

TITLE: The association between smoking and the development of rheumatoid arthritis: a population-based case-control study.

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ABSTRACT

Introduction: Smoking is one of the few modifiable risk factors associated with the development of rheumatoid arthritis (RA). We aimed to study the association between smoking and the development of RA in the Catalan population.

Methods: Case-control study. We included all patients with a new diagnosis of RA registered in the SIDIAP database between 2008 and 2018; and matched them to up to 1:5 controls by age, gender and general practitioner. Smoking was classified as never, ex- or current smoker. Odds Ratios and 95% confidence intervals for the association between smoking and RA were estimated using conditional logistic regression adjusted for potential confounders.

Results: A total of 13,920 RA cases and 69,535 controls were included. Compared with never smokers, current and ex-smokers were at increased risk of RA, with adjusted OR of 1.28 [95% CI 1.20 to 1.37] and OR 1.19 [1.12 to 1.26] respectively.

Conclusion: Our findings confirm an association between smoking and the risk of developing RA. The effect seems to prevail in the long-term and even in ex-smokers for 2 or more years after smoking cessation.

Keywords: Rheumatoid arthritis, smoking, environment, risk factor,
epidemiology

Palabras clave: Artritis Reumatoide, Tabaco, medio ambiente, factores de
riesgo, epidemiología

INTRODUCTION

Rheumatoid arthritis (RA) is a long-term autoimmune disease which is thought to be related with genetic and environmental risk factors. One of the few modifiable risk factors is smoking. The relationship between smoking and RA has been shown in a lot of studies and reviews previously. The first study that related smoking with an increased risk of developing RA was published in 1987,¹ and since then, numerous additional studies have been reported. Most of these studies were completed 10 or more years ago, and both the diagnosis and treatment/s available for RA have changed substantially in the last decade. Additionally, the routine collection of health data for research has now enabled the conduction of bigger studies in actual practice conditions and using the entire population, in contrast with previous cohorts or case-control studies mostly conducted in specialised research centres.² Finally, none of the studies published to date were conducted in Mediterranean populations, where both the incidence/prevalence and the severity of RA are lower than in Northern European and American people.^{3,4}

We therefore took advantage of the existence of routinely collected health data from electronic primary care records in Catalonia (Spain) to study the association between smoking and the development of rheumatoid arthritis in the general population.

METHODS

- DATA SOURCE

Data were extracted from the SIDIAP (*'Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària'*, English translation: Information System for Research in Primary Care) database. SIDIAP contains primary care electronic medical records covering over 80% of the Catalan population (approximately 6 million people's records). These records include socio-demographics, lifestyle risk factors and measurements (body mass index, smoking, alcohol consumption), and diagnoses coded using the ICD10 system, amongst other variables.

- STUDY DESIGN AND PARTICIPANTS

We conducted a population-based case-control study including all participants newly diagnosed with rheumatoid arthritis registered in SIDIAP in the period 2008-2018 and with at least 2 years of data available prior to RA diagnosis. Up to 5 RA-free controls registered in any of the practices contributing to SIDIAP and with a similar run-in period (2+ years) were identified and matched by age, gender and general practitioner to each RA case. Controls were given the same index date as their matched case.

- OUTCOME

The outcome of interest of this study was the diagnosis of RA, defined by a previously validated list of ICD10 codes, including M05, M06 and all

sub-codes. Previous validations of RA in SIDIAP ⁵ have shown face validity, with population-based incidence and prevalence similar to that previously reported for the source population. In addition, a total of 2,482/5,796 incident cases studied in the validation manuscript had evidence of rheumatoid factor testing in primary care, with a 73.9% being positive, in line with previous knowledge.

- EXPOSURE

Smoking is routinely recorded by family physicians in the Catalan healthcare system as part of their day-to-day job. Smoking status is recorded in a structured format into three categories: never smoker, ex-smoker, or current smoker. For the current study, we classified participants based on the most recent record in the two years prior to their index date.

- STATISTICAL ANALYSES

Baseline characteristics for study participants are reported as mean (standard deviation) or n (%) stratified by RA status (cases vs controls). Conditional logistic regression models were used to calculate unadjusted (sex- and age-matched) Odds Ratios and 95% confidence intervals for the association between current and ex-smoking and RA status. In addition, multivariable conditional logistic models were then used to adjust for potential confounders, including body mass index, socio-economic deprivation, alcohol drinking, cardiovascular/cerebrovascular disease,

history of osteoarthritis, peripheral artery disease, chronic kidney disease, diabetes mellitus, cancer, inflammatory bowel disease, and number of GP visits in the year before index date. Gender-stratified analyses were conducted as there were significant differences in effect size seen in previous literature.^{6,7} Multiple imputation with chained equations (MICE) was used to minimise the impact of missing data for smoking, alcohol drinking, and body mass index. Ten datasets were imputed using MICE, and the results were combined using Rubin's rules. All analyses were conducted using Stata for Windows version 15.0.

RESULTS

In total, we included 13,920 RA cases matched to 69,535 controls with a similar age, gender and same primary care practice. Average (standard deviation) age was therefore similar between cases (64.67 +/- 15.67 years) and controls (64.04 +/- 15.83), and the proportion of females was the same in both groups (70.42%). In addition, body mass index was also similar between cases and controls, and the prevalence of co-morbidity was also comparable, except for inflammatory bowel disease, peripheral artery disease and pulmonary embolism, all three being more common amongst RA cases. Detailed baseline characteristics for cases and controls are reported in Table 1.

Before imputation, a total of 2,227/13,920 (16.9%) of RA cases were current smokers, compared to 7,637/69,535 (13.45%) controls, and remained similar after imputation (see Table 1). Unadjusted (sex, age,

and GP-matched) OR for RA in ex-smokers was 1.09 [95% CI 1.03 to 1.14] and 1.35 [1.28 to 1.43] for current smokers. Multivariable adjusted ORs were 1.19 [1.12 to 1.26] and 1.28 [1.20 to 1.37] respectively. In the pre-specified gender stratified analysis, the observed association was stronger in men, with an adjusted OR 1.38 [1.27 to 1.50] for current smokers, compared to women (adjusted OR 1.20 [1.09 to 1.32] for current smoking). Full results for these models are depicted in Figure 1.

DISCUSSION

To our knowledge, this is the largest and most up-to-date epidemiological study on the association between smoking and the development of RA to date. Our analysis is also the first to include a Mediterranean population, with previous studies conducted in Northern European,⁷ American,⁶ and Asian patients.⁸ Our study supports previous findings of an association between smoking and the risk of developing RA, with an almost 30% higher risk for current smokers and a 20% increase for ex-smokers compared to never smokers. In addition, we found a stronger effect of smoking amongst men, with an almost 40% excess risk in current smokers and a 15% in ex-smokers.

Our data do not differ from the results obtained in other studies done previously in different populations: most previous case-control studies found similar associations between current smoking and the risk of developing RA, with ORs ranging from 1.42 [1.13 to 1.80] to 2.37 [1.56 to 3.60].^{6,9} Similarly, cohort studies have mostly found an excess risk associated with smoking.¹⁰⁻¹² Some controversial findings have however been published previously, that found no association between RA and smoking¹³.

Our study suggests that the effect of smoking on RA risk is long-lasting for years after smoking cessation, with ex-smokers still at an increased risk of developing RA compared to non-smokers. Interestingly, a recent

study supports these findings: in a report by Seror R. et al ¹⁴ passive smoking during childhood on the risk of developing RA.

Finally, other previous studies have shown ³ like ours a stronger effect of smoking amongst men compared to women. It has been speculated that the observed difference in gender may be due to the difference in smoking intensity³.

One of the limitations of our study is the lack of detail on exposure intensity, i.e. cigarettes smoked per day or pack-years. Previous studies have reported on this, and found that smoking more than 20 pack-years make increase the possibilities of having RA.³ Also, with our data it is impossible to assess the timing when a person stopped smoking, and this makes ex-smoking effects difficult to interpret. An additional limitation is the use of routinely collected data, which was not designed for research purposes. Primary care coding of RA is likely delayed and/or focussed on more severe cases, as shown by the average age at diagnosis in our series, which is older than a recent study in Catalan population.¹⁵

On the other hand, our study has several strengths. This study includes the largest number of RA participants to date on this topic, with previous reports ranging from 90 to 7,697 RA cases.^{12,16} Additionally, our study is the first one population-based, including all diagnosed cases of RA in a large population of around 6 million people, and in a Mediterranean region not previously studied. The diagnosis of RA has been previously validated in SIDIAP using laboratory and external rate comparisons.⁵ Finally, our

controls were sampled from a universal primary care database making them representative of the general population. Matching on general practitioner minimised differences in socio-economic status, environmental factors, and physician differences in diagnostic or coding practices.

We confirm an association between smoking and the risk of developing RA. Research is needed on the impact of smoking cessation on the risk of developing this disease, and on related health outcomes including cardiovascular disease and all-cause mortality in RA populations.

References

1. Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. *Contraception*. 1987 May;**35(5)**:457-64.
[https://doi.org/10.1016/0010-7824\(87\)90082-5](https://doi.org/10.1016/0010-7824(87)90082-5).
2. Hutchinson D, Shepstone L, Moots R, Lear JT, Lynch MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis*. 2001 Mar;**60(3)**:223-7.
<https://doi.org/10.1136/10.1136/ard.60.3.223>.
3. Sugiyama, D., Nishimura, K., Tamaki, K., Tsuji, G., Nakazawa, T., Morinobu, A., & Kumagai, S. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Annals of the rheumatic diseases* 2010; **69(1)**, 70–81.
<https://doi.org/10.1136/ard.2008.096487>.
4. Lahiri M, Morgan C, Symmons DP, Bruce IN. Modifiable risk factors for RA: prevention, better than cure? *Rheumatology (Oxford)*. 2012 Mar;**51(3)**:499-512. <https://doi.org/10.1093/rheumatology/ker299>.
5. Fina-Aviles F, Medina-Peralta M, Mendez-Boo L, Hermosilla E, Elorza JM, Garcia-Gil M, Ramos R, Bolibar B, Javaid MK, Edwards CJ, Cooper C, Arden NK, Prieto-Alhambra D. The descriptive epidemiology of rheumatoid arthritis in Catalonia: a retrospective study using routinely collected data. *Clin Rheumatol*. 2016 Mar;**35(3)**:751-7. <https://doi.org/10.1007/s10067-014-2801-1>.

6. Krishnan E. Smoking, gender and rheumatoid arthritis- epidemiological clues to etiology. Results from the behavioral risk factor surveillance system. *Joint Bone Spine*. 2003 Dec;**70**(6):496-502. [https://doi.org/10.1016/s1297-319x\(03\)00141-6](https://doi.org/10.1016/s1297-319x(03)00141-6).
7. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, Alfredsson L; EIRA study group. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis*. 2003 Sep;**62**(9):835-41. <https://doi.org/10.1136/ard.62.9.835>.
8. Yahya A, Bengtsson C, Lai TC, Larsson PT, Mustafa AN, Abdullah NA, Muhamad N, Hussein H, Klareskog L, Alfredsson L, Murad S. Smoking is associated with an increased risk of developing ACPA-positive but not ACPA-negative rheumatoid arthritis in Asian populations: evidence from the Malaysian MyEIRA case-control study. *Mod Rheumatol*. 2012 Aug;**22**(4):524-31. <https://doi.org/10.1007/s10165-011-0544-2>.
9. Mikuls TR, Sayles H, Yu F, Levan T, Gould KA, Thiele GM, Conn DL, Jonas BL, Callahan LF, Smith E, Brasington R, Moreland LW, Reynolds RJ, Bridges SL Jr. Associations of cigarette smoking with rheumatoid arthritis in African Americans. *Arthritis Rheum*. 2010 Dec;**62**(12):3560-8. <https://doi.org/10.1002/art.27716>.
10. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. *Am J Med*. 2006 Jun;**119**(6):503.e1-9.

<https://doi.org/10.1016/j.amjmed.2005.09.053>.

11. Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, Mudano AS, Burma M, Folsom AR, Saag KG. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. *Am J Med*. 2002 Apr 15; **112(6)**:465-71.
[https://doi.org/10.1016/s0002-9343\(02\)01051-3](https://doi.org/10.1016/s0002-9343(02)01051-3).
12. Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum*. 1999 May; **42(5)**:910-7. [https://doi.org/10.1002/1529-0131\(199905\)42:5<910::AID-ANR9>3.0.CO;2-D](https://doi.org/10.1002/1529-0131(199905)42:5<910::AID-ANR9>3.0.CO;2-D).
13. Hazes JM, Dijkmans BA, Vandenbroucke JP, de Vries RR, Cats A. Lifestyle and the risk of rheumatoid arthritis: cigarette smoking and alcohol consumption. *Ann Rheum Dis*. 1990 Dec; **49(12)**:980-2.
<https://doi.org/10.1136/ard.49.12.980>.
14. Seror R, Henry J, Gusto G, Aubin HJ, Boutron-Ruault MC, Mariette X. Passive smoking in childhood increases the risk of developing rheumatoid arthritis. *Rheumatology (Oxford)*. 2019 Jul 1; **58(7)**:1154-1162.
<https://doi.org/10.1093/rheumatology/key219>.
15. Castellanos-Moreira R, Rodríguez-García SC, Gomara MJ, Ruiz-Esquide V, Cuervo A, Casafont-Solé I, Ramírez J, Holgado S, Gómez-Puerta JA, Cañete JD, Haro I, Sanmarti R. Anti-carbamylated proteins antibody repertoire in rheumatoid arthritis: evidence of a

new autoantibody linked to interstitial lung disease. *Ann Rheum Dis*. 2020 May;**79(5)**:587-594. <https://doi.org/10.1136/annrheumdis-2019-216709>.

16. Symmons DP, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DG, Silman AJ. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. *Arthritis Rheum*. 1997 Nov;**40(11)**:1955-61. <https://doi.org/10.1002/art.1780401106>.

Tables/figures

Table 1 – Baseline characteristics for cases and controls, including smoking status before and after multiple imputation.

	RA cohort (n = 13,920)	Controls (n = 69,535)
Age in years, mean \pm SD	64.67 \pm 15.67	64.04 \pm 15.83
Women, n (%)	9,802 (70.42)	48,966 (70.42)
Body mass index, kg/m², mean \pm SD	27.70 \pm 5.22	27.22 \pm 5.06
BMI: missing values	1,579 (11.34)	19,098 (27.46)
Comorbid conditions, n (%)		
Cancer	916 (6.58)	4,791 (6.89)
Myocardial Infarction	546 (3.92)	2,133 (3.07)
Cerebrovascular Disease	302 (2.17)	1,540 (2.21)
Diabetes Mellitus	1,534 (11.02)	7,295 (10.49)
Inflammatory Bowel Disease	614 (4.41)	1,492 (2.15)
Kidney Disease	50 (0.36)	254 (0.37)
Peripheral Artery Disease	49 (0.35)	89 (0.13)
Pulmonary Embolism	62 (0.45)	179 (0.26)
Alcohol consumption, n (%)		
No/mild	8,782 (68.53)	34,240 (64.49)

Moderate	3,852 (30.06)	17,888 (33.69)
High/at risk drinker	180 (1.40)	965 (1.82)
Alcohol consumption: missing values	1,106 (7.94)	16,442 (23.64)
Socioeconomic Status, n (%)		
U1-2	4,667 (33.53)	23,395 (33.65)
U3-5	6,087 (43.74)	30,354 (43.66)
Smoking status, original data n (%)		
Current	2,227 (16.90)	7,637 (13.45)
Ex-smoker	2,800 (21.25)	12,079 (21.27)
Never smoked	8,152 (61.86)	37,075 (65.28)
Smoking status, after MICE* n (%)		
Current	25,784 (16.92)	102,261 (13.59)
Ex-smoker	32,498 (21.32)	159,956 (21.26)
Never smoked	94,097 (61.75)	489,924 (65.13)

*MICE = Multiple imputation with chained equations

Figure 1.- Multivariable adjusted ORs for the association between smoking and RA stratified by gender.

