**Jong, H.J.I. de, Klungel, O.H., Dijk, L. van, Vandebriel, R.J., Leufkens, H.G.M., Laan, J.W. van der, Cohen Tervaert, J.W., Loveren, H. van. Use of statins is associated with an increased risk of rheumatoid arthritis. Annals of the Rheumatic Diseases: 2012, 71(5), 648-654**



# Use of statins is associated with an increased risk of rheumatoid arthritis

H J I DE JONG[1,2,3], O H KLUNGEL[3], L VAN DIJK[4], R J VANDEBRIEL[1], H G M LEUFKENS[3], JW VAN DER LAAN[5], J W COHEN TERVAERT[6], H VAN LOVEREN[1,2]

[1]Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[2]Department of Toxicogenomics, Maastricht University Medical Centre, Maastricht, The Netherlands
[3]Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Faculty of Sciences, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[4]Pharmaceutical Care, Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands
[5]Centre for Biological Medicines and Medical Technology, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[6]Division of Clinical and Experimental Immunology, Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands
Correspondence to O H Klungel, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, PO Box 80 082, 3508 TB Utrecht, The Netherlands; o.h.klungel@uu.nl.

## ABSTRACT

Objectives Statins offer significant cardiovascular benefits. Their use, however, influences immune regulation, which may potentially facilitate autoimmunity, eventually resulting in autoimmune diseases such as rheumatoid arthritis (RA).The authors studied whether statin use was associated with an increased risk of developing RA by conducting a case–control study using the Netherlands Information Network of General Practice database.

Methods The authors identified 508 patients aged 40 years or older with a first-time diagnosis of RA in the period 2001–2006. Each RA case was matched to five controls for age, sex and index date, which was selected 1 year before the first diagnosis of RA. Odds ratios for the first-time diagnosis of RA were verified by a referral to a rheumatologist and/or at least one prescription of disease-modifying anti-rheumatic drugs and/or two prescriptions of corticosteroids after the date of first diagnosis.

Results Cases were more often users of statins (15.9%) compared to controls (8.6%). After adjustment for cardiovascular risk factors and use of comedication, statin use was associated with an increased risk of incident RA (adjusted OR, 1.71 (95% CI 1.16 to 2.53); p=0.007). A consistent trend of increasing risk with increased cumulative duration, cumulative defined daily doses and number of prescriptions was not observed. However, a small trend between the potency of statin treatment and the risk of RA was found.

Conclusions Statin use seems to be associated with an increased risk of developing RA. Our findings should be replicated by additional studies.

## INTRODUCTION

Epidemiological studies have shown an increasing prevalence of autoimmune diseases in highly industrialised countries, which cannot be attributed to better diagnosis alone but may be due to increased drug use.[1 2] Concerns about preventive therapies such as statins, which are widely prescribed to reduce the risk of cardiovascular morbidity and mortality in patients with hyperlipidaemia, hypertension or diabetes, have been raised.[3,–,5] Several studies have shown that statins, in addition to their cholesterol-lowering activity, have anti-inflammatory and immunomodulatory properties, suppressing the expression of ongoing autoimmune responses.[6,–,11] Such immunomodulating effects may hypothetically also facilitate the development of autoimmunity, potentially resulting in autoimmune diseases such as systemic lupus erythematosus and autoimmune hepatitis.[12 13] Recently, a meta-analysis showed an association between statins and an increased risk of diabetes.[14] As no distinction between the types of diabetes was made, no conclusions on mechanisms could be drawn.

Several studies demonstrated that statins may exacerbate or trigger cellular apoptosis[12 15 16] and induce a shift in Th1/Th2 balance, leading to production of autoantibodies.[12 17] An increasing number of case reports suggest that statins can trigger rare autoimmune diseases, raising the question on whether these commonly prescribed drugs may facilitate the development of more common autoimmune diseases such as rheumatoid arthritis (RA). So far, few studies have assessed the risk of developing RA after statin treatment. A population-based case–control and cohort study reported that statins may be protective against the development of RA in patients with hyperlipidaemia,[18 19] while two other population-based cohort studies did not observe an association between statin use and incident RA.[20 21] We conducted a case–control study to determine the risk of developing RA associated with different exposure aspects (duration, dose, type and potency) of statin use.

## METHODS

### Study population

We used the Netherlands Information Network of General Practice (LINH), a database derived from general practices that register data on morbidity, drug prescriptions and referrals in electronic medical records on a continuous basis. The LINH network includes 350 000 patients who were registered at 85 practices in 2001–2006.[22] For a number of practices, data on drug prescriptions were not available before the year 2001. Prescription data were classified according to Anatomical Therapeutic and Chemical (ATC) classification,[23] and morbidity was coded using the International Classification of Primary Care (ICPC).[24]

### Case definition

All patients who were first diagnosed as having RA and had a medical history of at least 1 year at index date were included in the study (figure 1). Subsequent diagnoses of RA were disregarded. The date exactly 1 year before the date of the first-time diagnosis of RA was subsequently used as the ‘index date’ because the diagnosis is usually made after the disease has been symptomatic for some period of time.[25 26] From the arthritis group (ICPC code L88), we verified the first-time diagnosis of RA registered by a general practitioner (GP) if:

1. The patient was referred to a rheumatologist, or
2. At least one disease-modifying anti-rheumatoid drug (DMARD; immunosuppressants, aminoquinolines, gold preparations and sulfasalazine) was prescribed after the index date, or
3. Two or more prescriptions of systemic corticosteroids (glucocorticoids and combinations) were distributed after the index date.

Since statins are widely prescribed for patients with cardiovascular diseases or cardiac risk factors that are more prevalent among older patients, patients younger than 40 years of age were excluded from the study. Furthermore, patients were excluded if they had a medical record of ankylosing spondylitis (ICPC code L88.2) or were taking at least one prescription of DMARDs before the index date, if they had been

diagnosed by the GP as having RA with no confirmation according to the above-mentioned criteria or if they had no registered medical history for 1 year.

**[FIGURE 1] [TABLE 1]**

### Control selection

Five controls were matched to each RA case on age (within 5 years), sex and index date. Controls were required to be registered in general practice for at least 1 year before the index date to minimise information bias. The exclusion criteria used in case selection were applied to controls.

**[TABLE 2]**

### Definition of exposure and potential confounders

Exposure to statins was defined as the use of any approved and commercially available statins (pravastatin, simvastatin, cerivastatin, atorvastatin and fluvastatin) in The Netherlands before the index date. The hazard function between statin use and RA is unknown; therefore, different aspects of statin use were defined. Statin users were patients who had received at least one prescription of statins before the index date. We determined the type of statins based on their last prescription before the index date. The potency of statins was determined by combining the type and the dose of statin into a single potency score to control for the fact that different types and doses of statins differ with respect to percentage reduction in total cholesterol (see online supplementary table 1).[27] Potency was divided into four categories of increasing potency: potencies 2 and 3, potency 4, potency 5, and potencies 6 and 7. The expected duration of statin use until the index date was based on treatment time and prescribed drug supply (determined by the number of prescribed tablets). We calculated the cumulative dose of statins according to defined daily dose (DDD), which is the assumed average daily dose of a drug for its main indication in adults (see online supplementary table 2).[23] Adherence to statin use was calculated by dividing the sum of the days' supply by the total number of days between the first prescription and the last prescription of statins in the year before the index date, multiplied by 100%. To determine adherence to statin use, we excluded patients who received one prescription of statins and did not use statins 1 year before the index date. Patients who received one prescription of statins before the index date were not excluded from other analyses.

Potential confounders included prescriptions (in the 6 months before the index date) for non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, proton pump inhibitors, aspirin, antibiotics and hormone replacement treatment, and comorbidity (diabetes, hyperlipidaemia, hypertension, cardiovascular disease and asthma).[28] The ICPC and ATC codes for comorbidity are presented in table 1.

### Statistical analysis

Logistical regression conditioned on matching factors was used to study the association between statin use and risk of RA. Odds ratios and 95% CI were estimated. We evaluated the effects of cumulative duration, cumulative DDDs, number of prescriptions, and the specific type and potency of statins on the risk of developing RA. In addition to controlling for age, sex and calendar time by matching, we adjusted the estimates for the above-mentioned confounders. Furthermore, we evaluated the confounding effects of asthma, aspirin and antibiotics, but we did not include these covariates in the regression models because we did not observe more than 10% differences in the estimate of exposure–outcome association by adding each time 1 of these three variables into the model.[29] We examined whether there was a linear trend across the categories of the potencies of statins by including the categorical variables as ordinal variables in the regression model. P values of $\leq 0.05$ were considered statistically significant. We used SAS V.9.1 (SAS Institute, Cary, North Carolina, USA) to analyse the data.

We performed 11 different sensitivity analyses to test the robustness of our findings, which are presented online (see online supplementary table 3).

[TABLE 3]

## RESULTS

In the study population, 3074 patients with a first-time diagnosis were identified, of whom 9 patients did not have a matched control and 642 patients had a medical record of ankylosing spondylitis. Of 2423 patients with RA, 848 patients were referred to a rheumatologist, 425 patients received at least one prescription of a DMARD and 817 patients were treated with two or more prescriptions of systemic corticosteroids after the index date. Regarding the 848 patients who were referred to a rheumatologist, 155 patients were treated with a DMARD after the index date. As a result of verifying the first-time diagnosis of RA, we identified 508 eligible cases that were matched to 2369 controls. Of the patients with RA, the average age was 63 years, approximately 67% of the patients were female and 3% of the patients were diagnosed as having psoriasis. Fourteen per cent of the patients with RA were users of statins. Two patients with RA used other lipid-lowering medications. Use of corticosteroids and NSAIDs was higher in patients with RA than in controls. The duration of registration with the GP was approximately 11.3 years in patients with RA and 10.3 years in controls. The baseline characteristics of the study population are presented in table 2.

Table 3 shows the results of analyses with different exposure aspects of statin use. Statin use was associated with an increased risk of developing RA (adjusted OR, 1.71 (95% CI 1.16 to 2.53); p=0.007). Regarding the number of prescriptions, an increased risk of developing RA was found for all categories of statin use compared to non-users. No trend between an increasing number of prescriptions and an enhanced risk of developing RA was observed. We explored the effect of the duration of statin use. After adjustment, an increased risk of developing RA was found for different categories of the duration of statin use. No clear relation between the duration of statin use and an increased risk of developing RA was observed. When data were analysed for different levels of DDD, we found no trend between the different DDD groups of statins and the risk of developing RA.

Regarding confounding effects on the different strata of DDD, duration of statin prescriptions and number of statin prescriptions, the association between statin use and the risk of developing RA was weaker compared to the result of our overall analysis with ever use of statins.[30] Categorising exposure according to level of adherence did reveal differences in effect. Only patients with an adherence rate of more than 80% had an increased risk of incident RA.

The association between individual statins, their potencies and the risk of RA is shown in table 4. All types and potencies of statins showed an enhanced risk of incident RA. Regarding the potency of statin treatment, we observed a small trend between the different categories of the potencies of statin treatment and the risk of RA (p for trend <0.01). The results of 11 different sensitivity analyses are presented online (see online supplementary table 3).

[TABLE 4]

## DISCUSSION

The findings were consistent with the hypothesis that statin use is associated with an increased risk of developing RA. We did not observe a consistent trend of increasing risk with increased cumulative duration, increased cumulative DDDs and increased number of prescriptions. However, we observed a small trend between the potency of statin treatment and the risk of RA. With our baseline characteristics taken into account, cardiovascular diseases and cardiovascular risk factors (eg, hyperlipidaemia) may have influenced our results.

Our hypothesis was made a priority for this study and was supported by several case reports describing the occurrence of autoimmune diseases during treatment with statins.[12 13] Our findings are not in line with previous studies which found that statins exert a protective effect or no effect on developing RA.[18,–,21] In a nested case–control study of 313 patients with incident RA and 1252 matched controls aged 40–89 years, current statin use was associated with a reduced risk of developing RA in patients with a diagnosis of hyperlipidaemia, whereas no association was found for patients without a diagnosis of hyperlipidaemia.[18]

Because of limited data on hyperlipidaemia in our study, we analysed the data of patients without a medical record for cardiovascular disease, diabetes and hypertension, and we still found an increased risk of developing RA associated with statin use. Recently, three population-based cohort studies of patients who were initially treated with statins have shown conflicting results.[19,–,21] Smeeth et al[21] reported no effect of statins on the development of RA, whereas Chodick et al[19] reported a reduction in the risk of developing RA when patients were treated with statins. Both the study of Smeeth et al[21] and the study of Chodick et al[19] excluded patients with RA in the first year after the index date. In contrast to our retrospective study, these two prospective studies hypothetically considered a lag time between exposure to statins and incident RA. This could explain the differences between these two cohort studies and our results because we found an increased risk of RA within 6 months of statin use. Another prospective population-based cohort study of more than 2 million patients from 368 general practices in England and Wales showed no association between statin use and the risk of developing RA.[20] In comparison with this population-based cohort study, we used a more sensitive definition of RA by verifying the patient electronic records with a referral to a rheumatologist and/or at least one DMARD prescription and/or two corticosteroid prescriptions after the date of the first diagnosis of RA. In the study of Hippisley-Cox and Coupland,[20] patients were included as cases if they only had a diagnostic code for RA. Using a more inclusive definition of RA may have diluted the association between statin use and incident RA.

The underlying mechanisms by which statins may facilitate RA are unknown, and it was not possible to investigate them in our study. Statins are suggested to have a direct immunomodulating effect on T cells that may promote a shift in Th1/Th2 balance, leading to production of autoantibodies.[12 17] Statins may affect regulatory T cells that are critical for maintaining peripheral tolerance and preventing the development of RA.[31,–,33] Recent studies have suggested that regulatory T cells can be unstable in the periphery and may promote autoimmunity.[34 35] According to these studies, we hypothesise that statins do not cause autoimmunity but may promote a pre-existing autoimmune-prone condition to progress towards a clinical disease such as RA. Another possibility is that self-tolerance is lost due to non-specific bystander activation provided by local inflammation (microbial infection), which could result in the formation of neo-antigens.[36] This mechanism may be induced by statins that have been proven to reduce Th1 responses.[8]

One of the strengths of our study is the use of a computerised database, allowing us to use routinely recorded medical and prescription data from GPs. Consequently, recall bias was minimised. Our study contains a relatively large number of patients with RA, which allowed an assessment of the association between statins and RA with sufficient precision. Finally, we performed a range of sensitivity analyses regarding outcome definition, exposure definition, and inclusion and exclusion criteria. All these analyses consistently showed an increased risk of incident RA associated with statin use.

Some limitations of this study should be considered. A concern may be the power of this study; therefore, we used a definition of RA that is based on GP diagnosis, a referral to a rheumatologist or prescriptions of DMARDs or corticosteroids after the index date. Thus, we may have used a relatively sensitive but non-specific diagnosis of RA because no specific ICPC codes were available for other rheumatic diseases (e.g., systemic lupus erythematosus and psoriatic arthritis) that may have attenuated the association between statins and RA. However, our results remained unchanged when the analyses were restricted to patients with RA who were referred to a rheumatologist or who received DMARDs after their first-time diagnosis, or when we excluded from the analysis patients with a diagnosis of psoriasis or patients who used corticosteroids and NSAIDs before the index date. In addition, we have attempted to verify the first-time diagnosis of RA by the GP: if patients were referred to a rheumatologist and received at least one DMARD prescription after the index date, or if patients were prescribed DMARDs after the index date. Using these two criteria for defining RA, we have only included patients who were referred to a rheumatologist and were prescribed DMARDs by their GP, or patients who were treated with DMARDs by their GP. When DMARDs were prescribed by the rheumatologist, the prescription of the patient may not always appear in the LINH data set. The LINH database does not provide medical information from the rheumatologist, but the Dutch guidelines for optimising GP–medical specialist communication enjoin medical specialists to inform GPs of the first results of the diagnostics and treatments of the referred patient.[37 38] Due to this possible underestimation of patients with RA, we may have introduced selection bias that may produce an underestimation of the association.

Using computerised prescription data from the GP may have introduced an overestimation of actual statin use. However, this misclassification is likely to be non-differential between cases and controls and,

therefore, would probably have resulted in an underestimation of the association between statin use and RA.

In this study, we found an effect of statin use on the risk of developing RA. We observed no effect of past statin use and no trend between different groups of duration, DDDs and prescriptions of statins and the risk of developing RA. This may be due to the small number of patients in the study.

There were no available data on dietary intake, physical activity and smoking, and there were limited available data on other examinations (eg, lipid levels, inflammatory and immunomodulatory markers (eg, anti-nuclear antibodies, anti-citrullinated protein antibodies)) that may be important confounders. By conducting simulation analyses with potential effects of smoking,[39] we estimated the impact of smoking on the association between statin use and the development of RA.[40] Our findings were similar after adjusting for smoking. Nonetheless, we cannot exclude the possibility of residual confounding.

Cardiovascular morbidity and mortality are enhanced in patients with RA, and this could be due to the inflammatory process and the increased prevalence of traditional cardiovascular risk factors such as hyperlipidaemia.[41,–,43] Several studies have demonstrated an unfavourable lipid profile in patients with RA.[41 44] Therefore, statin use could be a proxy for hyperlipidaemia, which may be responsible for an increased risk of developing RA in our study. With our baseline characteristics taken into account, cardiovascular diseases and cardiovascular risk factors (eg, hyperlipidaemia) may have influenced our results. Therefore, we should consider that the increased risk of RA was due to hyperlipidaemia and not due to statins. Conversely, several studies did not find significant differences between the lipid profile of patients with RA and the lipid profile of the general population.[45,–,47] These conflicting results can be attributed to inflammation and treatment with lipid-lowering drugs.[45 46 48] Myasoedova et al[45] reported that reduction of lipid levels in patients with RA is unlikely to be solely due to lipid-lowering treatment. Additionally, confounding by indication may have affected the results of this study. We have limited information on hyperlipidaemia due to under-registration of this diagnosis in the GPs' records. Therefore, to minimise confounding by indication, we conducted a subgroup analysis based on cardiovascular risk profile. Statin use was associated with an increased risk of incident RA in patients with a low cardiovascular risk profile.

With the potency of statins taken into account, certain assumptions about disease severity in the patients in our study can be made. We believe that a high potency of statins is related to severe cardiovascular disease/hyperlipidaemia. Based on this assumption, we would expect the association between the increased potency of statin treatment and the risk of developing RA to disappear or to be much more diminished among those cases with severe cardiovascular disease and/or hyperlipidaemia. However, we observed a small trend between an increased potency of statin treatment and an increased risk of RA. Taken together, it is not very likely that hyperlipidaemia is the only risk factor.

Selection bias might have been introduced in this study because GPs could have paid more attention to the comorbidities of patients with RA. Consequently, these patients may have an increased probability of receiving statins. A sensitivity analysis in which we included controls who were registered and visited the GP showed similar results. Additionally, the average duration of registration with the GP is almost equal between patients with RA and controls, indicating that the patients in our study had similar opportunities to have been prescribed a statin.

Differences between GPs could have biased the results of our study if there are differences in diagnoses and prescribing regimens per practice. However, because of the small number of patients with RA per GP, we did not control for general practice effects in our analysis. It is likely that statins were prescribed before the first-time diagnosis of RA. In our study, we could define the date of onset of RA by the first record of the GP for RA, but the date of onset of the RA symptoms is unknown.[49] Chan et al[25] reported that the median time between the onset of symptoms and the diagnosis of RA was less than 1 year. To prevent this possible type of bias (protopathic bias) of defining the date of onset, we performed several sensitivity analyses by modifying the index date exactly 2, 3 and 4 years before the first-time diagnosis of RA. Our results remained unchanged in all sensitivity analyses. Because of the small sample size of the study population, we used an index date exactly 1 year before the first-time diagnosis of RA. From approximately 500 000 eligible patients, we ultimately included 508 patients with RA in our study. Our restricted sample of patients with RA may hamper the external validity of the study.

Our study shows that even if statins are effective in suppressing symptoms of ongoing autoimmunity, they also seem to be associated with an increased risk of developing RA. Our findings should be replicated by

additional studies. When confirmed, these findings indicate that precaution should be taken when prescribing statins for individuals with a low risk of cardiovascular disease.

Acknowledgments:The authors would like to thank the staff of LINH for their help with data collection and data extraction, and R Janssen for her helpful suggestions. Funding: This work was supported by research grant S340040 from the National Institute for Public Health and the Environment. The funder had no role in study design, in the analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

Competing interests: All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author) and declare (1) no support from any company for the submitted work; (2) no relationship with any company that might have an interest in the submitted work in the previous 3 years; (3) that their spouses, partners or children have no financial relationships that may be relevant to the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed

## REFERENCES

1. WHO Collaborating Centre for Immunotoxicology and Allergic Hypersensitivity. Principles and Methods for Assessing Autoimmunity Associated with Exposure to Chemicals: Environmental Health Criteria 236. Bilthoven, The Netherlands: World Health Organization, 2006.
2. Mongey AB, Hess EV. Drug insight: autoimmune effects of medications—what's new? Nat Clin Pract Rheumatol 2008;4:136–44.
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
4. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.
5. Sever PS, Dahlöf B, Poulter NR, et al
6. . Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.
7. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009;373:1175–82.
8. McCarey DW, McInnes IB, Madhok R, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet 2004;363:2015–21.
9. Arnaud C, Braunersreuther V, Mach F. Toward immunomodulatory and anti-inflammatory properties of statins. Trends Cardiovasc Med 2005;15:202–6.
10. Kanda H, Yokota K, Kohno C, et al. Effects of low-dosage simvastatin on rheumatoid arthritis through reduction of Th1/Th2 and CD4/CD8 ratios. Mod Rheumatol 2007;17:364–8.
11. Funk JL, Chen J, Downey KJ, et al. Bone protective effect of simvastatin in experimental arthritis. J Rheumatol 2008;35:1083–91
12. Lodi S, Evans SJ, Egger P, et al. Is there an anti-inflammatory effect of statins in rheumatoid arthritis? Analysis of a large routinely collected claims database. Br J Clin Pharmacol 2010;69:85–94.
13. Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. J Eur Acad Dermatol Venereol 2007;21:17–24.
14. Alla V, Abraham J, Siddiqui J, et al. Autoimmune hepatitis triggered by statins. J Clin Gastroenterol 2006;40:757–61.
15. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735–42.
16. Mevorach D. Systemic lupus erythematosus and apoptosis: a question of balance. Clin Rev Allergy Immunol 2003;25:49–60.
17. Chapman-Shimshoni D, Yuklea M, Radnay J, et al. Simvastatin induces apoptosis of B-CLL cells by activation of mitochondrial caspase 9. Exp Hematol 2003;31:779–83.

18. Youssef S, Stüve O, Patarroyo JC, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature 2002;420:78–84.
19. Jick SS, Choi H, Li L, et al. Hyperlipidaemia, statin use and the risk of developing rheumatoid arthritis. Ann Rheum Dis 2009;68:546–51.
20. Chodick G, Amital H, Shalem Y, et al. Persistence with statins and onset of rheumatoid arthritis: a population-based cohort study. PLoS Med 2010;7:e1000336.
21. 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.
22. Smeeth L, Douglas I, Hall AJ, et al. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol 2009;67:99–109.
23. Linh.nl [internet]. Utrecht: Netherlands Institute for health services research; c1992 - [updated 2011 May 30; cited 2011 Sept 25]. Available from: http://www.linh.nl/
24. Whocc.no [internet]. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; c1996 [updated 2010 Dec 21; cited 2011 Sept 25]. Available from: http://www.whocc.no/atc_ddd_index/
25. Lamberts H, Wood M. ICPC. International Classification of Primary Care. Oxford: Oxford University Press, 1987.
26. Chan KW, Felson DT, Yood RA, et al. The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. Arthritis Rheum 1994;37:814–20.
27. Palm Ø, Purinszky E. Women with early rheumatoid arthritis are referred later than men. Ann Rheum Dis 2005;64:1227–8.
28. Penning-van Beest FJ, Termorshuizen F, Goettsch WG, et al. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. Eur Heart J 2007;28:154–9.
29. Pedersen M, Jacobsen S, Klarlund M, et al. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther 2006;8:R133.
30. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–37.
31. Greenland S, Robin MR, Pearl J. Confounding and collapsibility in causal inference. Stat Sci 1999;14:29–46.
32. Kagami S, Owada T, Kanari H, et al. Protein geranylgeranylation regulates the balance between Th17 cells and Foxp3+ regulatory T cells. Int Immunol 2009;21:679–89.
33. Esensten JH, Wofsy D, Bluestone JA. Regulatory T cells as therapeutic targets in rheumatoid arthritis. Nat Rev Rheumatol 2009;5:560–5.
34. Tang TT, Song Y, Ding YJ, et al. Atorvastatin upregulates regulatory T cells and reduces clinical disease activity in patients with rheumatoid arthritis. J Lipid Res 2011;52:1023–32.
35. Zhou X, Bailey-Bucktrout SL, Jeker LT, et al. Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells in vivo. Nat Immunol 2009;10:1000–7.
36. Komatsu N, Mariotti-Ferrandiz ME, Wang Y, et al. Heterogeneity of natural Foxp3+ T cells: a committed regulatory T-cell lineage and an uncommitted minor population retaining plasticity. Proc Natl Acad Sci U S A 2009;106:1903–8.
37. Kivity S, Agmon-Levin N, Blank M, et al. Infections and autoimmunity—friends or foes? Trends Immunol 2009;30:409–14.
38. Preston C, Cheater F, Baker R, et al. Left in limbo: patients' views on care across the primary/secondary interface. Qual Health Care 1999;8:16–21.
39. Kvamme OJ, Olesen F, Samuelson M, et al. Improving the interface between primary and secondary care: a statement from the European Working Party on Quality in Family Practice (EQuiP). Qual Health Care 2001;10:33–9.
40. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70–81.
41. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 1998;54:948–63.
42. van Halm VP, Nielen MM, Nurmohamed MT, et al. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann Rheum Dis 2007;66:184–8.
43. Solomon DH, Greenberg J, Reed G,
44. et al.. Cardiovascular risk among patients with RA in CORRONA: comparing the explanatory value of traditional cardiovascular risk factors with RA risk factors. Ann Rheum Dis 2008;67:482.

45. Peters MJ, Nielen MM, Raterman HG, et al. Increased cardiovascular disease in patients with inflammatory arthritis in primary care: a cross-sectional observation. J Rheumatol 2009;36:1866–8.
46. Steiner G, Urowitz MB. Lipid profiles in patients with rheumatoid arthritis: mechanisms and the impact of treatment. Semin Arthritis Rheum 2009;38:372–81.
47. Myasoedova E, Crowson CS, Kremers HM, et al. Total cholesterol and LDL levels decrease before rheumatoid arthritis. Ann Rheum Dis 2010;69:1310–4.
48. Hurt-Camejo E, Paredes S, Masana L, et al. Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile. Arthritis Rheum 2001;44:2761–7.
49. Goodson NJ, Silman AJ, Pattison DJ, et al. Traditional cardiovascular risk factors measured prior to the onset of inflammatory polyarthritis. Rheumatology (Oxford) 2004;43:731–6.
50. Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. Am J Med 2008;121(10 Suppl 1):S21–31.
51. Vandebroucke JP. Oral contraceptives and rheumatoid arthritis. Lancet 1983;2:228–9.

**FIGURE AND TABLES**

Figure 1 Study fl ow diagram.

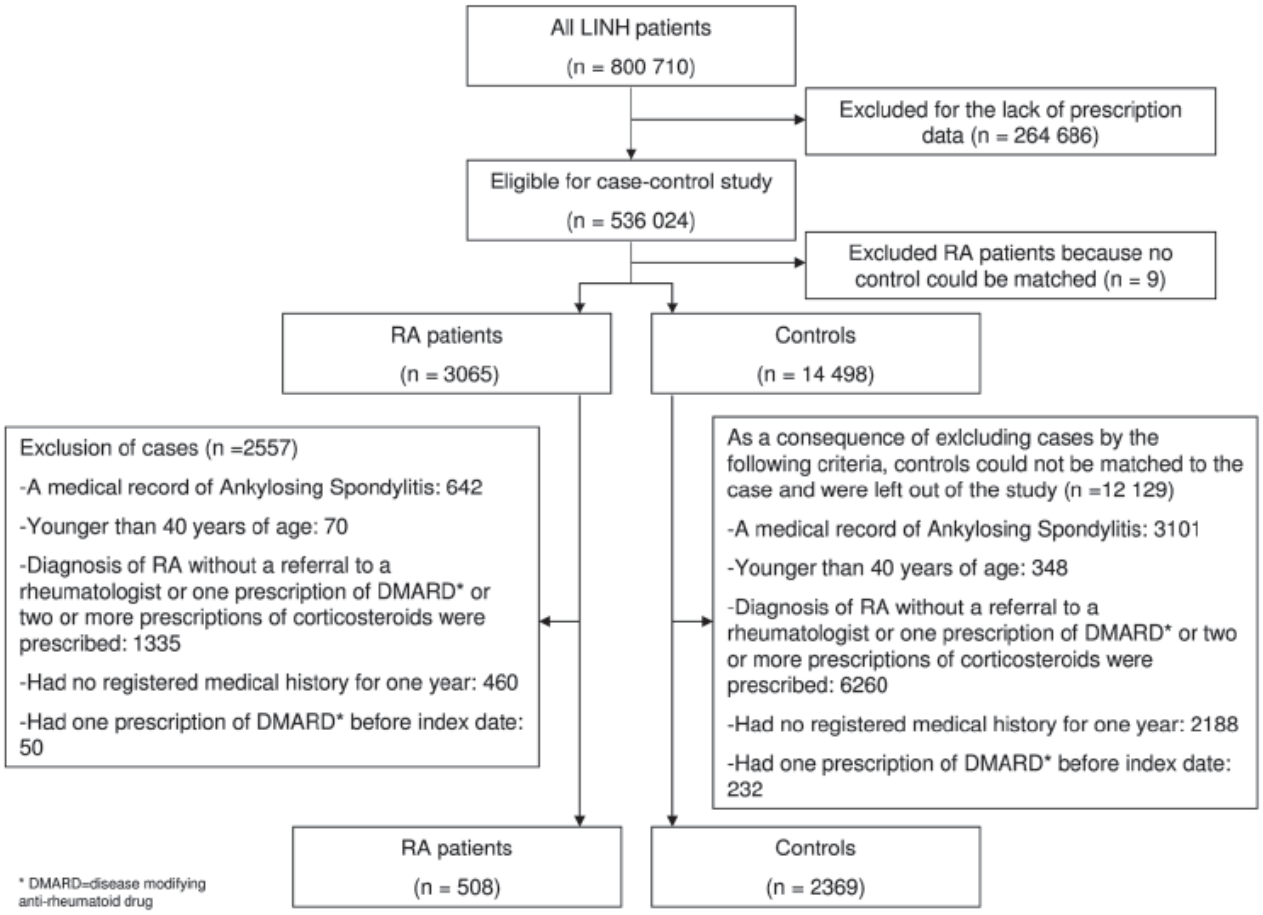

**Table 1** The definitions and ICPC and ATC codes for comorbidity

| | | |
|---|---|---|
| Comorbidity | At least one medical record of a disease (ICPC codes) | At least one prescription of drugs before the index date (ATC codes) |
| Diabetes | Diabetes (T90) | Insulin (A10A), oral-blood-glucose-lowering drugs (A10B) |
| Hyperlipidaemia | Lipid disorder (T93) | |
| Hypertension | Elevated blood pressure (K85), hypertension (K86, K87) | Anti-hypertensive drugs (C02), diuretics (C03), β blockers (C07), calcium channel blockers (C08), ACE inhibitors and angiotensin antagonists (C09) |
| Cardiovascular disease | Heart disease (K71), congenital anomaly cardiovascular (K73), ischaemic heart disease with angina (K74), acute myocardial infarction (K75), ischaemic heart disease without angina (K76), heart failure (K77), atrial fibrillation/flutter (K78), paroxysmal tachycardia (K79), cardiac arrhythmia (K80), heart/arterial murmur (K81), pulmonary heart disease (K82), heart valve disease (K83), heart disease other (K84), transient cerebral ischaemia (K89), stroke/cerebrovascular accident (K90), cerebrovascular disease (K91), atherosclerosis (K92), pulmonary embolism (K93), phlebitis/ thrombophlebitis (K94), varicose veins of leg (K95), haemorrhoids (K96), cardiovascular disease other (K99) | |
| Inflammatory bowel disease | Chronic enteritis/ulcerative colitis (D94) | |
| Asthma | Asthma (R96) | |

ATC, Anatomical Therapeutic and Chemical; ICPC, International Classification of Primary Care.

**Table 2** Baseline characteristics of the study population before the index date

| | Case (n=508) | Control (n=2369) |
|---|---|---|
| Sex | | |
| Male, % (n) | 32.5 (165) | 34.2 (810) |
| Female, % (n) | 67.5 (343) | 65.8 (1559) |
| Age in years, mean (SD) | 63.4 (12.9) | 62.8 (12.8) |
| Duration registration at general practice, % (n)* | | |
| 1–5.99 years | 24.3 (118) | 23.5 (487) |
| 6–11.99 years | 34.3 (174) | 33.8 (800) |
| ≥12 years | 38.2 (194) | 33.3 (790) |
| Disease history before the index date | | |
| Diabetes, % (n) | 8.7 (44) | 7.1 (167) |
| Hypertension, % (n) | 45.3 (230) | 30.6 (724) |
| Cardiovascular disease, % (n) | 24.6 (125) | 13.9 (330) |
| Hyperlipidaemia, % (n) | 5.5 (28) | 3.8 (89) |
| Hepatic disease, % (n) | 2.0 (10) | 0.7 (16) |
| Renal disease, % (n) | 1.6 (8) | 0.6 (13) |
| Asthma, % (n) | 8.7 (44) | 2.4 (57) |
| Cancer, % (n) | 2.6 (13) | 3.0 (71) |
| Inflammatory bowel syndrome, % (n) | 0.8 (4) | 0.3 (7) |
| Psoriasis, % (n) | 3.2 (16) | 1.4 (33) |
| Drug use 6 months before the index date | | |
| Corticosteroids, % (n) | 13.4 (68) | 1.9 (46) |
| NSAIDs, % (n) | 28.5 (145) | 5.1 (121) |
| Statins, % (n) | 13.8 (70) | 6.9 (163) |
| Other lipid-lowering agents, % (n) | 0.4 (2) | 0.6 (14) |
| Anti-hypertensive drugs, % (n) | 35.8 (182) | 22.4 (530) |
| Anti-diabetic drugs, % (n) | 6.7 (34) | 4.9 (115) |
| Aspirin, % (n) | 7.5 (38) | 4.4 (105) |
| HRT, % (n) | 6.1 (31) | 2.6 (62) |
| Antibiotics, % (n) | 15.9 (81) | 8.4 (199) |
| Vaccines, % (n) | 14.9 (76) | 11.2 (266) |
| Antipsychotics, % (n) | 0.6 (3) | 0.8 (19) |
| Antidepressants, % (n) | 8.7 (44) | 3.8 (89) |
| PPIs | 14.2 (72) | 3.6 (85) |

*Duration of registration with a general practitioner was defined by the date of registry at a general practice or by the first medical record of the patient. No data on the date of registry at a general practice before entrance to this study were available for 314 patients.
SD, standard deviation; HRT, hormone replacement treatment; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.

**Table 3** Association of statin use with rheumatoid arthritis, stratified by number of prescriptions, cumulative duration, cumulative daily dose and adherence

| Statin use | Case (n=508), n | Control (n=2369), n | OR (95% CI) | OR (95% CI)* | p value† |
|---|---|---|---|---|---|
| Non-users | 427 | 2165 | 1.00 | 1.00 | |
| Users | 81 | 204 | 2.12 (1.59–2.83) | 1.71 (1.16–2.53) | 0.007 |
| Number of prescriptions | | | | | |
| 1–4 | 29 | 61 | 2.62 (1.64–4.19) | 2.25 (1.27–3.98) | 0.05 |
| 5–8 | 23 | 66 | 1.83 (1.11–3.02) | 1.62 (0.86–3.03) | 0.13 |
| ≥9 | 29 | 77 | 2.03 (1.29–3.20) | 1.59 (0.90–2.81) | 0.11 |
| Cumulative duration | | | | | |
| 1–250 days | 19 | 55 | 1.85 (1.08–3.17) | 1.59 (0.85–2.95) | 0.15 |
| 251–600 days | 25 | 61 | 2.19 (1.35–3.56) | 1.50 (0.85–2.64) | 0.16 |
| ≥601 days | 37 | 88 | 2.24 (1.48–3.41) | 1.38 (0.85–2.23) | 0.20 |
| Cumulative daily dose‡ | | | | | |
| 1–300 | 21 | 54 | 2.03 (1.21–3.41) | 1.67 (0.92–3.04) | 0.09 |
| 301–900 | 23 | 66 | 1.90 (1.17–3.11) | 1.32 (0.74–2.35) | 0.35 |
| ≥901 | 37 | 84 | 2.36 (1.55–3.59) | 1.44 (0.90–2.33) | 0.13 |
| Adherence§ | | | | | |
| 0 | 427 | 2165 | 1.00 | 1.00 | |
| 1–80 | 12 | 47 | 1.39 (0.72–2.66) | 1.14 (0.55–2.39) | 0.73 |
| 81–99 | 13 | 20 | 4.15 (1.95–8.84) | 2.85 (1.20–6.77) | 0.02 |
| 100 | 44 | 98 | 2.35 (1.60–3.46) | 1.62 (1.00–2.61) | 0.05 |

*Adjusted for hypertension, cardiovascular disease, hyperlipidaemia, diabetes and use of non-steroidal anti-inflammatory drugs, corticosteroids, hormone replacement treatment and proton pump inhibitors.
†p values are for adjusted ORs.
‡Cumulative statin dose was defined as the total defined daily dose of drugs prescribed prior to the index date.
§Adherence in the year prior to the index date was the sum of the days' supply divided by the total number of days between the first prescription and the last prescription of statins, multiplied by 100%. Patients who received only one prescription of statins and who used statins more than 1 year before the index date were excluded from the study; therefore, the total number of patients in the analysis is 2826 (496 cases and 2330 controls).

**Table 4** Association between the different types and potencies of statin exposure and the risk of developing rheumatoid arthritis

| Statin use | Case (n=508), n | Control (n=2369), n | OR (95% CI) | OR (95% CI)* | p value† |
|---|---|---|---|---|---|
| Non-use | 427 | 2165 | 1.00 | 1.00 | |
| Specific type‡ | | | | | |
| Simvastatin | 29 | 97 | 1.59 (1.03–2.45) | 1.53 (0.89–2.62) | 0.12 |
| Pravastatin | 13 | 35 | 2.04 (1.07–3.89) | 1.66 (0.78–3.53) | 0.19 |
| Fluvastatin | 6 | 7 | 4.80 (1.60–14.35) | 2.65 (0.72–9.72) | 0.14 |
| Atorvastatin | 29 | 57 | 2.75 (1.70–4.44) | 2.35 (1.29–4.29) | 0.005 |
| Rosuvastatin | 4 | 7 | 3.03 (0.88–10.41) | 1.69 (0.38–7.61) | 0.49 |
| Potency§ | | | | | |
| 2+3 | 8 | 38 | 1.14 (0.53–2.48) | 0.89 (0.37–2.14) | 0.79 |
| 4 | 36 | 95 | 1.97 (1.31–2.94) | 1.72 (1.05–2.82) | 0.03 |
| 5 | 25 | 53 | 2.77 (1.65–4.67) | 2.25 (1.18–4.31) | 0.01 |
| 6+7 | 12 | 18 | 3.51 (1.64–7.51) | 2.36 (0.96–5.76) | 0.06 |

*Adjusted for hypertension, cardiovascular disease, hyperlipidaemia, diabetes and use of non-steroidal anti-inflammatory drugs, corticosteroids, hormone replacement treatment and proton pump inhibitors.
†p values are for adjusted ORs.
‡The type and the potency of statins were based on their last prescription before the index date.
§Potency was determined for statin use by combining the type and the dose of statins into a single potency score.