



Impact of smoking as a risk factor for developing rheumatoid arthritis : a meta-analysis of observational studies

Sugiyama, D ; Nishimura, K ; Tamaki, K ; Tsuji, G ; Nakazawa, T ; Morinobu, A ; Kumagai, S

(Citation)

Annals of the rheumatic diseases, 69(1):70-81

(Issue Date)

2009-01-27

(Resource Type)

journal article

(Version)

Version of Record

(URL)

<https://hdl.handle.net/20.500.14094/90001457>



Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies

D Sugiyama,¹ K Nishimura,^{2,3} K Tamaki,⁴ G Tsuji,¹ T Nakazawa,^{1,5} A Morinobu,¹ S Kumagai^{1,2}

► Additional supplemental file is published online only at <http://ard.bmj.com/content/vol69/issue1>

¹ Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, Kobe, Japan;

² Department of Evidence Based Laboratory Medicine (Sysmex), Kobe University Graduate School of Medicine, Kobe, Japan;

³ Department of Health Policy Management, Harvard School of Public Health, Boston, Massachusetts, USA;

⁴ Department of Respiratory Medicine, Kansai Electric Power Central Hospital, Osaka, Japan;

⁵ Department of Rheumatology, Kurashiki Central Hospital, Okayama, Japan

Correspondence to:
Dr S Kumagai, Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; kumagais@kobe-u.ac.jp

Accepted 13 January 2009
Published Online First
28 January 2009

ABSTRACT

Objectives: To assess whether smoking is a risk factor for developing rheumatoid arthritis (RA).

Design: Meta-analysis.

Method: Data sources were observational studies that examined the association between smoking history and the risk of developing RA identified through Medline and EMBASE (from 1966 to December 2006), relevant books and a reference search. Two authors independently extracted the following: authors' names, publication year, sample size, participant characteristics, odds ratios (OR) or relative risks, adjustment factors, study design and area where the study was conducted. Data syntheses were based upon random effects model. Summarised syntheses effects were expressed by OR.

Results: Sixteen studies were selected from among 433 articles. For men, summary OR for ever, current and past smokers were 1.89 (95% CI 1.56 to 2.28), 1.87 (1.49 to 2.34) and 1.76 (1.33 to 2.31), respectively. For rheumatoid factor-positive (RF+) RA, summary OR for ever, current and past smokers were 3.02 (2.35 to 3.88), 3.91 (2.78 to 5.50) and 2.46 (1.74 to 3.47), respectively. Summary OR for 20 or more pack-years of smoking was 2.31 (1.55 to 3.41). For women, summary OR for ever, current and past smokers were 1.27 (1.12 to 1.44), 1.31 (1.12 to 1.54) and 1.22 (1.06 to 1.40), respectively. For RF+ RA, summary OR for ever, current and past smokers were 1.34 (0.99 to 1.80), 1.29 (0.94 to 1.77) and 1.21 (0.83 to 1.77). Summary OR for 20 or more pack-years of smoking was 1.75 (1.52 to 2.02).

Conclusion: Smoking is a risk factor for RA, especially RF+ RA men and heavy smokers.

Rheumatoid arthritis (RA) is a major autoimmune disease, with typical clinical features of chronic inflammation in joints and the development of bone destruction.¹ Although the aetiology of RA is unknown, it is thought that the interaction of environment, genetics and the immune system may lead to the development of this disorder.¹

Smoking is thought to be a risk factor for the development of several autoimmune diseases, including systemic lupus erythematosus,² primary biliary cirrhosis,³ Graves' disease⁴ and RA.^{5–12} Smoking modulates the immune system¹³ by reducing natural killer cells, depressing hormonal cells and cell-mediated immunity, and leading to dysfunction of T lymphocytes.^{14–17}

Epidemiological studies of the past 20 years have investigated smoking as an important risk factor for RA and have reported several key findings.^{1–3,10} The first is a stronger influence of smoking on

developing RA in men, and the second is the association of smoking with rheumatoid factor (RF) positive RA in men, but not in women.^{7,18} However, the findings for women of various studies have been inconsistent.^{7,18–22} Moreover, although several reviews have dealt with the relation between smoking and the development of RA, no systematic analyses have been conducted.^{23–28}

We therefore conducted a meta-analysis to assess whether smoking habits affect the development of RA.

METHODS

To report our meta-analysis, we followed the Moose checklists, the proposal for reporting meta-analysis of observational studies.²⁹

Data sources and searches

An article search was conducted through Medline and EMBASE from 1966 to December 2006 using the keywords "Rheumatoid Arthritis" and "Smoking." We used both the Medline MeSH term ("Arthritis, Rheumatoid") and text words ("Rheumatoid Arthritis" and "smoking") for our Medline search. In addition, we performed a search of the references cited in each paper and a book that reviewed the relationship between RA and nutritional or environmental risk factors.¹ For study selection and data extraction, we also examined what other possible confounding factors (such as age, social class, body mass index, education, coffee consumption and menopause status), affect developing RA generally.

Study selection

Inclusion criteria: studies included in our meta-analysis comprised the following minimum requirements: (1) any type of observational study (case-control or cohort study) investigating the relationship between the development of RA and smoking habits, with no limit for smoking status (ever, current and past); and (2) effect size data (odds ratio (OR) or relative risk (RR) and CI) related to RA development among smokers compared with non-smokers were estimated. For different studies of the same populations (eg, the Nurses' Health Study), we used the results of the most recent study.

Excluded studies: case reports, basic medical reports about RA and smoking, and studies

concentrating on other environmental factors (eg, coffee intake) or severity of RA.

Data extraction and quality assessment

Data extraction was independently performed by two authors. We extracted the following data from each paper: author's name; publication year; sample size; effect size data (OR or RR) for risk of development of RA; study design (case-control or cohort); area where the study was conducted; adjustment factors (eg, age).

For the sample size, we also extracted subgroup data classified by gender. If we could not obtain effect size data adjusted with other confounders, we estimated the crude OR from sample size data. When mentioned, we also obtained data for RF-positive or RF-negative findings, anti-citrulline protein/peptide (CCP) positive or negative and effect size by pack-years of smoking for subgroup analyses. The quality of the selected studies was assessed with the checklist proposed by Rushton.³⁰ This check list contains 14 items answered by "Yes" or "No", and we used the number of "Yes" answers to determine the study quality with a score between 0 and 14, and these scores were used for meta-regression analysis.³¹ If results were significantly affected by study quality scores, we weighted study quality scores on data syntheses. We resolved any item discrepancies through discussion and adopted the more conservative results.

Data synthesis and analysis

Statistical models and software

All data syntheses were based upon a random effect model,³² which allowed us to compare the effect of factors other than smoking on the development of RA in any of the studies. Forest plots were used to express the effect size data of each study and summary OR with 95% CI estimated from each study. We used R version 2.60 (R Development Core Team, Vienna, Austria), S-Plus version 7.0 (Insightful Corp, Seattle, Washington, USA), and Comprehensive Meta Analysis version 2 (Biostat Inc, Englewood, California, USA).

Main outcome for evaluation

For the main outcome, the influence of any type of smoking (ever, current and past) on the development of RA in men and women was evaluated separately. The results were stratified by whether the study design was case-control or cohort. Weighted analysis of variance was used to evaluate differences between smoking status and study design.

Heterogeneity among studies

Meta-regression analysis³¹ was performed to explore the sources of statistically significant ($p < 0.05$) heterogeneity among studies. Possible sources for heterogeneity were smoking habit rates and study quality in each selected study.

Subgroup analysis

For subgroup analyses, the following three items were evaluated for assessment of the influence of smoking on the development of RA limited to the following three topics: (1) differences in expression of RF in the effect of smoking effect on the development of RF-positive as well as RF-negative RA; (2) differences in expression of anti-CCP; (3) effect of pack-years (years of smoking multiplied by packs of cigarettes per day) of smoking. We also performed a sensitivity analysis based on study quality. For example, if one study was lower in quality

than another, we performed data syntheses again after the exclusion of the low quality study and compared the results.

Assessment of publication bias

To evaluate publication bias, Rosenthal's fail-safe number³³ in terms of smoking status was calculated for numbers of the selected studies. This number is a standard for estimating how many "null-effect" studies are needed to increase the p value for the meta-analysis to make the summary OR statistically insignificant. As this number increases, so does the reliability of the study results. If the estimated number of unpublished studies according to Rosenthal's fail-safe number was larger than five times the number of identified studies plus 10 studies, we decided the influence of publication bias on our findings was minor.^{2 29 33}

RESULTS

Characteristics of included studies

Of the 433 articles screened we obtained data from 18 articles that met our inclusion criteria (fig 1, table 1), including 11 case-control and five cohort studies. The mean age of the total population, weighted by the size of each study, was 52.2 years and 94% were women. Smoking rates of ever, current and past were 50.6%, 26.5% and 26.3%, respectively. In the 11 case-control studies,^{8 9 11 12 18–22 34–36} 4764 cases and 13 647 controls were included, and in five cohort studies,^{5 7 10 37 38} 9121 cases were identified from among 566 044 participants. Seven case-control studies and one cohort study of male subjects and nine case-control and five cohort studies of female subjects were included. Only Pedersen *et al*³⁶ investigated the effect of smoking on the development of CCP-positive RA. Classification of pack-years smoked was very different in each of the articles, but all of

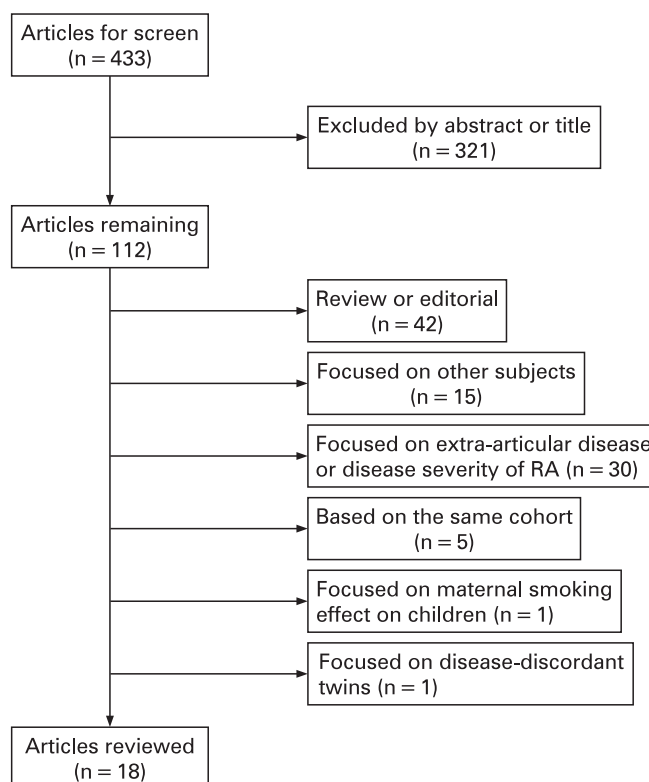


Figure 1 Flow diagram of considered articles. RA, rheumatoid arthritis.

Table 1 Summary of selected studies

Authors, year (ref no)	Gender	RR or OR (95% CI)		Smoking rate (%)					Adjustment	Cases/controls or cohort size	Smoking rate (%)			Study design	Study quality	Study area
		Ever smokers	Past smokers	Current smokers	Past smokers	Current smokers	Ever smokers	Past smokers			Current smokers	Past smokers	Current smokers			
Vessey <i>et al</i> , 1987 ⁵	Female	1.50 (0.93 to 2.44)		1.66 (1.00 to 2.78)	1.15 (0.54 to 2.43)		47.5	33.8	(No)	78/600	47.5	33.8	13.6	Cohort	5	Europe
Hazes <i>et al</i> , 1990 ⁴⁴	Female			0.61 (0.42 to 0.89)				43.9	Year of birth, age at onset of symptoms, parity, alcohol consumption, oral contraceptive, marital status, menopause	135/378						
Heliövaara <i>et al</i> , 2000 ³⁸	Both								Consumption of coffee, age, BMI, serum cholesterol, sex, level of education, smoking, intake of alcohol	512/52 809	47.6	35.6	12.1			
Heliövaara <i>et al</i> , 1993 ⁷	Male	2.04 (1.10 to 3.79)		1.60 (0.70 to 3.80)	1.40 (0.50 to 3.80)		69.7	51.1	Age	161/28 364	69.7	51.1	18.7	Cohort	13	Europe
	RF+ cases	3.86 (2.71 to 5.49)		4.31 (2.87 to 6.50)	2.80 (1.40 to 5.60)											
	RF- cases	0.81 (0.49 to 1.34)		0.66 (0.34 to 1.27)	1.10 (0.50 to 2.40)											
	Female	1.06 (0.84 to 1.35)		1.10 (0.84 to 1.44)	0.92 (0.53 to 1.58)		22.1	17.7	Age	351/24 445	22.1	17.7	4.5			
	RF+ cases	1.04 (0.78 to 1.40)		1.10 (0.80 to 1.52)	0.80 (0.40 to 1.70)											
	RF- cases	1.10 (0.73 to 1.66)		1.10 (0.70 to 1.80)	1.10 (0.50 to 2.60)											
Voigt <i>et al</i> , 1994 ⁸	Female	1.31 (1.07 to 1.60)		1.33 (1.00 to 1.77)	1.28 (0.96 to 1.71)		50.9	26.0	Age, BMI	349/1457	50.9	26.0	24.9	Case-control	10	USA
	PY <20	1.49 (1.06 to 2.10)														
	PY >20	1.16 (0.90 to 1.50)														
Symmonds <i>et al</i> , 1997 ⁹	Both	1.66 (0.95 to 3.06)		0.95 (0.56 to 1.61)			54.5		Sex, social class	90/93	54.5			Case-control	12	Europe
	RF+ cases	2.92 (0.92 to 9.21)														
	RF- cases	1.20 (0.70 to 2.09)														
Uhlir <i>et al</i> , 1999 ¹¹	Both			1.46 (1.10 to 1.94)				32.9	Age, sex, education, marital status, employment, BMI	361/5469		32.9				
	Male			2.38 (1.45 to 3.92)				33.4	Age, education, marital status, employment, BMI	99/2626		33.4				
	RF+ cases			4.77 (2.09 to 10.90)												
	RF- cases			1.57 (0.80 to 3.06)												
	Female			1.14 (0.8 to 1.62)				32.2	Age, education, marital status, employment, BMI	262/2843		32.2		Case-control	13	Europe
	RF+ cases			0.67 (0.37 to 1.20)												
	RF- cases			1.54 (0.99 to 2.39)												
Karlson <i>et al</i> , 1999 ¹⁰	Female	1.13 (1.08 to 1.18)		1.18 (1.07 to 1.31)	1.06 (0.96 to 1.13)		45.2	13.2	Age, race, education, age at menarche, pregnancy history, menopausal status, postmenopausal HRT (Not clearly shown)	7697/37 7481	45.2	13.2	32.0	Cohort	13	USA
Hutchinson <i>et al</i> , 2001 ¹²	Both	1.81 (1.22 to 2.19)														
Olsson <i>et al</i> , 2001 ¹⁸	Male	1.97 (1.18 to 3.29)		2.20 (1.10 to 4.20)			58.3	31.8	Age, socioeconomic status	239/239	58.3	31.8	26.6	Case-control	10	Europe
	RF+ cases	2.42 (1.36 to 4.32)					65.6			91/203	65.6					
	PY <20	1.39 (0.56 to 3.44)														
	PY >20	2.70 (1.20 to 5.80)														
	female	1.61 (1.06 to 2.45)														
	RF+ cases	1.94 (1.24 to 3.01)					38.0		Age, socioeconomic status	154/222	38.0			Case-control	12	Europe

Continued

Table 1 Continued

Authors, year (ref no)	Gender	RR or OR (95% CI)		Adjustment	Cases/controls or cohort size	Smoking rate (%)			Study design	Study quality	Study area
		Ever smokers	Past smokers			Current smokers	Ever smokers	Past smokers			
Criswell <i>et al</i> , 2002 ¹⁹	PY <20	1.57 (0.99 to 2.50)	1.30 (0.80 to 2.00)	Age, alcohol use, coffee consumption, marital status, BMI, age at menopause, oral contraceptives, HRT	154/31 336	2.20 (1.40 to 3.30)	33.0	17.1	Cohort	13	USA
	PY >20	1.80 (0.70 to 4.60)									
	Female	1.70 (1.02 to 2.85)									
	PY <20	1.10 (0.60 to 1.80)									
Krishnan <i>et al</i> , 2003 ³¹	PY >20	1.99 (1.41 to 2.81)	2.00 (1.20 to 3.20)	Age, BMI, education, HAQ index, general health assessment, pain	318/426	1.20 (0.70 to 2.00)	76.5	19.7	Case-control	12	Europe
	Male	1.56 (0.95 to 2.58)	2.30 (1.30 to 3.90)								
	RF+ cases	1.88 (1.24 to 2.86)	0.90 (0.40 to 1.90)								
	RF- cases female	1.16 (0.63 to 2.22)	0.90 (0.60 to 1.30)								
Krishnan, 2003 ³⁵	RF+ cases	0.81 (0.60 to 1.09)	0.80 (0.60 to 1.30)	Age, BMI, education, HAQ index, general health assessment, pain	777/1104	0.60 (0.30 to 1.00)	30.6	11.1	Case-control	10	USA
	RF- cases	0.74 (0.53 to 1.02)	0.80 (0.60 to 1.30)								
	Both	0.90 (0.63 to 1.28)	0.94 (0.60 to 1.50)								
	Male	1.34 (1.00 to 1.81)	1.08 (0.87 to 1.34)								
Stolt <i>et al</i> , 2003 ²⁰	Female	2.29 (1.35 to 3.90)	0.80 (0.50 to 1.40)	Age, race, education, income, living alone	644/1509	1.80 (1.20 to 2.30)	49.5	20.9	Case-control	13	Europe
	Male	0.98 (0.67 to 1.42)	0.80 (0.50 to 1.40)								
	RF+ cases	1.40 (0.80 to 2.30)	1.30 (0.70 to 2.40)								
	RF- cases	1.90 (1.00 to 3.50)	1.80 (0.80 to 4.10)								
Padyukov <i>et al</i> , 2004 ²²	RF+ cases	0.80 (0.40 to 1.60)	0.90 (0.40 to 1.90)	Age, residential area	203/543	1.40 (1.00 to 2.00)	64.4	33.6	Case-control	13	Europe
	Female	1.30 (1.00 to 1.70)	1.20 (0.90 to 1.70)								
	RF+ cases	1.70 (1.20 to 2.30)	1.60 (1.10 to 2.30)								
	RF- cases	0.80 (0.60 to 1.20)	0.80 (0.50 to 1.30)								
Olsson <i>et al</i> , 2004 ²¹	Both	1.50 (1.20 to 2.00)	1.50 (1.20 to 2.00)	Age(10 strata), sex, residential area	858/1048	2.20 (1.70 to 3.00)	23.6	25.5	Case-control	11	Europe
	RF+ cases	2.20 (1.70 to 3.00)	2.30 (1.20 to 4.40)								
	RF- cases	0.80 (0.60 to 2.20)	3.80 (1.40 to 10.20)								
	Male	1.70 (1.00 to 2.90)	1.80 (1.10 to 2.90)								
Olsson <i>et al</i> , 2004 ²¹	RF+ cases	3.30 (1.70 to 6.30)	1.80 (1.00 to 3.50)	Age	74/382	5.80 (1.90 to 17.10)	63.8	44.3	Case-control	11	Europe
	RF- cases	0.60 (0.30 to 1.30)	1.80 (1.00 to 3.50)								
	Female	1.50 (1.10 to 2.00)	1.80 (1.00 to 3.50)								
	RF+ cases	2.20 (1.60 to 3.00)	1.80 (1.00 to 3.50)								
Olsson <i>et al</i> , 2004 ²¹	RF- cases	0.80 (0.60 to 1.30)	1.80 (1.00 to 3.50)	Age	159/368	5.80 (1.90 to 17.10)	52.8	30.8	Case-control	11	Europe
	Male	2.54 (1.55 to 4.16)	1.80 (1.00 to 3.50)								
	RF+ cases	4.60 (2.20 to 9.60)	1.80 (1.00 to 3.50)								
	PY <20	2.20 (1.15 to 4.22)	1.80 (1.00 to 3.50)								
Olsson <i>et al</i> , 2004 ²¹	PY >20	2.50 (1.20 to 5.10)	1.80 (1.00 to 3.50)	Age	159/368	5.80 (1.90 to 17.10)	52.8	30.8	Case-control	11	Europe
	Female	1.52 (1.09 to 2.12)	1.80 (1.00 to 3.50)								
	RF+ cases	1.56 (1.03 to 2.36)	1.80 (1.00 to 3.50)								
	RF- cases	1.56 (1.03 to 2.36)	1.80 (1.00 to 3.50)								

Continued

Table 1 Continued

Authors, year (ref no)	Gender	RR or OR (95% CI)			Adjustment	Cases/controls or cohort size	Smoking rate (%)			Study design	Study quality	Study area
		Ever smokers	Current smokers	Past smokers			Ever smokers	Current smokers	Past smokers			
Costenbader <i>et al</i> , 2006 ³⁷	PY <20	1.33 (0.86 to 2.04)										
	PY >20	1.60 (0.90 to 3.10)										
	Female	1.46 (1.24 to 1.71)	1.43 (1.16 to 1.75)	1.47 (1.24 to 1.71)	BMI, alcohol intake, father's occupation,	680/103 818	55.5	17.5	38.1			
	RF+ cases	1.59 (1.29 to 1.97)	1.58 (1.21 to 2.06)	1.60 (1.27 to 2.02)	age at menarche, regularity of menses,							
	RF- cases	1.28 (1.00 to 1.65)	1.23 (0.88 to 1.70)	1.31 (1.00 to 1.73)	duration of breastfeeding, postmenopausal HRT					Cohort	14	USA
	PY <20	1.19 (0.95 to 1.50)										
Pedersen <i>et al</i> , 2006 ³⁸	PY >20	1.72 (1.41 to 2.11)										
	Both	1.70 (1.38 to 2.10)	1.80 (1.37 to 2.36)	1.57 (1.13 to 2.19)	Birth year, year of diagnosis							
	CCP+ cases	1.66 (1.23 to 2.24)	1.73 (1.17 to 2.56)	1.57 (0.99 to 2.48)	Sex, birth year, year of diagnosis, residence area, history of urinary tract infection, marital status, coffee consumption, alcohol consumption, BMI	515/769	64.7	44.2	28.9			
	CCP- cases	1.04 (0.65 to 1.68)	0.83 (0.49 to 1.39)	1.35 (0.76 to 2.39)	Physical activity, pets as adult, asthma, schizophrenia among 1st degree relatives							
	Male	1.75 (1.15 to 2.65)	1.89 (1.09 to 3.30)	1.58 (0.84 to 2.97)	Birth year, year of diagnosis	149/291	77.0	50.0	27.0	Case-control	12	Europe
	PY <20	1.63 (0.99 to 2.70)										
	PY >20	2.00 (1.12 to 3.58)										
	Female	1.78 (1.38 to 2.97)	1.84 (1.33 to 2.54)	1.69 (1.12 to 2.55)	Birth year, year of diagnosis	366/478	58.4	41.4	30.0			
	PY <20	1.68 (1.27 to 2.26)										
	PY >20	2.07 (1.35 to 3.16)										

BMI, body mass index; CCP, citrulline protein/peptide; HRT, hormone replacement therapy; OR, odds ratio; PY, pack-years smoked; RF, rheumatoid factor; RR, relative risk.

them included 20 pack-years. We therefore divided the classification of pack-years into “less than 20” or “20 or more”.

Excluded studies

A total of 321 articles was excluded based on their title or abstract and those focusing on in-vitro or non-human studies; case reports were excluded, but were read in full to make sure the topics were based on experimental data or case reports. Among the excluded items, 15 were studies focusing on other environmental factors (eg, diet), and were thus without enough data for our analysis; 42 were editorials or reviews about smoking and RA; 30 focused on extra-articular manifestations or disease severity of RA; five^{6 40–43} were based on the same cohorts as one of the studies already included, and three^{6 38 43} were based on the same cohort (the Nurses' Health Study). Because their report was the latest, we extracted data from Costenbader *et al.*³⁷ Stolt *et al.* 2005⁴¹ also used the results of the EIRA study (as did Stolt *et al.* 2003³⁰ and Padykov *et al.*²²), but we excluded one because it was an analysis of a subgroup. Criswell *et al.* 2002³⁹ published two articles^{40 42} based on the same cohort (the Iowa Women's Health Study) and both of them were excluded because they were reports of a subgroup analysis. We also excluded one study by Jaakkola *et al.*⁴⁴ because it examined the effect on children of their mother's smoking, and one by Silman *et al.*⁴⁵ because its risk estimation focused on twins rather than on individuals.

Overall analysis and evaluation of publication bias

The mean score of study quality according to the Rushton checklist was 11.4 (SD 2.2) with a maximum score of 13 and a minimum score of 5. The item of adequacy of the sample size was rarely assessed as satisfactory. As study quality scores of the selected studies did not have a significant effect as determined by meta-regression analysis, we did not adopt any weighting for our analyses. See supplemental file (published online only).

The summary OR for all of the selected studies were 1.40 (95% CI 1.25 to 1.58) for ever smokers in 14 studies, 1.35 (1.17 to 1.55) for current smokers in 15 studies and 1.25 (1.10 to 1.40) for past smokers in 11 studies. As for the evaluation of publication bias, estimated fail-safe numbers for the selected studies were 403 for ever smokers, 210 for current smokers and 76 for past smokers, suggesting the influence of publication bias was small.

Subgroup analysis by study design (fig 2)

The summary OR for all the selected case-control studies were 1.46 (1.27 to 1.69) for ever smokers in nine studies, 1.31 (1.06 to 1.63) for current smokers in 10 studies and 1.26 (1.21 to 1.41) for past smokers in six studies.

The summary OR for the selected cohort studies were 1.29 (1.10 to 1.51) for ever smokers in five studies, 1.37 (1.13 to 1.65) for current smokers in five studies and 1.20 (0.97 to 1.49) for past smokers in five studies. Differences in smoking status between the case-control group and the cohort group were not statistically significant.

Subgroup analysis for male population (table 2A, fig 3)

The summary OR for ever, current and past male smokers were 1.89 (1.56 to 2.28), 1.87 (1.49 to 2.34) and 1.76 (1.33 to 2.31), respectively. For RF-positive RA, the summary OR for ever, current and past smokers were 3.02 (2.35 to 3.88), 3.91 (2.78 to 5.50) and 2.46 (1.74 to 3.47). The summary OR for 20 or more pack-years of smoking compared with non-smokers was 2.31 (1.55 to 3.41).

In the seven case-control studies^{11 18–22 35 36} the summary OR for ever, current and past smokers were 1.87 (1.53 to 2.29), 1.89 (1.49 to 2.40) and 1.79 (1.34 to 2.38). Differences in smoking status were not significant.

For only RF-positive RA, the summary OR for ever, current and past smokers were 2.35 (1.64 to 3.35), 3.14 (1.70 to 5.82) and 2.35 (1.58 to 3.51), and for RF-negative RA only, the summary OR for ever, current and past smokers were 0.90 (0.52 to 1.27), 1.31 (0.62 to 2.76) and 0.96 (0.61 to 1.51).

Only one cohort study⁷ was identified in the male subgroup population.

Subgroup analysis for female population (table 2B, fig 4)

The summary OR for ever, current and past female smokers were 1.27 (1.12 to 1.44), 1.31 (1.12 to 1.54) and 1.22 (1.06 to 1.40), respectively. For RF-positive RA, the summary OR for ever, current and past smokers were 1.34 (0.99 to 1.80), 1.29 (0.94 to 1.77) and 1.21 (0.83 to 1.77). Summary OR for 20 or more pack-years of smoking was 1.75 (1.52 to 2.02). Heterogeneities were statistically significant, but meta-regression analyses findings for smoking rate and study quality were not significant.

For the nine case-control studies,^{8 11 18–22 34–36} the summary OR for ever, current and past smokers were 1.27 (1.05 to 1.54), 1.19 (0.88 to 1.61) and 1.24 (1.04 to 1.48). Differences among the three categories of smokers were not significant. For RF-positive RA, the summary OR for ever, current and past smokers were 1.32 (0.87 to 2.02), 1.15 (0.57 to 2.31) and 1.21 (0.76 to 1.90). For RF-negative RA, the summary OR for ever, current and past smokers were 0.89 (0.64 to 1.21), 1.47 (0.87 to 2.49) and 0.87 (0.63 to 1.21).

For the five cohort studies,^{5 7 10 37 39} the summary OR for ever, current and past smokers were 1.27 (1.07 to 1.50), 1.37 (1.13 to 1.65) and 1.20 (0.96 to 1.49). Differences among the three categories of smokers were not significant. For RF-positive RA, the summary OR for ever, current and past smokers were 1.30 (0.88 to 1.94), 1.33 (0.94 to 1.90) and 1.24 (0.64 to 2.38). For RF-negative RA, the summary OR for ever, current and past smokers were 1.15 (0.74 to 1.76), 1.22 (0.93 to 1.56) and 1.29 (0.99 to 1.67).

The study quality of one female cohort study⁵ was lower than that of the others, but our results remained robust even after the exclusion of this low quality study.

DISCUSSION

This is the first meta-analysis to examine the question of whether smoking is a risk factor for the development of RA, and our analysis clearly showed it is.

Our results indicate the risk of developing RA is approximately two times higher for male smokers than for non-smokers. For women, the risk for smokers is approximately 1.3 times greater than for non-smokers. However, for heavy smokers (20 or more pack-years of smoking), the risk was as high for women as for men. Although the results of previous studies^{5 7 11 18 20 34 35} did not show a significant relationship between smoking and the development of RA for women, our analysis provides quantitative evidence that smoking is an important risk factor for women in developing RA. We also demonstrated the risk for developing RA by smoking was not different for both men and women ever, current and past smokers. Finally, the difference between study designs was also not significant. We therefore thought the influence of these factors on our results were minor.

We determined that the risk of smoking for RA development is greater among men. Whereas the mechanism of hormonal

Figure 2 Forest plots of the odds ratio for the risk of developing rheumatoid arthritis (RA) and rheumatoid factor (RF)-positive RA.

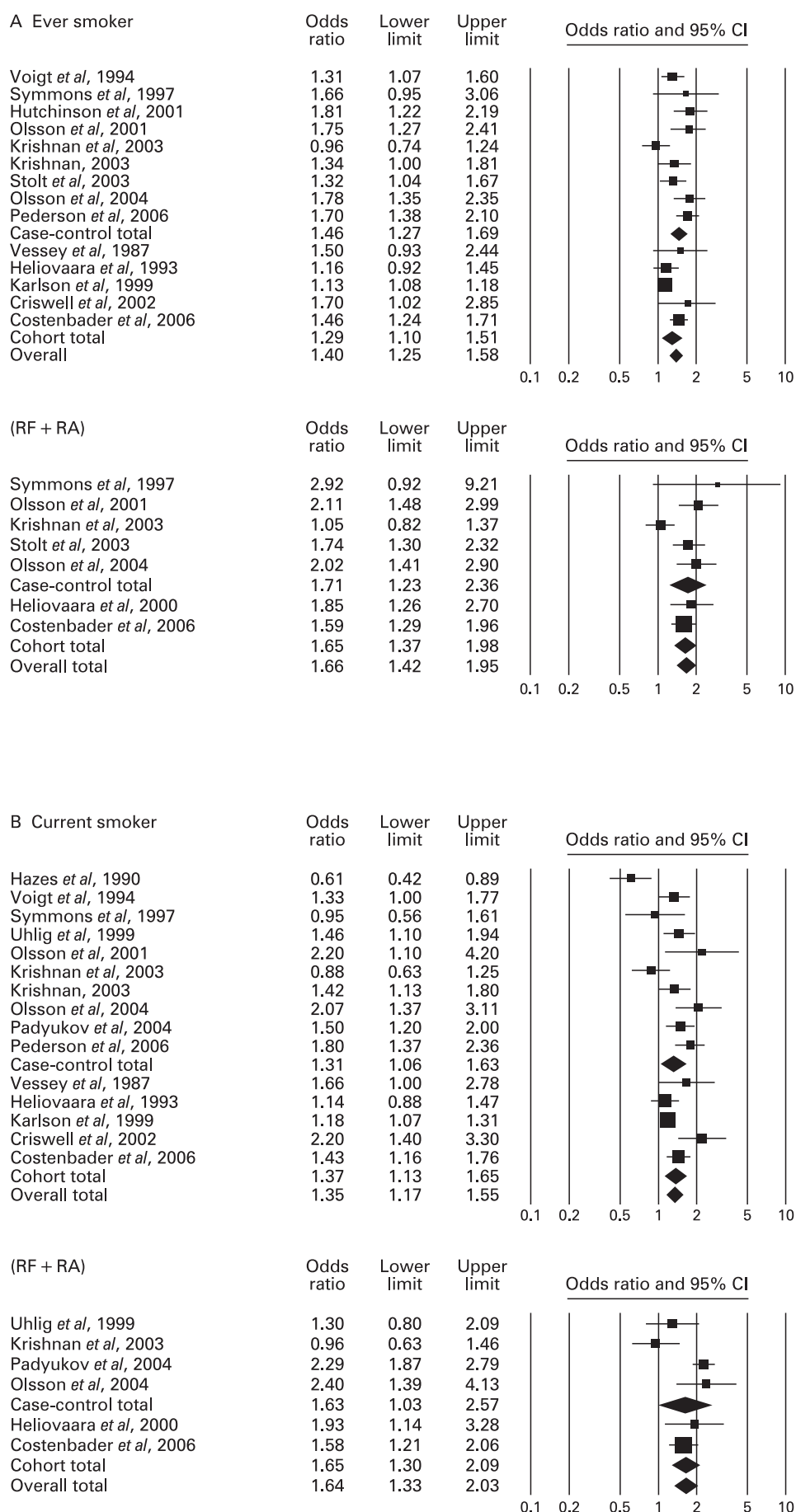
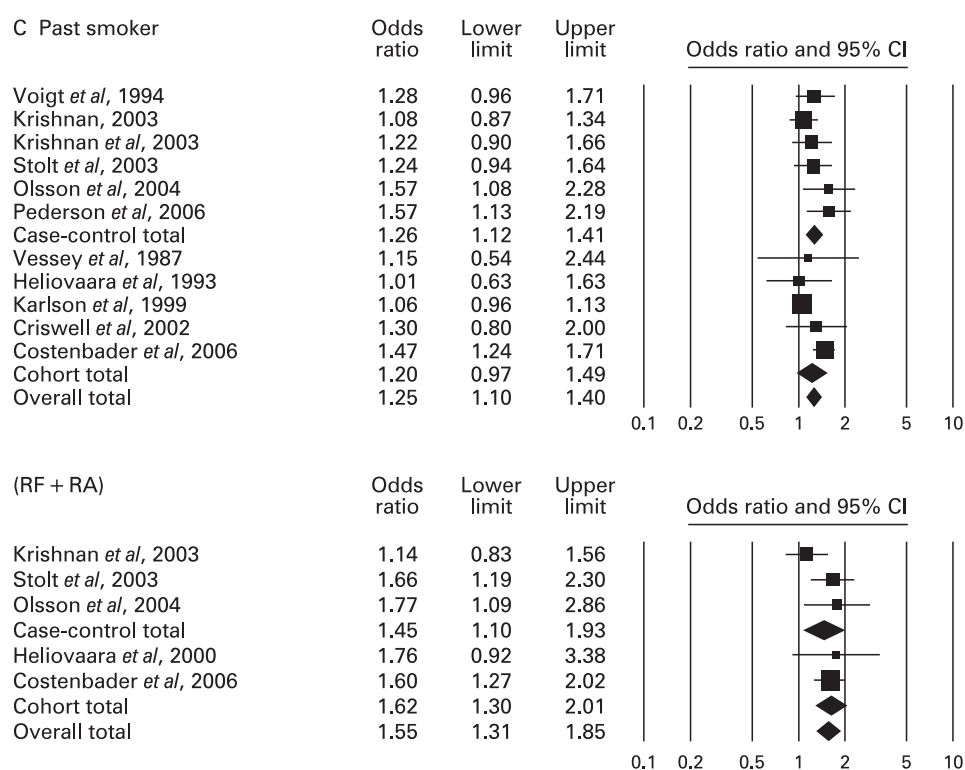


Figure 2 Continued.



effects on the development of RA is not clear, several biological and epidemiological studies investigated this issue.

Experimental studies have shown that oestrogen suppresses arthritis in an RA mouse model,^{46 47} and Salem⁴⁸ found that oestrogen inhibited the production of T-helper type 1 pro-

inflammatory cytokines such as tumour necrosis factor- α , which reduce the risk of RA development. In addition, oestrogen was shown to stimulate the production of anti-inflammatory cytokines such as IL-4. These cytokines play important roles in the development of RA by causing inflammation of synovial tissue.^{49 50}

Moreover, epidemiological studies^{51–53} have suggested that factors related to oestrogen production, such as oral contraceptive use, significantly influenced the development of RA.^{51–53}

To some extent, the discrepancy by gender may be the result of an artifact in that RA is inherently less common in men than women. However, the attributable risk proportion for men was found to be higher than that for women (2.1% vs 0.7%). The discrepant effect is attributable to gender as such and not to the difference in the prevalence of RA between men and women.

We also showed that the risk of developing RF-positive RA is greater than the risk of developing RF-negative RA and that this effect is modified by gender. Smoking is known to be associated with the production of RF.^{54 55} Although the molecular mechanisms connecting smoking and the development of RA have not been identified in detail yet, Padyukov *et al*²² investigated the interaction between smoking and RF and showed that HLA-DRB1 shared epitope alleles were a significant risk factor for the development of RF-positive RA only. In addition, the influence of HLA-DRB1 alleles was greater in the case of smokers. Our findings regarding the relation between smoking and RF-positive RA are compatible with these results. The modification by gender can be explained by the fact that production of RF may be affected by hormonal factors as well as smoking, so that the former may account for the gender-related differences in the effects of smoking on the development of RA.¹

Another possible explanation for the discrepancy between genders can be found in occupational factors. For example, Stolt *et al*⁴¹ reported that silica exposure was associated with an increased risk of developing RA in men. However, the mechanisms by which silica affects RA progression have not

Table 2 Summary of results

Smoking status	No of studies	OR (95% CI)
A. Men		
Ever smoker		
Total	7	1.89 (1.56 to 2.28)
Case-control studies	6	1.87 (1.53 to 2.29)
Cohort studies	1	2.04 (1.10 to 3.79)
Current smoker		
Total	7	1.87 (1.49 to 2.34)
Case-control studies	6	1.89 (1.49 to 2.40)
Cohort studies	1	1.60 (0.70 to 3.80)
Past smoker		
Total	5	1.76 (1.33 to 2.31)
Case-control studies	4	1.79 (1.34 to 2.38)
Cohort studies	1	1.40 (0.50 to 3.80)
B. Women		
Ever smoker		
Total	12	1.27 (1.12 to 1.44)
Case-control studies	7	1.27 (1.05 to 1.54)
Cohort studies	5	1.27 (1.07 to 1.50)
Current smoker		
Total	12	1.31 (1.12 to 1.54)
Case-control studies	6	1.19 (0.88 to 1.61)
Cohort studies	5	1.37 (1.13 to 1.65)
Past smoker		
Total	10	1.22 (1.06 to 1.40)
Case-control studies	5	1.24 (1.04 to 1.48)
Cohort studies	5	1.20 (0.96 to 1.49)

OR, odds ratio.

Figure 3 Forest plots of the odds ratio for the risk of developing rheumatoid arthritis (RA) and rheumatoid factor (RF)-positive RA in men.

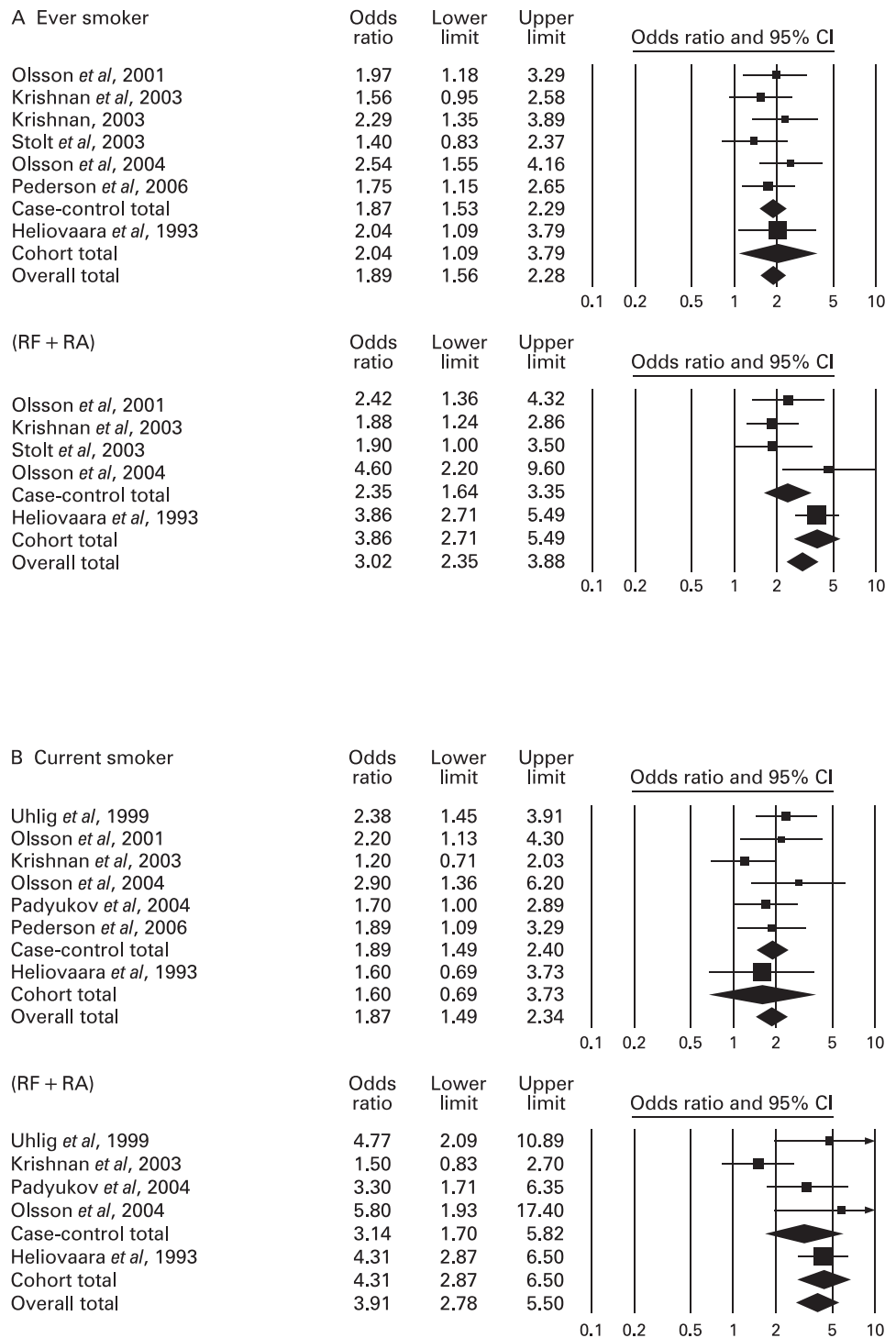
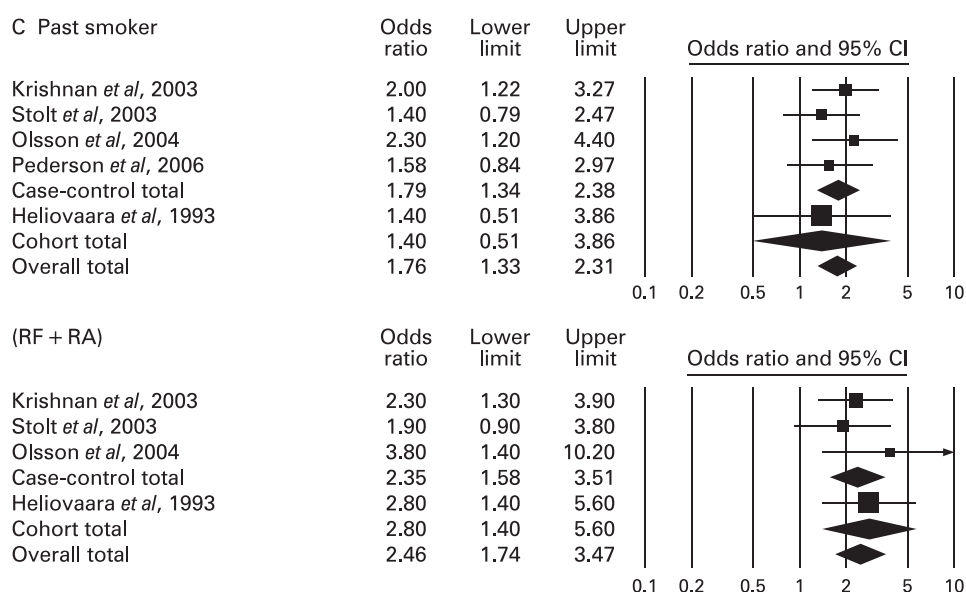


Figure 3 Continued.

yet been clearly established, and the overall risk of occupational exposure will need further study.

The difference in smoking intensity between men and women may also explain the risk difference in gender. However, among the studies reviewed, there was no significant difference in the smoking rate between men and women. Moreover, our results for pack-years of smoking suggest that heavy smokers, whether male or female, are at the same risk of developing RA. Therefore, the role of smoking intensity is likely to be minor.

The reason for the difference in the influence of smoking by gender might be due to a complex of several factors such as the hormonal effect, as mentioned above.

Some studies have recently reported anti-CCP was related to smoking habits and shared epitopes.^{36 56 57} Klareskog *et al*⁵⁶ first demonstrated that smoking was a significant risk factor for CCP-positive RA, but not for CCP-negative RA, and that the presence of HLA-DRB1 alleles was linked to the occurrence of CCP-positive RA. These findings were re-confirmed in later studies.^{36 57} However, we could not conduct a subgroup analysis for CCP-positive RA because of a lack of data.

Westwood *et al*⁵⁸ have suggested that RF-positive differ from RF-negative RA patients, and Klareskog *et al*⁵⁹ also reviewed the evidence that CCP-positive and CCP-negative RA consists of two subsets of RA.

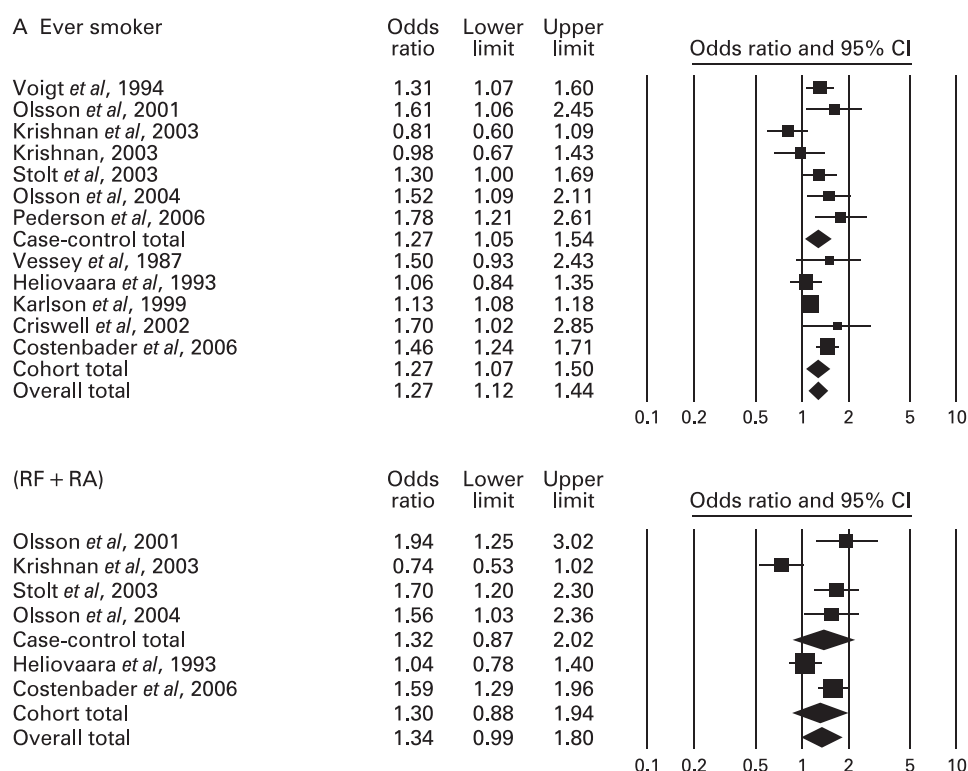
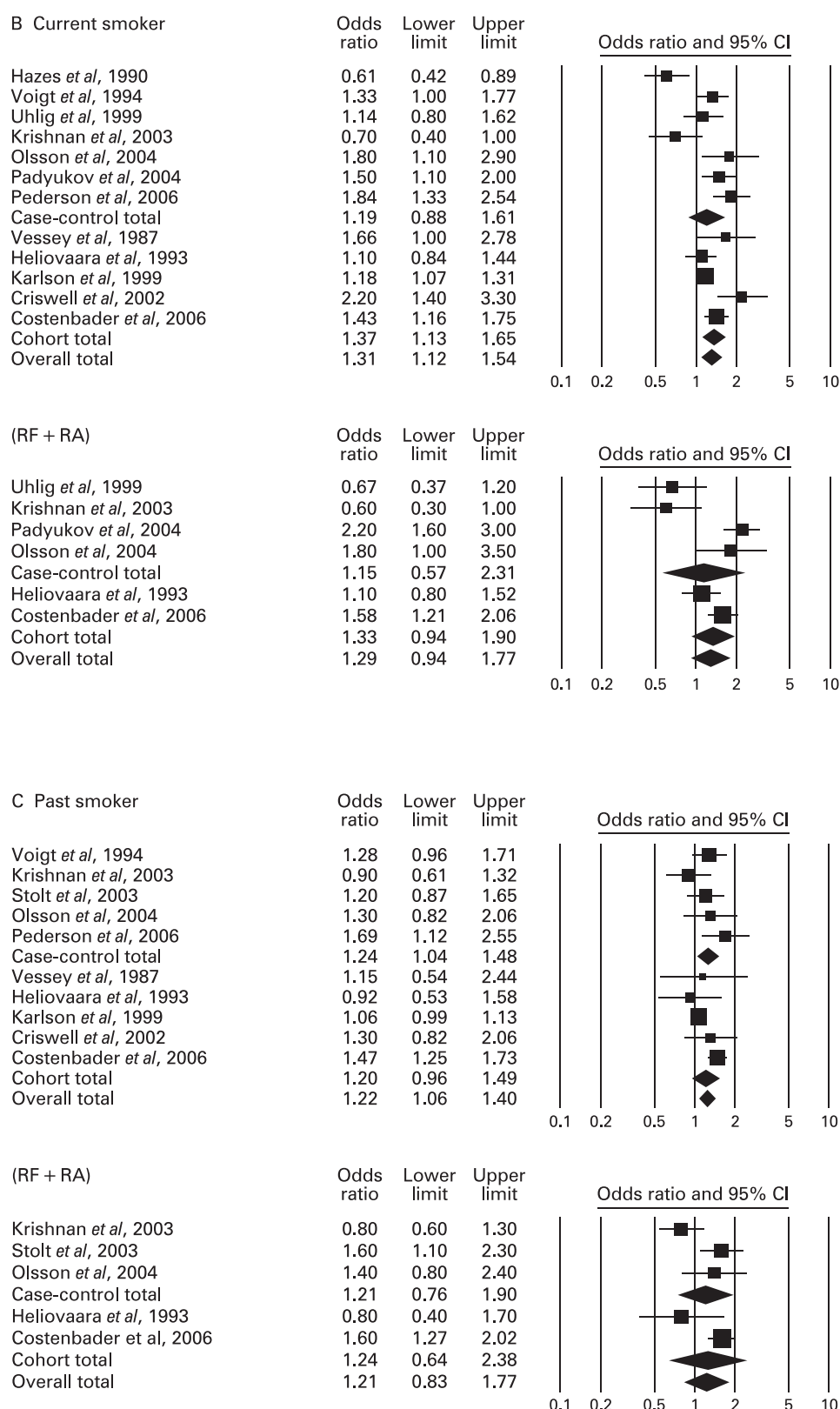
Figure 4 Forest plots of the odds ratio for the risk of developing rheumatoid arthritis (RA) and rheumatoid factor (RF)-positive RA in women.

Figure 4 Continued.



Our analysis has certain limitations. First, some of the studies selected for our meta-analysis also focused on other factors, such as the menopausal state, not only on smoking habits. These differences resulted in statistical heterogeneity among studies of female populations. Second, the selected studies were regionally restricted. All studies we found were performed in the

USA and Europe, so that the validity of extrapolation of the findings to other regions is questionable.

Our results showed that any type of smoking constitutes a significant risk factor for the development of RA, especially for RF-positive RA men and smokers of 20 or more pack-years of smoking. Because RA is associated with a poor quality of life

and life prognosis, we recommend cessation of smoking for current smokers, especially heavy smokers to prevent or reduce the risk of developing RA. Smoking is a preventable risk factor for the development of RA.

Acknowledgements: The authors would like to thank Drs Katsuyasu Saigo, Seiji Kawano, Takeshi Sugimoto and Chiyo Kurimoto for their helpful comments.

Funding: DS is supported by a Hyogo Science and Technology Association grant 18D022.

Competing interests: None.

REFERENCES

- Rayman M, Callaghan A. *Nutrition and arthritis*. Oxford, UK: Blackwell Publishing, 2006.
- Costenbader KH, Kim DJ, Peerzada J, et al. Cigarette smoking and the risk of systemic lupus erythematosus. *Arthritis Rheum* 2004;**50**:849–57.
- Parikh-Patel A, Gold EB, Worman H, et al. Risk factors for primary biliary cirrhosis in a cohort of patients from the United States. *Hepatology* 2001;**33**:16–21.
- Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA* 1993;**269**:479–82.
- Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. *Contraception* 1987;**35**:457–64.
- Hernandez Avila M, Liang MH, Willett WC, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. *Epidemiology* 1990;**1**:285–9.
- Heliovaara M, Aho K, Aromaa A, et al. Smoking and risk of rheumatoid arthritis. *J Rheumatol* 1993;**11**:1830–5.
- Voigt LF, Koepsell TD, Nelson JL, et al. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. *Epidemiology* 1994;**5**:525–32.
- Symmons DP, Bankhead CR, Harrison BJ, et al. 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;**40**:1955–61.
- Karlson EW, Lee IM, Cook NR, et al. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum* 1999;**42**:910–17.
- Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. *J Rheumatol* 1999;**26**:47–54.
- Hutchinson D, Shepstone L, Moots R, et al. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis* 2001;**60**:223–7.
- George J, Levy Y, Shoenfeld Y. Smoking and immunity: an additional player in the mosaic of autoimmunity. *Scand J Immunol* 1997;**45**:1–6.
- Ginnis LC, Ryu JH, Rogol PR, et al. Natural killer cell activity in cigarette smokers and asbestos workers. *Am Rev Respir Dis* 1985;**131**:831–4.
- Hersey P, Prendergast D, Edwards A. Effects of cigarette smoking on the immune system. *Med J Aust* 1983;**2**:425–9.
- Burton RC. Smoking, immunity and cancer. *Med J Aust* 1983;**2**:411–12.
- Hughes DA, Haslam PL, Townshend PJ. Numerical and functional alterations in circulating lymphocytes in cigarette smokers. *Clin Exp Immunol* 1985;**61**:459–66.
- Krishnan E, Sokka T, Hannonen P. Smoking-gender interaction and risk for rheumatoid arthritis. *Arthritis Res Ther* 2003;**5**:158–62.
- Olsson AR, Skogh T, Wingren G. Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann Rheum Dis* 2001;**60**:934–9.
- Stolt P, Bengtsson C, Nordmark B, et al. 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;**62**:835–41.
- Olsson AR, Skogh T, Wingren G. Aetiological factors of importance for the development of rheumatoid arthritis. *Scand J Rheumatol* 2004;**33**:300–6.
- Padyukov L, Silva C, Stolt P, et al. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum* 2004;**50**:3085–92.
- Albano SA, Santana-Sahagun E, Weisman MH. Cigarette smoking and rheumatoid arthritis. *Semin Arthritis Rheum* 2001;**31**:146–59.
- Harrison BJ. Influence of cigarette smoking on disease outcome in rheumatoid arthritis. *Curr Opin Rheumatol* 2002;**14**:93–7.
- Symmons DP. Environmental factors and the outcome of rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2003;**17**:717–27.
- Klareskog L, Padyukov L, Ronnelid J, Alfredsson L. Genes, environment and immunity in the development of rheumatoid arthritis. *Curr Opin Immunol* 2006;**18**:650–5.
- Oliver JE, Silman AJ. Risk factors for the development of rheumatoid arthritis. *Scand J Rheumatol* 2006;**35**:169–74.
- Costenbader KH, Karlson EW. Cigarette smoking and autoimmune disease: what can we learn from epidemiology? *Lupus* 2006;**15**:737–45.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–12.
- Rushton L. Reporting of occupational and environmental research: use and misuse of statistical and epidemiological methods. *Occup Environ Med* 2000;**57**:1–9.
- Egger M, Smith GD, Altman DG, eds. *Systematic reviews in health care. meta-analysis in context*. London, UK: BMJ Books, 2001.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
- Rosenthal R. The "file drawer problem" and tolerance for null results. *Psychol Bull* 1979;**86**:638–41.
- Hazes JM, Dijkmans BA, Vandenbroucke JP, et al. Lifestyle and the risk of rheumatoid arthritis: cigarette smoking and alcohol consumption. *Ann Rheum Dis* 1990;**49**:980–2.
- Krishnan E. Smoking, gender and rheumatoid arthritis—epidemiological clues to etiology. Results from the behavioral risk factor surveillance system. *Joint Bone Spine* 2003;**70**:496–502.
- 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.
- 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;**119**:503.e1–9.
- Heliovaara M, Aho K, Knekt P, et al. Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. *Ann Rheum Dis* 2000;**59**:631–5.
- Criswell LA, Merlino LA, Cerhan JR, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. *Am J Med* 2002;**15**:465–71.
- Criswell LA, Saag KG, Mikuls TR, et al. Smoking interacts with genetic risk factors in the development of rheumatoid arthritis among older Caucasian women. *Ann Rheum Dis* 2006;**65**:1163–7. Epub 3 August 2006.
- Stolt P, Kallberg H, Lundberg I, et al. EIRA study group. Silica exposure is associated with increased risk of developing rheumatoid arthritis: results from the Swedish EIRA study. *Ann Rheum Dis* 2005;**62**:582–6.
- Mikuls TR, Cerhan JR, Criswell LA, et al. Coffee, tea, and caffeine consumption and risk of rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum* 2002;**46**:83–91.
- Karlson EW, Mandl LA, Aweh GN, Grodstein F. Coffee consumption and risk of rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:3055–60.
- Jaakkola JJ, Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. *Int J Epidemiol* 2005;**34**:664–71. Epub 13 January 2005.
- Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. *Arthritis Rheum* 1996;**39**:732–5.
- Klareskog L, McDevitt H. Rheumatoid arthritis and its animal models: the role of TNF-alpha and the possible absence of specific immune reactions. *Curr Opin Immunol* 1999;**26**:1024–34.
- Holmdahl R, Jansson L, Anderson M. Female sex hormones suppress development of collagen-induced arthritis in mice. *Arthritis Rheum* 1986;**29**:1501–9.
- Salem ML. Estrogen, a double-edged sword: modulation of TH1- and TH2-mediated inflammations by differential regulation of TH1/TH2 cytokine production. *Curr Drug Targ: Inflamm Allergy* 2004;**3**:97–104.
- Klippel JH, ed. *Primer on the rheumatic diseases*, 12th edn. Atlanta, GA, USA: Arthritis Foundation, 2002.
- Petrovic-Rackov L, Pejnovic N. Clinical significance of IL-18, IL-15, IL-12 and TNF-alpha measurement in rheumatoid arthritis. *Clin Rheumatol* 2006;**25**:448–52.
- Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004;**50**:3458–67.
- Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology (Oxford)* 2002;**41**:793–800.
- Hannaford PC, Kay CR, Hirsch S. Oral contraceptives and rheumatoid arthritis: new data from the Royal College of General Practitioners' Oral Contraceptive Study. *Ann Rheum Dis* 1990;**49**:744–6.
- Tuomi T, Heliovaara M, Palosuo T. Smoking, lung function, and rheumatoid factors. *Ann Rheum Dis* 1990;**49**:753–6.
- Jonsson T, Thorsteinsson J, Valdimarsson H. Does smoking stimulate rheumatoid factor production in non-rheumatic individuals? *APMIS* 1998;**106**:970–4.
- Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006;**54**:38–46.
- Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. *Ann Rheum Dis* 2006;**65**:366–71.
- Westwood OMR, Nelson PN, Hay FC. Rheumatoid factors: what's new? *Rheumatology* 2006;**45**:379–85.
- Klareskog L, Ronnelid J, Lundberg K, et al. Immunity to citrullinated proteins in rheumatoid arthritis. *Annu Rev Immunol* 2008;**26**:651–75.