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

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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' disease[4] and RA.[5–12] Smoking modulates the immune system[13] 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 analysis[31] 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 number[33] 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

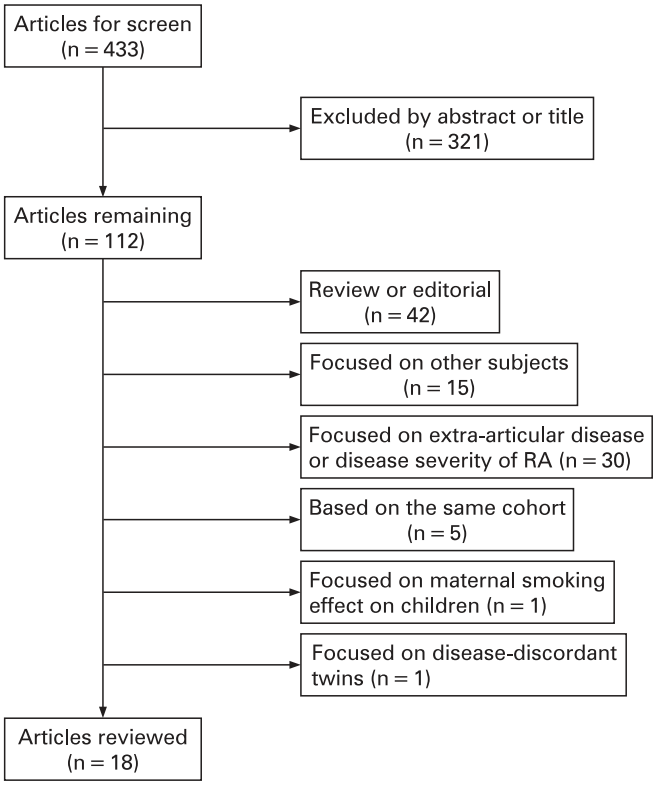


Figure 1 Flow diagram of considered articles. RA, rheumatoid arthritis.

Table 1 Summary of selected studies

Authors, year (ref no)	Gender	RR or OR (95% CI) Ever smokers	Current smokers	Past smokers	Adjustment	Cases/controls or cohort size	Smoking rate (%) Ever smokers	Current smokers	Past smokers	Study design	Study quality	Study area
Vessey *et al*, 1987[5]	Female	1.50 (0.93 to 2.44)	1.66 (1.00 to 2.78)	1.15 (0.54 to 2.43)	(No)	78/600	47.5	33.8	13.6	Cohort	5	Europe
Hazes *et al*, 1990[34]	Female		0.61 (0.42 to 0.89)		Year of birth, age at onset of symtoms, parity, alcohol consumption, oral cotraceptive, marital status, menopause	135/378		43.9		Case–control	10	Europe
Heliovaara *et al*, 2000[38]	Both					512/52 809	47.6	35.6	12.1			
	RF+ cases	1.85 (1.26 to 2.70)	1.93 (1.14 to 3.28)	1.76 (0.92 to 3.38)	Consumption of coffee, age, BMI, serum cholesterol, sex, level of education, smoking, intake of alcohol							
Heliovaara *et al*, 1993[7]	Male	2.04 (1.10 to 3.79)	1.60 (0.70 to 3.80)	1.40 (0.50 to 3.80)	Age	161/28 364	69.7	51.1	18.7			
	RF+ cases	3.86 (2.71 to 5.49)	4.31 (2.87 to 6.50)	2.80 (1.40 to 5.60)						Cohort	13	Europe
	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)	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 *et al*, 1994[8]	Female	1.31 (1.07 to 1.60)	1.33 (1.00 to 1.77)	1.28 (0.96 to 1.71)	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)										
Symmons *et al*, 1997[9]	Both	1.66 (0.95 to 3.06)	0.95 (0.56 to 1.61)		Sex,social class	90/93	54.5					
	RF+ cases	2.92 (0.92 to 9.21)								Case–control	12	Europe
	RF− cases	1.20 (0.70 to 2.09)										
Uhlig *et al*, 1999[11]	Both		1.46 (1.10 to 1.94)		Age, sex, education, marital status, employment, BMI	361/5469		32.9				
	Male		2.38 (1.45 to 3.92)		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)							Case–control	13	Europe
	Female		1.14 (0.8 to 1.62)		Age, education, marital status, employment, BMI	262/2843		32.2				
	RF+ cases		0.67 (0.37 to 1.20)									
	RF− cases		1.54 (0.99 to 2.39)									
Karlson *et al*, 1999[10]	Female	1.13 (1.08 to 1.18)	1.18 (1.07 to 1.31)	1.06 (0.96 to 1.13)	Age, race, education, age at menarche, pregnancy history, menopausal status, postmenopausal HRT	7697/37 7481	45.2	13.2	32.0	Cohort	13	USA
Hutchinson *et al*, 2001[12]	Both	1.81 (1.22 to 2.19)			(Not clearly shown)	239/239	58.3	31.8	26.6.	Case–control	10	Europe
Olsson *et al*, 2001[19]	Male	1.97 (1.18 to 3.29)	2.20 (1.10 to 4.20)		Age, socioeconomic status	91/203	65.6					
	RF+ cases	2.42 (1.36 to 4.32)										
	PY <20	1.39 (0.56 to 3.44)										
	PY >20	2.70 (1.20 to 5.80)								Case–control	12	Europe
	female	1.61 (1.06 to 2.45)			Age, socioeconomic status	154/222	38.0					
	RF+ cases	1.94 (1.24 to 3.01)										

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			
	PY <20	1.57 (0.99 to 2.50)										
	PY >20	1.80 (0.70 to 4.60)										
Criswell *et al*, 2002[39]	Female	1.70 (1.02 to 2.85)	2.20 (1.40 to 3.30)	1.30 (0.80 to 2.00)	Age, alcohol use, coffee consumption, marital status,	154/31 336	33.0	13.4	17.1	Cohort	13	USA
	PY <20	1.10 (0.60 to 1.80)			BMI, age at menopause, oral contraceptives, HRT							
	PY >20	1.99 (1.41 to 2.81)										
Krishnan *et al*, 2003[31]	Male	1.56 (0.95 to 2.58)	1.20 (0.70 to 2.00)	2.00 (1.20 to 3.20)	Age, BMI, education, HAQ index,	318/426	76.5	19.7	56.8			
	RF+ cases	1.88 (1.24 to 2.86)	1.50 (0.80 to 2.60)	2.30 (1.30 to 3.90)	general health assessment, pain							
	RF− cases	1.16 (0.63 to 2.22)	0.80 (0.30 to 1.80)	0.90 (0.40 to 1.90)						Case–control	12	Europe
	female	0.81 (0.60 to 1.09)	0.70 (0.40 to 1.00)	0.90 (0.60 to 1.30)	Age, BMI, education, HAQ index,	777/1104	30.6	11.1	19.5			
	RF+ cases	0.74 (0.53 to 1.02)	0.60 (0.30 to 1.00)	0.80 (0.60 to 1.30)	general health assessment, pain							
	RF− cases	0.90 (0.63 to 1.28)	0.84 (0.50 to 1.50)	0.94 (0.60 to 1.50)								
Krishnan, 2003[35]	Both	1.34 (1.00 to 1.81)	1.42 (1.13 to 1.80)	1.08 (0.87 to 1.34)	No	644/1509	49.5	20.9	28.9			
	Male	2.29 (1.35 to 3.90)			Age, race, education, income, living alone	203/543	68.3			Case–control	10	USA
	Female	0.98 (0.67 to 1.42)			Age, race, education, income, living alone	441/946	39.2					
Stolt *et al*, 2003[20]	Male	1.40 (0.80 to 2.30)	1.30 (0.70 to 2.40)	1.40 (0.80 to 2.50)	Age, residential area	190/245	74.7	37.0	37.7			
	RF+ cases	1.90 (1.00 to 3.50)	1.80 (0.80 to 4.10)	1.90 (0.90 to 3.80)								
	RF− cases	0.80 (0.40 to 1.60)	0.70 (0.30 to 1.60)	0.90 (0.40 to 1.90)						Case–control	13	Europe
	Female	1.30 (1.00 to 1.70)	1.40 (1.00 to 2.00)	1.20 (0.90 to 1.70)	Age, residential area	489/602	64.4	33.6	19.1			
	RF+ cases	1.70 (1.20 to 2.30)	1.80 (1.30 to 2.60)	1.60 (1.10 to 2.30)								
	RF− cases	0.80 (0.60 to 1.20)	0.90 (0.50 to 1.40)	0.80 (0.50 to 1.30)								
Padyukov *et al*, 2004[22]	Both		1.50 (1.20 to 2.00)		Age(10 strata), sex, residential area	858/1048		23.6				
	RF+ cases		2.20 (1.70 to 3.00)									
	RF− cases		0.80 (0.60 to 2.20)									
	Male		1.70 (1.00 to 2.90)		Age(10 strata), residential area	246/312		19.7				
	RF+ cases		3.30 (1.70 to 6.30)							Case–control	13	Europe
	RF− cases		0.60 (0.30 to 1.30)									
	Female		1.50 (1.10 to 2.00)		Age(10 strata), residential area	612/736		25.5				
	RF+ cases		2.20 (1.60 to 3.00)									
	RF− cases		0.80 (0.60 to 1.30)									
Olsson *et al*, 2004[21]	Male	2.54 (1.55 to 4.16)	2.90 (1.40 to 6.40)	2.30 (1.20 to 4.40)	Age	74/382	63.8	22.2	44.3	Case–control	11	Europe
	RF+ cases	4.60 (2.20 to 9.60)	5.80 (1.90 to 17.10)	3.80 (1.40 to 10.20)								
	PY <20	2.20 (1.15 to 4.22)										
	PY >20	2.50 (1.20 to 5.10)										
	Female	1.52 (1.09 to 2.12)	1.80 (1.10 to 2.90)	1.30 (0.80 to 2.00)	Age	159/368	52.8	19.7	30.8	Case–control	11	Europe
	RF+ cases	1.56 (1.03 to 2.36)	1.80 (1.00 to 3.50)	1.40 (0.80 to 2.40)								

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			
	PY <20	1.33 (0.86 to 2.04)										
	PY >20	1.60 (0.90 to 3.10)										
Costenbader *et al*, 2006[37]	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,					Cohort	14	USA
	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							
	PY <20	1.19 (0.95 to 1.50)										
	PY >20	1.72 (1.41 to 2.11)										
Pedersen *et al*, 2006[36]	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, maritul status,	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)	coffee consumption, alcohol consumption, BMI							
					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 Costenbarader *et al*.[37] Stolt *et al* 2005[41] also used the results of the EIRA study (as did Stolt *et al* 2003[20] and Padykov *et al*[22]), but we excluded one because it was an analysis of a subgroup. Criswell *et al* 2002[39] 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 study[7] 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 study[5] 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.

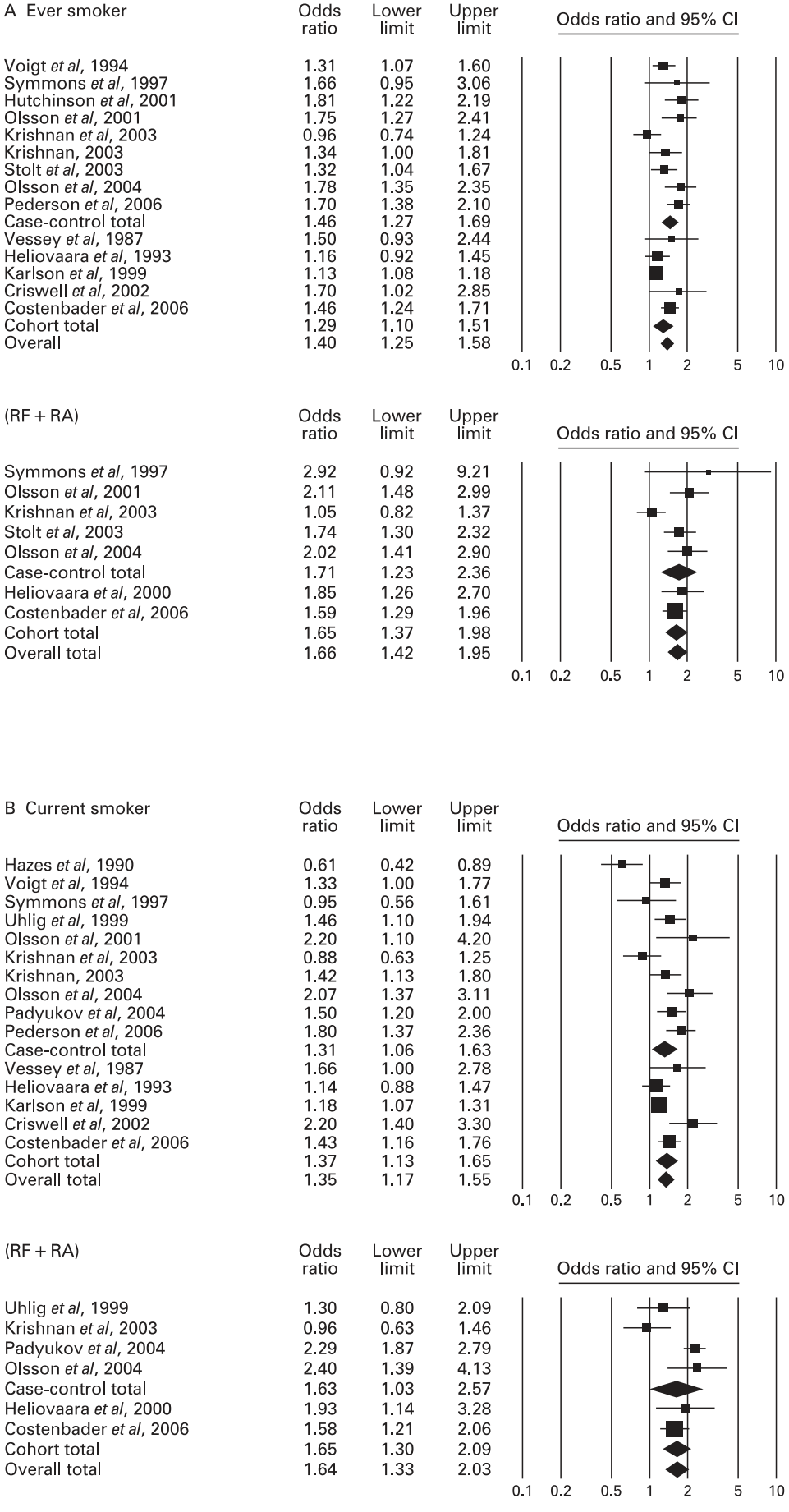
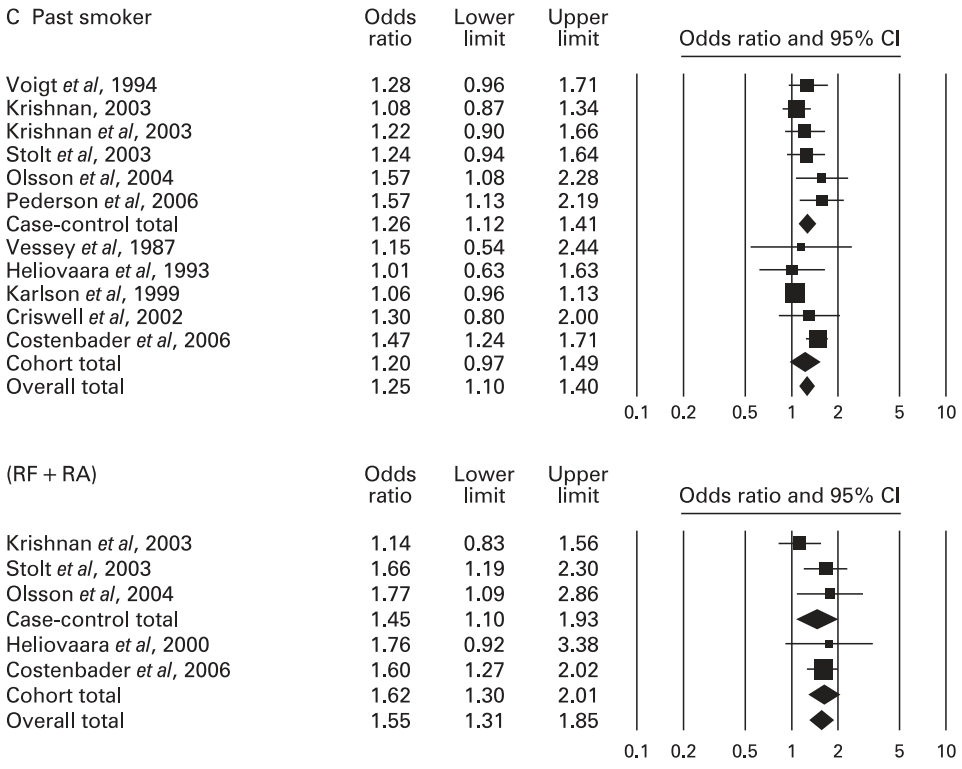


Figure 2 Continued.



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 Salem[48] found that oestrogen inhibited the production of T-helper type 1 pro-inflammatory cytokines such as tumour necrosis factor-alpha, 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]

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.

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

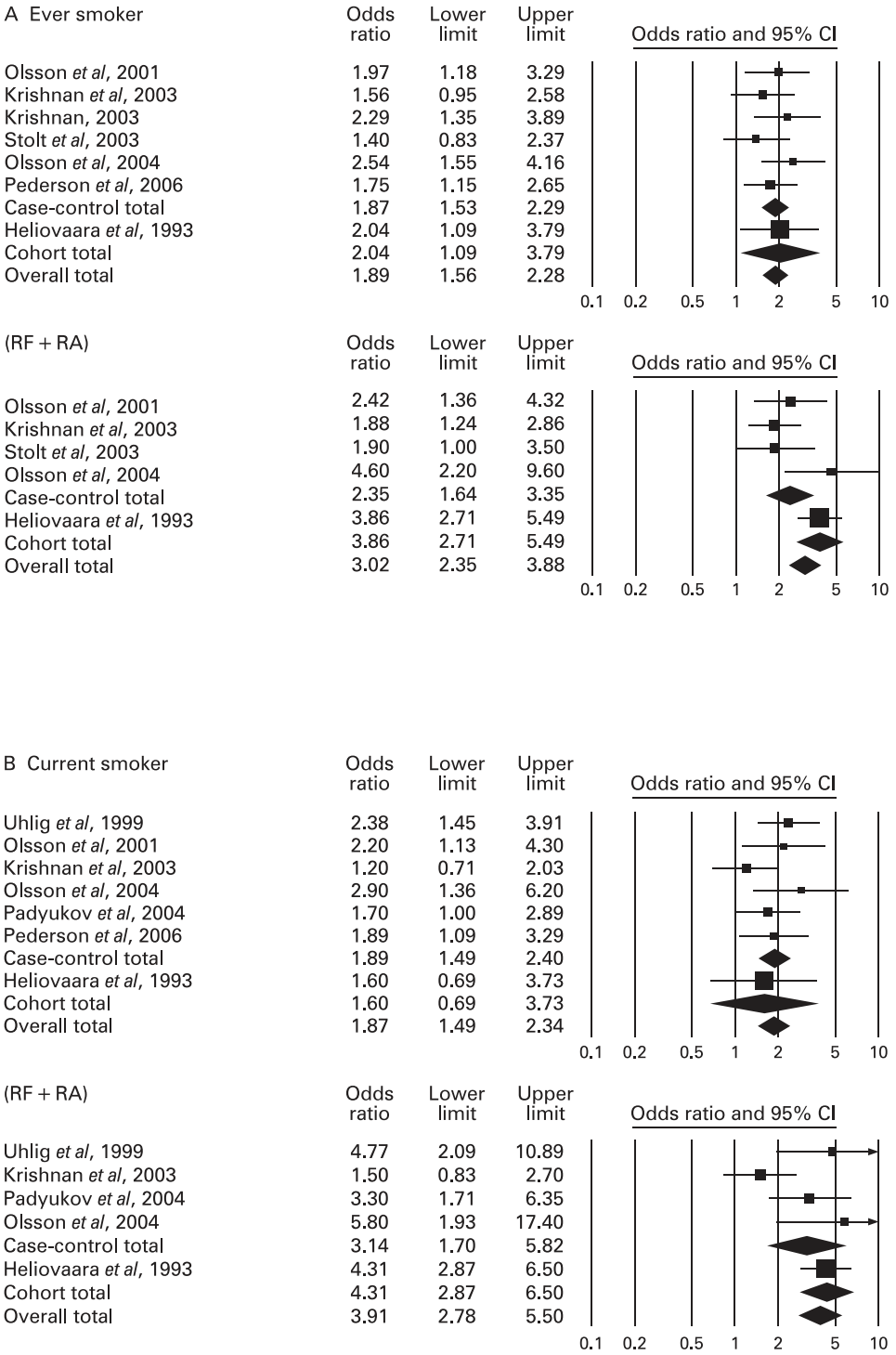
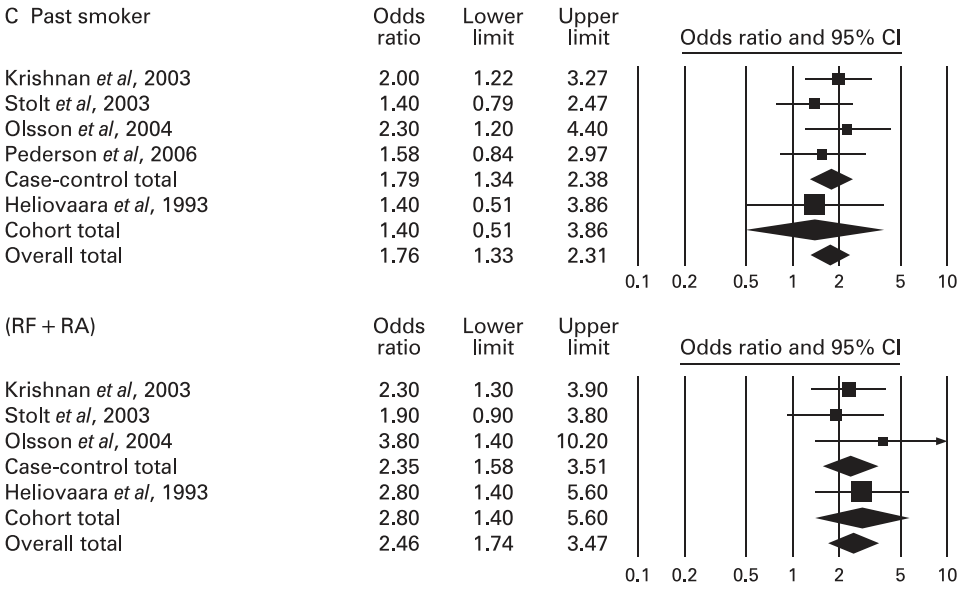


Figure 3 Forest plots of the odds ratio for the risk of developing rheumatoid arthritis (RA) and rheumatoid factor (RF)-positive RA in men.

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.

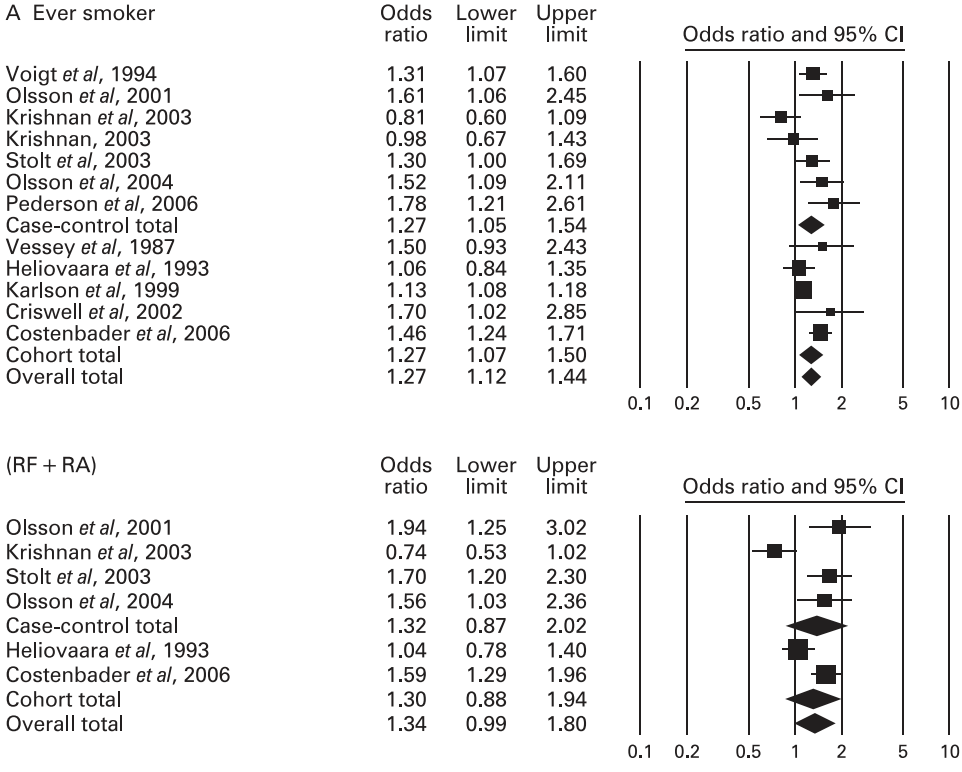
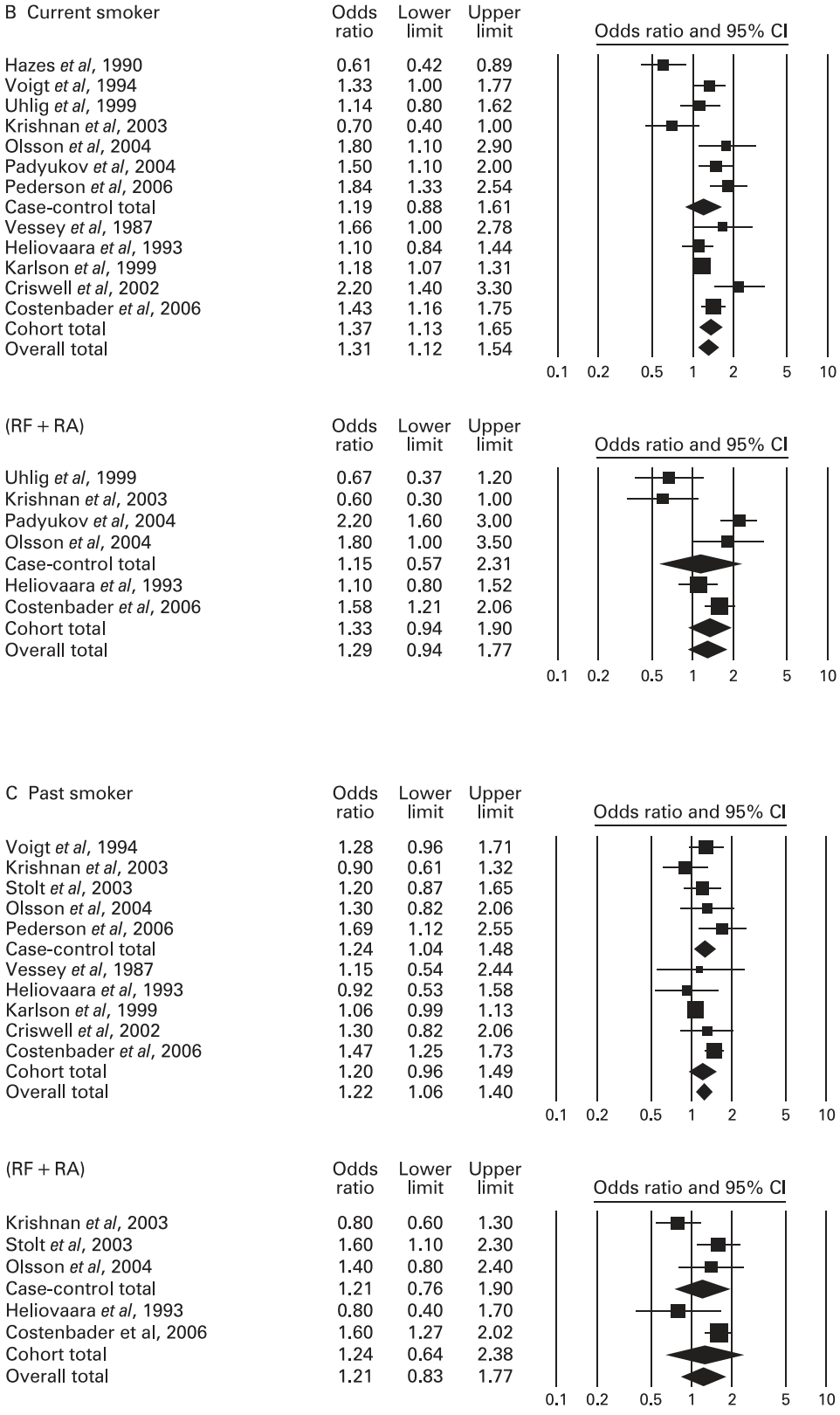


Figure 4 Continued.



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.

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