Statins and Risk of Rheumatoid Arthritis - A Nested Case-Control Study

Koray Tascilar MD[1,2], Sophie Dell'Aniello MSc[1], Marie Hudson MD, MPH, FRCPC[1, 3, 4], Samy Suissa PhD[1, 5]

[1]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Montreal Quebec, Canada
[2]Division of Rheumatology, Department of Internal Medicine, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey
[3]Division of Rheumatology, Jewish General Hospital, Montreal, Quebec, Canada
[4]Department of Medicine, McGill University Montreal, Quebec, Canada
[5]Department of Epidemiology and Biostatistics McGill University Montreal, Quebec, Canada

Word Count (Abstract): 249
Word Count (Text): 3708
Tables: 5
Figures: 2
Keywords: Rheumatoid arthritis, statins, prevention
Running head: Statins and Rheumatoid Arthritis

Correspondence:
Samy Suissa
Centre for Clinical Epidemiology, Jewish General Hospital
3755 Cote Ste-Catherine, H461, Montreal, Quebec, Canada H3T 1E2
e-mail: samy.suissa@mcgill.ca
Tel: 514.340.7593
Fax: 514.340.7564

Conflict of Interest Disclosures: None of the authors declare any conflict of interest concerning the content of this manuscript.

Funding/Support: This study was funded in part by the Canadian Institutes of Health Research and the Canadian Foundation for Innovation (CFI). Dr. Koray Tascilar's work at the Lady Davis Institute was supported by an award from the Turkish Society of Rheumatology and from the Canadian Network for Observational Drug Effects Studies (CNODES). Mrs. Sophie Dell'aniello has no financial disclosures. Dr. Marie Hudson is funded as a Chercheur-clinicien by the Fonds de recherche en santé du Québec and Dr. Samy Suissa is the recipient of the James McGill Chair. Canadian Institutes of Health Research and other funding sources had no role in the design of the study, analysis or interpretation of data, manuscript preparation or decision to submit the manuscript.

May 12, 2016

Abstract

Objective: Statins have anti-inflammatory/immunomodulatory effects that may be useful to prevent rheumatoid arthritis (RA) but previous observational studies about the risk of RA with statin use provided conflicting results. The aim of this study was to determine whether high-intensity statin treatment is associated with a lower risk of rheumatoid arthritis.

Methods: Using data from the UK Clinical Practice Research Datalink, we performed a nested case-control analysis in a population-based cohort of new statin users between 1997 and 2009, followed until a first diagnosis of RA, death, end of registration or end of 2009. For each case of RA, 10 age, sex and calendar year-matched controls were randomly selected from risk sets. We estimated the hazard ratio (HR) of incident RA in the highest quintile of duration-weighted average statin intensity compared with the lowest, using conditional logistic regression. Models were adjusted for smoking status, total cholesterol levels, obesity, history of cardiovascular disease, coexistent autoimmune diseases, hypothyroidism and persistence with treatment.

Results: The cohort included 528,654 new users of statins, with 1,357 new RA cases during a mean 3.3 years of follow-up, for an incidence rate of 7.9 per 10,000 person-years. Cases were more likely to be smokers, have other autoimmune diseases and lower total cholesterol levels at baseline. The incidence of RA was lower in the highest statin intensity quintile (adjusted HR 0.77; 95% CI: 0.63-0.95) in comparison to the lowest quintile.

Conclusions: In this large population-based study, high-intensity statin treatment was associated with a reduced risk of RA in comparison with low-intensity statins.

Introduction

Hypercholesterolemia is a major modifiable risk factor for cardiovascular disease, and robust, longstanding evidence shows that lowering cholesterol using hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) prevents cardiovascular events, both in primary and secondary prevention settings.(1, 2) In addition to their effect on cholesterol levels, statins also attenuate inflammation in individuals with atherosclerosis as shown in observational studies, and in a large randomized controlled trial where cardiovascular protection was accompanied by a reduction in C-reactive protein (CRP) levels (3). In the Trial of Atorvastatin in Rheumatoid Arthritis (TARA)(4), active rheumatoid arthritis (RA) patients randomized to receive 40 mg/day of atorvastatin experienced a small but significant reduction in the acute phase reactants and the number of tender and swollen joints. Results of the TARA trial strongly support the notion of an anti-inflammatory effect of statins outside the context of atherosclerosis and cardiovascular prevention. Statins have also been shown to attenuate immune responses with a dose response relationship,(5) and exert an immunomodulatory effect at the population level (6).

Despite the anti-inflammatory and immunomodulatory properties of statins, observational studies on the risk of RA with statin exposure have reported contradictory results (7-9). Two population-based studies showed a reduced risk of RA with statin use (7, 9) while one case-control study found an increased risk (8). On the other hand, two cohort studies looking at overall unintended effects of statins found no change in the risk of RA with statin use among a number of other outcomes (10, 11). The discrepancies may have resulted from

small numbers of exposed cases (7, 8), improper case validation (9-11), or study designs contrasting effects in statin users vs. non-users (7, 8) or adherers vs. non-adherers (9), which in the case of the pleiotropic benefits of statins have been shown to pose challenges concerning bias eradication (12, 13). Therefore, we undertook a nested case-control analysis in a large population-based cohort of new statin users to define the relationship between the risk of RA and the intensity of statin treatment. We hypothesized that the immunomodulatory effect would be more pronounced and the risk of RA would be lower in high-intensity statin users in comparison to that in low-intensity users.

Methods

Data Source and Setting

We assembled a cohort of new statin users from 623 general practices that contributed data to the Clinical Practice Research Datalink (CPRD). CPRD is a comprehensive primary care database generated by general practitioners in the United Kingdom (UK). Details of clinical encounters such as diagnoses, physical examination findings, procedures or referrals are encoded using the Read dictionary. Prescriptions issued by the GPs are encoded using the UK Prescription Pricing Authority Dictionary. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for the U.K. Medicines and Healthcare Products Regulatory Agency (# 14_051) and the Ethics Committee of the Jewish General Hospital, Montreal, Canada (# 14-053). All data used in this study were anonymized.

Cohort Definition

The cohort of statin users was formed from all adults of at least 40 years of age that were issued a statin prescription for the first time between 1/01/1997 and 31/12/2009. Subjects were required to have a medical history in the CPRD of at least 1 year before their first statin prescription. Cohort entry was taken as the date of the first statin prescription. Subjects with a diagnostic code for rheumatoid arthritis (RA), any prescription for a disease modifying anti-rheumatic drug (DMARD) or any other

immunosuppressive/immunomodulatory drug prior to cohort entry were excluded. The cohort was followed until death, end of registration with the practice, fulfillment of the case definition or January 1st 2010, whichever occurred first. Because of the complex time-dependent nature of the statin exposure and the large size of the cohort, we used a nested case-control design within the cohort.

Case Definition and Control Selection

Within this cohort, we identified all incident RA cases occurring during follow-up. We used an algorithm including 2 sets of qualifiers with 2 qualifiers each: Set-A - one diagnostic code for RA (Table S1) and one prescription for a DMARD (Table S2); and, Set-B - appearance of two diagnostic codes for RA at least 3 months apart. Subjects satisfying either one of these qualifier sets were classified as cases. Date of the earliest qualifier, that is earliest of the treatment or diagnostic codes in Set-A, or earliest of the two diagnostic codes in Set-B, was called the index date for our primary analysis.

For each case, we constructed the risk set of possible controls with at least an equal duration of follow-up at the case's index date. To be included in the risk set of a case, a candidate control had to be the same gender as the case, had to enter the cohort within one calendar year, had to be within 5 years of age as the case, while not satisfying the case definition at the assigned index date. We randomly selected 10 controls from each risk set and each control was assigned the index date that resulted in a follow-up duration equal to that of the corresponding case. As a result, controls were matched to cases with respect to sex, age at index date (within 5 years), calendar year of cohort entry (within one year) and follow-up duration from statin initiation. This risk-set sampling allows subjects to serve as

controls for more than one case at different time points or a case to serve as a control before the case definition is satisfied.

Exposure Assessment

We extracted statin prescriptions in cases and controls up to index date including prescription dates, compound, strength, number of units and dosing instructions of the physician. We divided the prescribed number of units by the daily number of units in dosing instructions and calculated the number of days supplied (NDS) with each prescription. In case of overlapping prescriptions (i.e. oversupply), NDS was truncated at the number of days between two consecutive prescriptions. Missing or unusual number of units in dosing instructions were replaced by the mode value for the product. We summed the NDS from cohort entry to index date to calculate the total NDS for each subject. Finally dividing the total NDS by the follow-up duration in days we calculated the proportion of days covered (PDC) by statins between cohort entry and index date as a measure of persistence.

The primary exposure variable was defined as the "duration-weighted average statin intensity". The intensity of a statin preparation was based on the percent reduction in low density lipoprotein (LDL) as quantified in two meta-analyses of randomized controlled trials (14, 15). We assigned simvastatin 20 mg a reference intensity value of 1 and all other statin compounds and doses were assigned a corresponding relative intensity (Table S3, Figure S2). We calculated the average statin intensity weighted by the number of days supplied between cohort entry and index date for each subject (further details provided in online supplement). Finally, we ranked the duration-weighted average statin intensity in

controls to define boundaries of intensity quintiles. Of note, the exact boundary for the highest quintile was 1.1977, which was also the intensity of Simvastatin 40 mg and included approximately 14% of all controls. Therefore, we made an arbitrary decision to include this value with the lower intensity quintile. Otherwise, our highest intensity quintile would have contained approximately 28% of all controls.

Statistical Analysis

Descriptive statistics were used to report the characteristics of cases and controls at cohort entry. We used conditional logistic regression to estimate the odds ratio (OR) and respective 95% confidence interval (CI) of RA for subjects in the highest duration-weighted average intensity quintile in comparison with the lowest. In a secondary analysis we estimated the odds ratios separately in follow-up duration categories in order to examine the time course of the effect. The effects of age, sex, calendar year of cohort entry and follow-up duration were controlled for by matching. The model was further adjusted for potential confounders, namely smoking status, body mass index (BMI), total cholesterol level, history of cardiovascular disease, coexistent autoimmune diseases (Table S4) and non-iatrogenic hypothyroidism (16-18). The main model was also adjusted for PDC as a continuous variable in order to account for the effect of treatment persistence. Baseline cholesterol was measured at the latest available time point within the 5 years before cohort entry and other covariates were measured over all time points available up-to cohort entry. Missing BMI, smoking, and cholesterol data were categorized as unknown and included as such in the models. The OR from a conditional logistic regression analysis in a nested case-control study with risk-set sampling is a reliable estimate of the hazard ratio (HR) from a

Cox model for a time-dependent exposure. Thus, the effect estimates from our analyses were reported as HRs (19, 20).

Since there is a delay from the clinical onset of RA to a physician diagnosis, we conducted two sensitivity analyses to assess the impact of such delay on our estimates. Firstly, the exposure was lagged by 1 year, excluding RA cases that were diagnosed in the first year after starting statin treatment. Secondly, we used indicator variables that are known to precede the diagnosis of RA in the CPRD (21) and repeated the analysis after assigning new index dates to cases and their respective controls using the earliest date of an indicator variable within the three years prior to the cases' original index dates.

Other sensitivity analyses were performed. Our case selection algorithm required multiple cumulative qualifiers to be fulfilled over time whereas the earliest of those qualifiers was assigned as the index date, i.e. our index dates were earlier in time than dates of case ascertainment in the primary analysis. Thus, alternatively, we used the dates of case ascertainment instead of the original index dates in order to assess the impact of such "peek into the future" on our estimates. We also repeated the analyses with an interaction term between duration-weighted average intensity quintiles and 3 PDC levels (<20%, 20-80% and >80%) in order to assess the impact of persistence on our effect estimate. As well, we repeated the analysis using the intensity value for the first statin prescription instead of the duration-weighted average intensity, to imitate an intention to treat analysis. Finally, we assessed the effect of recency of statin use using a regression model with current use (last use within 90 days prior to the index date) and recent use (last use 91 to 180 days prior to the index date), with a reference category of past use as last use over 180 days

prior to the index date). All analyses were carried out using SAS v. 9.3 (SAS Institute, Cary NC).

Results

We identified 528,654 individuals that were eligible for the study (Figure 1). In this cohort, 1357 new RA cases were identified and matched to 13,570 controls. Crude incidence rate of RA was 7.9/10.000 patient years. The mean age (SD) at index date was 67.1 (9.5), with an average follow up duration of 3.3 (2.5) years. Sixty percent of the subjects were females. Characteristics of the cases and controls are presented in Table 1. Controls were less likely to be smokers and to have a history of lung disease, hypothyroidism and other autoimmune diseases, and more likely to have a higher total cholesterol level at cohort entry. Baseline characteristics were also presented across duration-weighted average intensity categories in the supplementary appendix (Tables S5 and S6).

Our case-control population was highly persistent with statin use. Average duration of statin use was 27.8 (25.8) months in cases and 28.8 (26.0) months in controls. Overall median PDC was higher than 80% and 1304 individuals (8.7%) were poorly persistent with a PDC less than 20% of their follow-up (Table 2). Highest median PDC was observed in individuals in the first six months after statin initiation (95.0 and 96.8% for cases and controls respectively). In subsequent follow-up periods, median PDC was lower than the first six months but constantly over 80% both in cases and controls (Table-3). In addition, more than 70% of our case-control population was still current users of statin treatment, defined as within 3 months prior to the index date, in all follow-up periods, even after 5 years (Table 3). Overall, PDC and proportion of current users was higher in controls than in cases in all follow-up periods and duration-weighted average intensity quintiles with small differences (Table 2, Table 3, Table S7).

Adjusted HR of incident RA for subjects in the highest compared to the lowest intensity quintile of statin exposure was 0.77 (95% CI, 0.63-0.95, Table 4). In our secondary analysis by categories of follow-up duration, the effect appeared most prominent between 6 to 12 months after starting statin treatment (adjusted HR: 0.44, 95% CI, 0.19-1.00) and gradually decreased thereafter (Figure 2), though the numbers in these subgroups are small and confidence intervals wide.

In sensitivity analyses for diagnostic delay, lagging the exposure by 1 year resulted in 1079 new RA cases and an HR of 0.83 (95% CI, 0.66-1.04). When the index date was defined by the earliest date of an indicator variable instead of a constant 1 year lag, there were 1049 new RA cases and the HR was 0.74 (95% CI, 0.58-0.93). Using the date of case-ascertainment instead of the original index date resulted in an HR of 0.76 (95% CI, 0.62-0.94). There were differences in persistence between cases and controls as well as the higher and lower intensity statin users (Table 2, Table 3). However, there was no statistically significant interaction between levels of persistence and statin intensity on the risk of RA (adjusted HR 0.75, 95% CI, 0.57-0.98), though here again the numbers in these strata are very small. When we used the intensity value of the initial statin prescription instead of the weighted average, the adjusted HR was 0.77 (95%CI, 0.60-0.99). Finally, the adjusted HR of incident RA for current statin users was 0.67 (95% CI, 0.52-0.86) and for recent statin users it was 0.98 (95% CI, 0.73-1.31), relative to past users.

Discussion

Results of this large population based study showed that high-intensity statin treatment was associated with a 23% reduction in the risk of incident RA in comparison to low-intensity statins. Highest quintile of duration-weighted average statin intensity in our study corresponds to treatment with atorvastatin 20-80 mg, rosuvastatin 5-40 mg, or simvastatin 80 mg. The association appeared most pronounced after six months of initiating statin treatment up to 3 years and gradually abated at long term, though the confidence intervals are very wide. This is the largest study on the association of statins with RA risk to date and the first to assess the effect of relative statin strength.

The crude incidence of RA in our statin user population was 7.9/10.000 person years. This incidence is comparable to the incidence of RA in the UK general population in the similar age range as our study population, namely 6.7/10.000 person years for males and 9.4/10.000 person years for females (22). The similarity of the incidence in our study population to the UK general population is reassuring with respect to the validity of our case selection algorithm while it might also be considered as argument against a large protective effect of statins.

Our primary exposure definition (i.e. duration-weighted average statin intensity) instead of a cumulative dose/cumulative follow-up duration with a recency analysis (i.e. current, recent and past use versus non-use) may be considered non-conventional for a pharmacoepidemiology study. However, the latter could have resulted in a high intensity statin category that would have included only the highly persistent high-intensity statin users while high intensity users with lower persistence would have been classified into

lower exposure categories. This would increase the risk of healthy adherer bias, which is common in observational studies of statins resulting in spurious statin benefits when individuals with good adherence are compared to those with poor adherence (12, 23). Our approach allowed us to remove persistence from our primary exposure and deal with it separately in our analysis. Similarly, we chose not to compare statin users to non-users because preventive medications are more likely prescribed to healthier individuals (23, 24) again possibly introducing bias associated with use vs non-use comparisons (24, 25).

Inhibition of HMG-CoA reductase by statins has multiple effects on cellular physiology. The product of this reaction, mevalonate, is converted to isoprenyl intermediates essential for post-translational modification of a host of proteins with diverse functions such as cytoskeletal integrity, protein trafficking and cellular signaling (26). These effects translate into a reduced antigen presenting cell function at various steps from endocytosis to antigen processing and presentation, including reduced expression of MHC class-II proteins, disruption of the immunological synapse, and reduced co-stimulatory signaling (27). Statins also reduce Th-1 and Th-17 cell differentiation and secretion of Th-1 type cytokines, such as interferon gamma (26, 27). These mechanisms provide some biological plausibility for our findings.

The effect of statin use on the risk of RA was investigated in three previous studies (Table-5) (7-9). In a nested case-control study from the CPRD population, current use of statins was associated with a decreased risk of RA (7). However, this effect was only apparent in subjects with a diagnosis of hyperlipidemia (OR: 0.59, 95% CI 0.37 to 0.95) and dose response could not be assessed due to an insufficient number of exposed cases (7). In

another study from a health maintenance organization cohort, good persistence with statin treatment (PDC≥80%) was associated with a substantial decrease in the risk of RA (HR: 0.58, 95% CI 0.52 to 0.65) (9) in comparison with poor persistence (PDC<20%). As an attempt to test the adequacy of their statistical adjustments for healthy-adherer bias, the authors also looked at the effect of the same exposure on the risk of osteoarthritis as a control outcome (28). They assumed that if adequate adjustment for healthy-adherer bias had been made, no association would have been observed between persistence with statin treatment and risk of osteoarthritis. However, good persistence with statin treatment was associated with a lower risk of osteoarthritis (HR: 0.85, 95% CI 0.81-0.88). Therefore, it is difficult to quantify the exact contribution of a true effect versus healthy-adherer bias to the risk estimate in that study. Finally, a case-control study found an increased risk of RA with statin use (OR: 1.71, 95% CI 1.16-2.53). However, this increased risk was associated with less than 4 prescriptions suggesting protopathic bias, and there was no significant effect of cumulative dose or treatment duration (8).

Two observational studies from the UK investigated the overall unintended effects of statin use in large population based cohorts (Table-5) (10, 11) and did not find any association between statin use and risk of RA. However, these studies were primarily designed to detect harm signals, numbers of individuals exposed to statins were lower than in our study and relative strengths of statins were not considered in the analyses for RA risk. Interestingly, in one of the secondary analyses by Hippisley-Cox et al (11) hazard ratio of RA with rosuvastatin, all available doses of which were in the highest intensity quintile in our study, was 0.84 (95% CI, 0.44 to 1.61) for women and 0.72 (95% CI, 0.27 to 1.92) for men. However, that study included only 4496 individuals exposed to rosuvastatin, whereas

our cohort included approximately 75000 individuals (Table 4) in the equivalent intensity quintile. Finally, in an observational study, risk of connective tissue disease was lower in users of statins in comparison to non-users (OR, 0.80; 95% CI, 0.64-0.99). However, this study did not exclude subjects with prevalent outcome at baseline, and did not analyze RA separately (29).

We analyzed a cohort of more than half a million new statin users from a large population-based primary care database where exposure and covariate data collection were prospective and independent of the outcome in a real-life setting. In addition to detailed prescription information, CPRD also includes data on smoking status and body habitus thereby allowing adjustments that were not possible in some previous studies (8, 9, 29). Employing a new-user design, an active comparator instead of a user vs non-user or adherer vs non-adherer comparison and a time-dependent exposure definition allowed us to minimize the risks of confounding by indication, healthy-adherer bias and time-related biases. Our case definition algorithm was based on a previous validation study that provided a sensitivity and specificity of more than 80% for a correct diagnosis of RA (30). The results were robust in a number of sensitivity analyses.

This study is not without limitations. First, exposure definition in the CPRD is based on prescription records and actual receipt of the medication from a pharmacy cannot be verified. This may lead to overestimation of the exposure. Secondly, simvastatin 10 mg is available over the counter in the UK making an underestimation of exposure to this drug a possibility. However, less than 10% of eligible persons purchase over the counter simvastatin in the UK and most of those that do still use other prescription statins (31).

These limitations, however, would not be expected to affect cases and controls differentially, and are therefore unlikely to bias our results. Our exposure variable, the duration-weighted average statin intensity is a strength, since it constitutes a single summary variable for all available statin compounds across all dose ranges, and a limitation, since it obscures differential effects of individual compounds, and their temporal relation with the risk of RA.

A recent observational study provided a decision tool to predict the risk of developing RA in patients with recent onset arthralgia based on clinical and family history, lifestyle and autoantibody status (32). Patients identified as being at high risk with this decision tool developed clinical RA with a 2-year probability of approximately 65%. Thus, assuming the magnitude of effect observed in our study, in a putative 2-year randomized controlled trial enrolling 150 subjects at the high risk level identified with such a decision tool, high intensity statin treatment would be expected to prevent or delay the onset of RA in 11 subjects in the intervention arm.

In conclusion, our study provides robust evidence supporting a protective effect of high intensity statins on the risk of RA. It remains to be determined whether high-intensity statin treatment prevents or delays the onset of RA. In the meantime, our results may inform dosing decisions of clinicians who need to initiate cholesterol-lowering therapy in individuals at high risk of RA.

References

1. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.

2. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol. 2004;57(5):640-51.

3. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207.

4. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015-21.

5. Forero-Pena DA, Gutierrez FR. Statins as modulators of regulatory T-cell biology. Mediators Inflamm. 2013;2013:167086.

6. De Jong HJ, Damoiseaux JG, Vandebriel RJ, Souverein PC, Gremmer ER, Wolfs M, et al. Statin use and markers of immunity in the doetinchem cohort study. PLoS One. 2013;8(10):e77587.

7. Jick SS, Choi H, Li L, McInnes IB, Sattar N. Hyperlipidaemia, statin use and the risk of developing rheumatoid arthritis. Ann Rheum Dis. 2009;68(4):546-51.

8. de Jong HJ, Klungel OH, van Dijk L, Vandebriel RJ, Leufkens HG, van der Laan JW, et al. Use of statins is associated with an increased risk of rheumatoid arthritis. Ann Rheum Dis. 2012;71(5):648-54.

9. Chodick G, Amital H, Shalem Y, Kokia E, Heymann AD, Porath A, et al. Persistence with statins and onset of rheumatoid arthritis: a population-based cohort study. PLoS Med. 2010;7(9):e1000336.

10. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol. 2009;67(1):99-109.

11. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. Bmj. 2010;340:c2197.

12. Dormuth CR, Patrick AR, Shrank WH, Wright JM, Glynn RJ, Sutherland J, et al. Statin adherence and risk of accidents: a cautionary tale. Circulation. 2009;119(15):2051-7.

13. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. Journal of general internal medicine. 2011;26(5):546-50.

14. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. Journal of clinical pharmacy and therapeutics. 2010;35(2):139-51.

15. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. BMC family practice. 2003;4:18.

16. Warren JR, Falster MO, Fox D, Jorm L. Factors influencing adherence in long-term use of statins. Pharmacoepidemiol Drug Saf. 2013;22(12):1298-307.

17. Oliver JE, Silman AJ. Risk factors for the development of rheumatoid arthritis. Scand J Rheumatol. 2006;35(3):169-74.

18. Lahiri M, Morgan C, Symmons DP, Bruce IN. Modifiable risk factors for RA: prevention, better than cure? Rheumatology (Oxford). 2012;51(3):499-512.

19. Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. BMC medical research methodology. 2005;5(1):5.

20. Suissa S. The quasi-cohort approach in pharmacoepidemiology: upgrading the nested case-control. Epidemiology. 2015;26(2):242-6.

21. Nicholson A, Ford E, Davies KA, Smith HE, Rait G, Tate AR, et al. Optimising use of electronic health records to describe the presentation of rheumatoid arthritis in primary care: a strategy for developing code lists. PLoS One. 2013;8(2):e54878.

22. Wiles N, Symmons DP, Harrison B, Barrett E, Barrett JH, Scott DG, et al. Estimating the incidence of rheumatoid arthritis: trying to hit a moving target? Arthritis Rheum. 1999;42(7):1339-46.

23. Patrick AR, Shrank WH, Glynn RJ, Solomon DH, Dormuth CR, Avorn J, et al. The association between statin use and outcomes potentially attributable to an unhealthy lifestyle in older adults. Value Health. 2011;14(4):513-20.

24. Glynn RJ, Schneeweiss S, Wang PS, Levin R, Avorn J. Selective prescribing led to overestimation of the benefits of lipid-lowering drugs. J Clin Epidemiol. 2006;59(8):819-28.

25. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology. 2001;12(6):682-9.

26. Ulivieri C, Baldari CT. Statins: from cholesterol-lowering drugs to novel immunomodulators for the treatment of Th17-mediated autoimmune diseases. Pharmacological research : the official journal of the Italian Pharmacological Society. 2014;88:41-52.

27. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol. 2006;6(5):358-70.

28. Dusetzina SB, Brookhart MA, Maciejewski ML. Control Outcomes and Exposures for Improving Internal Validity of Nonrandomized Studies. Health services research. 2015.

29. Schmidt T, Battafarano DF, Mortensen EM, Frei CR, Mansi I. Frequency of development of connective tissue disease in statin-users versus nonusers. The American journal of cardiology. 2013;112(6):883-8.

30. Thomas SL, Edwards CJ, Smeeth L, Cooper C, Hall AJ. How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? Arthritis Rheum. 2008;59(9):1314-21.

31. Mainous AG, 3rd, Baker R, Everett CJ, King DE. Impact of a policy allowing for over-the-counter statins. Quality in primary care. 2010;18(5):301-6.

32. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis. 2013;72(12):1920-6.

Figure Legends

Figure 1 Flow diagram of cohort selection. RA, rheumatoid arthritis; DMARD, disease modifying anti rheumatic drug.
* Cohort members counted in multiple risk sets unless case definition satisfied.

Figure 2 Relative risk of RA in follow-up categories after initiation of statin treatment in comparison to the lowest duration-weighted average intensity quintile. Percentages next to case and control numbers are within follow-up duration category.

Tables

Table 1 Characteristics of cases and controls.

Variable	Cases (n=1357)	Controls (n=13,570)
Age at cohort entry, mean (SD)	63.7 (9.4)	63.8 (9.3)
Age at index date, mean (SD)*	67.0 (9.6)	67.1 (9.5)
Male, n (%)*	539 (39.7)	5,390 (39.7)
Follow up duration, months (SD)*	39.2 (30.3)	39.2 (30.3)
Duration of statin use, months (SD)	27.8 (25.8)	28.8 (26.0)
Smoking status, n (%)		
Never smoker	254 (18.7)	3,528 (26.0)
Ever smoker	861 (63.4)	7,364 (54.3)
Missing	242 (17.8)	2,678 (19.7)
Baseline total cholesterol level, n (%)		
Low (<5.2 mmol/L)	152 (11.2)	1282 (9.4)
Moderate (5.2-6.2 mmol/L)	412 (30.4)	3,884 (28.6)
High (>6.2 mmol/L)	564 (41.6)	6,148 (45.3)
Missing	229 (16.9)	2,256 (16.6)
Obesity		
Non-obese (BMI<25)	635 (46.8)	6,393 (47.1)
Obese (BMI≥25)	353 (26.0)	3,427 (25.3)
Unknown	369 (27.2)	3,750 (27.6)
Co-morbid diseases n (%)		
Cardiovascular disease	361 (26.6)	3,533 (26.0)
Diabetes mellitus	286 (21.1)	2,919 (21.5)
Lung disease	269 (19.8)	2,026 (14.1)
Renal disease	30 (2.2)	328 (2.4)
Liver disease	11 (0.8)	73 (0.5)
Cancer	58 (4.3)	698 (5.1)
Hypothyroidism	120 (8.8)	1052 (7.8)
Other autoimmune disease	191 (14.1)	1043 (7.7)

SD, standard deviation.
* Matching variables

Table 2 Distribution of RA cases and controls by levels of persistence and intensity quintiles

	Duration-Weighted Average Intensity Quintiles											
	≤0.93		>0.93-1		>1-1.09		>1.09-1.2		>1.2		Total	
Persistence Categories	**Cases** (%)*	**Controls** (%)	**Cases** (%)	**Controls** (%)	**Cases** (%)	**Controls** (%)	**Cases** (%)	**Controls** (%)	**Cases** (%)	**Controls** (%)	**Cases** (%)	**Controls** (%)
<20%	41 (13.6)	336 (12.2)	34 (13.2)	304 (11.1)	31 (11.5)	240 (9.2)	26 (7.1)	200 (5.7)	7 (4.3)	85 (4.4)	139 (10.2)	1165 (8.6)
20% to 80%	98 (32.4)	800 (29.1)	70 (27.1)	670 (24.5)	93 (34.6)	763 (29.1)	115 (31.6)	1009 (28.6)	57 (34.8)	576 (29.6)	433 (31.9)	3818 (28.1)
>80%	163 (54.0)	1609 (58.6)	154 (59.7)	1757 (64.3)	145 (53.9)	1615 (61.7)	223 (61.3)	2324 (65.8)	100 (61.0)	1282 (66.0)	785 (57.9)	8587 (63.3)
Total	302	2745	258	2731	269	2618	364	3533	164	1943	**1357**	**13570**

*All percentages are within columns.

,

,

Table 3 Persistence with and duration of statin use in cases and controls across follow-up duration categories.

Follow-up duration	Case-Control Status	N	Number of current users at index date (%)*	Average duration of statin use, months (SD)	Average PDC, % (SD)	Median PDC, %
<6 months	Case	128	116 (90.6)	2.7 (1,6)	83.5 (22.6)	95.0
	Control	1280	1174 (91.7)	2.8 (1,6)	87.2 (20.3)	96.8
6-12 months	Case	150	112 (74.7)	6.4 (2,6)	73.6 (26.8)	83.8
	Control	1500	1201 (80.1)	6.6 (2,7)	75.2 (26.7)	86.8
12-36 months	Case	464	338 (72.8)	16.2 (8,7)	69.8 (29.6)	83.6
	Control	4640	3718 (80.1)	17.0 (8,4)	73.6 (28.4)	86.8
36-60 months	Case	298	218 (73.2)	33.5 (15,1)	71.2 (29.9)	84.8
	Control	2980	2392 (80.1)	34.4 (14,1)	73.3 (27.8)	86.0
>60 months	Case	317	248 (78.2)	59.6 (28,2)	70.9 (28.3)	83.4
	Control	3170	2633 (83.1)	61.5 (27,8)	73.3 (27.3)	85.8

*Current use defined as statin use within the 90 days prior to index date.
SD, standard deviation; PDC, proportion of days covered.

Table 4 Crude and adjusted hazard ratios of incident rheumatoid arthritis for quintiles of duration-weighted average statin intensity in comparison to the lowest quintile.

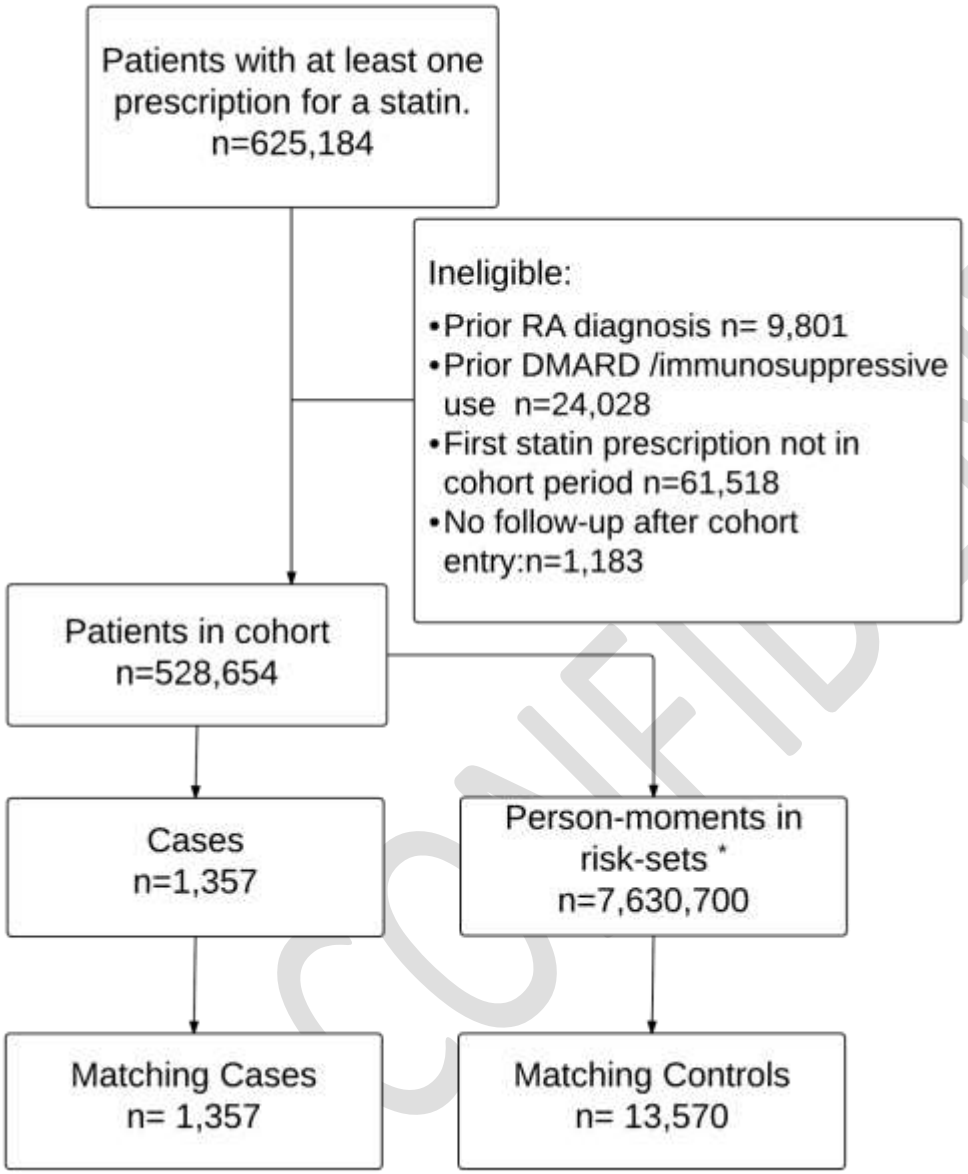
Duration-Weighted Average Statin intensity	Cases, n (%)	Controls, n (%)	Crude HR	*Adjusted HR (95% CI)
≤0.93	302 (22.3)	2,754 (20.2)	1.00	1.00 (Reference)
>0.93-1.00	258 (19.0)	2,731 (20.1)	0.85	0.86 (0.72-1.03)
>1.00-1.09	269 (19.8)	2,618 (19.3)	0.92	0.94 (0.79-1.13)
>1.09-1.2	364 (26.8)	3,533 (26.6)	0.92	0.94 (0.79-1.12)
>1.2	164 (12.1)	1,943 (14.3)	0.75	0.77 (0.63-0.95)

HR, hazard ratio.
*Adjusted for persistence with treatment (PDC), baseline cholesterol level, smoking, obesity, history of cardiovascular disease, non-iatrogenic hypothyroidism and autoimmune diseases.

Table 5 Summary of previous studies on the risk of RA with statin use.

Author, Year	Country, Setting, Study Type	RA cases, Exposed population	Reference for the effect estimate	Effect size (95%CI)	Limitations
Jick et al. 2009 (7)	UK, GPRD, Nested Case-Control	313 cases, 1252 controls 41 cases, 194 controls exposed to statins	283 controls with hyperlipidemia not exposed to statins, matched on age, sex and center.	OR: 0.59 (0.37 to 0.95) in current users of statins with hyperlipidemia.	- Small number of exposed cases - Current use defined as 2 or more prescriptions in pre-index year. - Low power to detect effects of individual statins
De Jong et al. 2011 (8)	Netherlands, LINH, Case-Control	496 cases, 2330 controls 81 cases, 204 controls exposed to statins	2165 controls not exposed to statins, matched on age and sex.	OR: 1.71 (1.16–2.53) overall. OR: 2.25 (1.27–3.98) in individuals with small number (1-4) of prescriptions	- Small number of exposed cases - Risk of protopathic bias; risk associated with statin use within 6 months before RA diagnosis.
Chodick et al. 2010 (9)	Israel, MHS, Cohort	2578 incident cases among 211,627 individuals exposed to statins.	57,690 individuals with a PDC less than 20% of follow-up.	HR: 0.58 (0.52–0.65) in individuals with≥80% PDC	- Case ascertainment; RA incidence very high in the age range comparable to the current study (47.8/10,000 py) - Risk of healthy-adherer bias; High PDC also preventive for osteoarthritis. - PDC assessment not time-dependent.
Smeeth et al. 2009 (10)	UK, THIN, Matched cohort	2532 incident cases in a matched cohort of 729,529 individuals. 227 cases exposed to statins among 129,288 exposed individuals	600,241 individuals matched on age, sex and center, not prescribed statins up-to the date of matching users' first statin prescription.	HR: 0.93 (0.73, 1.18)	-Not primarily designed to detect change in RA risk. -RA case definition not specified.
Hippisley-Cox et al. 2010 (11)	UK, QResearch, Cohort	5730 incident cases among 2,121,768 individuals. 225,922 new statin users among 342,998 exposed to statins.	1,778,770 individuals not exposed to statins.	*Highest HR: 1.13 (0.68 to 1.88) for pravastatin in men *Lowest HR: 0.72 (0.27 to 1.92) for rosuvastatin in men.	-Not primarily designed to detect change in RA risk. -RA case definition not specified.

*** HRs reported separately for men, women and individual drugs.**
GPRD, General Practice Research Database; LINH, Netherlands Information Network of General Practice; MHS, Maccabi Healthcare Services; THIN, The Health Improvement Network, PDC, proportion of days covered; OR, odds ratio; HR, hazard ratio; py, person-years.



Supplementary Appendix to Statins and the Risk of Rheumatoid Arthritis – A Nested Case-Control Study

Supplementary Methods, Tables and Figures

Calculation of duration-weighted average statin intensity

We determined the duration-weighted average statin intensity using the following formula:

$$Duration\text{-}weighted\ average\ intensity = \frac{\sum DPI \times NDS}{\sum NDS}$$

To do this, we used the statin intensity values in eTable-3. The number of days supplied (NDS) for each prescription was multiplied by the daily prescription intensity (DPI) value, providing "intensity-days" of the prescription. Then, the "intensity-days" of all prescriptions dispensed to a subject between cohort entry and index date were summed and divided by the total number of days supplied (and not the total number of days between cohort entry and index date). Therefore, if a patient received the same product for part of or the entire follow-up period, the average intensity was simply one of the corresponding values in eTable-3 (Figure S1A). However, if a patient received different doses of one statin or different statins during their follow-up, then the average intensity was an average value of the different intensities weighted by the number of days supplied (Figure S1B).Two study participants each with a 365-day follow-up duration are depicted in Figure-S1.The participant in Figure S1A would therefore have an average intensity value equal to that of Simvastatin 40mg, that is 1.1917 and a proportion of days covered (PDC) value of 0.52 (190/365) while the participant depicted in Figure S1B would have a final duration weighted average intensity value of 1.2333 [as calculated by the formula above (115x1.1917+140x1.2674)/(115+140)] and a PDC of 0.70 [(115+140)/365].

Figure S1 Exposure assessment showing 2 hypothetical study participants followed for 365 days between cohort entry and index date.

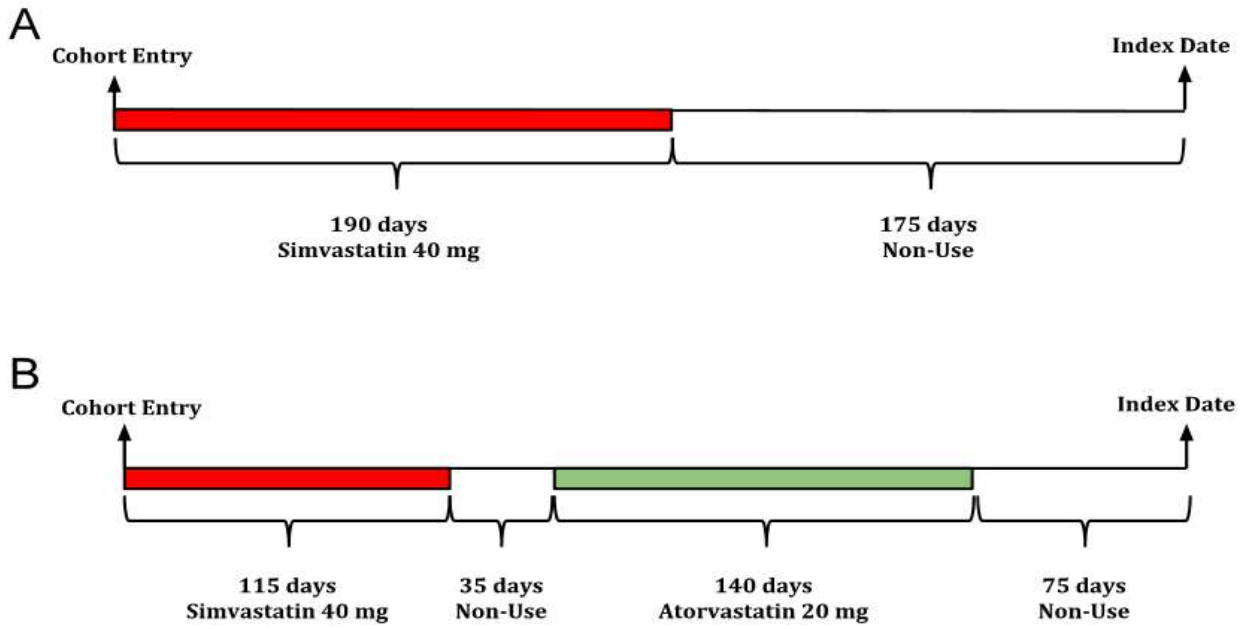


Table S1 Read codes used to define RA diagnosis.

Read Term	Read Code*
Rheumatoid arthritis	N040.00
Rheumatoid arthrit. monitoring	66H..13
Seronegative rheumatoid arthritis	N040P00
Flare of rheumatoid arthritis	N040T00
Seropositive rheumatoid arthritis, unspecified	N04X.00
Rheumatoid nodule	N042200
Rheumatoid arthritis and other inflammatory polyarthropathy	N04..00
Seropositive erosive rheumatoid arthritis	N047.00
Swan-neck finger deformity	N362200
Felty's syndrome	N041.00
Rheumatoid arthritis - multiple joint	N040S00
Fibrosingalveolitis associated with rheumatoid arthritis	N04y012
Rheumatoid lung	H570.00
O/E - ulnar deviation	2G25.11
Rheumatoid vasculitis	N040N00
Rheumatoid arthritis of knee	N040D00
Rheumatoid lung	N04y000
Rheumatoid nodule	N040R00
Rheumatoid arthritis of wrist	N040700
Rheumatoid arthritis of MCP joint	N040800
O/E-hands-rheumatoid spindling	2G27.00
Rheumatoid bursitis	N040Q00
Rheumatoid arthritis of ankle	N040F00
Other rheumatoid arthritis of spine	N040100
O/E - hands - ulnar deviation	2G25.00
Rheumatoid arthritis of PIP joint of finger	N040900

Table S1 Read codes used to define RA diagnosis.

Read Term	Read Code*
Rheumatoid arthropathy + visceral/systemic involvement NOS	N042z00
Rheumatoid carditis	G5yA.00
Rheumatoid arthritis of 1st MTP joint	N040K00
Rheumatoid arthritis of shoulder	N040200
Rheumatoid arthritis of elbow	N040500
Rheumatoid lung disease	N042100
Rheumatoid arthritis of hip	N040B00
Other rheumatoid arthropathy + visceral/systemic involvement	N042.00
[X]Seropositive rheumatoid arthritis, unspecified	Nyu1G00
Myopathy due to rheumatoid arthritis	F396400
Polyneuropathy in rheumatoid arthritis	F371200
Rheumatoid arthritis of cervical spine	N040000
[X]Other specified rheumatoid arthritis	Nyu1200
Rheumatoid arthritis of DIP joint of finger	N040A00
Rheumatoid myocarditis	G5y8.00
[X]Other seropositive rheumatoid arthritis	Nyu1100
Caplan's syndrome	N04y011
Rheumatoid arthritis of talonavicular joint	N040H00
Rheumatoid arthritis of subtalar joint	N040G00
Rheumatoid arthritis of other tarsal joint	N040J00
Rheumatoid arthritis of distal radio-ulnar joint	N040600

*Ordered in accordance with the frequency of appearance in the CPRD database.

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
Methotrexate		
	Maxtrex injection 2.5mg/ml [PHARMACIA]	27342
	Maxtrextablets 10mg [PHARMACIA]	21753
	Maxtrex tablets 2.5mg [PHARMACIA]	13428
	Methotrexate injection 10mg/0.4ml	7337
	Methotrexate injection 10mg/1ml	32865
	Methotrexate injection 12.5mg/0.5ml	7336
	Methotrexate injection 15mg/0.6ml	16540
	Methotrexate injection 15mg/1.5ml	27404
	Methotrexate injection 17.5mg/0.7ml	18890
	Methotrexate injection 20mg/0.8ml	14347
	Methotrexate injection 20mg/0.8ml [CENT HOME]	34258
	Methotrexate injection 20mg/2ml	26064
	Methotrexate injection 22.5mg/0.9ml	17672
	Methotrexate injection 25mg/1ml	16519
	Methotrexate injection 25mg/2.5ml	24634
	Methotrexate injection 25mg/ml	8583
	Methotrexate injection 27.5mg/1.1ml	27642
	Methotrexate injection 30mg/1.2ml	30703
	Methotrexate injection 50mg/2ml	24783
	Methotrexate injection 50mg/3ml	8327
	Methotrexate injection 5mg/0.2ml	30932
	Methotrexate injection 5mg/2ml	9528
	Methotrexate injection 7.5mg/0.3ml	16570
	Methotrexate injection 7.5mg/0.75ml	35402

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
	Methotrexate oral solution 10mg/5ml	36800
	Methotrexate oral suspension 10mg/5ml	36849
	Methotrexate oral suspension 12.5mg/5ml	28041
	Methotrexate oral suspension 7.5mg/5ml	35752
	Methotrexate sodium injection 25mg/ml	14748
	Methotrexate sodium tablets 2.5mg	18424
	Methotrexate sterile powder 500mg/vial	29069
	Methotrexate suspension 2.5mg/5ml	17035
	Methotrexate tablets 10mg	877
	Methotrexate tablets 10mg [MAYNE]	34929
	Methotrexate tablets 2.5mg	823
	Methotrexate tablets 2.5mg [GOLDSHIELD]	20951
	Methotrexate tablets 2.5mg [MAYNE]	32111
	Methotrexate tablets 2.5mg [PHARMACIA]	30780
	Metoject injection 10mg/1ml [MEDAC UK]	37117
	Metojectinjection 15mg/1.5ml [MEDAC UK]	27400
	Metoject injection 20mg/2ml [MEDAC UK]	14348
	Metoject injection 25mg/2.5ml [MEDAC UK]	33601
	Metoject injection 7.5mg/0.75ml [MEDAC UK]	35865
Leflunomide		
	Arava tablets 100mg [AVENTIS]	18460
	Aravatablets 10mg [AVENTIS]	16522
	Arava tablets 20mg [AVENTIS]	17642
	Leflunomide tablets 100mg	4970
	Leflunomidetablets 10mg	4971
	Leflunomide tablets 20mg	6934
Sulfasalazine		

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
	Salazopyrin EN- tablets 500mg [PHARMACIA]	380
	Salazopyrinsuspension 250mg/5ml [PHARMACIA]	14054
	Salazopyrin suspension 250mg/5ml [PHARMACIA]	17880
	Salazopyrintablets 500mg [PHARMACIA]	1566
	Salazopyrin tablets 500mg [PHARMACIA]	4978
	Sulazine EC enteric coated tablets 500mg [CHATFIELD]	23401
	Sulfasalazine enteric coated tablets 500mg	508
	Sulfasalazine enteric coated tablets 500mg [ACTAVIS]	20862
	Sulfasalazine enteric coated tablets 500mg [CERETRON]	34894
	Sulfasalazine enteric coated tablets 500mg [DDSA]	33682
	Sulfasalazine suspension 250mg/5ml	7497
	Sulfasalazine suspension 250mg/5ml	11767
	Sulfasalazine tablets 500mg	2920
	Sulfasalazine tablets 500mg	5427
	Sulfasalazine tablets 500mg [ACTAVIS]	31949
	Sulfasalazine tablets 500mg [APS]	33968
	Sulfasalazine tablets 500mg [GEN (UK)]	34473
	Sulfasalazine tablets 500mg [HILLCROSS]	31667
Anti-Malarials		
	Avloclor tablets 250mg [ASTRAZENEC]	3325
	Chloroquine phosphate syrup 80mg/5ml	10658
	Chloroquinephosphate tablets 250mg	422
	Chloroquinesulphate injection 272.5mg(200mg base)/5ml	15362
	Chloroquinesulphate syrup 68mg/5ml	265
	Chloroquinesulphate tablets 200mg	456
	Hydroxychloroquinesulphate oral solution 200mg/5ml	29566
	Hydroxychloroquine sulphate tablets 200mg	672

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
	Malarivon syrup 80mg/5ml [WALLACE]	23441
	Nivaquine injection 272.5mg(200mg base)/5ml [AVENTIS]	463
	Nivaquinesyrup 68mg/5ml [AVENTIS]	3169
	Nivaquine syrup 68mg/5ml [SANOFI/AVE]	14828
	Nivaquinetablets 200mg [AVENTIS]	3224
	Nivaquine tablets 200mg [BEACON]	13022
	Plaquenil tablets 200mg [SANOFI S]	4946
Gold Compounds		
	Auranofin tablets 3mg	3934
	Myocrisin injection 10mg/0.5ml [SANOFI/AVE]	283
	Myocrisininjection 20mg/0.5ml [SANOFI/AVE]	3329
	Myocrisin injection 50mg/0.5ml [SANOFI/AVE]	3267
	Ridaura TILTAB tablets 3mg [ASTELLAS]	13493
	Sodium aurothiomalate injection 10mg/0.5ml	10842
	Sodium aurothiomalate injection 20mg/0.5ml	16606
	Sodium aurothiomalate injection 50mg/0.5ml	4470
D-Penicillamine		
	Oprisine tablets 50mg [OPUS]	19072
	Pendraminetablets 125mg [VIATRIS]	29721
	Pendraminetablets 250mg [VIATRIS]	20255
	Penicillamine tablets 125mg	643
	Penicillaminetablets 125mg [ACTAVIS]	31216
	Penicillamine tablets 125mg [GEN (UK)]	40170
	Penicillamine tablets 125mg [IVAX]	31120
	Penicillamine tablets 250mg	604
	Penicillamine tablets 250mg [ACTAVIS]	30925
	Penicillamine tablets 250mg [GEN (UK)]	34684

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
	Penicillamine tablets 250mg [HILLCROSS]	31217
	Penicillamine tablets 50mg	267
Azathioprine		
	Azamune tablets 50mg [PENN]	12339
	Azathioprine capsules	770
	Azathioprine capsules 10mg	39115
	Azathioprine injection 50mg/vial	270
	Azathioprine oral solution 50mg/5ml	22982
	Azathioprine oral solution 50mg/ml	36792
	Azathioprine oral suspension 50mg/5ml	35518
	Azathioprine tablets 10mg	13320
	Azathioprine tablets 25mg	451
	Azathioprine tablets 25mg [GEN (UK)]	34816
	Azathioprine tablets 25mg [HILLCROSS]	32101
	Azathioprine tablets 50mg	571
	Azathioprine tablets 50mg [GEN (UK)]	34451
	Azathioprine tablets 50mg [HILLCROSS]	34687
	Azathioprine tablets 50mg [IVAX]	29340
	Azathioprine tablets 50mg [KENT]	31215
	Berkaprine tablets 50mg [RORER]	26261
	Distamine tablets 125mg [ALLIANCE]	3327
	Distaminetablets 250mg [ALLIANCE]	8904
	Distamine tablets 50mg [ALLIANCE]	11959
	Immunoprin tablets 50mg [ASHBOURNE]	21899
	Imuran injection 50mg/vial [WELLCOME]	14395
	Imuran tablets 10mg [WELLCOME]	30495
	Imuran tablets 25mg [WELLCOME]	671

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
	Imuran tablets 50mg [WELLCOME]	1899
Cyclosporine		
	Ciclosporin capsules 100mg	3896
	Ciclosporincapsules 10mg	16035
	Ciclosporin capsules 25mg	2838
	Ciclosporin capsules 50mg	2837
	Ciclosporinconcentrate for solution for infusion 50mg/1ml	38056
	Ciclosporin concentrate for solution for infusion 50mg/ml	19370
	Ciclosporinoral solution 100mg/ml	1626
	Neoral capsules 100mg [NOVARTIS]	973
	Neoralcapsules 10mg [NOVARTIS]	16137
	Neoral capsules 25mg [NOVARTIS]	972
	Neoral capsules 50mg [NOVARTIS]	4231
	Neoraloral solution 100mg/ml [NOVARTIS]	1905
	Sandman capsules 100mg [NOV/SANDOZ]	13556
	Sandimmuncapsules 25mg [NOV/SANDOZ]	3920
	Sandimmuncapsules 50mg [NOV/SANDOZ]	15596
	Sandimmunconcentrate for solution for infusion 50mg/ml [NOV/SANDOZ]	26790
	Sandimmunsugar free solution 100mg/ml [NOV/SANDOZ]	13494
Biologics		
	Adalimumab injection 40mg	6882
	Anakinra injection 100mg/0.67ml	36726
	Certolizumabpegol 200mg/1ml solution for injection pre-filled syringes	44100
	Cimzia 200mg/1ml solution for injection pre-filled syringes (UCB Pharma Ltd)	43703
	Enbrel injection solution 25mg [WYETH PHAR]	35419

Table S2 List ofDMARD products and product codes used to identify RA cases		
Compound	**Product**	**Product Code**
	Enbrel injection solution 50mg [WYETH PHAR]	36556
	Enbrel powder for solution for injection 25mg [WYETH PHAR]	14886
	Enbrel powder for solution for injection 50mg [WYETH PHAR]	19257
	Etanercept injection solution 25mg	36008
	Etanercept injection solution 50mg	35126
	Etanercept powder for solution for injection 25mg	15921
	Etanercept powder for solution for injection 50mg	26387
	Golimumab 50mg/0.5ml solution for injection pre-filled disposable devices	46370
	Golimumab 50mg/0.5ml solution for injection pre-filled syringes	47398
	Humira injection 40mg [ABBOTT]	23850
	Kineret injection 100mg/0.67ml [AMGEN]	32418
	Remicade powder for concentrate for solution for infusion 100mg [SCHERING-P]	22392
	Rituximab concentrate for intravenous infusion 10mg/ml	39111
	Rituximab concentrate for solution for infusion 100mg/10ml	28490
	Rituximab concentrate for solution for infusion 500mg/50ml	36294
	Simponi 50mg/0.5ml solution for injection pre-filled disposable devices (Merck Sharp &Dohme Ltd)	47740
	Tocilizumab 200mg/10ml solution for infusion vials	46348
	Tocilizumab 80mg/4ml solution for infusion vials	41502

Table S3 Relative statin intensities based on reduction in LDL

Compound, strength	*LDL reduction in RCTs, %	Assigned Intensity	Corresponding Intensity quintile
Atorvastatin 10 mg	37.2	1.07849	3
Atorvastatin 20 mg	43.7	1.26744	5
Atorvastatin 40 mg	48.7	1.40988	5
Atorvastatin 80 mg	50.1	1.45058	5
Cerivastatin 100 mcg	18.0**	0.52151	1
Cerivastatin 200 mcg	21.0**	0.60843	1
Cerivastatin 400 mcg	25.1**	0.72722	1
Cerivastatin 800 mcg	29.2**	0.84601	1
Fluvastatin 20 mg	18.5	0.53488	1
Fluvastatin 40 mg	23.6	0.68314	1
Fluvastatin 80 mg	34.3	0.99419	2
Lovastatin 10 mg	22.1	0.63953	1
Lovastatin 20 mg	26.7	0.77326	1
Lovastatin 40 mg	31.2	0.90407	1
Lovastatin 80 mg	39.0	1.13081	4
Pravastatin 10 mg	20.2	0.58430	1
Pravastatin 20 mg	24.1	0.69767	1
Pravastatin 40 mg	25.1	0.72674	1
Rosuvastatin 5 mg	41.6	1.20640	5
Rosuvastatin 10 mg	46.2	1.33721	5
Rosuvastatin 20 mg	50.1	1.45058	5
Rosuvastatin 40 mg	56.1	1.62500	5
Simvastatin 10 mg	30.2	0.87500	1
Simvastatin 20 mg	34.5	1.00000§	2

Simvastatin 40 mg	41.3	1.19767	4
Simvastatin 80 mg	47.4	1.37209	5

RCT, randomized controlled trial, LDL, low-density lipoprotein
* LDL reduction based on point estimates provided in Figure-1 of Weng et al. J Clin Pharm Ther. 2010;35(2):139-51
** LDL reduction based on point estimates provided in Figure-1 of Edwards et al. BMC FamPract. 2003;4:18.
§ Reference intensity

Table S4 Read codes used to define other autoimmune diseases.

Read Term	Read Code*
BILAG - British isles lupus assessment group score	ZR2l.11
Cerebral lupus	N000600
Disseminated lupus erythematosus	N000000
Lung disease with systemic lupus erythematosus	H57y400
Lupus erythematosus	M154.00
Lupus erythematosus NOS	M154z00
Lupus erythematosus profundus	M154400
Lupus erythematosus tumidus	M154500
Lupus nephritis	K01x411
Nephrotic syndrome in systemic lupus erythematosus	K01x400
Polyneuropathy in disseminated lupus erythematosus	F371000
SLAM - Systemic lupus activity measure	ZRq8.11
Subacute cutaneous lupus erythematosus	M154700
Systemic lupus activity measure	ZRq8.00
Systemic lupus erythematosus	N000.00
Systemic lupus erythematosus disease activity index	ZRq9.00
Systemic lupus erythematosus NOS	N000z00
Systemic lupus erythematosus with organ or sys involv	N000300
Systemic lupus erythematosus with pericarditis	N000400
Acute scleroderma renal crisis	K0H..00
Lung disease with systemic sclerosis	H572.00
Myopathy due to scleroderma	F396600
Progressive systemic sclerosis	N001000
Scleroderma	N001.00
Systemic sclerosis	N001.12
[X]Dermatopolymyositis, unspecified	Nyu4E00
Dermatomyositis	N003.00
Dermatopolymyositis, unspecified	N003X00

Table S4 Read codes used to define other autoimmune diseases.	
Read Term	**Read Code***
Gottron's papules	M21y800
Lung disease with polymyositis	H57y100
Polymyositis	N004.00
Polymyositisossificans	N231400
Idiopathic thrombocytopenic purpura	D313.12
Idiopathic thrombocytopenic purpura	D313000
ITP - idiopathic thrombocytopenic purpura	D313012
Coeliac disease	J690.00
Coeliac disease annual review	6648000
Coeliac disease annual review declined	8IAp.00
Coeliac disease monitoring	6648
Coeliac disease monitoring invitation	9mB..00
Coeliac disease monitoring invitation first letter	9mB1.00
Coeliac disease NOS	J690z00
Dietary advice for coeliac disease	ZC2C200
Gluten enteropathy	J690.13
Sprue - nontropical	J690.14
Benign multiple sclerosis	F204.00
Exacerbation of multiple sclerosis	F203.00
Generalised multiple sclerosis	F202.00
Kurtz multiple sclerosis rating scale	ZRVE.00
Management of multiple sclerosis in early disease phase	8Cc1.00
Management of multiple sclerosis in onset phase	8Cc0.00
Management of multiple sclerosis in palliative phase	8Cc4.00
Management of multiple sclerosis in stable disability phase	8Cc2.00
Multiple sclerosis	F20..00
Multiple sclerosis care plan agreed	8CS1.00
Multiple sclerosis monitoring administration	9mD..00
Multiple sclerosis multidisciplinary review	666B.00

Table S4 Read codes used to define other autoimmune diseases.	
Read Term	**Read Code***
Multiple sclerosis NOS	F20z.00
Multiple sclerosis of the brain stem	F200.00
Multiple sclerosis of the spinal cord	F201.00
Multiple sclerosis review	666A.00
Multiple sclerosis review declined	8IAb.00
Neuromyelitisoptica	F210.00
Primary progressive multiple sclerosis	F206.00
Referral to community multiple sclerosis team	8Hkv.00
Relapsing and remitting multiple sclerosis	F207.00
Secondary progressive multiple sclerosis	F208.00
Spec serv for pat with multiple sclerosis - enhserv admin	9kG..00
Guillain-Barre syndrome	F370000
Miller-Fisher syndrome	F370200
Churg-Strauss vasculitis	G758.00
Microscopic polyangiitis	G75A.00
Myopathy due to polyarteritisnodosa	F396300
Nephrotic syndrome in polyarteritis nodosa	K01x300
Polyarteritis nodosa	G750.00
Polyarteritis nodosa and allied conditions	G75..00
Polyarteritis nodosa and allied conditions NOS	G75z.00
Polyneuropathy in polyarteritis nodosa	F371100
Wegener's granulomatosis	G754.00
Autoimmune chronic active hepatitis	J614111
Autoimmune hepatitis	J63B.00
Primary biliary cirrhosis	J616000
[X]Other pemphigoid	Myu1200
[X]Other pemphigus	Myu1000
Benign mucous membrane pemphigoid	M146.00
Benign mucous membrane pemphigoid NOS	M146z00

Table S4 Read codes used to define other autoimmune diseases.	
Read Term	**Read Code***
Benign mucous membrane pemphigoid with no eye involvement	M146000
Benign pemphigus	M144000
Benign pemphigus NOS	M145100
Bullous pemphigoid	M145000
Cicatricial pemphigoid	M146011
Erythematous pemphigus	M144200
Foliaceous pemphigus	M144300
Ocular pemphigoid	F4Cy100
Ocular pemphigoid	M146100
Pemphigoid	M145.00
Pemphigoid NOS	M145z00
Pemphigus	M144.00
Pemphigus NOS	M144z00
Pemphigus vegetans	M144500
Pemphigus vulgaris	M144600
Wildfire pemphigus	M144700
[X]Other psoriatic arthropathies	Nyu1300
Arthritis mutilans	M160200
Chronic large plaque psoriasis	M161F11
Distal interphalangeal psoriatic arthropathy	M160100
Erythrodermic psoriasis	M161H00
Guttate psoriasis	M161600
Other psoriasis	M161.00
Palmoplantar pustular psoriasis	M166.00
Psoriasis and similar disorders	M16..00
Psoriasis and similar disorders NOS	M16z.00
Psoriasis annularis	M161100
Psoriasis circinata	M161200
Psoriasis diffusa	M161300

Table S4 Read codes used to define other autoimmune diseases.

Read Term	Read Code*
Psoriasis discoidea	M161400
Psoriasis geographica	M161500
Psoriasis gyrata	M161700
Psoriasis inveterata	M161800
Psoriasis NOS	M161z00
Psoriasis ostracea	M161900
Psoriasis palmaris	M161A00
Psoriasis plantaris	M161B00
Psoriasis punctata	M161C00
Psoriasis spondylitica	M160000
Psoriasis universalis	M161E00
Psoriasis unspecified	M161000
Psoriasis vulgaris	M161F00
Psoriatic arthritis	M160.11
Psoriatic arthropathy	M160.00
Psoriatic arthropathy NOS	M160z00
Pustular psoriasis	M161D00
Scalp psoriasis	M16y000
Leucoderma	M295.00
Leucoderma NOS	M295z00
Vitiligo	M295100
Vitiligo of eyelid	F4E5311
[X]Other ulcerative colitis	Jyu4100
Arthropathy in ulcerative colitis	N031000
Exacerbation of ulcerative colitis	J410400
Ulcerative (chronic) enterocolitis	J411.00
Ulcerative (chronic) ileocolitis	J412.00
Ulcerative colitis	J410100
Ulcerative colitis and/or proctitis	J41..12

Table S4 Read codes used to define other autoimmune diseases.	
Read Term	**Read Code***
Ulcerative ileocolitis	J410000
Ulcerative pancolitis	J413.00
Ulcerative proctocolitis	J410.00
Ulcerative proctocolitis NOS	J410z00
Giant cell arteritis	G755.00
Giant cell arteritis with polymyalgia rheumatica	N200.00
Polymyalgia	N20..11
Polymyalgia rheumatica	N20..00
Temporal arteritis	G755100
Horton's disease	G755200
Juvenile or adult myasthenia gravis	F380100
Myasthenia gravis	F380.00
Myasthenia gravis NOS	F380z00
Lung disease with Sjogren's disease	H57y300
Myopathy due to Sjogren's disease	F396700
Sicca (Sjogren's) syndrome	N002.00
Autoimmune haemolyticanaemias	D110.00
Evan's syndrome	D313.11
Acute and subacuteiridocyclitis	F440.00
Anterior uveitis	F443000
Chronic anterior uveitis	F441200
Chronic iridocyclitis	F441.00
Chronic iridocyclitis NOS	F441z00
Iridocyclitis	F44..12
Panuveitis	F401100
Posterior uveitis NOS	F432200
Primary iridocyclitis	F440200
Recurrent iridocyclitis	F440300
Unspecified acute iridocyclitis	F440000

Table S4 Read codes used to define other autoimmune diseases.	
Read Term	**Read Code***
Unspecified chronic iridocyclitis	F441000
Unspecified iridocyclitis	F443.00
Uveitis NOS	F443.11
[X]Sarcoidosis of other and combined sites	Cyu0600
Hepatic granulomas in sarcoidosis	J63A.00
Lupus pernio	AD53000
Meningitis due to sarcoidosis	F013.00
Multiple cranial nerve palsies in sarcoidosis	F326300
Myopathy due to sarcoidosis	F396500
Myositis in sarcoidosis	N233200
Polyneuropathy in sarcoidosis	F374900
Pulmonary sarcoidosis	H57y200
Sarcoid arthropathy	AD55.00
Sarcoid heart disease	G558300
Sarcoid myocarditis	G5y7.00
Sarcoidosis	AD5..00
Sarcoidosis of inferior turbinates	AD54.00
Sarcoidosis of lung	AD50.00
Sarcoidosis of lung with sarcoidosis of lymph nodes	AD52.00
Sarcoidosis of lymph nodes	AD51.00
Sarcoidosis of skin	AD53.00
Acute adrenal insufficiency	C154000
Addisonian crisis	C154600
Addisonian crisis	C154011
Addison's disease	C154100
Adrenal crisis	C154012
Adrenal hypofunction	C154z11
Adrenal insufficiency NEC	C154z12
Autoimmune polyglandular failure	C182.00

Table S4 Read codes used to define other autoimmune diseases.	
Read Term	**Read Code***
Corticoadrenal insufficiency	C154.00
Corticoadrenal insufficiency NOS	C154z00
Myopathy due to Addison's disease	F395000
[X]Other Crohn's disease	Jyu4000
Arthropathy in Crohn's disease	N031100
CDAI - Crohn's disease activity index	ZR3S.11
Crohn's colitis	J401z11
Crohn's disease	J40..11
Crohn's disease activity index	ZR3S.00
Crohn's disease NOS	J40z.11
Crohn's disease of the ileum NOS	J400400
Crohn's disease of the ileum unspecified	J400300
Crohn's disease of the large bowel NOS	J401z00
Crohn's disease of the small bowel NOS	J400z00
Crohn's disease of the terminal ileum	J400200
Exacerbation of Crohn's disease of large intestine	J401200
Exacerbation of Crohn's disease of small intestine	J400500
Juvenile arthritis in Crohn's disease	N045300
Orofacial Crohn's disease	J08z900
Regional enteritis - Crohn's disease	J40..00

Table S5 Characteristics of Controls by exposure category.

Variable	Duration Weighted Average Intensity ≤0.93	>0.93-1	>1-1.09	>1.09-1.2	>1.2
N	2,745	2,731	2,618	3,533	1,943
Age at Index date (mean±std)	67.9 ± 9.5	67.5 ± 9.4	67.3 ± 9.4	66.5 ± 9.5	65.9 ± 9.4
Male, n (%)	1,110 (40.4)	1,083 (39.7)	975 (37.2)	1,463 (41.4)	759 (39.1)
Follow-up, months (mean±std)	39.7 ± 31.1	34.1 ± 28.7	40.8 ± 30.8	37.8 ± 29.4	45.7 ± 31.0
Smoking status, n (%)					
Non-Smoker	659 (24.0)	773 (28.3)	657 (25.1)	991 (28.0)	448 (23.1)
Smoker	1,359 (49.5)	1,482 (54.3)	1,345 (51.4)	2,029 (57.4)	1,149 (59.1)
Missing	727 (26.5)	476 (17.4)	616 (23.5)	513 (14.5)	346 (17.8)
Body mass index n (%)					
Non-Obese	1,346 (49.0)	1,306 (47.8)	1,207 (46.1)	1,657 (46.9)	877 (45.1)
Obese	562 (20.5)	670 (24.5)	651 (24.9)	1,007 (28.5)	537 (27.6)
Missing	837 (30.5)	755 (27.6)	760 (29.0)	869 (24.6)	529 (27.2)
Baseline Cholesterol Level n (%)					
Low (<5.2 mmol/L)	255 (9.3)	260 (9.5)	211 (8.1)	410 (11.6)	146 (7.5)
Moderate (5.2-6.2 mmol/L)	811 (29.5)	868 (31.8)	736 (28.1)	1,067 (30.2)	402 (20.7)
High (>6.2 mmol/L)	1,047 (38.1)	1,209 (44.3)	1,209 (46.2)	1,606 (45.5)	1,077 (55.4)
Missing	632 (23.0)	394 (14.4)	462 (17.6)	450 (12.7)	318 (16.4)
Co-morbidity, n (%)					
Cardiovascular disease	845 (30.8)	624 (22.8)	674 (25.7)	877 (24.8)	513 (26.4)
Diabetes	524 (19.1)	517 (18.9)	636 (24.3)	816 (23.1)	419 (21.6)
Lung Disease	379 (13.8)	386 (14.1)	393 (15.0)	572 (16.2)	296 (15.2)

Renal Disease	47 (1.7)	83 (3.0)	42 (1.6)	119 (3.4)	37 (1.9)
Liver Disease	20 (0.7)	10 (0.4)	10 (0.4)	24 (0.7)	9 (0.5)
Cancer	140 (5.1)	139 (5.1)	136 (5.2)	189 (5.3)	94 (4.8)
Hypothyroidism (non-iatrogenic)	204 (7.4)	189 (6.9)	223 (8.5)	263 (7.4)	173 (8.9)
History of autoimmune disease	206 (7.5)	222 (8.1)	185 (7.1)	273 (7.7)	157 (8.1)

Std, standard deviation.
Percentages within exposure category.

Table S6 Characteristics of cases by exposure category

Variable	Duration Weighted Average Intensity ≤0.93	>0.93-1	>1-1.09	>1.09-1.2	>1.2
N	302	258	269	364	164
Age at Index date (mean±std)	68.4 ± 9.7	67.3 ± 9.5	66.8 ± 9.2	66.7 ± 9.7	65.1 ± 9.8
Male	107 (35.4)	106 (41.1)	112 (41.6)	152 (41.8)	62 (37.8)
Follow-up Time, in months (mean±std)	39.0 ± 31.7	35.0 ± 27.3	42.0 ± 31.3	35.1 ± 27.7	50.3 ± 32.8
Smoking status, n (%)					
Non-Smoker	57 (18.9)	48 (18.6)	57 (21.2)	63 (17.3)	29 (17.7)
Smoker	175 (57.9)	172 (66.7)	148 (55.0)	255 (70.1)	111 (67.7)
Missing	70 (23.2)	38 (14.7)	64 (23.8)	46 (12.6)	24 (14.6)
Body mass index n (%)					
Non-Obese	145 (48.0)	127 (49.2)	123 (45.7)	174 (47.8)	66 (40.2)
Obese	66 (21.9)	59 (22.9)	68 (25.3)	106 (29.1)	54 (32.9)
Missing	91 (30.1)	72 (27.9)	78 (29.0)	84 (23.1)	44 (26.8)
Baseline Cholesterol Level n (%)					
Low (<5.2 mmol/L)	30 (9.9)	32 (12.4)	31 (11.5)	45 (12.4)	14 (8.5)
Moderate (5.2-6.2 mmol/L)	93 (30.8)	80 (31.0)	80 (29.7)	121 (33.2)	38 (23.2)
High (>6.2 mmol/L)	121 (40.1)	106 (41.1)	101 (37.5)	146 (40.1)	90 (54.9)
Missing	58 (19.2)	40 (15.5)	57 (21.2)	52 (14.3)	22 (13.4)
Co-morbidity					
Cardiovascular disease	88 (29.1)	61 (23.6)	79 (29.4)	86 (23.6)	47 (28.7)
Diabetes	65 (21.5)	49 (19.0)	67 (24.9)	66 (18.1)	39 (23.8)

Lung Disease	66 (21.9)	55 (21.3)	43 (16.0)	72 (19.8)	33 (20.1)
Renal Disease	7 (2.3)	5 (1.9)	6 (2.2)	8 (2.2)	4 (2.4)
Liver Disease	4 (1.3)	3 (1.2)		3 (0.8)	1 (0.6)
Cancer	13 (4.3)	15 (5.8)	6 (2.2)	19 (5.2)	5 (3.0)
Hypothyroidism (non-iatrogenic)	26 (8.6)	19 (7.4)	26 (9.7)	33 (9.1)	16 (9.8)
History of autoimmune disease	45 (14.9)	31 (12.0)	40 (14.9)	51 (14.0)	24 (14.6)

Std, standard deviation.
Percentages within exposure category.

Table S7 Numbers of current statin users by exposure category

		Duration Weighted Average Intensity					
	Current Use	**≤0.93**	**>0.93-1**	**>1-1.09**	**>1.09-1.2**	**>1.2**	**Total**
Controls	No	630	565	473	537	247	2452
	(%)	(23.0)	(20.9)	(18.1)	(15.2)	(12.7)	(18.1)
	Yes	2115	2166	2145	2996	1696	11118
	(%)	(77.0)	(79.1)	(81.9)	(84.8)	(87.3)	(81.9)
Cases	No	88	69	78	69	21	325
	(%)	(29.1)	(26.7)	(29.0)	(19.0)	(12.8)	(23.9)
	Yes	214	189	191	295	143	1032
	(%)	(70.9)	(73.3)	(71.0)	(81.0)	(87.2)	(76.1)

Percentages within exposure categories separately for cases and controls.

Figure S2 Relative treatment intensities for statin compounds, interpolated using splines.