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Disease-Modifying Antirheumatic Drugs and Risk of Parkinson Disease: Nested Case-Control Study of People With Rheumatoid Arthritis

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Abstract

Background

Epidemiological studies have suggested a link between rheumatoid arthritis and Parkinson's disease (PD). Disease-modifying anti-rheumatic drugs (DMARDs) might explain this association.

Objective

To evaluate the association between DMARDs and risk of PD in persons with rheumatoid arthritis.

Methods

Nested nationwide case-control study was conducted within the Finnish Parkinson's disease (FINPARK) cohort that includes 22,189 Finnish persons with clinically verified PD diagnosed in 1996-2015. The cases had recorded diagnosis of PD in the Special Reimbursement Register and had no exclusion diagnoses whose symptoms may be confused with PD within two years of PD diagnosis. This study included cases with PD diagnosed during 1999-2015

and rheumatoid arthritis diagnosed >3 years before PD. Rheumatoid arthritis was identified using Finnish Care Register for Health Care and Special Reimbursement Register. Cases were matched with up to seven control persons by age, sex, duration of rheumatoid arthritis and region. DMARDs were categorised into five classes and data on purchased prescriptions was identified from the Prescription Register since 1995. Associations were studied with conditional logistic regression adjusted for confounders.

Results

Altogether 315 cases with PD and 1,571 matched controls were included. Majority (> 60%) were women and median duration of rheumatoid arthritis on matching date was 11.6 years for controls and 12.6 years for cases. Use of DMARDs was not associated with risk of PD with three-year lag period applied between exposure and outcome, except chloroquine/hydroxychloroquine which associated with decreased risk (adjusted odds ratio 0.74; 95% confidence interval 0.56-0.97). Other DMARDs, including sulfasalazine, methotrexate, gold preparations and immunosuppressants, were not associated with PD.

Discussion

Our results suggest that the lower risk of PD in people with rheumatoid arthritis is not explained by DMARD use as these drugs in general did not modify the risk of PD among persons with rheumatoid arthritis. Association between chloroquine/hydroxychloroquine and lower risk of PD as well as the possible underlying mechanisms should be further investigated.

Classification of evidence: This study provides Class II evidence that in individuals with rheumatoid arthritis using DMARDs, only chloroquine/hydroxychloroquine was associated with a potentially decreased risk of developing PD (adjusted OR 0.74, 95% CI 0.56-0.97).

ACCEPTED

Introduction

Rheumatoid arthritis has been linked to lower risk of Parkinson's disease (PD)¹⁻³, although some studies have also observed an increased risk of PD in people with rheumatoid arthritis⁴, or no association between rheumatoid arthritis and PD⁵.

One suggested explanation for the protective association are medications used to treat rheumatoid arthritis¹. Disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, inhibit the rheumatic inflammation and progression of structural joint damage⁶, and they could modify the risk of PD by interfering with immune system dysfunction, which has been suggested to be present in PD⁷. However, there is very little research on the association of DMARDs with risk of PD. Although one study demonstrated lower risk of PD in users and nonusers of DMARDs with rheumatoid arthritis compared to people without rheumatoid arthritis¹, that study did not compare the risk between DMARD users and nonusers with rheumatoid arthritis. A case-control study which investigated several DMARDs reported that use of either azathioprine, leflunomide or mycophenolate were associated with lower risk of PD⁸.

The primary research question of our study is whether use of different DMARDs is associated with risk of PD. We investigated this in a nested nationwide case-control study restricted to persons with rheumatoid arthritis diagnosed at least 3 years before clinically verified PD. This restriction of study population allowed us to minimize confounding by indication of DMARD treatment. To control for increased contact with healthcare professionals due to diagnostic process of PD, which could differentially affect the exposure in cases, we applied a three-year lag period between DMARD use and PD diagnosis. In addition, due to the long onset period of PD, it is unlikely that DMARDs initiated within close proximity to PD diagnosis would impact the risk.

Methods

FINPARK study population

A nested case-control study was conducted within the Finnish Parkinson's disease (FINPARK) cohort that contains all community-dwelling Finnish persons who received special reimbursement for PD drugs in 1996-2015 (N=22,189). These persons were identified using the Special Reimbursement Register which includes information on entitlements to higher reimbursements for drugs because of chronic diseases. PD diagnosis was based on United Kingdom Parkinson's disease Society Brain Bank criteria⁹ and exclusion diagnoses for FINPARK cohort has been reported previously¹⁰. For every person with PD, up to 7 comparison persons without PD were identified from the Social Insurance Institution (SII) database covering all residents and they were matched for age, sex, and region of residence (N=148,009). Each Finnish resident is given a unique personal identification number which enables data linkage across several registers. The FINPARK study has been described in detail previously¹⁰.

Identification of cases and controls for this study

Formation of study population is described in Figure 1. Persons diagnosed with PD in 1999-2015 (N=19,568) were included in this study as drug exposure data were available since 1995 and we used a three-year lag period in exposure assessment. To control for confounding by indication we restricted the study to people who had been diagnosed with rheumatoid arthritis at least three years before PD diagnosis. Rheumatoid arthritis was defined from the Finnish Care Register for Health Care (1987-2012) and Special Reimbursement Register (1972-2012) using International Classification of Diseases (ICD) ICD-

9 and ICD-10 codes as described in eTable 1. In addition, ICD-8 codes (1972-1986) were used to get the earliest diagnosis date of rheumatoid arthritis for those who had rheumatoid arthritis based on ICD-9 or ICD-10 codes. Final diagnosis date for rheumatoid arthritis was defined either as the earliest date of the hospitalization, specialized healthcare outpatient visit or as the first date of the entitlement to reimbursement for drugs used to treat rheumatoid arthritis, whichever occurred first.

For each PD case with rheumatoid arthritis (n=318), up to seven controls without PD but with rheumatoid arthritis were matched from the controls of the FINPARK study. Date of the PD diagnosis was defined as the index date. Controls were matched based on sex, age (+/- 2 years) on index date, time since rheumatoid arthritis diagnosis on index date (+/- 2 years) and university hospital district. If no controls were identified from the same district, controls were allowed to come from neighboring district. Same exclusion criteria were applied for cases and controls. In addition, controls were not allowed to have diagnosis of Dementia in Parkinson's disease (ICD-10 code F02.3). The final study population included 315 cases and 1,571 controls. Three cases without matched controls were excluded.

Drug exposure

Data on DMARD and corticosteroid purchases were extracted from the Prescription register since 1995 until the index date. The Prescription register includes data on all reimbursed drug purchases, while drug use during hospital stays or in public nursing homes is not recorded in this register. Drugs are categorized according to Anatomical Therapeutic Chemical (ATC) classification system. Drug use was defined based on ATC codes (eTable 2) and DMARDs were categorized as follows: sulfasalazine (A07EC01), chloroquine (P01BA01) or hydroxychloroquine (P01BA02), gold preparations (M01CB) including auranofin and

sodium aurothiomalate and immunosuppressants (L04A) which consist of azathioprine, certolizumab pegol, ciclosporin, mycophenolic acid and biological DMARDs (bDMARDs): abatacept, adalimumab, anakinra, etanercept, golimumab and leflunomide. Methotrexate (L04AX03) was studied separately from immunosuppressants throughout the study due to its common usage in the treatment of rheumatoid arthritis. Due to small number of bDMARD users during the study period, they were combined with immunosuppressants in the main analysis. In addition, we performed sensitivity analysis investigating bDMARDs as a separate category.

Corticosteroids (H02AB) covered prednisolone, prednisone, and methylprednisolone. Dexamethasone was excluded due to low amount of reimbursed purchases. All the above-mentioned drugs are available only as prescription drugs and all reimbursed purchases can be reliably identified from the register. The first date of purchase was determined for each drug or drug group for each person and person was defined as user if there was at least one purchase.

To control for biases caused by 1) prodromal symptoms or ongoing diagnosis process of PD affecting drug exposure, or 2) newly diagnosed rheumatoid arthritis or changes in rheumatoid arthritis pharmacotherapy increasing likelihood of being diagnosed with PD, we applied a three-year lag period for assessing drug exposure. Three years was chosen based on our previous study demonstrating that incidence of muscle relaxants, an indicator of motor symptoms of PD, occurs within this three-year period in FINPARK cohort¹¹. In the main analysis drug use was determined prior to three-year lag period indicating that exposure had occurred at least three years before index date. Time before lag period refers

to exposure assessment period. Additionally, drug exposure was measured within lag period only (within three years of index date) or without lag period (ever before index date).

Furthermore, exposure histories based on the different types of DMARDs used during the exposure assessment period were derived.

Covariates

Comorbidities that were considered to be associated with exposure and outcome were used as covariates (eTable 3). History of asthma or chronic obstructive pulmonary disease (COPD), stroke, diabetes, cardiovascular diseases including any of the following: hypertension, coronary artery disease, chronic heart failure and chronic arrhythmias, substance abuse and head injury were identified using the Special Reimbursement Register, Care Register for Health Care Register or Prescription Register. Cancer history was derived from Cancer Register using ICD-10 codes from IARC CRG Tools. All covariates were defined until the start of the three-year lag period and ever before index date.

Statistical analyses

Characteristics of cases and controls were compared with χ^2 -test for categorical variables. For continuous variables, t-test was applied for normally distributed and Mann-Whitney U test for non-normally distributed data. Conditional logistic regression was used to estimate the unadjusted and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for the association between exposures and PD. Analyses were conducted with different lag periods i.e., without lag period, with three-year lag and use only during the three-year lag period. We analyzed the association between individual DMARD categories (use vs. no use) to assess the association of specific DMARDs. To account for changes in pharmacotherapy for

rheumatoid arthritis (i.e., one person using more than just one type of DMARDs during the exposure assessment period), we grouped the persons based on the types of drugs they had purchased (sulfasalazine, methotrexate, chloroquine/hydroxychloroquine, gold preparations and immunosuppressants). The association between different exposure histories for DMARDs was investigated in comparison to most common exposure type category. Only categories with >5% frequency were reported.

The minimum detectable ORs for different exposure prevalence levels among controls are shown in eFigure 1. We had 80% power to detect ORs ≥ 1.41 (or ≤ 0.71) with exposure prevalence of 50% and ORs ≥ 1.92 (or ≤ 0.52) with exposure prevalence of 5% ($\alpha=0.05$).

Analyses were performed with SAS v9.4 (SAS Institute, Cary, North Carolina). Power calculations were performed with Stata MP14.0 using power mcc-function.

Standard Protocol Approvals, Registrations, and Patient Consents

According to Finnish legislation, ethics committee approval or informed consent is not needed, because included persons cannot be identified due to pseudonymised register data, and the persons were not contacted.

Data availability

The data used to conduct this research is not publicly available due to restrictions by the register maintainers and Finnish legislation. However, the data are available from the corresponding author, provided that appropriate permission of the register maintainers is sought and demonstrated.

Results

The characteristics of cases (N=315) and matched controls (N=1,571) are described in Table 1. The age ranged between 46 and 93 years (mean 73.1 years). Most of the study participants were women. Median duration of rheumatoid arthritis on index date was 11.6 years for controls and 12.6 years for cases, respectively. Prevalence of different comorbidities was comparable between PD cases and controls and cardiovascular diseases were the most common comorbidities.

Use of DMARDs and corticosteroids in different time periods are summarized in Table 2. The three most commonly used DMARDs in both cases and controls were sulfasalazine, methotrexate and chloroquine/hydroxychloroquine (Table 2). Gold preparations were used by approximately one quarter of cases and controls during exposure assessment period and immunosuppressant were the least commonly used DMARD. Corticosteroids were used by nearly two thirds of cases and controls during exposure assessment period.

Use of DMARDs or corticosteroids during exposure assessment was not associated with risk of PD except for use of chloroquine/hydroxychloroquine which associated with decreased risk (aOR 0.74; 95% CI 0.56-0.97) (Table 2). The use of bDMARDs was infrequent in the study period, with less than 3% of cases and controls having used before the three-year lag time. They were not associated with risk of PD (aOR 0.98; 95% CI 0.46-2.09).

When any use before the index date was considered, regardless of whether it was initiated during actual exposure assessment or during lag time, the associations were similar. When initiations in the three-year lag period were considered, no associations were observed.

The negative association of chloroquine/hydroxychloroquine was stronger when any use before the index date was considered (aOR 0.69; 95% CI 0.53-0.89) than in the main analysis

with exposure that had occurred before the three-year lag period (aOR 0.74; 95% CI 0.56-0.97).

When changes in DMARDs during exposure assessment period (i.e., exposure histories) were considered, the most common exposure type was sulfasalazine, with 10% prevalence in both cases and controls (Table 3). Second most common was the combination of chloroquine/hydroxychloroquine, methotrexate, and sulfasalazine. The frequency of other types was <10% in cases and controls. No associations were observed between different exposure histories for DMARDs and PD risk when adjusted with different covariates (Table 3).

Classification of Evidence: This study provides Class II evidence that in individuals with rheumatoid arthritis using DMARDs, only chloroquine/hydroxychloroquine was associated with a potentially decreased risk of developing PD (adjusted OR 0.74, 95% CI 0.56-0.97).

Discussion

Studies on the association between DMARDs and risk of PD in population restricted to rheumatoid arthritis are lacking, although they would aid in understanding whether the inverse association between rheumatoid arthritis and PD is explained by DMARD-treatment of rheumatoid arthritis. Our nationwide nested case-control study of people with rheumatoid arthritis found no association between the use of DMARDs or corticosteroids and risk of PD on a general level. However, the use of chloroquine/hydroxychloroquine was associated with lower risk of PD, even when the analyses were restricted to exposure that had occurred at least three years before PD diagnosis.

These results extend the findings of earlier studies which have implied the role of immune system in PD pathogenesis⁷. Genome-wide association studies have shown that autoimmune diseases, including rheumatoid arthritis, and PD share genetic pathways¹². Lower risk of PD has been observed in people with rheumatoid arthritis in some¹⁻³ but not all studies^{4,5}, and similarly conflicting findings have been reported for systemic lupus erythematosus^{4,13}, another autoimmune disease. Given these inconsistent findings, it is difficult to conclude whether autoimmune diseases alter the PD pathophysiology and to what extent. However, the evidence of involvement of immune system dysfunction in PD pathogenesis⁷ supports the presumption that long-term use of DMARDs, which have anti-inflammatory properties, could explain the reduced risk of PD in rheumatoid arthritis. Surprisingly, the number of pharmacoepidemiological studies on DMARDs is still small.

Differences in our study design prevent direct comparison to earlier studies which have mainly studied how rheumatoid arthritis as a disease is associated with risk of PD¹⁻⁵ or how DMARDs are associated with risk of PD without restricting study population to persons with rheumatoid arthritis⁸. We wanted to focus on DMARDs and avoid confounding by indication by restricting study to people with rheumatoid arthritis. This allowed us to evaluate the association of DMARDs and PD instead of rheumatoid arthritis and PD. Secondly, we considered drug exposure that had occurred at least three years before PD diagnosis, since PD has long latency period before actual diagnosis and potentially increased contact with healthcare, as evident from the initiation of muscle relaxants already three years before PD diagnosis¹¹, can also affect drug exposure. By contrast, previous case-control study⁸ applied only one-year lag between drug exposure and PD diagnosis. We also conducted sensitivity analyses considering exposure that had occurred until PD diagnosis and during the lag period. The results of these additional analyses were in line with the main analyses.

In Finland, we have a long-lasting tradition to aim to remission in the treatment of rheumatoid arthritis. Thus, DMARDs have been used actively during the whole study period. Sulfasalazine was the most used DMARD in our study followed by methotrexate and chloroquine/hydroxychloroquine. These three DMARDs, so called Triple therapy, have been the recommended treatment according to Finnish guidelines for rheumatoid arthritis¹⁴. In addition to individual drugs, we assessed whether exposure histories for different types of DMARDs at least three years before PD diagnosis would differ in the risk of PD but observed no differences compared to sulfasalazine.

Some of the DMARDs have been previously associated with reduced risk of PD. In an earlier case-control study⁸, users of azathioprine, leflunomide or mycophenolate, had reduced risk of PD compared to nonusers with or without one-year lag between drug exposure and outcome. However, we did not observe risk reduction for immunosuppressants class in which these drugs, along with bDMARDs, were defined in our study. In a cohort study, people with rheumatoid arthritis had lower risk of PD than those without rheumatoid arthritis regardless of DMARD use¹. The relative risk reduction was similar in DMARD users and nonusers with rheumatoid arthritis in comparison to persons without rheumatoid arthritis, meaning that use of DMARDs did not explain the protective association of rheumatoid arthritis. Despite differences in study setting, this reflects our results since in general we found no association between DMARDs use and risk of PD among people with rheumatoid arthritis.

In a previous case-control study, corticosteroids were associated with lower risk of PD when the exposure had occurred at least one year before or up to PD diagnosis⁸ while we did not observe association between corticosteroids and PD. One explanation for our null result might be that despite their immunosuppressive effects, corticosteroids are aimed to be

used with low dose and only for relatively short-term in the treatment of rheumatoid arthritis due to their possible adverse effects in long-term use, such as osteoporosis¹⁵. It is possible to reach remission with active use of DMARDs, even without long-term use of systemic corticosteroids.

Our finding on the association between chloroquine/hydroxychloroquine, and lower risk of PD is, however, consistent with the previous case-control study⁸, which reported a protective association for hydroxychloroquine when any exposure before PD diagnosis was considered (relative risk=0.77; 95% CI 0.65-0.90), and a weaker association when exposure occurring at least one year before the outcome was investigated (relative risk=0.83; 95% CI 0.68-1.00). This attenuation may imply that the association in that study was partially due to increased healthcare contact in close proximity to PD diagnosis. Our findings provide additional support to this earlier observation as we were able to use longer lag time in exposure assessment.

Neuroprotective potential of chloroquine and hydroxychloroquine has been speculated previously^{16,17}. Both chloroquine and hydroxychloroquine, interfere with lysosomal activity and autophagy, can inhibit both innate and adaptive immune processes and reduce production of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)¹⁸. These immunomodulatory effects could have a role in modulating inflammatory processes in PD. However, methotrexate, the first-line DMARD for rheumatoid arthritis, that is more powerful immunosuppressant than hydroxychloroquine¹⁹, was not associated with risk of PD in our study. Therefore, the protective association of chloroquine/hydroxychloroquine might be explained by other reasons than its immunosuppressive effects. Hydroxychloroquine has been implied to have pleiotropic effects, as it was recently shown to improve lipid profiles and reduce diabetes incidence in

rheumatoid arthritis²⁰, a population in increased risk of cardiovascular diseases²¹. It is possible that the effects on metabolic and cardiovascular risk factors²² might partly explain our findings. It should be noted that hydroxychloroquine is better tolerated than chloroquine, and thus it is nowadays more commonly used in the treatment of rheumatoid arthritis²³. Chloroquine was included in our study because we used drug exposure data since 1995.

The protective association of chloroquine/hydroxychloroquine is also supported by experimental models of PD; chloroquine protected dopaminergic (DA) neurons against 6-hydroxydopamine induced neurotoxicity¹⁷ and hydroxychloroquine ameliorated motor functions of rotenone-induced parkinsonian rats in behavioral tests¹⁶. Neuroprotective effects of these drugs was suggested to be mediated through orphan nuclear receptor Nurr1, which is important in the development and maintenance of midbrain dopaminergic neurons²⁴ and whose expression was activated by both chloroquine¹⁷ and hydroxychloroquine¹⁶. In terms of other neurodegenerative diseases, hydroxychloroquine did not, however, slow the progression of dementia in persons with Alzheimer's disease compared to the placebo in double-blind clinical trial²⁵.

Our study has several strengths. Definition of PD is based on clinically verified diagnosis. Using large nationwide registries, we could restrict the study population on persons who have the indication to use DMARDs thereby controlling for confounding by indication. Due to long, up to 17 years, exposure assessment time we were able to apply three-year lag period. Short lag period between drug exposure and outcome of PD has been a key limitation in previous studies. If drug exposure is measured too close to the diagnosis of PD, it is more likely to reflect different contact density with prescribers than actual risk factor.

Further, as PD progresses slowly over time, immediate exposure just before diagnosis is unlikely to have significant effect on PD pathophysiology.

Our study was based on data on purchased drugs in which case medication adherence is based on presumption. On the other hand, all the drugs included are only available as prescription drugs which minimizes classification bias. DMARDs administered in hospitals, for example infliximab, are not included in the prescription register. However, these drugs are never used as the first, or only, DMARD and every patient getting infliximab is also treated with other DMARD(s). Therefore, the drugs administered in hospital should not have a major impact on our results.

Although we had nationwide data, restriction of analyses to those with rheumatoid arthritis and at least three years of exposure assessment decreased the sample size. This means that we had limited power to detect weak associations. However, the power issue unlikely explains the null findings, as we were able to observe the association between chloroquine/hydroxychloroquine and PD risk and the point estimates for other DMARDs in the main analyses were close to the null. Further, based on the exposure prevalence we do not think that a clinically relevant signal was missed because of lack of power, and restriction of study population aided us to avoid indication bias. We did not perform dose-response or duration of treatment analyses due to limitations posed by the sample size. Some of the newer immunosuppressants included in our study, mainly bDMARDs such as golimumab, have entered the market at the end of the study period, therefore they have been used in lesser extent compared to older DMARDs, such as sulfasalazine, methotrexate, and chloroquine/hydroxychloroquine. Findings of additional analysis regarding bDMARDs should be interpreted cautiously due to limited number of users in our study.

A possible limitation of our study is the lack of information on severity of rheumatoid arthritis which could affect chosen pharmacotherapy and have differential impact on developing PD regardless of DMARDs use. Our data included both seropositive and seronegative rheumatoid arthritis. This is common approach in register-based studies on rheumatoid arthritis, and unlikely to have major impact on our results.

The sex distribution of our study population may appear surprising considering that PD is more common in men²⁶. However, rheumatoid arthritis is more common in women than in men¹⁵, which explains the sex distribution in our study. As the earlier studies on rheumatoid arthritis or other autoimmune rheumatic diseases and the risk of PD^{1,4} have reported sex distribution comparable to our study and the findings on the association between rheumatoid arthritis and PD have been inconsistent, it is difficult to speculate whether sex has implications for the analyses. We matched cases and controls by sex and thus our results are unlikely explained by sex.

Linkage of several registers enable to account for multiple confounding factors although adjustment with comorbidities did not change the results. We lacked data on smoking, which has been associated with an increased risk of rheumatoid arthritis¹⁵ and oppositely with decreased risk of PD²⁷. However, we used smoking-associated comorbidities, including cancer from Cancer registry, as proxies, but residual confounding is still possible. Additionally, the association between chloroquine/hydroxychloroquine and lower risk of PD can be confounded by another variable that was not identified in our study. The association may also be explained by survival bias: both chloroquine and hydroxychloroquine are old drugs and persons treated with them, especially in monotherapy, might have less severe rheumatoid arthritis and better overall health status than those treated with other DMARDs. However, hydroxychloroquine is also included in the drug-combination with

methotrexate and sulfasalazine which is widely used also on moderate and severe rheumatoid arthritis.

In conclusion, the hypothesis that decreased risk of PD among rheumatoid arthritis patients could be explained by use of DMARDs was not confirmed in our study. Further studies on newer DMARDs, especially on bDMARDs such as TNF- α inhibitors and target specific DMARDs (JAK inhibitors), and assessment of dose-response relations between DMARDs and risk of PD are needed. The potential ability of chloroquine/hydroxychloroquine to modify the PD disease process should be studied further.

Appendix 1
Authors

Name	Location	Contribution
Anne Paakinaho, MSc (Pharm)	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. Approval of the submitted version.
Marjaana Koponen, PhD (Pharm)	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, data preprocessing and analysis supervision, revising the manuscript. Approval of the submitted version.
Miia Tiihonen, PhD (Pharm)	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, interpretation of the data, revising the manuscript. Approval of the submitted version.
Markku Kauppi, MD, PhD, Professor of rheumatology	Department of rheumatology, Päijät-Häme Central Hospital, Lahti and Clinicum, Faculty of Medicine, University of Helsinki, Helsinki	Interpretation of the data, revising the manuscript. Approval of the submitted version.

Sirpa Hartikainen, MD, PhD	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, interpretation of the data, revising the manuscript. Approval of the submitted version.
Anna-Maija Tolppanen, PhD	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, interpretation of the data, revising the manuscript. Approval of the submitted version.

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Figure 1. Flow chart of formation of Parkinson disease (PD) cases and controls.

*age $\pm$ years, sex, time since rheumatoid arthritis diagnosis $\pm$ 2 years, university hospital district

Table 1. Description of Parkinson's disease (PD) cases and matched controls. Data are given as mean (SD) for age, median (IQR) for duration of rheumatoid arthritis and n (%) for other variables.

	Controls N=1,571	PD cases N=315	P
Age at PD diagnosis (years)	73.1 (7.7)	73.1 (8.2)	1.00 ^a
Sex			0.39 ^b
Men	539 (34.3)	116 (36.8)	
Women	1032 (65.7)	199 (63.2)	
Duration of rheumatoid arthritis on index date, median years (IQR)	11.6 (7.5– 19.2)	12.6 (8.4– 20.5)	0.08 ^c
University hospital district on index date			0.36 ^b
Helsinki	409 (26.0)	74 (23.5)	
Tampere	363 (23.1)	79 (25.1)	
Kuopio	348 (22.2)	61 (19.4)	
Oulu	227 (14.5)	57 (18.1)	
Turku	224 (14.3)	44 (14.0)	
Covariates before three-year lag			
Cardiovascular diseases	639 (40.7)	136 (43.2)	0.41 ^b
Asthma or COPD	198 (12.6)	34 (10.8)	0.37 ^b
Cancer history	134 (8.5)	24 (7.6)	0.59 ^b
Diabetes	132 (8.4)	34 (10.8)	0.17 ^b
Head injury	80 (5.1)	13 (4.1)	0.47 ^b
Stroke	54 (3.4)	10 (3.2)	0.81 ^b
Substance abuse	36 (2.3)	4 (1.3)	0.25 ^b

^a t-test, ^b Chi-Square test, ^c Mann-Whitney U test

COPD=chronic obstructive pulmonary disease, IQR=interquartile range, PD=Parkinson's disease

Table 2. Association between disease-modifying anti-rheumatic drugs (DMARDs) and Parkinson's disease (PD).

	Controls N=1571 n (%)	PD cases N=315 n (%)	P	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Drug or drug group	Use before three-year lag				
Sulfasalazine	794 (50.5)	161 (51.1)	0.85	1.02 (0.79-1.33)	1.01 (0.78-1.32)
Methotrexate	751 (47.8)	163 (51.8)	0.20	1.17 (0.90-1.52)	1.17 (0.90-1.52)
Chloroquine/ hydroxychloroquine	704 (44.8)	118 (37.5)	0.016	0.73 (0.56-0.96)	0.74 (0.56-0.97)
Gold preparations	388 (24.7)	84 (26.7)	0.46	1.09 (0.82-1.45)	1.11 (0.83-1.47)
Immunosuppressants	231 (14.7)	53 (16.8)	0.34	1.07 (0.76-1.53)	1.06 (0.75-1.51)
Corticosteroids	1062 (67.6)	210 (66.7)	0.75	0.96 (0.73-1.26)	0.98 (0.74-1.29)
	Use only in three-year lag period				
Sulfasalazine	52 (3.3)	9 (2.9)	0.68	0.90 (0.43-1.87)	0.91 (0.44-1.91)
Methotrexate	102 (6.5)	19 (6.0)	0.76	0.98 (0.59-1.63)	0.98 (0.59-1.64)
Chloroquine/ hydroxychloroquine	90 (5.7)	10 (3.2)	0.06	0.57 (0.29-1.12)	0.57 (0.29-1.13)
Gold preparations	27 (1.7)	3 (1.0)	0.32	0.47 (0.14-1.59)	0.46 (0.13-1.56)
Immunosuppressants	68 (4.3)	13 (4.1)	0.87	1.01 (0.55-1.88)	1.03 (0.55-1.91)
Corticosteroids	120 (7.6)	18 (5.7)	0.23	0.76 (0.45-1.28)	0.75 (0.44-1.26)
	Use ever before index date				
Sulfasalazine	846 (53.9)	170 (54.0)	0.97	1.01 (0.78-1.31)	1.01 (0.77-1.31)
Methotrexate	853 (54.3)	182 (57.8)	0.26	1.16 (0.90-1.51)	1.18 (0.91-1.53)
Chloroquine/ hydroxychloroquine	794 (50.5)	128 (40.6)	0.001	0.67 (0.51-0.87)	0.69 (0.53-0.89)
Gold preparations	415 (26.4)	87 (27.6)	0.66	1.03 (0.78-1.37)	1.05 (0.79-1.39)
Immunosuppressants	299 (19.0)	66 (21.0)	0.43	1.06 (0.77-1.46)	1.06 (0.77-1.46)
Corticosteroids	1182 (75.2)	228 (72.4)	0.29	0.87 (0.66-1.16)	0.90 (0.68-1.20)

*Asthma or chronic obstructive pulmonary disease (COPD), cancer history, cardiovascular diseases, diabetes, head injury, stroke, substance abuse

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Table 3. The most common exposure histories for disease-modifying anti-rheumatic drugs (DMARDs) and their association with Parkinson's disease (PD) risk during the exposure assessment period before three-year lag in both PD cases and controls.

	Controls N=1571 n (%)	PD cases N=315 n (%)	Adjusted* OR (95% CI)
Sulfasalazine	165 (10.5)	32 (10.2)	reference
Chloroquine/hydroxychloroquine, methotrexate, and sulfasalazine	163 (10.4)	32 (10.2)	1.02 (0.58-1.79)
Chloroquine/hydroxychloroquine	109 (6.9)	13 (4.1)	0.64 (0.32-1.29)
Methotrexate and sulfasalazine	95 (6.1)	26 (8.3)	1.47 (0.82-2.65)
Methotrexate	81 (5.2)	19 (6.0)	1.19 (0.63-2.25)
Chloroquine/hydroxychloroquine and sulfasalazine	91 (5.8)	8 (2.5)	0.46 (0.20-1.06)
Gold preparations	80 (5.1)	14 (4.4)	0.95 (0.47-1.91)
Chloroquine/hydroxychloroquine and methotrexate	79 (5.0)	13 (4.1)	0.95 (0.46-1.94)

*Asthma or chronic obstructive pulmonary disease (COPD), cancer history, cardiovascular diseases, diabetes, head injury, stroke, substance abuse

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