Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database

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ABSTRACT
Objective To quantify the unintended effects of statins according to type, dose, and duration of use.

Design Prospective open cohort study using routinely collected data.

Setting 368 general practices in England and Wales supplying data to the QResearch database.

Participants 2 004 692 patients aged 30-84 years of whom 225 922 (10.7%) were new users of statins: 159 790 (70.7%) were prescribed simvastatin, 50 328 (22.3%) atorvastatin, 8103 (3.6%) pravastatin, 4497 (1.9%) rosvuastatin, and 3204 (1.4%) fluvastatin.

Methods Cox proportional hazards models were used to estimate effects of statin type, dose, and duration of use. The number needed to treat (NNT) or number needed to harm (NNH) were calculated and numbers of additional or fewer cases estimated for 10 000 treated patients.

Main outcome measure First recorded occurrence of cardiovascular disease, moderate or serious myopathic events, moderate or severe liver dysfunction, acute renal failure, venous thromboembolism, Parkinson's disease, dementia, rheumatoid arthritis, cataract, osteoporotic fracture, gastric cancer, oesophageal cancer, colon cancer, lung cancer, melanoma, renal cancer, breast cancer, or prostate cancer.

Results Individual statins were not significantly associated with risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, colon cancer, lung cancer, melanoma, renal cancer, breast cancer, or prostate cancer. Statin use was associated with decreased risks of oesophageal cancer but increased risks of moderate or serious liver dysfunction, acute renal failure, moderate or serious myopathy, and cataract. Adverse effects were similar across statin types for each outcome except liver dysfunction where risks were highest for fluvastatin. A dose-response effect was apparent for acute renal failure and liver dysfunction. All increased risks persisted during treatment and were highest in the first year. After stopping treatment the risk of cataract returned to normal within a year in men and women. Risk of oesophageal cancer returned to normal within 1-3 years in women and within 1-3 years in men. Risk of acute renal failure returned to normal within 1-3 years in men and women, and liver dysfunction within 1-3 years in women and from three years in men. Based on the 20% threshold for cardiovascular risk, for women the NNT with any statin to prevent one case of cardiovascular disease over five years was 37 (95% confidence interval 27 to 64) and for oesophageal cancer was 1266 (850 to 3460) and for men the respective values were 33 (24 to 57) and 1082 (711 to 2807). In women the NNH for an additional case of acute renal failure over five years was 434 (284 to 783), of moderate or severe myopathy was 259 (186 to 375), of moderate or severe liver dysfunction was 136 (109 to 175), and of cataract was 33 (28 to 38). Overall, the NNHs and NNTs for men were similar to those for women, except for myopathy where the NNH was 91 (74 to 112).

Conclusions Claims of unintended benefits of statins, except for oesophageal cancer, remain unsubstantiated, although potential adverse effects at population level were confirmed and quantified. Further studies are needed to develop utilities to individualise the risks so that patients at highest risk of adverse events can be monitored closely.

INTRODUCTION
Cardiovascular disease is the leading cause of premature death and a major cause of disability in the United Kingdom.1 Some meta-analyses and national policies support the use of statins to reduce the risk of cardiovascular disease among high risk patients.2-5 Given that statins are already among the most widely prescribed medicines and that their use is likely to continue to increase, both their intended and their unintended effects and how these vary by type, dose, and duration of use need to be quantified in large representative populations. This information can then be used to inform policy and clinical practice by supplementing information from meta-analyses of clinical trials, which tend to lack sufficient detail, duration of follow-up, or sufficient power to make some of the relevant comparisons.2 5 8-9 Also, meta-analyses can be subject to selection bias as trial...
Table 1 | Baseline characteristics of study population of new users and non-users of statins. Values are numbers (percentages) unless stated otherwise

| Characteristics                        | New users (n=225 922) | Non-users (n=1 778 770) |
|----------------------------------------|-----------------------|-------------------------|
| **Gender**                             |                       |                         |
| Women                                  | 104 774 (46.4)        | 990 423 (51.1)          |
| Men                                    | 121 148 (53.6)        | 869 347 (48.9)          |
| **Ethnicity**                          |                       |                         |
| Recorder                               | 121 355 (53.7)        | 569 466 (32.0)          |
| White or not stated                    | 215 077 (95.2)        | 1 699 991 (95.6)        |
| Indian                                 | 2861 (1.3)            | 13 398 (0.8)            |
| Pakistani                              | 1 658 (0.7)           | 7 562 (0.4)             |
| Bangladeshi                            | 679 (0.3)             | 3 226 (0.2)             |
| Other Asian                            | 759 (0.3)             | 7 321 (0.4)             |
| Caribbean                              | 1788 (0.8)            | 9 853 (0.6)             |
| Black African                          | 834 (0.4)             | 15 358 (0.9)            |
| Chinese                                | 316 (0.1)             | 401 (0.2)               |
| Other ethnic group                     | 1950 (0.9)            | 18 046 (1.0)            |
| **Mean (SD) age (years)**              | 57.2 (11.7)           | 44.4 (13.7)             |
| **Mean (SD) Townsend score**           | ~0.5 (3.3)            | ~0.3 (3.4)              |
| **Mean (SD) systolic blood pressure (mm Hg)** | 141.1 (19.1) | 129.9 (19.1) |

**Liver function test:**
- Recorded at baseline or before statins: 131 354 (58.1) 162 207 (9.1)
- Recorded at follow-up: 193 586 (85.7) 594 750 (33.4)

**Creatine kinase concentration:**
- Recorded at baseline or before statins: 15 724 (7.0) 8642 (0.5)
- Recorded at follow-up: 62 706 (27.8) 43 333 (2.4)

**Body mass index recorded:** 207 644 (91.9) 1 341 863 (75.4)

**Mean (SD) body mass index:** 28.3 (4.9) 26.6 (4.6)

**Smoking status recorded:** 224 982 (99.6) 1 615 527 (90.8)

**Body mass index and smoking status recorded:** 207 494 (91.8) 1 330 320 (74.8)

**Non-smoker** 109 406 (48.4) 912 149 (51.3)

**Former smoker** 74 277 (32.9) 285 271 (16.0)

**Current smoker:**
- Amount not recorded: 2286 (1.0) 55 859 (3.1)
- Light: 14 447 (6.4) 116 035 (6.5)
- Moderate: 13 880 (6.1) 142 469 (8.0)
- Heavy: 10 686 (4.7) 107 744 (5.8)

**Comorbidities:**
- Atrial fibrillation: 11 656 (5.2) 13 730 (0.8)
- Congestive cardiac failure: 7457 (3.3) 9026 (0.5)
- Cardiovascular disease: 56 943 (25.2) 31 038 (1.7)
- Peripheral vascular disease: 8801 (3.9) 12 656 (0.7)
- Treated hypertension†: 97 782 (43.3) 106 582 (6.0)
- Chronic kidney disease stage 3b+: 18 768 (8.3) 17 114 (1.0)
- Type 1 diabetes: 2843 (1.3) 2633 (0.2)
- Type 2 diabetes: 47 703 (21.1) 18 243 (1.0)
- Endocrine disorders: 2749 (1.2) 9347 (0.5)
- Malabsorption: 2156 (1.0) 11 079 (0.6)
- Rheumatoid arthritis: 3652 (1.6) 11 762 (0.7)
- Systemic lupus erythematosus: 264 (0.1) 1070 (0.1)
- Asthma: 23 307 (10.3) 1 394 85 (7.8)
- Falls: 10 333 (4.6) 21 805 (1.2)
- Endocrine disorders: 2749 (1.2) 9347 (0.5)
- Any cancer: 10 727 (4.8) 32 883 (1.9)
- Hypothyroidism: 12 378 (5.5) 30 357 (1.7)
- Chronic liver disease: 1016 (0.5) 3966 (0.2)
- Colorectal polyps: 1215 (0.5) 1989 (0.1)
- Family history of breast cancer (women only): 3492 (1.6) 40 519 (2.3)
- Benign breast disease (women only): 4343 (1.9) 32 187 (1.8)

**Prescribed drugs:**
- Corticosteroids: 13 868 (6.1) 44 517 (2.5)
- Selective serotonin reuptake inhibitors: 16 614 (7.4) 97 712 (5.5)
- Tricyclic antidepressants: 18 469 (8.2) 69 674 (3.9)
- Depression: 13 487 (6.0) 71 557 (4.0)
- Hormone replacement therapy: 5343 (2.4) 63 972 (3.6)
- Oral contraceptives: 303 (0.1) 72 334 (4.1)
- Non-steroidal anti-inflammatory drugs (including aspirin): 125 127 (55.4) 362 589 (20.4)
- Antipsychotic drugs: 10 955 (4.9) 42 683 (2.4)

*Composite variable that includes recorded diagnosis of hypertension and treatment, which could include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone, β blockers, thiazides, or calcium channel blockers.

Other patients tend to be predominantly white, younger, and more healthy than real world populations, thus limiting generalisability and external validity.8

We carried out a large population based study to examine a range of clinical outcomes that have been found to be positively or negatively associated with statin use, including moderate or serious myopathic events,9-13 Parkinson’s disease,14 dementia,15 16 liver dysfunction,8 9 17 venous thromboembolism,14 rheumatoid arthritis,19 cataract,20 common cancers,9 21-24 and osteoporotic fracture.25 27 We also included acute renal failure as an outcome because of concerns published both in The Lancet9 and on the Food and Drug Administration website,29 together with reports of proteinuria in patients prescribed rosuvastatin.30

**METHODS**

We carried out a prospective cohort study in a large population of primary care patients using version 24 of the general practice research database, QResearch. All practices in England and Wales that had been using the computer based Egton Medical Information System (EMIS) for at least a year were included. Two thirds of the practices were randomly allocated to the study dataset and one third was retained for a subsequent study. We identified an open cohort of patients aged 30-84 years from those registered with the practices between 1 January 2002 and 30 June 2008. We excluded patients without a postcode related Townsend score (about 4% of the population) and those who had been prescribed statins before, or were current users on, the date the study started. Entry to the cohort was the latest of the date the study started, 12 months after the patient registered with the practice, or, for new users of statins, the date of their first prescription. We censored patients at the earliest date of the diagnosis of interest, death, deregistration with the practice, last upload of computerised data, or the date the study ended (31 December 2008).

**Clinical outcomes**

We examined several outcomes, identified from Read codes recorded in the patients’ electronic records (codes available from authors on request): acute renal failure,28 30; venous thromboembolism;14 Parkinson’s disease14; dementia15 16; rheumatoid arthritis,19 cataract,20 common cancers,9 21-24 and osteoporotic fracture (spine, hip, or wrist); common cancers (gastric, colon, oesophageal, lung, renal, breast, prostate, melanoma); moderate or severe liver dysfunction, defined as an alanine transaminase concentration >120 IU/l (that is, more than three times the upper limit of normal) among patients without diagnosed chronic liver disease, as this is the severity at which guidelines recommend treatment is discontinued33 1; and moderate or serious myopathic events,9 11 12 which for our study was defined as a diagnosis of myopathy or rhabdomyolysis or a raised creatine kinase concentration of four or more times the upper limit of normal.)
Table 2: Crude incidence per 10 000 person years for study outcomes in both men and women

| Outcomes                  | Women                      | Men                        |
|---------------------------|----------------------------|----------------------------|
|                           | Incident cases | Person years | Rate per 10 000 person years (95% CI) | Incident cases | Person years | Rate per 10 000 person years (95% CI) |
| Cataract                  | 22 010         | 4 638 731     | 47.45 (46.83 to 48.08) | 14 531         | 4 434 520     | 32.77 (32.24 to 33.31) |
| Osteoporotic fracture     | 13 475         | 4 646 441     | 29.0 (28.52 to 29.49) | 4802           | 4 444 729     | 10.80 (10.50 to 11.11) |
| Breast cancer             | 9823           | 4 700 328     | 20.90 (20.49 to 21.32) | NA             | NA            | NA             |
| Prostate cancer           | NA             | NA            | NA             | 7129           | 4 486 286     | 15.89 (15.53 to 16.26) |
| Moderate or serious liver dysfunction | 7218         | 4 752 020     | 15.19 (14.84 to 15.54) | 7802           | 4 491 763     | 17.37 (16.99 to 17.76) |
| Venous thromboembolism    | 6628           | 4 708 712     | 14.08 (13.74 to 14.42) | 5571           | 4 475 491     | 12.45 (12.13 to 12.78) |
| Dementia                  | 5305           | 4 759 939     | 11.57 (11.26 to 11.87) | 3279           | 4 512 950     | 7.27 (7.02 to 7.52)   |
| Rheumatoid arthritis      | 3961           | 4 717 553     | 8.40 (8.14 to 8.66)   | 1769           | 4 498 971     | 3.93 (3.75 to 4.12)   |
| Lung cancer               | 2401           | 4 776 399     | 5.03 (4.83 to 5.23)   | 3600           | 4 519 197     | 7.97 (7.71 to 8.23)   |
| Parkinson’s disease       | 1534           | 4 768 474     | 3.22 (3.06 to 3.38)   | 2019           | 4 509 935     | 4.48 (4.29 to 4.68)   |
| Colon cancer              | 1970           | 4 769 095     | 4.13 (3.95 to 4.32)   | 2182           | 4 512 911     | 4.84 (4.64 to 5.04)   |
| Melanoma                  | 1174           | 4 767 753     | 2.46 (2.33 to 2.61)   | 896            | 4 516 849     | 1.98 (1.86 to 2.12)   |
| Acute renal failure       | 860            | 4 777 274     | 1.80 (1.68 to 1.92)   | 1109           | 4 519 879     | 2.45 (2.31 to 2.60)   |
| Oesophageal cancer        | 584            | 4 778 945     | 1.22 (1.13 to 1.33)   | 1225           | 4 521 683     | 2.71 (2.56 to 2.87)   |
| Moderate or serious myopathy | 518          | 4 777 929     | 1.08 (0.99 to 1.18)   | 888            | 4 520 960     | 1.96 (1.84 to 2.10)   |
| Gastric cancer            | 380            | 4 779 154     | 0.80 (0.72 to 0.88)   | 713            | 4 522 171     | 1.58 (1.47 to 1.70)   |
| Renal cancer              | 959            | 4 775 022     | 2.01 (1.89 to 2.14)   | 2037           | 4 512 131     | 4.51 (4.32 to 4.71)   |

Predic tor and exposure variables

We identified new users of statins during the study period, with the remaining patients classified as non-users. To correspond to an intention to treat analysis we classified statin use by type of statin first prescribed (atorvastatin, simvastatin, fluvastatin, pravastatin, or rosvuastatin). We examined starting dose using categories similar to those published elsewhere. When we found significant associations we used fractional polynomials to collapsing categories when data were insufficient to support analysis. We compiled a list of potential predictor variables, which included established risk factors for each outcome from the literature or existing risk prediction scores, using similar definitions when possible.

Statistical modelling

To estimate the hazard ratios for each outcome for type of statin first prescribed for men and women separately, we used Cox proportional hazards models to compare new users with non-users, adjusting for potential confounding variables. So that we considered first events only we excluded patients from the analysis of each outcome when they had a diagnosis of the outcome at or before the baseline date. We used multiple imputation to replace missing values for body mass index and smoking status and used these values in our main analyses. We carried out five imputations. When appropriate we used fractional polynomials to model non-linear risk relations with continuous variables. When we found significant associations for individual statins we examined the effects of dose. We tested for interactions between statin use and age and between smoking and deprivation and included significant interactions in the final models. We carried out two global tests; one to check that there was no overall effect of individual statins, and, if that test gave significant results a test for equality of effects of individual statins. When the hazard ratio was less than 0.80 or greater than 1.20 and was statistically significant at the 0.01 level we considered the effect of statins to be significant.

Time varying analyses

When associations for individual statins were significant, we used a time varying Cox regression analysis to examine the effects of duration of use and time since stopping any statin. We examined statins overall and by type. To determine the risk of each outcome within a year, 1-3 years, 3-5 years, and five or more years of taking statins we compared non-users with new users. We also determined change in risks after stopping statins, categorised as stopping treatment within a year, 1-3 years, and three or more years. The date of stopping statins was taken to be 90 days after the date of the last recorded prescription.

Self controlled case series analysis

In addition, we undertook post hoc self controlled case series analyses for the significant outcomes other than cancer. The case series methodology was originally developed to assess adverse events to vaccination but has a wider application. It can be used to determine the relative incidence of the outcome of interest for periods of drug use compared with periods of non-use in people with the outcome of interest. Inference is within individuals and hence implicitly controls for covariates that do not change over the study period.

For each outcome we selected the patients within the study cohort with the outcome of interest during the study period and ascertained dates when they started and finished taking statins. To improve adjustment for
age we included non-users along with new users during the study period. To estimate relative rate ratios we used conditional Poisson regression and adjusted for age in five year bands. We then determined the relative rate ratios for individual statins during the period of use and the washout period [1-182 days after stopping statins] compared with the baseline periods of non-use during each person’s observation time. We removed the time period in the 28 days before starting statins and the day on which the first prescription was issued. For these analyses we combined men and women. As the occurrence of an event may alter the probability of subsequent statin use we carried out an additional case series analysis restricted to new statin users and started the observation period at first use.44

Number needed to treat or number needed to harm
We calculated the number needed to treat (NNT) or number needed to harm (NNH) over five years for patients at high risk of cardiovascular disease based on a QRISK2 score of 20% or more, since this group is eligible for statin treatment. For each outcome we used Kaplan-Meier estimates to calculate the disease-free probability at five years for non-users of statins in those aged 35-74 years. For these calculations we identified a cohort of patients who entered the study on the latest of their registration date and 1 January 2002 and who had not been prescribed statins, or had the outcome of interest by that date. These patients were censored at the earliest date of the diagnosis of interest, first statin prescription, death, deregistration with the practice, last upload of computerised data, or date at end of study. We calculated adjusted hazard ratios for each outcome for all types of statin treatment combined, adjusting for potential confounding variables. We then used these adjusted hazard ratios and the disease-free probability to calculate the NNT or NNH for each outcome according to a published formula.45 To enable comparisons and supplement data published elsewhere we also used these values to calculate the number of additional cases per 10 000 patients treated over five years.

For cardiovascular disease, we used information from a recent meta-analysis of 10 primary prevention trials totalling over 70 000 patients with risk factors for cardiovascular disease but without cardiovascular disease at baseline who were treated with statins or placebo and followed up for a median of 4.1 years.7 The meta-analysis reported that the effects of statins on major coronary events and cerebrovascular events were not significantly different according to age, sex, or diabetes status.2 We combined the published results for major coronary events and cerebrovascular events using a random effects model to calculate a summary relative risk for cardiovascular disease in statin users compared with non-users. We only included trials that reported both outcomes, assuming that individual patients did not have both outcomes. The overall odds ratio for cardiovascular events associated with statin use in this meta-analysis was 0.76 (95% confidence interval 0.67 to 0.86), which is similar to that reported

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**Table 3** Risk associated with statin type both in men and in women for non-significant and marginal outcomes

| Outcomes                             | Adjusted hazard ratio (95% CI) |
|--------------------------------------|--------------------------------|
|                                      | Women | Men     |
| Rheumatoid arthritis:                |       |         |
| No statin                            | 1.00  | 1.00    |
| Simvastatin                          | 0.96  | (0.84 to 1.09) |
| Atorvastatin                         | 0.97  | (0.91 to 1.04) |
| Rosuvastatin                         | 1.00  | (0.92 to 1.09) |
| Pravastatin                         | 0.96  | (0.84 to 1.09) |
| Fluvastatin                         | 0.97  | (0.91 to 1.04) |
| No statin                            | 1.00  | 1.00    |
| Simvastatin                          | 0.96  | (0.84 to 1.09) |
| Atorvastatin                         | 0.97  | (0.91 to 1.04) |
| Rosuvastatin                         | 1.00  | (0.92 to 1.09) |
| Pravastatin                         | 0.96  | (0.84 to 1.09) |
| Fluvastatin                         | 0.97  | (0.91 to 1.04) |

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See web extra for variables that were adjusted for in hazard ratios. NA not applicable.
and to have comorbidities such as atrial fibrillation, tended to be older and were more likely to be men.

Of the new users, 159,790 (70.7%) had been prescribed simvastatin, 50,328 (22.3%) atorvastatin, 8,103 (3.6%) pravastatin, 4,497 (1.9%) rosuvastatin, and 3204 (1.4%) fluvastatin.

Table 4 shows the crude incidence of each outcome in men and women separately per 10,000 person years. Overall, there were 1,969 incident cases of acute renal failure, 12,199 of venous thromboembolism, 5,730 of rheumatoid arthritis, 36,541 of cataract, 3,553 of Parkinson’s disease, 8,874 of dementia, 18,277 of osteoporotic fracture, 1,093 of gastric cancer, 1,809 of oesophageal cancer, 4,152 of colon cancer, 6,001 of lung cancer, 2,070 of melanoma, 2,996 of renal cancer, 9,823 of breast cancer, 7,129 of prostate cancer, 15,020 of moderate or serious liver dysfunction, and 1,406 of moderate or serious myopathy. Sixty-two patients had both acute renal failure and moderate or serious myopathy.

### Non-significant and marginal clinical outcomes

The associations between statins and Parkinson’s disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, lung cancer, melanoma, renal cancer, breast cancer, and prostate cancer were not clinically significant and the overall tests for statins were not statistically significant (at \(P<0.01\)) (table 3).

Although the association between any statin and colon cancer was not significant in women, a significant effect was present in men (overall \(P=0.002\)). The risk of colon cancer was lowest among men prescribed pravastatin (adjusted hazard ratio 0.47, 95% confidence interval 0.28 to 0.86), although there was no evidence of a dose-response relation, and increased among men prescribed rosuvastatin (2.07, 1.29 to 3.21). Time varying analysis showed that the risk was increased after three years of treatment (3.27, 1.69 to 6.32) but returned to normal within a year of stopping treatment.

### Significant clinical outcomes

Outcomes significantly associated with statin use were myopathy, cataract, acute renal failure, oesophageal cancer, and moderate or serious liver dysfunction (table 4).

### Moderate or serious liver dysfunction

Overall, statins were associated with an increased risk of liver dysfunction in both men and women (table 4). In women there was some indication of differences between the effects of individual statins (overall test \(P=0.058\)). The highest risk was associated with fluvastatin (2.53, 1.84 to 3.47), which was significantly higher than that with simvastatin (1.52, 1.38 to 1.66). In men, differences between the effects of individual statins were significant (overall test \(P=0.0045\)). The highest risk was associated with fluvastatin (1.97, 1.43 to 2.72) and the lowest with pravastatin (1.21, 0.93 to 1.58).

A dose-response effect was evident in women, with an increased risk associated with higher doses.
| Risk of significant outcomes associated with type and dose of statin both in men and in women |
|-----------------------------------------------|
| Women                                      | Cases/total | Adjusted hazard ratio (95% CI) |
|-----------------------------------------------|
| Moderate or serious myopathy:                |            |                                |
| No statin                                   | 325/908 822 | 1.00                           |
| Simvastatin 10/20 mg/day                    | 81/46 056  | 2.91 (2.19 to 3.88)           |
| Simvastatin 40/80 mg/day                    | 43/27 775  | 3.30 (2.32 to 4.69)           |
| Atonvastatin 10 mg/day                      | 42/17 065  | 2.98 (2.09 to 4.26)           |
| Atonvastatin 20/40/80 mg/day                | 11/6488    | 2.62 (1.42 to 4.84)           |
| Fluvastatin 20 mg/day                       | 0/575      | Insufficient data             |
| Fluvastatin 40/80 mg/day                    | 0/906      | Insufficient data             |
| Pravastatin 10/20 mg/day                    | 4/1779     | 2.60 (0.96 to 7.04)           |
| Pravastatin 40 mg/day                       | 4/1913     | 2.68 (0.99 to 7.25)           |
| Rosuvastatin all                            | 8/2151     | 5.41 (2.64 to 11.07)          |
| Acute renal failure:                        |            |                                |
| No statin                                   | 579/908 720 | 1.00                           |
| Simvastatin 10/20 mg/day                    | 106/46 009 | 1.38 (1.10 to 1.74)           |
| Simvastatin 40/80 mg/day                    | 63/27 746  | 1.75 (1.32 to 2.32)           |
| Atonvastatin 10 mg/day                      | 57/17 048  | 1.43 (1.07 to 1.92)           |
| Atonvastatin 20/40/80 mg/day                | 24/6479    | 2.03 (1.34 to 3.09)           |
| Fluvastatin 20 mg/day                       | 7/577      | 4.35 (2.05 to 9.23)           |
| Fluvastatin 40/80 mg/day                    | 2/905      | 0.80 (0.20 to 3.21)           |
| Pravastatin 10/20 mg/day                    | 8/1777     | 1.94 (0.96 to 3.92)           |
| Pravastatin 40 mg/day                       | 10/1907    | 2.18 (1.16 to 4.09)           |
| Rosuvastatin all                            | 4/2150     | 1.03 (0.38 to 2.78)           |
| Cataract:                                   |            |                                |
| No statin                                   | 16 543/896 717 | 1.00                           |
| Simvastatin 10/20 mg/day                    | 2350/42 755 | 1.30 (1.24 to 1.36)           |
| Simvastatin 40/80 mg/day                    | 1090/25 877 | 1.31 (1.23 to 1.40)           |
| Atonvastatin 10 mg/day                      | 1180/15 861 | 1.31 (1.23 to 1.40)           |
| Atonvastatin 20/40/80 mg/day                | 334/6113   | 1.24 (1.11 to 1.39)           |
| Fluvastatin 20 mg/day                       | 47/553     | 1.27 (0.95 to 1.69)           |
| Fluvastatin 40/80 mg/day                    | 71/833     | 1.26 (1.00 to 1.60)           |
| Pravastatin 10/20 mg/day                    | 124/1662   | 1.24 (1.04 to 1.48)           |
| Pravastatin 40 mg/day                       | 158/1778   | 1.55 (1.32 to 1.82)           |
| Rosuvastatin all                            | 113/2029   | 1.25 (1.04 to 1.51)           |
| Moderate or serious liver dysfunction:      |            |                                |
| No statin                                   | 6055/907 313 | 1.00                           |
| Simvastatin 10/20 mg/day                    | 470/45 573  | 1.47 (1.32 to 1.63)           |
| Simvastatin 40/80 mg/day                    | 247/27 476  | 1.62 (1.41 to 1.86)           |
| Atonvastatin 10 mg/day                      | 221/16 948  | 1.37 (1.19 to 1.58)           |
| Atonvastatin 20/40/80 mg/day                | 106/6440   | 2.00 (1.64 to 2.44)           |
| Fluvastatin 20 mg/day                       | 10/574     | 1.64 (0.88 to 3.06)           |
| Fluvastatin 40/80 mg/day                    | 30/897     | 3.08 (2.14 to 4.43)           |
| Pravastatin 10/20 mg/day                    | 19/1765    | 1.06 (0.68 to 1.67)           |
| Pravastatin 40 mg/day                       | 37/1897    | 1.91 (1.37 to 2.65)           |
| Rosuvastatin all                            | 23/2132    | 1.31 (0.87 to 1.97)           |
| Oesophageal cancer:                         |            |                                |
| No statin                                   | 506/908 816 | 1.00                           |
| Simvastatin 10/20 mg/day                    | 31/46 067  | 0.62 (0.43 to 0.91)           |
| Simvastatin 40/80 mg/day                    | 19/27 788  | 0.82 (0.51 to 1.31)           |
| Atonvastatin 10 mg/day                      | 16/17 078  | 0.67 (0.40 to 1.11)           |
| Atonvastatin 20/40/80 mg/day                | 7/6489     | 0.94 (0.44 to 2.00)           |
| Fluvastatin 20 mg/day                       | 0/577      | Insufficient data             |
| Fluvastatin 40/80 mg/day                    | 0/905      | Insufficient data             |
| Pravastatin 10/20 mg/day                    | 0/1779     | Insufficient data             |
| Pravastatin 40 mg/day                       | 4/1913     | 1.37 (0.91 to 1.37)           |
| Rosuvastatin all                            | 1/2152     | 0.41 (0.06 to 2.92)           |

Hazard ratios are adjusted for same variables as table 4 (see web extra).
compared with lower doses (table 5). For example, the adjusted hazard ratio for fluvastatin was 3.08 (2.14 to 4.43) at high dose (≥20 mg) compared with 1.64 (0.88 to 3.06) at low dose (≤20 mg). The corresponding values for men were 2.37 (1.66 to 3.38) and 1.20 (0.60 to 2.40). This pattern was similar with the other statins.

The risk of liver dysfunction was highest within the first year of treatment with any statin: the adjusted hazard ratio for women was 2.38 (2.11 to 2.70) and for men was 2.32 (2.07 to 2.59). The hazard ratio in the 1-3 years after starting treatment for women was 1.39 (1.23 to 1.57) and for men was 1.35 (1.21 to 1.51). After stopping statins the risks returned to normal between one and three years in women and from three years in men. Further details on the analyses of duration are available from the authors.

**Moderate or serious myopathy**

All statins were associated with an increased risk of myopathy (table 4) apart from fluvastatin in women, where numbers were too small for analysis. The direct comparison test showed no significant difference between the effects of individual statins either in men ($P=0.57$) or in women ($P=0.61$).

The adjusted hazard ratios in table 5 show some evidence of a dose-response in men prescribed atorvastatin and pravastatin: 6.11 (4.79 to 7.80) for low dose (10 mg/day) atorvastatin compared with 8.18 (5.82 to 11.50) for high dose (≥20 mg/day) atorvastatin, and 3.62 (1.49 to 8.78) for low dose (≤20 mg/day) pravastatin compared with 5.79 (3.07 to 10.91) for high dose (40 mg/day) pravastatin. The confidence intervals were, however, wide owing to small numbers in each dose category.

The time varying analysis showed that the risk was highest within the first year of starting treatment: the adjusted hazard ratio in women was 4.30 (2.98 to 6.21) and in men was 9.96 (7.66 to 12.96). The increase persisted during treatment as well as on stopping treatment. From three years after stopping statins, the adjusted hazard ratio in women was 4.65 (2.32 to 9.28) and in men was 5.86 (2.84 to 12.06).

**Cataract**

Each statin was associated with an increased risk of cataract in both men and women, apart from fluvastatin in men, owing to small numbers. The direct comparison test showed no significant difference between the effects of individual statins in men ($P=0.32$) or in women ($P=0.82$).

There was no evidence of a dose-response relation (table 5). The time varying analysis showed the risk was significantly increased within a year of starting statins, persisted during treatment, and returned to normal within the first year after stopping treatment.

**Oesophageal cancer**

The risk of oesophageal cancer decreased in both men and women prescribed simvastatin (0.69, 0.50 to 0.94 and 0.82, 0.68 to 0.99, respectively). The risk was also significantly decreased in men prescribed atorvastatin (0.73, 0.55 to 0.96). The hazard ratios for the other statins were not statistically significant.

### Table 6: Relative incidence rate ratios from case series analysis for men and women combined for significant outcomes associated with statin type

| Outcomes | Incidence rate ratio (95% CI) |
|----------|------------------------------|
|          | Acute renal failure | Cataract | Moderate or serious liver dysfunction | Moderate or serious myopathy |
| Simvastatin: | | | | |
| Period of non-use | 1.00 | 1.00 | 1.00 | 1.00 |
| Period of use | 1.57 (1.27 to 1.95) | 1.18 (1.13 to 1.24) | 1.49 (1.36 to 1.63) | 20.66 (14.68 to 29.06) |
| Washout period* | 2.21 (1.40 to 3.5) | 0.94 (0.8 to 1.11) | 1.10 (0.86 to 1.41) | 3.81 (2.04 to 7.11) |
| Atorvastatin: | | | | |
| Period of non-use | 1.00 | 1.00 | 1.00 | 1.00 |
| Period of use | 1.17 (0.83 to 1.67) | 1.18 (1.09 to 1.29) | 1.62 (1.38 to 1.91) | 8.48 (5.14 to 13.99) |
| Washout period* | 1.60 (0.74 to 3.49) | 0.77 (0.56 to 1.06) | 0.90 (0.58 to 1.41) | 2.84 (1.22 to 6.59) |
| Fluvastatin: | | | | |
| Period of non-use | 1.00 | 1.00 | 1.00 | 1.00 |
| Period of use | Insufficient data | 1.50 (1.04 to 2.15) | 2.38 (1.24 to 4.57) | 9.20 (0.84 to 100.97) |
| Washout period* | Insufficient data | 1.06 (0.37 to 2.99) | 0.73 (0.10 to 5.55) | Insufficient data |
| Pravastatin: | | | | |
| Period of non-use | 1.00 | 1.00 | 1.00 | 1.00 |
| Period of use | 1.72 (0.69 to 4.25) | 1.13 (0.92 to 1.4) | 1.47 (0.95 to 2.26) | 28.71 (5.51 to 149.56) |
| Washout period* | 2.68 (0.53 to 13.51) | 1.23 (0.67 to 2.24) | 0.81 (0.25 to 2.69) | Insufficient data |
| Rosuvastatin: | | | | |
| Period of non-use | 1.00 | 1.00 | 1.00 | 1.00 |
| Period of use | 5.11 (1.05 to 24.92) | 1.33 (1.01 to 1.75) | 1.95 (1.11 to 3.41) | 4.77 (1.27 to 17.88) |
| Washout period* | 5.66 (0.55 to 58.49) | 1.26 (0.54 to 2.93) | 0.62 (0.08 to 4.64) | Insufficient data |

*1-182 days after stopping.
Table 7 | Numbers needed to harm (NNH) or numbers needed to treat (NNT) and numbers of extra or prevented cases for each outcome over five years in patients aged 35-74 free of cardiovascular disease at baseline with QRISK2 score of ≥20% or ≥15%

| Variables | High risk patients (QRISK2 score ≥20%) | Medium risk patients (QRISK2 score ≥15%) |
|-----------|----------------------------------------|----------------------------------------|
|           | Adjusted hazard ratio for statin use (95% CI) | 5 year risk of outcome in patients unexposed to statins (95% CI) | Estimated No of extra (or prevented) cases per 10 000 patients treated (95% CI) |
|           |                                           | NNH or NNT (95% CI) | |
|           |                                           |                         | 5 year risk of outcome in patients unexposed to statins (95% CI) | Estimated No of extra (or prevented) cases per 10 000 patients treated (95% CI) |
| Women     |                                         |                         |                         | |
| Potential benefits: Cardiovascular disease* | 0.76 (0.67 to 0.86) | 0.1184 | −37 (−64 to −27) | −271 (−374 to −157) | 0.0989 | −44 (−76 to −32) | −228 (−315 to −132) |
| Oesophageal cancer | 0.68 (0.52 to 0.88) | 0.0025 | −1266 (−3460 to −850) | −8 (−12 to −3) | 0.0021 | −1483 (−4053 to −996) | −7 (−10 to −3) |
| Potential harms: Acute renal failure | 1.56 (1.31 to 1.86) | 0.0041 | 434 (284 to 783) | 23 (13 to 35) | 0.0030 | 593 (388 to 1070) | 17 (9 to 26) |
| Cataract | 1.3 (1.26 to 1.35) | 0.1089 | 33 (28 to 38) | 307 (260 to 355) | 0.0882 | 40 (34 to 47) | 252 (213 to 292) |
| Liver dysfunction | 1.53 (1.41 to 1.66) | 0.0140 | 136 (109 to 175) | 74 (57 to 91) | 0.0123 | 154 (125 to 199) | 65 (50 to 80) |
| Myopathy | 2.97 (2.36 to 3.74) | 0.0020 | 259 (186 to 375) | 39 (27 to 54) | 0.0016 | 313 (225 to 453) | 32 (22 to 44) |
| Men       |                                         |                         |                         | |
| Potential benefits: Cardiovascular disease* | 0.76 (0.67 to 0.86) | 0.1326 | −33 (−57 to −24) | −301 (−417 to −174) | 0.1156 | −38 (−65 to −27) | −265 (−366 to −153) |
| Oesophageal cancer | 0.78 (0.66 to 0.91) | 0.0042 | −1082 (−2807 to −711) | −9 (−14 to −4) | 0.0037 | −1236 (−3207 to −812) | −8 (−12 to −3) |
| Potential harms: Acute renal failure | 1.61 (1.39 to 1.87) | 0.0047 | 346 (245 to 539) | 29 (19 to 41) | 0.0037 | 447 (316 to 696) | 22 (14 to 32) |
| Cataract | 1.32 (1.26 to 1.37) | 0.0630 | 52 (44 to 63) | 191 (158 to 225) | 0.0495 | 66 (56 to 80) | 151 (125 to 178) |
| Liver dysfunction | 1.53 (1.42 to 1.66) | 0.0133 | 142 (115 to 180) | 71 (56 to 87) | 0.0122 | 155 (126 to 197) | 64 (51 to 79) |
| Myopathy | 6.15 (5.19 to 7.3) | 0.0021 | 91 (74 to 112) | 110 (90 to 134) | 0.0018 | 106 (87 to 130) | 95 (77 to 116) |

Negative numbers indicate numbers needed to treat or cases prevented. Positive numbers indicate numbers needed to harm or extra cases.

*Odds ratios based on meta-analysis by Brugts et al.2
†Adjusted hazard ratios for all statins combined adjusted for same variables as in tables 4 and 5 (see web extra).

few patients were prescribed rosuvastatin to draw firm conclusions.

Evidence suggested a dose-response effect (table 5). For example, for women prescribed simvastatin 10/20 mg the adjusted hazard ratio was 1.38 (1.10 to 1.74) and for simvastatin 40/80 mg was 1.75 (1.32 to 2.32). For men the corresponding values were 1.39 (1.14 to 1.70) and 2.02 (1.63 to 2.52).

The increased risk of acute renal failure was apparent within the first year of starting treatment (adjusted hazard ratios 1.54 (1.09 to 2.17) for women and 1.67 (1.26 to 2.21) for men), and persisted for the first five years of treatment. The risk remained increased during the first year of stopping treatment and then returned to normal 1-3 years after stopping treatment: adjusted hazard ratios 1.23 (0.69 to 2.20) for women and 1.57 (0.95 to 2.60) for men.

Case series analysis
As in the cohort analysis the case series analysis for moderate or serious myopathy showed increased risks during statin use compared with no use, although the magnitude of incidence rate ratios was larger than that in the cohort analysis but also had wide confidence intervals (table 6). The incidence rate ratios tended to be smaller but still significant when the case series analysis was restricted to new users and the observation...
period started at first use—for example, the rate ratio for simvastatin was 8.59 (95% confidence interval 5.2 to 14.19) and for atorvastatin was 4.37 (2.27 to 8.44). The rate ratio for pravastatin was higher (33.89, 3.87 to 297.14). Data for fluvastatin and rosuvastatin were insufficient for this analysis.

The case series analysis confirmed the significantly increased risk of cataract during the period of use of each statin compared with the period of non-use, except for pravastatin: adjusted incidence rate ratio 1.13 (95% confidence interval 0.92 to 1.40). The risk of acute renal failure was increased during simvastatin use (1.57, 1.27 to 1.95) and also rosuvastatin use (5.11, 1.05 to 24.92) compared with non-use. The increased risk of moderate or serious liver dysfunction during simvastatin use compared with the period of non-use showed a similar pattern and magnitude to the cohort analyses.

Numbers needed to treat and numbers needed to harm Table 7 shows the NNTs and NNHs for each outcome among patients aged 35-74 who were at high risk of cardiovascular disease, as defined by two thresholds (≥20% and ≥15%) for cardiovascular risk based on the QRISK2 10 year cardiovascular risk score. Using the 20% threshold in women, the NNT with any statin to prevent one case of cardiovascular disease over five years was 37 (95% confidence interval 27 to 64) and for oesophageal cancer was 1266 (850 to 3460). For men, the corresponding values were 33 (24 to 57) and 1082 (711 to 2807).

In women, the NNH for an additional case of acute renal failure over five years was 434 (284 to 783), for moderate or severe myopathy was 259 (186 to 375), for moderate or severe liver dysfunction was 136 (109 to 175), and for cataract was 33 (28 to 38).

Overall, using the 20% threshold, the NNH or NNTs for women were similar to those for women except for myopathy where the NNH was 91 (74 to 112). This is lower than in women, mainly due to the higher hazard ratio in men.

Table 7 also shows the NNH or NNT for men and women selected using the 15% threshold for QRISK2 score. The event rates for each outcome in non-users of statins tended to be lower than when using the 20% threshold. The effect of this was to increase both the NNT and the NNH for each outcome. Table 7 also shows the estimated numbers of extra cases or cases prevented per 10 000 people treated with statins at both thresholds. For example, using the 20% threshold there would be 271 fewer cases (95% confidence interval 157 to 374) of cardiovascular disease for every 10 000 women compared with 228 fewer cases (132 to 315) using the 15% threshold.

**DISCUSSION**

We examined and quantified the unintended risks and benefits of statins in a large representative primary care population over a six year period. Our study has good face validity because it was carried out in a setting where most patients in the United Kingdom are assessed, treated, and followed up. We were unable to confirm some potential unintended effects of statins, such as a protective effect on risk of Parkinson’s disease, venous thromboembolism,10 rheumatoid arthritis,10 osteoporotic fracture,25 46 and dementia.15 16 This may be because compared with most previous studies our study was larger, prospective, and included more potential confounders.

Our findings largely confirm other studies that reported no clear association between statins and risk of cancers.9 21 23 47 48 There were two potential exceptions: oesophageal cancer, where we found a decreased risk, and colon cancer where there was an apparent decreased risk in men prescribed pravastatin and an increased risk in men prescribed rosuvastatin. These findings could represent a genuine association or could be due to chance, given the large number of outcomes under consideration in this study. Previous studies have not distinguished between the type of statin and specific cancer to this degree22 23 or undertaken independent patient level analyses. Some of the older meta-analyses did not include rosuvastatin, which has been licensed relatively recently. Further studies using independent datasets should be undertaken to confirm or refute these findings, particularly as the use of statins is likely to increase.

We were able to quantify adverse effects associated with statins, including myopathy, liver dysfunction, acute renal failure, and cataract. These seem to be class effects, with a dose-response effect apparent for acute renal failure and liver dysfunction consistent with that reported elsewhere.9 22 We found a suggestion of a dose-response for myopathy among men prescribed pravastatin and atorvastatin, although the confidence intervals were wide owing to small numbers.

As in previous studies, we found that adverse effects tended to be similar across the types of statins for most outcomes except for liver dysfunction, where the highest risks were associated with fluvastatin. All risks persisted during treatment and were highest in the first year of treatment. After stopping treatment the risk of cataract returned to normal within a year in men and women. Risk of oesophageal cancer returned to normal within a year in women and within 1-3 years in men. Risk of acute renal failure returned to normal within 1-3 years in men and women, and liver dysfunction within 1-3 years in women and from three years in men.

**Comparison with other studies**

Clinical trials and their associated meta-analyses provide valuable information on the effectiveness and efficacy of drugs. They are, however, limited in providing information on adverse events since such data are not always recorded or reported in a consistent fashion. Trials tend to be of short duration, under-powered for the detection of adverse events, and susceptible to selection bias, with participants tending to be predominantly white, younger, and healthier than the general population. Most statin trials and meta-analyses are designed to investigate the effectiveness of statins...
Individual statins were not significantly associated with risk of Parkinson’s disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, and several common cancers.

The risk of oesophageal cancer was reduced but for liver dysfunction, acute renal failure, myopathy, and cataract it was increased.

Adverse effects were similar across the statin types for each outcome except liver dysfunction where fluvastatin was associated with the highest risks.

One observational study examined the comparative safety of individual statins for selected outcomes, including myopathy, acute renal failure, and acute liver injury. This study used the general practice research database and involved 100,000 statin users followed for under three years. Our study adds to this trial by examining a larger population of statin users as well as including non-users, additional outcomes, and a longer duration of follow up. There are two main differences between our study and the general practice research database study. Firstly, we compared new users of statins with non-users whereas the general practice research database study was designed to compare different types of statins directly and did not include a non-user group. Secondly, we used more inclusive outcome definitions and identified many more cases. In the general practice research database study, in order for patients to be included as cases they needed both a computer recorded code of the outcome (for example, acute renal failure) and a computer code indicating admission to hospital, and if only one criterion was met the patient was not identified as a case. In our study we assumed that most patients with, for example, acute renal failure would be admitted to hospital and that the general practitioner would record the diagnostic code rather than the hospital admission itself.

Methodological considerations

Observational studies, with their large representative and ethnically diverse populations and their potential for longer term follow-up, have limitations, notably bias and unmeasured confounding. Recall bias is not of concern here because information on statin use was prospectively recorded on computer before the outcomes. Misclassification bias of use—that is, statin prescriptions—is possible because low dose simvastatin became available over the counter in August 2004. However, it is likely that most prescriptions are issued in primary care and recorded electronically, especially among elderly people and those with comorbidities, who will have free prescriptions. Any classification of statin use (or outcome) if non-differential, would tend to bias the hazard ratios towards 1 thus under-estimating a potential association. Misclassification of outcome is possible, although validation studies undertaken on similar general practice databases relating to similar outcomes where the general practitioner has been contacted for further detail have shown good results.

Ascertainment bias could occur as people starting statins tend to have more blood tests than those not starting statins thereby increasing the likelihood of detection of abnormal liver function tests or myopathy associated with a raised creatine kinase concentration. None the less, our study confirms the results of other studies that statins are associated with liver dysfunction and gives information on the likely volumes of affected people who need careful follow up. This not only has planning implications for general practitioner workload but may cause anxiety for patients. Our analysis, however, suggests that the risk of abnormal liver function tests is dose dependent and that it can be reversed on stopping treatment, both of which could help guide therapy and reassure people. Ascertainment or recording bias might also partly account for the increased risk of cataract because people prescribed statins may consult their general practitioner more often than the general population thereby increasing the opportunity for people to report on visual problems and be examined.

Indication bias is particularly important for intended outcomes such as the reduction in risk of cardiovascular disease. Initially, we carried out an additional preliminary analysis using the prior event rate ratios approach and obtained similar point estimates to those from the published meta-analyses. However, the prior event rate ratios approach is not valid for...
analyses of first events and cannot be applied if a diagnosis of an outcome before starting study drugs was an exclusion criterion.\textsuperscript{12} We have therefore used odds ratios\textsuperscript{2} derived from meta-analyses to work out the numbers needed to treat at population level for cardiovascular disease, combined with event rates from QResearch.

Our case series analysis generally confirms the results of our main cohort analyses. It removes the effects of fixed cofounders and largely removes the effect of indication bias, although it could still be susceptible to ascertainment bias.

Clinical implications
At national level, our study is likely to be useful for policy and planning purposes because we have given the expected numbers of additional adverse events per 10 000 patients that would occur if all patients likely to be at high risk of cardiovascular disease were prescribed statins, assuming the associations we found are causal. We undertook our analyses for NNHs and NNTs at two thresholds of cardiovascular risk (≥15% and ≥20%) and showed that the potential benefits and harms both tend to increase as the threshold for intervention increases.

Our study may also be useful for informing guidelines on the type and dose of statins. Although adverse outcomes tended to be class effects overall with no significant differences between the statins, the risk of liver dysfunction was highest with fluvastatin. The risk of liver dysfunction, acute renal failure, and possibly myopathy were dose related and, as liver dysfunction is common and the other two outcomes potentially life threatening, the findings would tend to support a policy of using lower doses of statins in people at high risk of the adverse event.

While we have shown adverse associations between statin use and four outcomes and one protective association, our study was not designed to show causality. Although we have shown some evidence of dose-response relation and reversibility (in that risk for most outcomes decreases on stopping treatment), consideration of potential biological mechanisms is outside the scope of this study.

Conclusions
In summary, we have reported a detailed epidemiological analysis of the unintended effects of statins in a large representative primary care population for a range of outcomes by type of statin, dose, and duration of use. We have given estimates on the number of additional events potentially caused or prevented per 10 000 patients treated. The current paper quantifies risks and benefits of statins at population level, but the underlying algorithms also can be applied at the individual level. In a companion paper,\textsuperscript{23} therefore, we validate the algorithms at individual level so that they can be used to explain absolute and relative risks and benefits for an individual patient as well as to identify those at high risk of adverse events from statins for more proactive monitoring.

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Contributors: JH-C initiated the study, reviewed the literature, extracted and manipulated the data, carried out the primary data analysis, and wrote the first draft of the paper. CC contributed to the design, analysis, interpretation, and drafting of the paper. Both authors are guarantors.

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Competing interests: JH-C is codirector of QResearch (a not for profit organisation that is a joint partnership between the University of Nottingham and EMIS, the leading commercial supplier of IT for 60% of general practices in the United Kingdom) and director of ClinRisk, which produces software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to improve patient care. CC is a consultant statistician for ClinRisk. This work and any views expressed within it are solely those of the authors and not of any affiliated bodies or organisations.

Data sharing: The patient level data from the QResearch are specifically licensed according to its governance framework. See www.qresearch.org for further details. The Read codes groups used are available from the authors on request.

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