 1134)	1040 (689, 1386)	1866 (1286, 2392)	670 (71, 1355)	806 (539, 1074)	825 (505, 1170)	1175 (696, 1642)	1052 (347, 1834)
Incremental Total cost, discounted (£) (95% CI)	365 (251, 480)	347 (190, 505)	574 (313, 821)	21 (-300, 381)	355 (246, 472)	328 (200, 470)	394 (201, 597)	282 (-37, 632)
ICER (£/QALY) (95% CI)	2945 (2173, 3766)	1762 (1060, 2390)	1655 (1020, 2185)	116 (-1977, 1839)	3502 (2513, 4783)	2276 (1502, 3095)	1782 (1054, 2490)	1725 (-275, 3531)

CI, confidence interval. CVD, cardiovascular disease. ICER, Incremental Cost-Effectiveness Ratio with costs and QALYs discounted at 3.5% per year. LDL, low density lipoprotein. QALY, quality-adjusted life years.

Supplemental Table 4: Predicted incremental health outcomes, costs and cost-effectiveness of higher intensity statin treatment compared to standard statin, in categories by sex, prior cardiovascular disease and pre-treatment LDL cholesterol level

Sex	Men				Women			
CVD history and LDL-C levels	**Without CVD, LDL-C < 3.4**	**Without CVD, LDL-C 3.4-4.1**	**Without CVD, LDL-C ≥4.1**	**With prior CVD**	**Without CVD, LDL-C < 3.4**	**Without CVD, LDL-C 3.4-4.1**	**Without CVD, LDL-C ≥4.1**	**With prior CVD**
Incremental Life years (95% CI)	0.08 (0.05, 0.1)	0.12 (0.09, 0.15)	0.21 (0.17, 0.25)	0.14 (0.1, 0.18)	0.08 (0.06, 0.1)	0.11 (0.08, 0.14)	0.17 (0.13, 0.21)	0.15 (0.11, 0.2)
Incremental Life years, discounted (95% CI)	0.04 (0.02, 0.05)	0.06 (0.04, 0.07)	0.1 (0.08, 0.12)	0.07 (0.05, 0.09)	0.03 (0.02, 0.04)	0.05 (0.03, 0.06)	0.07 (0.05, 0.08)	0.07 (0.05, 0.09)
Incremental QALYs (95% CI)	0.05 (0.03, 0.06)	0.08 (0.06, 0.1)	0.13 (0.1, 0.16)	0.06 (0.04, 0.09)	0.04 (0.02, 0.06)	0.07 (0.05, 0.09)	0.1 (0.07, 0.12)	0.06 (0.04, 0.09)
Incremental QALYs, discounted (95% CI)	0.02 (0.01, 0.03)	0.04 (0.03, 0.05)	0.06 (0.05, 0.08)	0.03 (0.02, 0.05)	0.02 (0.01, 0.03)	0.03 (0.02, 0.04)	0.04 (0.03, 0.05)	0.03 (0.02, 0.04)
Incremental Hospital cost (95% CI)	79 (26, 127)	89 (25, 164)	187 (86, 295)	-31 (-143, 94)	62 (11, 124)	48 (-6, 114)	93 (10, 177)	18 (-114, 164)
Incremental Hospital cost, Discounted (95% CI)	9 (-14, 34)	-1 (-29, 34)	14 (-30, 65)	-99 (-158, -33)	10 (-13, 39)	-2 (-25, 25)	5 (-30, 41)	-51 (-112, 17)
Incremental Primary care cost (95% CI)	99 (64, 141)	105 (71, 146)	184 (130, 241)	156 (105, 213)	120 (70, 187)	105 (65, 155)	172 (113, 243)	189 (120, 268)
Incremental Primary care cost, discounted (95% CI)	47 (28, 71)	46 (27, 68)	81 (54, 113)	78 (50, 109)	53 (28, 86)	43 (24, 66)	71 (42, 105)	82 (50, 119)
Statin cost (95% CI)	152 (147, 157)	159 (154, 165)	159 (153, 164)	134 (128, 140)	189 (184, 193)	195 (190, 199)	196 (191, 201)	177 (168, 185)
Statin cost, discounted (95% CI)	106 (104, 108)	110 (107, 112)	109 (107, 112)	96 (94, 99)	122 (120, 124)	125 (123, 127)	126 (124, 128)	117 (114, 120)
Statin Monitoring cost (95% CI)	-1 (-1, -1)	-1 (-2, -1)	-2 (-2, -2)	2 (1, 2)	-1 (-1, -1)	-1 (-1, -1)	-1 (-2, -1)	2 (1, 2)
Statin Monitoring cost, discounted (95% CI)	-1 (-1, 0)	-1 (-1, -1)	-1 (-1, -1)	1 (1, 1)	0 (-1, 0)	-1 (-1, 0)	-1 (-1, -1)	1 (1, 1)

Incremental Total cost (£) (95% CI)	329 (247, 408)	352 (264, 460)	528 (383, 682)	262 (105, 435)	370 (275, 491)	348 (262, 451)	460 (331, 602)	385 (192, 599)
Incremental Total cost, discounted (£) (95% CI)	162 (123, 204)	154 (112, 203)	204 (135, 277)	76 (-3, 168)	185 (137, 245)	165 (127, 212)	201 (143, 266)	149 (61, 251)
ICER (£/QALY) (95% CI)	7427 (4615, 15088)	4176 (2790, 6511)	3182 (2132, 4700)	2213 (-106, 5104)	11778 (6155, 23971)	5864 (4132, 9791)	4951 (3218, 7804)	5083 (2165, 10585)

CI, confidence interval. CVD, cardiovascular disease. ICER, Incremental Cost-Effectiveness Ratio with costs and QALYs discounted at 3.5% per year. LDL, low density lipoprotein. QALY, quality-adjusted life years.

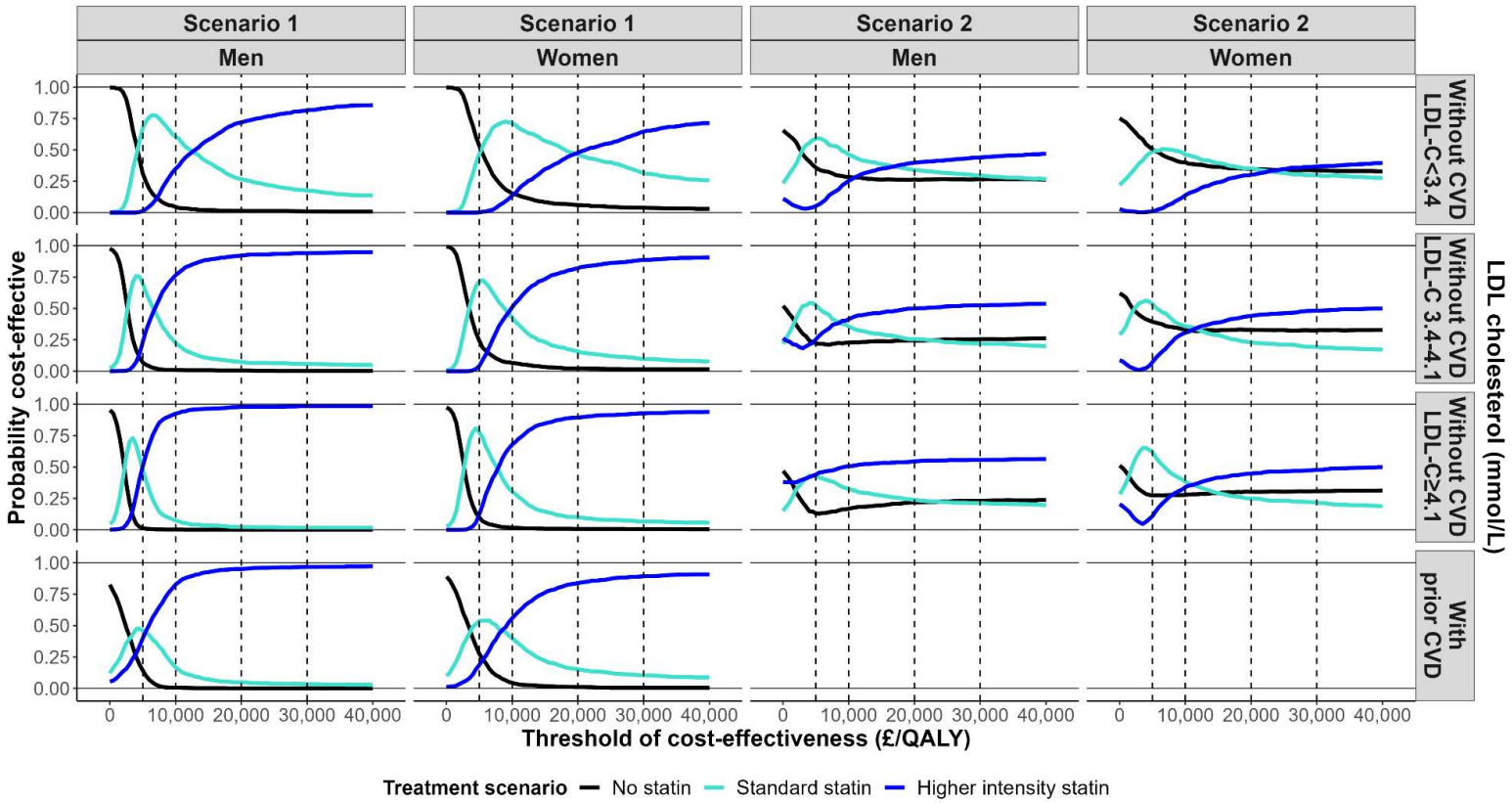
Supplemental Table 5: Predicted discounted incremental health outcomes, costs and cost-effectiveness of standard statin treatment compared to no statin, in categories by sex, prior cardiovascular disease and pre-treatment LDL cholesterol level: base case and selected sensitivity analyses

Sex	Men				Women			
CVD history and LDL-C levels	Without CVD, LDL-C < 3.4	Without CVD, LDL-C 3.4-4.1	Without CVD, LDL-C ≥4.1	With prior CVD	Without CVD, LDL-C < 3.4	Without CVD, LDL-C 3.4-4.1	Without CVD, LDL-C ≥4.1	With prior CVD
Base case								
Discounted Incremental QALYs	0.12	0.2	0.35	0.18	0.1	0.14	0.22	0.16
Discounted Incremental Primary care and Hospital admissions costs	100	75	302	-358	60	29	93	-170
Discounted Statin and Statin Monitoring costs	265	271	272	379	296	300	301	452
Discounted Incremental Total cost	365	347	574	21	355	328	394	282
ICER (£/QALY)	2945	1762	1655	116	3502	2276	1782	1725
Statin effects among participants >75 years old in RCTs								
Discounted Incremental QALYs	0.08	0.14	0.24	0.14	0.07	0.10	0.15	0.12
Discounted Incremental Primary care and Hospital admissions costs	82	83	249	-45	34	13	88	-89
Discounted Statin and Statin Monitoring costs	265	272	272	376	295	300	300	449
Discounted Incremental Total cost	347	354	520	332	329	313	388	360
ICER (£/QALY)	4116	2603	2154	2311	5050	3285	2587	3080
Statin effects among participants >75 years old without cardiovascular disease at entry in RCTs								
Discounted Incremental QALYs	0.05	0.07	0.13	NA	0.03	0.05	0.07	NA
Discounted Incremental Primary care and Hospital admissions costs	-141	-241	-320	NA	-144	-210	-283	NA
Discounted Statin and Statin Monitoring costs	263	270	268	NA	294	297	298	NA
Discounted Incremental Total cost	122	29	-52	NA	150	89	16	NA
ICER (£/QALY)	2602	399	-398	NA	4385	1856	218	NA
Lower relative risk reduction of vascular death of 7% (instead of 12%) per 1mmol/L LDL-C reduction with statin therapy								
Discounted Incremental QALYs	0.10	0.17	0.30	0.14	0.08	0.12	0.19	0.13
Discounted Incremental Primary care and Hospital admissions costs	-12	-78	30	-630	-26	-72	-70	-400
Discounted Statin and Statin Monitoring	265	271	270	377	295	299	300	450

costs								
Discounted Incremental Total cost	253	193	300	-253	269	227	230	51
ICER (£/QALY)	2416	1152	1010	-1781	3183	1877	1235	386
Results with 1.5% discount rate (instead of 3.5%) for outcomes and costs								
Discounted Incremental QALYs	0.18	0.30	0.51	0.25	0.16	0.23	0.35	0.25
Discounted Incremental Primary care and Hospital admissions costs	287	330	826	-133	193	178	363	64
Discounted Statin and Statin Monitoring costs	312	321	321	443	360	366	367	553
Discounted Incremental Total cost	598	651	1146	310	552	543	730	617
ICER (£/QALY)	3239	2199	2240	1240	3407	2350	2081	2495

CVD, cardiovascular disease. ICER, Incremental Cost-Effectiveness Ratio with costs and QALYs discounted at 3.5% per year (unless otherwise specified). LDL, low density lipoprotein. QALY, quality-adjusted life years. NA, not applicable.

Supplemental Figure 1: Probability of statin therapy being cost-effective in older people in scenario analyses with CVD reductions with statin therapy in people>75 years old informed from effects of statin therapy among participants >75 years old (Scenario 1) or >75 years old without CVD (Scenario 2) from Cholesterol Treatment Trialists' collaborative meta-analysis



The probability that the treatment scenario provides the highest QALYs gain at the particular threshold of cost-effectiveness plotted. Statin effects up to age 75 as in base-case analysis; statin effect thereafter as per respective scenario analysis. CVD, cardiovascular disease. LDL, low density lipoprotein. QALY, quality-adjusted life years.

Supplemental methods

The CVD micro-simulation model

The model(2) was developed using the individual participant data of 16 large randomised clinical trials comparing statin versus control, and calibrated using the UK Biobank study's(3) individual participant data. The model employs a broad range of patient socio-demographic characteristics (age, sex, ethnicity, physical activity, diet quality, quintile of socio-economic deprivation, body mass index (BMI), smoking status, blood pressure, serum lipid and creatinine levels, treated hypertension, and histories of CVD, diabetes (or HbA1c level for those without diabetes), cancer or mental illness) to project annually the first occurrence of four major CVD events: myocardial infarction, stroke, coronary revascularisation and vascular death, and three non-vascular events: incident diabetes, incident cancer and non-vascular death. Participant characteristics, disease histories and incident events determined health-related quality of life(2) and primary care and hospital admission costs(4) in each year of the model. The model was validated in categories of participants in UK Biobank and, separately, the Whitehall II study, and against national mortality, cancer incidence rates, and other published data. (2)

Identifying participants 70 years and older

1. **UK Biobank**

Between 2006 and 2010, the UK Biobank study(3) recruited more than 500,000 40-70 years old men and women across the UK and followed them in resurveys and routine health records thereafter. At recruitment into the UK Biobank, given the general aim to recruit 40-69 year olds, only 2400 people aged 70-73 were recruited. By the time of the three further re-assessments of some UK Biobank participants (e.g. a random participant sample to assess variation in continuous biomarkers; re-assessment to collect baseline information for participants undergoing imaging assessments), some UK Biobank participants had reached age 70 years. Therefore, individuals aged ≥70 years at any UK Biobank assessment attendance from all four (re-)surveys were included from the earliest such attendance. A small number of participants with end stage kidney disease were excluded (see **supplemental methods table 1** for the details of inclusion).

Supplemental methods table 1: distribution of included participants from all four UK Biobank surveys

	N	Data collection date	Age (years	Age>=70 years	Included*
1st attendance (entry)	502459	2006-03-13 to 2010-10-01	37-73	2423	2419
2nd attendance	20343	2009-12-12 to 2013-06-07	43-78	2716	2630
3rd attendance	56012	2014-04-30 to 2020-03-05	44-83	16896	12747
4th attendance	5305	2019-05-22 to 2020-03-05	49-83	1486	325

*Participants ≥70 years old with end stage kidney disease and those who were included from a previous attendance were excluded.

Definitions and specifications are the same as data preparation in the analyses of the main UK Biobank cohort data that was published previously. In general, analytical variables were coded using

the UK Biobank nurse interview and linked electronic health records. Participants' characteristics at baseline or reassessments were derived based on data from interviews and linked records. Follow-up events, such as myocardial infarction (MI), stroke, coronary revascularization (CRV), incident diabetes, incident cancer, and mortality, were derived from linked death, hospital inpatient, cancer, and primary care (GP) records. Disease variables were coded referring to the International Classification of Diseases (ICD) 10 and 9 systems, UK Biobank cancer codes, UK Biobank non-cancer codes, and other UK Biobank algorithms. Procedure variables were coded referring to the Office of Population Censuses and Surveys (OPCS) 3 and 4 systems and UK Biobank operation codes. For more details, please refer to our earlier study's supplemental table S1, and supplemental methods 1(2).

The end of follow-up date for these participants is the earliest from date of death, date of loss of follow-up, or 29/02/2020 (i.e. predating covid pandemic in UK). The average duration of follow-up is 3.5 years for the included individuals. The numbers of events during follow-up are summarised in **Supplemental methods table 2**.

Supplemental methods table 2: Number of participants experiencing events during follow-up

Cohort	Myocardial infarction	Stroke	Coronary revascularisation	Incident Cancer	Incident Diabetes	Vascular death	Nonvascular death
Without prior CVD	165	176	172	789	159	64	406
With prior CVD	67	92	136	285	99	75	152
Total	232	268	308	1074	258	139	558

CVD, cardiovascular disease.

2. Whitehall II

Whitehall II is a cohort study(5) among 10,308 participants aged 35-55 at entry, recruited from the British Civil Service in 1985, with periodic re-surveys of participants (called phases in Whitehall II). The Whitehall II study data includes Phases 1-9 and 11 at present. Due to attrition/no response and deaths, the numbers of participants declined from 10,308 in Phase 1 (1985-1988) to 6,308 in Phase 11 (2012-2014). We used participants from Phase 9 onwards for this external validation.

During odd-number phases, more detailed data was collected and biomarkers were measured. Routine healthcare data were linked for selected clinical events and mortality for participants. Electronic death records, NHS hospital records and cancer registry entries were linked for Whitehall II participants and used to identify events during follow-up. However, this data were made available until particular time points for different types of events. For example, the data for strokes was available until about Phase 9, while the data for MI, cancer and death were available over longer time period. We used the linked clinical events and mortality data to identify events during follow-up, but also used questionnaire data to complement data for some events (see **Supplemental methods table 3** for more details). For incident CRVs and incident diabetes, only partial questionnaire data were available (for CRV including only coronary artery bypass graft surgery, date of incident diabetes not systematically recorded); linked healthcare data were not available. Therefore, we did not validate the model for these endpoint.

Supplemental methods table 3: Identifying incident events for the older Whitehall II cohort

	Linked electronic health data	**Whitehall II questionnaire data**
Myocardial infarction (MI)	Electronic hospital and death records of "MI (HES/death)" until the mid of 2019	Not used
Stroke	Electronic hospital and death records of "All stroke (HES/death)" until the mid of 2019	
Cancer	Electronic cancer registry "All malignant cancer" with follow-up until March 2015 used.	Variables indicating self-reported "ever told cancer" were used to identify further baseline cancer as a complement. As only told years were available, 30th June of the told year was assumed as the told date. Told cancers with an unknown year, mostly from Phase 1, were assumed to occur on 1st January 1985, the year when Whitehall II project started.
Vascular death (VD)	Electronic death certificate data (until February 2021) were used; CVD death category; cut at 28 February 2020 to avoid the impact of covid19	Electronic death certificate data (until February 2021) were used; CVD death category; cut at 28 February 2020 to avoid the impact of covid19
Nonvascular death (NVD)	Electronic death certificate data (until February 2021) were used; non-CVD death category; cut at 28 February 2020 to avoid the impact of covid19	Electronic death certificate data (until February 2021) were used; non-CVD death category; cut at 28 February 2020 to avoid the impact of covid19

CVD, cardiovascular disease. HES, hospital episodes statistic.

For the participants in Phase 9, deaths have the longest follow-up periods, with an average of 10.9 years, followed by MI with an average of 9.4 years and stroke 9.3 years. The follow-up periods of cancers are shorter, with an average of 6.1 years. The numbers of follow-up events for the older cohort are summarised in Supplemental methods table 4.

Supplemental methods table 4: Number of Whitehall II participants 70 years and older at Phase 9 experiencing events

	Myocardial infarction (MI)	**Stroke**	**Incident Cancer**	**Vascular death (VD)**	**Nonvascular death (NVD)**
Without history of CVD (n=1247)	46	56	170	75	290
With history of prior CVD (n=754)	84	63	90	93	210
Total (N=2001)	130	119	260	168	500

CVD, cardiovascular disease.

Handling missing data

1. UK Biobank

We initially created a panel dataset for all individuals who attended as least one of the three follow-up surveys of UK Biobank, so in this dataset an individual has a baseline value and 1-3 follow-up values for each characteristic. The summary of missingness and imputation methods is presented in **Supplemental methods table 5**. In general, characteristics such as sex, ethnicity and Townsend score are invariant across time. A small numbers of missing smoking status were imputed using the Last observation carried forward (LOCF) method. The diet categorisation used the same method as previously, in which a small number of uncertain diet types due to missing values in consumption of some food types were combined with unhealthy diet. Physical activity levels are missing for all follow-up surveys, and they were imputed as the baseline levels.

We multiply imputed the missing biomarker values in a wide form (one individual one row and multiple measures for one characteristic) by chained equations using the Markov chain Monte Carlo (MCMC) simulation using a R package "mice". All characteristics of analyses were included, plus a binary variables of statin use at survey administration. All characteristics with missing values at entry into UK Biobank have been imputed as specified in our previous analysis. 80 imputations and 40 maximum iterations were used in the multiple imputation and the means across all the imputations were used to impute the missing values.

LDL, HDL, creatinine and HbA1c values were not measured at second and third follow-up re-surveys, and therefore they were missing. They were not imputed in the wide-form multiple imputation. Instead, we implemented a long-form multiple imputation. In the long form, all multiple measures of a characteristic such as LDL were stacked in one variable, which had values from baseline and the first follow-up survey and therefore can be imputed. Additionally, durations from entry to the current attendance were used, so that the trend was taken into account. The long-form multiple imputation model specification and parameters were then identical to the wide-form multiple imputation.

Supplemental methods table 5: Summary of missing data and imputation method in UK Biobank re-assessments

	Reassessment 1	**Reassessment 2**	**Reassessment 3**	**Imputation method**
Baseline Characteristics	**Numbers of missing values**			
Age at recruitment	As baseline	As baseline	As baseline	NA
Age at re-assessment	0	0	0	NA
Sex	As baseline	As baseline	As baseline	NA
Ethnicity	As baseline	As baseline	As baseline	NA
Townsend score	As baseline	As baseline	As baseline	NA
Smoking	60	518	38	LOCF
BMI (kg/m^2)	46	1638	19	Wide-form multiple imputation
Systolic blood pressure (mmHg)	13	5952	266	As above
diastolic blood pressure (mmHg)	13	5952	266	As above
CVD history	0	0	0	NA

Type 1 diabetes	0	0	0	NA
Hypertension treatment	0	0	0	NA
LDL (mmol/L)	2508	ALL	ALL	Wide-form multiple imputation for re-assessment 1; long-form multiple imputation for re-assessments 2&3
HDL (mmol/L)	4654	ALL	ALL	As above
Creatinine (umol/L)	2502	ALL	ALL	As above
HbA1c (mmol/mol)	6077	ALL	ALL	As above
Physical activity	ALL	ALL	ALL	As baseline
Severe mental illness	0	0	0	NA
Diet	130	661	43	Combined missing with unhealthy/ uncertain

BMI, body mass index. CVD, cardiovascular disease. HbA1c, hemoglobin A1c. HDL, high density lipoprotein. LOCF, last observation carried forward. LDL, low density lipoprotein. NA, not applicable.

2. Whitehall II

We focused on Whitehall II Phase 9 data. Referring to the specification of model input characteristics, there are small numbers of missing values for ethnicity, Townsend score, smoking status and disease histories, moderate numbers of missing values for biomarkers (8%-15%), and data was not available for prior Type 1 diabetes, severe mental illness and diet quality. We assigned the missing values to the most common categories in UK Biobank older cohort, referred to the available values in the last phase, or used multiple imputation by chain equations to address missing data (**Supplemental methods table 6**). The parameter specification of multiple imputation was the same as for the older UK Biobank cohort, and data about individuals across all ages and data from Phase 5, Phase 7 and Phase 11 were additionally included to provide information for multiple imputation.

Particularly, Whitehall II only provides two categories of ethnicity, White and non-White. We made the assumption that all non-White were South Asians, the second largest ethnicity group in England. The Whitehall II's physical activity categories include the moderate level and the low level (high-level physical activity category was possibly combined with the moderate level in Whitehall II). We assumed that participants did not have Type 1 diabetes, nor sever mental illness and all had "healthy" diet, the most common category in UK Biobank.

Supplemental methods table 6: Summary of missing data and imputation method in Whitehall II

Variables	**Numbers of missing values**	**Methods**
Age at attendance	0	Age at phase attendance; no missing
Sex	0	No missing

Ethnicity	5	Missing values assigned to "White"; Non-white assigned to "South Asian"
Townsend score	100	Multiply imputed
Smoking	145	Refer to status in last phase; otherwise assigned to the most common category, i.e. non-smoker
BMI	248	Multiply imputed
CVD history	93	Myocardial infarction (MI), stroke and other coronary heart diseases (total angina) used clinical follow-up prevalence data, complemented by questionnaire data. Peripheral artery disease (PAD) used only questionnaire data referring to the algorithm used in Health Survey for England 2017.
Prior cancer	2	Based on Clinical follow-up data, complemented by questionnaire data "ever told cancer" (available at Phase 1, 4 & 5). Only years of being told are available (for Phase 4 & 5), so assume the day as 30th June of that year; other unknown dates (mostly from Phase 1) were assumed to be "1st January 1985" (WH2 starting year).
Prior diabetes	3	Questionnaire data only "self-reported diabetes"; assume diagnosis date of diabetes before Phase 1 to be "1st January 1985"
Type 1 diabetes	0	Coding was based on self-reported other long-term illness. Participants who did not report any long-term illness were assumed no prior such illness
Treated hypertension	5	Minor missing, assigned to "no treated hypertension"
LDL-C (mmol/L)	305	Multiply imputed
HDL-C (mmol/L)	298	Multiply imputed
Creatinine (umol/L)	298	Creatinine was not measured at Phase 7 but measured at phase 9. Missing values multiply imputed.
HbA1c (mmol/mol)	301	Multiply imputed
Systolic blood pressure (mmHg)	240	Multiply imputed
diastolic blood pressure (mmHg)	240	Multiply imputed
Physical activity	65	Only three levels: low, moderate & missing (missing is a separate category, corresponding to the UK Biobank data)
Prior severe mental illness	0	Coding was based on self-reported other long-term illness. Participants who did not report any long-term illness were assumed no prior such illness
Healthy diet	443	All assigned to unhealthy diet, corresponding to the method used in the UK Biobank data

BMI, body mass index. CVD, cardiovascular disease. HbA1c, hemoglobin A1c. HDL, high density lipoprotein. LDL, low density lipoprotein.

Derivation of pre-treatment LDL cholesterol levels for statin-treated UK Biobank and WHITEHALL II participants

For UK Biobank participants, we adjusted upwards the LDL cholesterol levels of participants who were on statin treatment at entry into UK Biobank to derive "pre-treatment" LDL cholesterol levels using the potency of their statin regimen (see Supplemental Table 1). Statin dosage information was not collected at UK Biobank baseline interview but for participants with linked primary care prescription records both type of statin and dosage were available. However, more than half of the UK Biobank participants did not have linked primary care data, and, therefore, no linked primary care prescription records. Additionally, there were some discrepancies between reported statin use at UK Biobank recruitment and available statin prescription records; for such cases a report of statin use in either source was accepted and, if more than one source available, the more intensive regimen was used.

The statin treatment reports with an exact drug type and dosage were directly associated with the proportional LDL-C reductions according to Supplemental Table 1. The statin treatment with unknown dosage were assumed to derive the average proportional LDL cholesterol reduction according to weighted frequency of statin regimens within the primary or secondary prevention populations with known statin regimens.

Due to a complete lack of information about the exact drug type and dosage for statin treatment in Whitehall II Phase 9 participants, proportional LDL-C reductions among participants without prior CVD and with prior CVD were assumed to be 35% and 45%, respectively, informed by the corresponding average values in the UK Biobank participants.

The **pre-treatment LDL cholesterol (LDL-C)** of statin-treated participants was calculated as:

$$\text{LDL-C}_{\text{pre-treatment}} = \text{LDL-C}_{\text{entry}} / (1 - \%\text{LDL-C reduction on statin treatment})$$

Integrating treatment effects of statin therapy in the CVD model

Statin treatment effects based on the rate ratios (RR) per 1mmol/L reduction in LDL cholesterol, as reported by Cholesterol Treatment Trialists' Collaborative meta-analysis(6), were used for effects on myocardial infarction, stroke, coronary revascularisation and vascular death and further meta-analyses informed effects of statin therapy on incident diabetes in the model(7, 8) (see Table 1). In the base-case analysis, it was assumed that statins do not affect cancer incidence and non-vascular death.

The transition probabilities (tp) of events in the absence of statin treatment in the model in each cycle are calculated as:

$tp(t_u) = 1 - exp[H(t-u) - H(t)]$, where

u is the length of the cycle (i.e. 1 year), H(t-u) and H(t) are the cumulative hazards at time t-u and t, respectively.

The treatment effects of statin (tx) are calculated as: **tx = exp[ALR * ln(RR)]**, where RR is the rate ratio per 1 mmol/L LDL cholesterol reduction with statin (see Table 1) and ALR is the absolute LDL cholesterol reduction with the statin therapy, which is product of pre-treatment LDL cholesterol level and the proportional reduction in LDL cholesterol with corresponding statin regimen (see Supplemental Table 1).

The transition probabilities for events with statin treatment (tp_{tx}) in each cycle of the model is calculated as:

$$tp_{tx}(t_u) = 1 - exp[H(t-u) - H(t)]^{tx}$$

The excess rates on myopathy and rhabdomyolysis of statin treatment (see Table 1) were applied as constant annual rate each year on statin treatment in the model.

In the CVD microsimulation model, the first occurrences of MI, stroke and coronary revascularisation (CRV) were modelled followed by vascular death. The statin treatment effects, estimated using intention-to-treat analyses for times to first occurrences of these endpoints across the randomised studies in the Cholesterol Treatment Trialists' Collaborative meta-analysis, informed the treatment effects in the model. Therefore, we considered whether we may double count some treatment effects by simulating the effects on cardiovascular events concurrently (e.g. modelling statin impact on vascular death both through its effects on MI, stroke, CRV as well as its direct effect on risk of VD). We therefore internally validated the differences in predicted cumulative incidences of these endpoints due to statin therapy against the differences between observed censoring-adjusted cumulative incidences of these endpoints in the Cholesterol Treatment Trialists' Collaborative database (using the initial CVD model developed in this database(3)). The predicted effects were consistently within the 95% confidence intervals of the observed differences across the 5 years of follow-up in the trials. Nevertheless, to explore sensitivity of finding to somewhat smaller effect on cardiovascular death, in a sensitivity analysis the effect of statin therapy on vascular death was set at RR 0.93 (instead of the base case RR of 0.88 per 1mmol/L LDL cholesterol reduction), corresponding to the estimated effect of allocation to statin per 1mmol/L LDL cholesterol reduction with time-varying adjustment for first post randomisation occurrences of MI, stroke and CRV).

Specification of sensitivity and scenario analyses

Supplemental methods table 7: Sensitivity analyses parameterisation in the model

Scenario	Parameters
Base-case analysis (see Table 1)	• Overall effect of statin therapy on cardiovascular events (per 1 mmol/L LDL cholesterol reduction)(6): MI: Major coronary event Rate Ratio (RR) 0.76 (95% CI 0.73, 0.79) Stroke RR 0.84 (95% CI 0.80, 0.89) CRV RR 0.75 (95% CI 0.73, 0.78) VD RR 0.88 (95% CI 0.85, 0.91) • Statin does not have any effect on cancer • Compliance with statin therapy 100% • No disutility of daily statin • 3.5% discount rate for costs and outcomes • All healthcare costs included • Cost of statin therapy as per NHS Drug Tariff December 2021
Statin treatment effects on cardiovascular events after age 75 years corresponding to statin effects among participants >75 years of age in Cholesterol Treatment Trialists' Collaborative meta-analysis (Scenario 1)	The applied effects based on Cholesterol Treatment Trialists' individual participant data meta-analysis, reporting effects only among participants >75 years of age at randomisation (per 1 mmol/L LDL cholesterol reduction) (6) were: MI: Major coronary event RR 0.82 (99% CI 0.70, 0.96) Stroke RR 0.89 (99% CI 0.71, 1.10) CRV RR 1.02 (99% CI 0.75, 1.40) VD RR 0.95 (99% CI 0.83, 1.07)
Statin treatment effects on	The applied effects based on Cholesterol Treatment Trialists'

cardiovascular events after age 75 years corresponding to statin effects among participants >75 years of age and without CVD at randomisation in Cholesterol Treatment Trialists' Collaborative meta-analysis (Scenario 2)	individual participant data meta-analysis: effects only among participants >75 years of age and without CVD at randomisation (per 1 mmol/L LDL cholesterol reduction) (6) (personal communication): MI: Major coronary event RR 0.87 (99% CI 0.65, 1.15) Stroke RR 0.88 (99% CI 0.59, 1.30) CRV RR 0.93 (99% CI 0.50, 1.74) VD RR 1.04 (99CI 0.76, 1.43)
Smaller statin treatment effect on vascular death	Relative reduction in vascular death with statin RR 0.93 per 1 mmol/L LDL cholesterol reduction).
Vary statin treatment effect on cancer incidence	RR of 0.96 or 1.05, respectively, applied for incident cancer with statin therapy based on 95% confidence interval of the Cholesterol Treatment Trialists' individual participant data meta-analysis reporting RR of 1.00 (95% CI 0.96, 1.05).(9)
Real-world compliance with statin therapy	Using observed statin discontinuation and restarting rates for the first discontinuation and first restarting,(10) the derived probabilities of complying with statin therapy (Supplemental methods table 8) were applied to each individual in the respective years in model simulation. Both statin effects and costs were discontinued with no statin use.
Quality of life disutilities of daily statin pill	0.001, 0.002 or 0.005 QALYs were deducted in each model year. (11)
Higher risk of nonvascular death and lower general QoL	Includes three scenarios across all alternatives: 1) doubling individual's risk of nonvascular death; 2) reducing individual's QoL by 0.1 each year; 3) both doubling NVD risk and reducing QoL by 0.1
Discount rates for costs and outcomes of 1.5%	Annual discount rates to 1.5% were used for costs and QALYs (instead of the 3.5% base-case rates)
Include healthcare costs only for CVD and incident diabetes	Healthcare costs associated with CVD and incident diabetes only included (ie, unrelated healthcare costs were excluded).
Increased cost of statin therapy	The base-case costs of statin therapy increased 1.5, 2 or 5 times.

RR, rate ratio. MI, myocardial infarction. CRV, coronary revascularisation. QALY, quality-adjusted life years. QoL, quality of life. RR, relative risk. VD, vascular death.

Supplemental methods table 8: Probabilities for first discontinuation and first restarting of statin treatment and the derived probabilities of compliance with statin therapy over the first 10 years

	Cumulative probability (%)(10)		On statin treatment (%)	
Year	Discontinuation	Restarting	On	Off
1	30%	50%	70%	30%
2	38%	59%	77%	23%
3	43%	64%	79%	21%
4	47%	68%	80%	20%
5	50%	70%	81%	19%
6	52%	72%	81%	19%
7	54%	74%	82%	18%
8	56%	76%	82%	18%
9	58%	77%	83%	17%
10	60%	79%	83%	17%

The first two columns present cumulative probabilities for the first discontinuation and first restarting of statin treatment(10), followed by the derived compliance with statin treatment in first 10 years of treatment.

Supplemental material references

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