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Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The effect of statins on cardiovascular outcomes is well established.
- Effects on numerous other health outcomes have been claimed, but results have been inconsistent.
- Previous observational studies may have been affected by selection bias and confounding.

WHAT THIS STUDY ADDS

- This study was larger and more statistically powerful than the combined total of data from all randomized trials of statins undertaken to date.
- The validity of the study is supported by findings for vascular outcomes being comparable to those observed in large randomized controlled trials.
- There was little evidence to support effects of statins beyond their established effects on cardiovascular disease.

AIMS

To assess the effect of statins on a range of health outcomes.

METHODS

We undertook a population-based cohort study to assess the effect of statins on a range of health outcomes using a propensity score-based method to control for differences between people prescribed and not prescribed statins. We validated our design by comparing our results for vascular outcomes with the effects established in large randomized trials. The study was based on the United Kingdom Health Improvement Network database that includes the computerized medical records of over four and a half million patients.

RESULTS

People who initiated treatment with a statin ($n = 129\,288$) were compared with a matched sample of 600 241 people who did not initiate treatment, with a median follow-up period of 4.4 years. Statin use was not associated with an effect on a wide range of outcomes, including infections, fractures, venous thromboembolism, gastrointestinal haemorrhage, or on specific eye, neurological or autoimmune diseases. A protective effect against dementia was observed (hazard ratio 0.80, 99% confidence interval 0.68, 0.95). There was no effect on the risk of cancer even after ≥8 years of follow-up. The effect sizes for statins on vascular end-points and mortality were comparable to those observed in large randomized trials, suggesting bias and confounding had been well controlled for.

CONCLUSIONS

We found little evidence to support wide-ranging effects of statins on health outcomes beyond their established beneficial effect on vascular disease.

Introduction

Large randomized trials have demonstrated that statins are effective in preventing vascular disease [1, 2]. The use of statins has increased markedly, and in drug sales worldwide they are the highest ranked therapy class [3]. In recent years, there has been increasing interest in pleiotropic effects of statins [4]. Many disease processes have been suggested to be affected by statin use, including protection from infectious processes [5]; effects on cancer [6, 7]; protection against dementia [8] and fractures [9]; effects on the eye [10, 11] and a range of neurological [12, 13] and immune-mediated diseases [14]. However, outside clinical trials, exposure to statins is not randomized, but is determined by a wide range of health-related factors. The various reported pleiotropic effects could therefore be attributable to differences between people who are prescribed and not prescribed statins. For many of these outcomes, the existing data from randomized trials are insufficient to assess reliably whether the effects are true. The established effects of statins on vascular outcomes make further large population-based trials unlikely for ethical reasons. Therefore a large, high-quality observational study that overcomes confounding is needed to assess the association between statin use and a wide range of health outcomes. We undertook a population-based cohort study based on computerized medical records derived from primary care in the UK. To overcome biases associated with prescribing patterns we used a propensity score-based approach. We validated the study design by comparing our results for vascular outcomes with the effects seen in large randomized trials.

Methods

The Health Improvement Network database

The Health Improvement Network database (THIN) is a collection of computerized medical records derived from general practice that aims to include complete prescribing and diagnostic information. Recorded rates of consultations and drug prescriptions as well as pregnancy and death rates are similar to national data sources [15], and the validity of the data for pharmacoepidemiological research has been demonstrated [16]. Information obtained is anonymous. Ethical approval for the study was obtained from the South Thames Multi-centre Research Ethics Committee.

Participants

The source population was all patients registered with a general practice contributing to the THIN database between January 1995 and December 2006, comprising the electronic medical records for 5.5 million patients derived from 303 general practices.

Statin users (exposed group) All patients aged 40–80 years who received their first prescription for a statin on or after 1 January 1995 and with >12 months prior continuous registration with a general practice contributing to the database were included in the study. The date of first statin prescription was defined as the index date.

Statin non-users (unexposed group) Up to five non-users were matched to each user on sex and age within 5 years. Non-users had to be registered at the same general practice as their matched user on the index date, thus controlling for doctor prescribing habits and temporal trends. At least 12 months' registration with the practice prior to the index date was required. Both users and non-users also had to have had some form of contact recorded with the practice within 6 months before or after the index date in order to ensure all participants were active within their general practices. Non-users had to have no record of a statin prescription before the index date. However, non-users could go on to be prescribed a statin at a later date. This was specified partly in order to follow most closely the procedures adopted in randomized trials, but also to avoid assembling a biased comparison group who were not at risk of being prescribed a statin.

Analysis

Propensity score The decision to prescribe a statin for a patient is inextricably bound up with their health. Indeed, systematic differences between statin users and non-users have been found to influence estimates of the effect of exposure to the drugs [17, 18]. A propensity score is a measure of how likely an individual is to be prescribed a particular drug. Use of propensity scores offers a method of reducing selection bias and confounding in pharmacoepidemiological studies [19, 20]. Propensity scores were estimated for all patients using conditional logistic regression, with statin prescription at the index date as the outcome, taking the matching into account. Factors chosen for inclusion in the model were those judged possibly likely to influence statin prescribing. Included factors were: observation time in the THIN database, body mass index (BMI), socioeconomic status, consultation rate, prescribing rate, smoking status, drinking habits, diabetes, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, other circulatory disease, dementia, cancer, atrial fibrillation, heart failure, recent hepatic disease, recent renal disease, thyroid disease, hyperlipidaemia, hypertension, recent use of hormone replacement therapy, antipsychotics, antidepressants, steroids (oral or inhaled), fibrates, cytochrome P450 3A4 inhibitors, any prior use of non-statin or fibrate lipid-lowering medication, nitrates, aspirin, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs.

Outcomes Two groups of outcomes were considered. First, those effects that might reasonably be expected to occur and be attributable to statin even with short-term exposure (i.e. including the first 12 months of follow-up after initiating treatment). This included myositis or myolysis, acute liver disease, hypersensitivity, pancreatitis, anaemia, thrombocytopenia, alopecia, and Guillain–Barre syndrome. We assessed the effect on incident pneumonia, other serious respiratory infections (such as acute bronchitis and influenza) and urinary tract infections. Rather than protecting people against new infections, it has been suggested that statins lessen severity once someone has an infection [5]. To assess this, we compared the risk of developing pneumonia or of dying within 6 months of the diagnosis of influenza.

The second group of outcomes was of conditions more likely to be associated with longer term use. This group includes diseases likely to exhibit a lag period between the onset of disease process and clinical manifestation and diagnosis. Outcomes observed in the first year following initiation of statin treatment may therefore not be attributable to statin use, and thus the first year of follow-up was excluded. This second group of outcomes included the following: cancer – all forms and a separate analysis of breast, prostatic and gastrointestinal cancers; effects on the eye – cataract and age-related macular degeneration; fractures – both all and hip fractures separately; venous thromboembolism – including both deep vein thrombosis and pulmonary embolism; dementia – with Alzheimer's disease considered separately; depression – defined as the initiation of antidepressant pharmacotherapy; the following autoimmune conditions – psoriasis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus. In addition, the following outcomes were considered: Parkinson's disease, amyotrophic lateral sclerosis, upper gastrointestinal haemorrhage, and pulmonary fibrosis.

Modelling strategy Cox regression was used with Stata 9 [StataCorp, College Station, TX, USA]. The initial model was age and sex adjusted. We then adjusted for propensity score and further for year of index date; first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia; first use of any of the following post-index date: aspirin, nitrates, fibrates, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs. For chronic outcomes (such as cancer), only first ever recorded events were included in the analysis, in order to avoid the inclusion of non-incident records of a previous event. People with a previous history of the outcome prior to the index date were therefore excluded from the analysis of that outcome.

In the primary analysis, outcomes were compared between people who were initiated on statin therapy and people who had not been initiated on a statin at the index date, analogous to an intention-to-treat analysis. As a sensitivity analysis, we assessed the effect of censoring follow-up for each individual if their exposure status changed; e.g. if someone in the statin group stopped taking statins, or someone in the unexposed group was prescribed a statin. As secondary analyses, to assess whether effects varied with longer term exposure, we repeated the analysis of each outcome stratified on follow-up period. For cancer, we also analysed lipophilic and lipophobic statins separately because of a previous suggestion of a differential effect.

Validation of study design The effects of statin use on risk of myocardial infarction, stroke and mortality are well established from randomized controlled trials [2]. In order to assess how successful our design was in controlling for selection bias and confounding, we estimated the incidence hazard ratio (HR) for fatal and nonfatal myocardial infarction and stroke and for all-cause mortality using Cox regression and compared our results with the estimates obtained in the Heart Protection Study, the largest randomized trial to date [1]. The earliest of first recorded myocardial infarction, first stroke, or death were identified and assessed as outcomes. Patients with a diagnosis of myocardial infarction or stroke prior to index date were excluded from analyses for these outcomes, and all analyses were performed according to exposure status at the index date, as would be undertaken in a randomized trial. In order to mimic closely previous randomized trials of statins, analysis was restricted to patients with a diagnosis of atherosclerosis prior to their index date or at any point before the end of their observation period. Because of the likelihood that patients perceived to be at very high risk of an impending acute vascular event would be prescribed a statin, the first 12 months' follow-up time after the index date was excluded.

Results

People who received prescriptions for statins ($n = 129\,288$) were matched to 600 241 people not prescribed a statin (an average of 4.6 non-users per user). Table 1 shows the characteristics of statin users and non-users at the index date. Of note, users were more likely to be current or ex-smokers, have higher BMI and be diagnosed with hyperlipidaemia, diabetes or a range of cardiovascular diseases. Non-users were more likely to have other serious chronic disease such as dementia or cancer. Median follow-up after the index date was 4.4 years.

Table 2 shows the types of statin prescribed to the exposed group. The lipophilic statins, simvastatin and atorvastatin accounted for more than half of all users. Around

Table 1

Characteristics of study population at index date

	Unexposed *n* (%)	Exposed *n* (%)
All Patients	600 241	129 288
Age* (years)		
40–49	74 451 (12.4)	14 871 (11.5)
50–59	163 896 (27.3)	33 931 (26.2)
60–69	170 677 (31.2)	41 707 (32.3)
70–79	128 380 (21.4)	29 755 (23.0)
80+	46 327 (7.72)	9 024 (7.0)
Sex*		
Male	299 158 (49.8)	65 517 (50.7)
Female	301 083 (50.2)	63 771 (49.3)
Smoking status		
Nonsmoker	201 062 (33.5)	31 578 (24.4)
Ex-smoker	152 273 (25.4)	46 018 (35.6)
Current smoker	221 779 (37.0)	50 383 (39.0)
Unknown status	25 127 (4.2)	1 309 (1.0)
Body mass index		
<20	24 098 (4.0)	2 619 (2.0)
20–25	175 760 (29.3)	33 971 (26.3)
>25	308 695 (51.4)	83 919 (64.9)
Unknown	91 688 (15.3)	8 779 (6.8)
Diagnosis of		
Diabetes	53 955 (9.0)	35 699 (27.6)
Coronary heart disease	40 449 (6.7)	49 656 (38.4)
Cerebrovascular disease	26 302 (4.4)	16 010 (12.4)
Peripheral vascular disease	11 277 (1.9)	7 671 (5.9)
Unspecified atheroma	466 (0.1)	379 (0.3)
Atrial fibrillation	15 927 (2.7)	6 246 (4.8)
Heart failure	12 946 (2.2)	6 551 (5.1)
Hepatic disease (within 6 months)	2 215 (0.4)	474 (0.4)
Renal disease (within 6 months)	4 122 (0.7)	1 942 (1.5)
Thyroid disease	27 128 (4.5)	8 423 (6.5)
Hyperlipidaemia	16 244 (2.7)	38 575 (29.8)
Hypertension	173 101 (28.8)	68 538 (53.0)
Other circulatory disease	239 900 (40.0)	79 879 (61.8)
Dementia	3 932 (0.7)	329 (0.3)
Cancer	32 535 (5.4)	6 246 (4.8)
Prior use of:		
HRT (within 1 year)	42 796 (7.1)	8 394 (6.5)
Antipsychotics (within 6 months)	10 360 (1.7)	1 552 (1.2)
Antidepressants (within 6 months)	56 947 (9.5)	15 165 (11.7)
Oral steroid (within 6 months)	9 033 (1.5)	2 240 (1.7)
Inhaled steroid (within 6 months)	40 316 (6.7)	9 664 (7.5)
Aspirin	68 776 (11.5)	62 728 (48.5)
Nitrates	42 338 (7.1)	37 393 (28.9)
Nonstatin/fibrate lipid lowerers	3 792 (0.6)	5 529 (4.3)
Fibrates (within 3 months)	2 383 (0.4)	3 454 (2.7)
CYP450 3A4 inhibitor (within 3 months)	11 423 (1.9)	8 610 (6.7)
β-Blocker	115 213 (19.2)	62 254 (48.2)
Ca^{++} blocker/K^{+} activator	80 938 (13.5)	46 894 (36.3)
Diuretics	143 879 (24.0)	56 433 (43.7)
Positive inotrope	14 703 (2.5)	5 434 (4.2)
Antihypertensives	86 838 (14.5)	52 500 (40.6)
Other cardiovascular drugs	21 141 (3.5)	14 230 (11.0)

*Matching variable.

Table 2

Type of statin used

	n	%
Any statin exposure	129 288	
Rosuvastatin only*	1 126	0.9
Simvastatin only	50 465	39.0
Atorvastatin only	26 628	20.6
Pravastatin only*	6 904	5.3
Fluvastatin only	1 323	1.0
Cerivastatin only	597	0.5
Mixed use	42 245	32.7

*Lipophobic statin, the others are lipophilic.

one-third of patients prescribed a statin were prescribed more than one type of statin at some time. Relatively few patients, <7% of all those exposed, had received treatment with lipophobic statins only (pravastatin or rosuvastatin).

Table 3 shows the results for outcomes for which both short- and long-term effects might be expected. There was no clear evidence for an effect on the risk of infection. A small reduced risk of pneumonia was seen [HR 0.84, 99% confidence interval (CI) 0.74, 0.95], but the risk of urinary tract infections (HR 1.05, 99% CI 1.00, 1.11) and of other respiratory infections (HR 1.09, 99% CI 1.05, 1.13) was marginally increased. Among people diagnosed with influenza, there was no clear evidence of a protective effect of statins on the risk of pneumonia or death in the subsequent 6 months (HR 0.84, 99% CI 0.39, 1.80), although power was limited. There was a markedly increased risk of myositis or myolysis in the first year after the index date (adjusted HR 5.57, 99% CI 1.93, 16.07): the risk remained elevated but to a lesser extent (HR 2.38) throughout the follow-up period. There was an increased risk of incident liver disease in the first year after the index date (adjusted HR 1.51, 99% CI 1.19, 1.91), but little or no increased risk after this time. Even in the first year, the absolute increased risk of liver disease was relatively low (0.44% in the exposed group compared with 0.28% in the unexposed). There was a small but significant increased risk of diagnosed hypersensitivity reactions both in the first year and during longer follow-up. There was no evidence of an increased risk of anaemia, thrombocytopenia, Guillain–Barre syndrome, alopecia or pancreatitis.

Table 4 shows the results for outcomes for which we excluded the first year of follow-up. Overall, there was no effect on the incidence of all cancers or on gastrointestinal, prostatic and breast cancer individually. Statin use was not associated with an effect on all fractures or specifically on hip fractures. No effect was observed on the risk of venous thromboembolism, Parkinson's disease, amyotrophic lateral sclerosis or upper gastrointestinal haemorrhage. The risks of both cataract (HR 1.09, 99% CI 1.02, 1.16) and age-related macular degeneration (HR 1.17, 99% CI 1.00, 1.38) were slightly raised but of borderline statistical significance. No effect was seen on a range of autoimmune diseases: multiple sclerosis, rheumatoid arthritis, psoriasis or systemic lupus erythematosus. A protective effect against dementia was observed (HR 0.81, 99% CI 0.69, 0.96). The majority of cases were diagnosed with vascular

Table 3

Outcomes where short-term effects may be apparent—all time periods after the index date and first 12 months shown separately

Outcome	Statin exposure	Median follow-up (years)	No. of outcomes (%)	Hazard ratio (99% CI) adjusted for age and sex	Hazard ratio (99% CI) fully adjusted*
Infections:					
UTI	Unexposed	4.0	46 894 (9.1)	1.23 (1.19, 1.28)	1.05 (1.00, 1.11)
	Exposed	3.6	5 829 (9.9)		
Pneumonia	Unexposed	4.2	8 004 (1.4)	1.04 (0.95, 1.14)	0.84 (0.74, 0.95)
	Exposed	3.8	833 (1.2)		
Pneumonia/death 6 months post-flu†	Unexposed		262 (5.8)	0.63 (0.38, 1.03)	0.84 (0.39, 1.80)
	Exposed		29 (3.6)		
Other RTI	Unexposed	3.8	71 224 (15.7)	1.27 (1.23, 1.31)	1.09 (1.05, 1.13)
	Exposed	3.4	9 052 (18.1)		
Myositis/myolysis‡	Unexposed	4.2	192 (0.03)	3.82 (2.66, 5.49)	2.38 (1.36, 4.16)
	Exposed	3.6	69 (0.11)		
1st year only	Unexposed		35 (0.01)	8.05 (4.17, 15.53)	5.57 (1.93, 16.07)
	Exposed		30 (0.04)		
Guillain–Barre syndrome	Unexposed	4.2	75 (0.01)	1.40 (0.61, 3.22)	0.74 (0.23, 2.37)
	Exposed	3.8	11 (0.02)		
1st year only§	Unexposed		16 (<0.01)	–	–
	Exposed		3 (<0.01)		
Hepatic disorders	Unexposed	4.2	7 808 (1.3)	1.34 (1.23, 1.46)	1.11 (0.98, 1.24)
	Exposed	3.8	1 093 (1.6)		
1st year only	Unexposed		1 618 (0.28)	1.66 (1.41, 1.95)	1.51 (1.19, 1.91)
	Exposed		296 (0.44)		
Anaemia	Unexposed	4.2	12 242 (2.1)	1.47 (1.38, 1.57)	0.99 (0.91, 1.08)
	Exposed	3.8	1 785 (2.6)		
1st year only	Unexposed		2 172 (0.37)	1.46 (1.26, 1.70)	1.12 (0.91, 1.37)
	Exposed		334 (0.49)		
Thrombocytopenia	Unexposed	4.2	855 (0.14)	1.28 (0.99, 1.66)	1.05 (0.74, 1.48)
	Exposed	3.8	111 (0.16)		
1st year only	Unexposed		41 (0.04)	1.16 (0.62, 2.18)	0.82 (0.37, 1.84)
	Exposed		14 (0.04)		
Hypersensitivity	Unexposed	4.1	18 242 (3.1)	1.31 (1.24, 1.38)	1.14 (1.05, 1.23)
	Exposed	3.7	2 569 (3.7)		
1st year only	Unexposed		4 554 (0.76)	1.42 (1.28, 1.57)	1.35 (1.17, 1.56)
	Exposed		740 (1.1)		
Pancreatitis	Unexposed	4.2	1 213 (0.20)	1.22 (0.98, 1.52)	0.91 (0.68, 1.22)
	Exposed	3.8	156 (0.23)		
1st year only	Unexposed		244 (0.04)	1.22 (0.75, 1.96)	0.83 (0.44, 1.57)
	Exposed		33 (0.05)		
Alopecia	Unexposed	4.2	3 280 (0.55)	1.37 (1.21, 1.56)	1.16 (0.98, 1.39)
	Exposed	3.8	489 (0.71)		
1st year only	Unexposed		706 (0.12)	1.46 (1.13, 1.89)	1.35 (0.93, 1.94)
	Exposed		120 (0.17)		

*Adjusted for age, sex, propensity score, year of index date, first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia, first use of any of the following post-index date: aspirin, nitrates, fibrates, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs. †Analysis restricted to patients with a diagnosis of influenza between 1 October and 1 March in any year from 1995 to 2006. ‡Excluding 4953 patients exposed to cerivastatin (now withdrawn because of its established effects on rhabdomyolysis). §Too few outcomes to calculate an effect measure.

dementia or unspecified dementia. The effect was similar for Alzheimer's and non-Alzheimer's dementia, but the number of people diagnosed with Alzheimer's disease was relatively small.

Cancer: secondary analyses

Table 5 presents the results for all cancers stratified by duration of follow-up. There was no clear pattern of effect with increasing duration of follow-up. Similarly, analyses stratified on duration of follow-up for the individual cancer types (gastrointestinal, prostate, breast) showed no significant effects (data not shown, available on request). There was also no evidence of a dose–response relationship, with the HR (all cancers) for an average daily dose of 10 mg being 1.11, for 20 mg 1.00 and for 30 mg 0.96. The results for lipophilic or lipophobic statins were similar (data not shown).

The results for outcomes other than cancer did not vary with longer follow-up. For example, after ≥4 years of follow-up, the HR for all fractures was 1.06 (compared with 1.02 overall) and for cataract was 1.05 (compared with 1.08 overall).

Table 4

Outcomes with more longer term onset: first 12 months after index date excluded

Outcome	Statin exposure	Median follow-up (years)	No. of outcomes (%)	Hazard ratio (99% CI) adjusted for age & sex	Hazard ratio (99% CI) fully adjusted*
Cancer					
All forms	Unexposed	4.4	24 013 (4.6)	1.03 (0.98, 1.09)	1.03 (0.96, 1.11)
	Exposed	4.3	2 471 (4.2)		
GI	Unexposed	4.4	2 715 (0.49)	1.05 (0.89, 1.23)	1.08 (0.86, 1.36)
	Exposed	4.3	278 (0.46)		
Prostate†	Unexposed	4.7	3 213 (1.2)	1.02 (0.88, 1.19)	1.06 (0.86, 1.30)
	Exposed	4.5	312 (1.1)		
Breast‡	Unexposed	4.2	2 880 (1.1)	1.06 (0.91, 1.23)	1.17 (0.95, 1.43)
	Exposed	4.1	324 (1.1)		
Dementia					
All forms	Unexposed	4.5	4 765 (0.86)	0.89 (0.78, 1.02)	0.81 (0.69, 0.96)
	Exposed	4.3	407 (0.67)		
Alzheimer's	Unexposed	4.5	682 (0.12)	0.66 (0.44, 0.99)	0.81 (0.49, 1.35)
	Exposed	4.3	43 (0.07)		
Non-Alzheimer's	Unexposed	4.5	4 341 (0.79)	0.92 (0.80, 1.05)	0.82 (0.69, 0.97)
	Exposed	4.3	380 (0.62)		
AMD	Unexposed	4.4	3 867 (0.70)	1.42 (1.26, 1.61)	1.17 (1.00, 1.38)
	Exposed	4.3	528 (0.87)		
Cataract	Unexposed	4.4	24 446 (4.7)	1.41 (1.35, 1.48)	1.09 (1.02, 1.16)
	Exposed	4.2	3 254 (5.6)		
Fractures					
All forms	Unexposed	4.4	21 771 (4.7)	1.06 (1.01, 1.12)	1.02 (0.95, 1.10)
	Exposed	4.2	2 424 (4.7)		
Hip	Unexposed	4.4	4 151 (0.76)	0.96 (0.84, 1.10)	0.97 (0.82, 1.16)
	Exposed	4.3	391 (0.64)		
Venous thromboembolism	Unexposed	4.4	5 550 (1.0)	1.18 (1.06, 1.31)	1.02 (0.88, 1.18)
	Exposed	4.3	649 (1.1)		
Multiple sclerosis	Unexposed	4.5	257 (0.05)	0.92 (0.54, 1.57)	1.08 (0.51, 2.27)
	Exposed	4.3	26 (0.04)		
Parkinson's disease	Unexposed	4.4	2 102 (0.38)	1.12 (0.94, 1.34)	0.97 (0.77, 1.23)
	Exposed	4.3	227 (0.37)		
Rheumatoid arthritis	Unexposed	4.4	2 305 (0.4)	0.95 (0.80, 1.14)	0.93 (0.73, 1.18)
	Exposed	4.3	227 (0.4)		
Psoriasis	Unexposed	4.4	4 797 (0.89)	1.23 (1.10, 1.37)	1.08 (0.92, 1.26)
	Exposed	4.3	622 (1.1)		
Gastrointestinal bleed	Unexposed	4.4	4 241 (0.77)	1.34 (1.19, 1.50)	0.93 (0.79, 1.09)
	Exposed	4.3	558 (0.93)		
Depression	Unexposed	4.3	45 330 (10.7)	1.26 (1.22, 1.31)	1.01 (0.96, 1.06)
	Exposed	4.2	5 680 (13.0)		
Systemic lupus erythematosus	Unexposed	4.5	156 (0.03)	1.62 (0.94, 2.77)	1.08 (0.50, 2.36)
	Exposed	4.3	27 (0.04)		
Pulmonary fibrosis	Unexposed	4.5	635 (0.11)	1.34 (0.99, 1.81)	0.97 (0.65, 1.45)
	Exposed	4.3	82 (0.13)		
Amyotrophic lateral sclerosis	Unexposed	4.5	183 (0.03)	0.93 (0.48, 1.78)	1.11 (0.46, 2.65)
	Exposed	4.3	17 (0.03)		

*Adjusted for age, sex, propensity score, year of index date, first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia, first use of any of the following post-index date: aspirin, nitrates, fibrates, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs. †Analysis restricted to men only. ‡Analysis restricted to women only.

Effects of treatment status changing during follow-up

Our primary analysis was analogous to a randomized controlled trial: people newly prescribed a statin were matched to people who had not been prescribed a statin, and subsequent health outcomes compared. The effect measures obtained therefore provide estimates of the health consequences of the decision to initiate statin therapy in clinical practice. The design also meant we avoided assembling biased comparison groups: either an unexposed group of people who were never at risk of exposure, or an exposed group selected because they adhered to their therapy [21]. Our design therefore closely resembled the Heart Protection Study randomized trial for which the effect sizes reported were based on initial treatment allocation. Among people allocated to placebo in the Heart Protection Study, 17% initiated a statin during follow-up, whereas among those allocated to a statin, 15%

Table 5

All cancers stratified by duration of follow-up

Patient group	Statin exposure	No. of outcomes – (%)	Hazard ratio (99% CI) adjusted for age & sex	Hazard ratio (99% CI) fully adjusted*
All patients				
Year of follow-up				
Year 1	Unexposed	6112 (1.1)	0.80 (0.71, 0.91)	0.93 (0.80, 1.09)
	Exposed	509 (0.8)		
Year 2	Unexposed	5303 (1.0)	0.94 (0.83, 1.06)	1.01 (0.86, 1.18)
	Exposed	501 (0.9)		
Year 3	Unexposed	4762 (1.0)	0.97 (0.85, 1.10)	0.93 (0.79, 1.09)
	Exposed	462 (0.9)		
Year 4	Unexposed	4241 (1.1)	1.02 (0.89, 1.16)	0.98 (0.82, 1.16)
	Exposed	428 (1.1)		
Year 5	Unexposed	3318 (1.1)	1.12 (0.97, 1.29)	1.15 (0.95, 1.39)
	Exposed	374 (1.2)		
Year 6	Unexposed	2470 (1.2)	1.03 (0.87, 1.21)	1.06 (0.84, 1.33)
	Exposed	268 (1.1)		
Year 7	Unexposed	1718 (1.2)	1.14 (0.94, 1.38)	1.23 (0.94, 1.60)
	Exposed	210 (1.3)		
Year 8+†	Unexposed	2201 (2.3)	1.11 (0.87, 1.43)	1.39 (0.97, 1.98)
	Exposed	228 (2.1)		

*Adjusted for age, sex, propensity score, year of index date, first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia, first use of any of the following post-index date: aspirin, nitrates, fibrates, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs. †Median duration of follow-up after 8 years was 1.4 years in the unexposed group and 1.2 years in the exposed group.

were not taking a statin after 5 years [1]. These rates were broadly similar in our study: during the observation period, 9.9% (59 643/600 241) of the unexposed group initiated statin therapy and 10.9% (14 119/129 288) of the exposed group stopped statin therapy. Among the unexposed group, starting a statin after the index date was predicted by adverse risk factors for a range of outcomes, such as smoking, higher BMI and male sex. Thus only including data for these people up until the time they started statin therapy would have the effect of making the unexposed group more healthy compared with the exposed group, a form of selection bias that introduced a new layer of confounding not dealt with in the study design. The result was that a re-analysis in which peoples' observation periods were censored at the time of changing treatment found small increased risks for a range of adverse outcomes not seen in the primary analysis. However, the observed HRs were all very small (not shown: available on request) and likely to have arisen from uncontrolled confounding.

Validation of design: vascular outcomes

Table 6 shows the HRs for major vascular outcomes and mortality amongst patients with a diagnosis of atherosclerosis, along with comparison data from the Heart Protection Study, the largest randomized trial to date [1]. The fully adjusted HRs with 95% CIs were 0.78 (0.74, 0.82) for mortality, 0.86 (0.76, 0.97) for myocardial infarction and 0.86 (0.77, 0.97) for stroke. These results are consistent with those seen in the Heart Protection Study. Comparing the two studies, the CIs for all three outcomes overlap, although the protective effect against mortality was slightly greater in our study, whereas the effect on myocardial infarction and stroke was marginally lower.

Discussion

Other than the known effects on cardiovascular disease and a protective effect against dementia, we found little evidence to support wide-ranging effects of statins on health outcomes. We found no evidence of an increased risk of cancer even after ≥8 years follow-up.

Strengths and weaknesses

When assessing drug effects in observational studies, selection bias and confounding are major challenges. We validated our study design by demonstrating similar results for vascular outcomes and mortality to those found in randomized controlled trials. This suggests that our use of matching, propensity scores and adjustment for a wide range of factors was successful in reducing confounding that may have affected the results of previous observational studies. The other main strengths of the study were that it was very large and statistically powerful; Drug prescriptions in the THIN database are generated by practice computers ensuring the accuracy of the electronic prescribing records; prescription data were highly detailed and recorded prior to people developing the outcome, with no potential for recall bias. Our study was based on routine clinical data and a potential weakness might relate

Table 6
Major vascular outcomes and all cause mortality

Outcome	Statin exposure	*n* (median patient-years at risk)	No. of outcomes (%)	Hazard ratio (95% CI) adjusted for age and sex	Hazard ratio (95% CI) fully adjusted*	Hazard ratio observed in RCT†
Mortality	Unexposed	53 598 (5.0)	10 996 (20.5)	0.75 (0.72, 0.78)	0.79 (0.75, 0.83)	0.87 (0.81, 0.94)
	Exposed	30 024 (5.0)	3 373 (11.2)			
First MI	Unexposed	42 860 (4.8)	1 589 (3.7)	1.20 (1.09, 1.31)	0.87 (0.77, 0.98)	0.73 (0.67, 0.79)
	Exposed	18 431 (4.6)	661 (3.6)			
First stroke	Unexposed	44 858 (5.0)	1 701 (3.8)	0.91 (0.83, 0.99)	0.86 (0.77, 0.96)	0.75 (0.66, 0.85)
	Exposed	26 706 (5.0)	743 (2.8)			

*Adjusted for age, sex, propensity score, year of index date, first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidaemia, hypertension, other circulatory disease, cancer, dementia, first use of any of the following post-index date: aspirin, nitrates, fibrates, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, or other cardiovascular drugs. †Data from the Heart Protection Study [1].

to the quality of the morbidity data. The THIN research database overlaps considerably with the well-established General Practice Research Database (GPRD), for which high levels of data quality have been established [22]. The clinical software system used to enter data is the same in THIN and GPRD, and >100 general practices (over one-third of the total) that contribute data to THIN contribute the same data to the GPRD. Data quality in the two databases has been shown to be similar [16]. Well-established associations between diseases and between drug exposures and health outcomes have been reproduced using THIN, supporting validity [16].

Not all people prescribed statins will adhere to the therapy. However, in sensitivity analyses, scenarios such as noncompliance of 20% amongst statin users and undetected statin use of 10% amongst non-users had no material effect on the results. In June 2004 statins became available for sale in pharmacies without prescription in the UK, so incomplete ascertainment of exposure was a possibility after this date. Restricting our analyses to the period prior to June 2004 did not affect our results.

Comparison of results with previous studies

Experimental studies in humans and animals have demonstrated anti-inflammatory effects of statins [23]. There are no published randomized trials assessing the effects of statins on infection, although two trials in severe infection are underway (ClinicalTrials.gov identifiers NCT00452608 and NCT00450840). A large cohort study has found a reduced risk of hospital admission for sepsis (HR 0.81, 95% CI 0.72, 0.91) [24]. A subsequent study found no protective effect of statins among people admitted to hospital with pneumonia [25], and it has been suggested that previously reported beneficial effects could have been due to a healthy user effect [17]. We found no clear evidence of a protective effect against infections. The lack of any effect on fractures in our study disagrees with earlier reports of a protective effect [26]. However, later work has suggested that the protective effect observed may have been due to confounding [27, 28]. A protective effect against venous thromboembolism has been found in some [29, 30] but not all [31] studies. We found no evidence to support a beneficial effect. Previous reports of effects on cataract [10, 32, 33] and age-related macular degeneration [11, 34] have been inconsistent. Our study suggests that statins have minimal or no effect on these eye diseases. We found no evidence to support a reported protective effect against Parkinson's disease [35], multiple sclerosis [36], rheumatoid arthritis [37, 38], psoriasis [39] or effects on systemic lupus erythematosus [39, 40]. Concern that statins are associated with an increased risk of upper motor neuron lesions was raised based on spontaneous reports to the World Health Organization Programme for International Drug Monitoring [13]. We found no evidence to support these concerns.

The risk of cancer in our study was not increased among statin users during follow-up overall, nor was there

any clear evidence of increased risk even after ≥8 years of follow-up. Concerns about possible carcinogenic effects of statins have previously been raised [7], notably following the increased risks of cancer observed among people allocated to statins in the CARE [41] and PROSPER [42] randomized trials. A recent re-analysis of low-density lipoprotein-cholesterol (LDL-C) levels among people allocated to statins in randomized trials found an increased risk of cancer associated with lower LDL-C levels [43]. Although we did not have data on LDL-C levels post treatment, we found no evidence of any dose–response effect of statins on cancer risk. Recent systematic reviews of both trials and observational studies have concluded there was no evidence to support an increased short-term risk of cancer, but that longer term risks could not be excluded [12, 44]. In the recently published 10-year follow-up of the West of Scotland Coronary Prevention Trial, statins had no effect on cancer risk [45]. The trial findings for cancer were almost identical to those observed in our study, further increasing the credibility of our results for a range of other outcomes.

We observed a protective effect against dementia. Previous studies have been inconsistent, with marked protective effects seen in some [8, 46], but no effect in others [47, 48]. The protective effect we observed was similar for both Alzheimer's disease and for non-Alzheimer's. Although the diagnostic classification was likely to be somewhat imprecise, the overlap between vascular and Alzheimer's dementia is increasingly recognized [49]. A protective effect against vascular dementia is consistent with the established effects of statins on cerebrovascular disease. A protective effect against Alzheimer's disease is consistent with a recent report of a brain autopsy study of 110 people who were cognitively normal when first recruited [50]. Lower levels of neurofibrillary tangles were found in the brains of statin users compared with non-users.

Adverse drug reactions: risks in routine clinical practice

In randomized trials, the excess rate of myopathy was around 1/10 000 person-years of treatment [51]. In our study the rate of any diagnosed muscle problems was 4.1/10 000 in the first year of treatment. An excess risk of rhabdomyolysis of around 3–4/100 000 person-years was observed in randomized trials [51]; we observed no cases in >500 000 person-years of observation time exposed to statins. Thus, although our data suggest the level of milder muscle problems associated with statins is higher in clinical practice than in randomized trials, the incidence of severe problems may be lower. Although in randomized trials a small excess risk of elevated liver transaminases was seen, this did not translate into an increased risk of clinical liver disease [51]. However, we did see an increased risk of clinically diagnosed liver disease among statin users in the first year after the initiation of therapy. We identified no excess risk of other adverse effects that have been suggested to be caused by statins: anaemia [52], thrombocytopenia [53], Guillain–Barre syndrome [32], alopecia [54] or pancreatitis [55].

Overall, our results suggest that most of the reported pleiotropic effects of statins may be attributable to selection bias and confounding [17, 18]. Statins may reduce the risk of dementia, but a range of other reported benefits was not found. Although our results provide some reassurance about the medium to long-term effects of statins on cancer risk, there is clearly a need for continued study of the long-term effects of these commonly used drugs. Among statin users, adverse effects on muscle sufficient to present to the general practitioner are somewhat less common in clinical practice than observed in randomized trials, whereas clinically diagnosed liver disease is more common. However, these adverse effects remain rare and are outweighed by the established beneficial effects of statins on cardiovascular disease and mortality.

Competing interests

None to declare.

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